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
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The chemistry of carboxylic acids and esters
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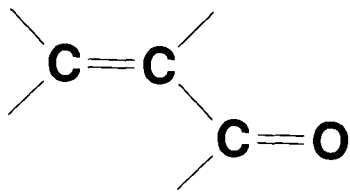
UPDATES

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



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Part 1

Edited by

SAUL PATAI

and

ZVI RAPPOPORT

The Hebrew University, Jerusalem

1989

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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.

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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)
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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.

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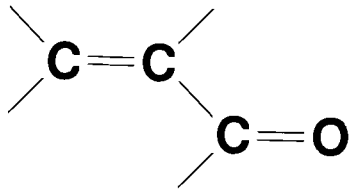

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Foreword

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(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.

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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

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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···C=Ö can be partitioned into two simple 'chromophores' (C=C, C=Ö). 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=Ö, 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···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.

(1) **(2)** **(3)** **(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

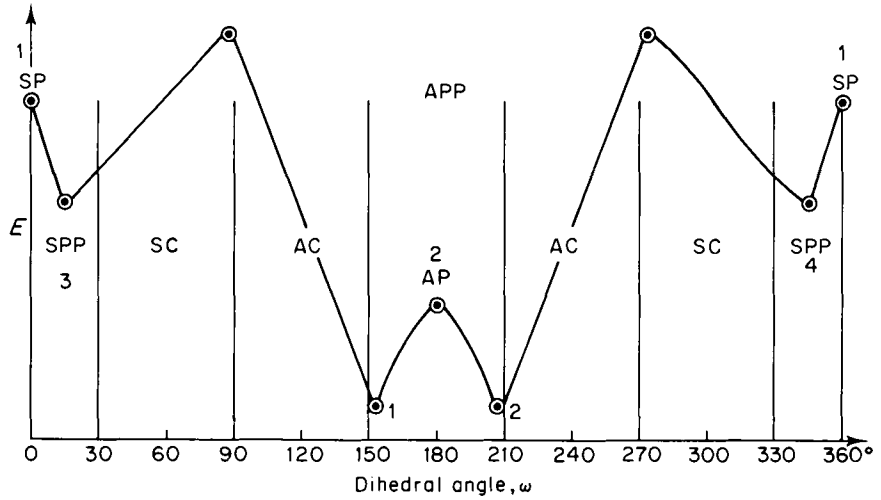


FIGURE 1. $E(\omega)$ curve for internal rotation about C^2—C^3 in $C^4{=}C^3$—$C^2{=}O^1$ in the most eventful case (schematic). In particular cases, some of the sketched features disappear

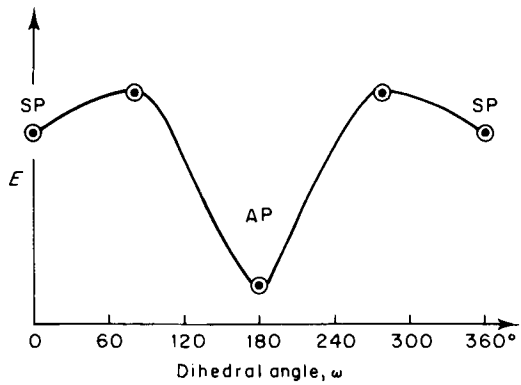


FIGURE 2. $E(\omega)$ curve for internal rotation about $C^2—C^3$ in $C^4=C^3—C^2=O^1$ in the least eventful case (schematic)

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.

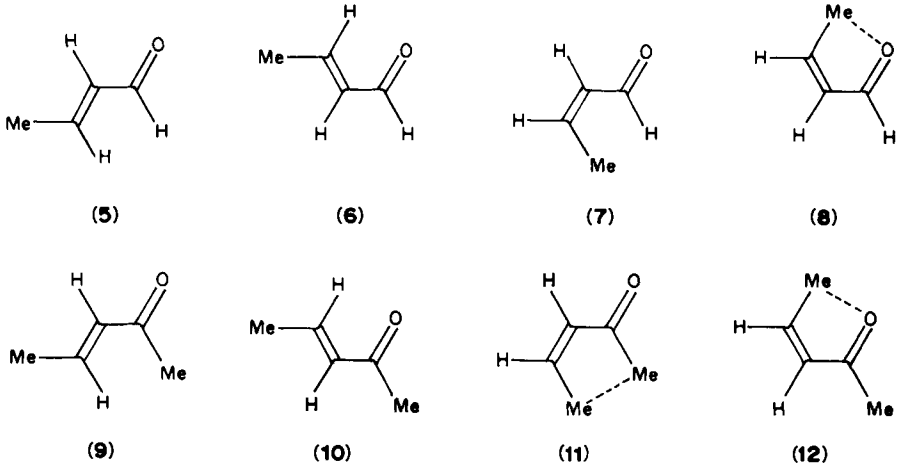
To illustrate the gradation in steric effects, let us examine two pairs of π diastereomers (formulas **5–12**). (π Diastereomers are isomers of the type formerly referred to as '*cis–trans* isomers about double bonds'. In the *E* diamer of XCH=CHCHO, X and CHO are on opposing sides of C=C ('entgegen'); 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.



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

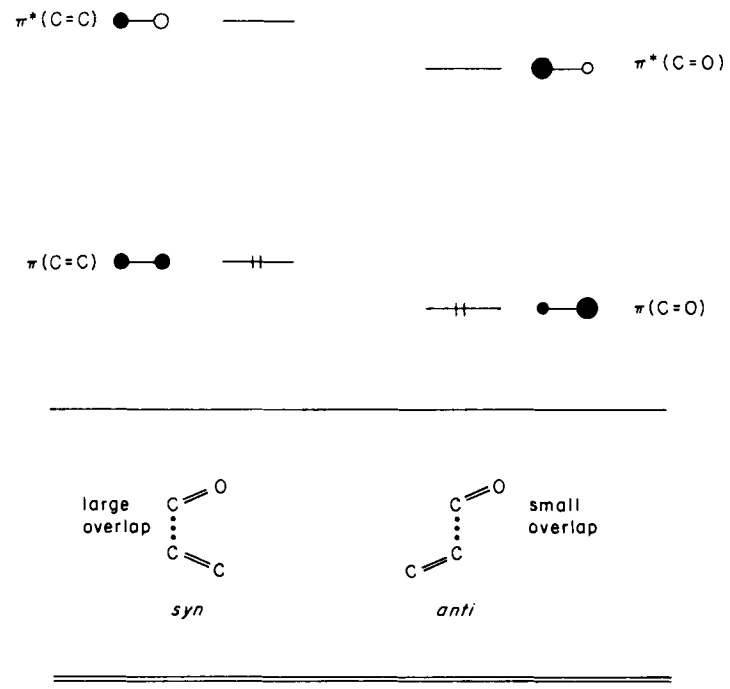


FIGURE 3. Top: Molecular orbitals of the π type in C=C (left) and C=O (right). Bottom: Disposition of fragments in the *syn* and *anti* varieties of C=C···C=O

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 $700 \pm 40\,cm^{-1}$, which corresponds to about $2.0\,kcal\,mol^{-1}$. 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 $530 \pm 40\,cm^{-1}$, that is $1.5\,kcal\,mol^{-1}$, 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).

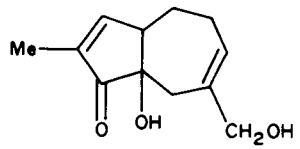
To summarize, stabilizing factors affect *anti* more than *syn*, while the destabilizing factor affects *syn* more than *anti*.

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].

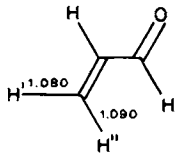
V. TWO PROTOTYPES

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**.



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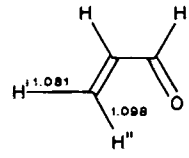


(15)

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.

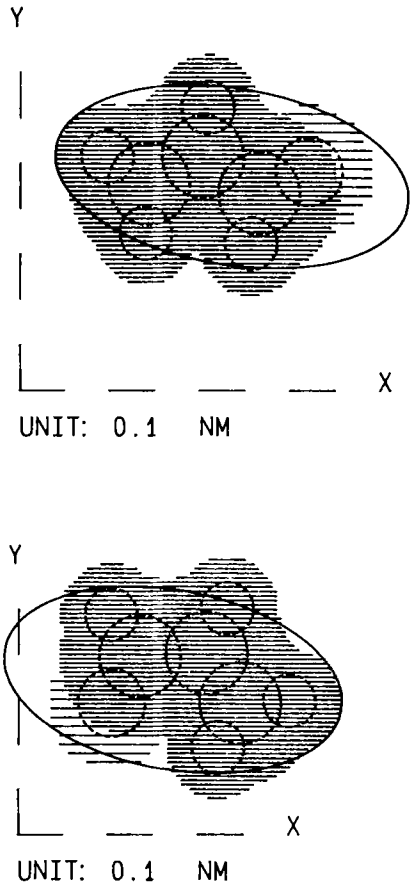


FIGURE 4. Cut through the van der Waals body of *anti* planar (top) and *syn* planar acrolein (bottom), in the first plane (xy) of their respective systems of principal coordinates. Circles represent atoms at half the van der Waals atomic radii. The hatched area cuts through the body, as defined by the 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)

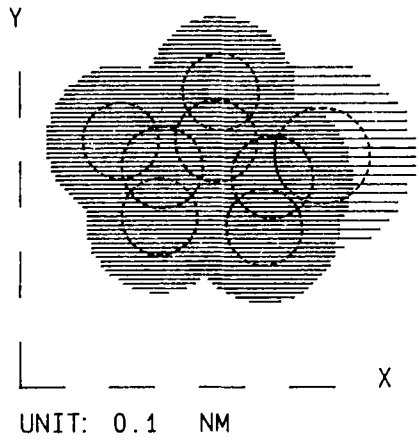
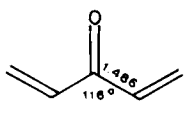


FIGURE 5. Cut through the 'inflated body' of *anti* planar acrolein. For details see caption to Figure 4

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.



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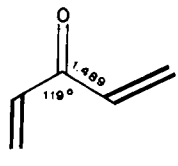

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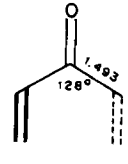


(18)

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 $\chi_1-\chi_4$ constitutes the basis of π-type molecular orbitals (π MOs), and the entire set $\chi_1-\chi_5$ 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:

For C=C,	$\phi_1 = a(\chi_1 + \chi_2)$	π
	$\phi_2 = a(\chi_1 - \chi_2)$	π^*
For C=O,	$\phi_3 = r\chi_3 + s\chi_4$	π
	$\phi_4 = s\chi_3 - r\chi_4$	π^*
	$\phi_5 = \chi_5$	n

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

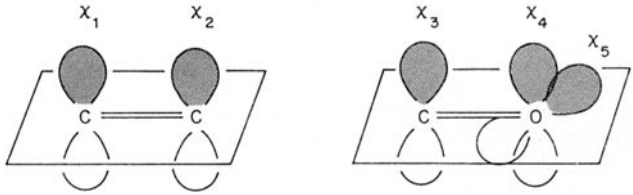


FIGURE 6. Basis set for component interaction in C=C···C=O. Atomic orbitals χ_1 to χ_4 are perpendicular to the skeletal planes. Orbital χ_5 is in plane

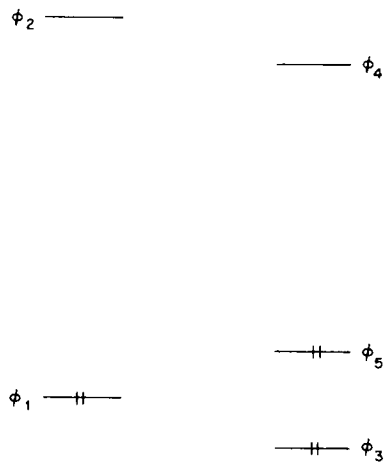


FIGURE 7. Sequencing of some molecular orbitals of C=C and C=O in C=C···C=O

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.

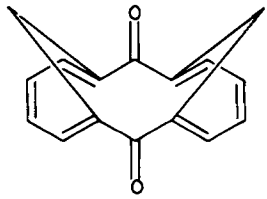
By vertical ionization potentials (IPs), the highest occupied MO of α,β-unsaturated aldehydes and ketones resides mainly in the nonbonding oxygen orbital. In the notation of

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).



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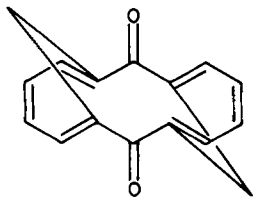


(20)

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

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

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,

$$\Psi_5 = 2^{-\frac{1}{2}}\{A_{41} + A_{14}\} \tag{2}$$

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 ν 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):

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

(c) K integrals (also bielectronic):

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

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 $P_1 = -I_1 - J_{11}$. By introducing P_1 and striking out the nul Ks, equation 10 reduces to

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

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 $\pi(\mathrm{C{=}C}) \rightarrow \pi^*(\mathrm{C{=}O})$.

(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 $\beta_{ab} = \beta_{ba}$,

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

(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 $(\chi_1, \chi_2, \cdots)$ 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,

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

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

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

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

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

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 ($\sim$ 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)↔C—C=C—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 $n \rightarrow \pi^*$ 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 $\dot{N}$, and the effect of alkyl substituents was taken account of by modifying the atomic parameters of C and of $\dot{N}$. 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

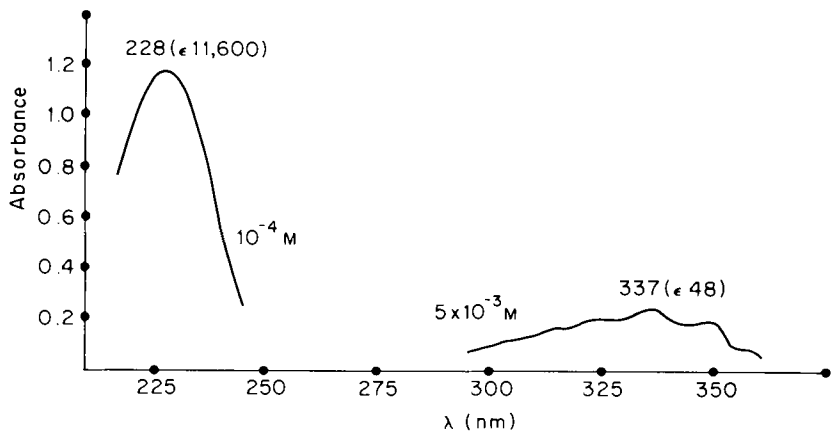
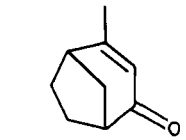


FIGURE 8. Ultraviolet spectrum of 4-methylbicyclo[3.2.1]oct-3-en-2-one (**21**) in cyclohexane

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**).



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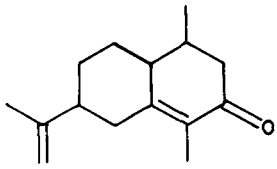

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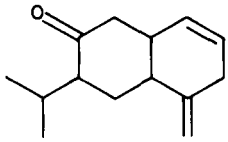

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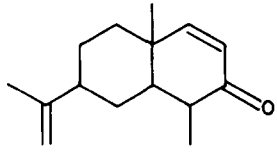


(24)

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

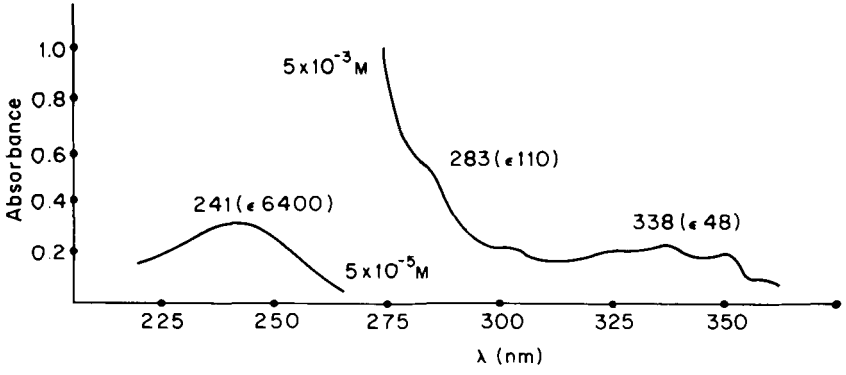
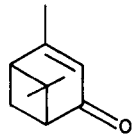


FIGURE 9. Ultraviolet spectrum of verbenone (**25**) in cyclohexane

$\pi \rightarrow \pi^*$ 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.



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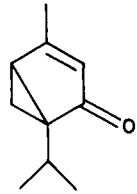
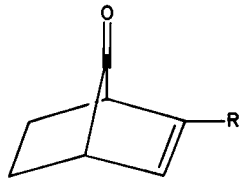


(26)

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.

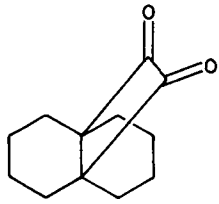
The compound in question is bicyclo[2.2.1]hept-2-en-7-one (7-norbornenone, **27**, R = H). In this and germane compounds, a strong absorption in the far UV tails into the near UV, and it was hard to tell whether the tail is practically smooth or carries a weak 'mystery band'. The problem was solved by 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 (ε73) 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.



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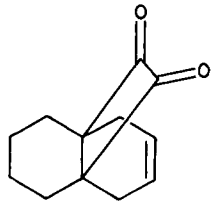

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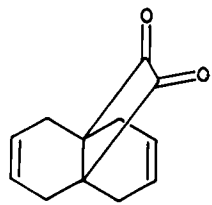

(30)

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, $\arccos(-1 \times 0.6791) = 133°$ or 47°;

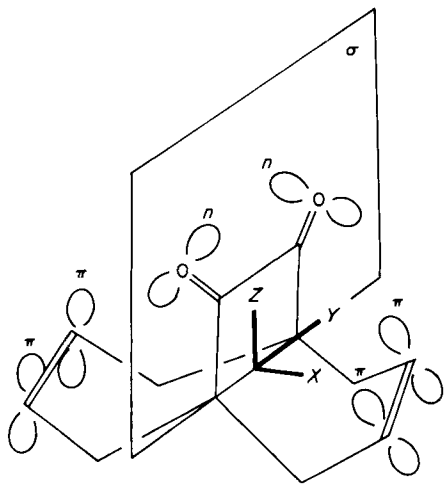

FIGURE 10. Conformation, orbitals (n and π) and symmetry plane (σ) in the calculation of the diene-dione **30**

(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 $n, \pi(C{=}C), \sigma \rightarrow \pi^*(C{=}O)$.

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 $\sim 170°$. 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–CI 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.

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The Chemistry of Enones
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CHAPTER **2**

Structural chemistry of enones

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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.

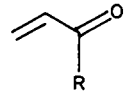
If the number of structures for a certain class of enones was big enough, a histogram of the C=O, C–C and C=C bond lengths of the enone group is given. The observations with the maximum and minimum values and single outliers were examined specially and removed for the calculation of the mean value if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

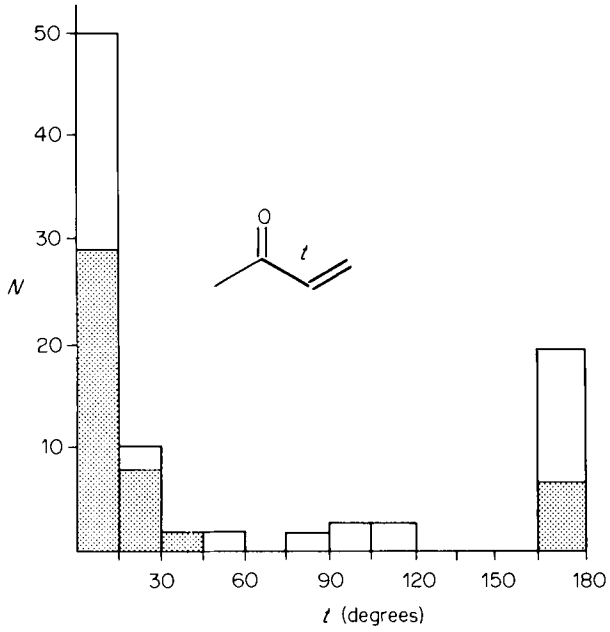
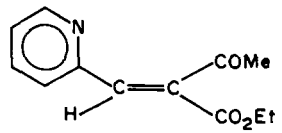
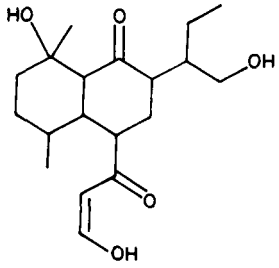


FIGURE 1. Histogram of the torsion angle C=C—C=O (deg, absolute value) in acyclic enones with aliphatic substituent at the carbonyl carbon. The shaded area shows enone fragments with a hydrogen atom on C(2)

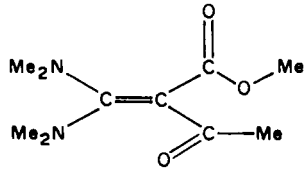


(1)

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



(2)



(3)

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

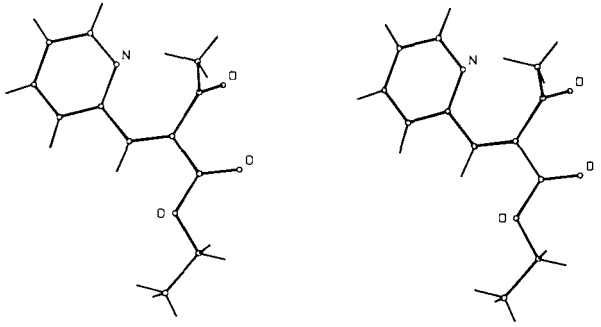


FIGURE 2. Stereoscopic drawing of the structure of 1. Example of a nonplanar enone fragment

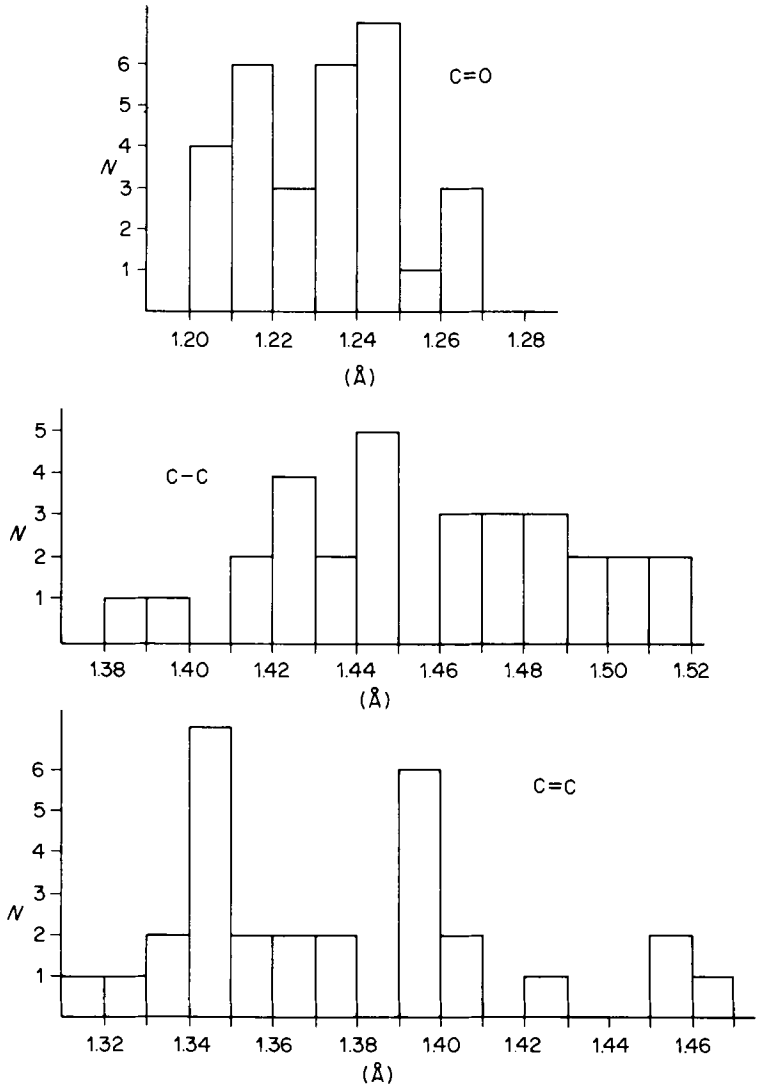


FIGURE 3. Histograms of bond lengths of the enone fragments of the acyclic enones with aliphatic substituent at the carbonyl group

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

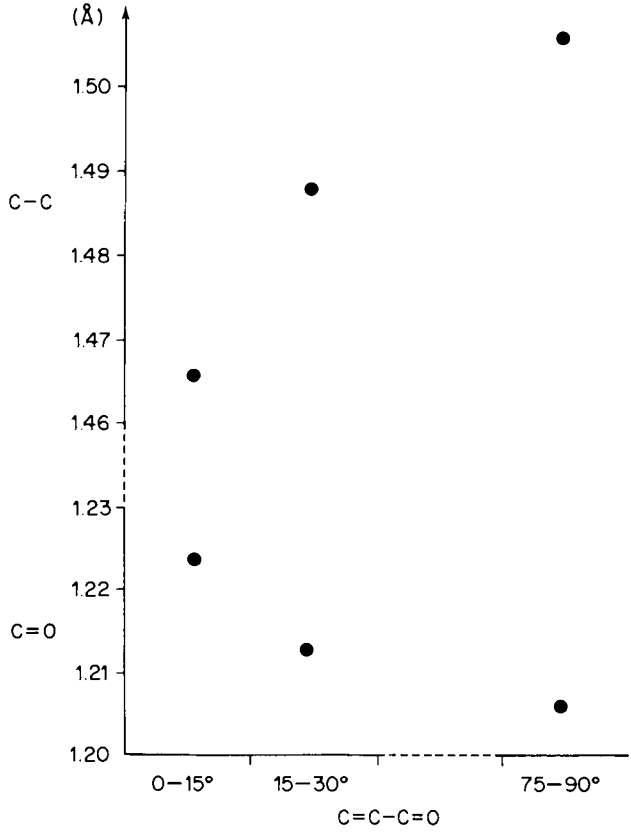
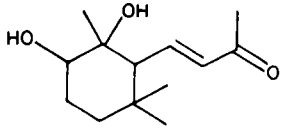


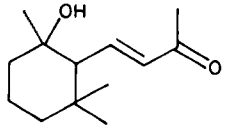
FIGURE 4. Mean value of the C—C and C=O bond lengths at different dihedral angles C=C—C=O of acyclic enones (for selection see text)

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**)

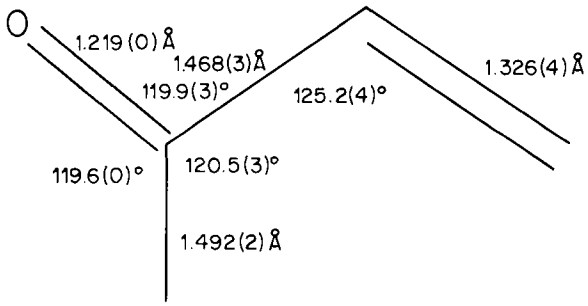


FIGURE 5. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the enone fragment of the acyclic enones (**4**) and (**5**) with aliphatic substituent at the carbonyl group

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

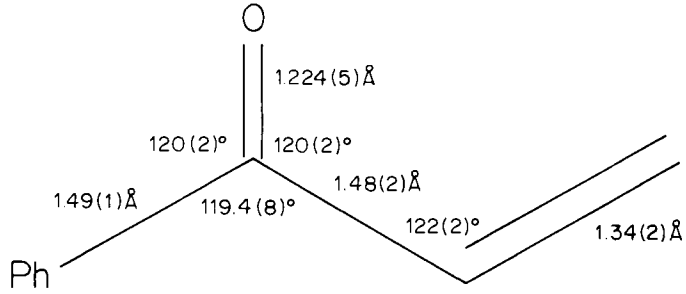


FIGURE 6. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the enone fragment of the acyclic enones with aromatic substituent at the carbonyl group

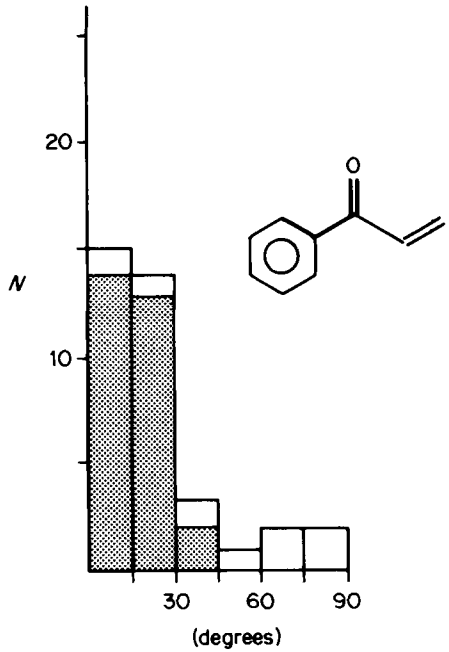
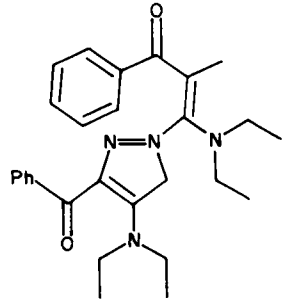


FIGURE 7. Histogram of the absolute value of the O=C—C_{ar}—C_{ar} torsion angles (deg) in enones with aromatic substituent at the carbonyl group. Only the smaller of the two possible values is used. Shaded area includes only aromatic substituents with H atoms in *ortho* position

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.

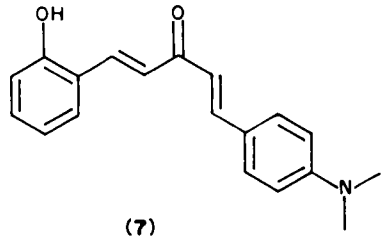


(6)

3. *Acyclic dienones*

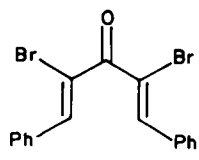
There are very few examples of known structures of acyclic dienones. In fact, there is only one structure with a reported accuracy of AS = 1, the *m*-dinitrobenzene clathrate of 1-

(*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

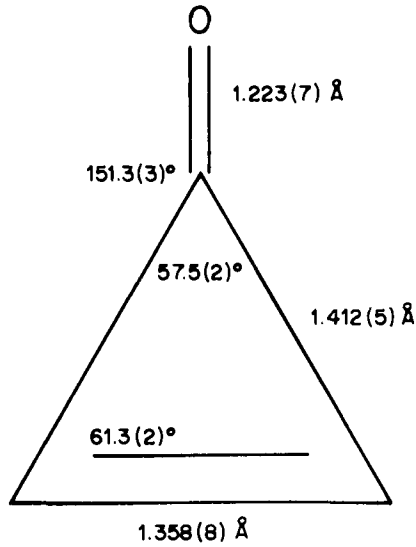
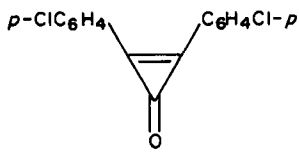
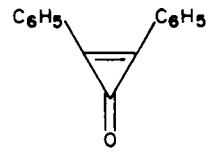


FIGURE 8. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the cyclopropenone fragment

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-

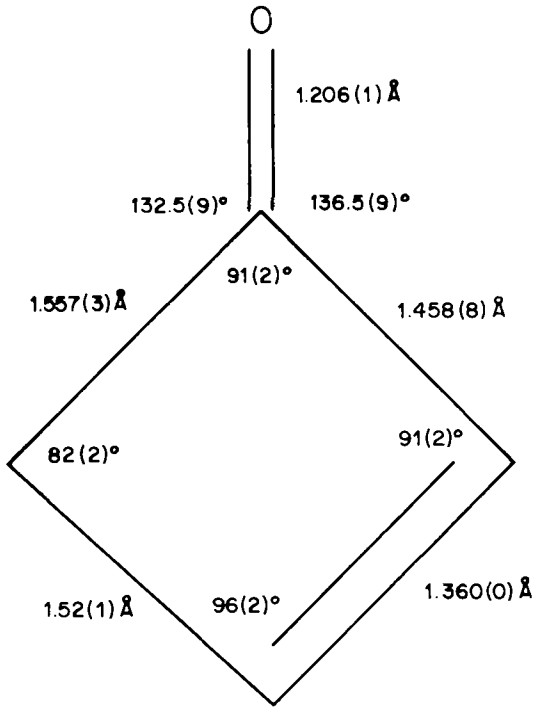
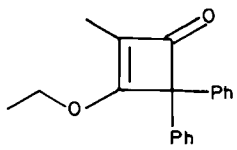
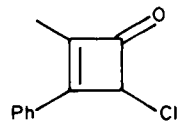


FIGURE 9. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the cyclobutenone fragment

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**

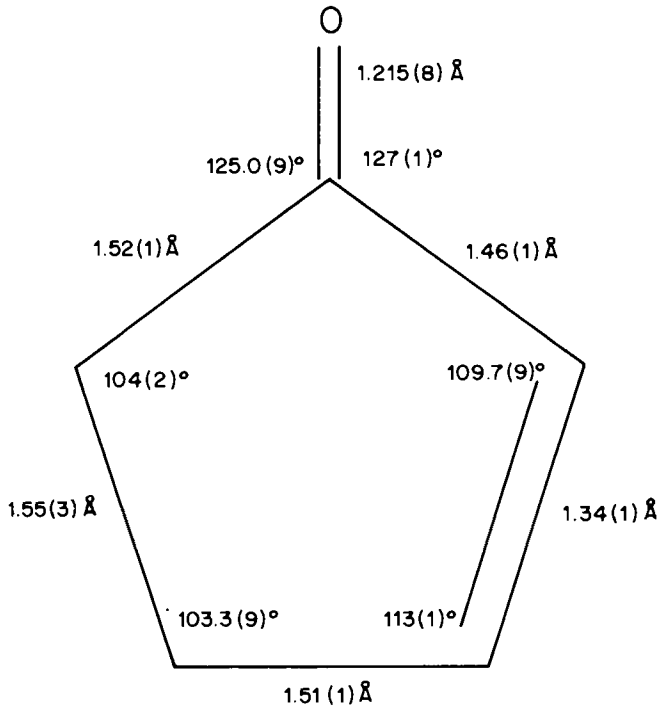


FIGURE 10. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the cyclopenten-2-one fragment

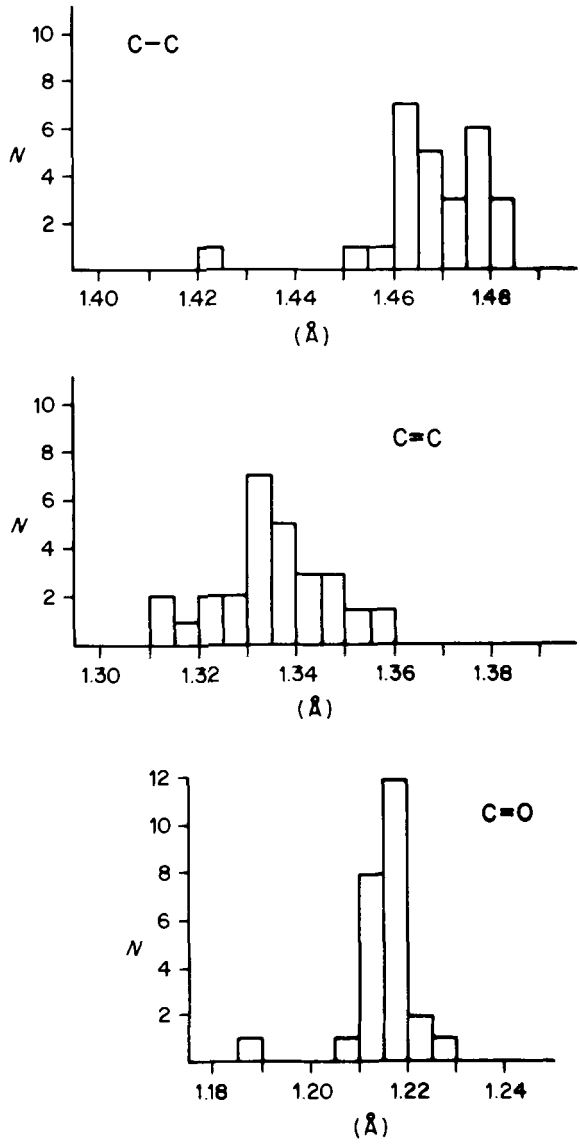
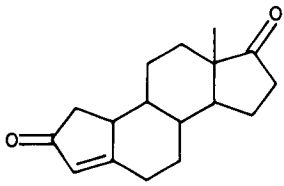


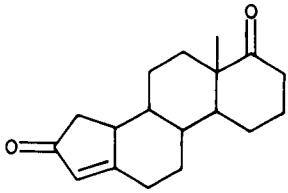
FIGURE 11. Histograms of the bond lengths (Å) of the enone fragments in cyclopent-2-en-1-ones

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

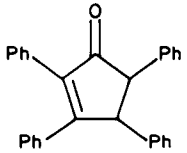
substituted enones like *trans*-2, 3, 4, 5-tetraphenylcyclopent-2-en-1-one (**15**)[20] (1.351 Å) or *trans*-4-cyano-2, 3, 4, 5-tetraphenylcyclopent-2-en-1-one (**16**)[21] (1.358 Å). The two phenyl groups attached to the double bond are turned out of the plane of the enone fragment by 40° and 45° in **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.



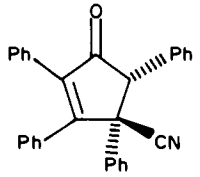
(13)



(14)

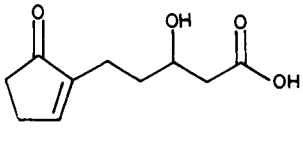


(15)

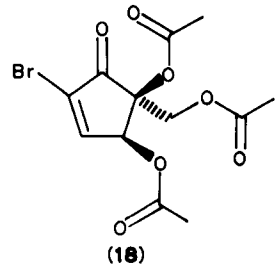


(16)

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)

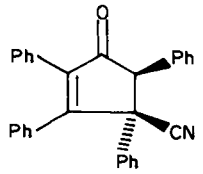


(18)

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

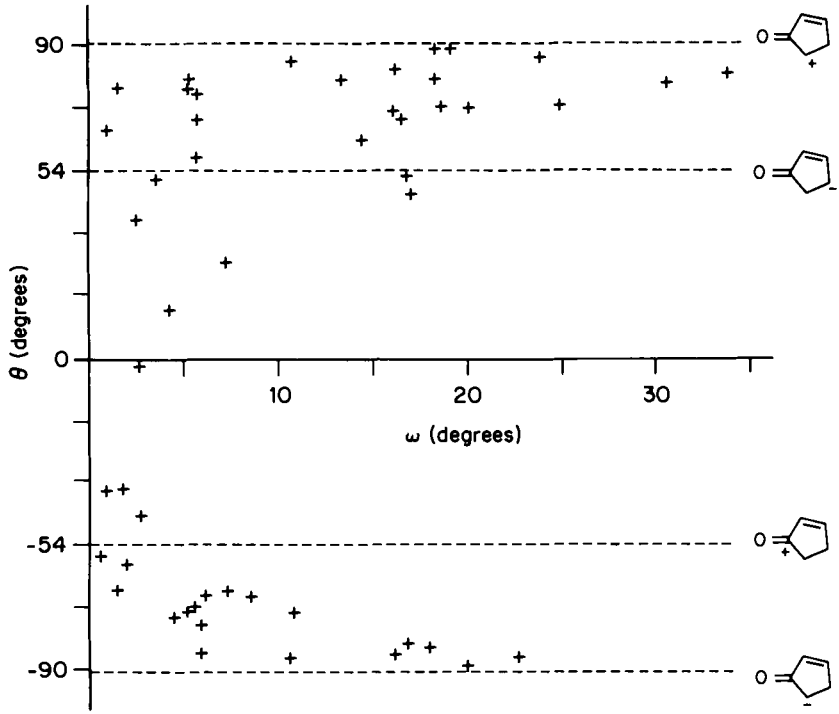
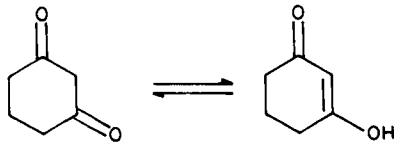


FIGURE 12. Scattergram of the plane deformation ω (deg) vs. conformation phase angles θ (deg) in cyclopent-2-en-1-one rings. The dashed lines indicate phase angles of envelope forms with the marked ring atom as the out-of-plane atom

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



(20)

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

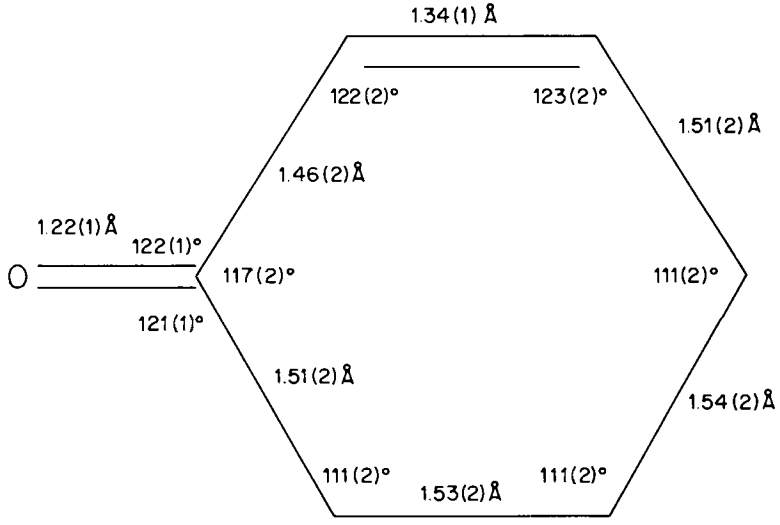


FIGURE 13. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the cyclohex-2-en-1-one fragment

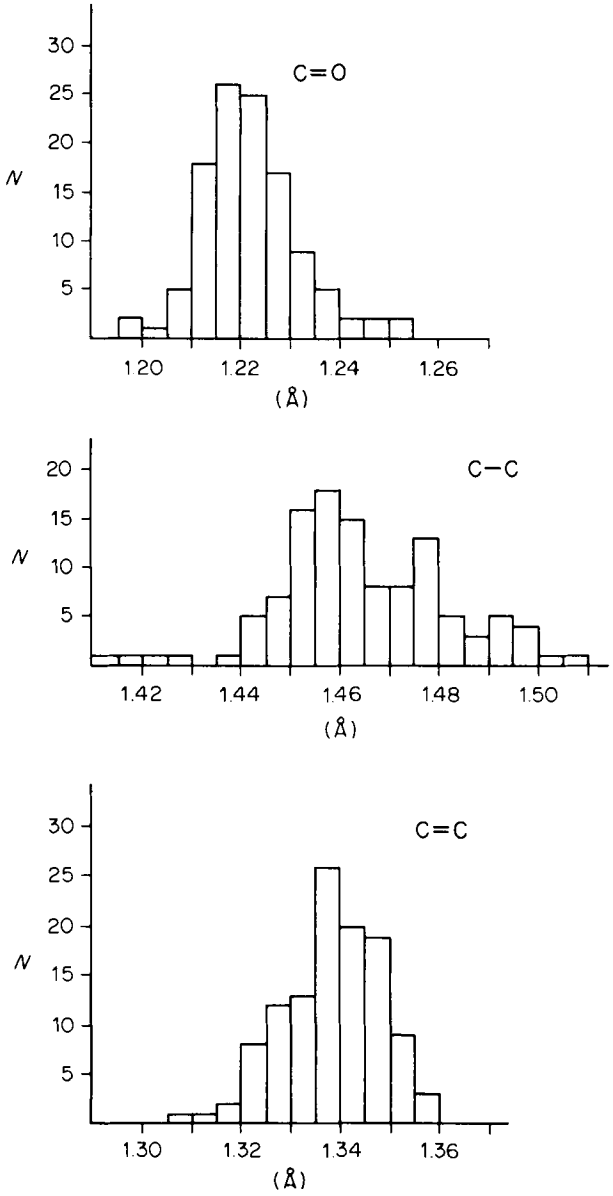
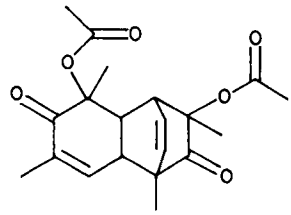


FIGURE 14. Histograms of the bond lengths (Å) of the enone fragments in cyclohexenones

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 struc-



(21)

ture 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),

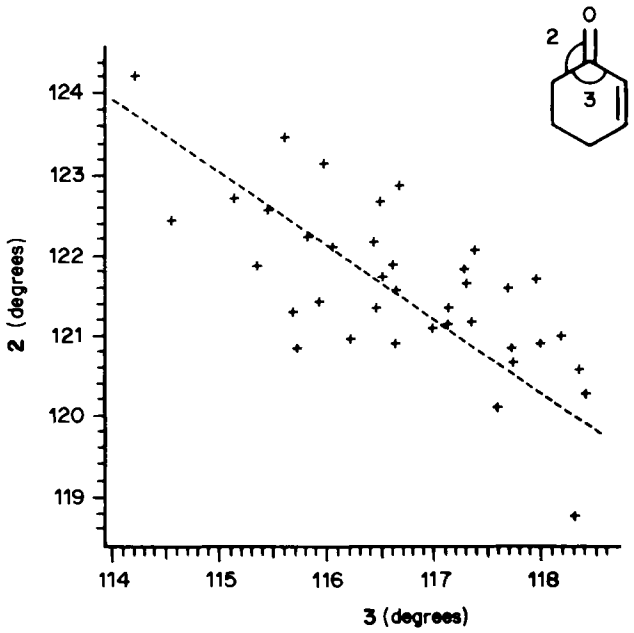
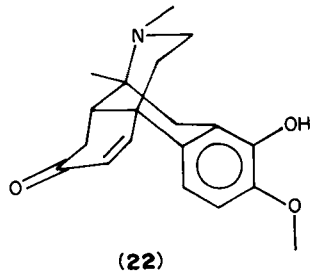


FIGURE 15. Scattergram of the bond angles O=C—C(6) (2) and C(2)—C(1)—C(6) (3) in cyclohexenone rings. The slope of the linear regression line is −0.94, the correlation coefficient is 0.71

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.

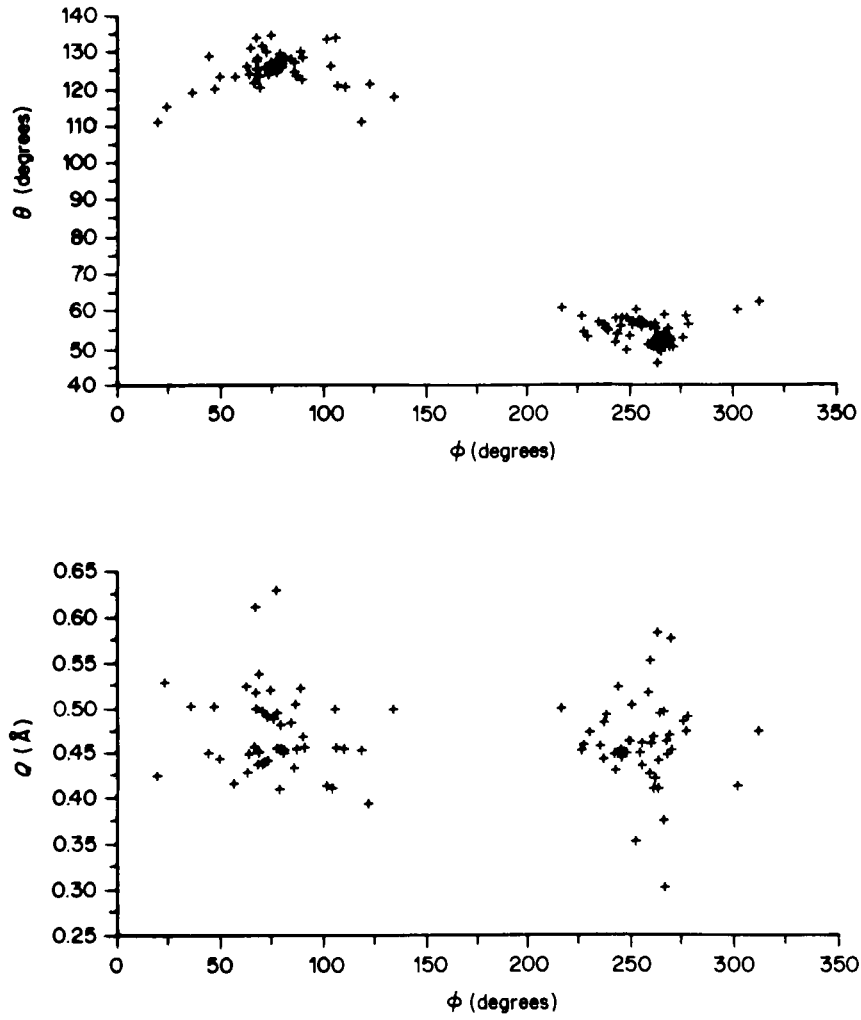


FIGURE 16. Scattergrams of the puckering parameters of cyclohexenone rings. Top: diagram of the two phase angles θ (deg) and ϕ (deg). Bottom: diagram of the total puckering amplitude Q (Å) with the phase angle ϕ is given

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.

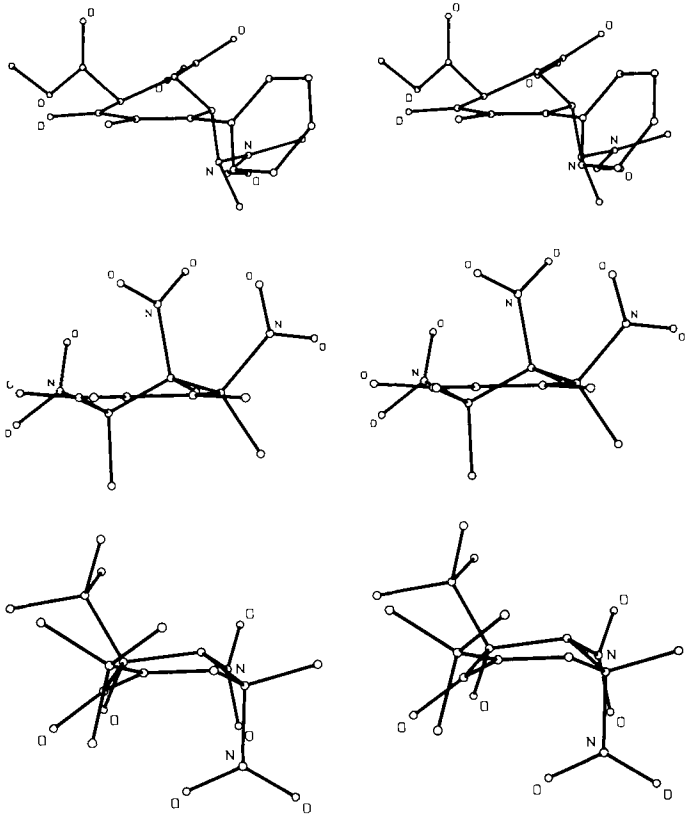
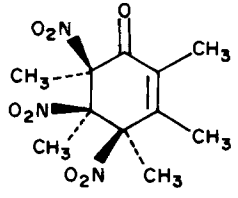
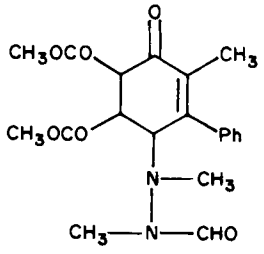


FIGURE 17. Stereoscopic drawings of typical ring conformations in cyclohexenones: half boat in the structure of **24** (top), half-chair form of the ring in **23** (middle) and boat form of the ring in **25** (bottom)

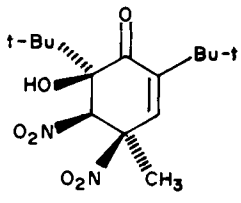
The bottom of Figure 17 shows the structure of 2, 6-di-*t*-butyl-c-6-hydroxy-4-methyl-4, c-5-dinitrocyclohex-2-en-1-one (**25**)[33], which is the only example of a boat form.



(23)



(24)



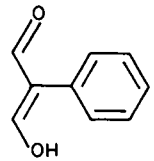
(25)

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.

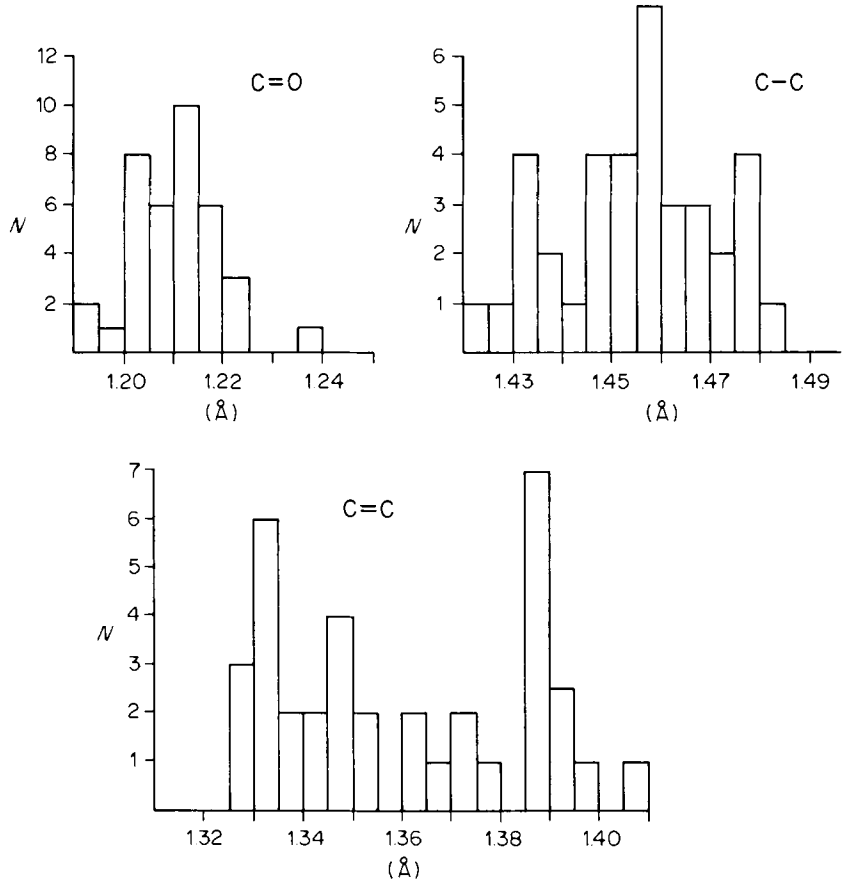
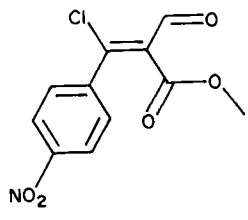
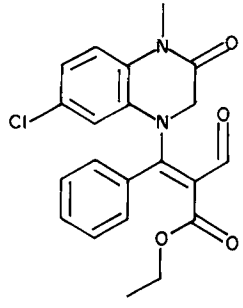


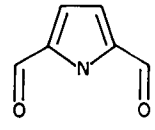
FIGURE 18. Histograms of the bond lengths (Å) in enal fragments



(27)



(28)



(29)

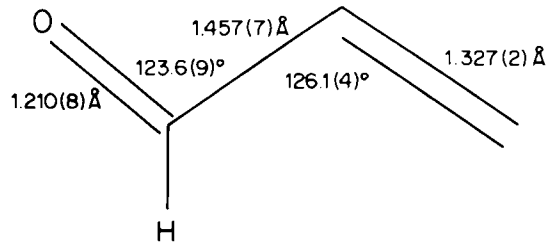


FIGURE 19. Averaged bond lengths (Å) and bond angles (deg) with standard deviations of the enal fragment

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

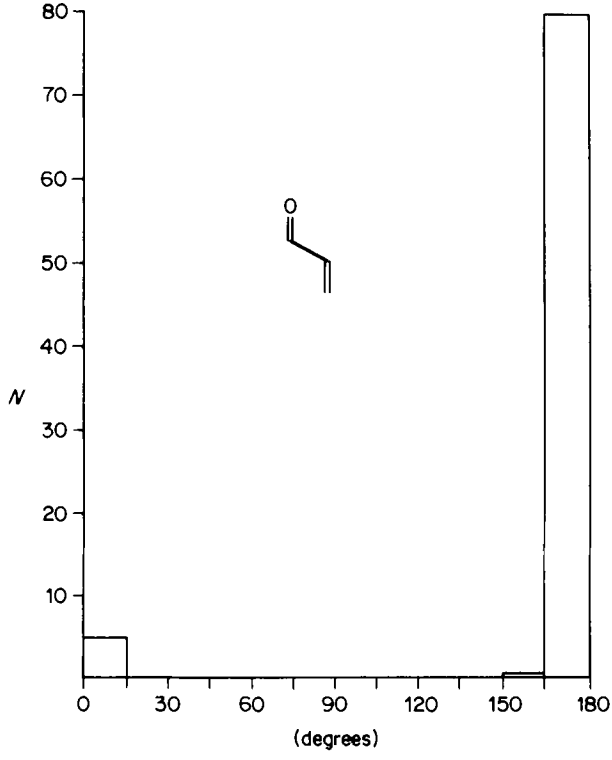
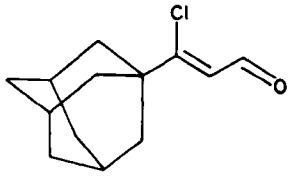
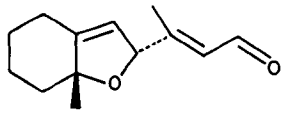


FIGURE 20. Histogram of the C=C—C=O torsion angle (deg, absolute value) in the enal fragments

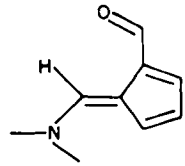
128° can be found in two independent molecules of 2-formyl-6-(*N*,*N*-dimethylamino)pentafulvene (**32**)[41], where the widening can be attributed to steric repulsion between the carbonyl oxygen and the C(6) hydrogen.



(30)

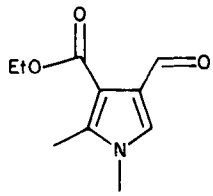


(31)

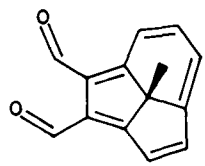


(32)

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)



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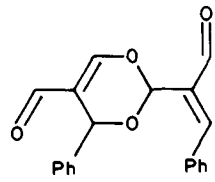

(35)

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The Chemistry of Enones
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CHAPTER 3

Conformations, chiroptical and related spectral properties of enones

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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.

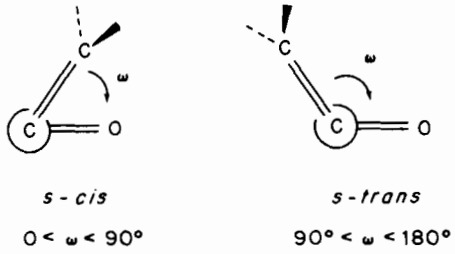
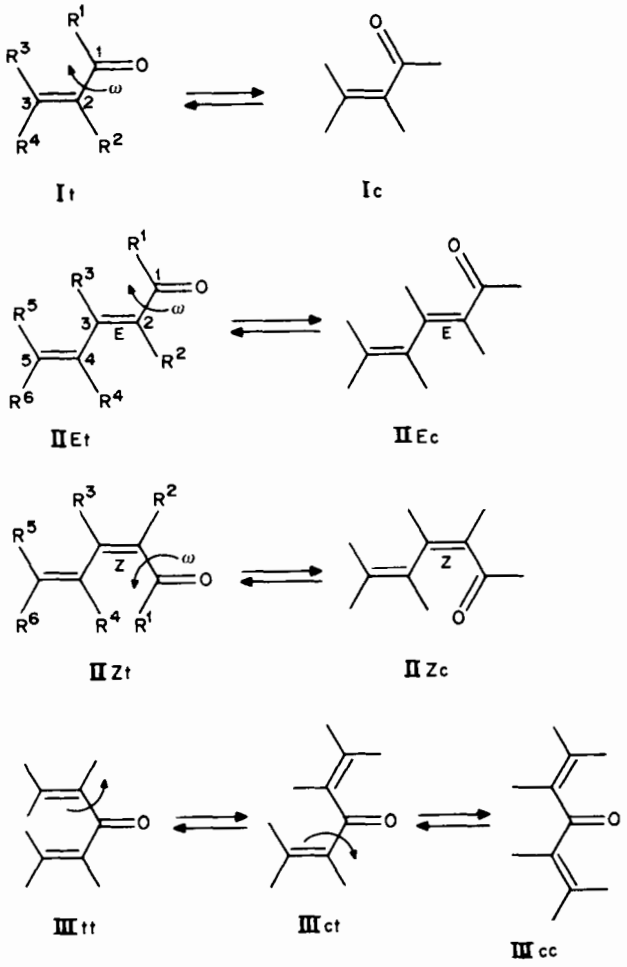


FIGURE 1. Conformation of an enone group with positive helicity ($\omega > 0$)



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.

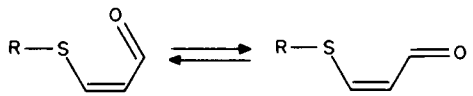
The scope of this chapter includes discussion of conformation of enones (**I**, R^1 = alkyl) and enals (**I**, R^1 = H), linearly conjugated dienones (**II**, R^1 = alkyl) and dienals (**II**, R^1 = H), as well as cross-conjugated dienones (**III**). The substituents R can constitute a part of a ring 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 $\omega = 180°$.

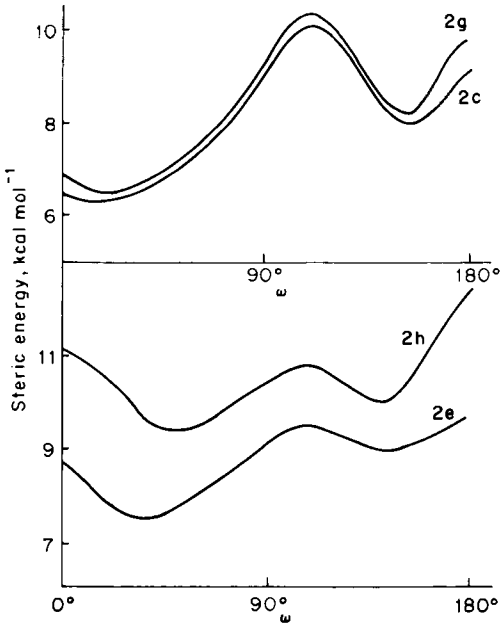
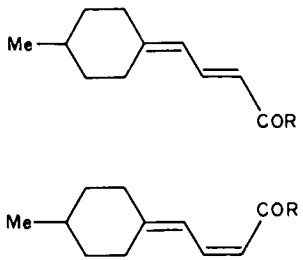


FIGURE 2. Calculated potential curves for enones **2c**, **2e**, **2g** and **2h**. Reprinted with permission from T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **98**, 2745 (1976). Copyright (1976) American Chemical Society

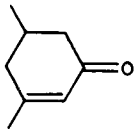
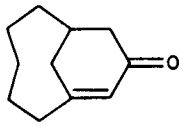
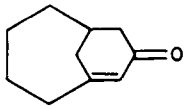
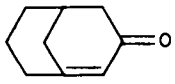
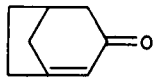
As expected, the calculated steric energy differences between planar *s-cis* and *s-trans* conformations of *E* and *Z* dienals and dienones **3–6** follow the trend already discussed for structurally equivalent enals **1c**, **1d** and enones **2c**, **2d**[6].



	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 $\quad \Delta\nu > 60\text{–}70\,cm^{-1}$

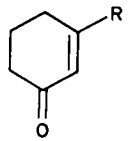
s-trans $\quad \Delta\nu < 60\text{–}70\,cm^{-1}$

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].

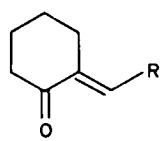
As can be seen enals ($R^1 = H$) prefer *s-trans* conformation, in agreement with the calculated vibrational spectra for this conformation[11]. As shown by the IR spectra, the amount of *s-cis* acrolein (**1a**), normally about 5%, could be enriched to about 28% by trapping from thermal molecular beams 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[a]	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})		$\nu_{C=C}$ (cm^{-1})		$\Delta\nu$ (cm^{-1})	
	Ic	It	Ic	It	Ic	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]

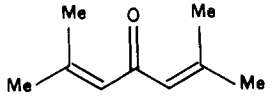
Compound		R	$\nu_{C=O}$	$\nu_{C=C}$	Solvent
R, COMe	**3**		1680	1630 1570	neat
	5		1665	1630 1570	neat
	18	Me	1690 1670	1643 1596	CCl_4
	19	Ph	1693 1676 1657	1626 1615 1601 1592	CCl_4
Me, COMe	**20**		1681 1663	1640 1611 1580	neat
	21	Me	1690	1634 1580	CCl_4
R, COMe	**22**	Ph	1685	1615 1581 1568	CCl_4

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).

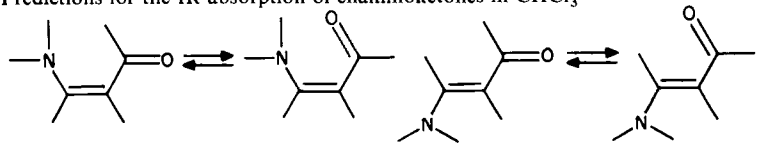
The conformations of $C_{(3)}$-heterosubstituted enones are comparable to those of the corresponding methyl analogs (cf. Table 4). Due to lowering of the $\nu_{C=C}$ frequencies the $\Delta\nu$ values for $C_{(3)}$-heterosubstituted enones are higher than those of alkyl-substituted enones. Thus, $\Delta\nu$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

TABLE 7. IR data for heterosubstituted acyclic enones **1** (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'' ($\sigma_{CC,CH}-\pi_1^*$)	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.

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

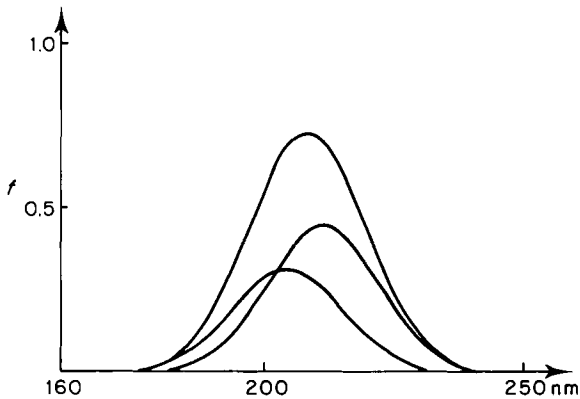


FIGURE 3. Summation of Gaussian curves for acrolein (**1a**)[5]. Reprinted with permission from T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **98**, 2745 (1976). Copyright (1976) American Chemical Society

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

[a] Reprinted with permission from T. Liljefors 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 [λ_{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 $\pi-\pi^*$ 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 $\pi-\pi^*$ 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 $n-\pi^*$ and the lowest singlet $\pi-\pi^*$ 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 $n-\pi^*$ transition, although directly not observable, remains the lowest energy singlet transition in retinals in non-hydrogen bonded solvents[48].

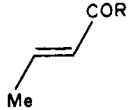
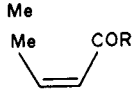
2. $\pi-\pi^*$ Band: substitution and conformational effects

The position of the enone (enal) $\pi-\pi^*$ 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_2Bu^t	226	11,500
	Me (**2c**)	221.5	8,500
	Bu^t (**14c**)	222	8,600
	CMe_2Bu^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 λ_{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 λ_{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 λ_{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 λ_{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 λ_{max} for a given substitution pattern (Figure 4) requires knowledge of ω; on the other hand knowledge of λ_{max} enables one to estimate the enone torsional angle ω.

Several regularities in the calculated λ_{max}/ω 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 λ_{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 λ_{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:

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

where f_{planar} and ε_{planar} are respectively the oscillator strength and molar absorption

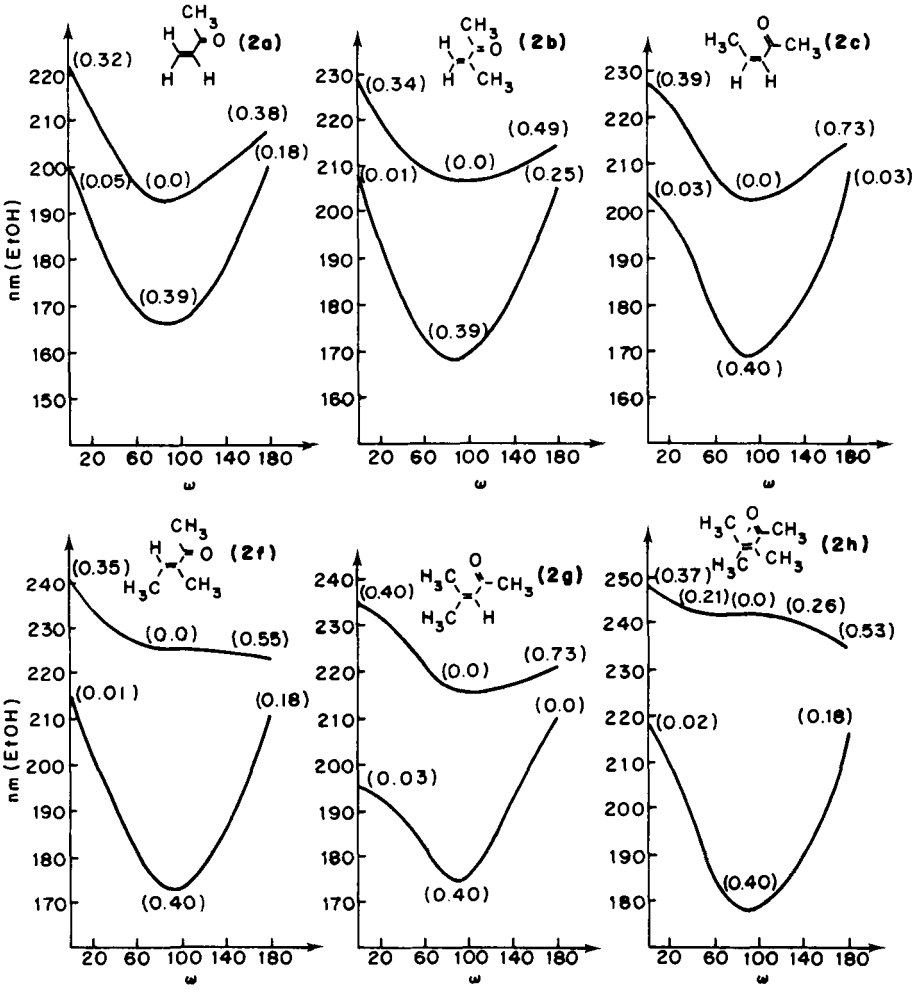
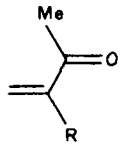


FIGURE 4. The two $\pi-\pi^*$ transitions of lowest energy calculated for various substitution patterns of enones. Reprinted with permission from T. Liljefors and N. L. Allinger, *J. Am. Chem. Soc.*, **100**, 1068 (1978). Copyright (1978) American Chemical Society

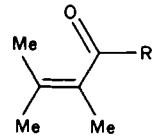
coefficient for the planar conformation. UV data for the two enones, **2b** and **14b**, show the difference in their conformation. Enone **2b** is *s-trans* planar, while **14b** is nonplanar, with $\omega = 135°$ according to equation 1[22]:



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

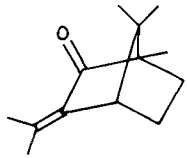
(**14b**) R = Bu^t $\varepsilon_{217.5}^{\text{hexane}} = 5{,}250$

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**:



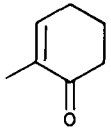
(**2h**) R = Me $\varepsilon_{244.5}^{EtOH} = 5{,}300$[9] ω 48°

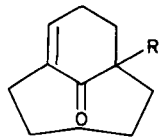
(**14f**) R = Bu^t $\varepsilon_{240}^{EtOH} = 2{,}490$[9] 63°

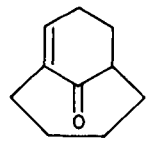


(**40**) $\varepsilon_{241}^{methylcyclohexane} = 12{,}000$[52] 0°

The relative sensitivity of λ_{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*-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 λ_{max} in **8** and **9** compared to **7** is due to the C=C bond distortion from planarity[7,54].

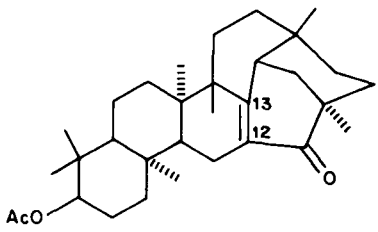




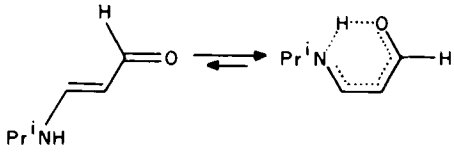


	(**41**)	(**42**) R = H	(**43**)
λ_{max}^{EtOH} (nm)	235	238	238
ε	10,000	5,630	3,000
	(**7**)	(**8**)	(**9**)
λ_{max}^{MeCN} (nm)	232	240	250
ε	13,800	14,800	5,070

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 λ_{max} calculated from the Woodward–Fieser rules must originate from the C=C bond deformation.



(**44**) λ_{max}^{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* → *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

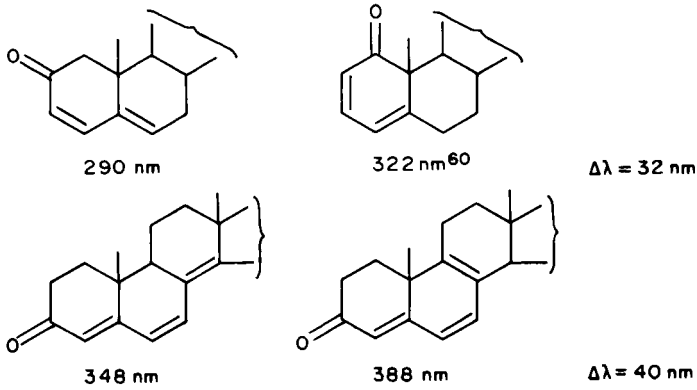
TABLE 17. Woodward–Fieser increments for calculation of $\lambda_{max}^{ethanol}$ of alkyl substituted dienones **II** (in nm)

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**.

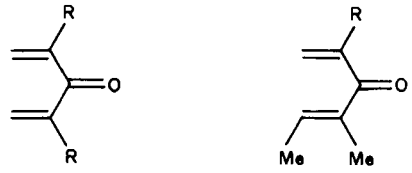
Dienones **47** and **52** both have *s-cis* conformation but, unlike **47**, **52** has a nonplanar diene portion of the chromophore, due to the 1,3-repulsion of the two substituents R^3 and R^5. Consequently, the ε value of the latter is much lower than that of the former.

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**,



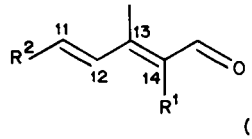
(λ_{max} in ethanol)

(**53**) R = H 230 nm (**55**) R = H 252 nm

(**54**) R = Me 225 nm (**56**) R = Me 234 nm

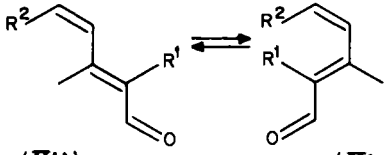
respectively. Apparently, when the carbonyl group in the divinyl ketone (**53**) is flanked by the two additional α,α'-substituents, the dienone chromophore is forced to nonplanarity.

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)

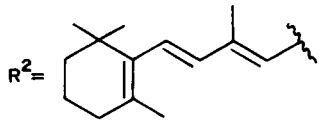
	R^1	λ_{max}(nm)	ε
(**57**)	H	368	47,500
(**58**)	Me	373	46,000



(IItt) (IItc)

(**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)

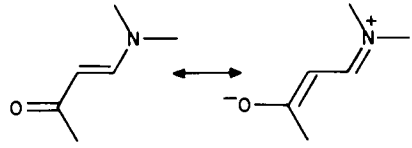
Compound	$\delta(R^3)$	$\delta(R^4)$	$\delta(R^3)-\delta(R^4)$	Reference
2c	2.12	6.09	—	66
2d	6.71	1.90	—	66
2g	2.11	1.86	0.25	66
2h	1.82	1.76	0.06	67
40	2.10	1.76	0.34	52

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

Compound	R^1	R^2	R^3	R^4	$\Delta = \delta(CCl_4) - \delta(\text{benzene})$ R^2	R^3	R^4	Ref.
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** ($R^1 = R^5 = Me$, $R^2 = R^3 = R^4 = H$, $R^6 = alkyl$)[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

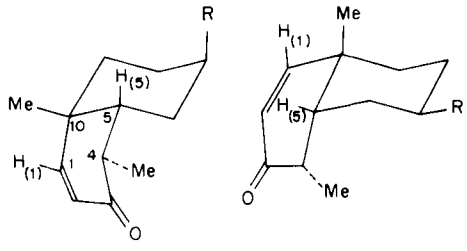


FIGURE 5. Nonsteroidal (**A**) and steroidal (**B**) conformation of *cis*-1-octalen-3-one derivatives

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 ± 0.2 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 = Me and R^2 = 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 $^3J_{(COMe,H)}$ 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
	IIt	199.17	128.67	145.14			25.18
18					129.57	140.33	
	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	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	$\frac{Ic}{It}$	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].

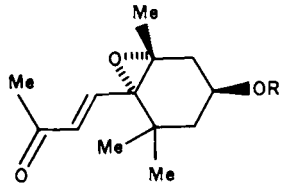
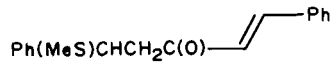
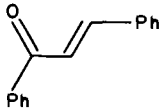
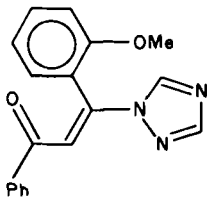
E. X-Ray Crystallography

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.

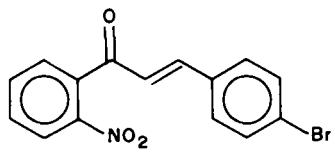
Nonplanar enone *s-cis* conformations are found in the X-ray-determined structures of several cyclic chalcone analogs **76–79** (Table 23).

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

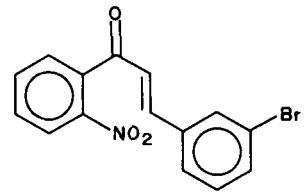
		ω(deg)	Reference
71		−172.3	83
72		178.8[a] −11.0[b]	84 84
17		16.9	85
73		23.4	86

SCHEME 3

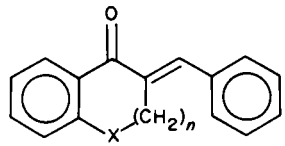
[a]Crystals grown from ethanol at temperatures higher than 55 °C.
[b]Crystals grown from ethanol at temperatures 20–45 °C.



(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

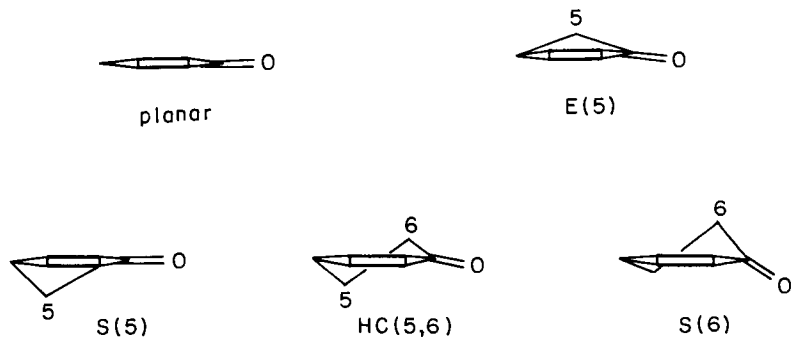
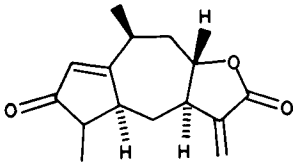
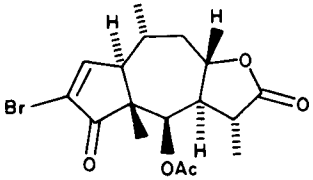
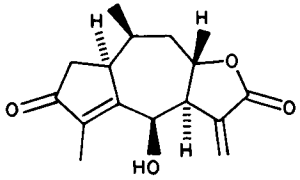
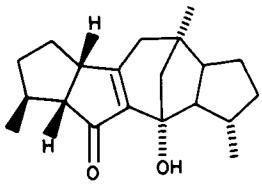
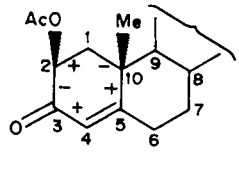


FIGURE 6. Typical conformations of 2-cyclopentenones (top) and 2-cyclohexenones (bottom). Only one enantiomer of each conformer is shown

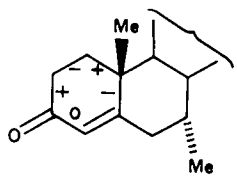
TABLE 24. Conformations of polycyclic 2-cyclopentenones

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

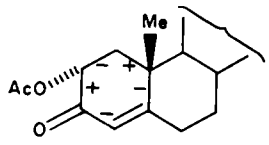
[a]Two independent molecules.



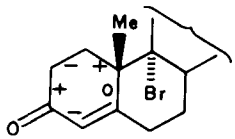
HC(1β, 2α)
ω = − 161.0[96]



S(1α)
ω = − 179.8[97]



HC(1α, 2β)
ω = + 169.2[98]

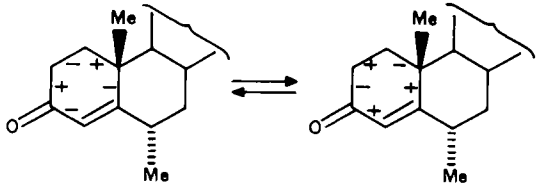


S(2β)
ω = + 162.3[99]

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:

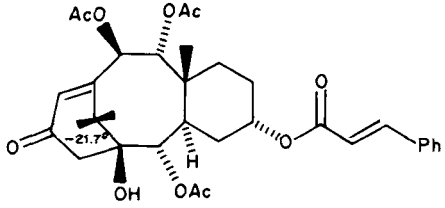


HC(1α, 2β) HC(1β, 2α)

The small energy difference between 4-en-3-one conformers causes flexibility of ring A in

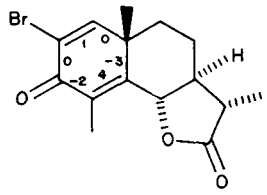
steroids and this in turn may show its importance in binding the hormone molecule in the receptor active site.

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].

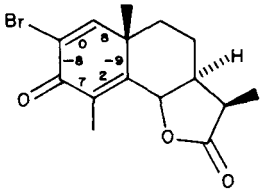


(80)

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].

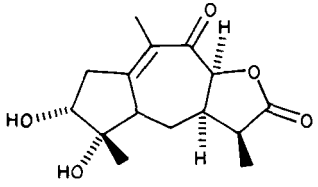


(81)

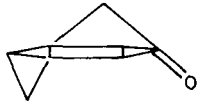


(82)

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

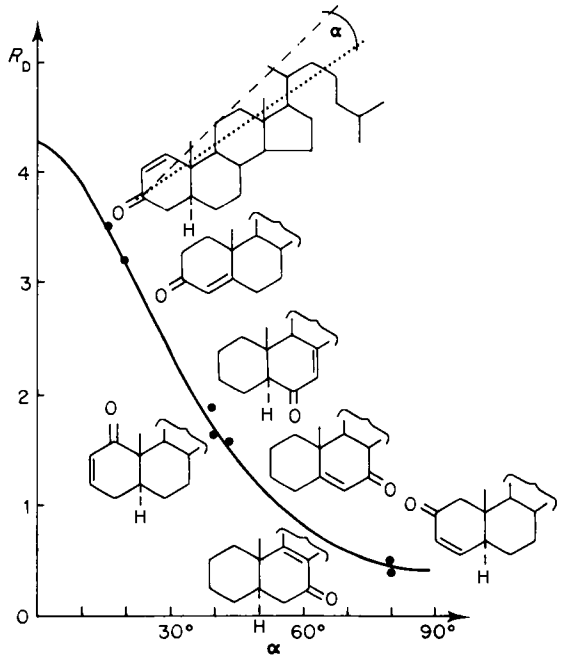


FIGURE 7. Plot of the dichroic ratio R_D *vs.* α according to equation 4 for the distribution factor $f = 0.5$. The circles are measured R_D values of cholestenones plotted against α values calculated from a geometrical model, line ------ is the π–π^* transition moment vector and ····· is the orientation 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

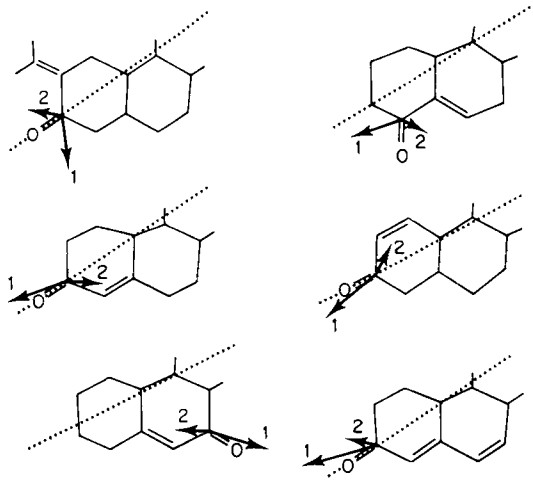


FIGURE 8. Calculated transition moment vectors (twice the calculated length, per unit charge) for the two π–π^* transitions above 200 nm (the longest wavelengths are denoted 1). The geometries of the compounds are shown as calculated by molecular mechanics. The dotted lines represent the assumed directions 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):

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

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.

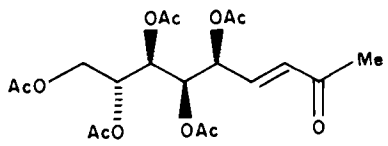
B. Circular Dichroism

1. General

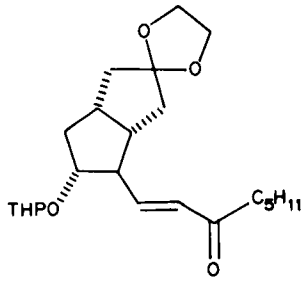
Unlike techniques discussed in the preceding parts of this chapter, circular dichroism measurements provide information on a variety of aspects of molecular chirality and are

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^*, $\Delta\varepsilon$	+ 0.11 (313 nm)	in MeCN	+ 0.03 (327 nm)	in MeOH
π–π^*, $\Delta\varepsilon$	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

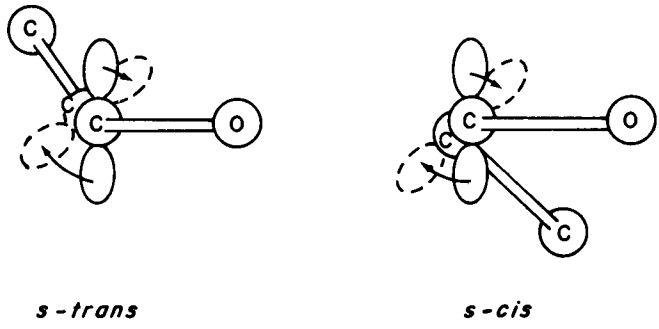


FIGURE 9. Orbital helicity rule applicable to either *s-cis* or *s-trans* enone. Reprinted with permission from D. N. Kirk, *Tetrahedron*, **42**, 777 (1986). Copyright (1986) Pergamon Journals Ltd

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.

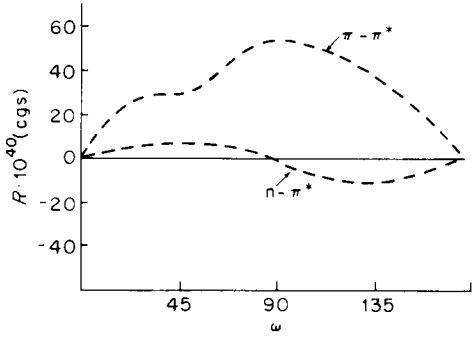


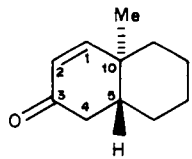
FIGURE 10. Calculated rotational strength R *vs.* the torsional angle ω in acrolein (**1a**) (redrawn from the data of Reference 124)

2. Planar enones and dienones

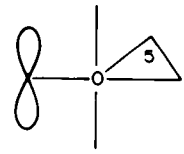
Nonplanar enones fall into the class of inherently dissymmetric chromophores, where local symmetry planes are lost and no sector rules, such as the octant rule for the n–π^* transition in saturated ketones, are applicable. In the case of a planar chromophore, nonzero rotational strength of a given transition 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

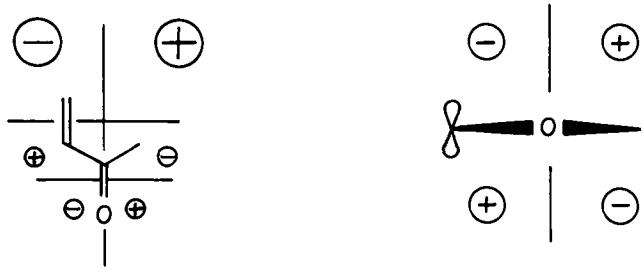


FIGURE 11. Sector rule for the n–π^* transition of planar *s-trans* enones [128,129]. (a) Signs of contributions in upper sectors (large circles are for the signs in rear sectors). (b) Sign pattern for the rear sectors. Reproduced by permission of D. Reidel Publishing Company

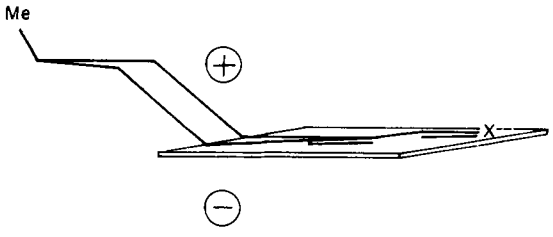
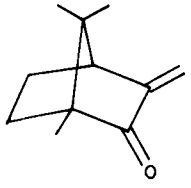


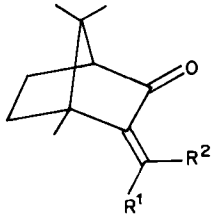
FIGURE 12. Planar rule for the π–π^* Cotton effect of *s-trans* dienes (X = CH_2) and enals (X = O)[131]

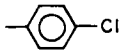
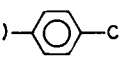
(R) absolute configuration is oriented as in Figure 12, bonds above the plane of the chromophore make a positive contribution to the π–π^* transition Cotton effect[131]. Incidentally, the sign of the n–π^* Cotton effect of **87** is correctly predicted by the sector rule mentioned earlier. Both rules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



	R^1	R^2
(**89**)	H	H
(**90**)	H	
(**91**)		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	$\Delta\varepsilon + 0.3$ (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

Compound	$\Delta\varepsilon$ (λ_{max}, nm)		Solvent	Reference
	n–π^*	π–π^*		
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 $90° < \omega < 180°$ 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

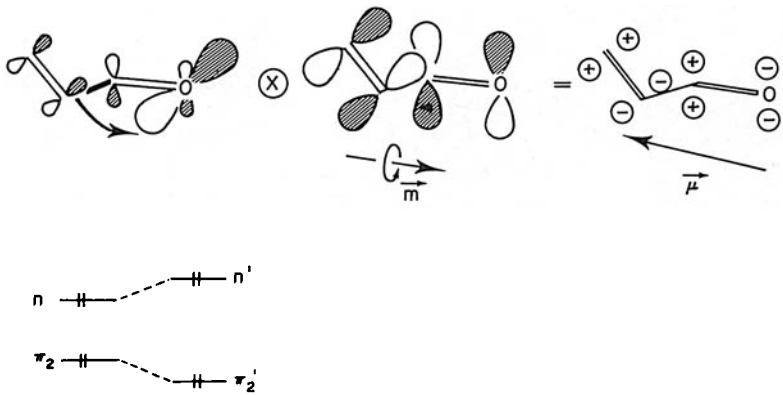


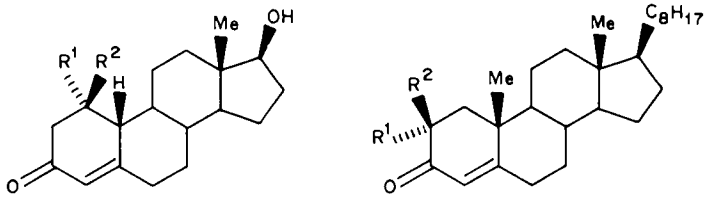
FIGURE 13. The rule for the n–π^* Cotton effect of nonplanar *s-trans* enones (the negative Cotton effect is obtained for the enone helicity shown). Taken from G. Snatzke, *Angew. Chem., Int. Ed. Engl.*, **18**, 363 (1979) and reproduced by permission of Verlag Chemie, GmbH, Weinheim

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

Compound	$\Delta\varepsilon(\lambda_{max}, nm)$		
	n–π*	π–π*	
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–π* and π–π* 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–π* and long-wavelength π–π* Cotton effects is observed. Note that the second π–π* 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–π* (*ca* 350 nm) and π–π* (*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

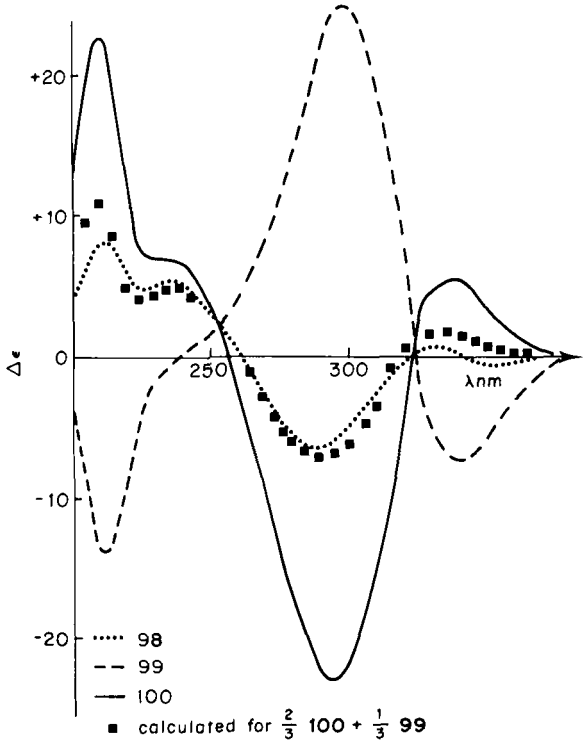
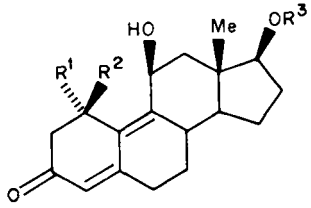


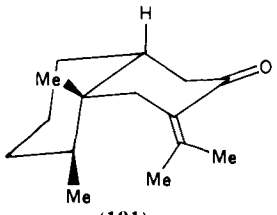
FIGURE 14. CD curves of 11β-hydroxy-4,9-dien-3-ones (solvent ethanol). Reprinted with permission from V. Delaroff, N. Dupuy, L. Nedelec and M. Legrand, *Tetrahedron*, **35**, 2681 (1979). Copyright (1979) Pergamon Journals Ltd

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 ΔG° value 0.9 kcal mol^{-1} [135].

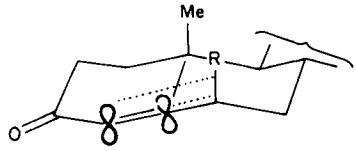


(101)

	297 K	83 K
n–π*, Δε (325 nm)	−0.38	−0.46
π–π*, Δε (243 nm)	+3.4	+7.2

4. Substitution effects

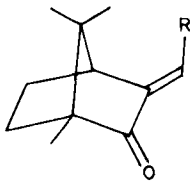
Nonplanar *s-cis* enones frequently give π–π* Cotton effects of opposite sign to those predicted by the application of the enone helicity rule[122,136]. In order to eliminate the discrepancy Burgstahler and coworkers have proposed that chiral interactions of allylic axial bonds with the enone (or diene) 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	$\Delta\varepsilon(\lambda_{max}, nm)$
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

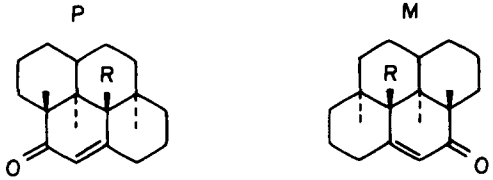
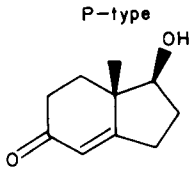
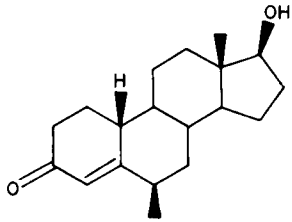
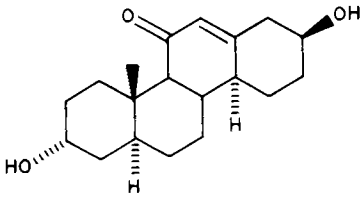
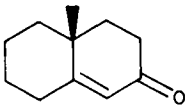
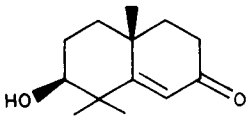
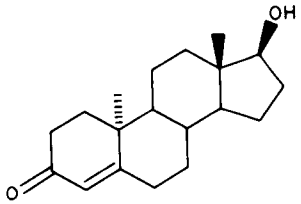


FIGURE 15. Configurational dependence of the 220–200 nm π–π^* Cotton effect of polycyclic cyclohexenones[120]

	$\Delta\varepsilon(\lambda_{max}, nm;$ in methanol) $n-\pi^*$	$\pi-\pi^*$
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

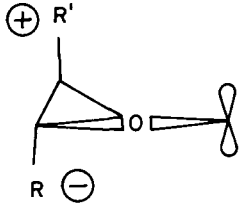
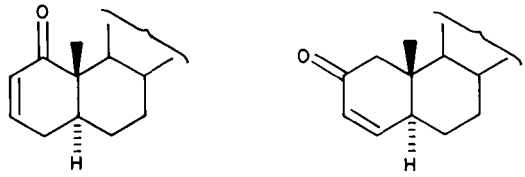


FIGURE 16. Substituent contributions to the Cotton effect below 200 nm of cyclohexenones with a planar enone chromophore. Reprinted with permission from J. Gawronski, *Tetrahedron*, **38**, 3 (1982). Copyright (1982) Pergamon Journals Ltd

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.

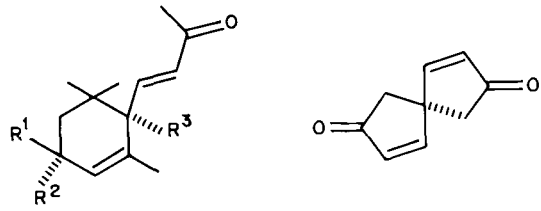


(108) **(109)**

in hexane: $\Delta\varepsilon + 28.0$ (198 nm) in MeCN: $\Delta\varepsilon + 2.3$ (189 nm)
in $(CF_3)_2CHOH$: $\Delta\varepsilon + 12.3$ (207 nm)
$+ 11.4$ (191 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)	19,300 (237)	ethanol	147
				a			
114	O		OH	+38.4 (242)	21,300 (234)	methanol	147
				−30.2 (208)			
115				+38 (228)	16,000 (223)	isooctane	148
				−16 (210)			

[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

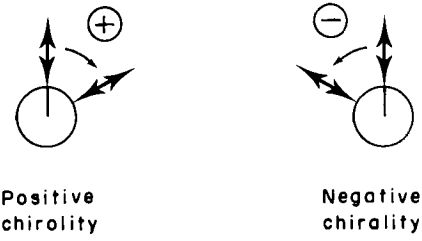


FIGURE 17. Qualitative definition of exciton chirality

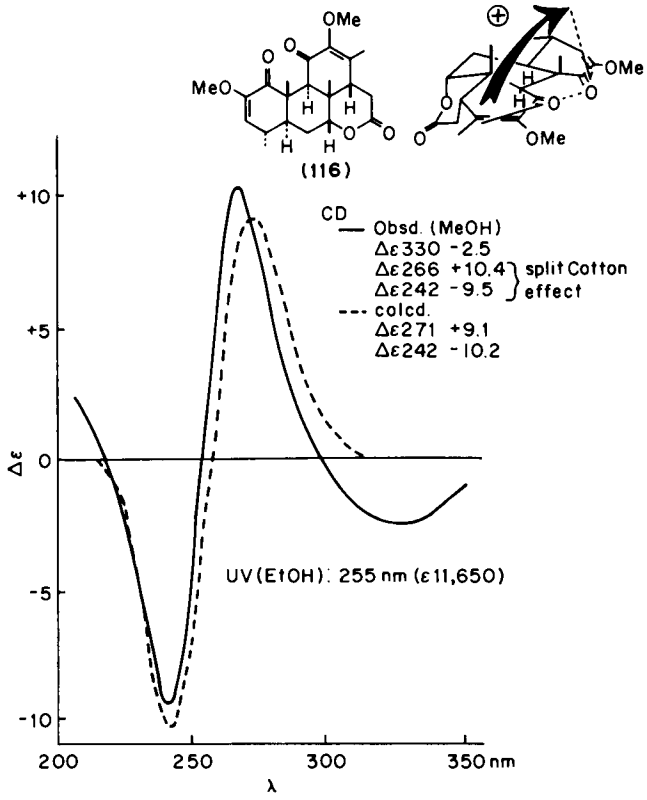
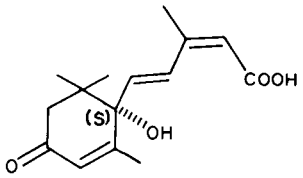


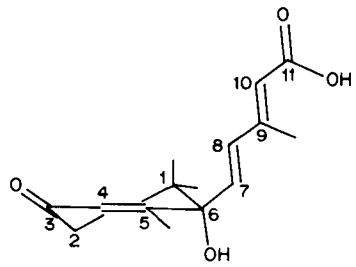
FIGURE 18. CD spectra of quassin (**116**):———observed (in methanol), - - - calculated. Reprinted with permission from M. Koreeda, N. Harada and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 266 (1974). Copyright (1974) American Chemical Society

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)

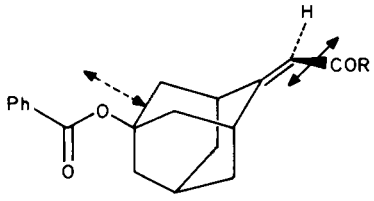


(118)

$\Delta\varepsilon$	+ 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)
		ε	35,000 (232)
(120)	R = Me	$\Delta\varepsilon$	− 12.9 (239)
			+ 9.1 (223)
		ε	27,700 (230)

(in cyclohexane)

IV. ACKNOWLEDGEMENTS

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The Chemistry of Enones
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CHAPTER 4

Thermochemistry of enones and related species

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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	ΔH_f(s) or ΔH_f(lq) (kcal mol^{-1})	Ref.	Year	ΔH_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	ΔH_f(s) or ΔH_f(lq) (kcal mol^{-1})	Ref.	Year	ΔH_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-methano-naphthalene-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-ethano-naphthalene-5, 8-dione (**14b**)	[− 53.1]	17	1964			
$C_{13}H_5N_5O_{11}$	2, 2′, 4, 4′, 6-pentanitro-benzophenone	[− 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	ΔH_f(s) or ΔH_f(lq) (kcal mol^{-1})	Ref.	Year	ΔH_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[c]	[−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.

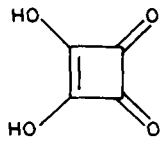
[c]While it is safe to assume that β-diketones are predominantly in their enol form, to the authors' knowledge only for acetylacetone are there separate thermochemical data on both the keto and enol forms. (See the discussion in References 11 and 27).

[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.

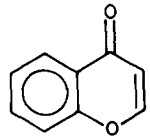
[e]Substitution site was unspecified.

[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)



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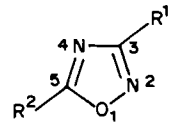
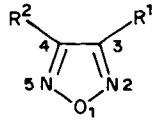


(3)(a) $R^1 = PhCO$, $R^2 = OH$

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



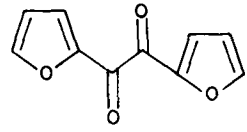
(4)(a) $R^1 = NH_2$, $R^2 = PhCO$

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



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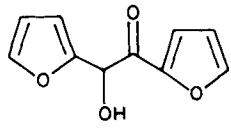

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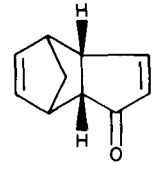

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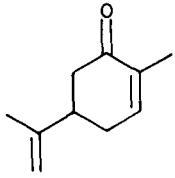

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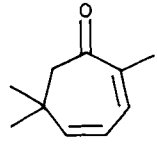

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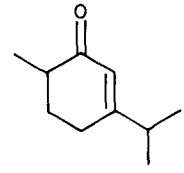

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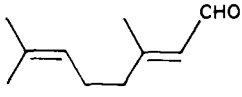

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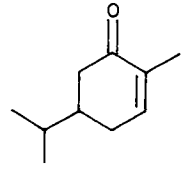

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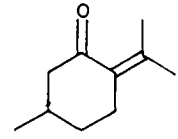

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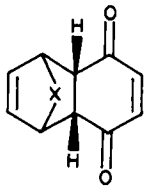
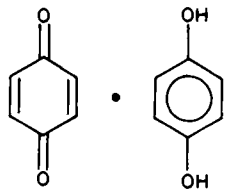


(14) (a) X = CH_2

(b) X = CH_2CH_2



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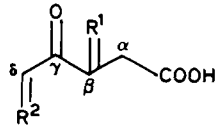
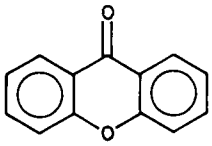


(16) (a) R^1 = PhCH, R^2 = H

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



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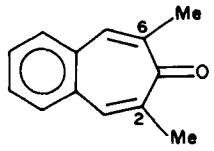

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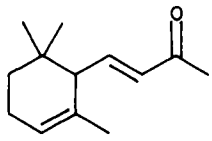

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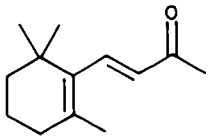

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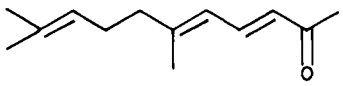

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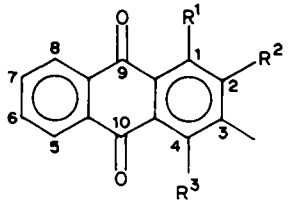
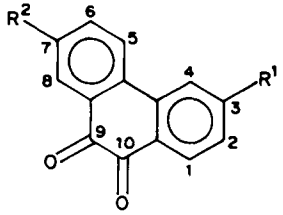


(22) (a) $R^1 = R^2 = R^3 = H$

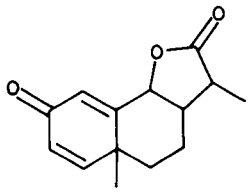
(b) $R^1 = R^2 = OH$, $R^3 = H$

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



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

(b) R^1 = Me, R^2 = *i*-Pr



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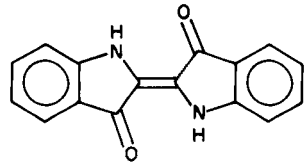

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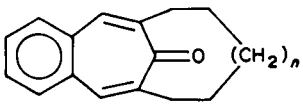
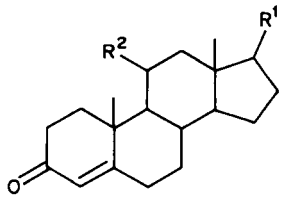


(26) (a) $n = 1$

(b) $n = 6$



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

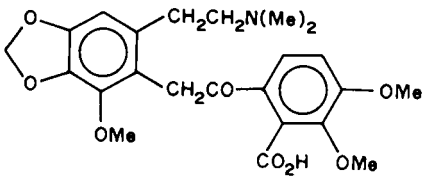
(b) R^1=β-OH, R^2=H

(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



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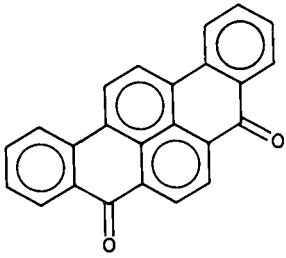

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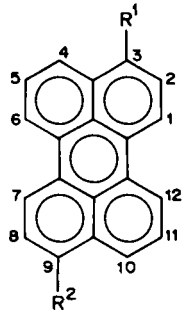


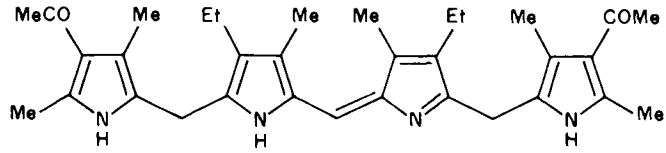
(30) (a) R^1=R^2=COMe

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

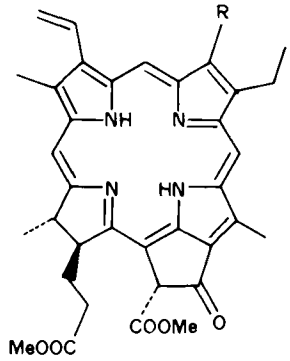
(c) R^1=R^2=COPr

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

(e) R^1=R^2=*P*-MeC_6H_4CO

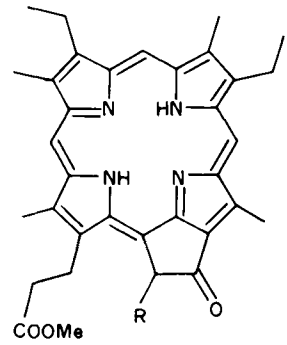


(31)



(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 kcal mol^{-1}, leading to values of the stabilization energy for crotonaldehyde of 2.4 kcal mol^{-1}(g) and 3.1 kcal mol^{-1}(l), relative to *trans*-2-butene.

	MeCH=CHCHO =	MeCH=CHMe +	$MeCH_2CH_2CHO$ −	$MeCH_2CH_2Me$	
ΔH_f(g)	$-21.6 = -2.7$	$+(-48.9)$	$-(-30.0)$		(1)
ΔH_f(l)	$-30.0 = -7.9$	$+(-57.1)$	$-(-35.0)$		
(kcal mol^{-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 ($D_{CHO} - D_R$) is *ca* 1.3 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.

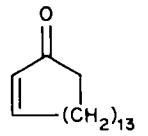
It is of interest that the vaporization enthalpies of butane and 2-butene are approximately the same (5.0 kcal mol^{-1} and 5.2 kcal mol^{-1}, respectively), whereas that of crotonaldehyde (9.1 kcal mol^{-1}) is somewhat higher than butyraldehyde (8.2 kcal mol^{-1})[8]. How much this is due to the dipolar 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 (± 0.4 kcal mol^{-1} for crotonaldehyde and ± 0.3 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 kcal mol^{-1} and 0.9 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 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 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.

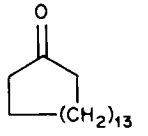
	MeCH=CHCHO =	$MeCH=CHCH=CH_2$ +	$MeCH_2CH_2CHO$ − $MeCH_2CH_2CH=CH_2$		
ΔH_f(g)	$-25.6 = 18.2$	$+(-48.9)$	$-(-5.1)$		(2)
ΔH_f(l)	$-34.0 = 11.9$[36]	$+(-57.1)$	$-(-11.2)$		
(kcal mol^{-1})					

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 kcal mol^{-1} compared to

the experimental value of $-97.6\,kcal\,mol^{-1}$. Despite the potential idiosyncracies of 17-membered rings, the resulting stabilization energy of nearly 15 kcal mol^{-1} seems excessive, even considering the $\pm 3\,kcal\,mol^{-1}$ 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 $-113\,kcal\,mol^{-1}$, 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.



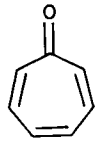
$= MeCH{=}CHMe +$



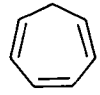
$- MeCH_2CH_2Me$ (3)

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 kcal mol^{-1} (g) and $-2.4\,kcal\,mol^{-1}$ (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 kcal mol^{-1}) and cycloheptanone (12.4 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.



$=$



$+ MeCH_2COCH_2Me - MeCH_2CH_2CH_2Me$ (4)

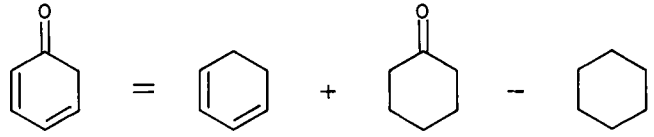
ΔH_f(g)	$16.7 = 43.2$	$+(-61.6)$	$-(-35.1)$
ΔH_f(l)	$4.6 = 34.0$	$+(-70.9)$	$-(-41.5)$
(kcal mol^{-1})			

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 $-17 \pm 3\,kcal\,mol^{-1}$ and of the 2,5-isomer equal to $-13 + 3\,kcal\,mol^{-1}$. Several comparisons have been made by these authors. The heat of formation of phenol is $-23\,kcal\,mol^{-1}$, 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.



ΔH_f(g) (kcal mol^{-1})	0.9 =	25.4	+	−54.0	−	(−29.5)	(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.

	PhCHO		PhMe			
ΔH_f(g) (kcal mol^{-1})	−8.8	−	12.0	=	−20.8	(6)

	CH_2=CHCHO		CH_2=CHMe			
ΔH_f(g) (kcal mol^{-1})	−24.0	−	(−2.7)	=	−21.3	(7)

	PhCOEt		PhCH$_2$COMe			
ΔH_f(g) (kcal mol^{-1})	−26.0	−	(−24.1)	=	−1.9	(8)

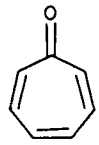
This equivalence between the effects of phenyl and vinyl substituents can be used to predict heats of formation of substituted vinyl ketones of the type C=C—C(=O)R

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}.

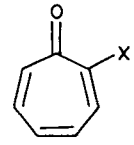
	PhCMe (O)	+	CH_2=CHEt	−	PhEt	=	CH_2=CHCMe (O)	
ΔH_f(g) (kcal mol^{-1})	−20.7	+	0	−	7.1	=	−27.8	(9)

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).



(**34**)



(10)

X = OH

ΔH_f(g) (kcal mol^{-1})	10.5	+ (−23.0)	−	19.7	=	−32.2 (calcd)
						−37.1 (expt)
					Δ =	4.9

X = NH_2

ΔH_f(g) (kcal mol^{-1})	+10.5	+	20.8	−	19.7	=	11.6 (calcd)
							9.4 (expt)
						Δ =	2.2

	MeCHO	+	PhOH	−	PhH	=	$MeCO_2H$	(11)
X = OH								
ΔH_f(g) (kcal mol^{-1})	−39.7	+	(−23.0)	−	19.7	=	−82.4 (calcd)	
							−103.4 (expt)	
							Δ = 21.0	

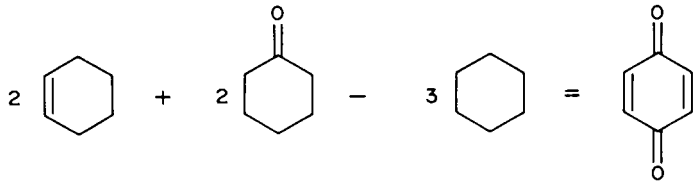
	MeCHO	+	$PhNH_2$	−	PhH	=	$MeCONH_2$	
X = NH_2								
ΔH_f(g) (kcal mol^{-1})	− 39.7	+	20.8	−	19.7	=	− 38.6 (calcd) − 57.0 (expt) Δ = 18.4	(12)

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.

	MeCCH=CHMe	+	PhOH	−	PhH	=	MeCCH=C(OH)Me	
ΔH_f(g) (kcal mol^{-1})	− 35.4	+	(− 23.0)	−	19.7	=	− 78.1 (calcd) − 91.1 (expt) Δ = 13.0	(13)

	PhCMe	+	(*E*)-MeCH=CHMe	−	PhMe	=	MeCCH=CHMe	
ΔH_f(g) (kcal mol^{-1})	− 20.7	+	(− 2.7)	−	12.0	=	− 35.4 (calcd)	(14)

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



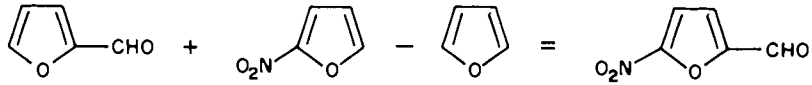
(15)

(35)

ΔH_f(g) (kcal mol^{-1})	2 × (− 1.2)	+	2 × (− 54.0)	−	3 × (− 29.5)	=	− 21.9 (calcd) − 29.4 (expt) Δ = 7.5

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) (kcal mol^{-1})	−36.0	+	(−6.9)	−	(−8.3)	=	−34.6 (calcd) −35.2 (expt) Δ = 0.6

(16)

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≡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.

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CHAPTER **5**

NMR spectroscopy of enones

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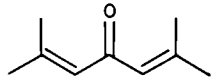
I. INTRODUCTION

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. ^{1}H 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

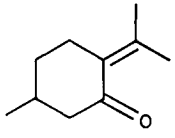
The chemical shift of carbon is less affected than that of hydrogen by medium and anisotropy effects, and therefore it is more indicative of the degree of conjugation and

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].

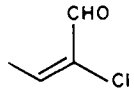
More recently, Loots, Weingarten and Levin used carbon shifts quantitatively in order to calculate electron deficiencies at the β-carbon (they estimated a ratio of 240 ppm per unit charge) in a variety of α,β-unsaturated carbonyl compounds, cyclic and acyclic[10,11]. For acyclic aldehydes and ketones, 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**)



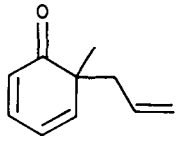
(**3**)

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}.



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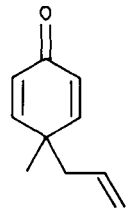
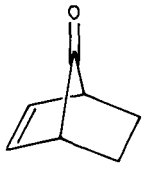


(5)

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.



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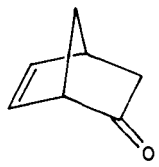


(7)

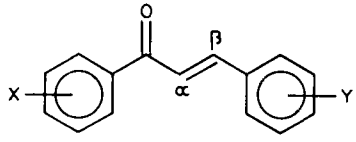
3. Acetylenic systems

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

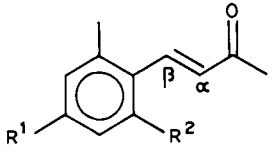
In enone systems that are substituted by aryl groups, the effect of the conjugation of these peripheral rings with the central chromophore has to be taken into account. A measure of this type of influence can be found in a ^{13}C study of chalcones which are *meta*- or *para*-substituted in one of the 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].



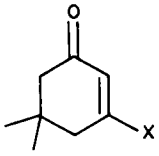
(**8**)

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 quanti-

tatively, 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**) $R^1 = R^2 = CH_3$



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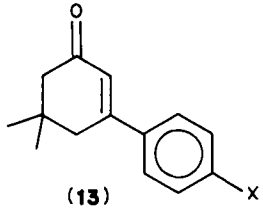
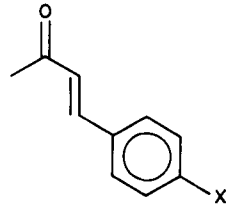


(**13**)



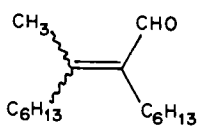
(**14**)

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.

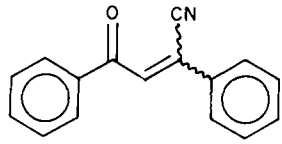


(**15**)

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 $^3J_{CH_3,H}$ 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.

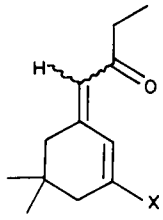
In this section we will deal first with the NMR techniques for conformational assignment (useful information is also obtained from other spectroscopic methods such as UV or IR) and then with the results reported in the literature.

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 $\Delta\delta$ 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

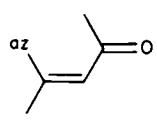
with different configurations (*cis* and *trans*), and the results seem slightly less reliable. When pairs of *cis* and *trans* isomers are available, they can serve as models for each other, and then even more highly substituted enones can be analysed[44]. Rouillard, Geribaldi and Azzaro[45] have used 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].



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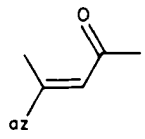


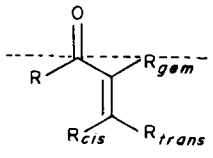
(19)

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 ^{1}H 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.



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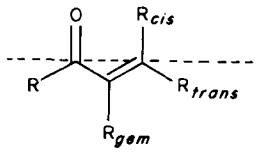

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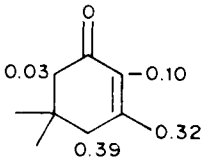

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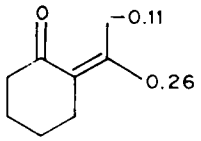

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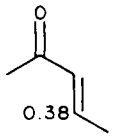

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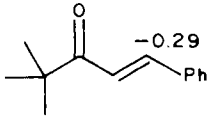


(25)

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

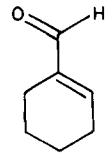
is unpredictable, especially since these may also have specific interactions of their own with the aromatic solvent.

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	R_{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

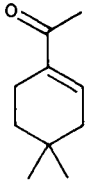
	R	R_{gem}	R_{cis}	R_{trans}	Results[a] (Reference)
1.	H	Cl	H	Me	12% (59)
2.	H	Br	H	Me	19% (59)
3.	H	Me	Cl	Me	6% (59), mainly s-*trans* (65)
4.	H	Me	Me	Cl	4% (59), mainly s-*trans* (65)
5.	H	H	Cl	Me	11% (59)
6.	H	H	Br	Me	5% (59)
7.	H	H	Me	Cl	9% (59)
8.	Me	H	Me	Cl	mainly s-*cis* (65)
9.	Me	H	Cl	Me	mainly 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.



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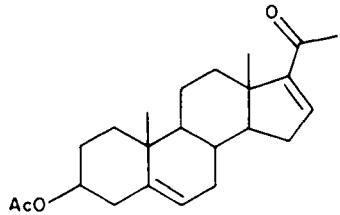

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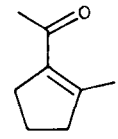

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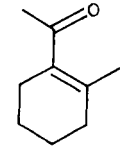
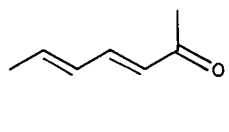


(30)

5. Dienones and polyenones

Conformational studies on α,β,γ,δ-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**).



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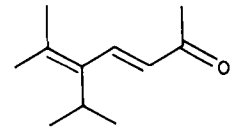

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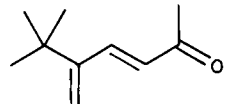

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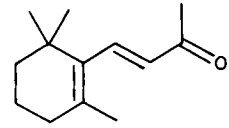
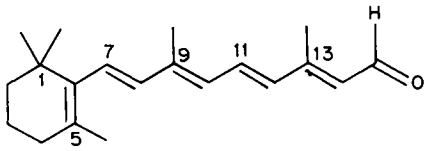


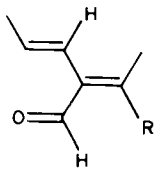
(34)

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.



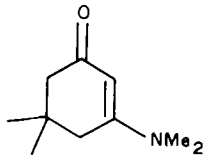
(**36**) R = H
(**37**) R = CH_3

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.

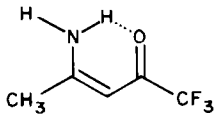
The first question of interest in this field is the degree of electron delocalization. Dabrowski, Skup and Sonelski have looked at the ^{14}N NMR chemical shifts of several R—CO—CH=CH—NR′R″ systems and shown that they fall between the values for the corresponding amides (R—CO—NR′R″) and amines (R—NR′R″) 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)

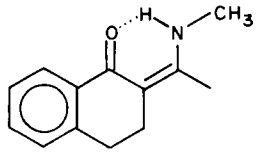
A. Tautomerism

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)

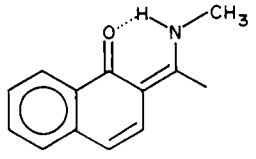
In fact, simple β-aminoenones exist mainly in the ketoenamine form, as proved in the case of **40** by a 5 Hz coupling constant between the N-methyl and NH protons[73–75]. In these hydrogen chelates, the NH signal appears within a wide range of chemical shifts (5 to 20 ppm), which correlate well with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



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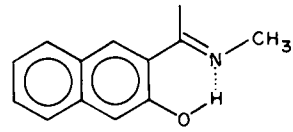
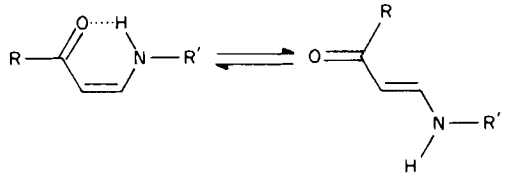


(42)

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

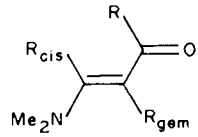
1. s-cis, s-trans *Isomerism*

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.

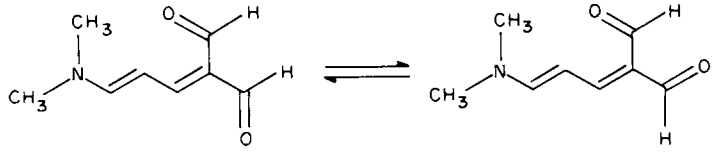
TABLE 4. =C—N Rotation barriers in β-aminoenones[a]

	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 ($\Delta G^{\neq} < 10.5$ 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 kcal mol^{-1}; a *p*-nitrophenyl group has an even stronger effect ($\Delta G^{\neq} = 16.9$ kcal mol^{-1})[89]. For the dienone (entry 7) the corresponding value goes up to 13.0 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 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 ^1H 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' (^1H 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-β > C = O ≫ 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 $Mg^{++} \gg Li^+ > Na^+$.

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The Chemistry of Enones
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CHAPTER 6

The chemistry of ionized enones in the gas phase

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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

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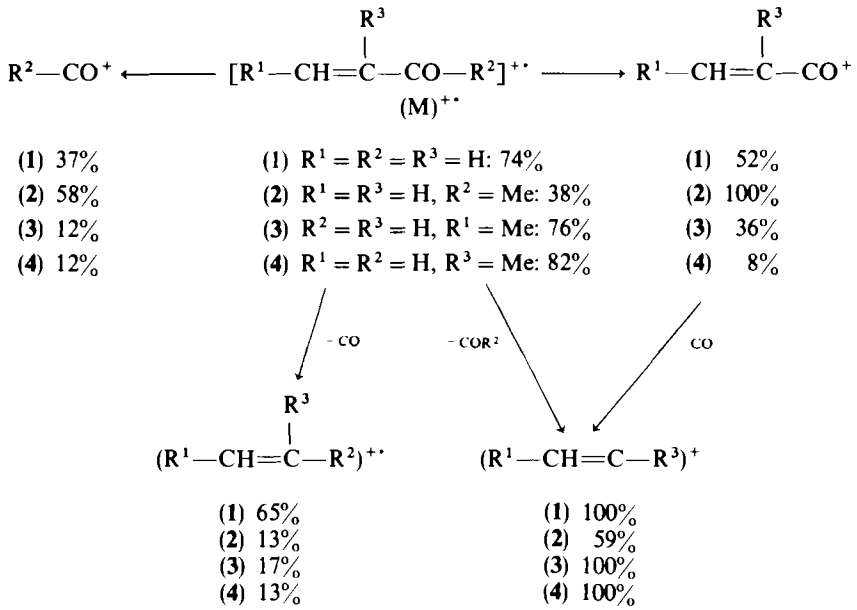
radical cations derived from unsaturated ketones have been summarized in an early paper[1]. Since then a wealth of information has been accumulated which shed more light on some of the more intricate features of enone ion chemistry in the gas phase. The EI-induced decompositions of simple aliphatic enones 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 $[\mathbf{1}]^{+\cdot}$, $[\mathbf{2}]^{+\cdot}$ and $[\mathbf{3}]^{+\cdot}$ (Table 1).

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



SCHEME 1

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

Precursor	ΔH_f° (kJ mol^{-1})	Products	ΔH_f°(kJ mol^{-1})	BDE (kJ mol^{-1})
$[1]^{+\cdot}$	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)
$[2]^{+\cdot}$	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)
$[3]^{+\cdot}$	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]

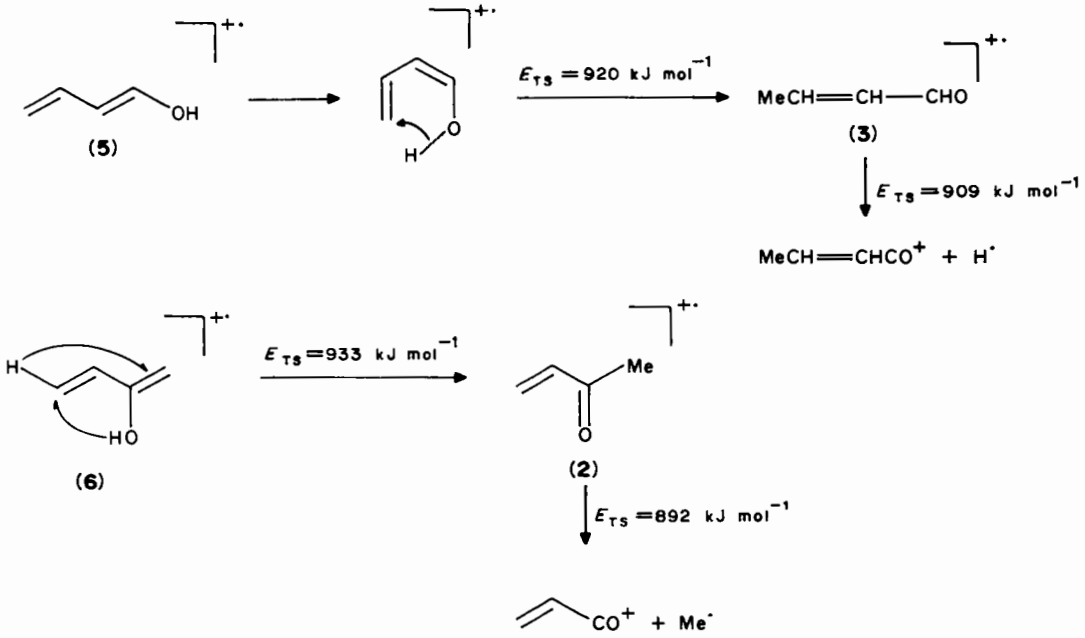
[a]The $CH_3CH{-}CH^+$ ion is calculated to be thermodynamically unstable[15].

decomposition of $[1]^{+\cdot}$, $[2]^{+\cdot}$ and $[3]^{+\cdot}$. 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} [16] to proceed and is therefore energetically more demanding than the direct formation of $CH_2{=}CH^+$ from both $[1]^{+\cdot}$ and $[2]^{+\cdot}$ (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 $[2]^{+\cdot}$ and $[3]^{+\cdot}$, 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 $[2]^{+\cdot} \rightarrow CH_2{=}CH{-}CO^+ + CH_3^\cdot$ and $[3]^{+\cdot} \rightarrow CH_3{-}CH{=}CH{-}CO^+ + H^\cdot$ 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 $[2]^{+\cdot}$ and $[3]^{+\cdot}$ in whose spectra the $[M-CO]^+$ ions represent the most abundant products[3,14].

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


(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}
(2)
E_{TS} = 892 kJ mol^{-1}
CO$^+$ + Me$^\cdot$

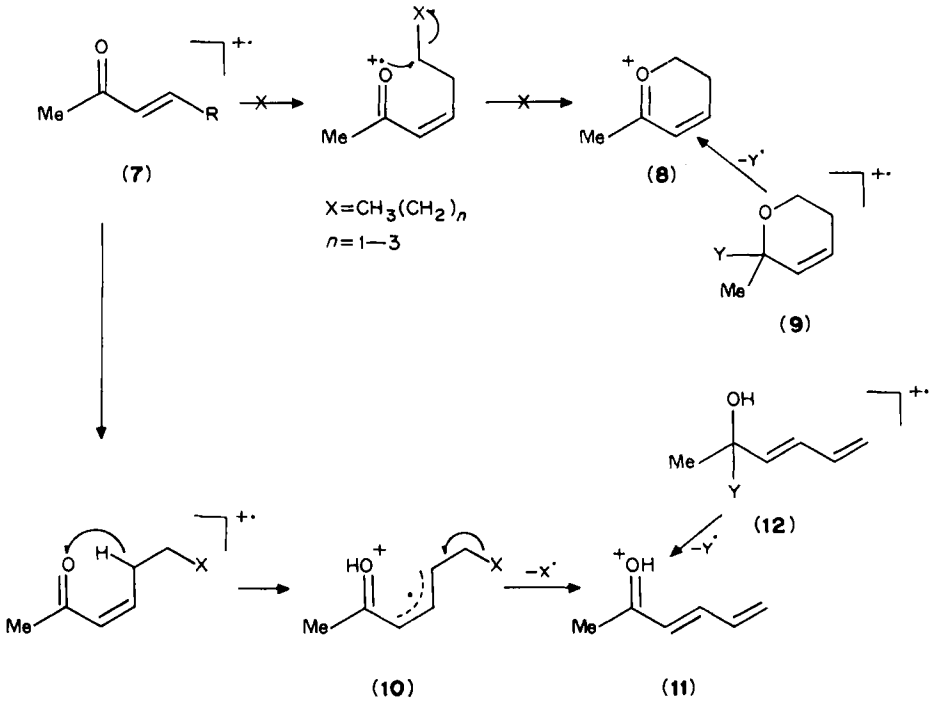
SCHEME 2

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

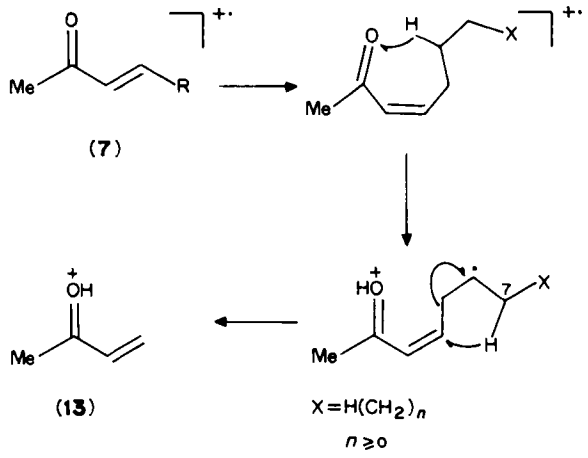
B. Rearrangements in Higher Enones

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.



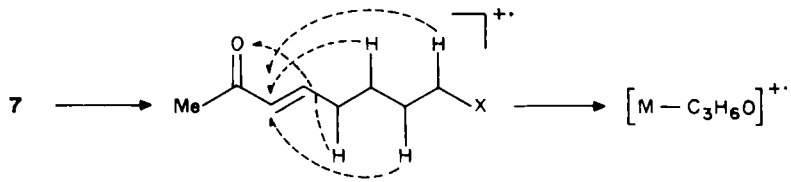
SCHEME 3



SCHEME 4

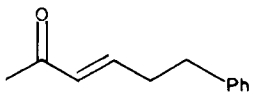
Hydrogen migrations, both hidden and directly observable, play an important role in the decompositions of ionized enones of type **7**. For instance, double hydrogen migration accounts for the formation of $C_4H_7O^+$ ions (**13**) from enones **7** having R larger than *n*-C_3H_7 (Scheme 4)[1]. As established 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 12eV 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**

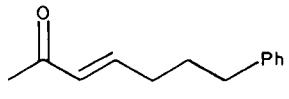


SCHEME 5

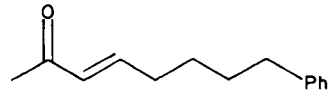
the two hydrogen atoms being transferred onto the enone group originate specifically from the benzylic (C-6) and vinylic (C-4) positions, respectively. In **7b** the benzylic methylene group (C-7) remains the major source for one hydrogen atom to be transferred, while the other comes largely from the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



(7a)



(7b)

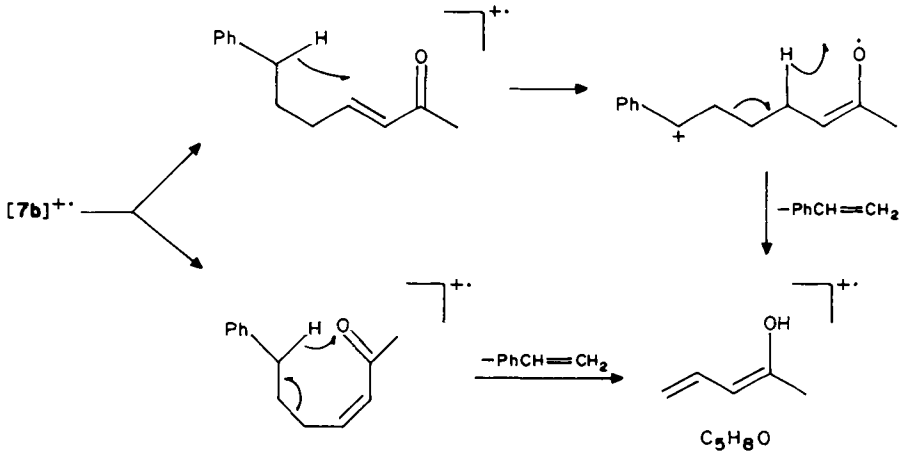


(7c)

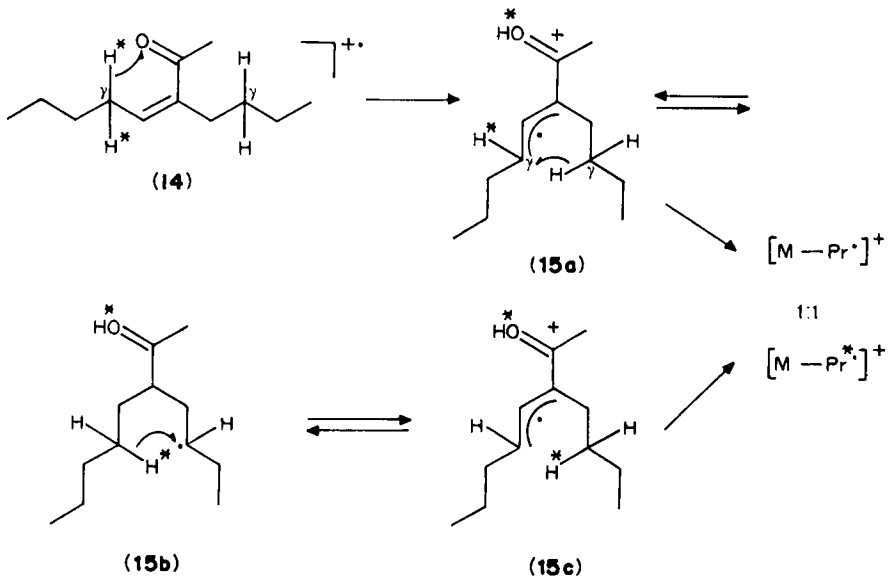
The molecular ion of **7b** undergoes yet another fragmentation which leads to complementary (by both labelling and elemental composition) $[C_5H_8O]^{+\cdot}$ and $[C_8H_8]^{+\cdot}$ ions. The possible mechanistic paths leading to the former ion are shown in Scheme 6. Deuterium labelling in **7b** revealed 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

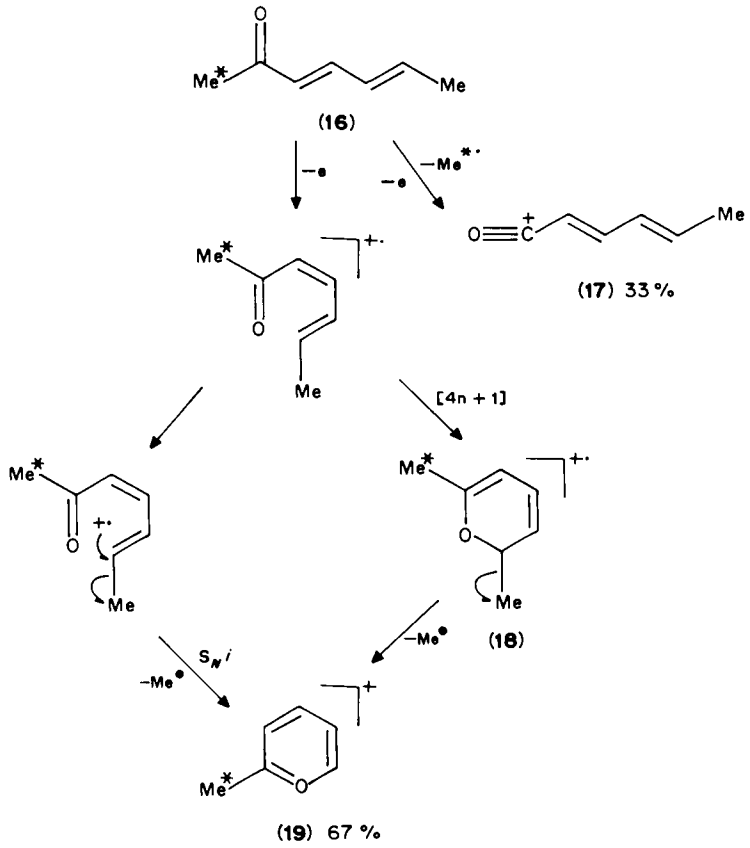


SCHEME 7

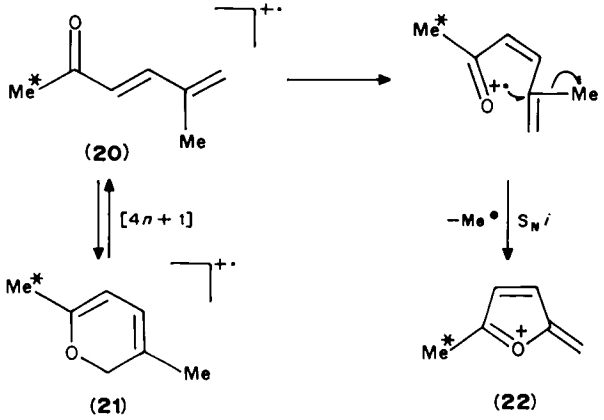
despite a stable acylium ion (**17**) being accessible directly by conventional loss of the C-1 methyl[27]. The unusual reactivity of **16** was explained by assuming two competing mechanisms for the methyl loss. Following a *trans*-to-*cis* isomerization in ionized **16**, the molecular ion can undergo 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 **20** → **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].

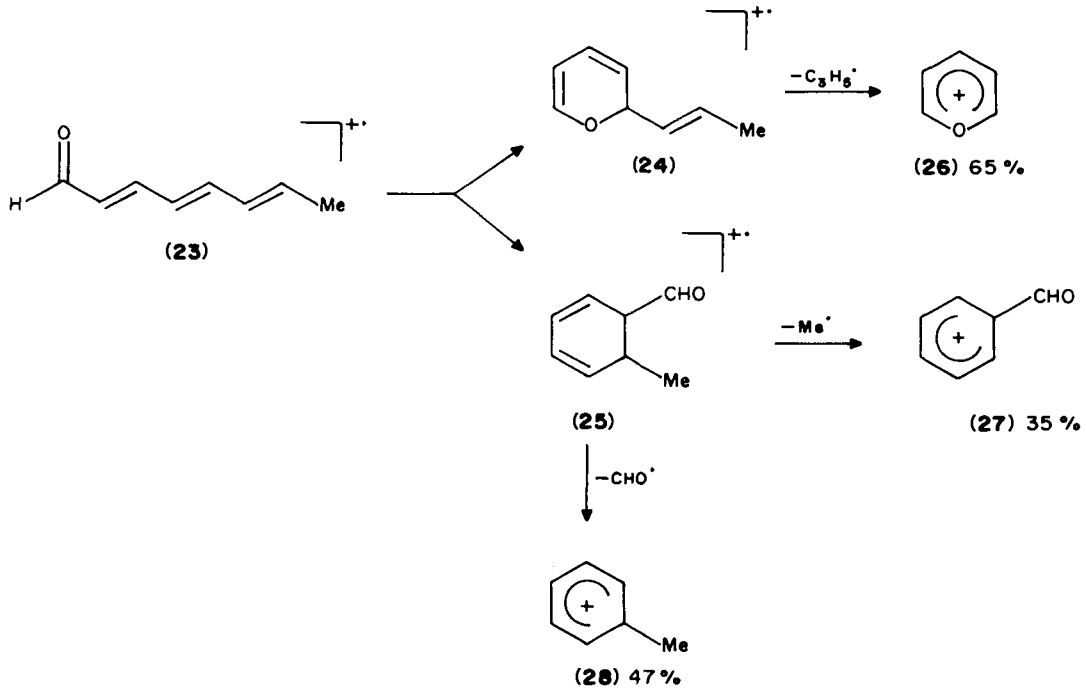
Skeletal rearrangements and hydrogen migrations evidently play a role in the as yet unexplained, complex loss of a methyl from ionized 5-hexen-2-one (**29**, Scheme 11)[29]. While the molecular ion of **29** decomposing in the ion source eliminates cleanly the original methyl group, metastable ions $[\mathbf{29}]^{+\cdot}$ 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].



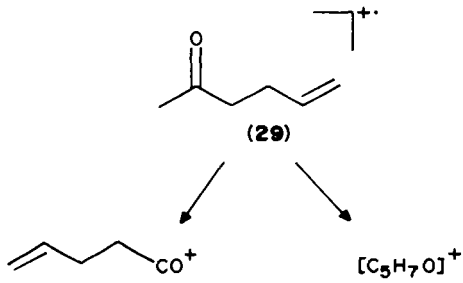
SCHEME 8



SCHEME 9


O
H
Me
(23)
(24)
Me
$-C_3H_5^{\cdot}$
(26) 65 %
CHO
Me
(25)
$-Me^{\cdot}$
CHO
(27) 35 %
$-CHO^{\cdot}$
Me
(28) 47 %

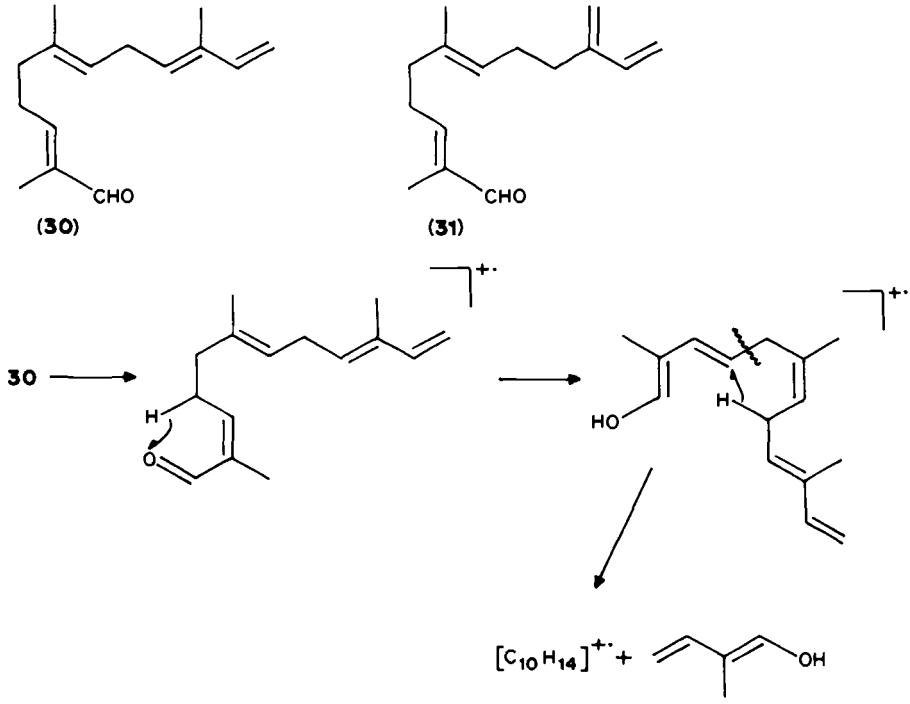
SCHEME 10



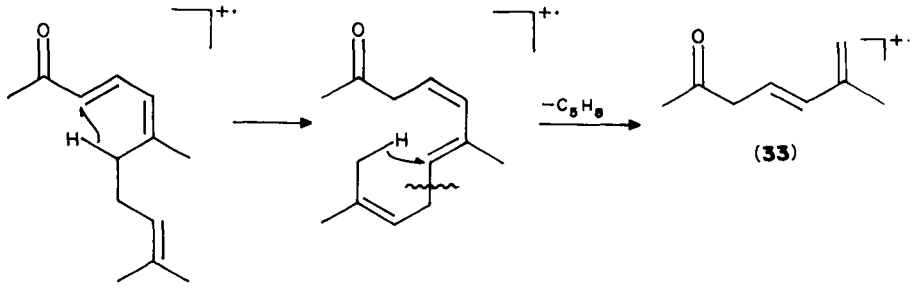
SCHEME 11

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].

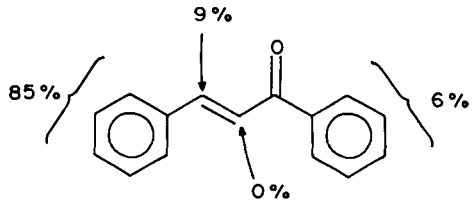
C. Cyclizations, *ortho*-Effects and Related Phenomena

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.

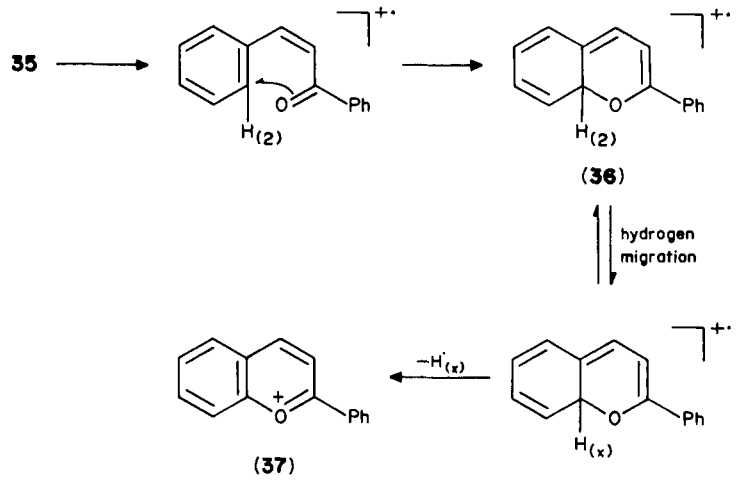
(34) (35)

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,

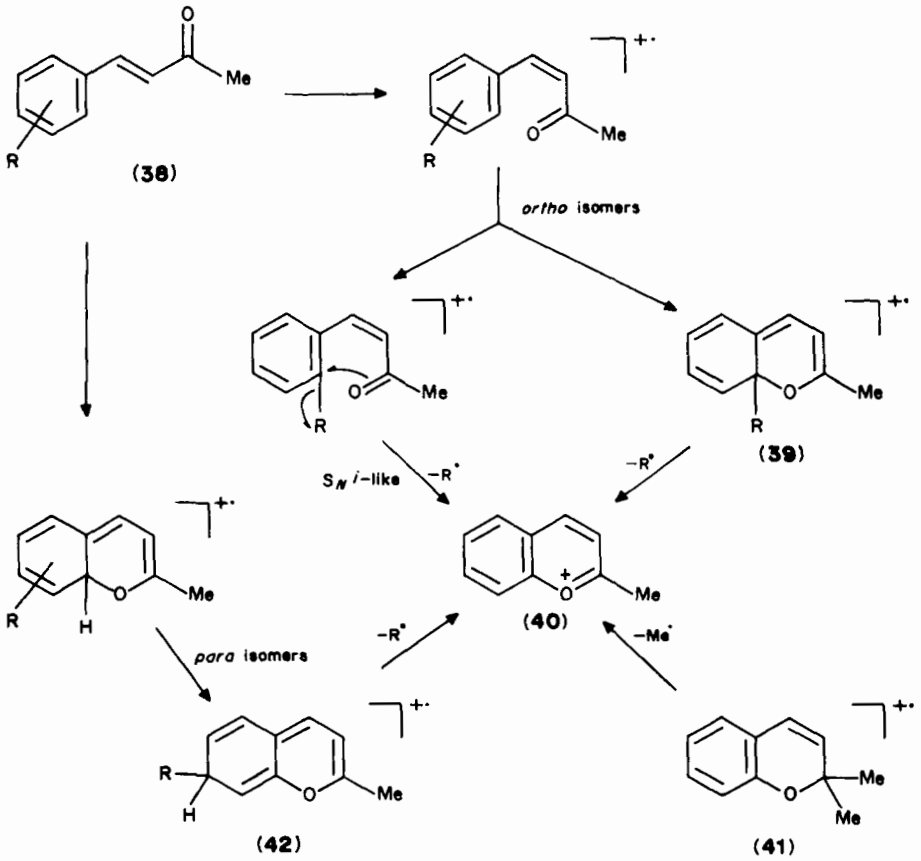


SCHEME 14



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· 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· 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·. For all the groups R the transition state energies have been assessed to lie above the corresponding thermochemical thresholds, defined by $\Delta H_f[C_{10}H_9O^+] + \Delta H_f(R^\cdot)$. 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



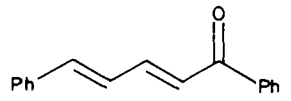
SCHEME 16

weakly bound substituents, e.g. Br, I and NO_2, the intermediates **39** may be unstable, such that the overall reaction resembles a S_Ni substitution rather than a two-step process (Scheme 16)[36]. The loss of R· 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· 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].

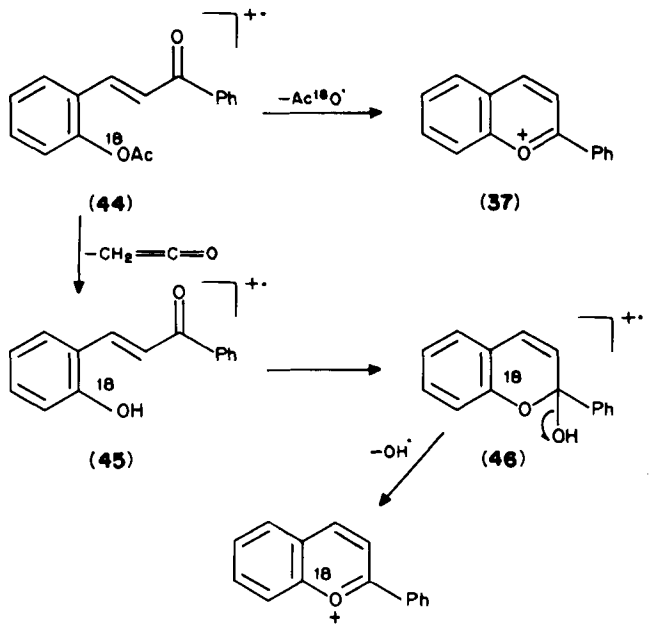


(43)

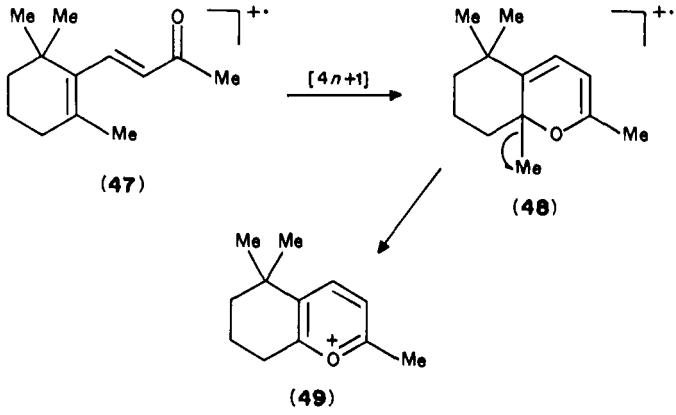
In an interesting ^{18}O-labelling study[41], different mechanisms were distinguished for the loss of the acetoxy and hydroxy group from substituted chalcones **44** and **45**, respectively (Scheme 17). The ^{18}O-labelled acetate **44** cleanly eliminates the acetoxy group to give ion **37** (Scheme 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].

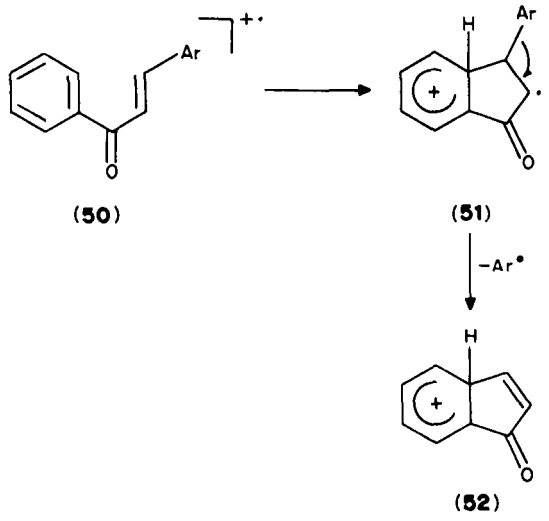
Ionized chalcones undergo another rearrangement which resembles the Nazarov cyclization known from solution chemistry[43,44], and leads to loss of the styryl aromatic



SCHEME 17



SCHEME 18



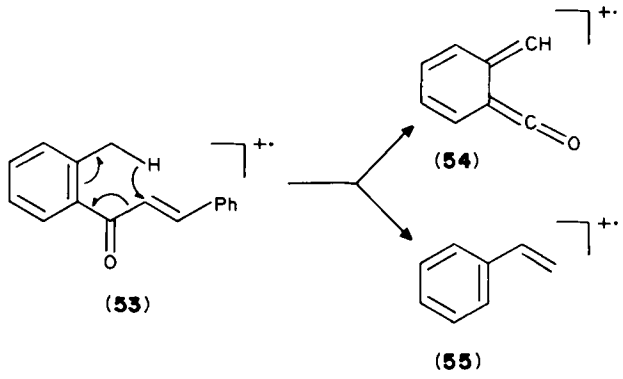
SCHEME 19

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].

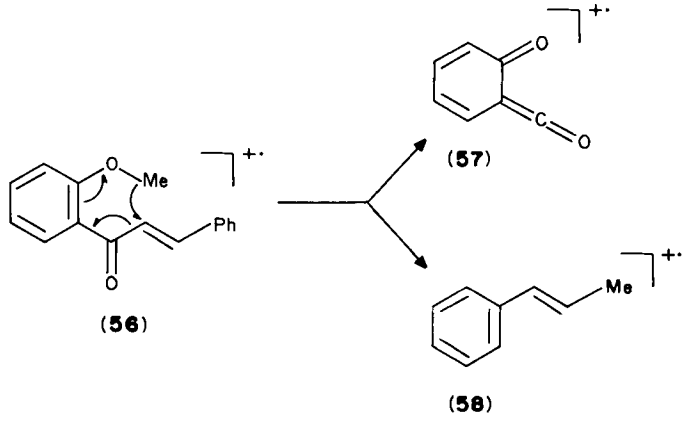
Beside reacting as an electrophile, the enone group can also function as an acceptor for radicals being transferred from the *ortho* positions of the benzoyl ring. This *ortho* effect, which is a general phenomenon in the mass spectra of *ortho*-disubstituted aromatic compounds[47,48], takes up different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

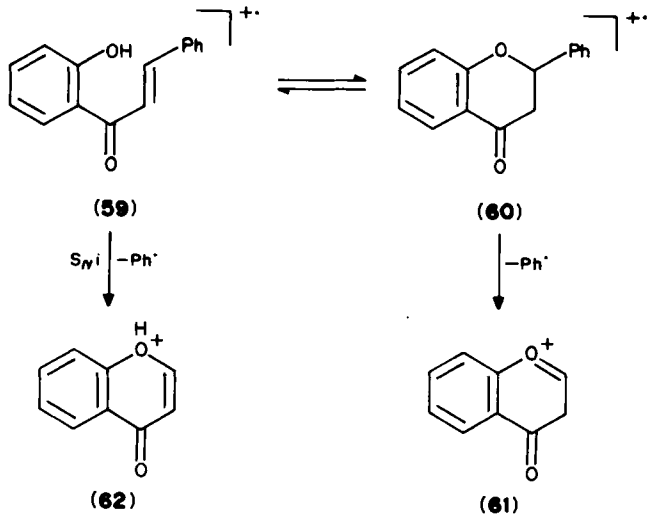
The *ortho*-hydroxy group in ionized chalcone **59** can attack the β-carbon atom of the enone group in an intramolecular Michael addition (Scheme 22), yielding the isomeric flavanone **60**[45,49]. The isomers **59** and **60** give similar mass spectra which indicate that the corresponding molecular 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 $Ar^2—\dot{C}=CH—Ar^3$ ion being formed. Consequently, the Ar^1CO^+ and $Ar^2—\dot{C}=CH—Ar^3$ 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.

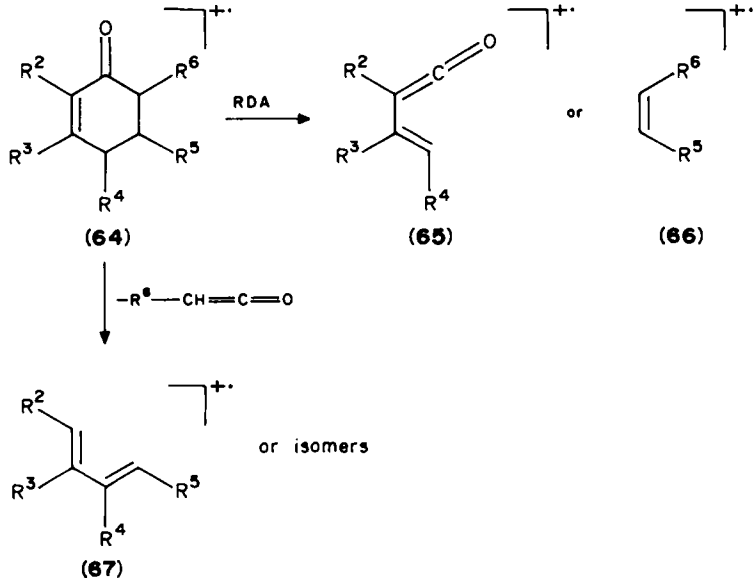
$$Ar^1CO—\underset{\displaystyle Ar^2}{\overset{|}{C}}=CHAr^3$$

(**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

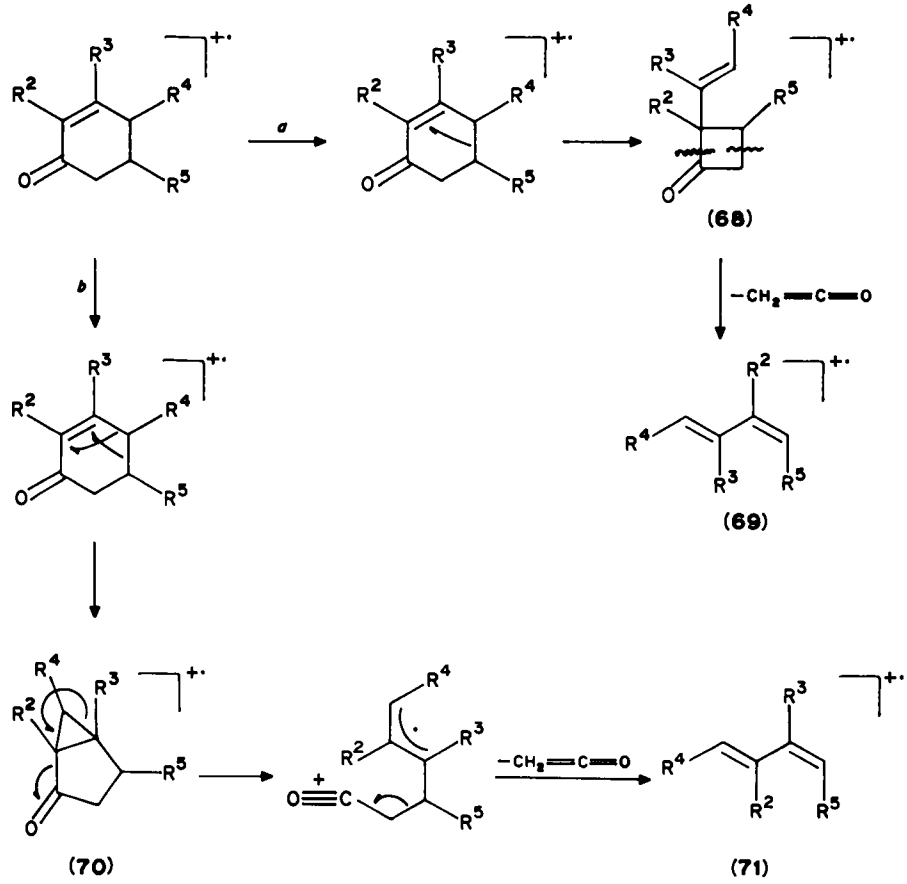
Compounds containing a cyclohexenone or a cyclopentenone ring are often of great biological importance (e.g. steroid hormones, phorbol esters, etc.), and the need for their analytical determination has prompted detailed mass spectral studies of model cyclic enones[51–59]. Under electron impact, cyclohexenone 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.

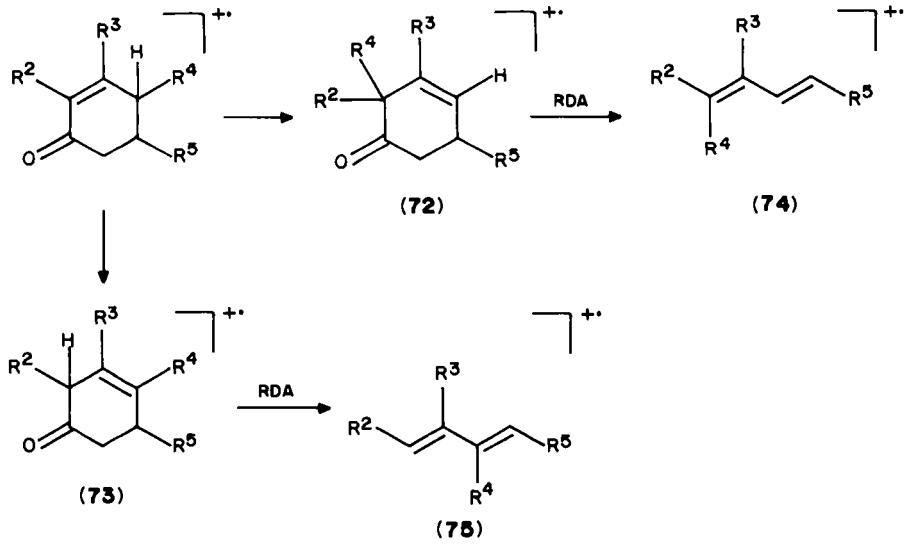
The elimination of ketene occurs for R^6 = H and necessitates the presence of an alkyl or an aryl group at C-4 of the cyclohexenone ring[51,52]. The identity of the ketene molecule has been established beyond any doubt by deuterium labelling in various cyclohexenone derivatives[51,53]. On the other hand, 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



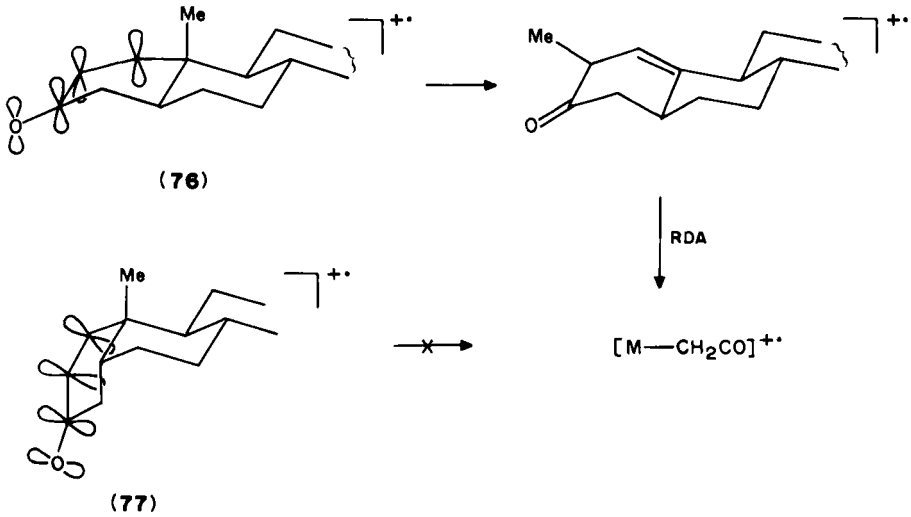
SCHEME 24

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

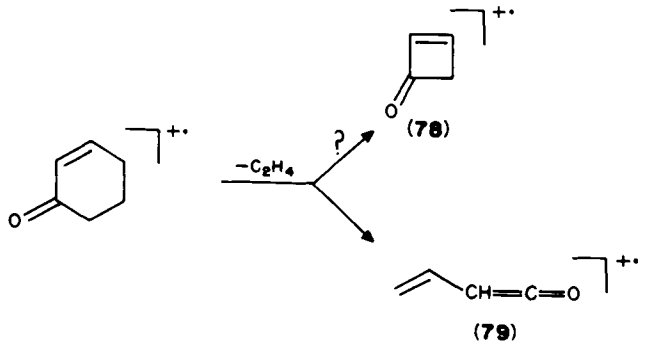


SCHEME 25



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 $[C_4H_4O]^{+\cdot}$ from cyclohexenone release on average 6.6 kJ mol^{-1} during the

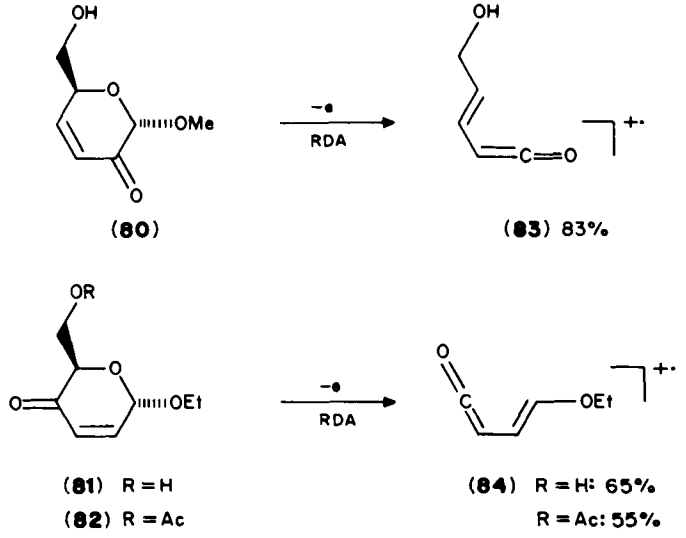


SCHEME 27

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].

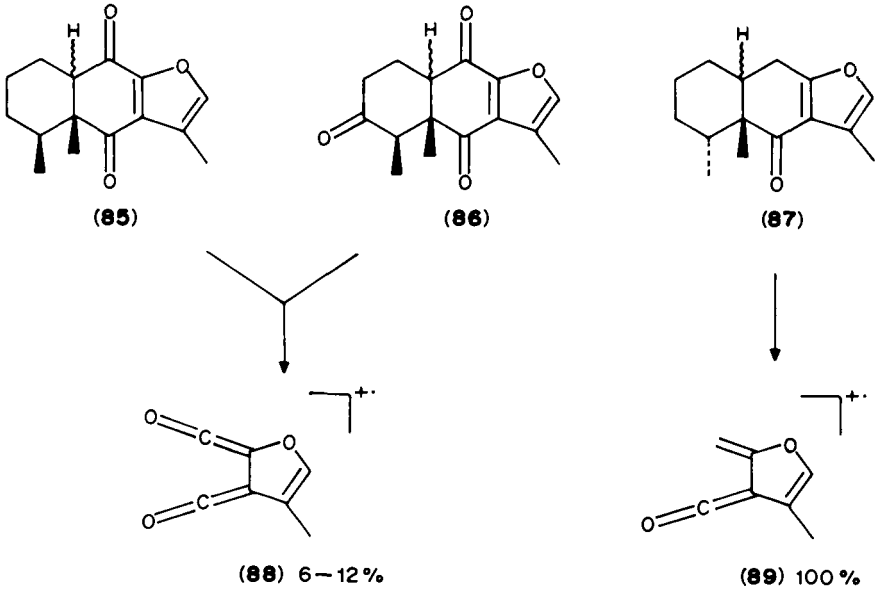


SCHEME 28

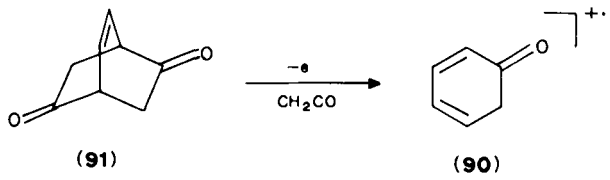
Stereochemistry of the retro-Diels–Alder reaction has been investigated with tricyclic enones **85–87** (Scheme 29), but only weak effects of ring annulation on the relative intensities of the RDA fragments have been found[70]. Of interest is the much greater relative abundance of the ketene ions **89** 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].

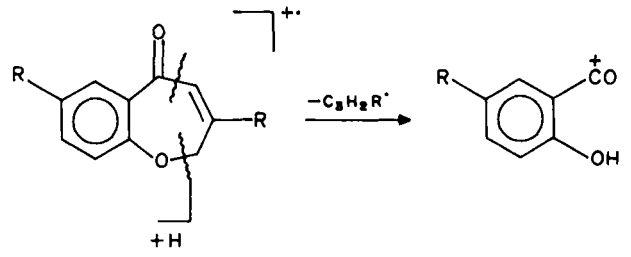
The 2,4-cyclohexadienone radical cation (**90**) has been the subject of numerous mass spectral studies owing to its role in decompositions of ionized phenyl ethers and phenyl esters[71] (for more recent accounts of the earlier work cf. References 72 and 73). Ion **90** is readily generated by the electron-impact-induced 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_2OH, CHO

SCHEME 31

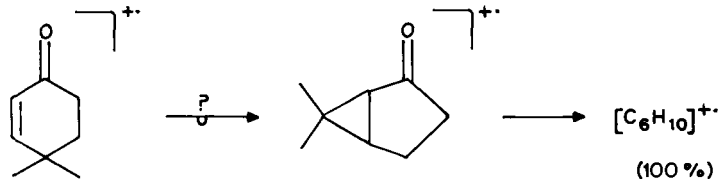
stable dienone ion behaves as a unique species[72,74,75]. Both unimolecular and collision-induced decompositions of **90** are dominated by expulsion of carbon monoxide to give a $[C_5H_6]^{+\cdot}$ ion[72,75]. The kinetic energy release accompanying the loss of carbon monoxide from metastable $[\mathbf{90}]^{+\cdot}$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

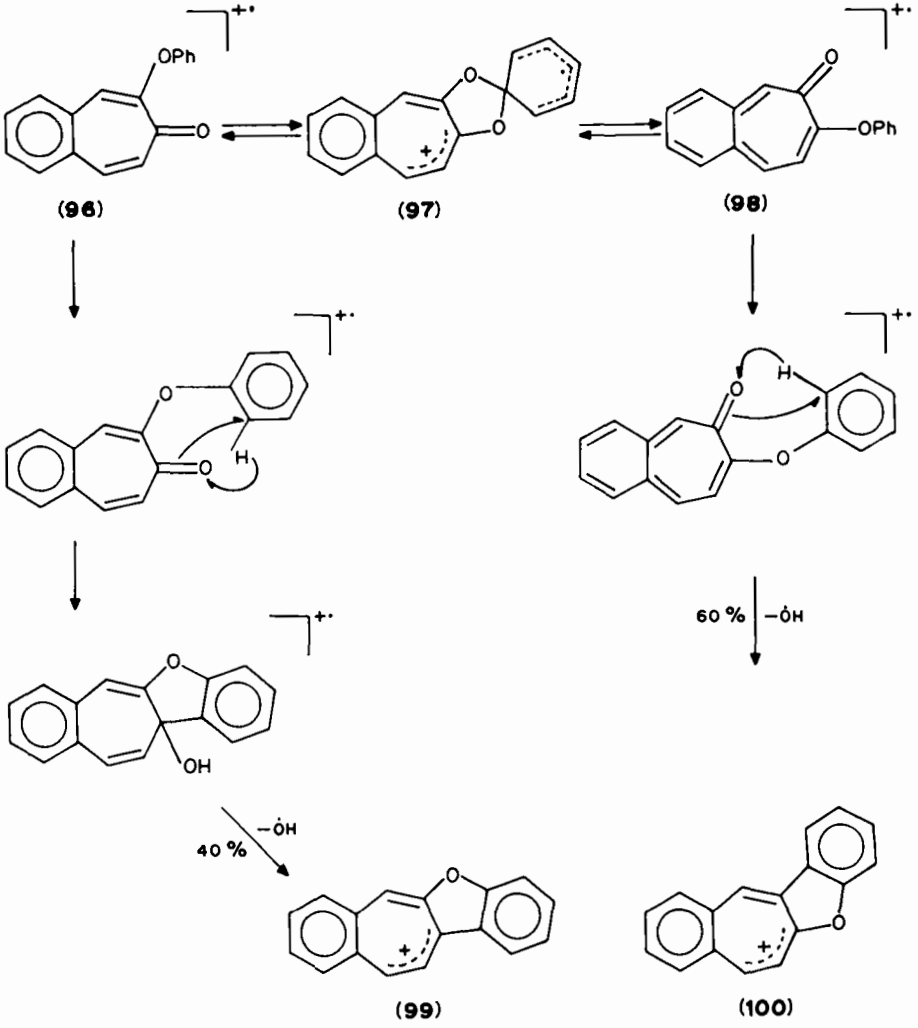
The chemistry of gaseous radical cations shares some common features with the chemistries of other open-shell species, e.g. radicals[77] and photoexcited molecules[55,78–80]. As mentioned earlier in this chapter, one of the ways to explain the loss of ketene from the 4,4-dimethylcyclohexenone molecular 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 ^2H, ^{13}C and ^{18}O labelling (Scheme 33)[80]. The hydroxyl eliminated involves both the carbonyl and the ether



(94) (95)

SCHEME 32



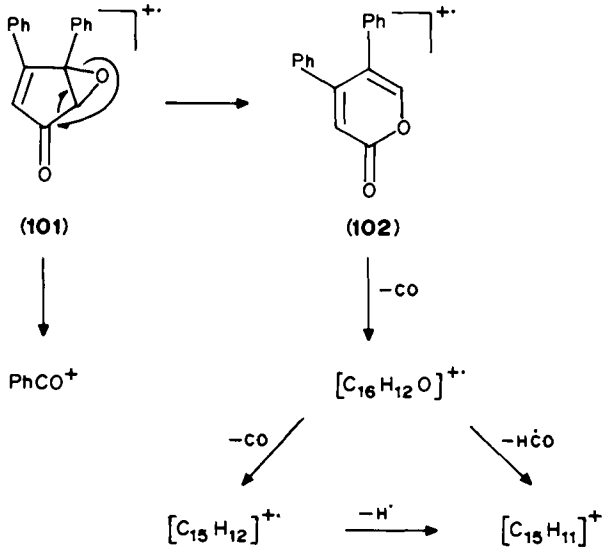
SCHEME 33

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

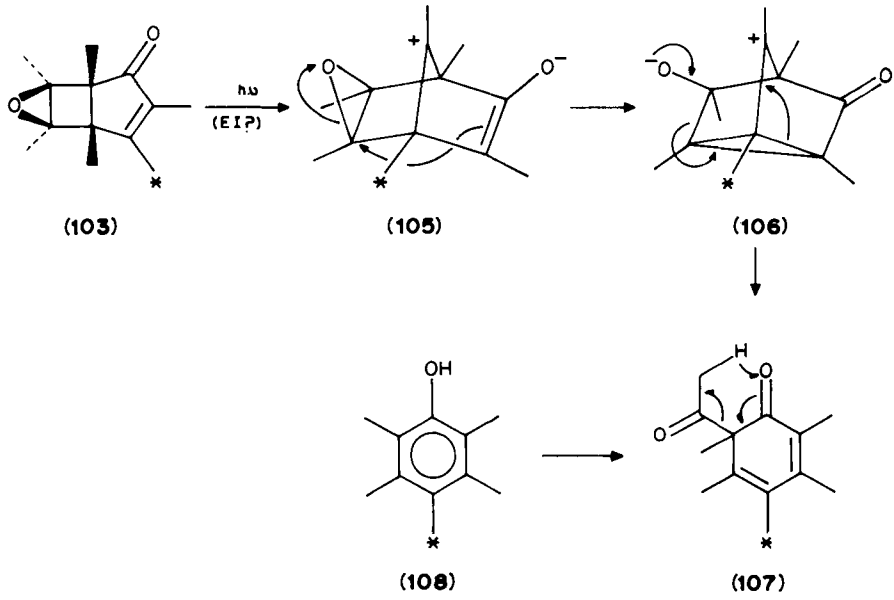
phenoxy group which is the subunit of the lowest ionization energy[10]. The bond formation in ionized **96** to give the intermediate **97** (Scheme 33) can thus be regarded as a nucleophilic attack by the enone oxygen atom at the electron-deficient centre of the ionized phenoxy group.

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

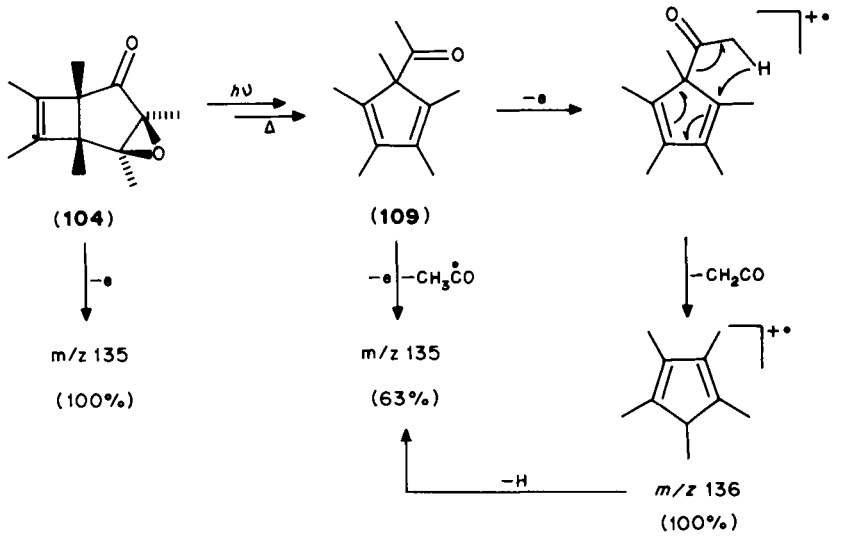


SCHEME 35

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

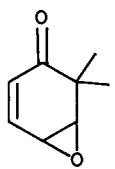
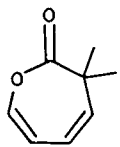
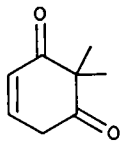
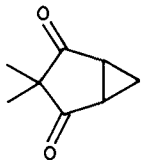
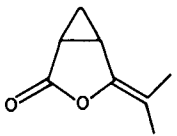
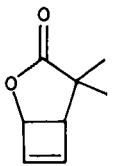


SCHEME 36

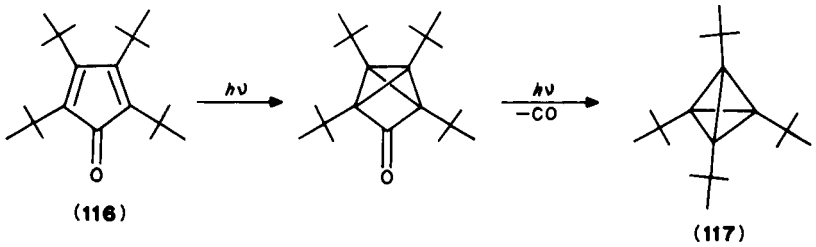
112–114 are similar, each showing the base peak at *m/z* 70, presumably due to $[(CH_3)_2C{=}C{=}O]^{+\cdot}$ ions. Hence it can be inferred that a large part of decomposing **[113]**$^{+\cdot}$ and **[114]**$^{+\cdot}$ undergo isomerization to **[112]**$^{+\cdot}$ which then fragments via RDA cleavage. 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].

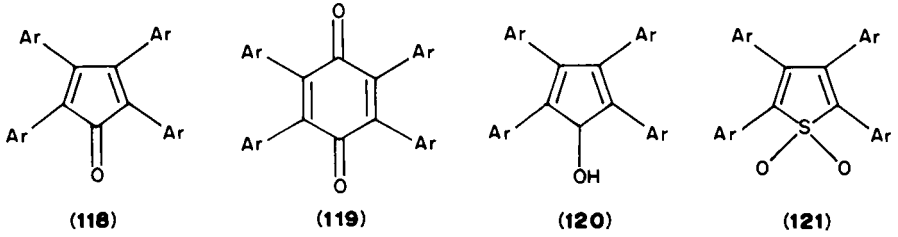
The intermediacy of tetrahedral structures in decompositions of $[C_4Ar_4]^{+\cdot}$ ions was definitely disproved by Schwarz and coworkers[95] who used the central-ring labelled

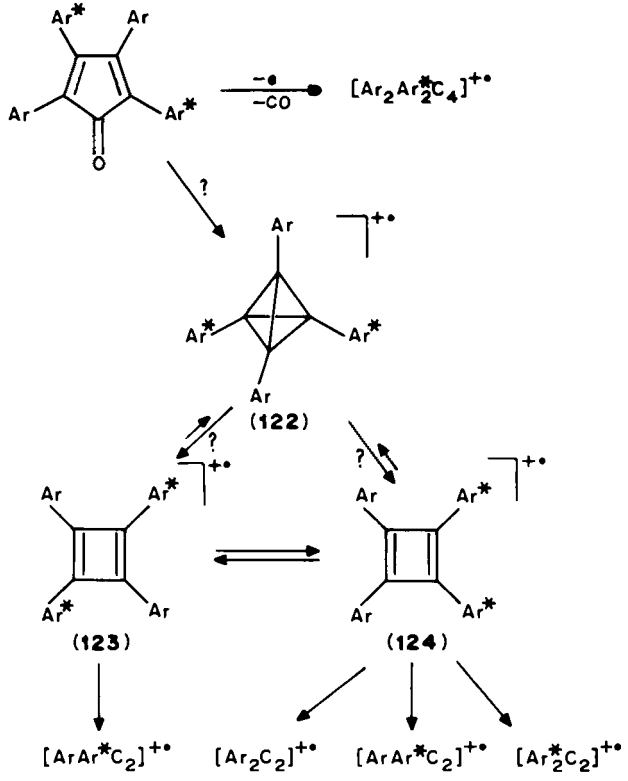
m/z	(110)	(111)	(112)	(113)	(114)	(115)
						
138	7	12	42	47	50	1.5
123	10	—	1	9	18	2
122	29	—	—	—	—	—
110	—	—	12	21	15	15
109	45	2	—	16	20	36
95	44	100	22	70	80	100
82	100	—	—	10	—	—
81	—	5	—	15	—	—
79	60	6	—	24	35	66
77	30	4	4	8	25	35
70	20	—	100	100	100	—

SCHEME 37

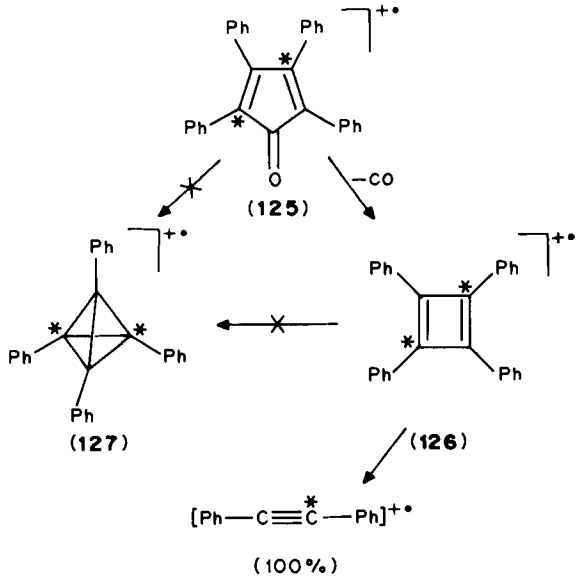


SCHEME 38





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 $n-\pi^*$ or $\pi-\pi^*$ 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:

$$\text{Enone} + BH^+ \overset{K_{eq}}{\rightleftharpoons} [\text{Enone} + H]^+ + B \tag{1}$$

$$GB(\text{Enone}) = GB(B) - \Delta G_r(1) \tag{2}$$

The proton affinity is defined as the negative enthalpy change in reaction 3:

$$\text{Enone} + H^+ \longrightarrow [\text{Enone} + H]^+ \tag{3}$$

i.e. $PA(\text{Enone}) = -\Delta H_r(3) = \Delta H_f^\circ(\text{Enone}) + \Delta H_f^\circ(H^+) - \Delta H_f^\circ([\text{Enone} + H]^+)$. The GB and PA quantities are interrelated by equation 4:

$$PA = GB - T\Delta S_r(3) \tag{4}$$

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**

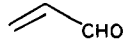
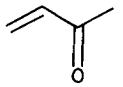
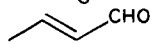
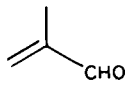
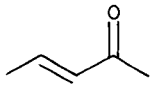
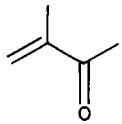
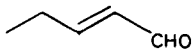
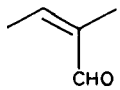
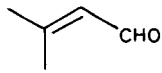
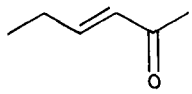
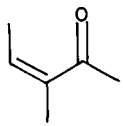
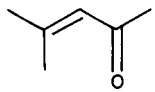
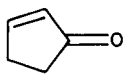
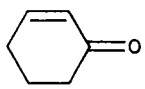
Compound	$\Delta H_{f,298}^\circ(M)$	PA	GB	$\Delta H_f^\circ(MH)^+$	IE_{vert}
(**1**) 	−74[a]	811[b]	778[c]	645	978[d]
(**2**) 	−124[a]	838[b]	805[c]	568	931[e]
(**3**) 	−104[f]	836[b]	803[c]	590	946[g]
(**4**) 	−109[a]	817[b]	784[c]	604	957[h]

TABLE 2. (*continued*)

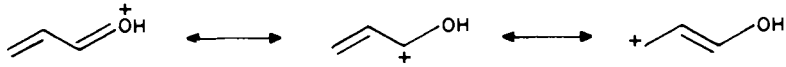
Compound		$\Delta H^\circ_{f,298}$(M)	PA	GB	$\Delta H^\circ_f(MH)^+$	IE_{vert}
(128)		−157[a]	867[i]	834[i]	506	906[h]
(129)		−157[a]	851[i]	819[i]	522	917[h]
(130)		−127[a]	848[j]	815[j]	555	936[h]
(131)		−137[a]	853[j]	819[j]	539	926[h]
(132)		−137[a]	861[j]	828[j]	531	
(133)		−177[a]	867[j]	834[j]	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 CH_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*).

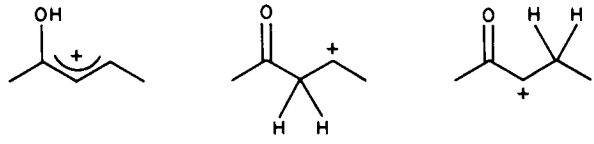
$CH_2 \cdots CH \cdots \overset{+}{C}H—OH$ (**138**) $\quad$ $Me—\overset{+}{C}H—CHO$ (**139**) $\quad$ $\overset{+}{C}H_2—CH_2—CHO$ (**140**)

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 ΔH_f°(**138**) − ΔH_f°(**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:



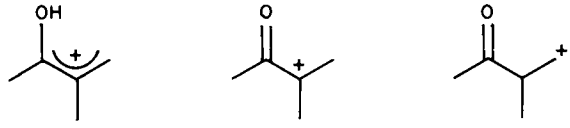
Gas-phase basicities of a series of aliphatic and cyclic enones have been determined from measurements of proton-transfer equilibrium constants in ion-cyclotron resonance experiments (Table 2)[115,119,120]. The thermochemical data show again that the protonation in higher aliphatic and cyclic enones 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



(128a) (128b) (128c)

ΔE (kJ mol^{-1}) 0 168 191



(129a) (129b) (129c)

ΔE (kJ mol^{-1}) 0 123 172

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 $\Delta H_f^\circ(MH)^+$ values should be regarded as the least accurate ones.

The effects of methyl substituents on the $\Delta H_f^\circ(MH)^+$ 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 $\Delta H_f^\circ(MH)^+$ 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.

$$\Delta H_f^\circ(MH)^+ = \alpha - \beta \ln n \tag{5}$$

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. $\Delta PA = 33$ 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

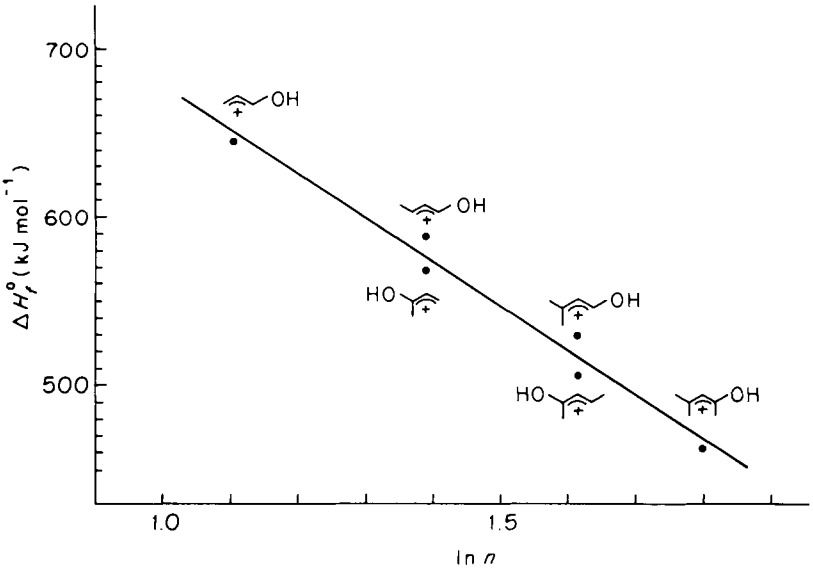


FIGURE 1. Correlation between the heats of formation of protonated enones and the number of carbon atoms in the ions

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**) $\approx$ 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_{vert} and PA values shows that the latter also

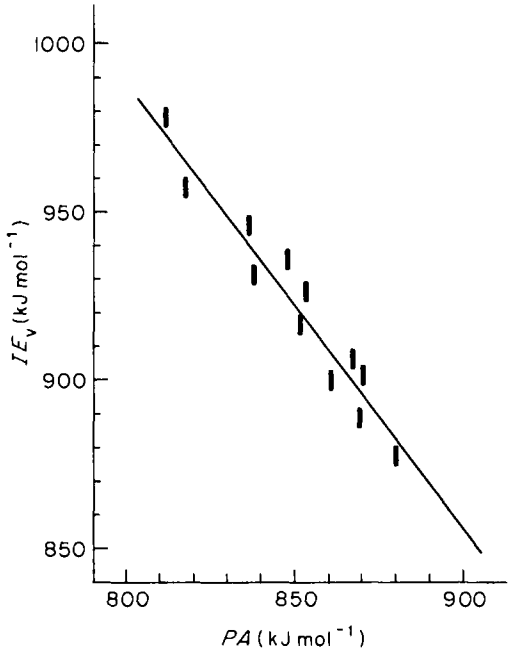


FIGURE 2. Correlation between proton affinities and vertical ionization energies in **1–4**, **128–131** and **134–137**

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:

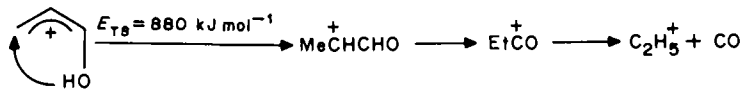
$$\begin{aligned} \mathrm{BDE(O{-}H)} &= \Delta H_f^\circ(\mathrm{M})^{+\cdot} + \Delta H_f^\circ(\mathrm{H}^\cdot) - \Delta H_f^\circ(\mathrm{MH})^+ \\ &= \mathrm{IE(M)} + \mathrm{PA(M)} - \mathrm{IE(H}^\cdot) \end{aligned} \tag{6}$$

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 $\Delta H_f^\circ(\mathrm{M})^{+\cdot}$ 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 $[C_2H_5^+ + CO]$ (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 $[C_2H_5^+ + CO]$ 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 $C_3H_5O^+$ and $C_2H_5^+$ investigated in a



	(138)	(139)	(141)	
ΔH_f^0 (kJ mol^{-1})	645	834	591	793

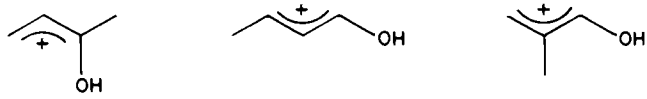
SCHEME 42

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)$^{+\cdot}$, giving E_{TS} = 868 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 kJ mol^{-1} using the Haney-Franklin formula[132] which gives T_{av} = 8–9 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.

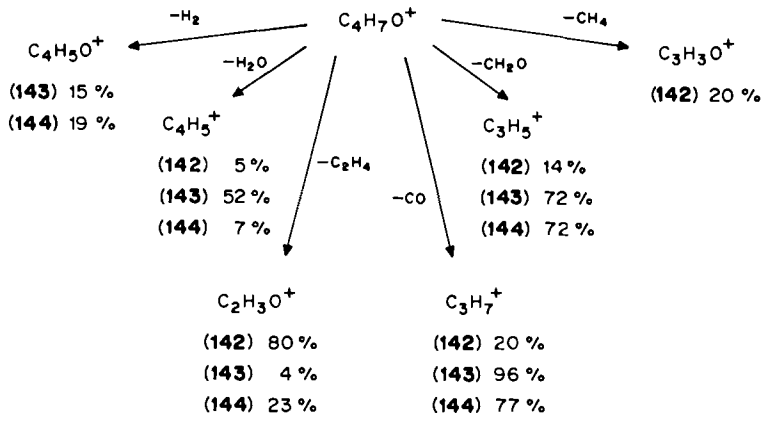
Collisional activation of stable **138** opens new, higher-energy, decomposition channels in addition to those encountered with metastable **138**. Of particular importance are the dehydrogenation, **138** → $C_3H_3O^+$, followed by decarbonylation, $C_3H_3O^+ \rightarrow C_2H_3^+$, and the formation 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

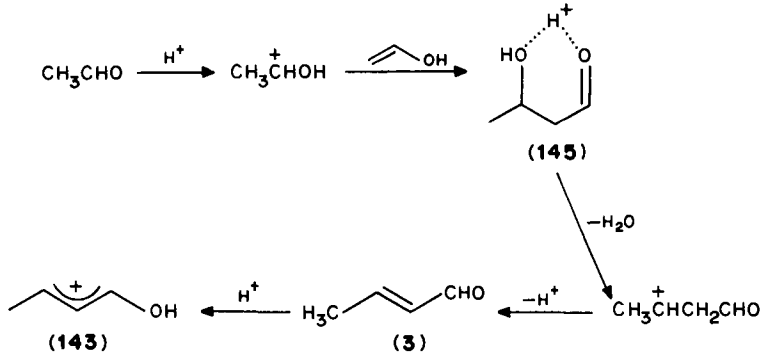


SCHEME 43

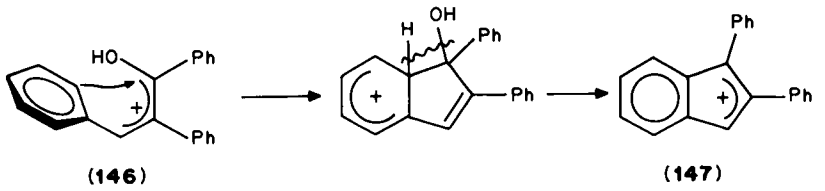
of CO vs. C_2H_4 from metastable **142–144** follows the same line as with decompositions in the ion source[99,134,135].

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.

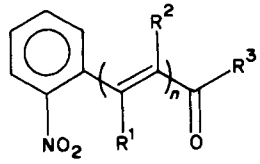
$$M + NH_4^+ \overset{K_a}{\rightleftharpoons} [M + NH_4]^+ \tag{7}$$

$$M + NH_4^+ \overset{K_p}{\rightleftharpoons} [MH]^+ + NH_3 \tag{8}$$

IV. THE CHEMISTRY OF ENONE ANIONS

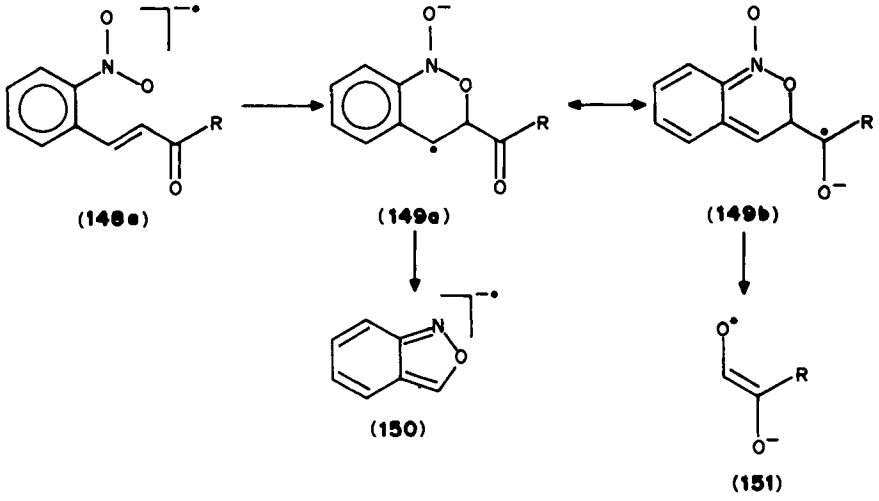
While the gas-phase chemistry of enone positive ions has been studied in depth, its anionic counterpart resembles a terra incognita awaiting exploration[147,148]. Formation of an observable radical anion $[M]^{-\cdot}$ from an organic molecule requires that the latter possess a low-lying LUMO which can accept a thermal electron and keep it until $[M]^{-\cdot}$ 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 $[M]^{-\cdot}$ 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].

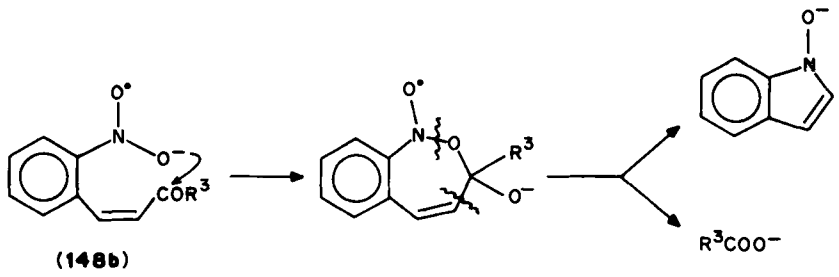


(148)

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

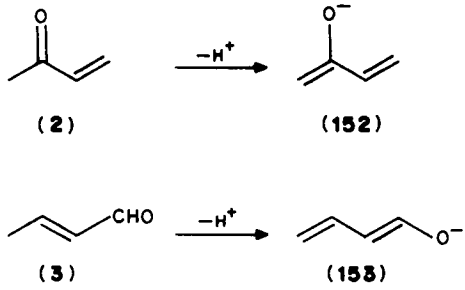
Even-electron anions, $[M-H]^-$, are formed readily from cyclic enones under conditions of CH_4/H_2O negative chemical ionization (NCI) which uses gaseous hydroxyl anion as the base[151]. Steroid enones, e.g. cholest-4-en-3-one, cholesta-3,5-dien-7-one and cholest-4-ene-3,6-dione, give mostly $[M-H]^-$ 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 $[M]^{-\cdot}$ 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

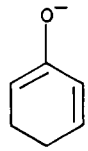


(**2**) (**152**)

(**3**) (**153**)

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.



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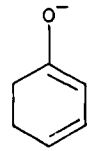

(155)

V. ACKNOWLEDGEMENTS

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The Chemistry of Enones
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CHAPTER 7

Synthesis of enones

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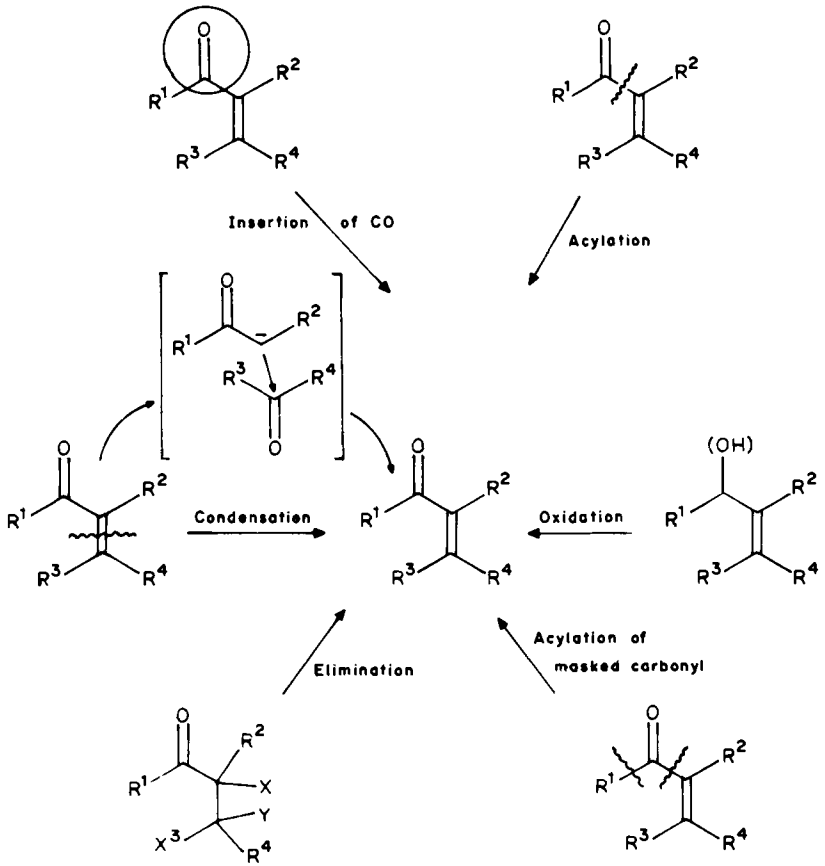
I. INTRODUCTION

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

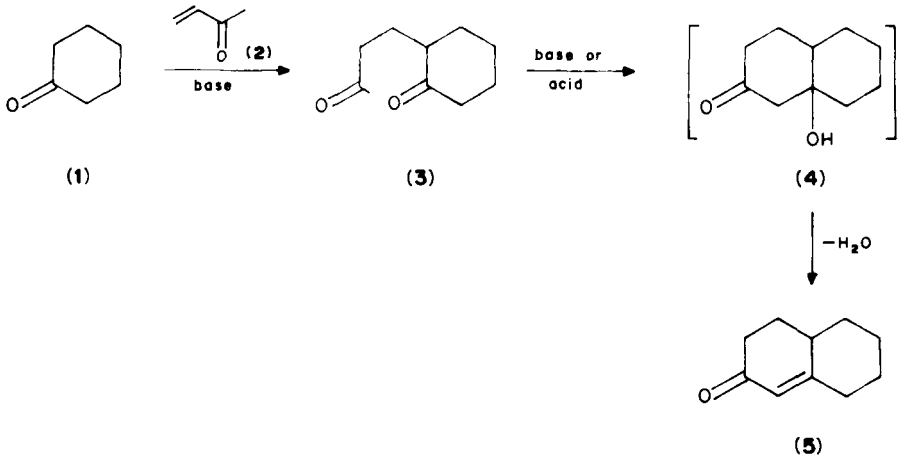


SCHEME 1

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.

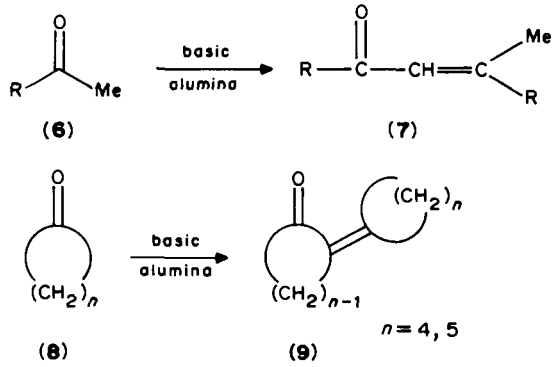
This sequence, however, is not without problems in many cases, especially low yields because of polymerization of the Michael acceptor (e.g. **2**), and lack of control of the direction of enolate formation in unsymmetrical ketones. Hence the sequence has been the target of constant development which 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

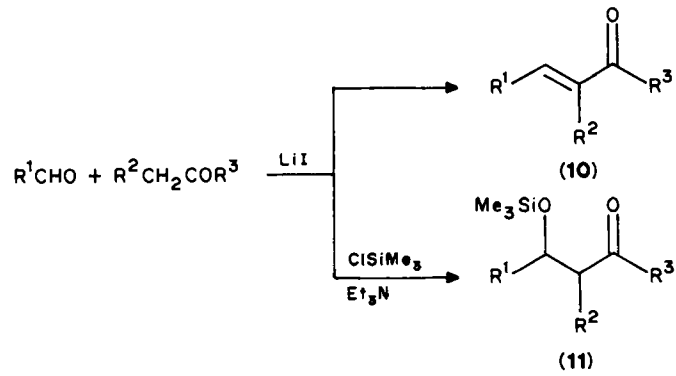
alumina for a few days, the corresponding enones can be obtained, while solid ketones require heating at 80 °C for one or two days.



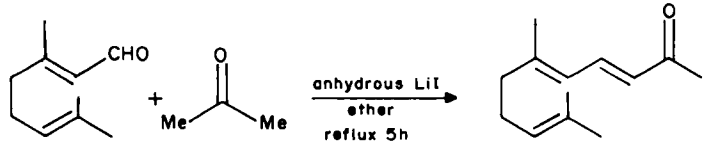
The method, however, has certain disadvantages: first, although product yields are reasonable, the percentage of conversion is rather low, and a large amount of starting material is recovered (although it can be recycled); second, the reaction is very slow or completely fails when hindered ketones are 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



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.

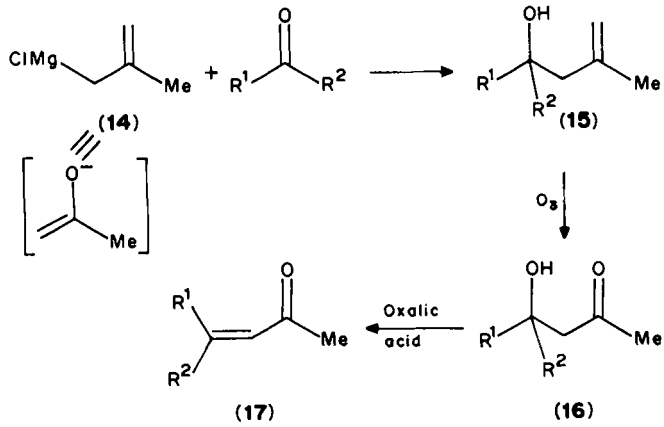


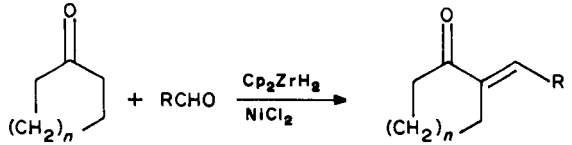
(12) (13)

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].

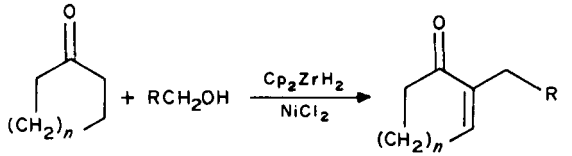
A recent discovery is that dicyclopentadienylzirconium dihydride (Cp_2ZrH_2, $Cp = C_5H_5$), first prepared by Wailes and Weigold[14], catalyzes hydrogen transfer from alcohol to carbonyl compound, i.e. simultaneously oxidizes the alcohol and reduces the carbonyl compound[15]. The same group of workers[16] 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.

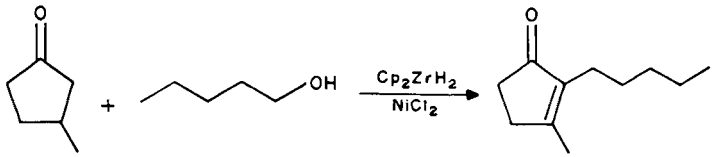
This catalyst system is also able to effect condensation between ketones and alcohols to give 2-substituted cycloalkenones **19**. Therefore, by using commercially available 3-methylcyclopentanone **20** and pentanol as starting materials, dihydrojasmone **21** can be synthesized in one step in 35% yield, albeit accompanied by 8% of the regioisomer **22**.

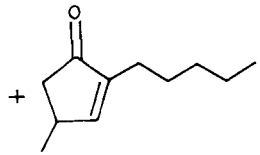

ClMg
Me
(14)
OH
R1
R2
(15)
O3
Oxalic acid
(16)
(17)


Cp2ZrH2
NiCl2
(CH2)n
R
(18)

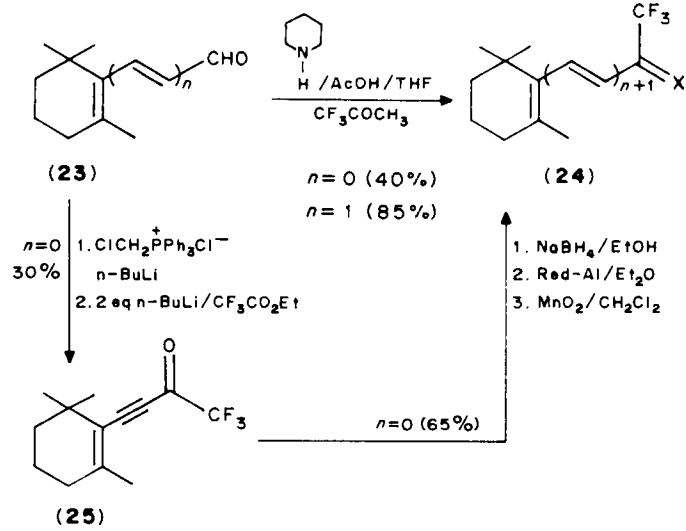
n = 1, 2 R = H, alkyl


+ RCH2OH
Cp2ZrH2
NiCl2
(CH2)n
R
(19)

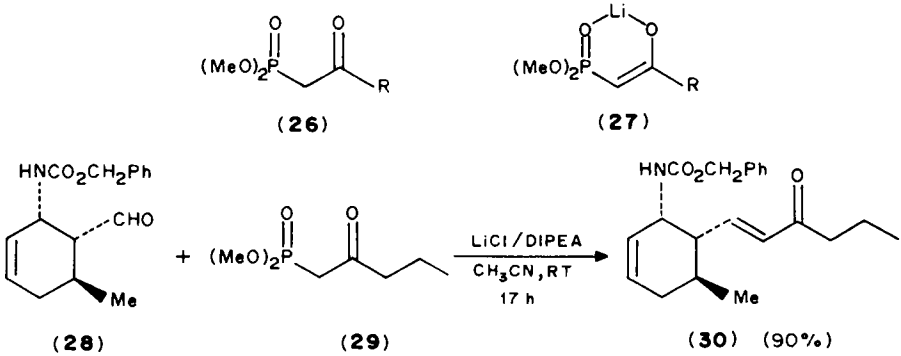

OH
Cp2ZrH2
NiCl2
(20)
(21)


(22)

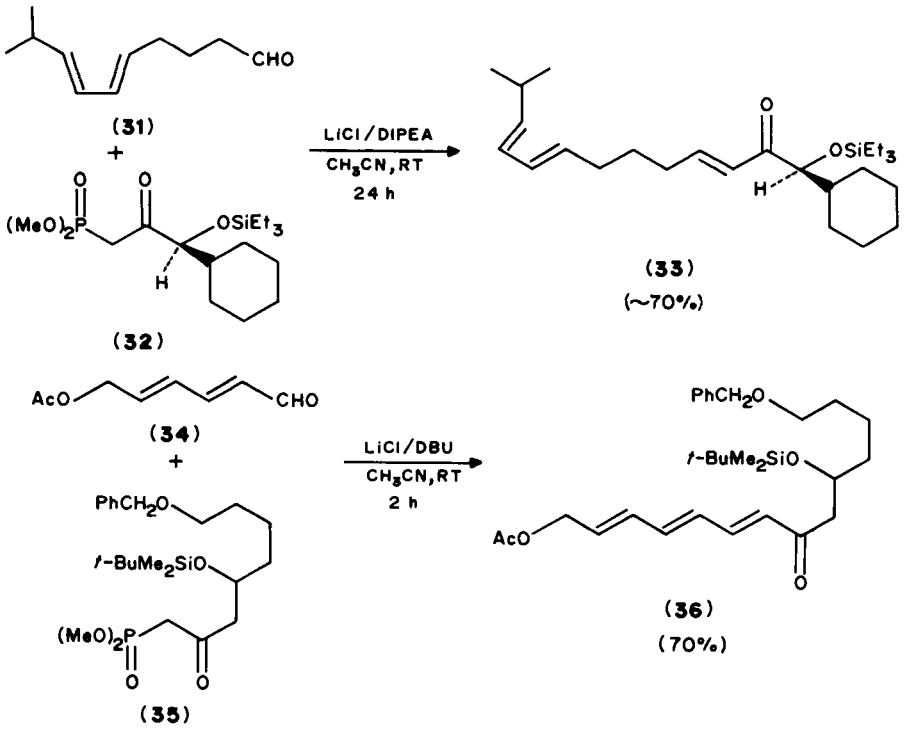
In recent years fluorine has not only found common usage in NMR spectroscopy, but is increasingly utilized as a label for probing structural information and mechanistic details of bioorganic molecules and their processes. Isoprenoid enones such as **24** with trifluoromethyl labels can be synthesized 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].



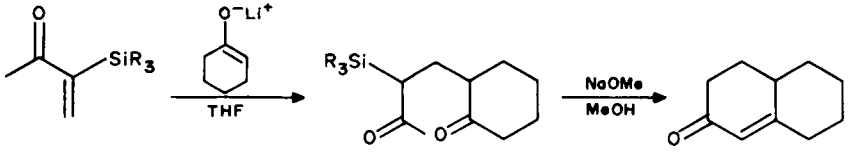
Condensations between carbonyl compounds and phosphonates (Horner–Wadsworth–Emmons reaction) provide another good method for the preparation of enones, as is evident from several reports[20–22]. Moreover, the method is further enhanced by the subsequent discovery[23] that, in the presence of a lithium 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.



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.

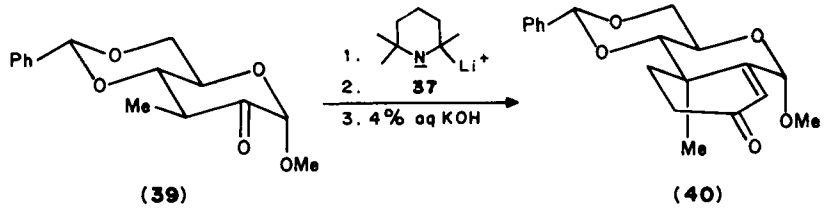


(**37**)
(R=Me,Et)

(**38**)

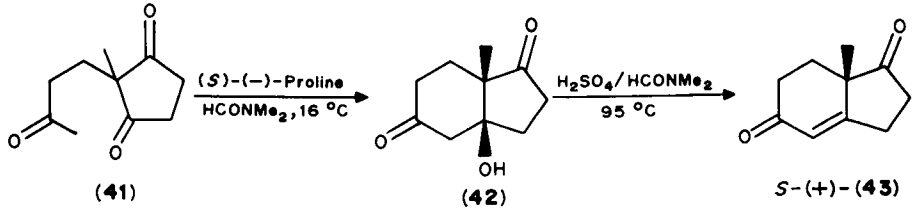
(**5**)

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.

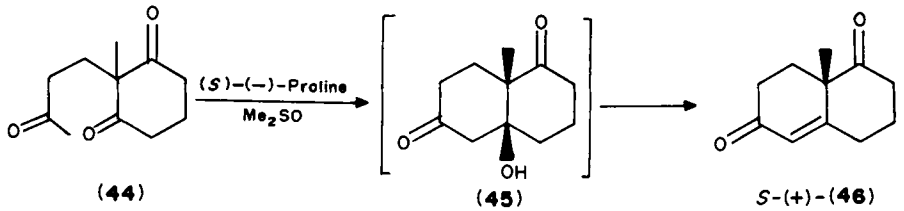


(39) (40)

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)

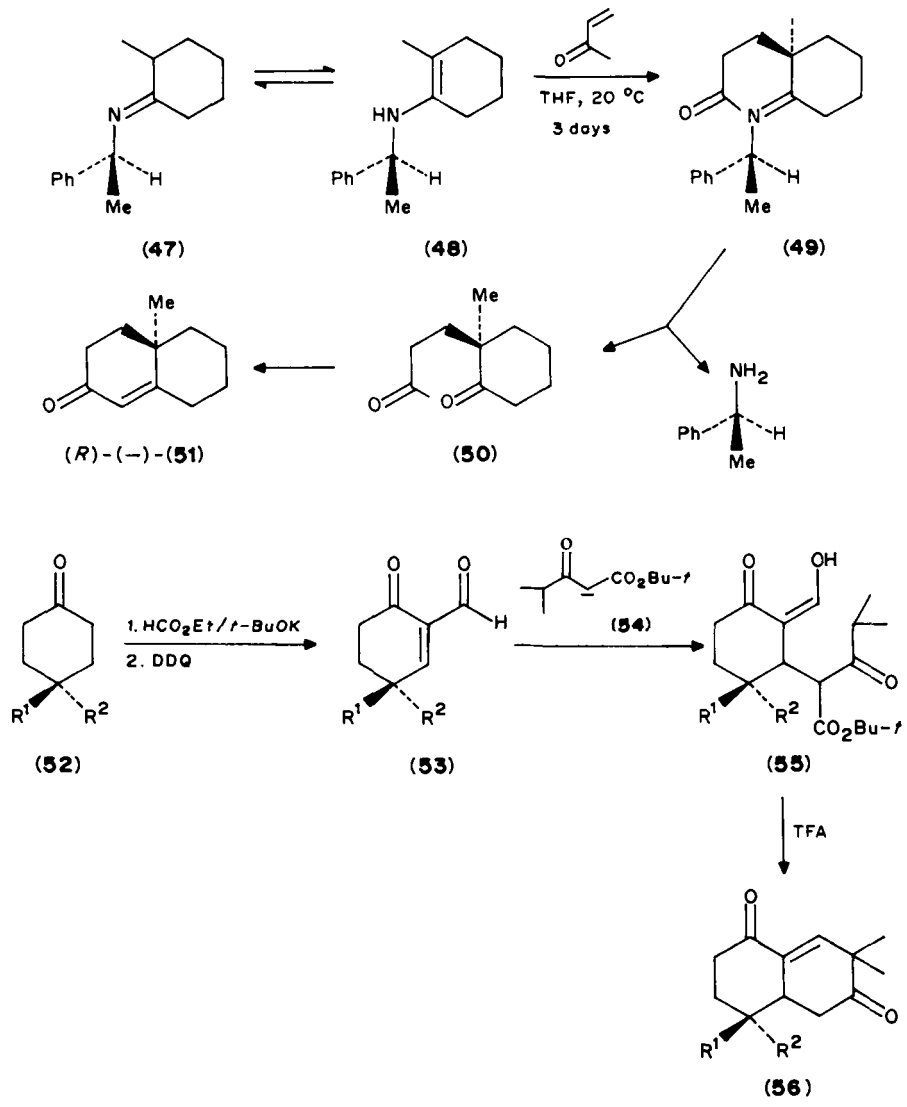


(44) (45) *S*-(+)-(46)

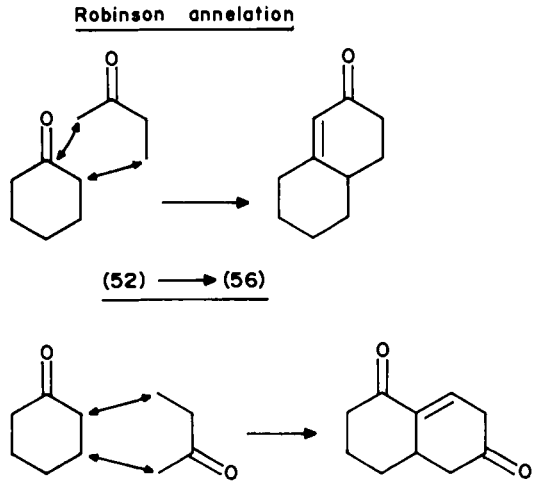
It is now also possible to achieve asymmetric Michael addition in the first step in the Robinson annelation. Optically active enamine **48**, prepared from the corresponding cyclohexanone and amine, undergoes asymmetric Michael addition to give **49** which, after acid hydrolysis, gives **50** in 88% 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.

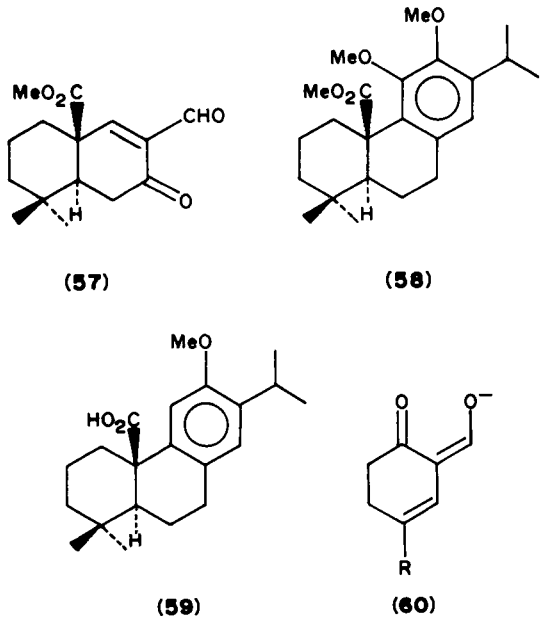
This mode of annelation is strategically applied in the total synthesis of several important natural products, for example, di-*O*-methyl carnosic acid **58**[38] and *O*-methyl pisiferic acid **59**[40], starting from precursor **57**.



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



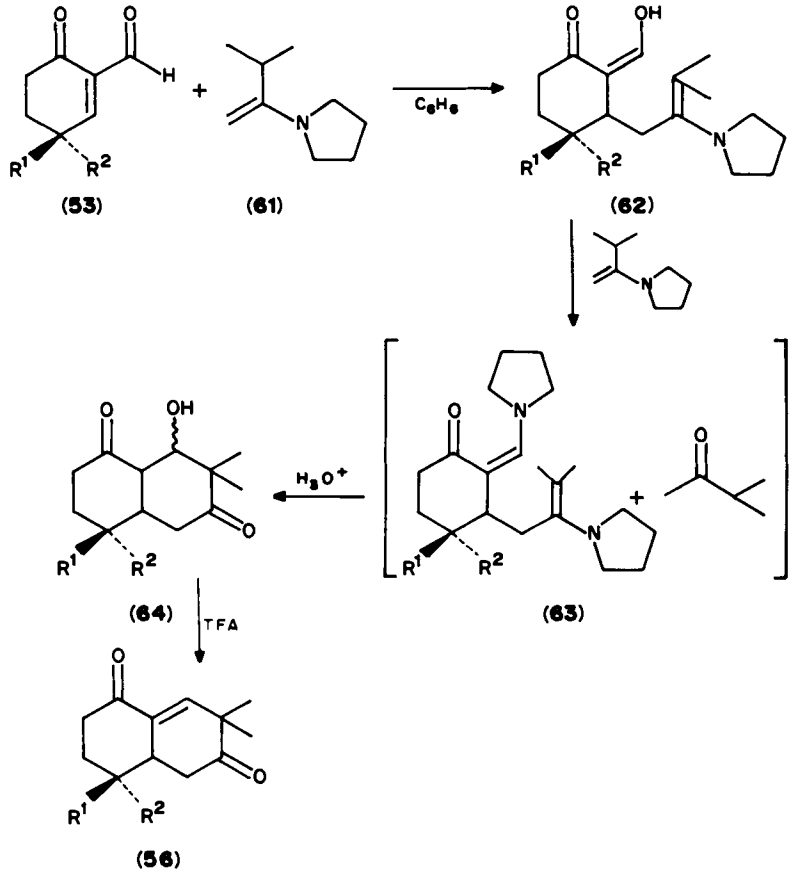
SCHEME 3



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.

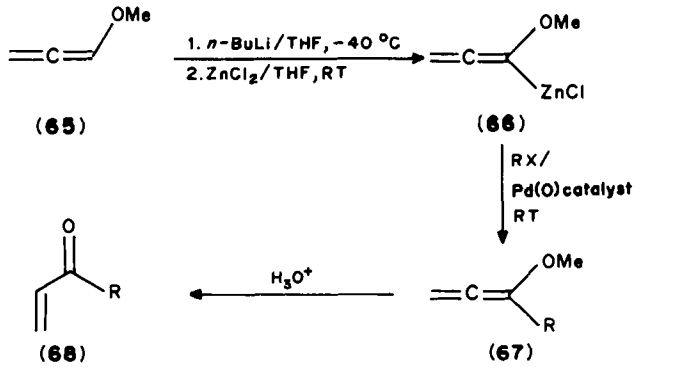


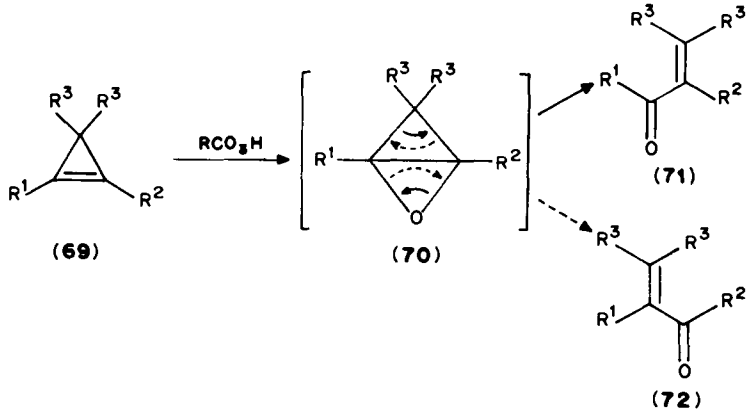
(53) (61) (62) (63) (64) (56)

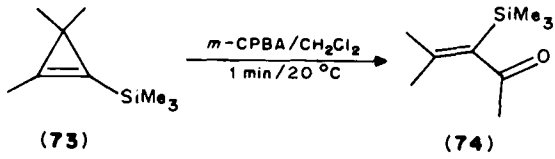
One technique[46] begins with lithiation of allenic ether **65** by *n*-butyllithium in THF at −40 °C followed by transmetallation with zinc chloride to give the zinc salt **66**, which can react with a variety of alkyl and aryl halides in the presence of palladium(0) catalyst to yield the substituted allenic ether **67**, acid hydrolysis of which affords the vinyl ketone **68**.

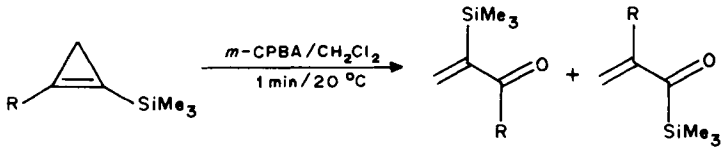
Since the report of Prinzbach and Fischer[47], twenty years ago, that peracid oxidation of the cyclopropene **69** gives **71** and/or **72**, the mechanism of this reaction has been extensively studied[48–50]. The process is now generally believed to involve the oxabicyclo[1.1.0]butane **70** as an 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**.

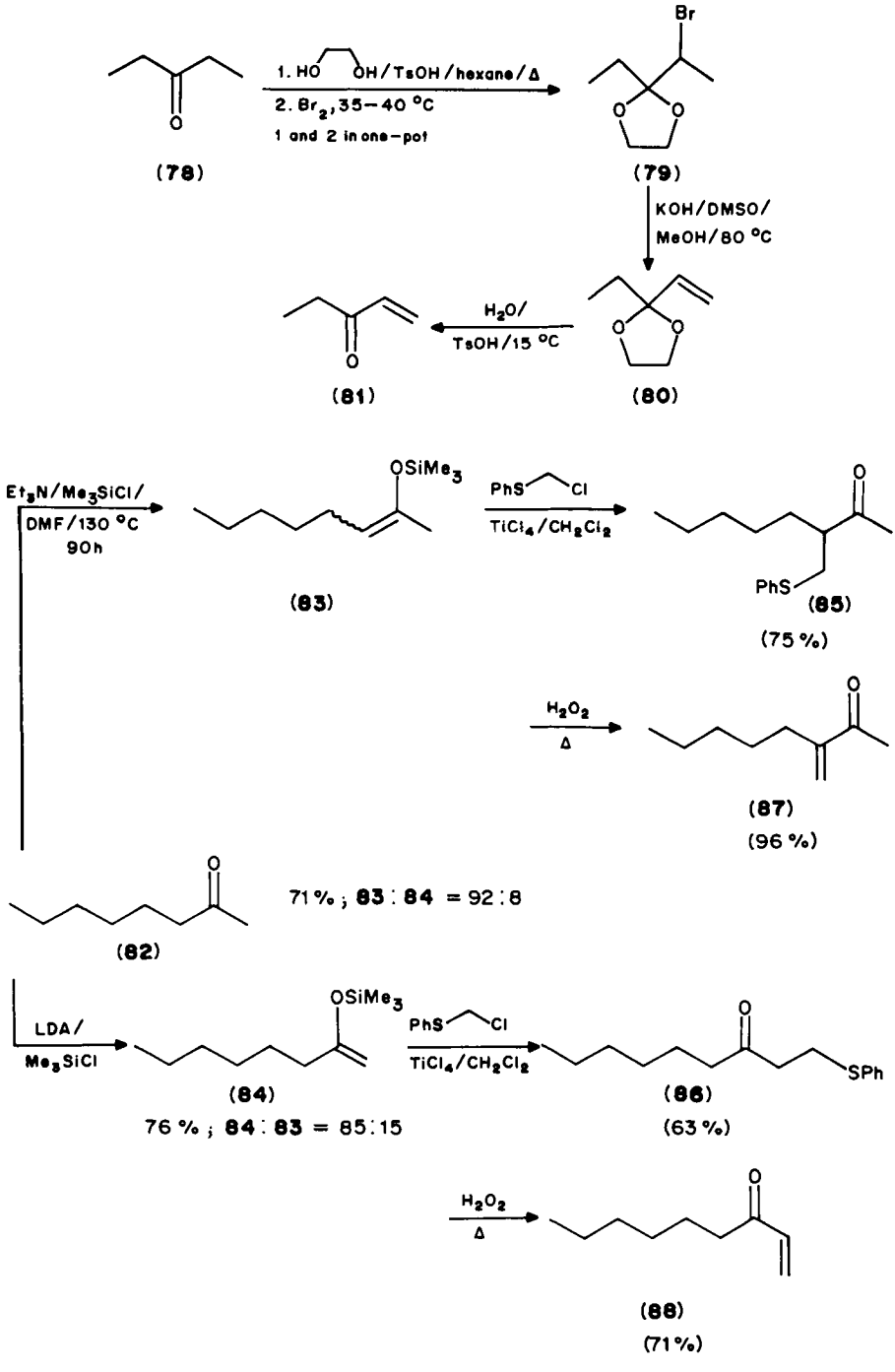








	(76)	(77)
R = *i*-Pr	66.5%	15%
R = *t*-Bu	66%	17%


1. HO OH/TsOH/hexane/Δ
2. Br2, 35–40 °C
1 and 2 in one-pot
Br
(78)
(79)
KOH/DMSO/
MeOH/80 °C
H2O/
TsOH/15 °C
(81)
(80)
Et3N/Me3SiCl/
DMF/130 °C
90h
OSiMe3
(83)
PhS Cl
TiCl4/CH2Cl2
PhS
(85)
(75 %)
H2O2
Δ
(87)
(96 %)
(82)
71 %; 83 : 84 = 92 : 8
LDA/
Me3SiCl
(84)
76 %; 84 : 83 = 85 : 15
SPh
(86)
(63 %)
(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.

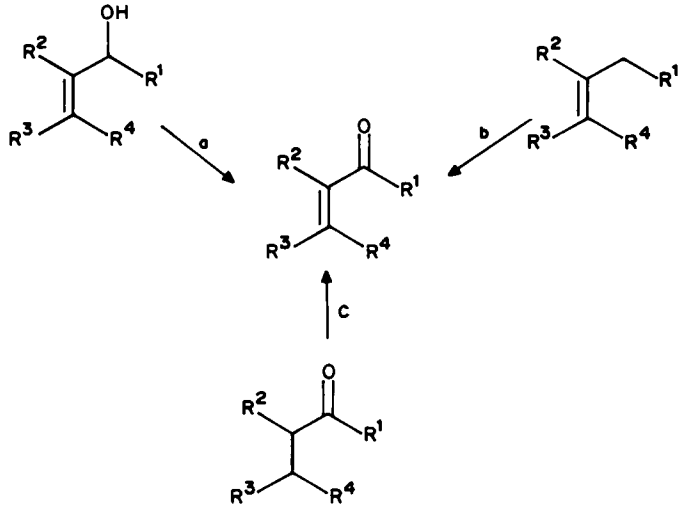
Yet another synthesis of vinyl ketones advantageously employs the 'thermodynamic' **83** and 'kinetic' **84** silyl enol ethers of 2-octanone. These are reacted with chloromethyl phenyl sulfide (titanium chloride as catalyst) to give **85** and **86** respectively. Conventional oxidative elimination 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-

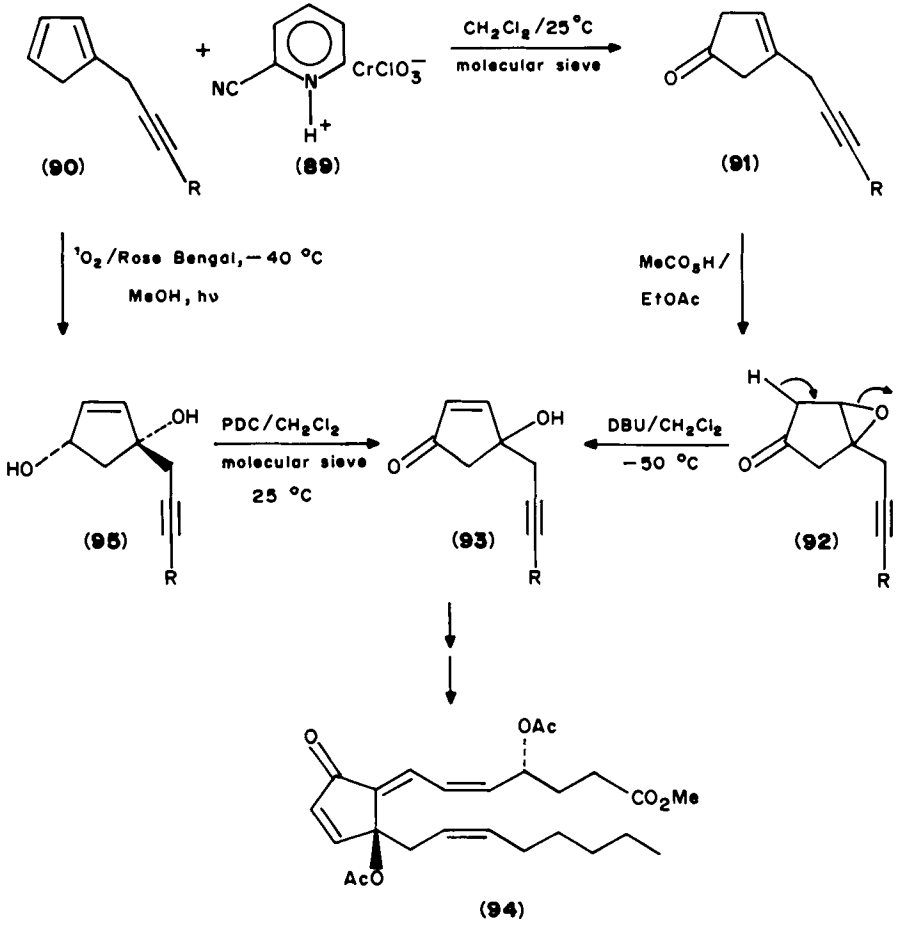


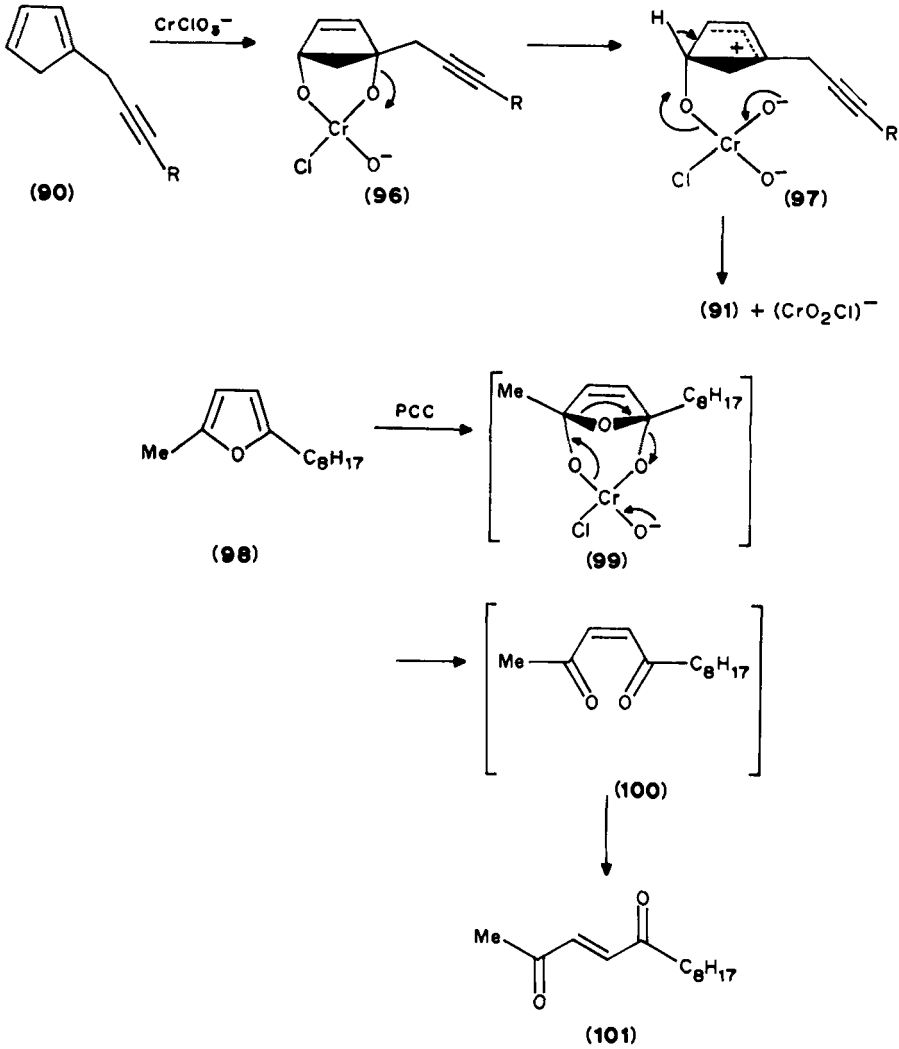
SCHEME 4

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].

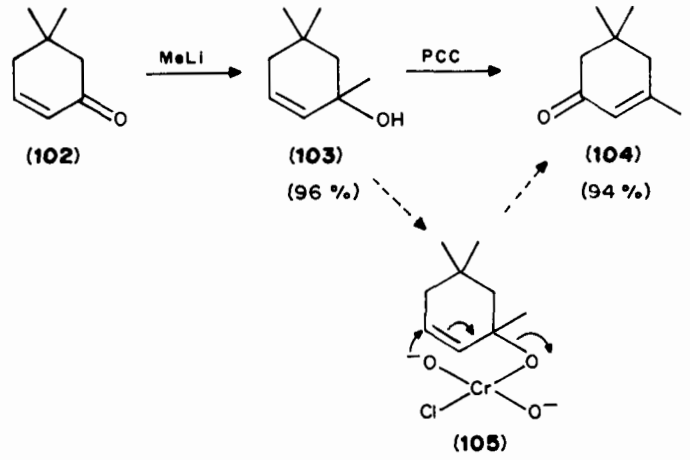


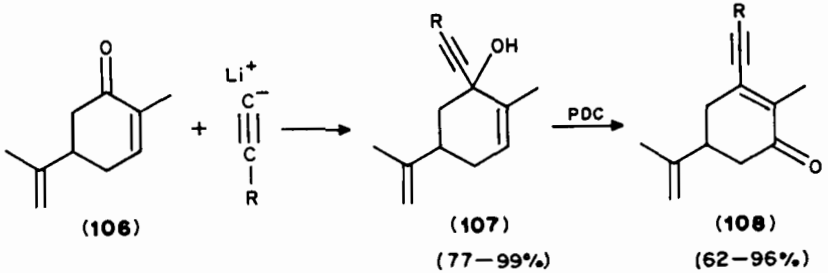


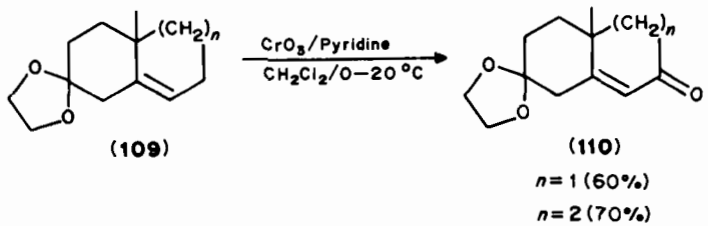
A related use of PCC effects the conversion of allylic alcohol **103** into enone **104**, the overall reaction **102** → **104** being an alkylative carbonyl transposition[74]. When modified by using PDC the reaction provides yne-enones **108**[75].

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 $[Cr(CO)_3(CH_3CN)_3]$ prepared *in situ* from chromium hexacarbonyl and acetonitrile[78]. This interesting system oxidizes cholestenyl acetate **111**

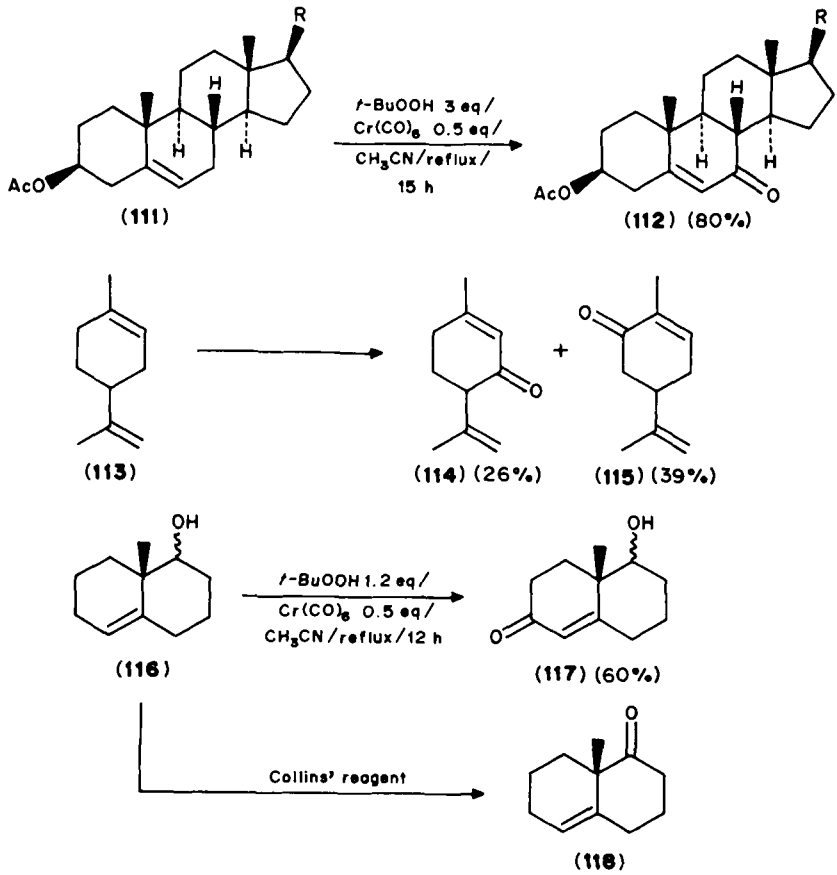




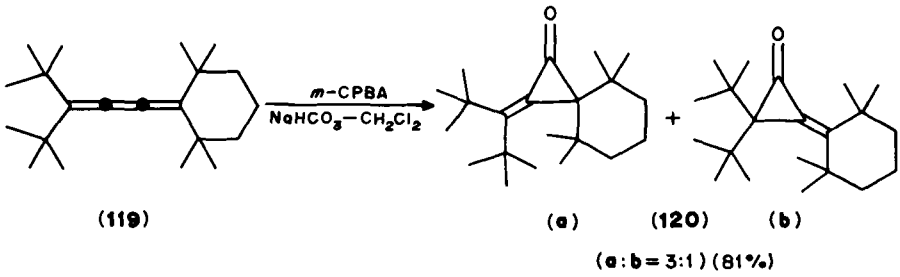


to the enone derivative **112** in 80% yield[79], but in other cases the reagent fails to afford regiospecificity; for example, the oxidation of limonene **113** under the same reaction conditions results in a mixture of **114** and **115**. The exceptional value of this oxidizing agent, however, is 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**.

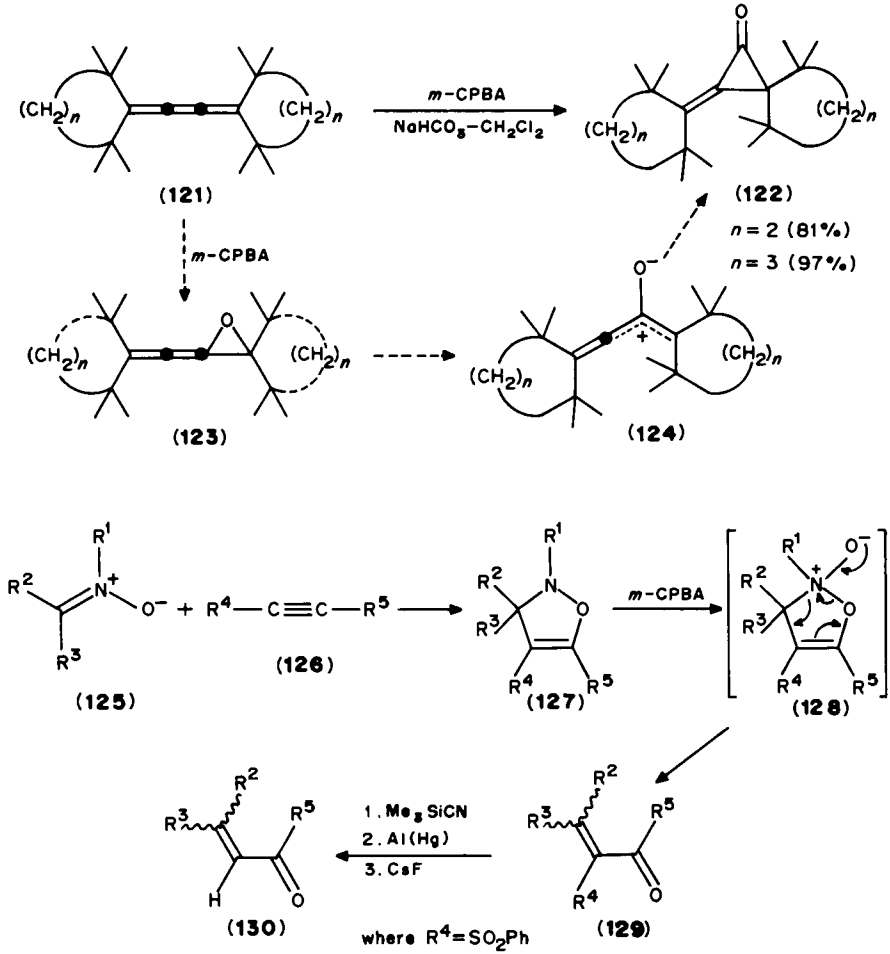
Direct dehydrogenation of saturated ketones to the corresponding enones as outlined in Scheme 4 (route c) cannot be regarded as a general synthetic method for the preparation of enones because yields are generally low, and, in the case of unsymmetrical ketones, products are complicated as a result of lack of regiospecificity. Nevertheless there are reports on dehydrogenation, using $Pd(II)Cl_2$ catalyst, leading to enones[80,81].



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_2Cl_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.

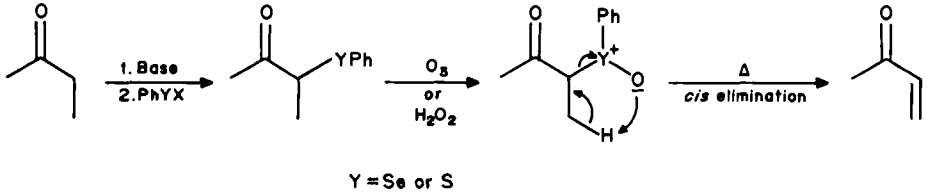


Recently, Δ^4-isoxaxoline **127**, derived from the dipolar cycloaddition reaction of nitrone **125** with acetylene **126**, is reported[84] to undergo oxidation with *m*-CPBA to give the enone **129** in excellent yield (> 90%). The oxidation is believed to proceed via the intermediate *N*-oxide **128**, 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

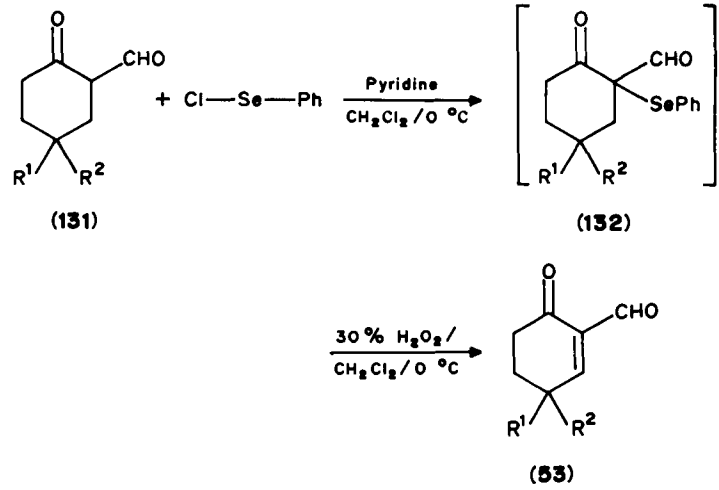
The use of elimination reactions in the synthesis of enones is very well established. The classical method involves consecutive α-bromination of the ketone and elimination of



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).

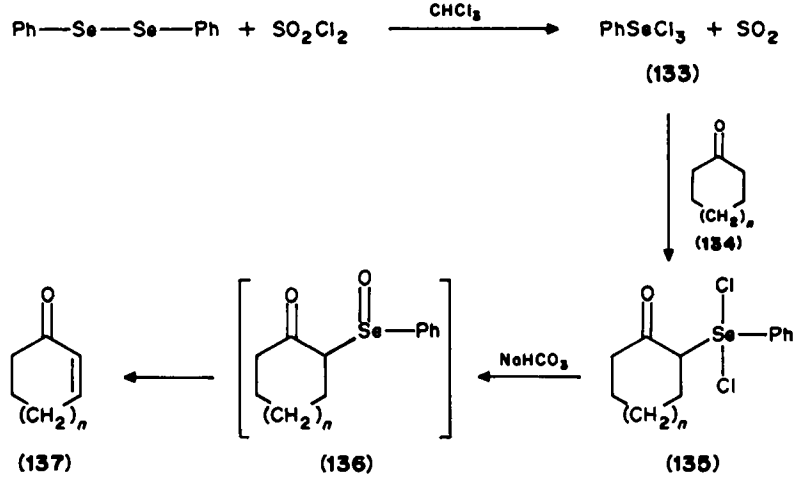
A good example of the application of the reaction is the preparation of enone **53**, an important intermediate in the synthesis of complex natural product molecules. In the synthesis of **53** shown below, reaction conditions are compatible with a variety of functional groups and yields are nearly quantitative[90].



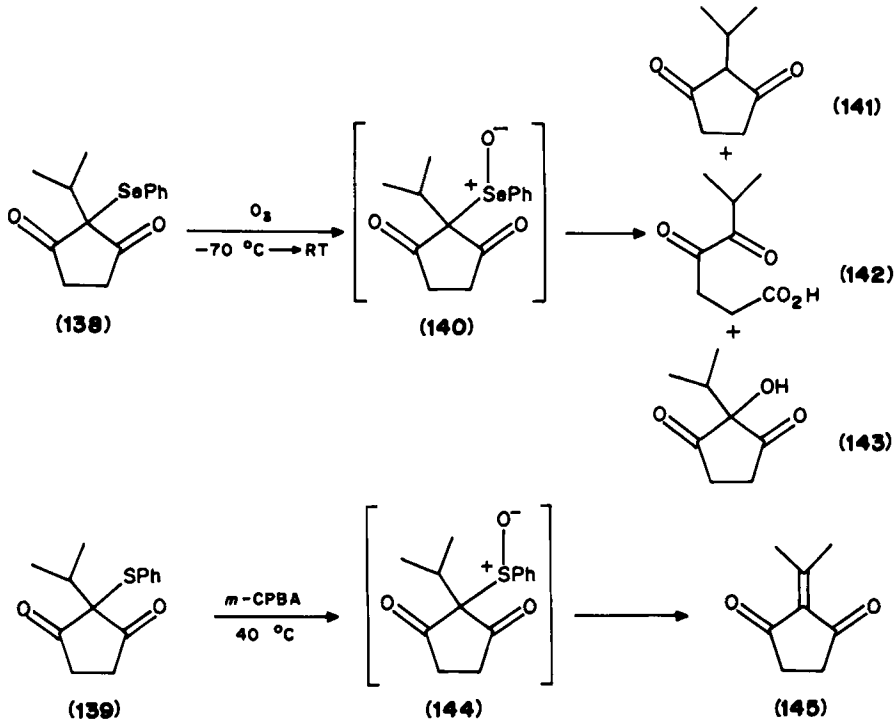
(131) **(132)** **(53)**

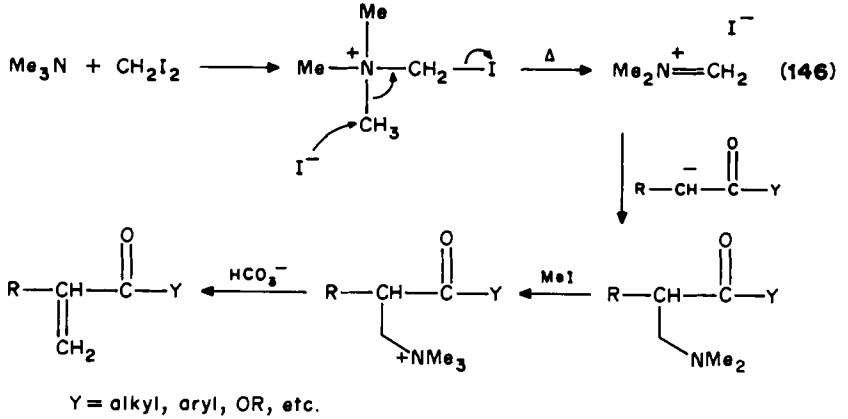
Phenyl selenium trichloride, recently made available by a convenient preparation from diphenyl diselenide and sulfuryl chloride, readily introduces the $PhCl_2Se$— group into ketones at the α-position. This is important because the functional group can be easily hydrolyzed by sodium bicarbonate to the 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



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].





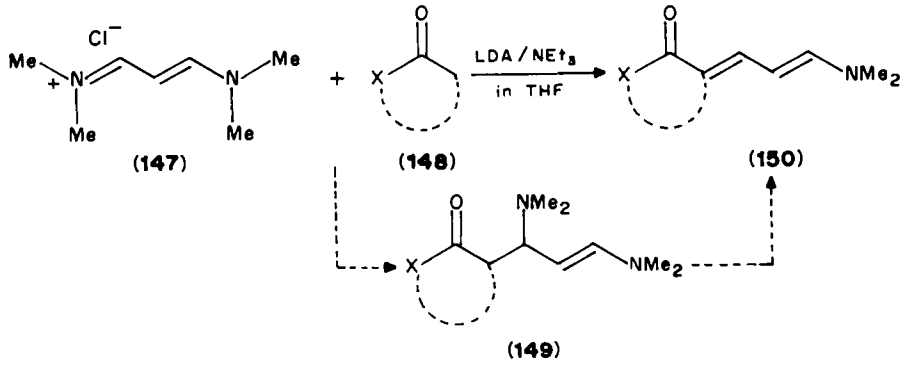
SCHEME 6

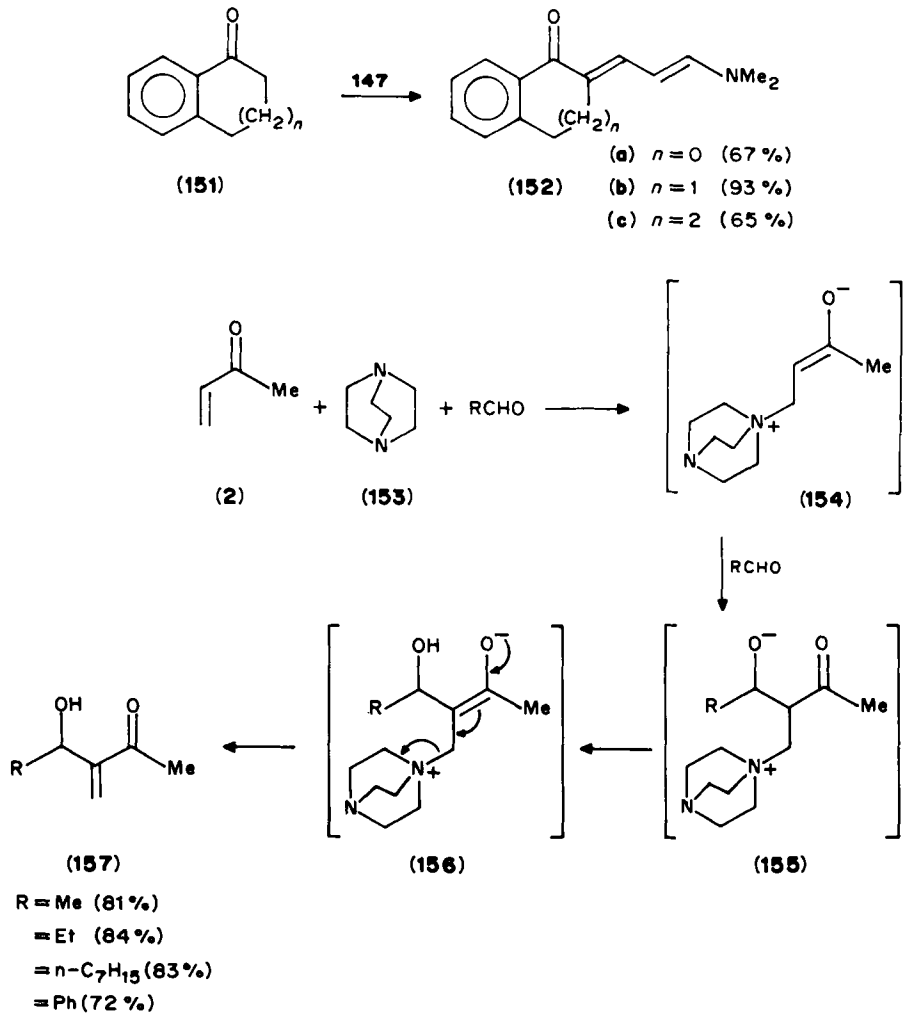
A good reagent for the synthesis of α-methylene carbonyl compounds[95–97] is *N,N*-dimethylmethyleneammonium iodide **146**, which operates via a different mode of elimination. The compound is an important Mannich intermediate which can easily be prepared by the method of Eschenmoser and coworkers[95] (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.

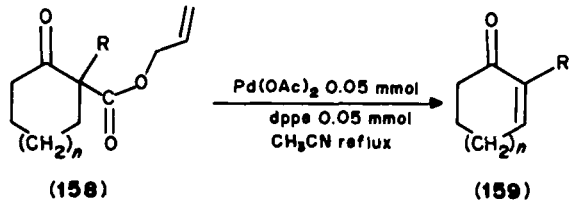
The elimination of ammonium salts is also cleverly applied in the functionalization of enones exemplified by the addition–elimination reaction of methyl vinyl ketone with the commercially available 1,4-diazabicyclo[2.2.2]octane (DABCO) **153**[102]. DABCO adds in a Michael addition fashion to methyl 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.



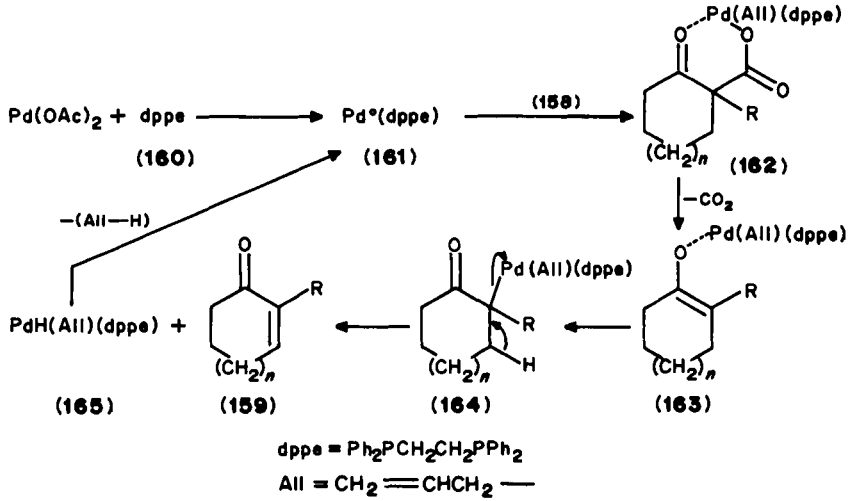


Palladium-catalyzed elimination is also a good route to enones[103,104]. The first example was the decarboxylation–dehydrogenation of allyl β-keto carboxylate **158** with palladium acetate and 1,2-bis(diphenylphosphino)ethane (dppe) **160** as catalysts, yielding enone **159**. A reasonable mechanism 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.

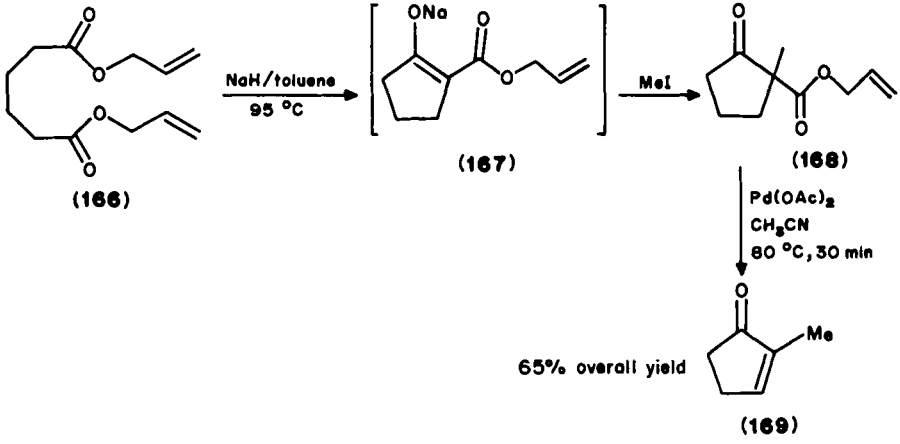
The favourable nature of the palladium-catalyzed decarboxylation–dehydrogenation reaction is reflected in its being the reaction of choice for the synthesis of 2-methyl-2-cyclopentenone **169**. Although a simple-looking molecule, **169** is a very important starting material for the construction of 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],

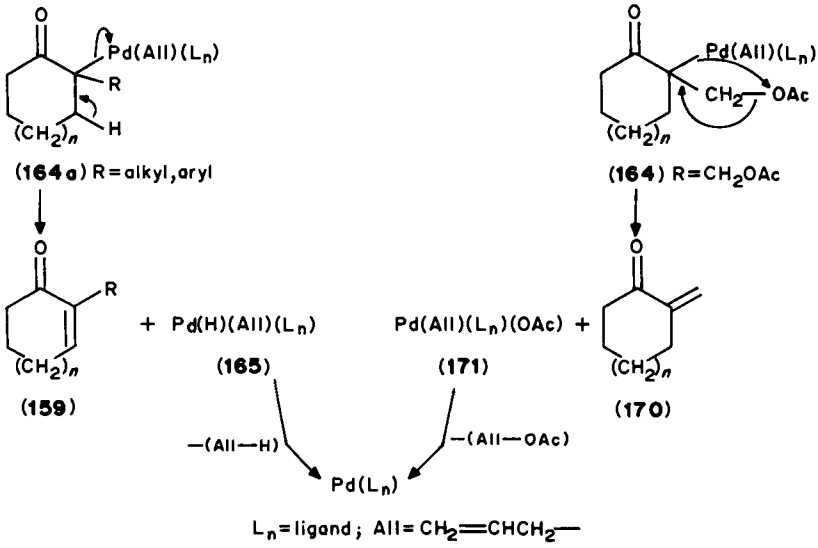


SCHEME 7



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**.

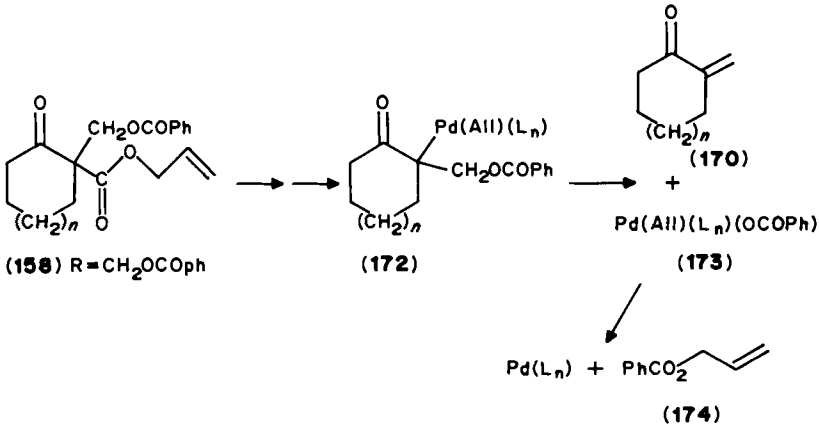




SCHEME 8

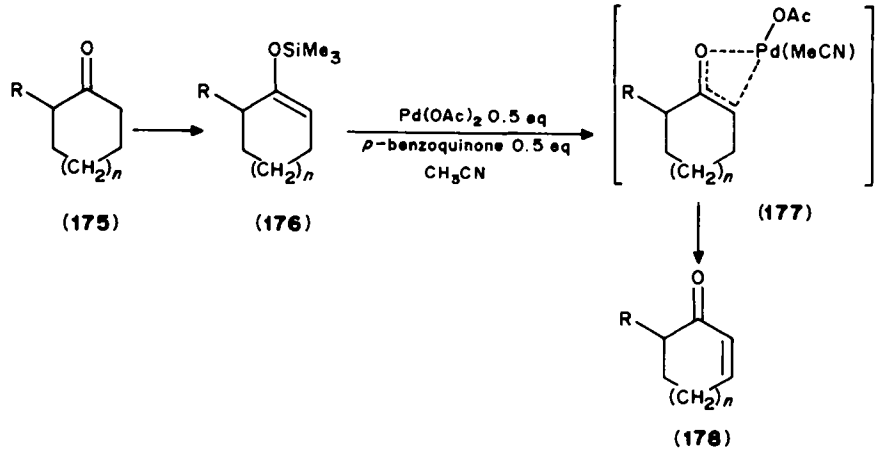
It should be noted that, in the sequence depicted in Scheme 7, when R is an acetoxymethyl group the mechanism of elimination deviates from that shown. That is, the dehydrogenation of **164a** to enone **159** does not occur; and instead, elimination of the acetoxy group takes place to yield α-methylene 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.

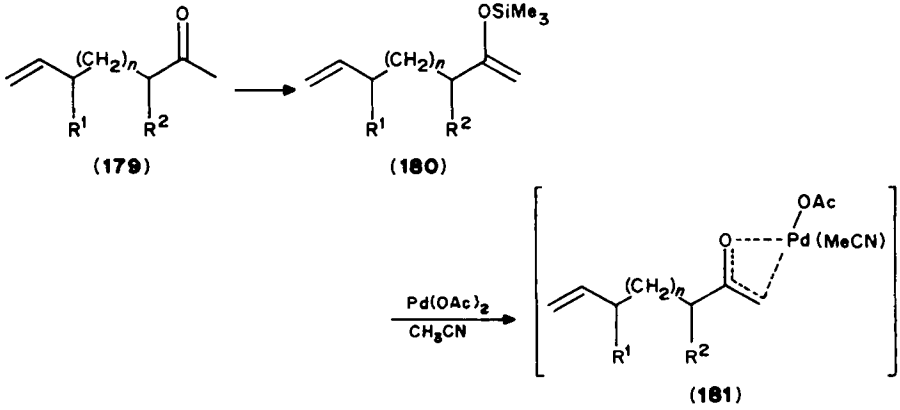
Silyl enol ether **176** undergoes a palladium(II) catalyzed dehydrosilylation[110], probably via an oxo-π-allylpalladium(II) complex **177**, to give a very high yield (> 90%) of enone **178**. The reaction allows the introduction of a double bond into an unsymmetrical ketone via the corresponding enol ether as shown below.



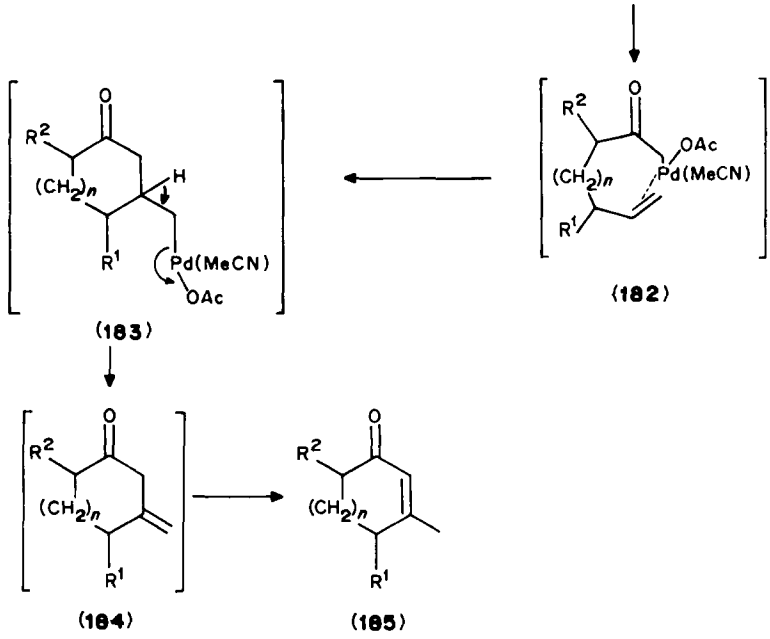
(175) (176) (177) (178)

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].

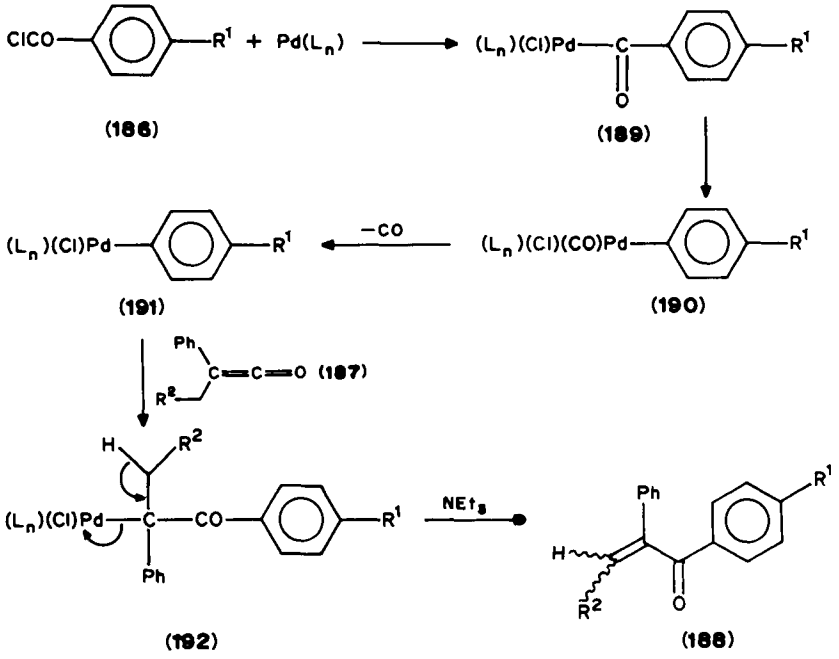
The reaction between aroyl chloride **186** and alkyl phenyl ketene **187** in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium, [$Pd(PPh_3)_4$], results in decarbonylation and dehydrogenation to give a mixture of *E*- and *Z*-enones **188**[114]. Detailed mechanistic study 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].

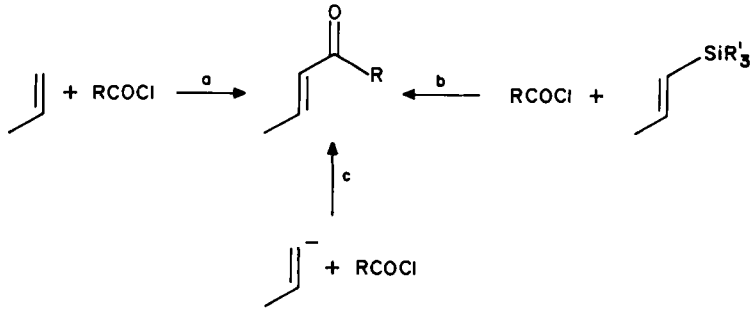


(179) (180) (181)


(182)
(183)
(184)
(185)

SCHEME 9


ClCO
R1
+ Pd(Ln)
(Ln)(Cl)Pd
C
O
(186)
(189)
(190)
(191)
−CO
(Ln)(Cl)(CO)Pd
(Ln)(Cl)Pd
Ph
C=C=O (187)
R2
H
CO
Ph
NEt3
(192)
(188)



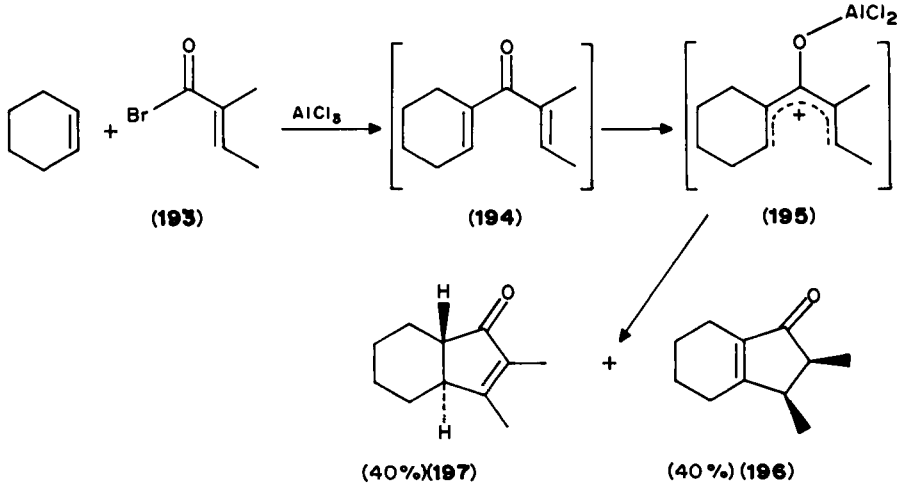
SCHEME 10

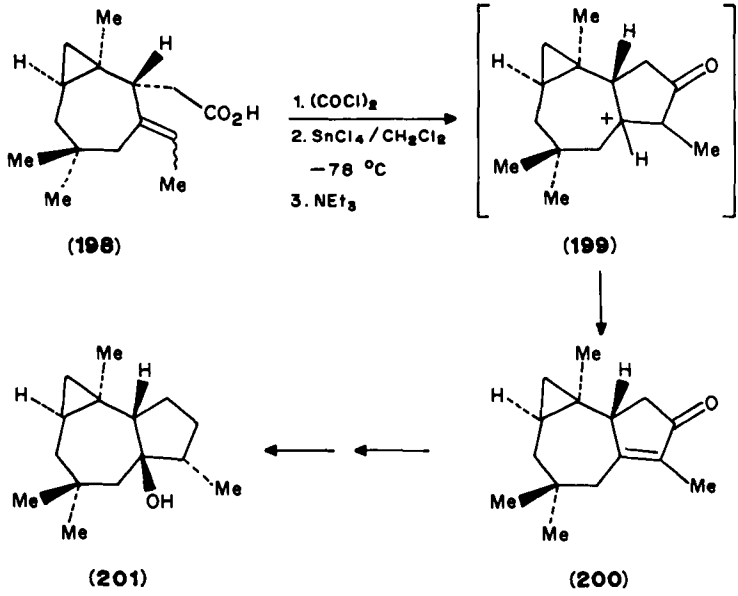
V. ACYLATION

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.

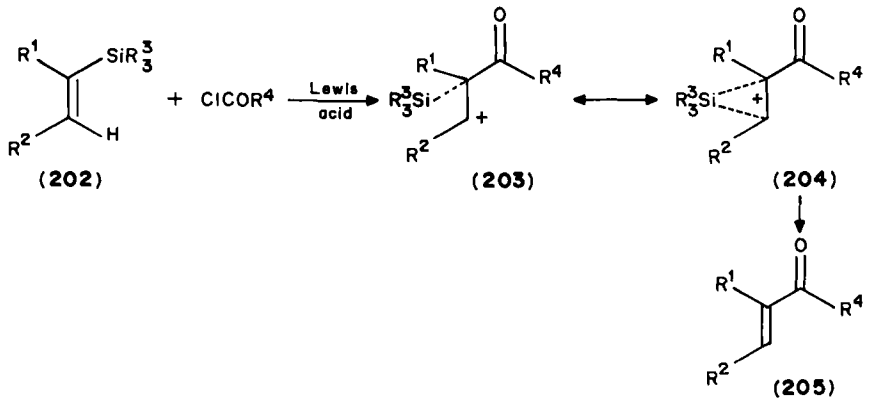
(a) The Friedel–Crafts acylation is a long-established classical method which can still be employed effectively in certain cases, especially in the preparation of cyclopentenone derivatives. A simple example is found in the Friedel–Crafts acylation of cyclohexenone with acid bromide **193**, which gives **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].

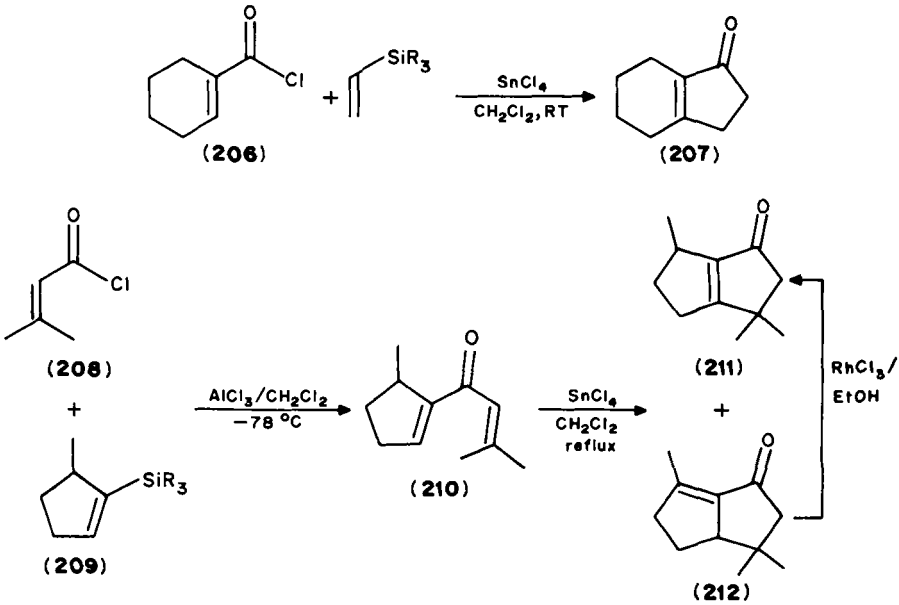


Lewis acids which can be used in vinylsilane acylations include aluminium chloride ($AlCl_3$), stannic chloride ($SnCl_4$), titanium chloride ($TiCl_4$), zinc chloride ($ZnCl_2$), ferric chloride ($FeCl_3$) and boron trifluoride etherate ($BF_3 \cdot Et_2O$)[65].

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-

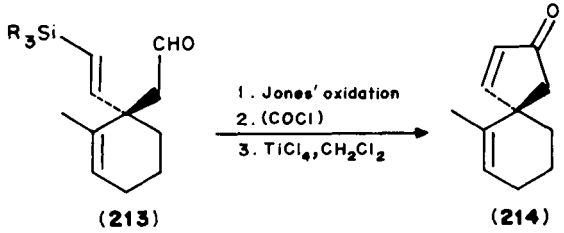
catalyzed acylation of **209** with **208** gives a divinyl ketone **210** that yields **211** and **212** when treated with stannic chloride[126].

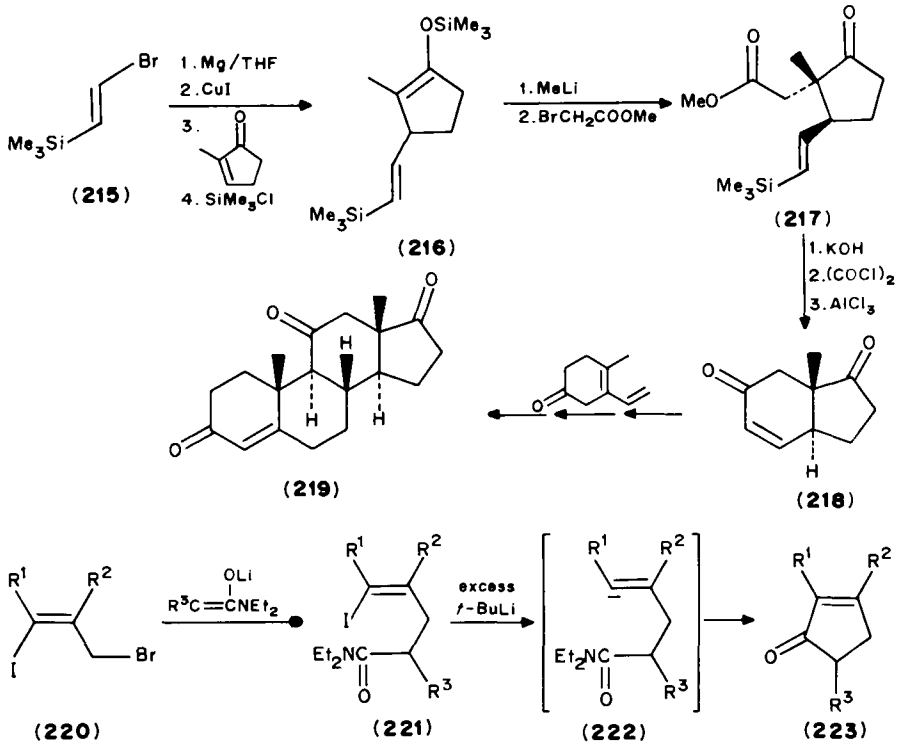
The use of vinylsilanes to promote acylation and/or cyclization reactions has since been widely investigated[127–129] and applied in organic synthesis, for example in the synthesis of spiro-compound **214**[130] and the C,D ring portion (**218**)[131–133] of the corticosteroids **219**.



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.

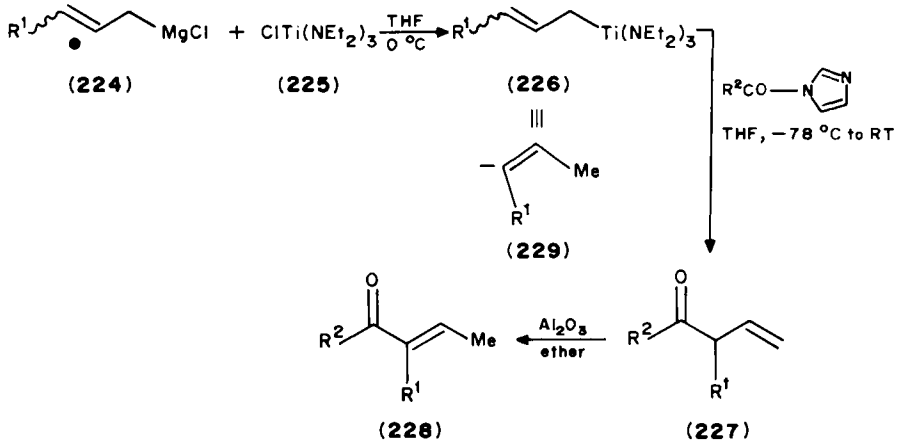
(c) The third main acylation route to enones, route c in Scheme 10, involves the use of the vinyl anion or its equivalent. For example, trisubstituted cyclopentenones such as **223** can be synthesized by direct intramolecular acylation of vinyl anion **222**, prepared from iodoolefin **221** by treatment 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.





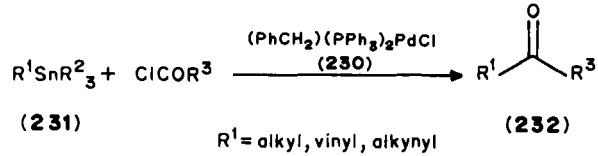
(215) (216) (217) (218) (219) (220) (221) (222) (223)

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) (228) (227)

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].



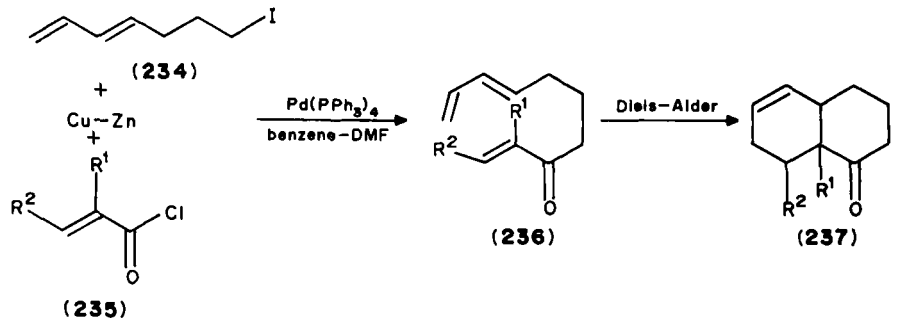
Apart from the Stille reaction which employs organotin, variations on organometallic compounds in acylation include the use of organozinc which can undergo coupling reactions very efficiently, for example the reaction between organozinc halide **233** and acid chloride with tetrakis(triphenylphosphine)palladium as catalyst[145].

$$R^1ZnX + R^2COCl \xrightarrow{Pd(PPh_3)_4/THF} R^1COR^2$$

(**233**)

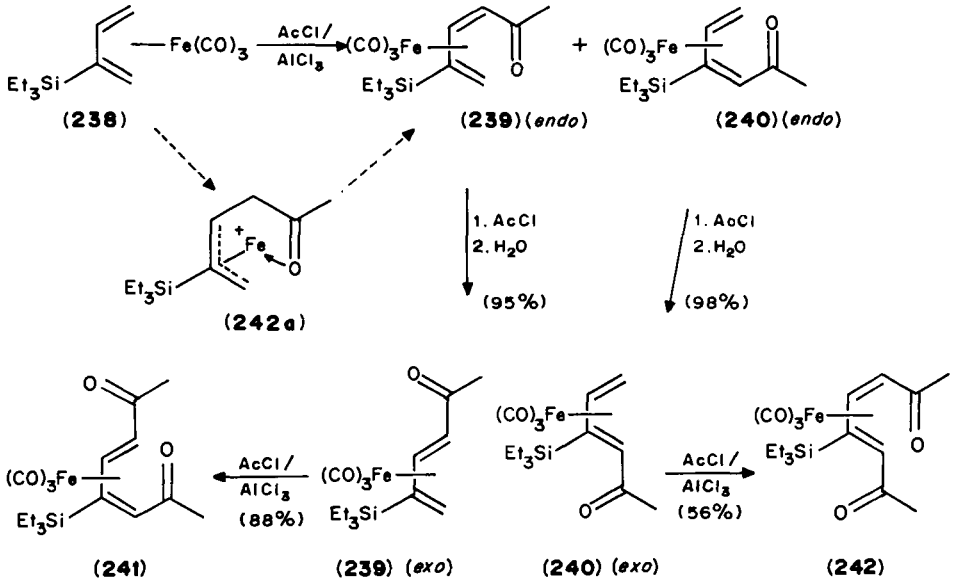
R^1 = alkyl, aryl; R^2 = alkyl, aryl, vinyl, OMe
X = Cl, I

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].



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].

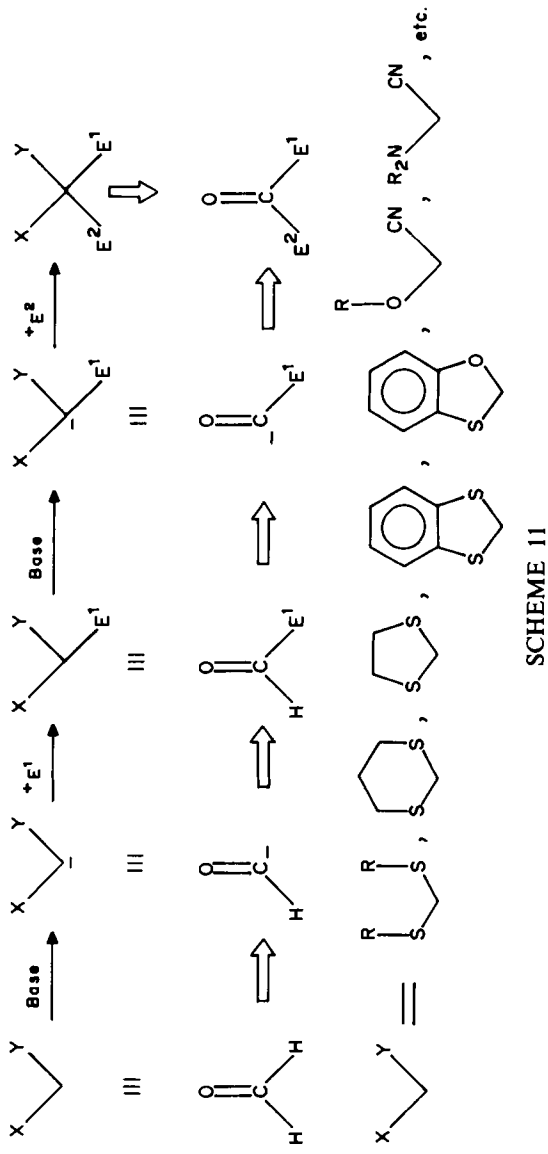


In addition to direct acylation, the last twenty years or so have witnessed the growth of an exciting complementary approach to acylation syntheses of carbonyl compounds. 'Reverse activity' or 'Umpolung', a new idea in organic synthesis, is applied to carbonyl compound synthesis through the use of a '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.

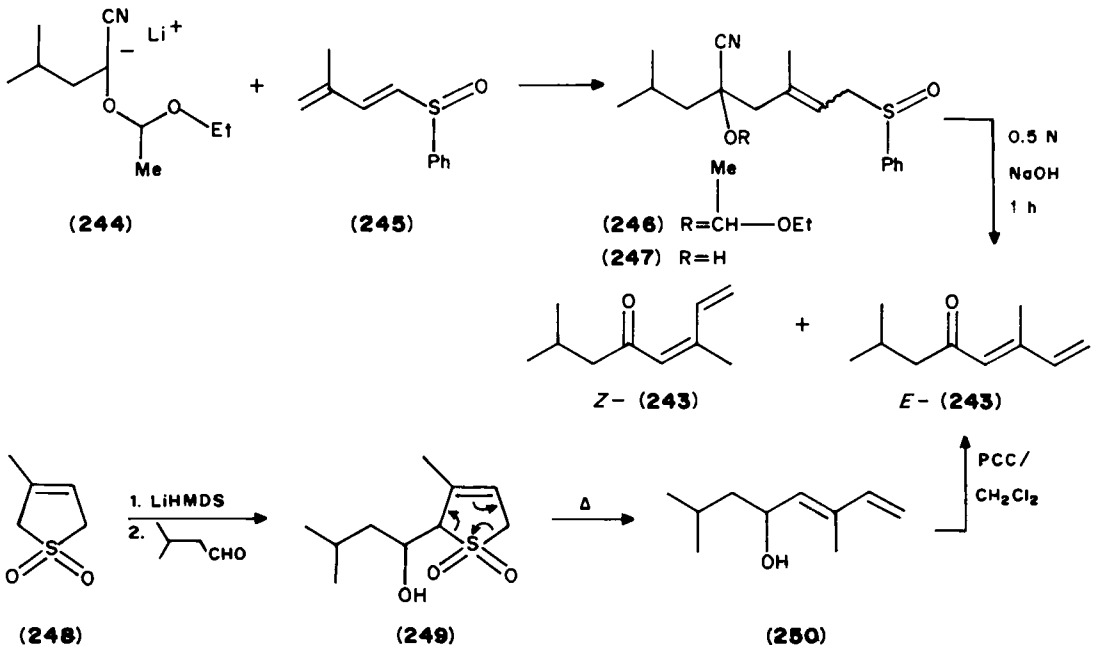
The synthesis of the monoterpenoid dienone, tagetone **243**, can be accomplished by two different methods. The first utilizes **244** as the masked-acyl anion[44] in a conjugate addition reaction with sulfoxide **245** to yield adduct **246**. Acid hydrolysis followed by treatment of the resulting cyanohydrin **247** with 0.5N sodium hydroxide for 1 h gives a 1:1 mixture of *E*- and *Z*-tagetone **243** (50% overall yield from **245**)[157].

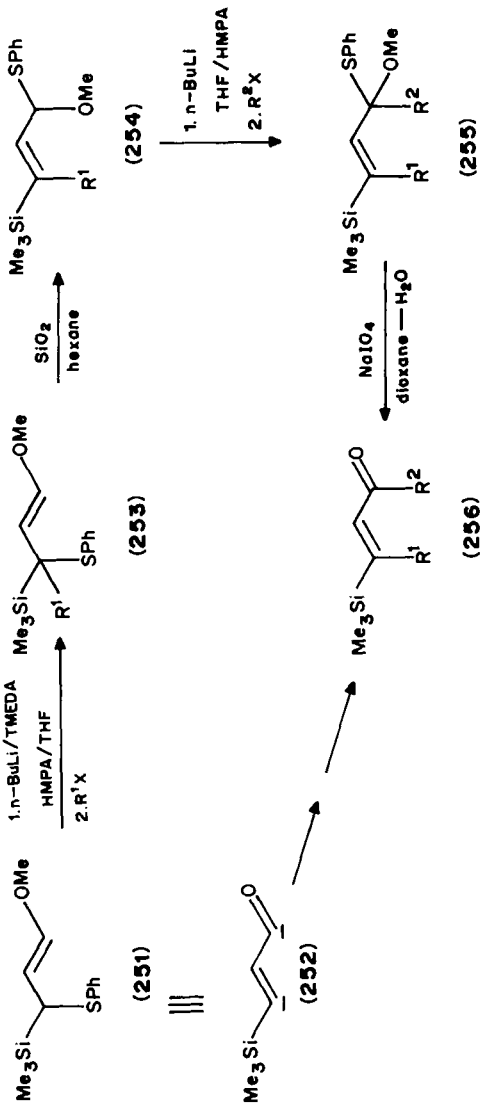
The second method, on the other hand, is a stereoselective synthesis starting with 3-methyl-2,5-dihydrothiophene *S,S*-dioxide **248** as the masked isoprene unit. The anion obtained from **248** using lithium hexamethyldisilazide (LiHMDS) reacts with isovaleraldehyde to give **249** which, upon desulfonylation 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

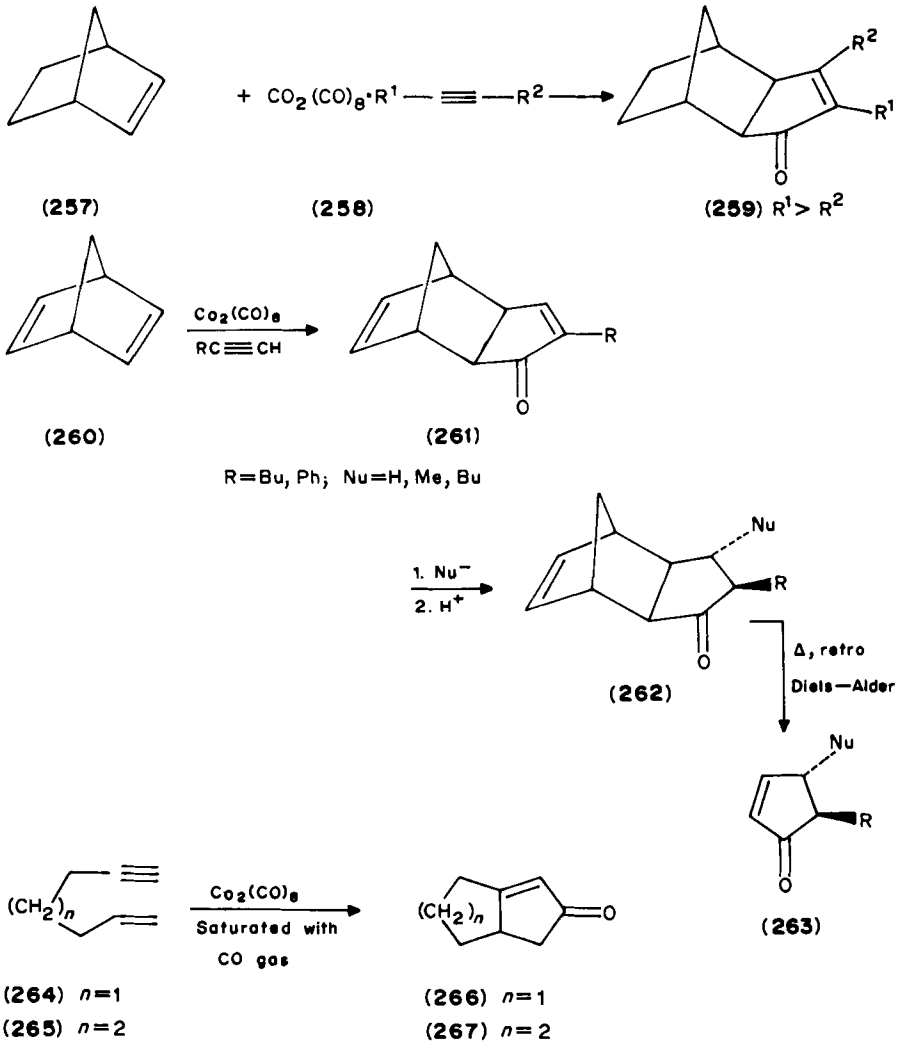

CN
Li+
O
O
Et
Me
(244)
+
S
O
Ph
(245)
CN
OR
Me
R=CH—OEt
(246)
R=H
(247)
S
O
Ph
0.5 N
NaOH
1 h
O
Z- (243)
+
O
E- (243)
1. LiHMDS
2.
CHO
S
O
O
(248)
OH
(249)
Δ
OH
(250)
PCC/
CH2Cl2


Me3Si
OMe
SPh
(251)
1.n-BuLi/TMEDA
HMPA/THF
2.R1X
(253)
SiO2
hexane
(254)
1.n-BuLi
THF/HMPA
2.R2X
(255)
NaIO4
dioxane—H2O
(256)
(252)

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].

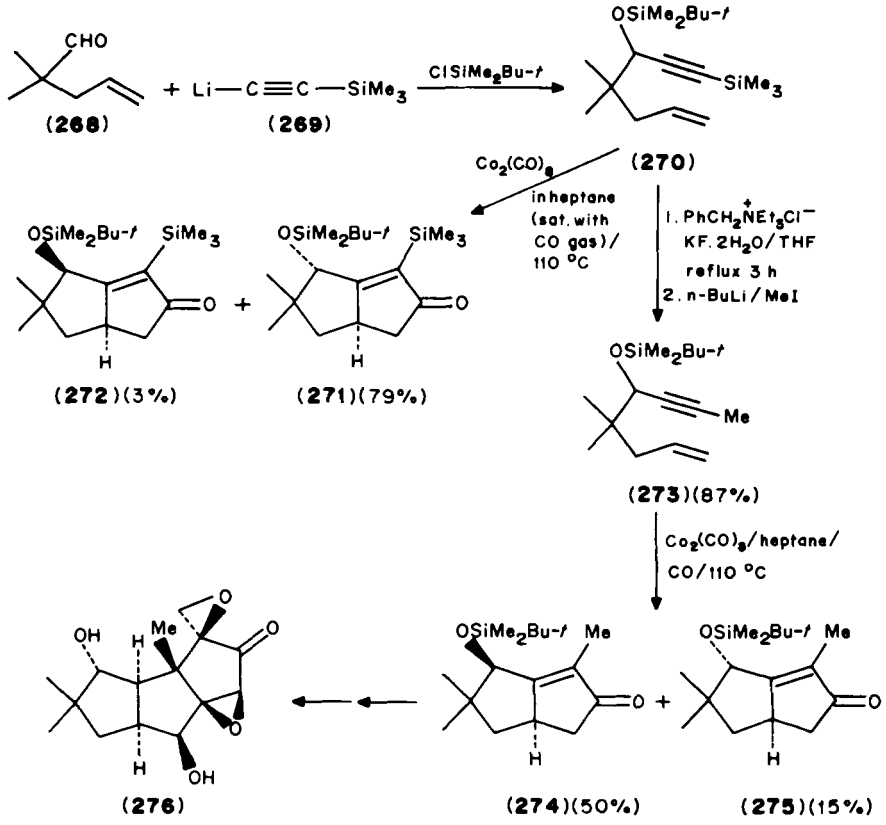
VI. INSERTION OF CARBON MONOXIDE

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**.



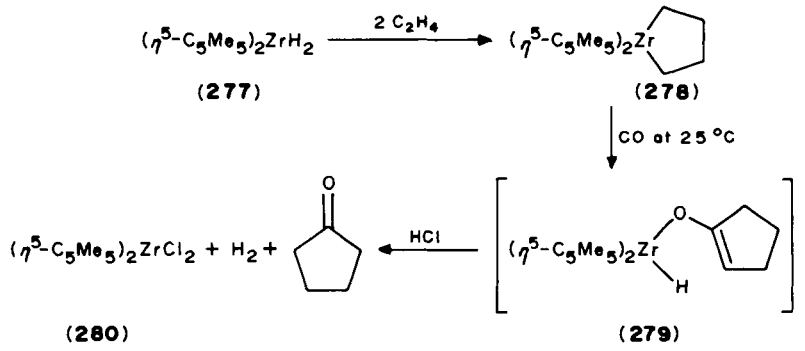
More recently Exon and Magnus[167] emphasized the usefulness of this reaction by the synthesis of (dl)-coriolin **276**, a hirsutane antitumor sesquiterpene isolated from the culture broth of Basidiomycete *Coriolus consors*[168], via the key intermediate **274**.

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].



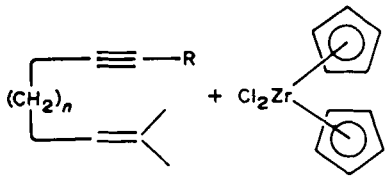
It was earlier mentioned that zirconium complexes, such as dicyclopentadienylzirconium dihydride $[(C_5H_5)_2ZrH_2]$[14], catalyze cross aldol condensations and are employed[16] in the synthesis of α-methylene cycloalkanones (e.g. **18**) and cycloalkenones (e.g. **19**). In addition, similar reagents 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



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].

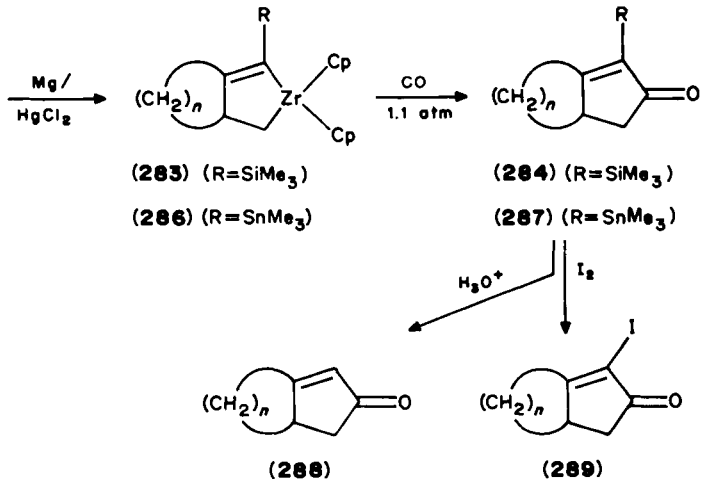


(281) (R=$SiMe_3$)

(285) (R=$SnMe_3$)

$n = 3$ or 4

(282)



(283) (R=$SiMe_3$)

(286) (R=$SnMe_3$)

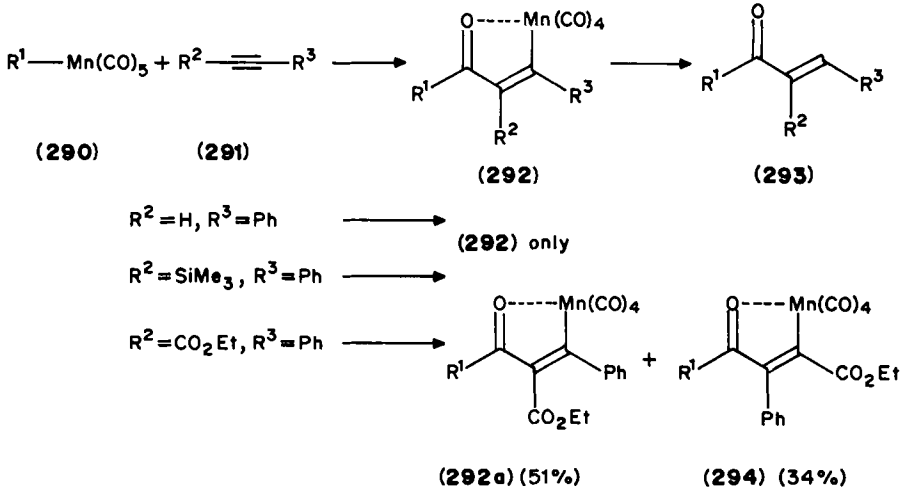
(284) (R=$SiMe_3$)

(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.



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.

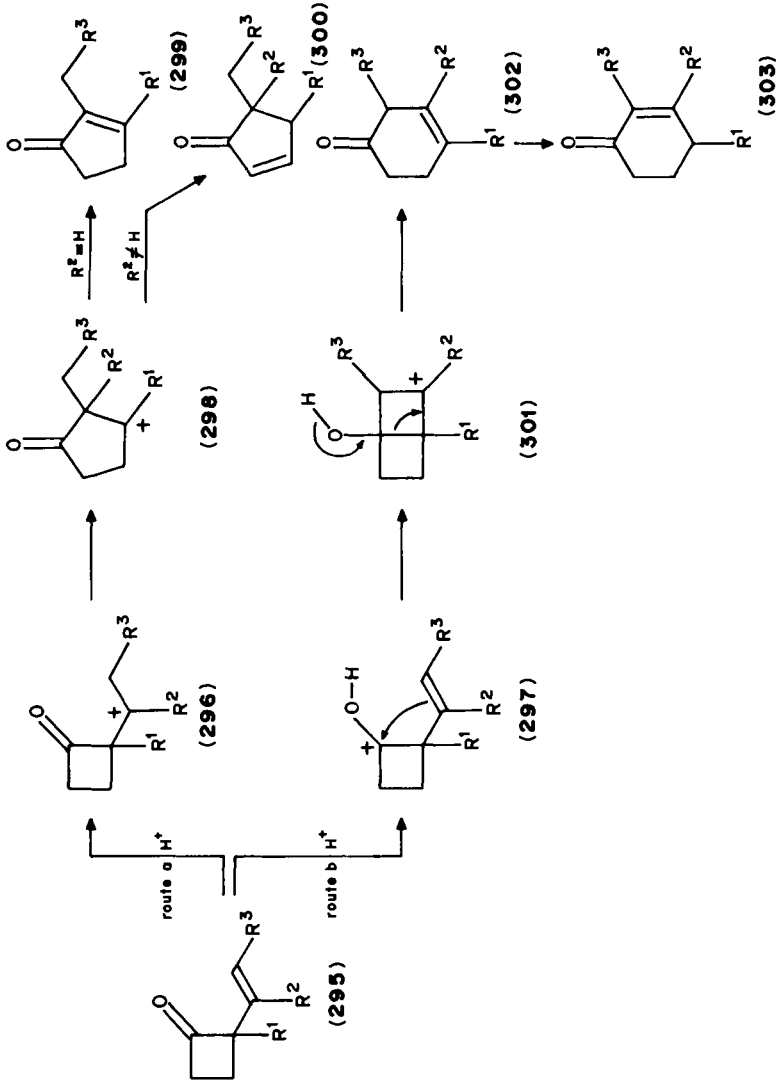
VII. OTHER METHODS

A. Ring Expansion and Ring Contraction

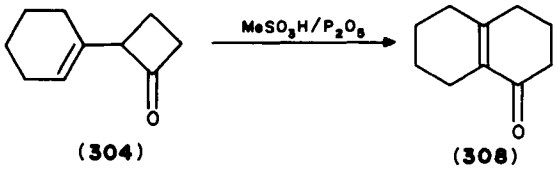
2-Vinylcyclobutanones such as **295** undergo acid-catalyzed rearrangements via cationic intermediates **296** (route a) to the corresponding cyclopentenones **299** or **300** and via **297** (route b) to cyclohexenones **303**, depending on the substituents, as depicted in Scheme 12. The overall reaction 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].

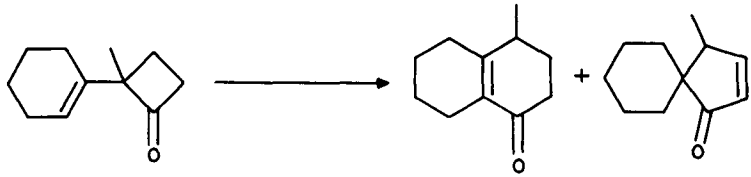
Substituted keteniminium salts **314** have been shown to add alkyl and arylacetylenes **315** in a cycloaddition fashion to give, after basic hydrolysis, a good yield of cyclobutenones **316**[181]. Addition of anion **317** to the cyclobutenone results in enol **318**, which can be made to undergo 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].



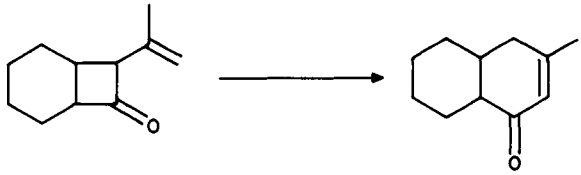
SCHEME 12



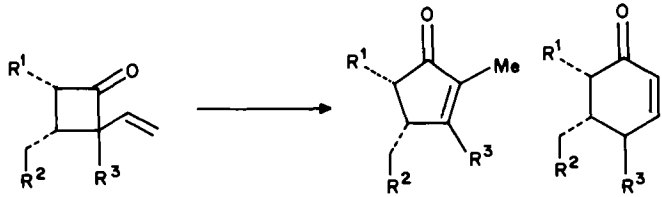
(304) (308)



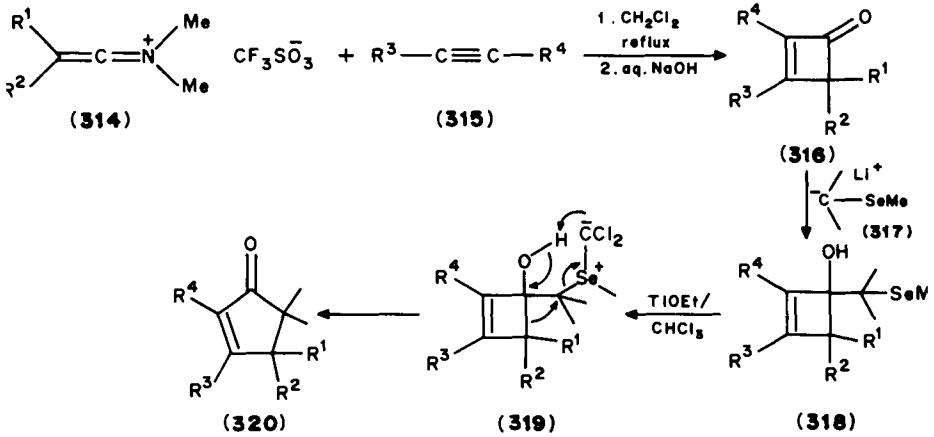
(305) (309)(13%) (310)(51%)



(306) (311)

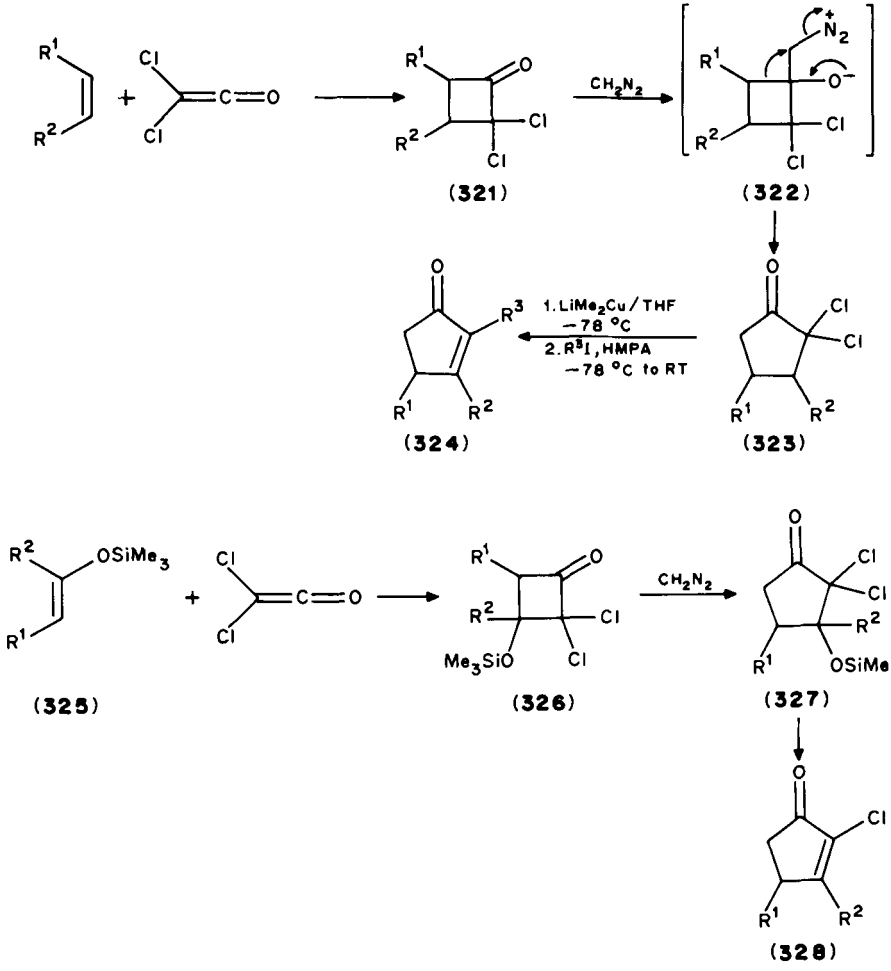


(307) (312) only (313) none



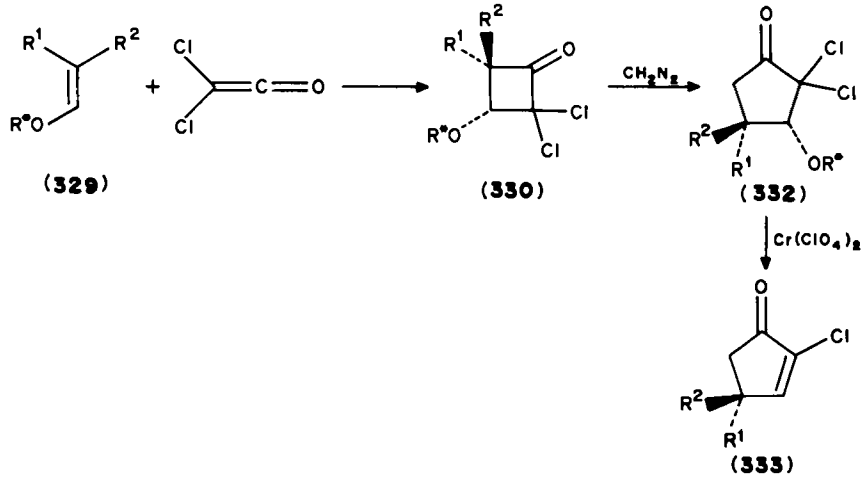
(314) (315) (316) (317) (318) (319) (320)

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**.

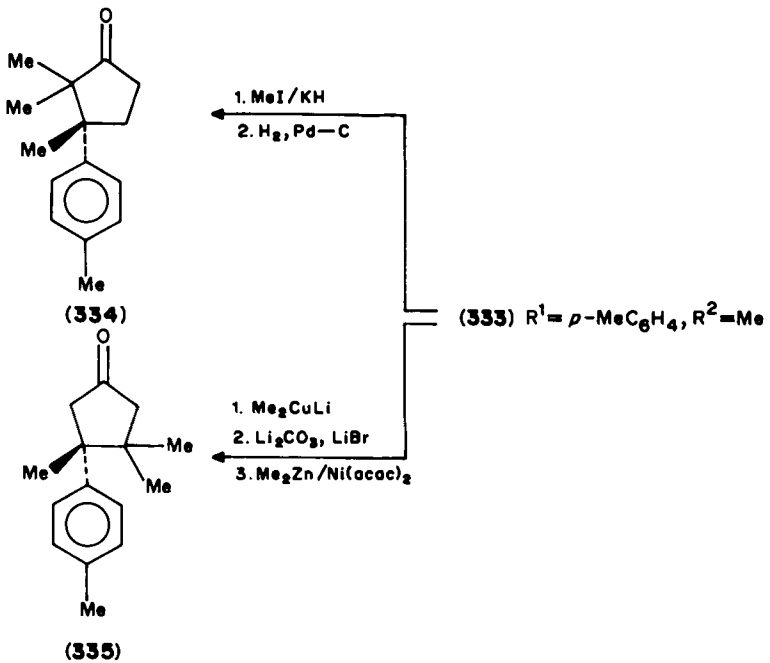


Further elaboration using a chiral enol ether such as **329** in the cycloaddition provides a 9:1 mixture of cyclobutanones **330** and **331** and leads to the preparation of optically active cyclopentenone **333**[187]. This is an important intermediate (where $R^1 = p\text{-}MeC_6H_4$, $R^2 = Me$) 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].

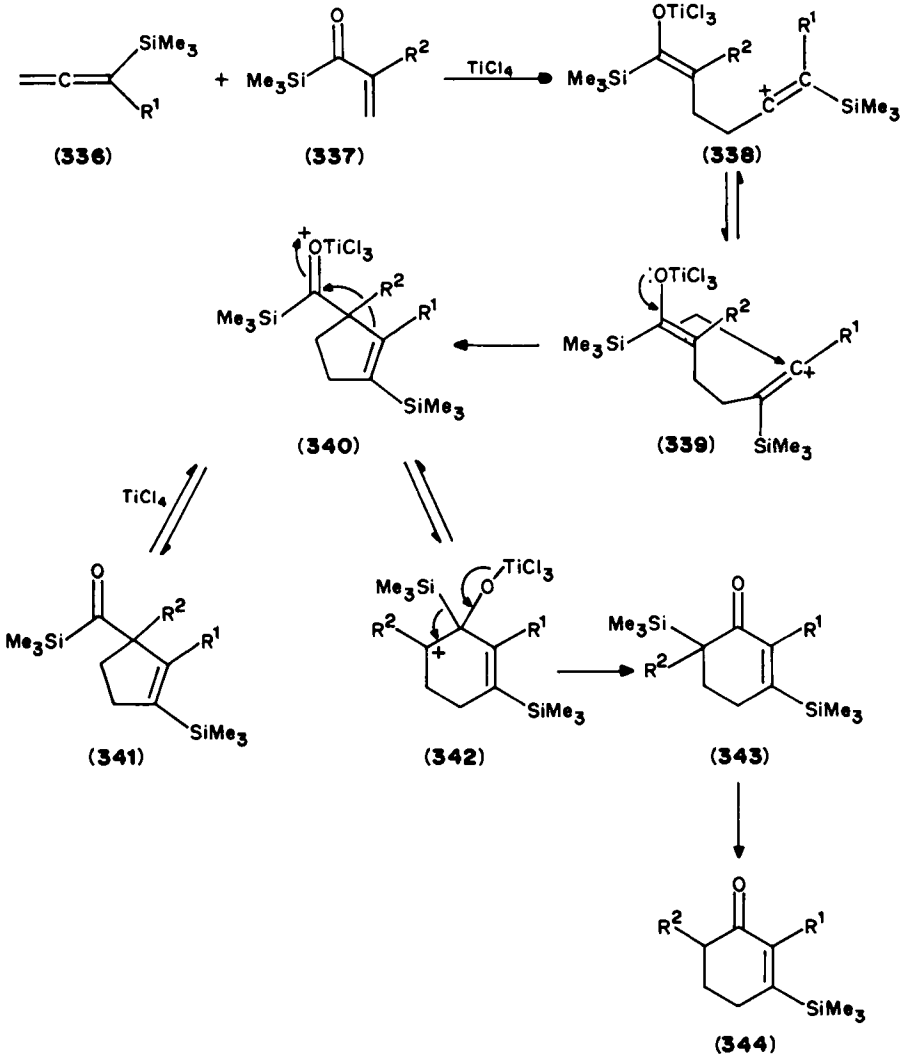
The reaction between allenylsilanes, e.g. **336**, and α,β-unsaturated acylsilanes, e.g. **337**, in the presence of titanium tetrachloride at −78 °C for a short period affords acylcyclopentenes **341** in good yields. On exposure to $TiCl_4$ at higher temperatures **341** undergoes ring enlargement to produce β-silylcyclohexenone **344**[190]. It is therefore


(329)
(330)
(332)
(333)


OR*=
Ph
(331)

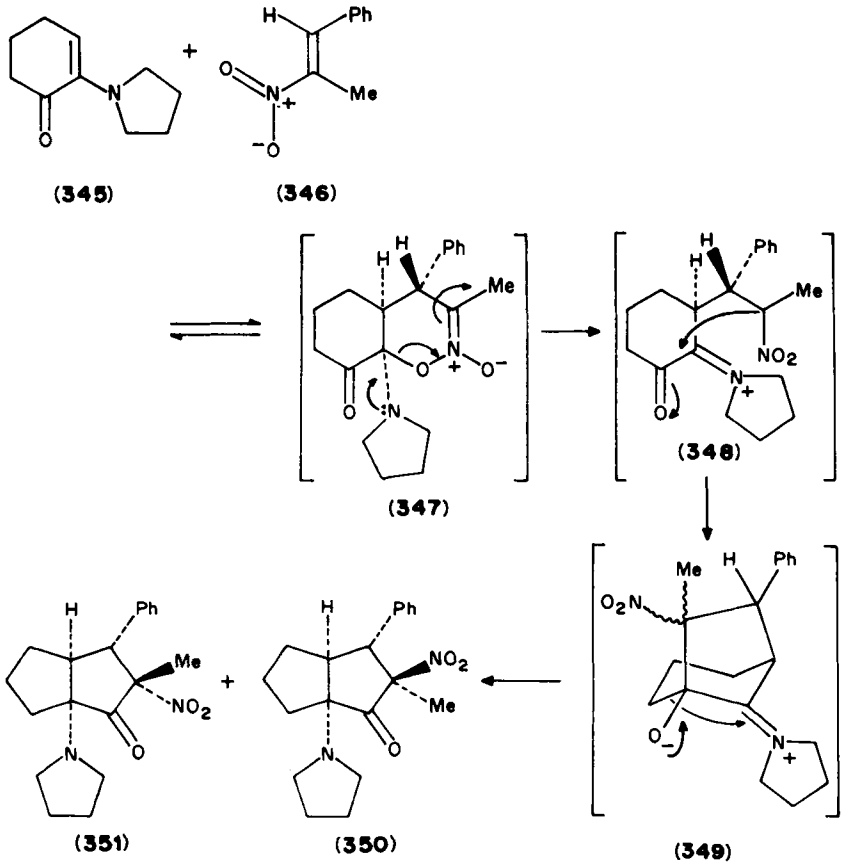

1. MeI/KH
2. H2, Pd—C
(334)
(333) R1= p-MeC6H4, R2=Me
1. Me2CuLi
2. Li2CO3, LiBr
3. Me2Zn/Ni(acac)2
(335)

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].

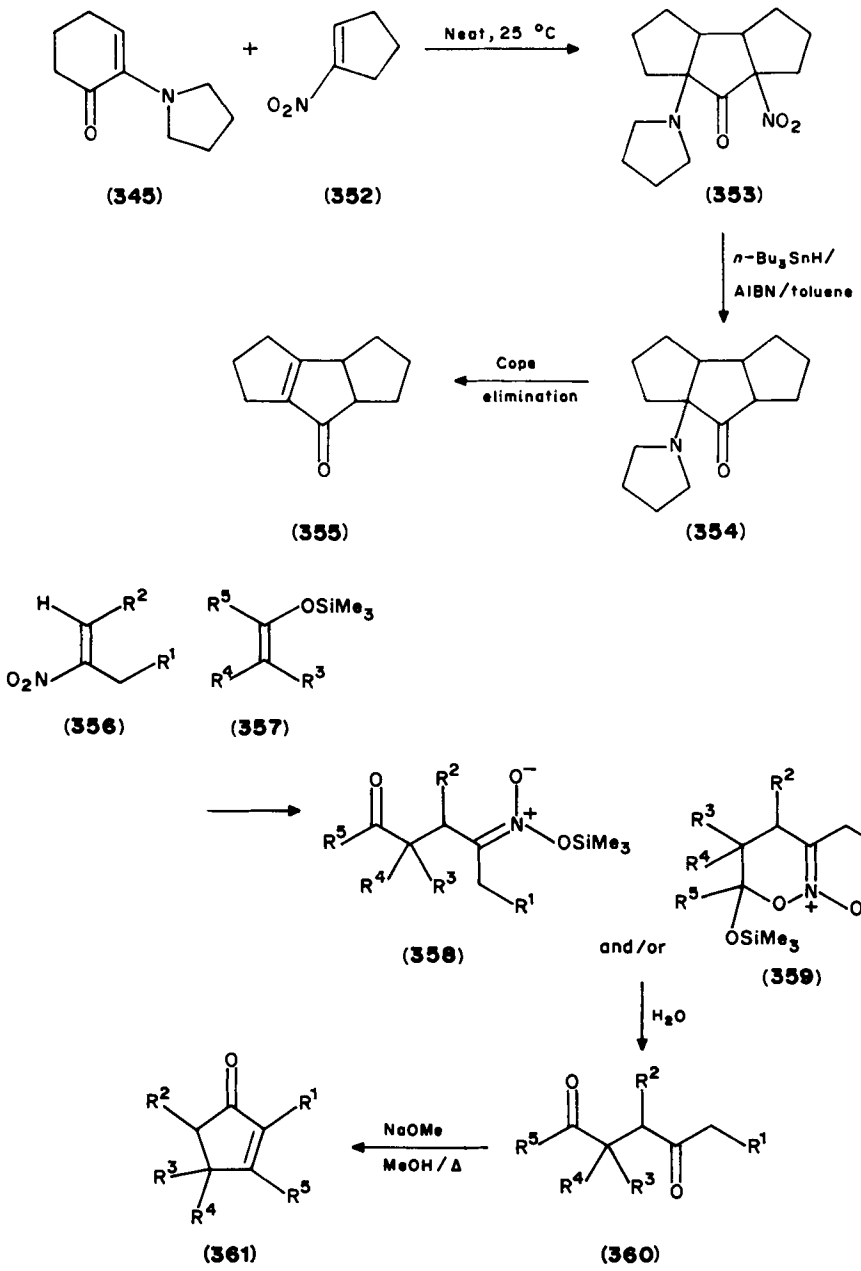


An application of this reaction is exemplified in the synthesis of the triquinane system **355**[193] from ketoenamine **345** and nitrocyclopentene **352**. A neat mixture of **345** and **352** at 25 °C furnishes a quantitative yield of **353**. Reductive removal of the nitro group with tributyltin 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.

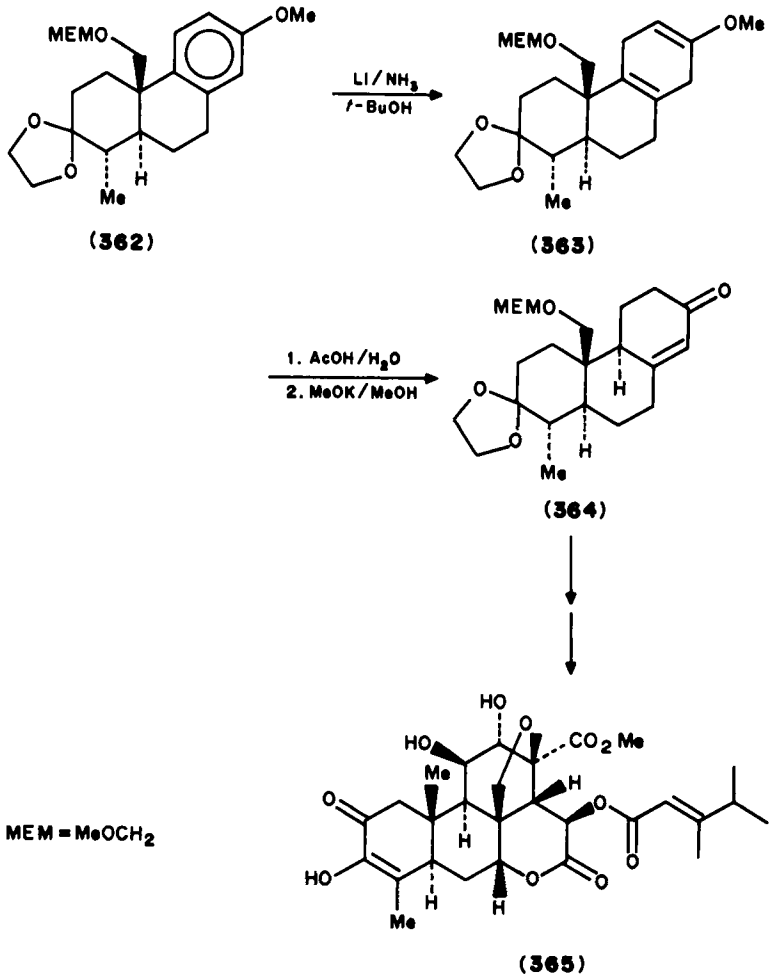
It is worth noting that the use of nitroalkene in cycloaddition reactions can be applied to the synthesis of 1,4-diketone derivatives **360**[195], themselves important precursors in the synthesis of cyclopentenones by the classical condensation method[196].

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.

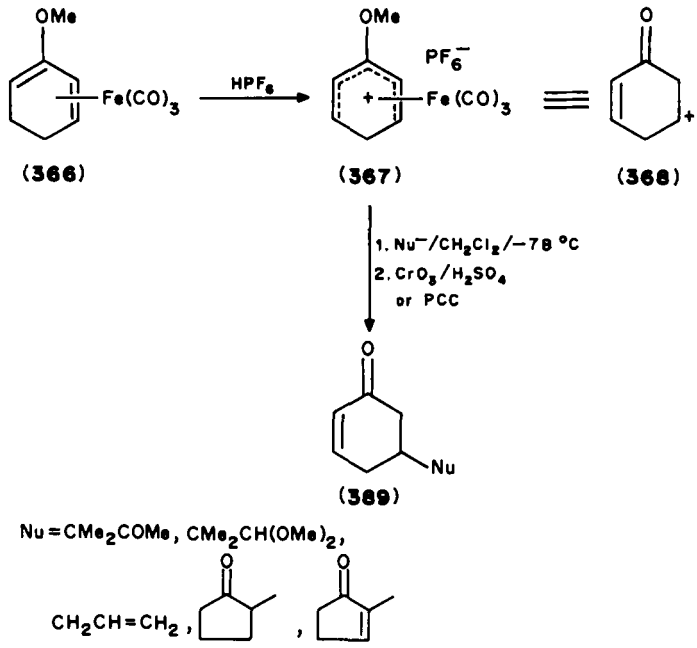


The total synthesis of bruceantin **365**, the antileukemic quassinoid from *Brucea antidysenterica*[197], employs enone **364** as the key intermediate. This is synthesized[198] from **362** by Birch reduction, followed by acid hydrolysis and double-bond isomerization as shown below.



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].

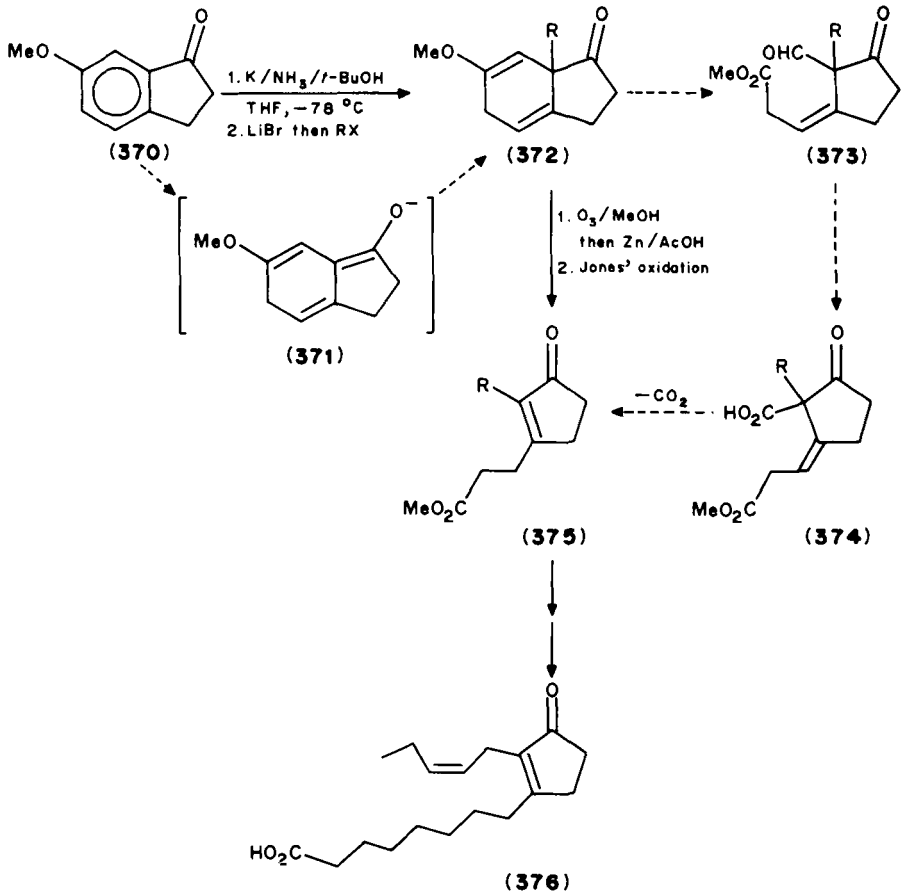


Complementary to the reduction of aromatic ethers is the oxidation of phenols which constitutes a straightforward route to six-membered ring dienones. For example, direct oxygenation[204] of **377** with a cobalt catalyst leads immediately to **378**. Alternatively, bubbling oxygen through a solution 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

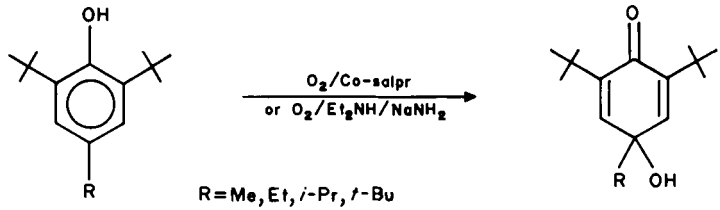


undergoes Nazarov cyclization with an excess of boron trifluoride etherate to yield 4,5-disubstituted cyclopentenone **392** as a mixture of *cis* and *trans* isomers in very good overall yields[213].

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].

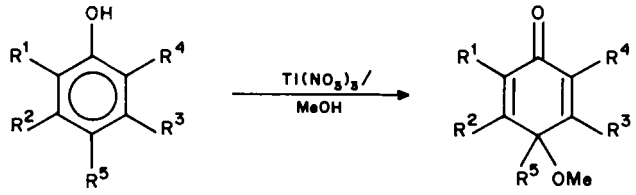
It is quite possible that nature itself also exploits the pericyclic reaction, for instance in the biosynthesis of clavulone **94** by the Pacific coral, *Clavularia viridis*[69]. It is believed[215–217] that preclavulone **402** is first formed via the allene oxide **400**, which undergoes allene oxide 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.



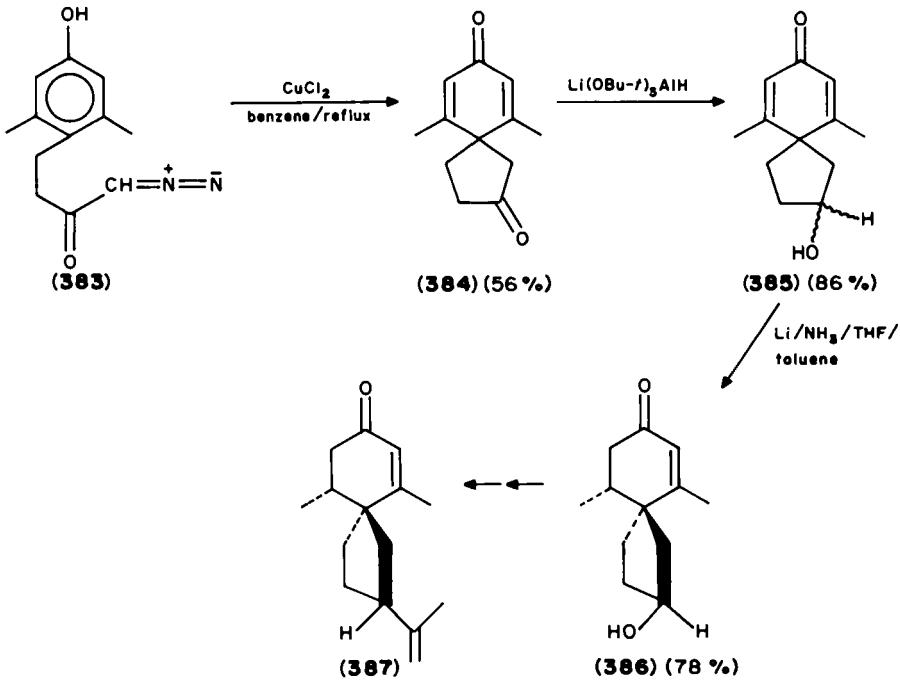
R=Me, Et, *i*-Pr, *t*-Bu

(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)



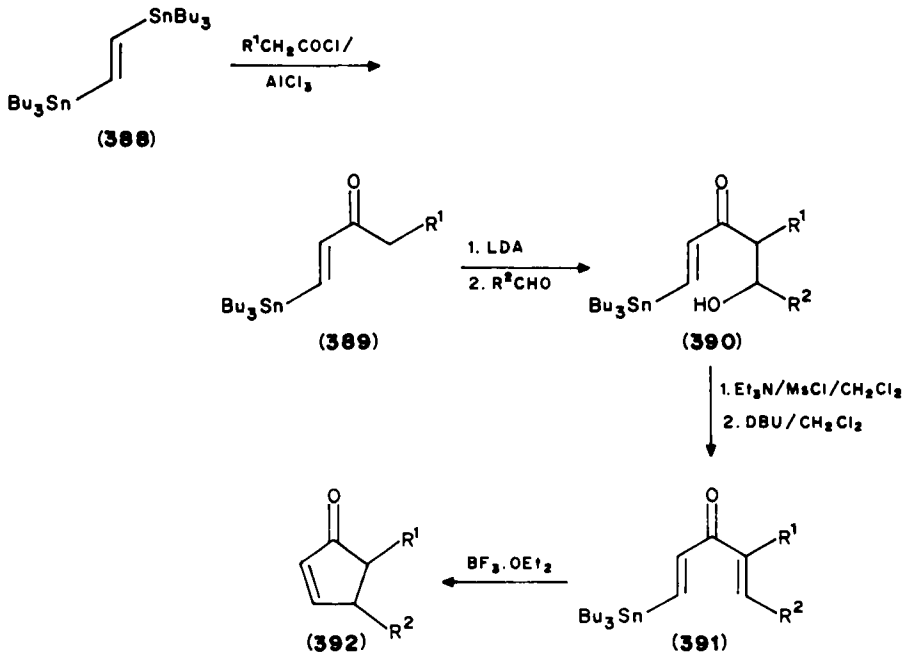
(383)

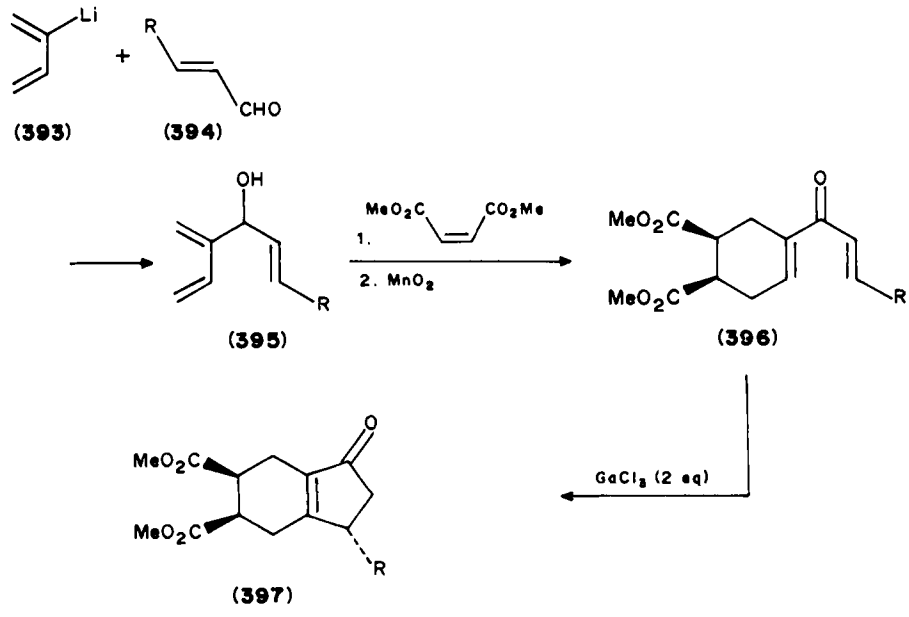
(384) (56 %)

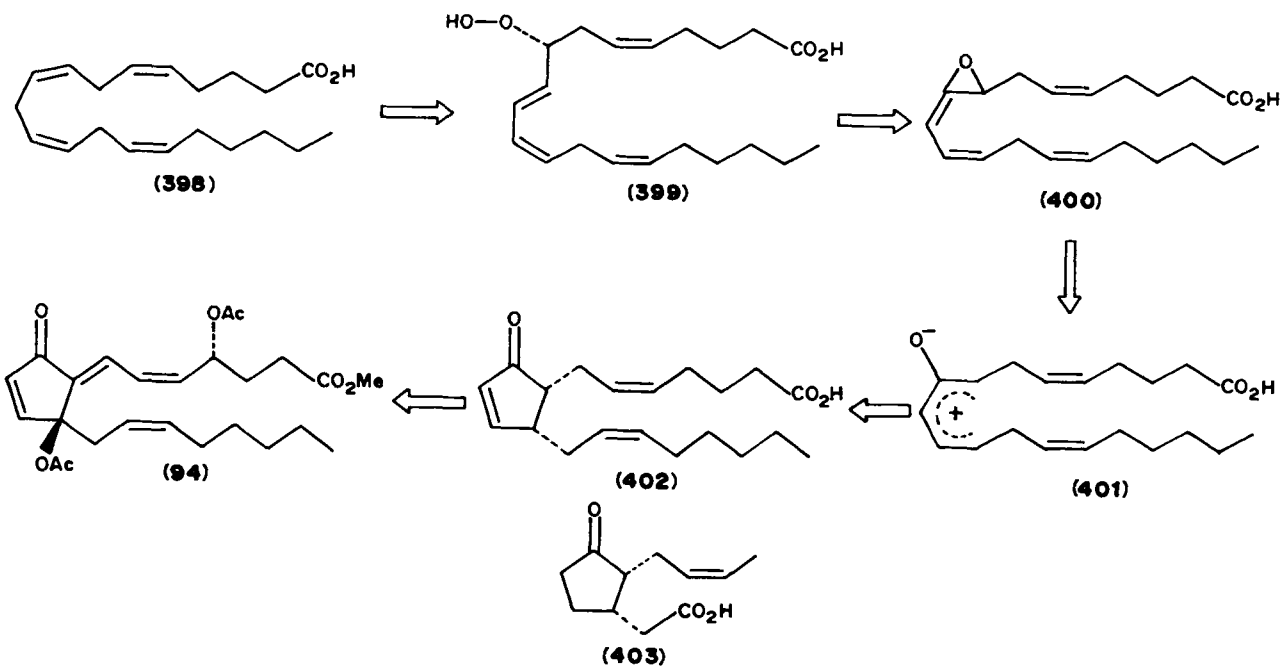
(385) (86 %)

(386) (78 %)

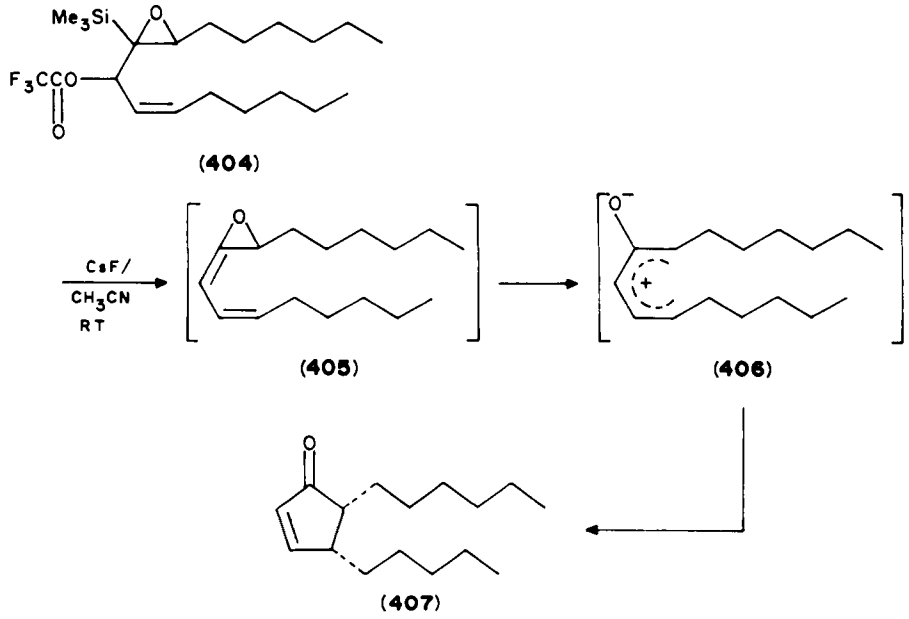
(387)


SnBu3
Bu3Sn
R1CH2COCl/
AlCl3
(388)
O
R1
Bu3Sn
1. LDA
2. R2CHO
HO
R2
(389)
(390)
1. Et3N/MsCl/CH2Cl2
2. DBU/CH2Cl2
BF3.OEt2
(392)
(391)


Li
+
R
CHO
(393)
(394)
OH
MeO2C
CO2Me
1.
2. MnO2
MeO2C
MeO2C
(395)
(396)
GaCl3 (2 eq)
(397)



SCHEME 13

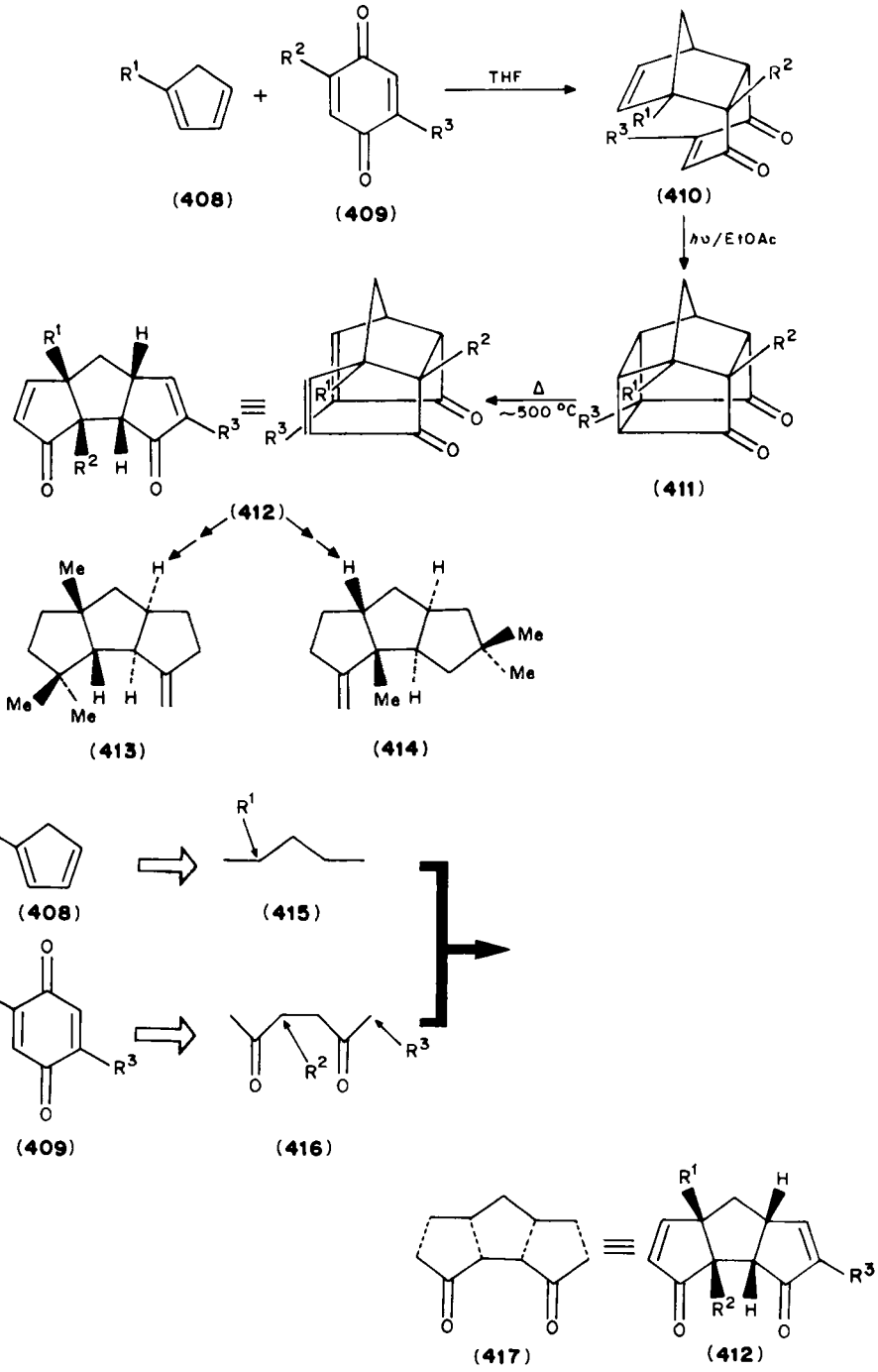


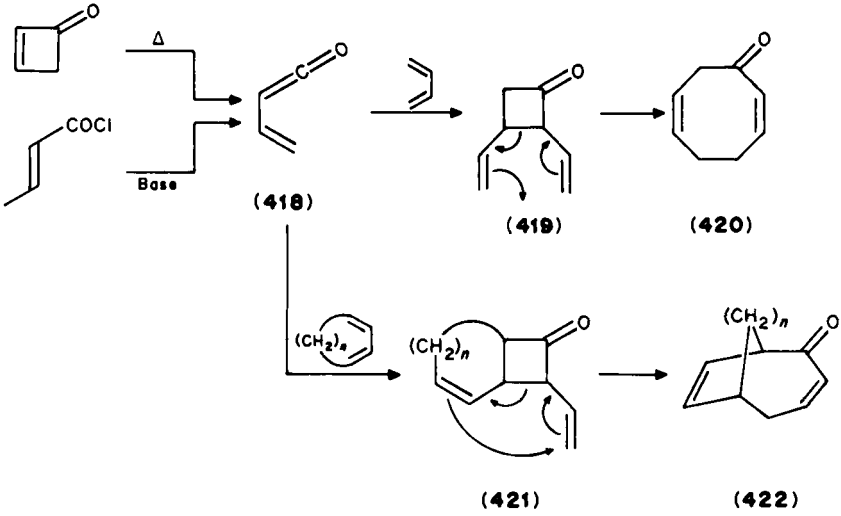
One of the most beautiful syntheses of fused enones to employ the pericyclic reaction is the construction of the *cis–syn–cis* triquinane carbon skeleton **412** by consecutive Diels–Alder reaction, photochemical [2 + 2]cycloaddition and ground-state cyclobutane ring-opening reaction. The cycloaddition 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.

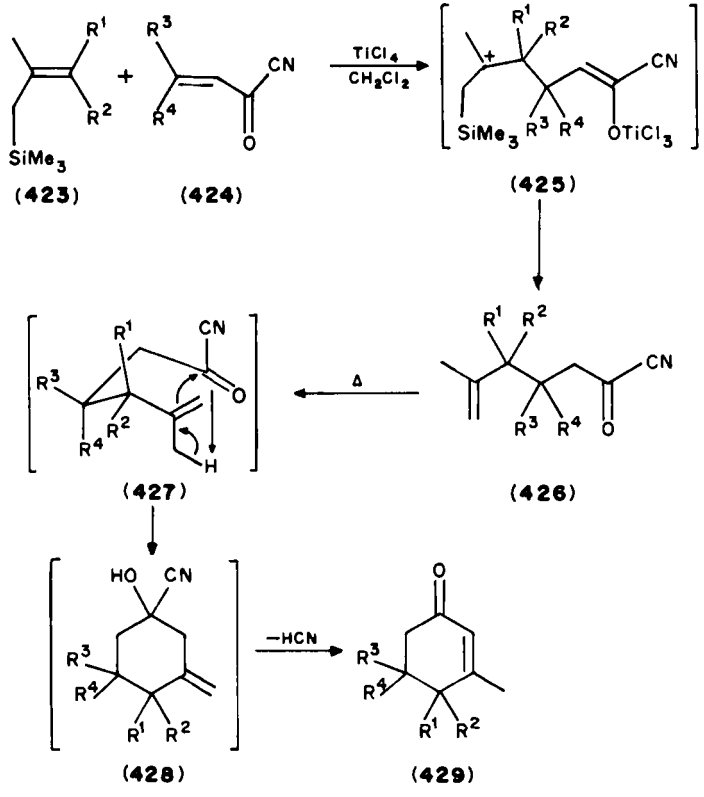
In tracing the carbon framework of product **412** back to the starting compounds **408** and **409**, the clever use of cyclopentadiene **408** as the synthon for pentane unit **415** and of *p*-benzoquinone **409** for hexanedione **416** can be better appreciated when emphasized by the construction 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].


THF
hν/EtOAc
Δ
~500 °C
(408)
(409)
(410)
(411)
(412)
(413)
(414)
(415)
(416)
(417)

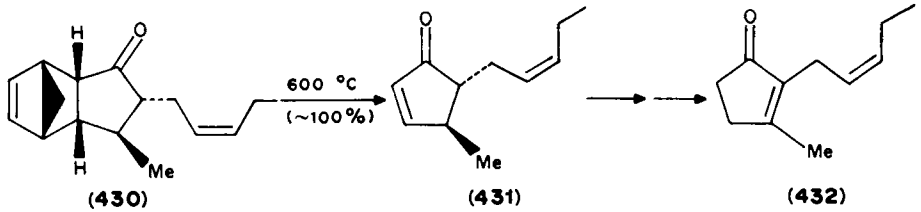

COCl
Δ
Base
(418)
(419)
(420)
(421)
(422)


SiMe3
(423)
(424)
TiCl4
CH2Cl2
(425)
(426)
Δ
(427)
HO
CN
−HCN
(428)
(429)

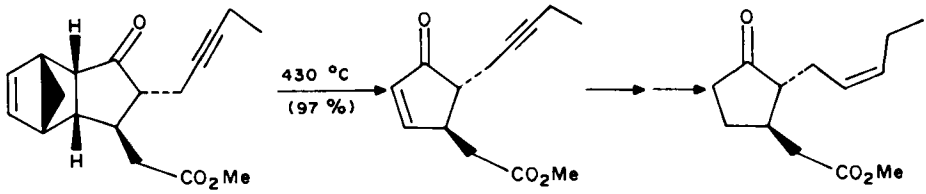
D. Retro Diels–Alder Reaction

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)**

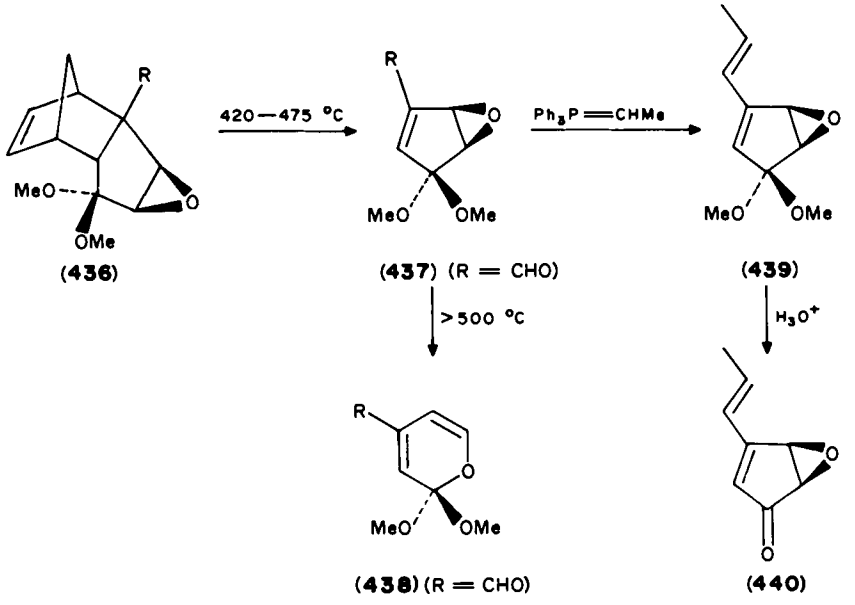


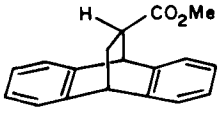
(433) **(434)** **(435)**

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].

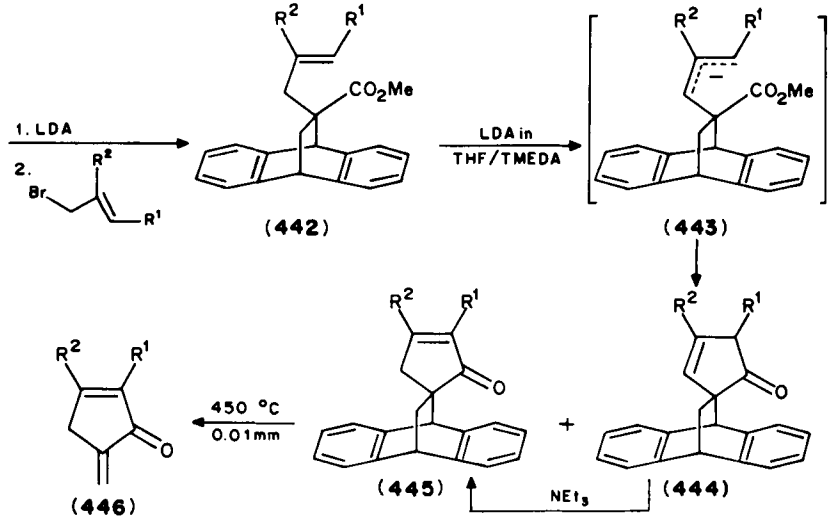
The use of anthracene-methyl acrylate adduct **441** as a masked acrylate anion[235] allows easy construction of cyclopentenones via 3-carbon annelation reactions[236]. This technique, coupled with retro Diels–Alder flash-vacuum pyrolysis of the resulting spirocyclopentenones **445**, provides the most 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.

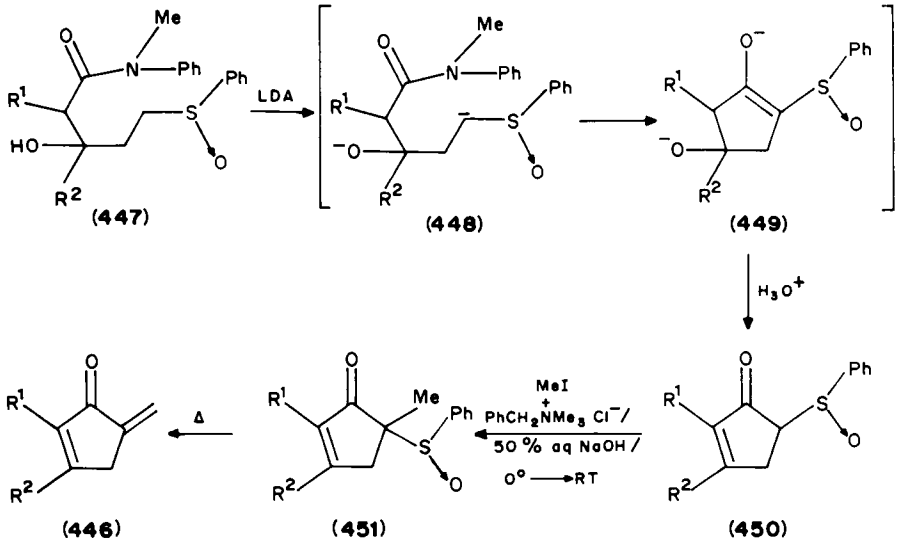
As a matter of fact the first synthesis[240] of methylenomycin B, which led to a revision and hence the first true understanding of its structure (in 1979), had employed the classical condensation of 1,4-diketones[196] in constructing the cyclopentenone nucleus, followed by an elimination reaction to 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.


R
MeO
OMe
420—475 °C
Ph3P=CHMe
>500 °C
H3O+
(436)
(437) (R = CHO)
(439)
(438) (R = CHO)
(440)


H
CO2Me

(441)


1. LDA
2.
Br
R2
R1
CO2Me
LDA in
THF/TMEDA
(442)
(443)
450 °C
0.01mm
(445)
(444)
NEt3
(446)

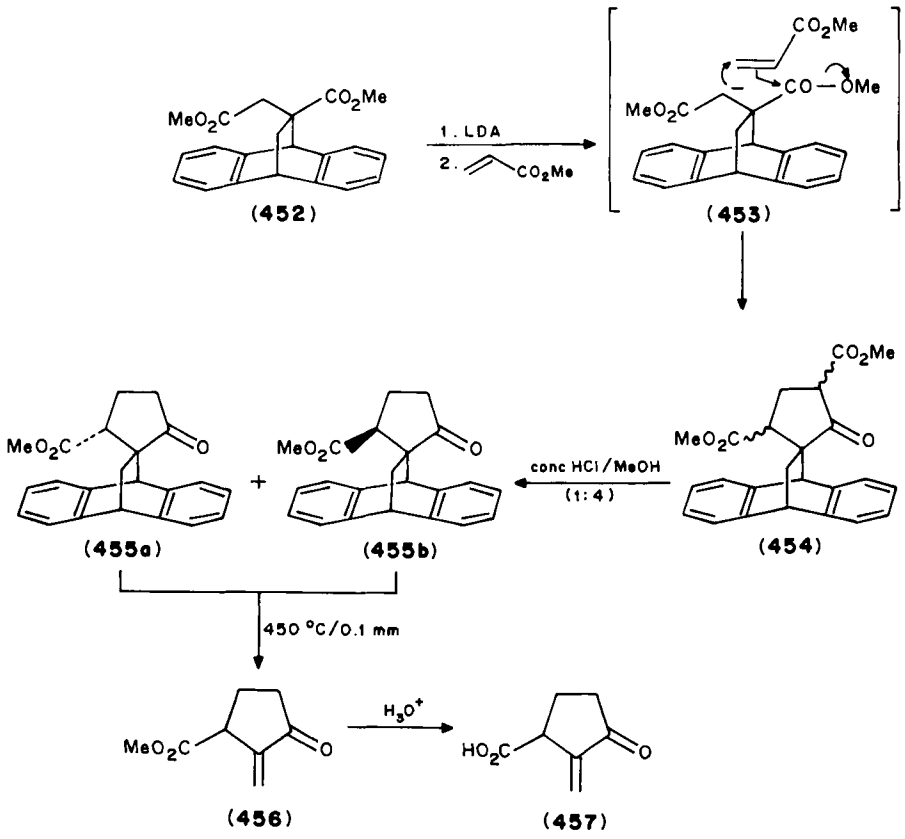


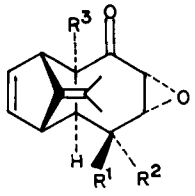
The high versatility of the anthracene adduct coupled with the synthetic utility of the retro Diels–Alder reaction is again demonstrated in the synthesis of sarkomycin **457**, a deceptively simple-looking molecule isolated from the culture broth of Streptomyces[245]. Because of its very interesting 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.

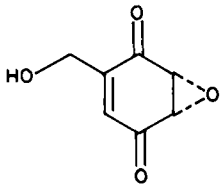
The rate of the retro Diels–Alder reaction, in contrast to the forward reaction, has not been widely studied[259,260]. However, recent results show that the spiropentanedione **464** undergoes the acid-catalyzed retro Diels–Alder reaction extremely readily, even at room temperature, giving 2-methylene-1,3-cyclopentanedione **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].



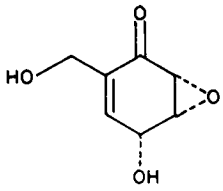


(458)

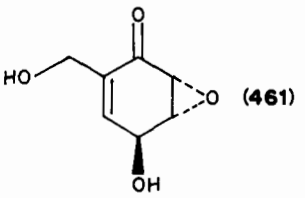
(a) $R^1, R^2 = =O, R^3 = CH_2OH$
(b) $R^1 = H, R^2 = OH, R^3 = CH_2OH$
(c) $R^1 = OH, R^2 = H, R^3 = CH_2OH$
(d) $R^1 = H, R^2 = OH, R^3 = Me$
(e) $R^1 = OH, R^2 = H, R^3 = Me$



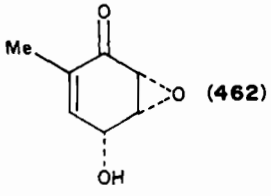
(459)



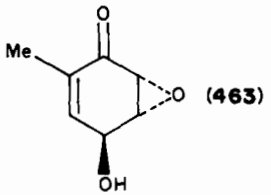
(460)



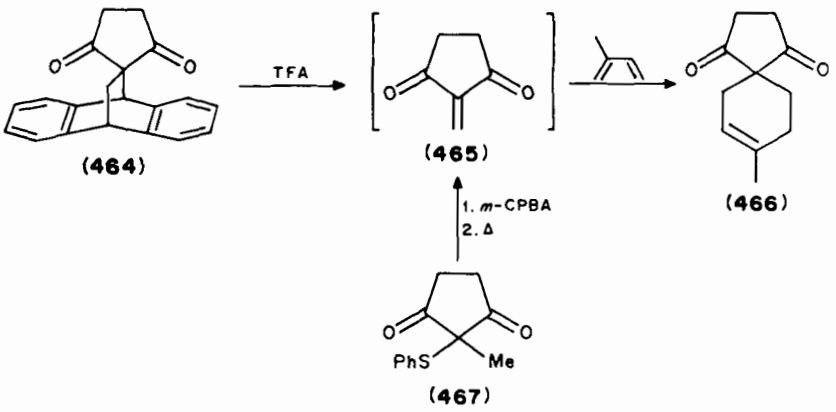
(461)



(462)



(463)

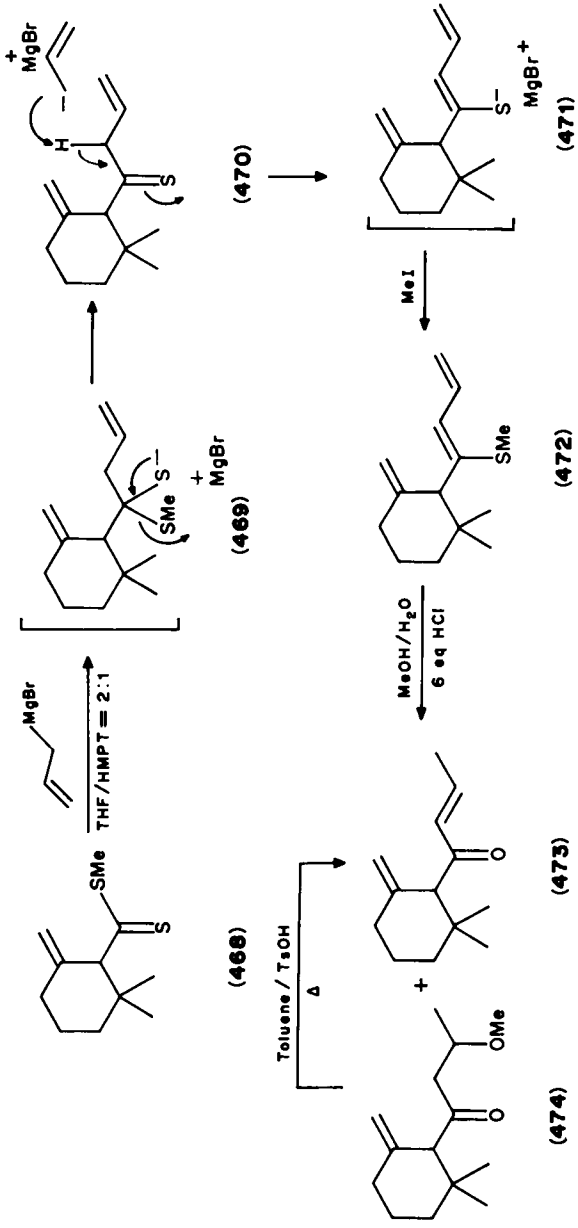


(464) (465) (466) (467)

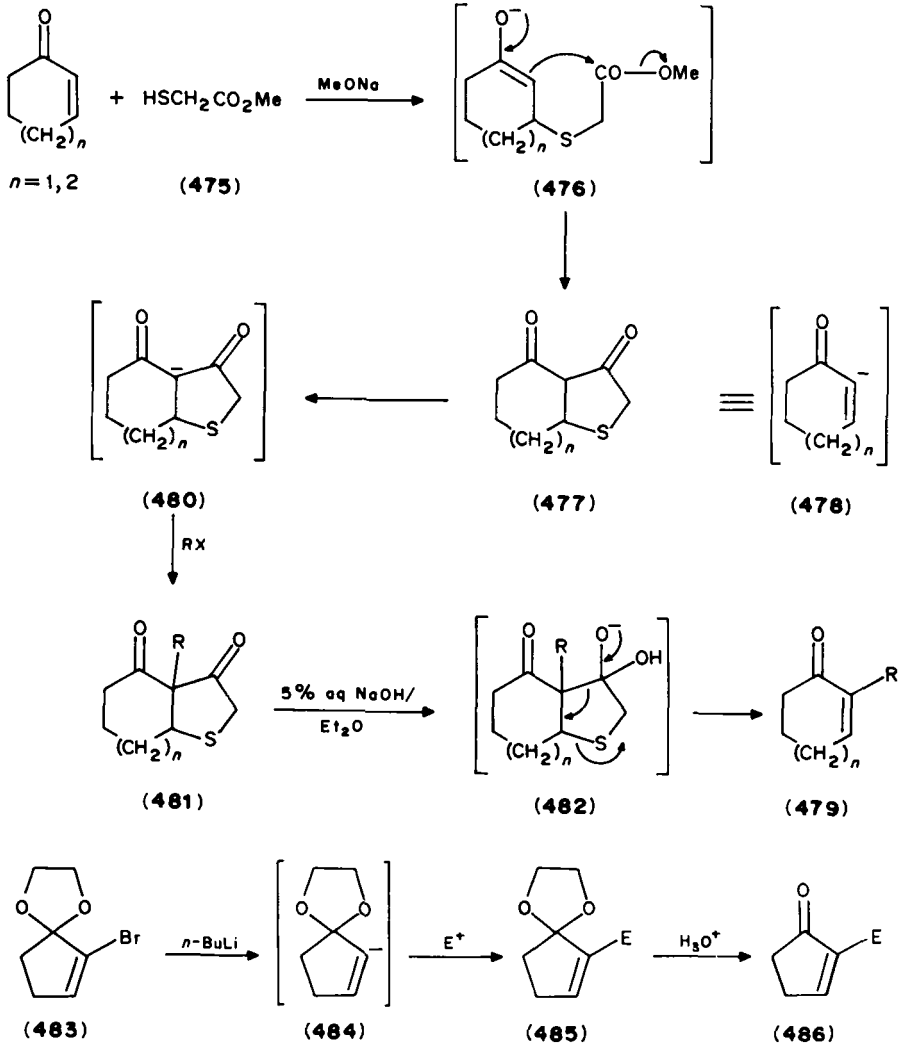
E. Miscellaneous

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.

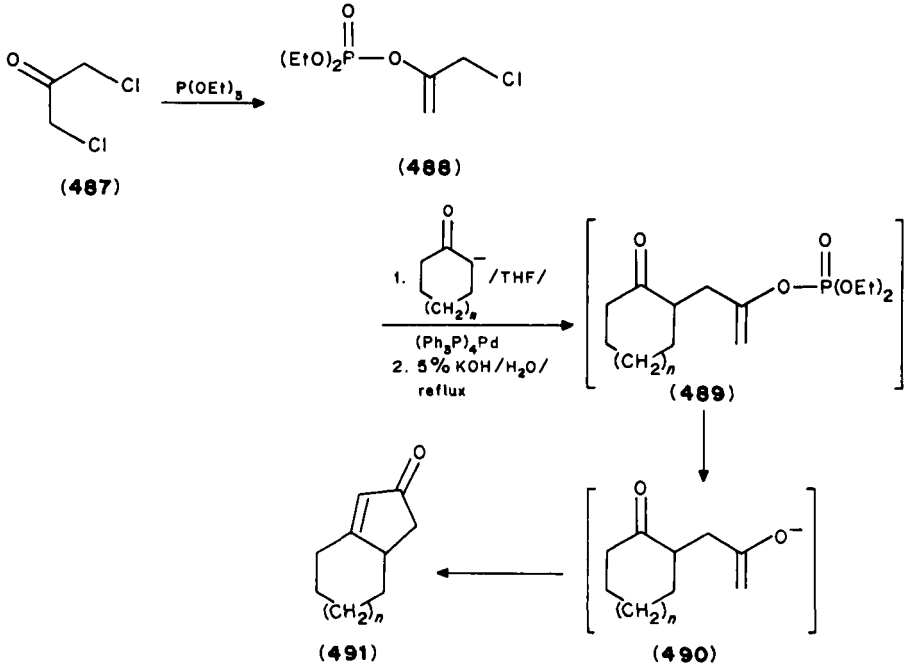

MgBr
THF/HMPT = 2:1
SMe
S
(468)
SMe
S⁻
+ MgBr
(469)
(470)
MgBr⁺
(471)
MeI
SMe
(472)
MeOH/H₂O
6 eq HCl
Toluene / TsOH
Δ
O
(473)
+
OMe
O
(474)

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].



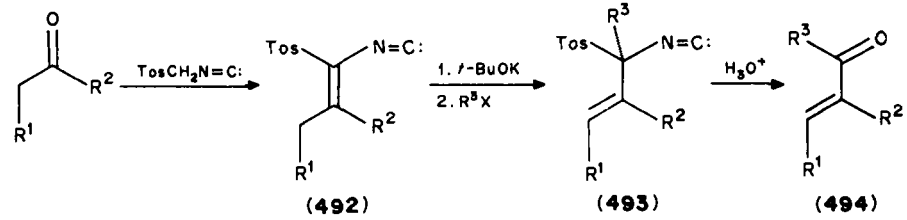
A new reagent, 3-chloro-2-diethylphosphoryloxypropene **488**, prepared from **487** by Perkow reaction[266], is employed as a three-carbon source in a 'one-pot' synthesis of cyclopentenones. The significant advantage here is that intermediate **489** can be

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].



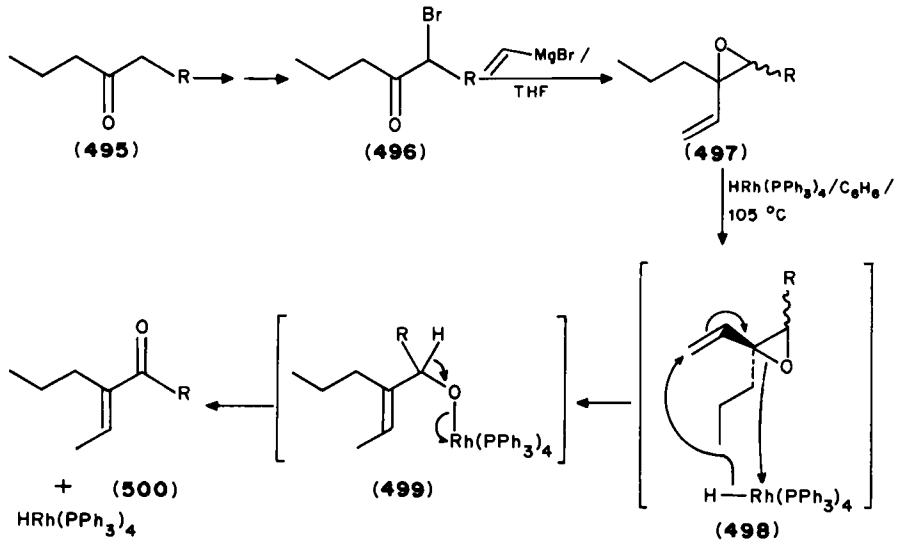
Homologation and 1,2-carbonyl transposition reactions also provide access to the enone system. Two examples which are simple, short and give good to excellent yields, are cited here.

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].

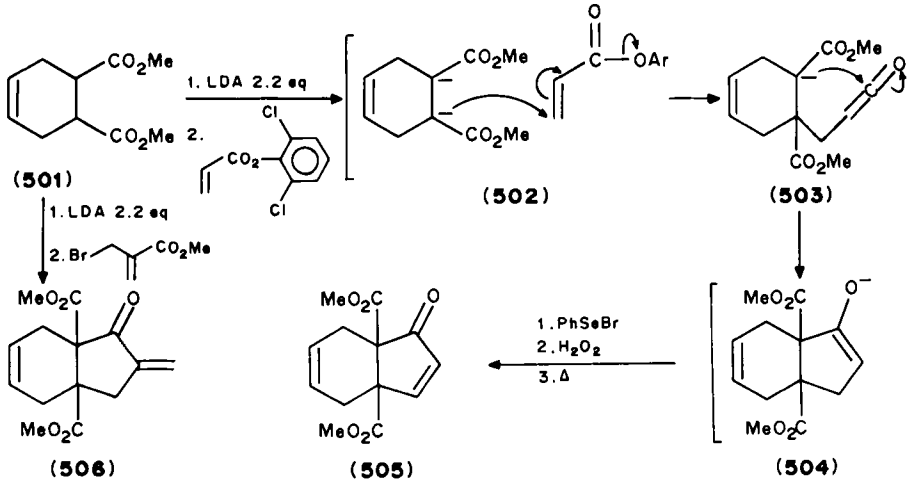


R^1, R^2 = H, alkyl, or $-(CH_2)_n-$ (n = 2—4), R^3 = alkyl

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.



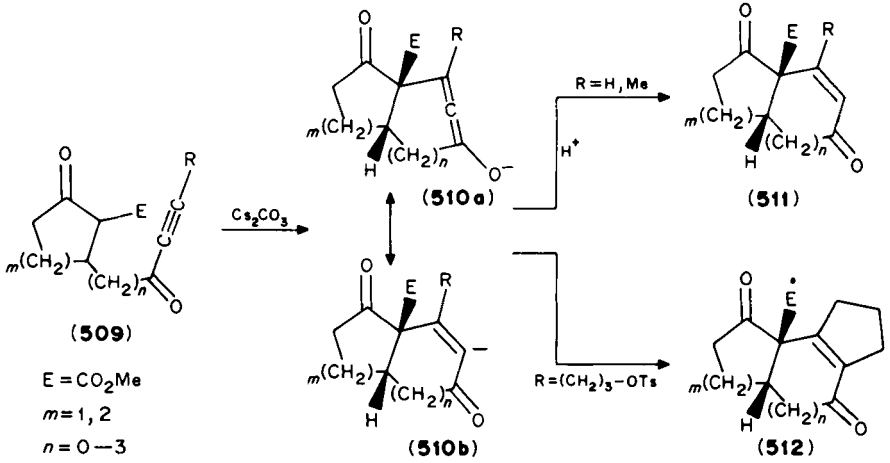
Although not widely exploited, inter- and intra-molecular addition to the electrophilic acetylenic bond, particularly in conjugated acetylenic ketone, provides another mode of access to enones[273]. An example is the addition of HF to the activated triple bond.

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].

$$\underset{\textbf{(507)}}{R{-}C{\equiv}C{-}A} \xrightarrow{n\text{-}Bu_4N^+H_2F_3^-} \underset{\textbf{(508)}}{R{-}CF{=}CH{-}A}$$

R = alkyl, phenyl : A = CN, CO_2Me, COPh, CHO

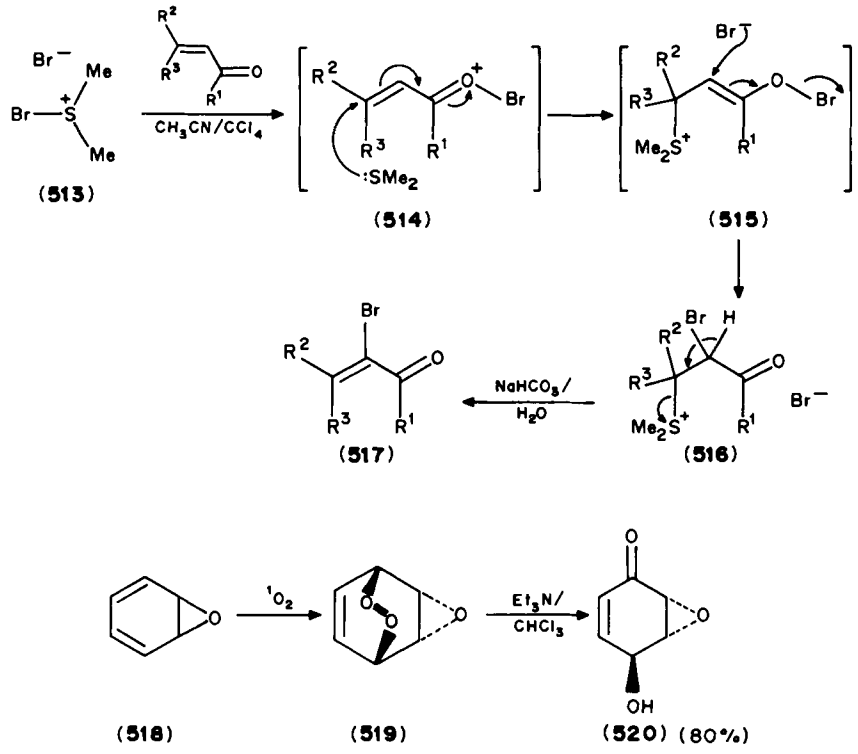
The intramolecular addition of nucleophiles to ynones was investigated very recently with the result that a variety of enones with the general skeletons **511** and **512** can now be prepared[275–277] from cesium carbonate-induced intramolecular cyclization of **509**.



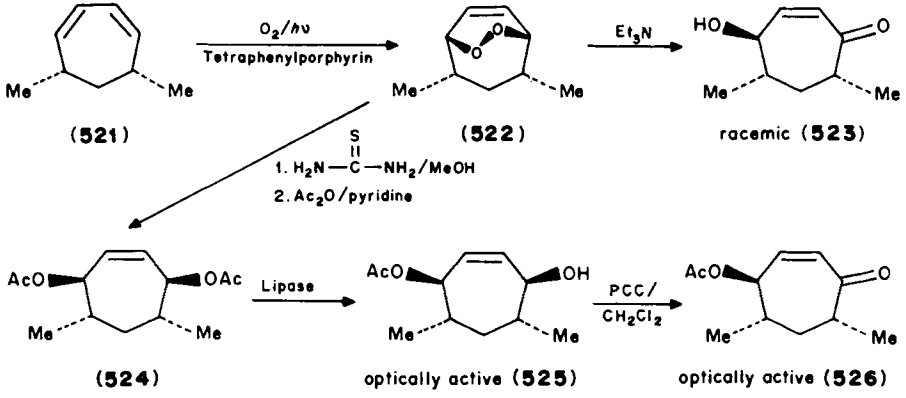
Apart from β-fluoroenones (e.g. **508**), α-bromoenones (e.g. **517**) are also readily available through the use of dimethylbromosulfonium bromide **513**. This versatile reagent, easily prepared from the reaction of dimethyl sulfide with bromine[278], has several uses; for example as a dethioacetalization 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**.

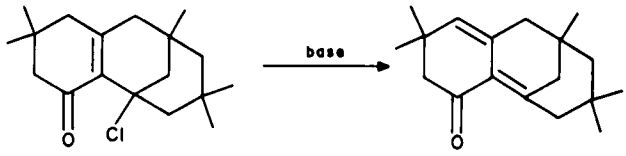
Recently this reaction was applied[283,284] to *cis*-5,7-dimethylcyclohepta-1,3-diene **521** to yield racemic **523**. Because of the importance of **523** as a synthetic intermediate, efforts were made to develop the synthesis further and the preparation of optically active **523** (in



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**.

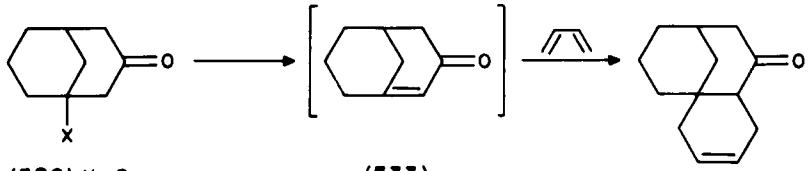


A mention should also be made here of strained enones and their synthesis. In this class are the bridgehead enones wherein either the α- or β-carbon atom of the enone is at the bridgehead[286]. The synthetic study of enones with strained double bonds is largely the work of House and his group[287] who 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**)

Dimer

(**534**)

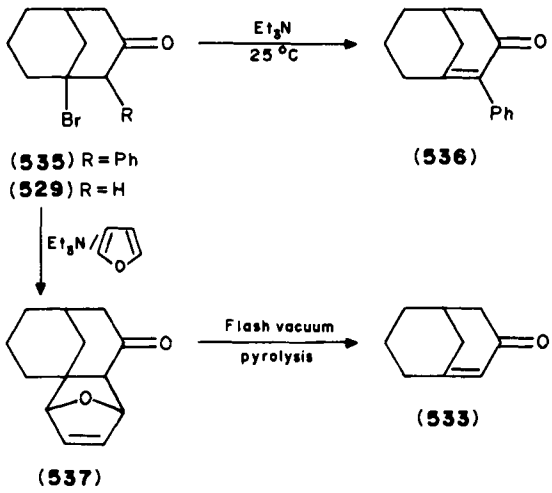
Interestingly, it was found that, by placing a bulky substituent at the α-position of the enone system, self-dimerization could be markedly retarded; hence **536** was obtained in a pure state from the base-catalyzed elimination of **535**. Although it reacts readily with nucleophiles, oxygen and dienes, **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].

VIII. OPTICALLY ACTIVE CYCLOPENTENONES

Many biologically important natural products are cyclopentenone derivatives, for example the prostaglandins, pentenomycins and jasmones. Attempts to synthesize these



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.

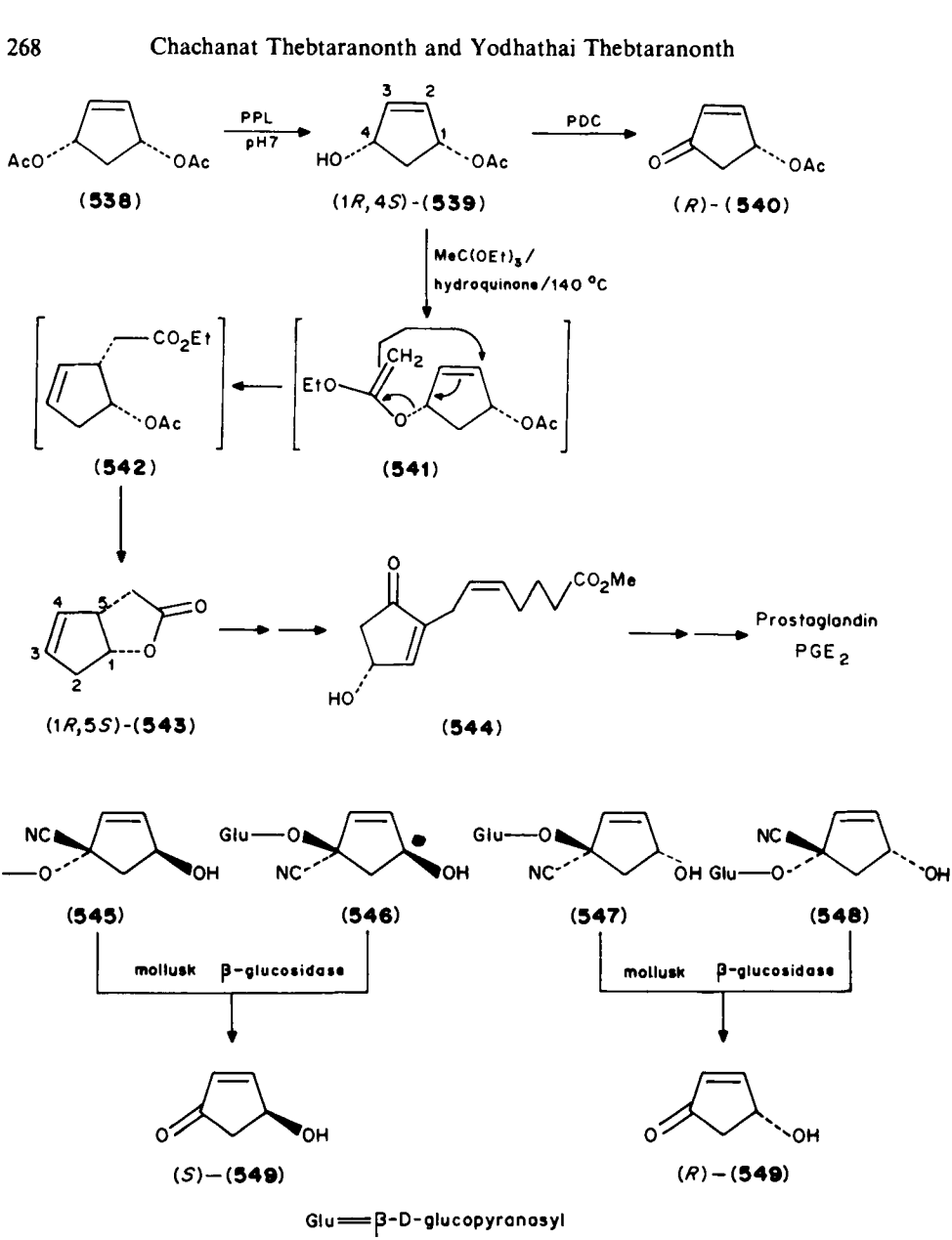
In the same manner as the selective (*S*)-ester hydrolysis of diacetate **524** to optically active **525** by lipase[284], the hydrolysis of prochiral **538** with commercially available and comparatively inexpensive porcine pancreatic lipase (PPL) provides (*1R,4S*)-**539** with hardly a trace of the 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].

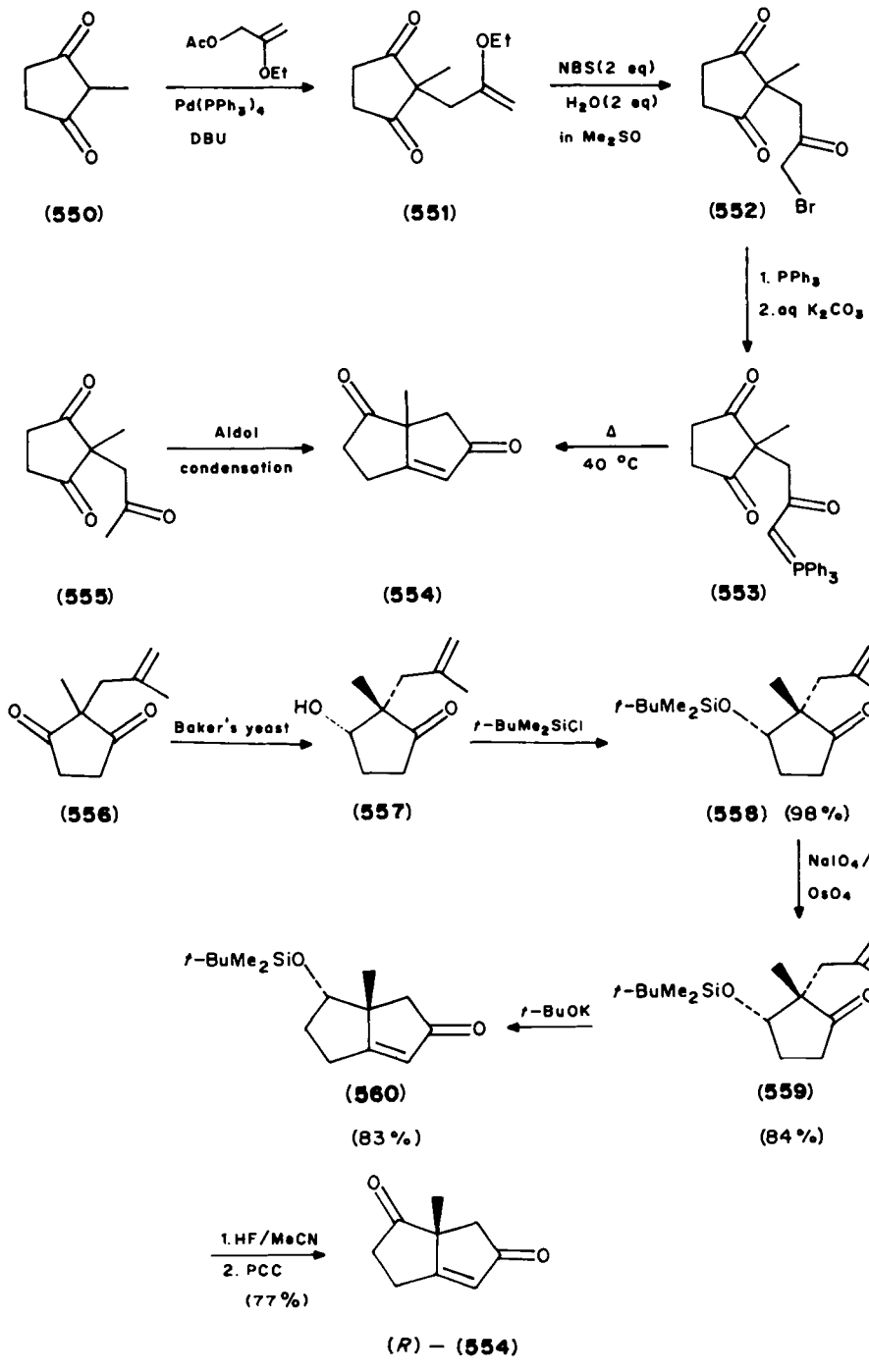
A further example of enantiomeric synthesis utilizing the enzymatic process is the synthesis of optically active enedione **554**, a potential intermediate[307] for the synthesis of coriolin **276**. Racemic **554** had been synthesized by Trost and Curran[308] via palladium-catalyzed C-alkylation of 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**).

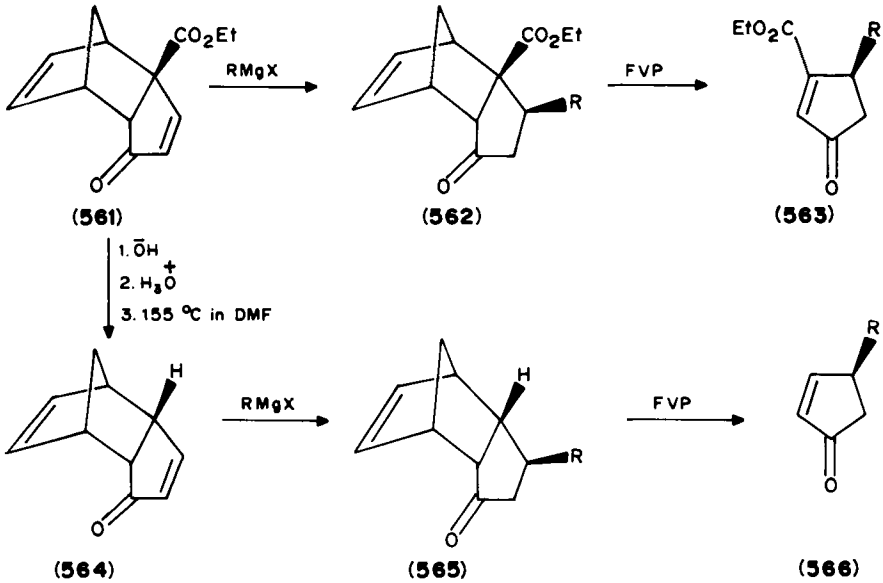


However, a more efficient enantioselective synthesis of **554** has since been achieved. Chiral ketol **557** can be produced in high yield, with more than 98% enantiomeric purity, by taking advantage of the asymmetric monoreduction of prochiral dione **556** with fermenting baker's yeast[310,311]. From there on the conversion of **557** into (*R*)-**554** is a straightforward process.

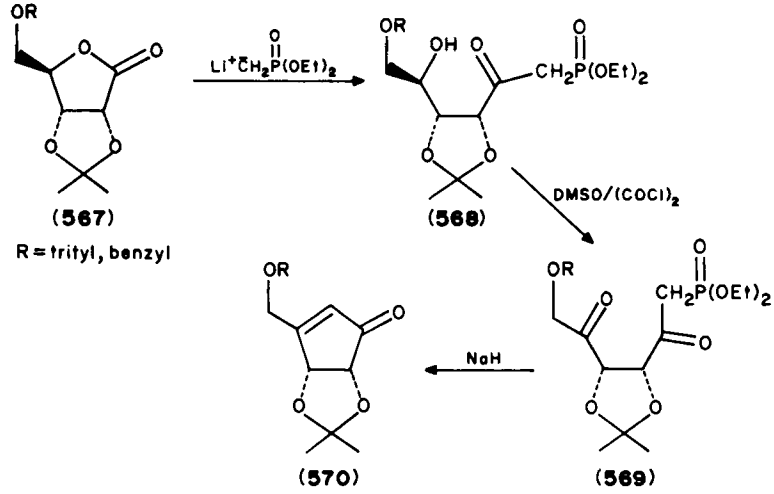
Optically active adduct **561** (cf. **436**) can be obtained by enzymatic resolution of the racemate using porcine liver esterase (PLE)[312]. The rigid *endo* configuration of **561**, whose

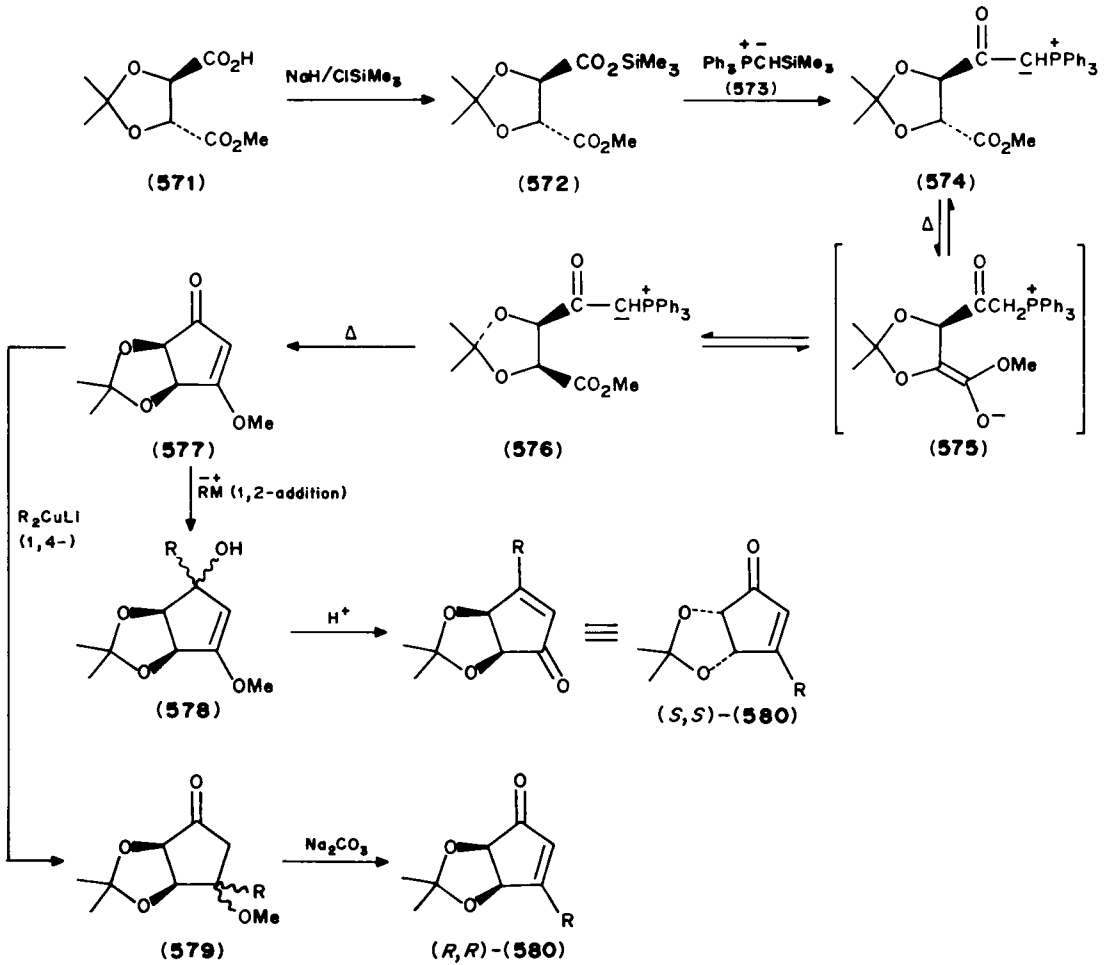

AcO
OEt
Pd(PPh3)4
DBU
OEt
NBS(2 eq)
H2O(2 eq)
in Me2SO
Br
(550)
(551)
(552)
1. PPh3
2.aq K2CO3
Aldol
condensation
Δ
40 °C
PPh3
(555)
(554)
(553)
Baker's yeast
HO
t-BuMe2SiCl
t-BuMe2SiO
(556)
(557)
(558) (98%)
NaIO4/
OsO4
t-BuMe2SiO
t-BuOK
t-BuMe2SiO
(560)
(83%)
(559)
(84%)
1. HF/MeCN
2. PCC
(77%)
(R) – (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**.



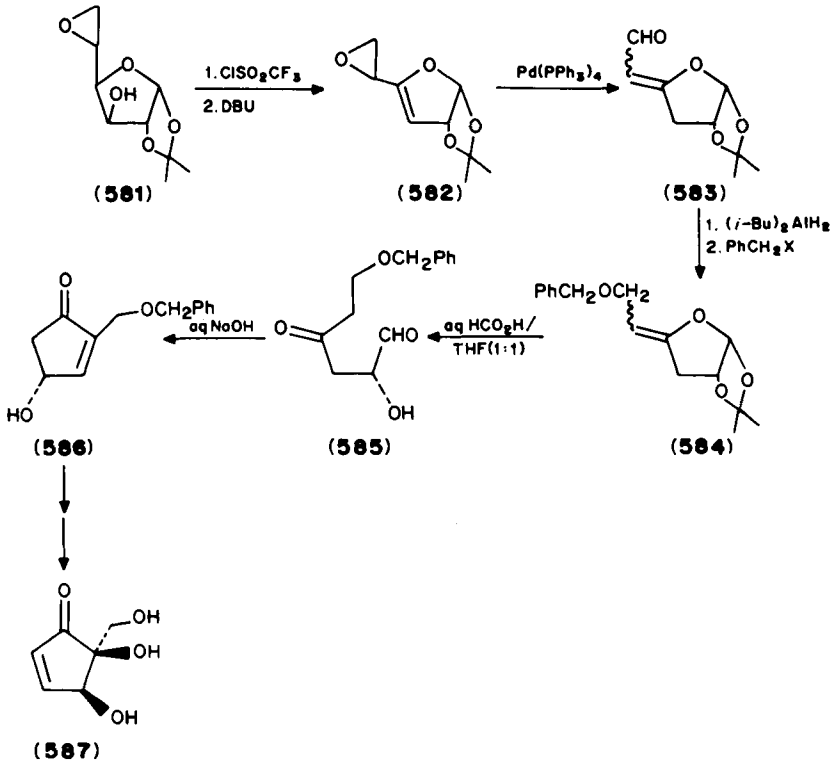
A partial synthesis of optically active **570** (a precursor of 3-substituted 4,5-dihydroxycyclopentenones) from *R*-ribolactone **567** has been described[315]. Reacting **567** with the lithium phosphonate salt followed by oxidizing the resulting ketol **568** with a mixture of dimethyl sulfoxide/oxalyl chloride the authors obtained 1,4-diketone **569** which, when subjected to the Horner–Wittig reaction, yielded **570**.




NaH/ClSiMe3
Ph3PCHSiMe3
(573)
(571)
(572)
(574)
Δ
(577)
(576)
(575)
RM (1,2-addition)
R2CuLI
(1,4-)
(578)
H+
(S,S)-(580)
(579)
Na2CO3
(R,R)-(580)

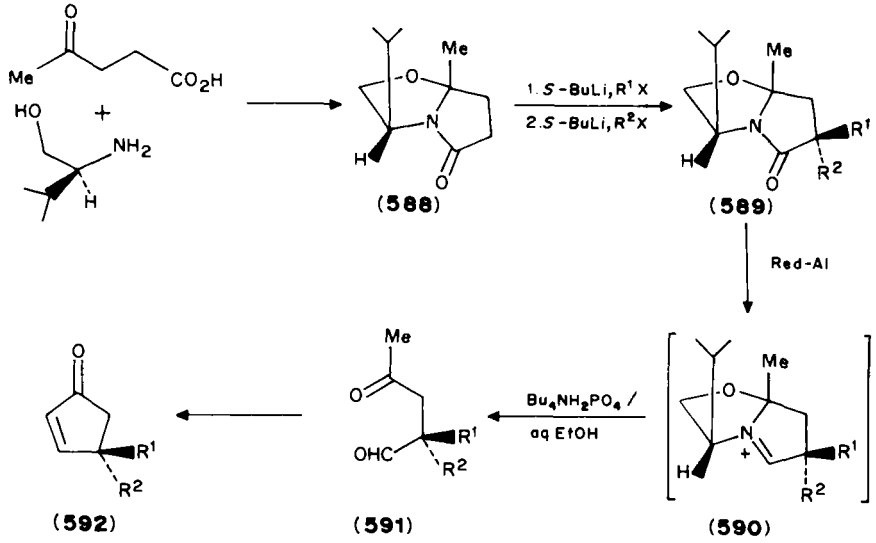
A similar method[316] which provides optically active cyclopentenones such as **570** in either the (*R*,*R*)- or (*S*,*S*)- form makes use of the readily available acetonide of (*R*,*R*)-tartaric acid monomethyl ester **571**. The reaction between phosphorane **573** and trimethylsilyl ester derivative **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 (*4S*,*5R*)-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**.

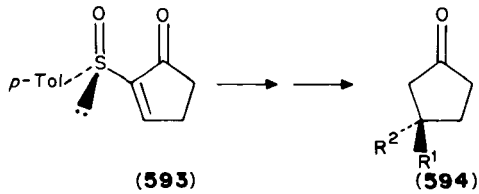


The use of chiral templates in asymmetric synthesis is fast growing in popularity, especially in the area of nucleophilic addition[320] and cycloaddition reactions[188], whilst in asymmetric alkylation it has already led to the synthesis of many optically active cyclopentenone and cyclohexenone derivatives[321-323].

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.

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The Chemistry of Enones
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CHAPTER **8**

Synthetic uses of enones

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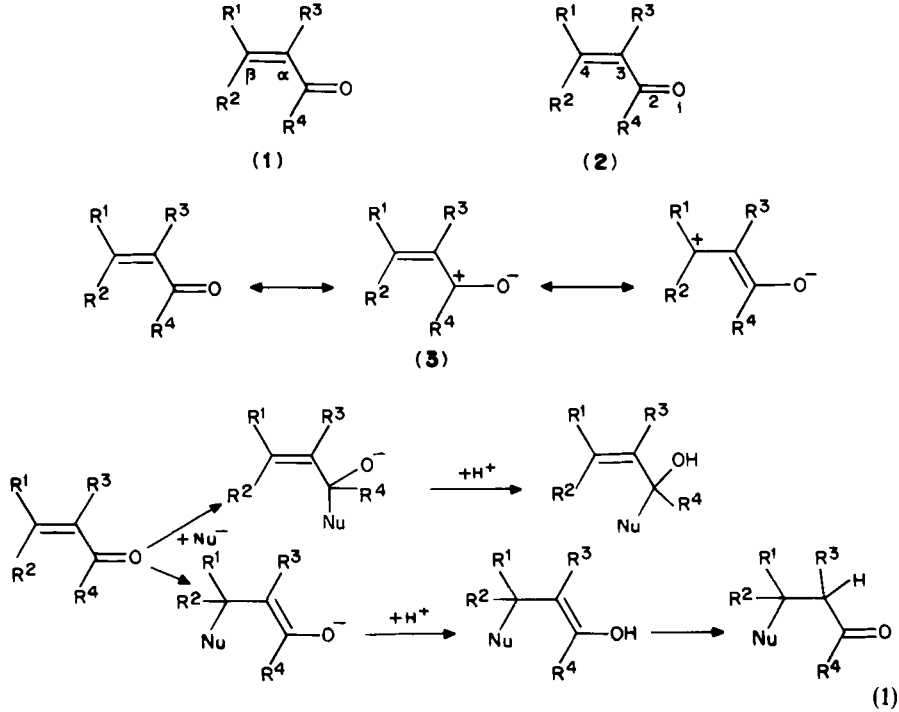
I. INTRODUCTION

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).



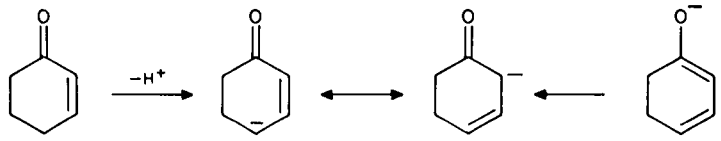
(1)

The question of 1,2- versus 1,4-addition is one of the most important features of the chemistry of enones[5].

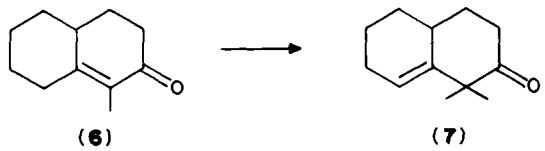
II. REACTIONS WITH NUCLEOPHILES

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).

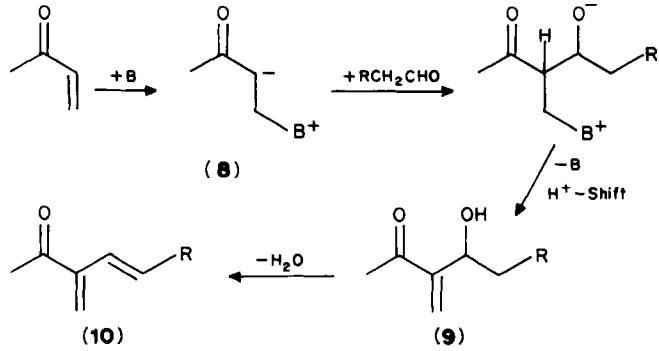


(2)



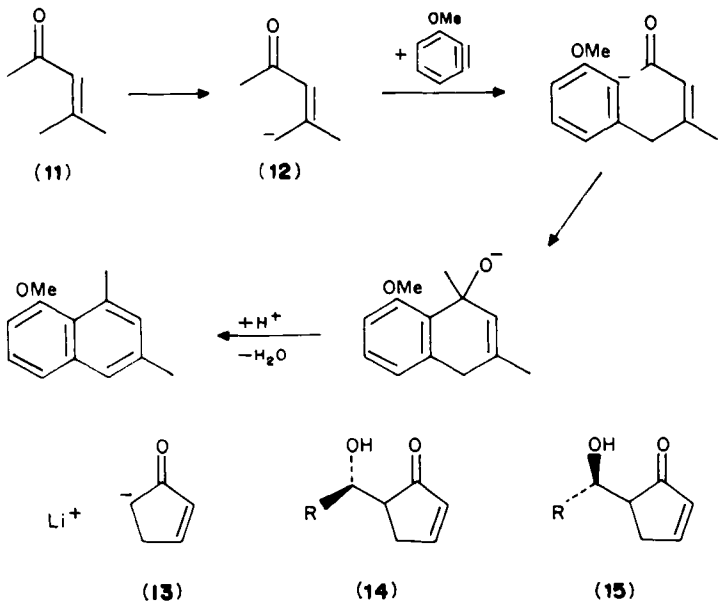
(6) (7)

(3)



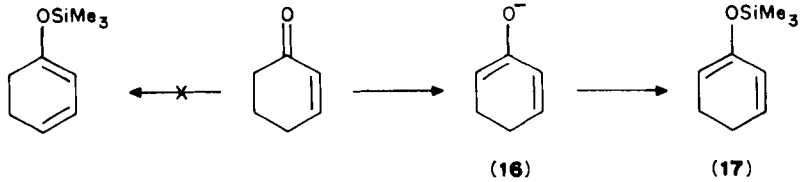
(4)

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].



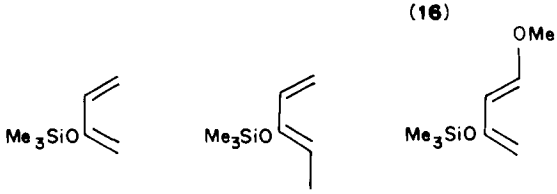
(5)

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].

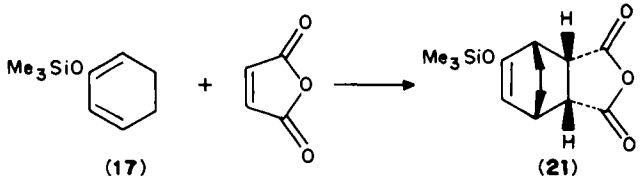


(16) (17)

(6)

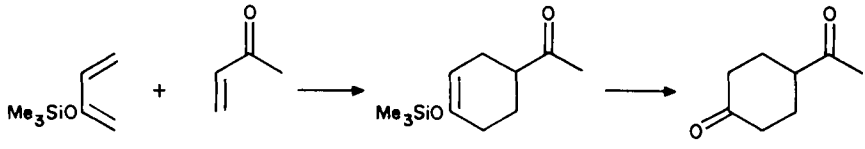


(18) (19) (20)



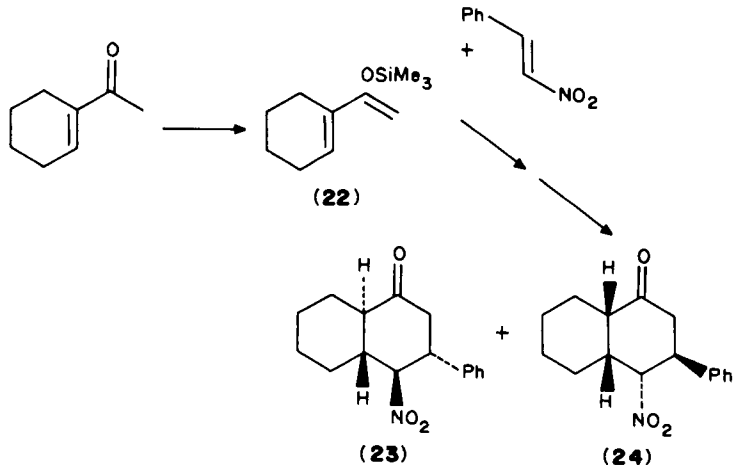
(17) (21)

(7)

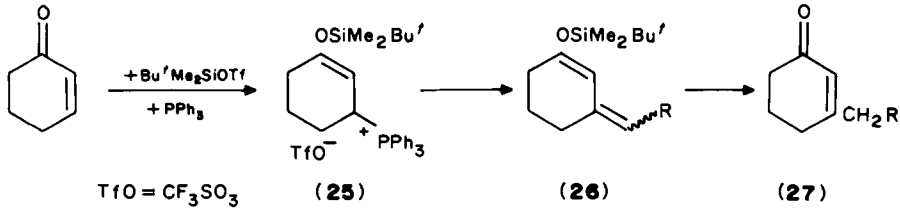


(18)

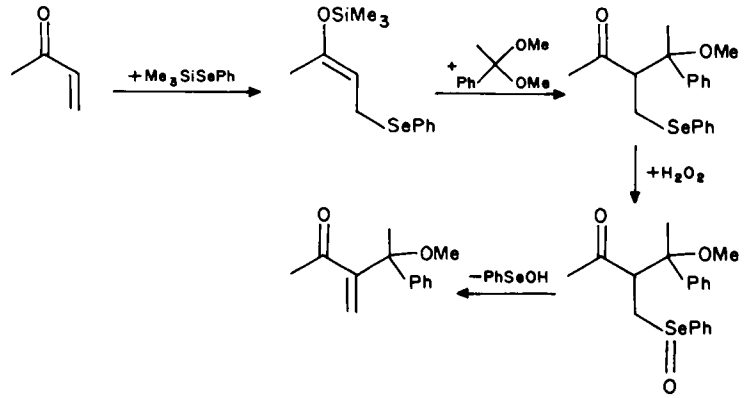
(8)



(9)



(10)

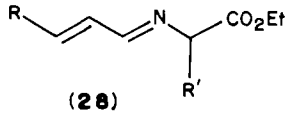


(11)

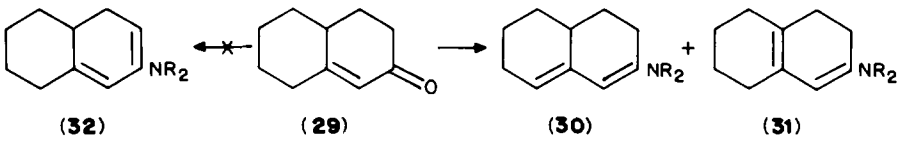
B. Reactions at the Carbonyl Carbon Atom

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.

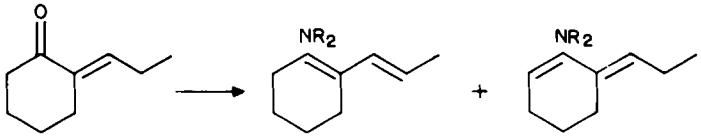


(**28**)



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

(12)



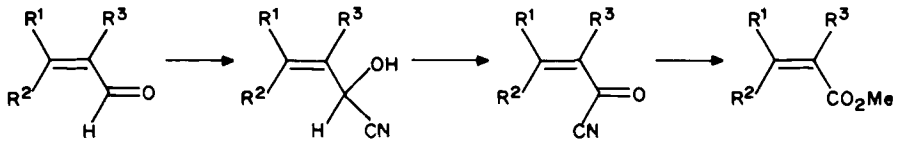
(**33**) (**34**) (**35**)

(13)

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.

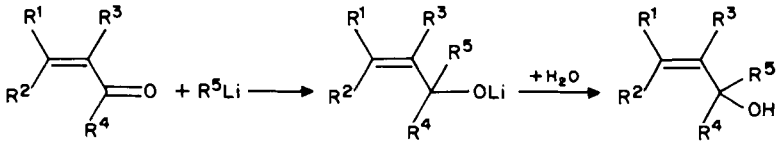
(**36**)



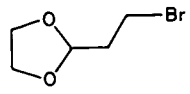
(14)

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,

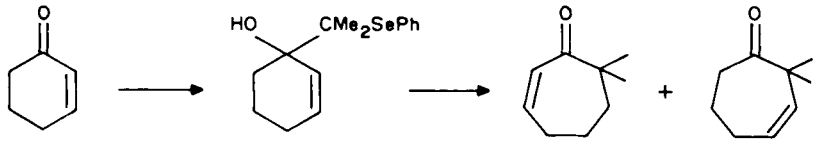
the Grignard reagent derived from the acetal **37** adds to cyclopentenone and cyclohexenone at low temperatures to give mainly 1,4-adducts[22]. Metal derivatives of allyl ethers add exclusively to the carbonyl group of enones[23]. The action of the selenide $Me_2C(SePh)Li$ on cyclohex-2-enone produces 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**)

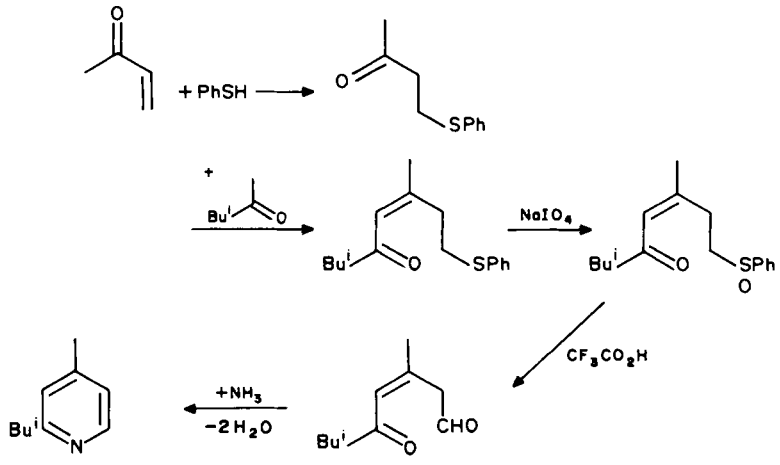


(16)

C. Reactions at the β-Carbon Atom (Conjugate Additions)

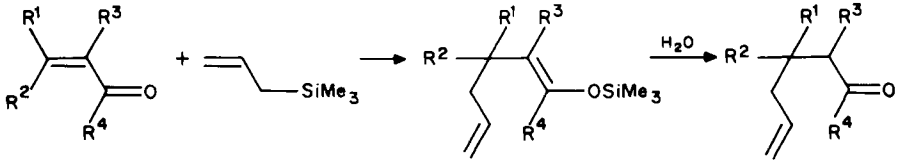
1. With various nucleophiles

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

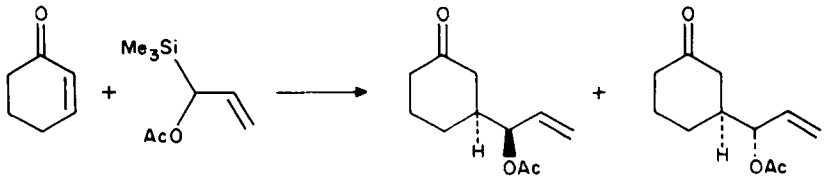


(17)

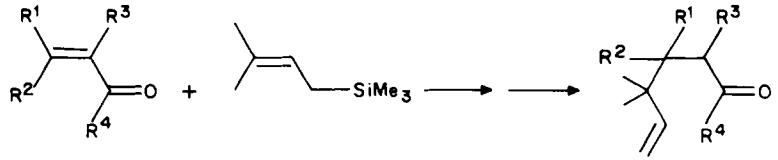
pyridines has been obtained by this method[25]. The conjugate addition of allyltrimethylsilane to enones is promoted by Lewis acids or fluoride ion (equation 18)[26]. (1-Acetoxy-2-propenyl)trimethylsilane reacts with enones, such as cyclohexenone, in the presence of tetrabutylammonium fluoride to yield 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].



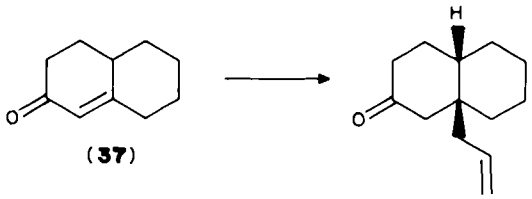
(18)



(19)

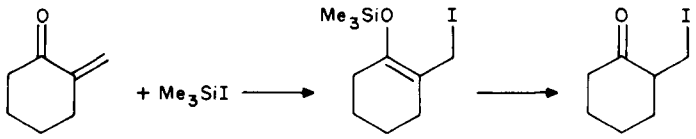


(20)

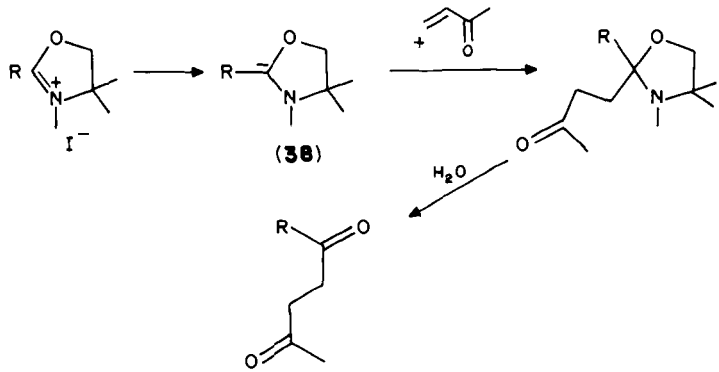


(21)

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].

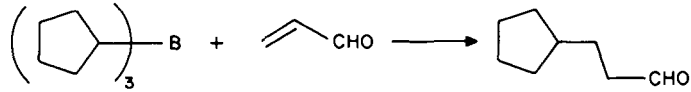


(22)



(23)

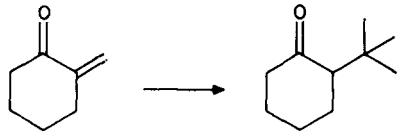
β-Alkylation of enals and enones can be achieved by using trialkylboranes, followed by hydrolysis, as in the cyclopentylation of acrolein (equation 24)[31].



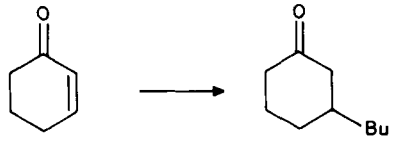
(24)

2. With organometallic reagents

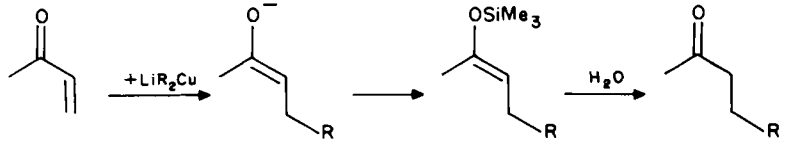
In contrast to the reaction of organolithium and Grignard reagents with α,β-unsaturated carbonyl compounds, discussed in Section II.B, clean conjugate addition is brought about by the use of organocopper reagents, which are produced from lithium or Grignard compounds and copper(I) salts[32]. Thus 2-isopropylidenecyclohexanone 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].



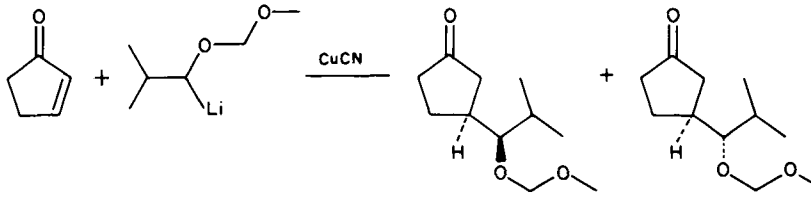
(25)



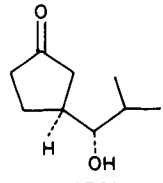
(26)



(27)

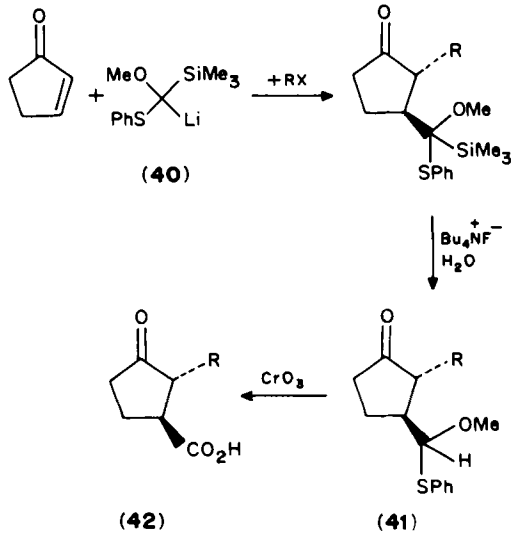


(28)



(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].



(40)

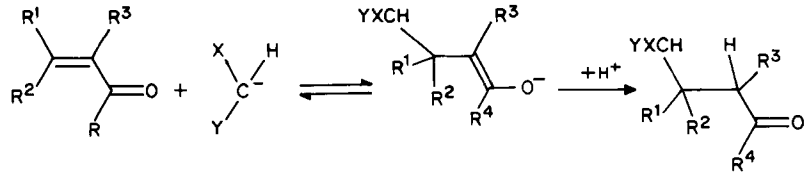
(41)

(42)

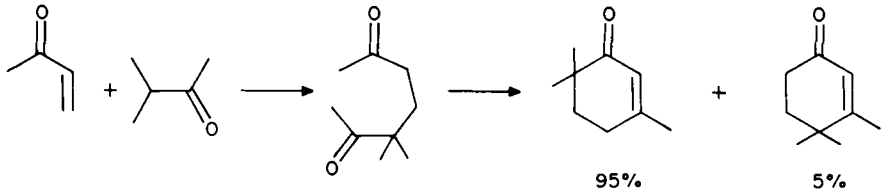
(29)

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].



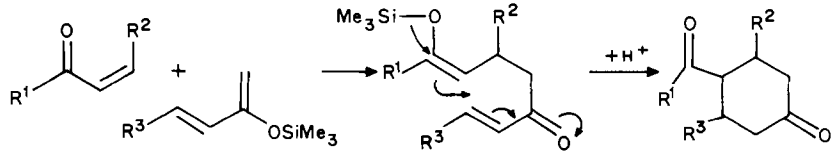
(30)



(31)

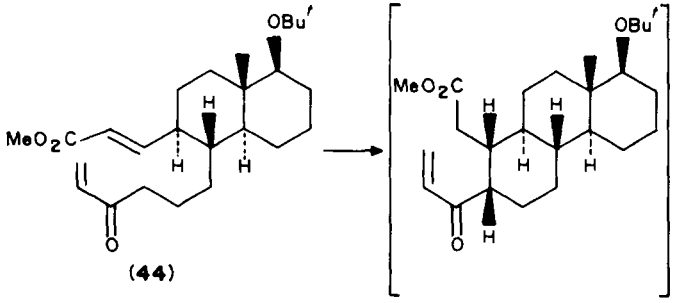
Triphenylmethyl perchlorate catalyses the addition of trimethylsilyloxybutadienes to enones; the products **43**, in which the trimethylsilyloxy group has been transferred, undergo an intramolecular Michael reaction to give 4-acylcyclohexanones in good yield (equation 32)[40]. A twofold Michael reaction 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].

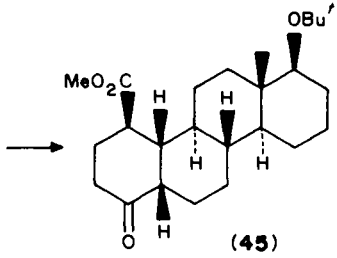
Wittig reagents undergo conjugate addition to enones. This type of reaction is particularly fruitful if (triphenyl)propylidenephosphorane (**46**) is employed. Its Michael adduct **47** to 4-methyl-3-penten-2-one undergoes a proton shift, followed by an intramolecular Wittig reaction, to yield a cyclohexadiene (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].



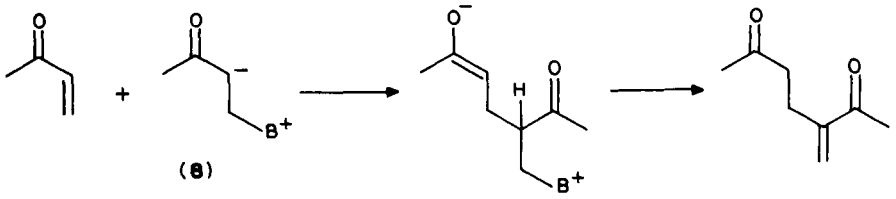
(**43**)

(32)

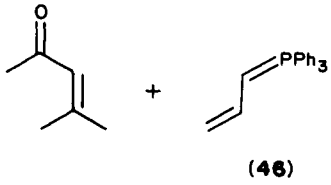

OBu'
MeO2C
H
H
H
O
(44)
OBu'
MeO2C
H
H
H
H
O
H

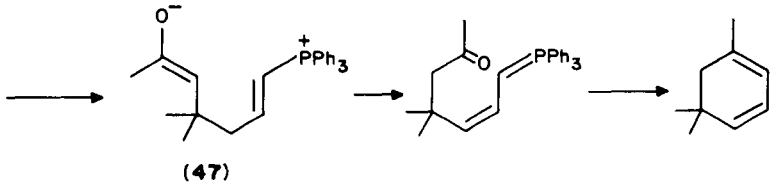

OBu'
MeO2C
H
H
H
H
O
H
(45)

(33)

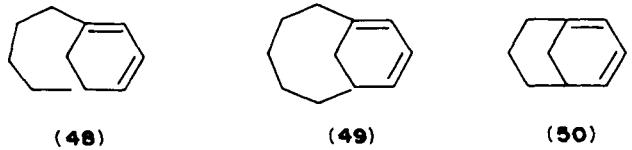

O
O
O
B+
(8)
O
H
O
B+
O
O

(34)

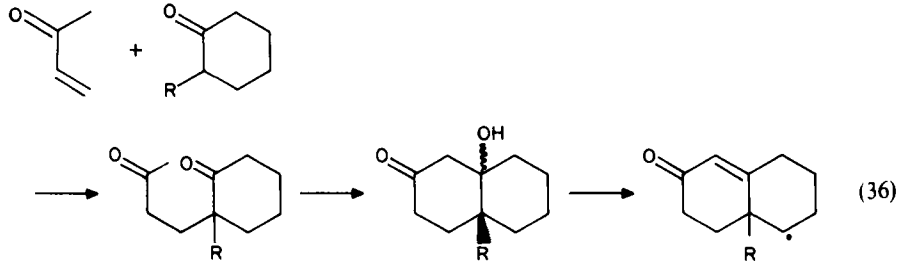

O
PPh3
(46)


O
PPh3
(47)
O
PPh3

(35)

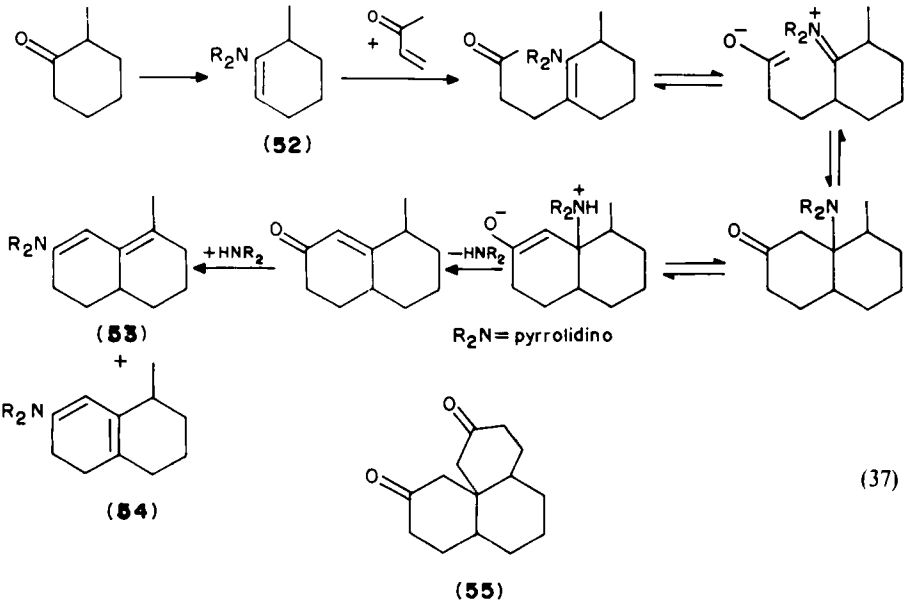

(48)
(49)
(50)

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)

(51)



(37)

(52)

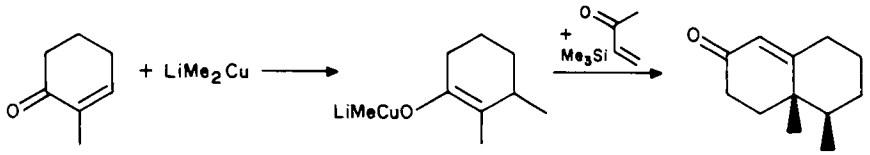
(53)

(54)

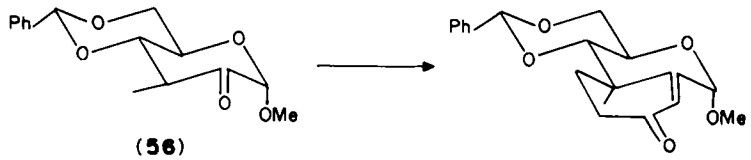
(55)

R_2N = pyrrolidino

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].

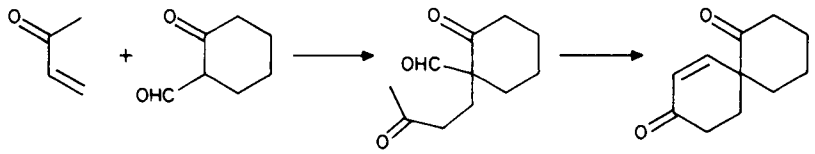


(38)



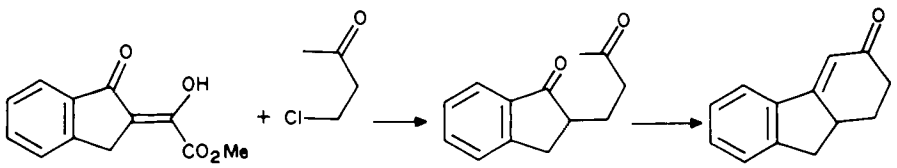
(**56**)

When 2-formylcycloalkanones are the donors in the Robinson reaction spiro-compounds result (equation 39)[53].



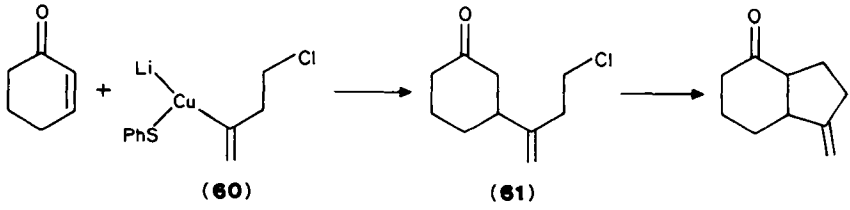
(39)

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].

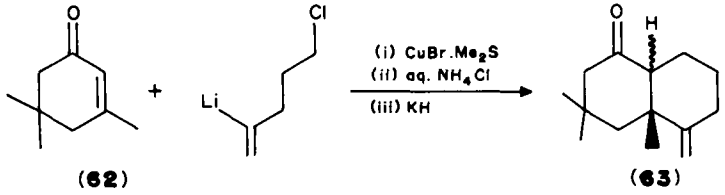


(**57**) (**58**) (**59**)

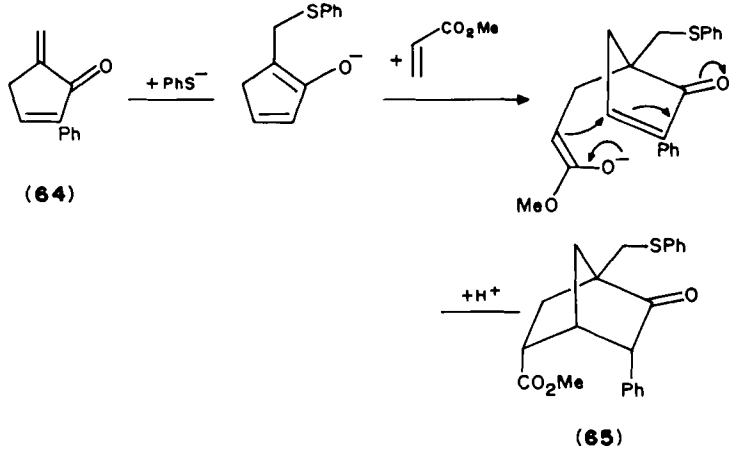
(40)



(41)



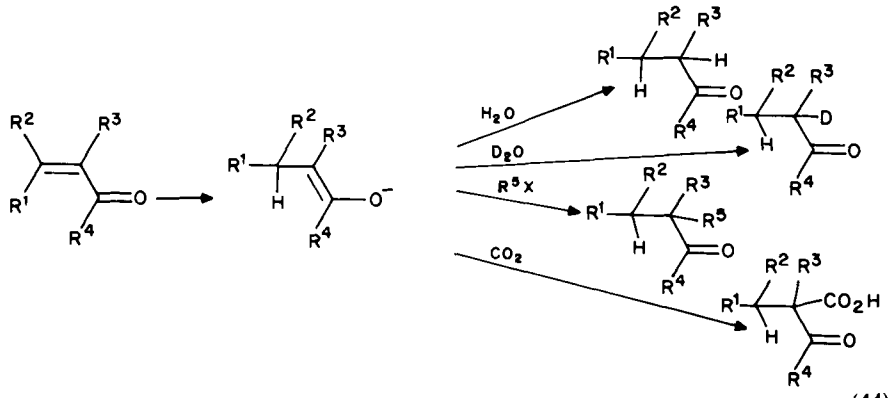
(42)



(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].



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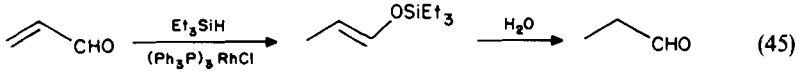
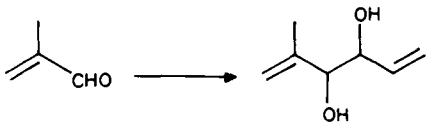


(45)

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].



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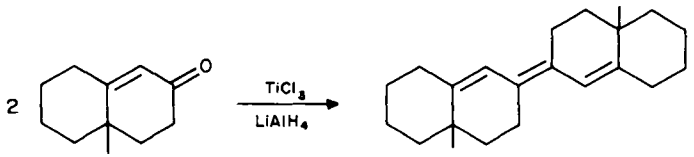
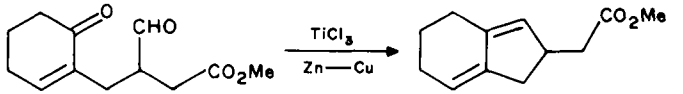


(47)

(**66**)



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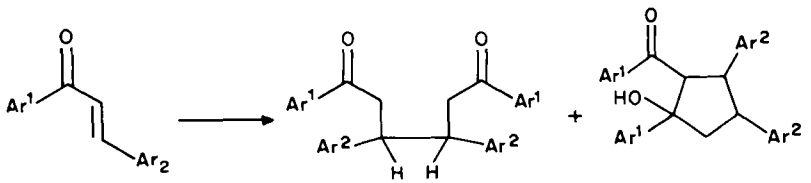
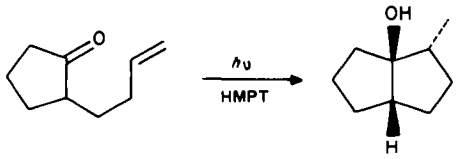
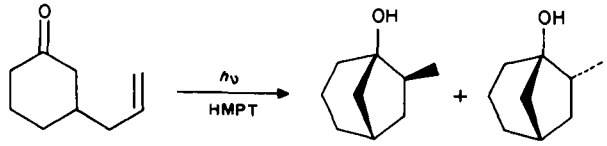


(49)



(50)

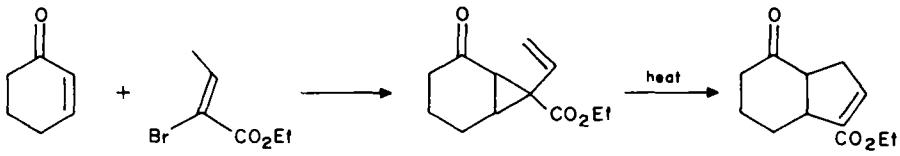


(51)

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].



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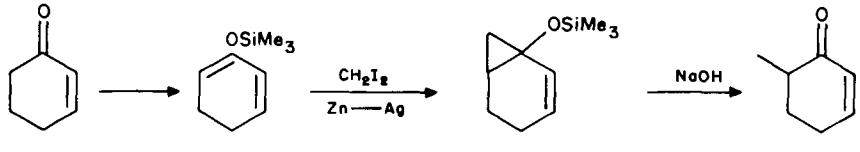
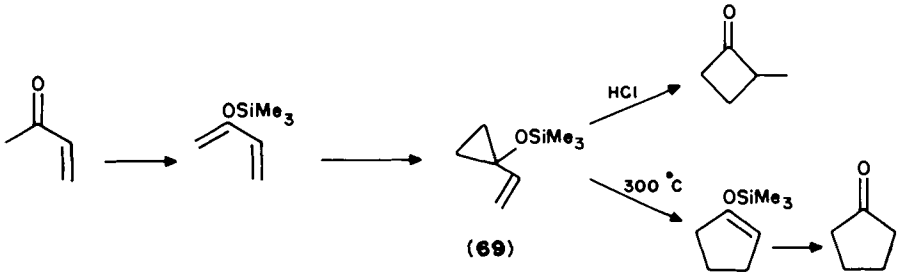


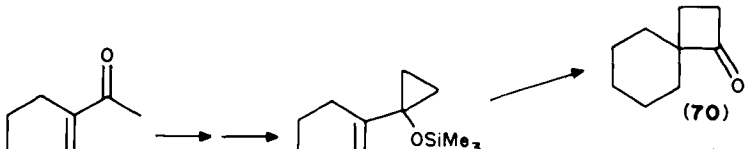
(68)

(53)



(69)

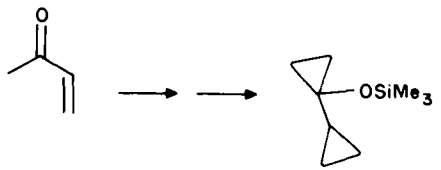
(54)



(70)

(71)

(55)



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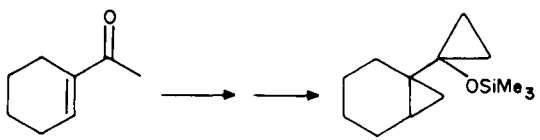

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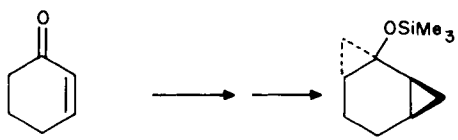
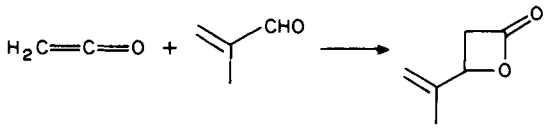


(58)

B. Formation of Four-membered Rings

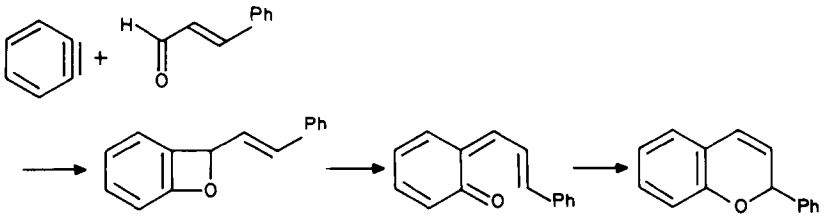
The boron trifluoride-catalysed reaction of ketene with methacrolein leads to the β-lactone **72** by addition to the carbonyl group of the aldehyde (equation 59)[76]; similarly, benzyne and cinnamaldehyde form the cyclic ether **73**, which rearranges to the benzopyran

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].



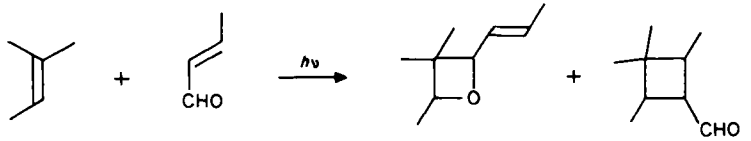
(59)

(72)



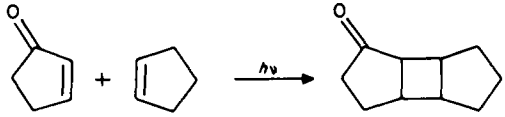
(60)

(73) (74)



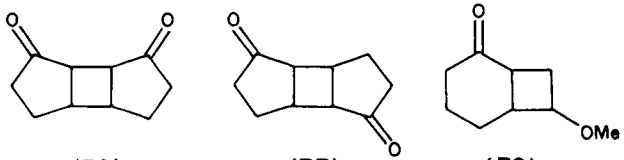
(61)

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].



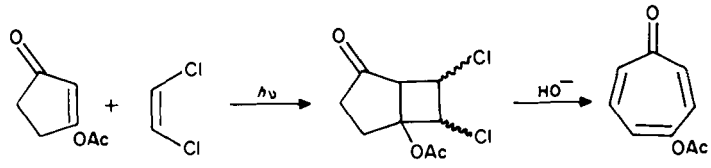
(62)

(75)

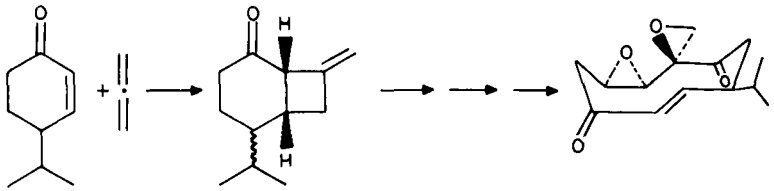


(76) (77) (78)

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].



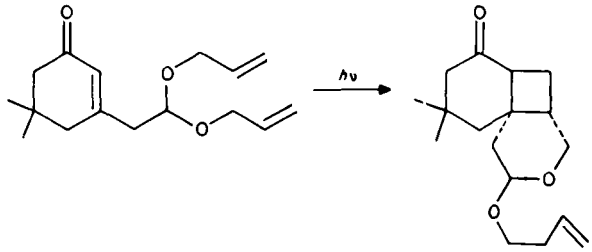
(63)



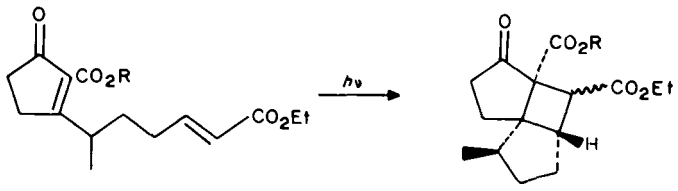
(64)

(**79**) (**80**)

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)



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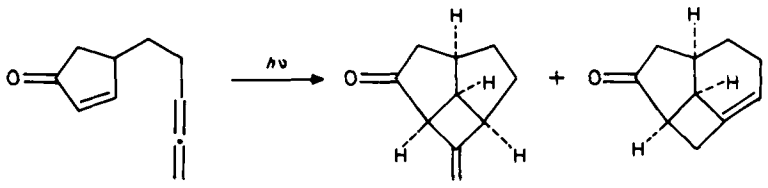

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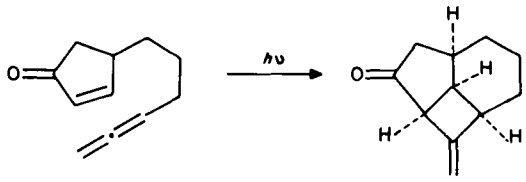

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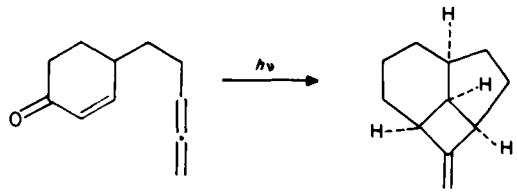

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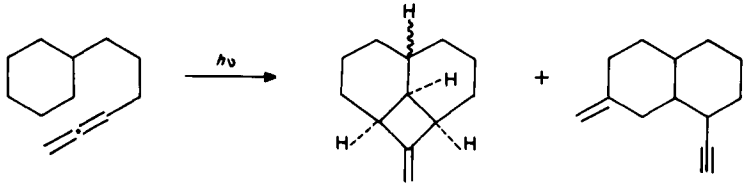

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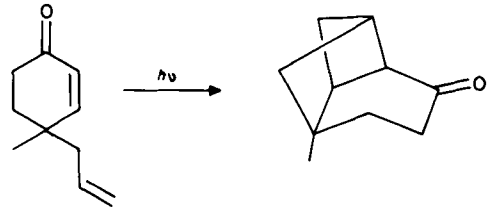

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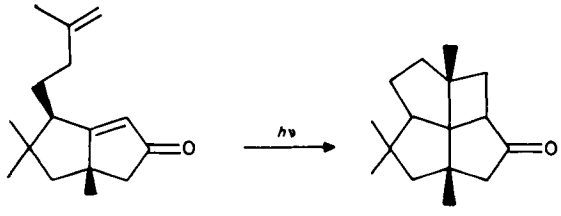

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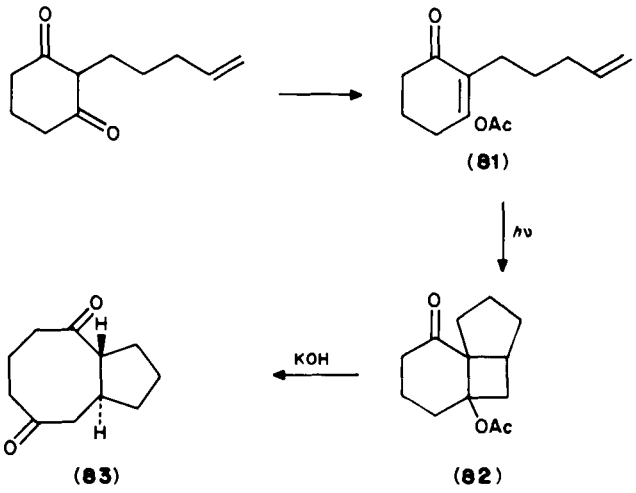
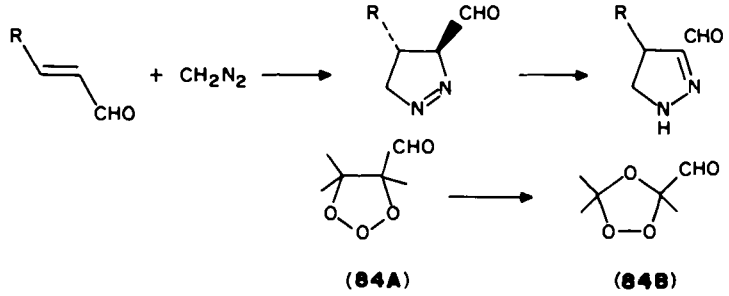


(73)

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)

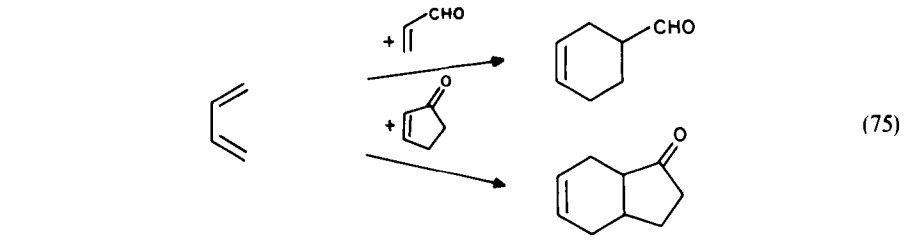
D. Formation of Six-membered Rings

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].



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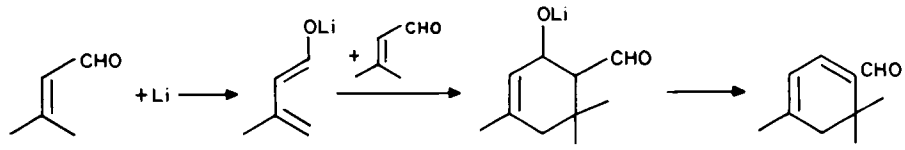
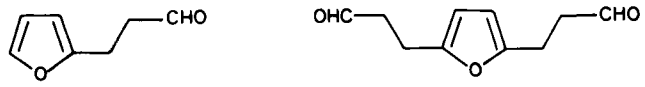
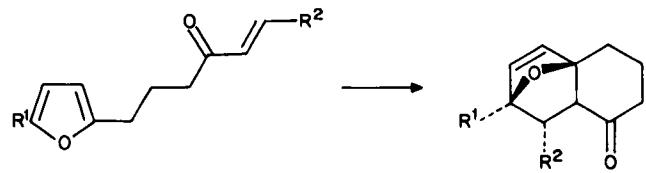


(85)

(76)

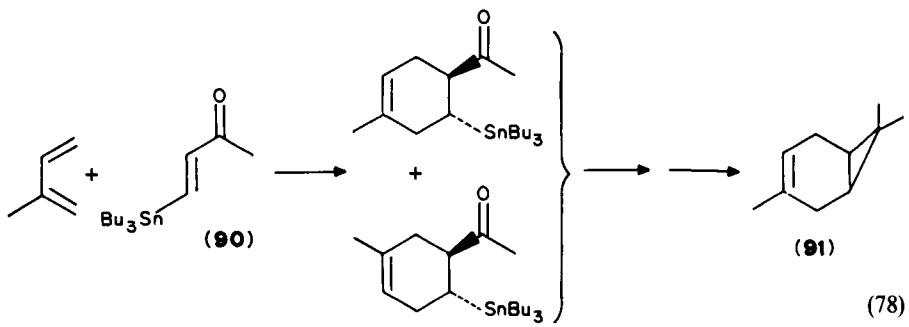


(86) (87)



(77)

(88) (89)



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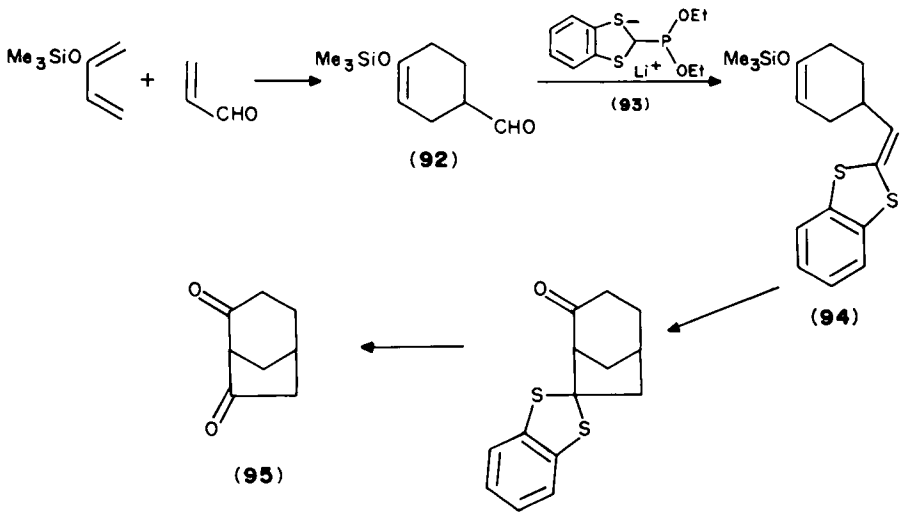
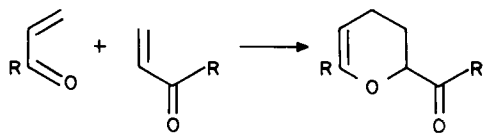


(79)

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].



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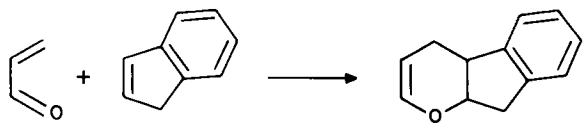

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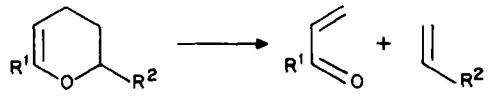

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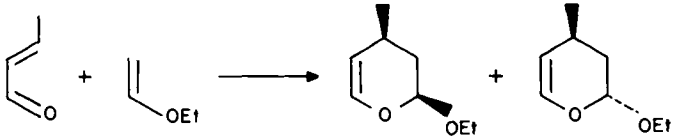
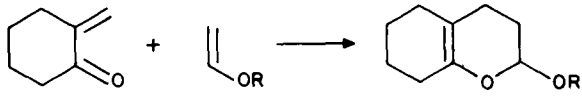


(83)



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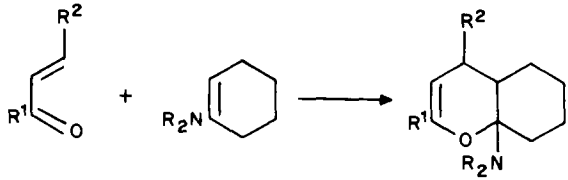

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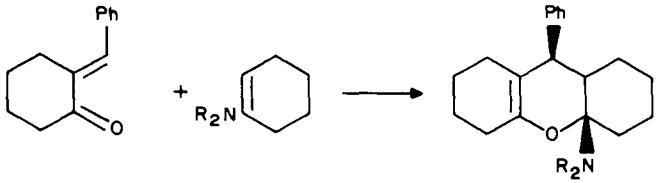

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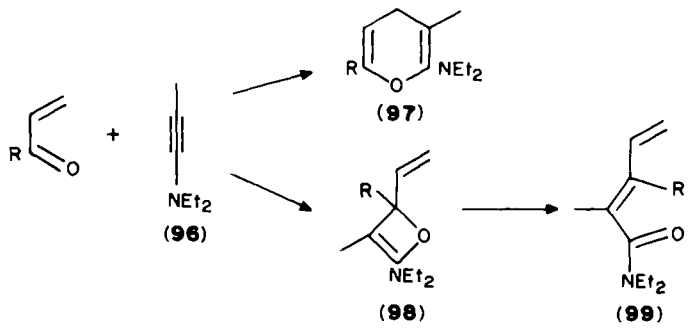

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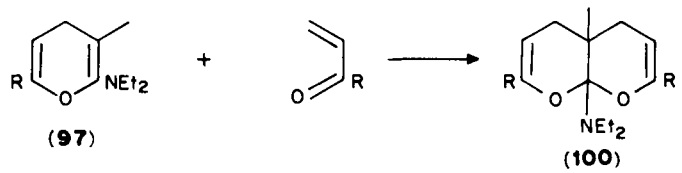
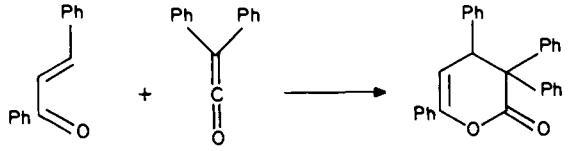
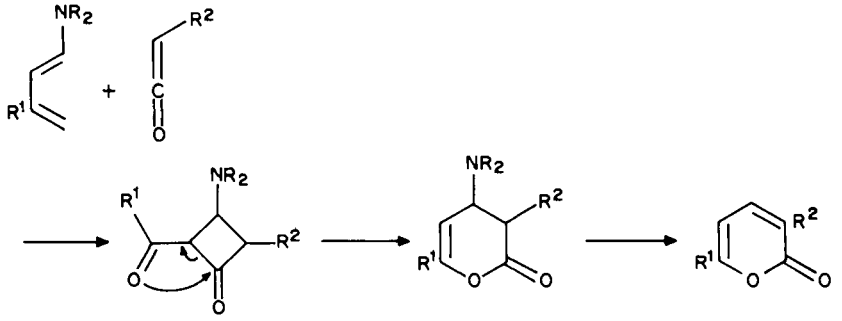


(97) (100) (89)

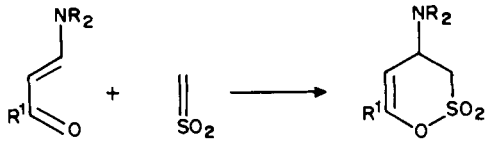
The addition of ketenes to enones was discovered by Staudinger in 1913 (equation 90)[106]. Enaminoketones are particularly reactive towards ketenes[107]. The formation of the adducts is thought to proceed by way of the cyclobutanones **101**; the products often eliminate dialkylamine to produce α-pyrones **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)

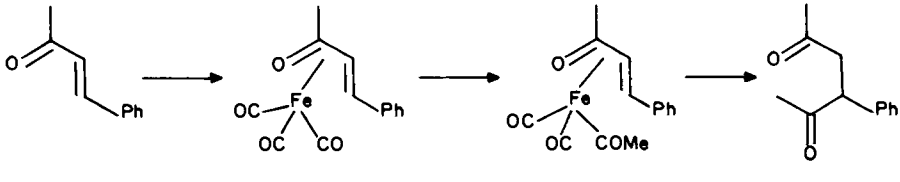


(103) (92)

V. MISCELLANEOUS REACTIONS

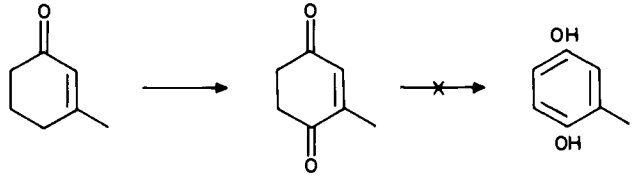
α,β-Unsaturated ketones form iron tricarbonyl complexes, e.g. **104** from benzylideneacetone and diiron enneacarbonyl[109], which reacts with methylmagnesium bromide to yield the 1,4-diketone **106**, possibly via the intermediate **105** (equation 93)[110]. 3-Methylcyclohex-2-enone is oxidised by 2,3,5-triphenyltetrazolium chloride to the cyclo-

hexenedione **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].



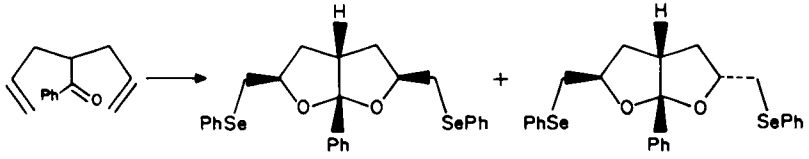
(104) **(105)** **(108)**

(93)

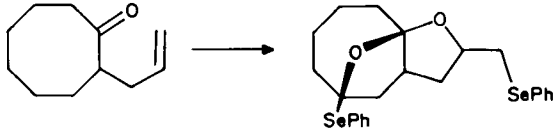


(107) **(108)**

(94)



(95)



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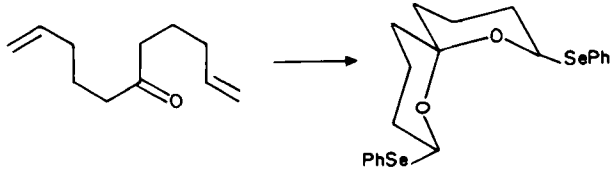

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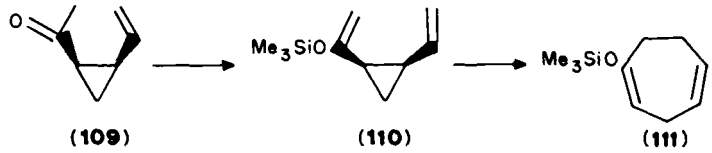


(109) (110) (111) (98)

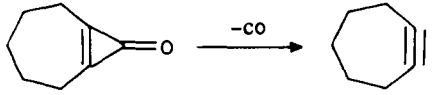
VI. SYNTHESES WITH SMALL-RING ENONES

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.

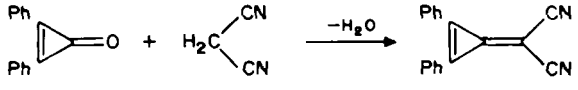
(112) (112A)

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].

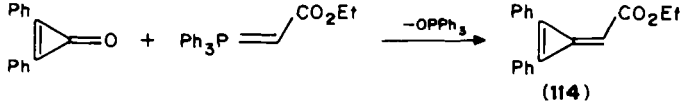


(99)

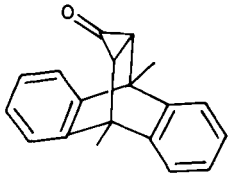
Only a few reactions of cyclopropenone are known in which the cyclopropene structure is preserved: diphenylcyclopropenone condenses with malononitrile under the influence of acetic anhydride to yield the methylenecyclopropene **113** (equation 100)[116] and its Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane affords compound **114** (equation 101)[117].



(113) (100)

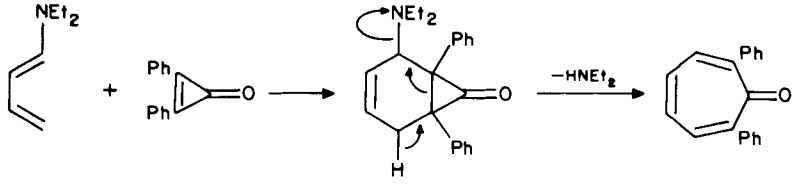


(114) (101)

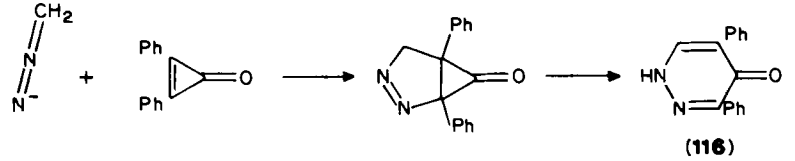


(115)

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].

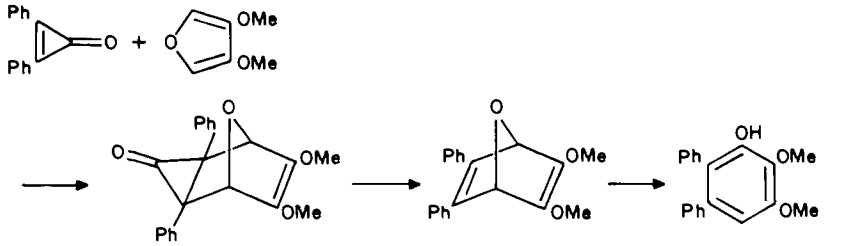


(102)

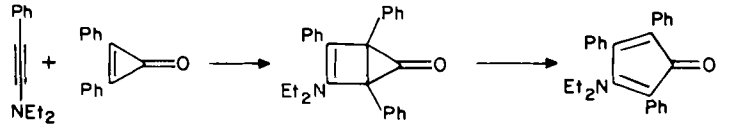


(103)

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].

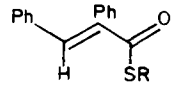


(104)

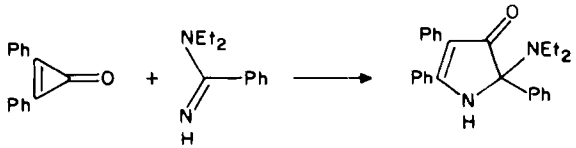


(105)

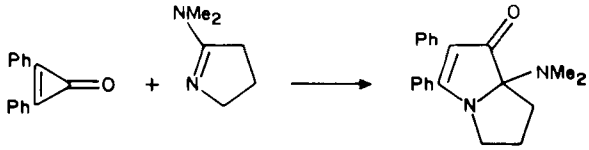
The action of nucleophilic reagents on diphenylcyclopropenone usually leads to products in which the unit —CPh=CPh—CO— has been inserted. Thus aliphatic and aromatic thiols RSH afford the thioesters **119**[123] and amidines yield pyrrolinones (equations 106[124] and 107[125]).



(119)

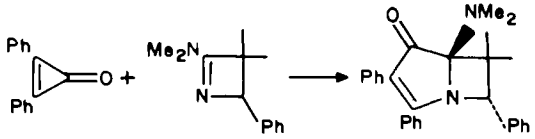


(106)



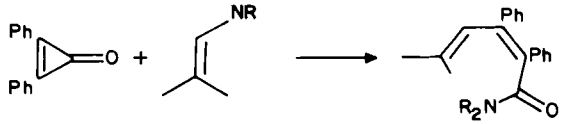
(107)

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].



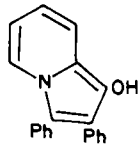
(108)

(120)

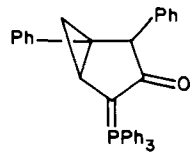


(109)

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)



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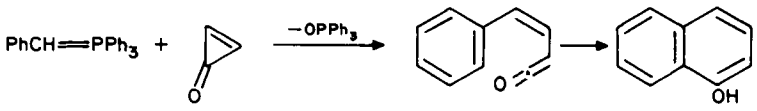
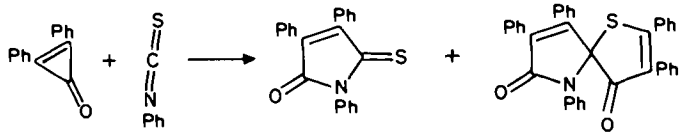


(110)

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].

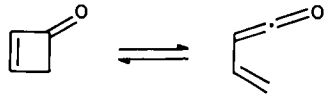


(111)

(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].



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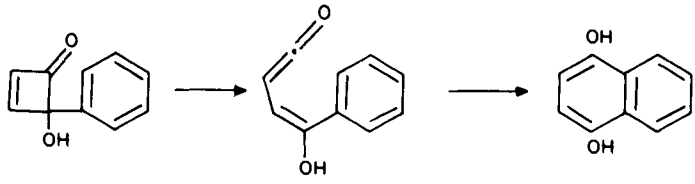

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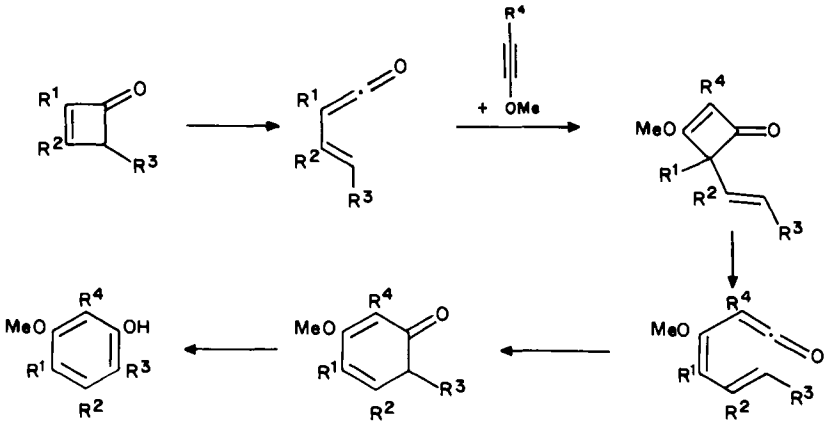

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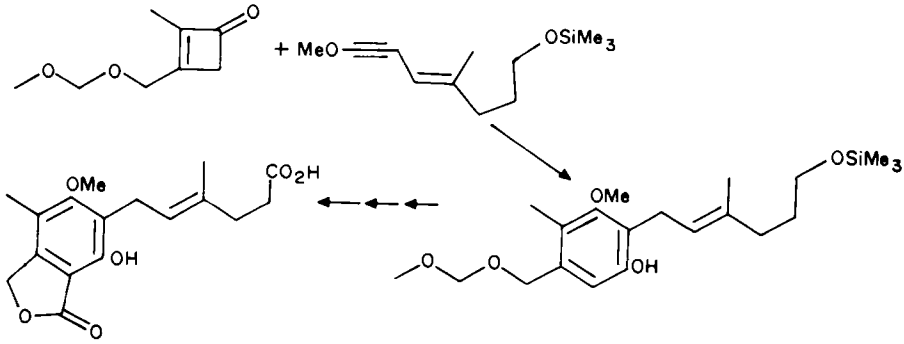
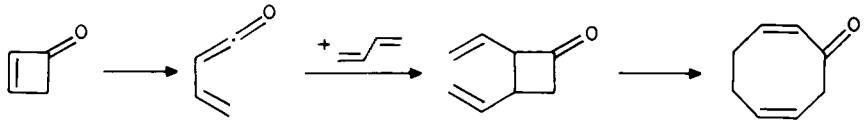


(125)

(115)



(116)

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CHAPTER 9

Acid–base behaviour of enones

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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].

$$H_0 = -\log c_{H^+} - \log(\bar{f}_B f_{H^+}/f_{BH^+}) \tag{5}$$

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.

$$\log K/K_0 = (1 - \phi)(H_0 + \log c_{H^+}) \tag{6}$$

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].

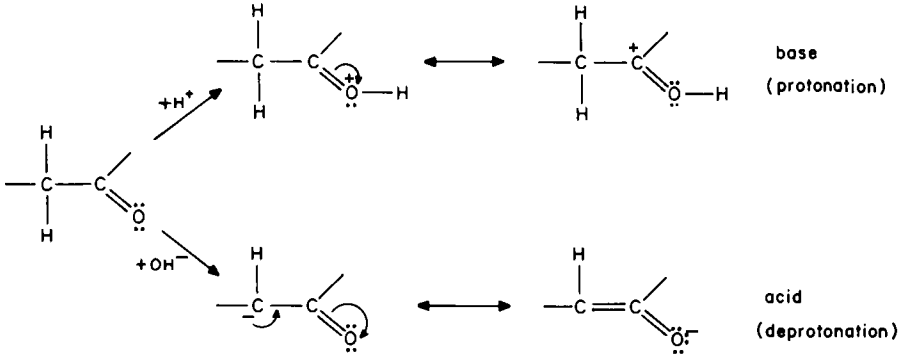
$$AH + OH^- \rightleftharpoons A^- + H_2O \tag{7}$$

$$H_- = -\log a_{H^+}\frac{f_{A^-}}{f_{AH}} = -\log\frac{K_w a_{H_2O}}{a_{OH^-}}\cdot\frac{f_{A^-}}{f_{AH}} \tag{8}$$

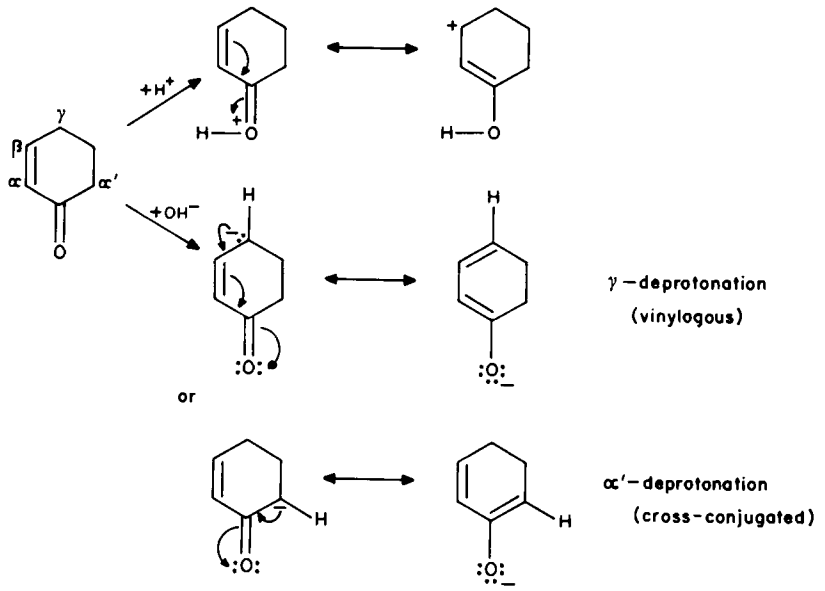
II. KETONES AS WEAK ACIDS AND BASES

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 $pK_{BH^+} = H_0$. 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.

$$pK_{BH^+} = H_0 - \log(C_B/C_{BH^+}) = H_0 - \log Q \tag{9}$$

pK_{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 pK_{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.

$$\log K = (1 - \phi)(H_0 + \log C_{H^+}) + \log K_0 \tag{10}$$

Substitution for K yields equation 11 or 12:

$$\log \frac{C_{H^+} C_B}{C_{BH^+}} = (1 - \phi)(H_0 + \log C_{H^+}) + \log K_0 \tag{11}$$

$$-\log C_{H^+} + \log \frac{C_{BH^+}}{C_B} = (1 - \phi)(H_0 + \log C_{H^+}) + pK_0 \tag{12}$$

and after rearranging:

$$H_0 + \log \frac{C_{BH^+}}{C_B} = \phi(H_0 + \log C_{H^+}) + pK_0 \tag{13}$$

The value of pK_0 (or pK_{BH^+}) can be found as the intercept of the plot of $[H_0 + \log(C_{BH^+}/C_B)]$ vs. $(H_0 + \log C_{H^+})$, 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:

$$-\log C_{H^+} + \log \frac{C_{BH^+}}{C_B} = m^* X + pK_{BH^+} \tag{14}$$

where pK_{BH^+} is the intercept of the plot of $[\log(C_{BH^+}/C_B) - \log C_{H^+}]$ 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 (pK_{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

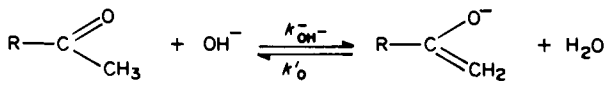
Besides the above-described two strategies, thermodynamic properties of ketones in alkaline media may be evaluated from kinetic measurements. The relations between ketone, enol and enolate are presented in Scheme 3. In general, the equilibrium between a ketone and its corresponding enol is usually shifted 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:



(16)

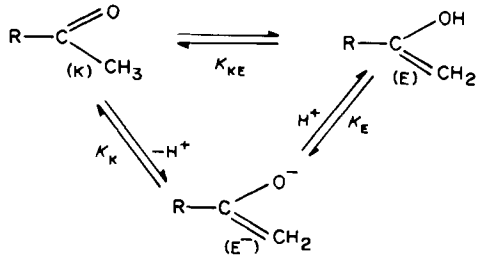
for which

$$k'_0/k^0_{OH^-} = K_w/(K_{KE}K_E) \tag{17}$$

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

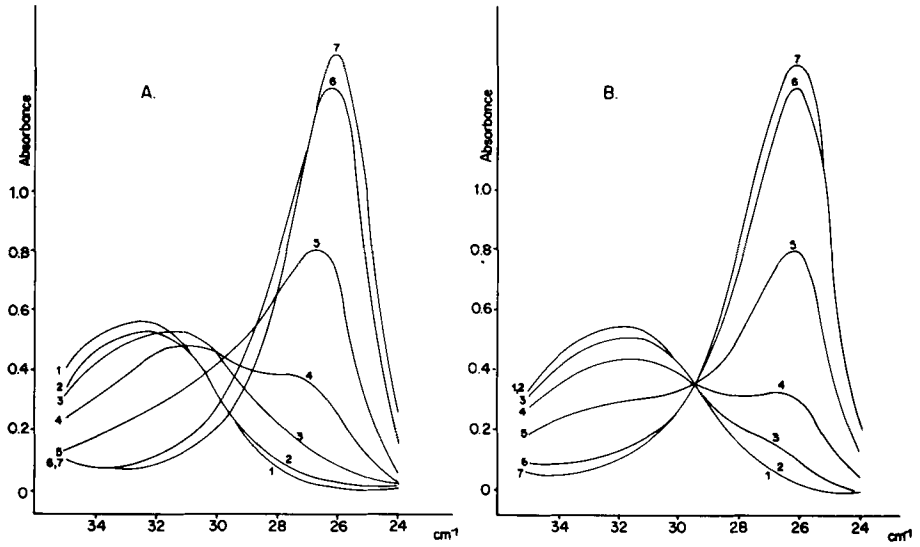


FIGURE 1. Experimental (A) and re-calculated (B) family of UV spectra of α-ionone in sulphuric acid: (1) 19.19%, (2) 29.08%, (3) 38.73%, (4) 45.13%, (5) 53.00%, (6) 64.58%, (7) 75.94%.

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

$$I = C_{BH^+}/C_B = \frac{A - A_B}{A_{BH^+} - A} \tag{19}$$

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.

$$A_{n,p} = C_{1,p}L_{n,1} + C_{2,p}L_{n,2} + \varepsilon \tag{20}$$

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, ^{1}H NMR was used with success to obtain fairly good pK 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 ^{1}H NMR measurement of ketone basicity are the following: relatively low sensitivity (± 0.2 pK 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 pK determinations are the advantages of ^{1}H 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 ^{1}H 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].

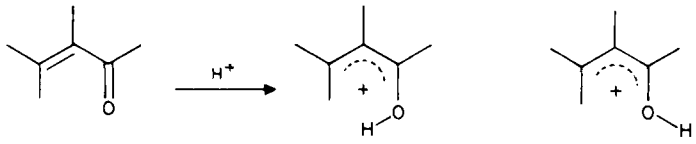
The titration curves resulting from ^{1}H or ^{13}C NMR may be used to estimate rough values of acidity functions at half-protonation (at the inflection point). Accurate pK_{BH^+} calculations require computation of the ionization ratio I from the standard equation:

$$I = C_{BH^+}/C_B = (\Delta\nu - \Delta\nu_B)/(\Delta\nu_{BH^+} - \Delta\nu) \tag{21}$$

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. ^{1}H 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.



syn *anti*

^{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:

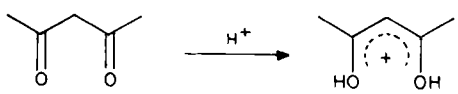
syn *anti*

-12.3 ppm -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 ^1H 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 ΔH° for various classes of carbonyl compounds (N-ammoniobenzamidates[96], unsaturated ketones[97,98]) depends linearly on pK_{BH^+} and follows an extrathermodynamic relationship. The ΔH° 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]:

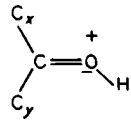
$$A^- + BH \rightleftharpoons B^- + AH$$

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 $\delta\Delta G^\circ_{acid} = -RT \ln K$ from which, by incorporating some standard reactions in the relative scale of acidity, one can establish an absolute basicity scale. Larger values of $\delta\Delta G^\circ_{acid}$ 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.

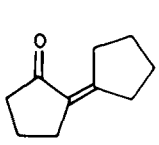
Data on basicity of unsubstituted cyclic enones of other ring sizes are not available in the literature. The accessible data on mono- and disubstituted alkyl or phenyl cyclopropenones[103–106] were derived from NMR data and the H_0 acidity function and have the status of 'half-protonation' values. Assuming 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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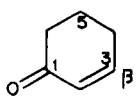
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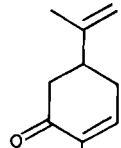
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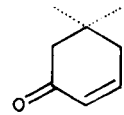
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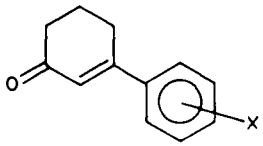
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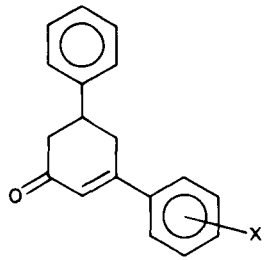
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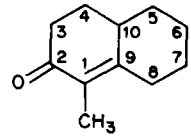
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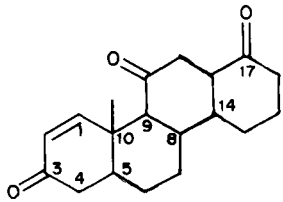
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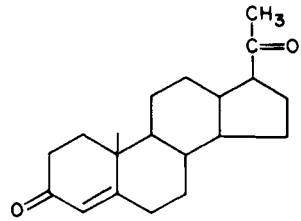
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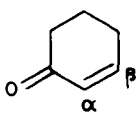
CHART 1

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.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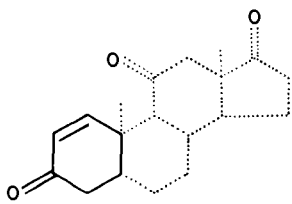
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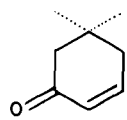
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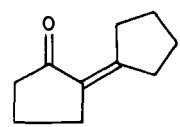
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TABLE 1. A. Basicity data for monocyclic enones in sulphuric acid

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'_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		Ref.	$HClO_4$ (Ref. 107)	
		pK_{BH^+}	Slope[a]		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.

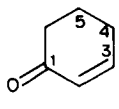
b. Long-range structural effects. This term will comprise, within this work, all structural elements and substituents more or less remote from the enone moiety. By this definition only α and β carbons are excluded from such a description. In other words, long-range effects do not need a through-the-bonds 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.

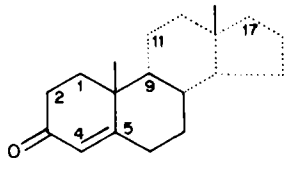
It is obvious from data in Table 2 that remote alkyl groups and aromatic rings do not affect the basicity of the carbonyl group; nor do substituents in a steroid molecule beyond C_{11}. Presence of a C=O group or a fluorine atom decreases basicity of the enone in some way which is dependent on distance. 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**)



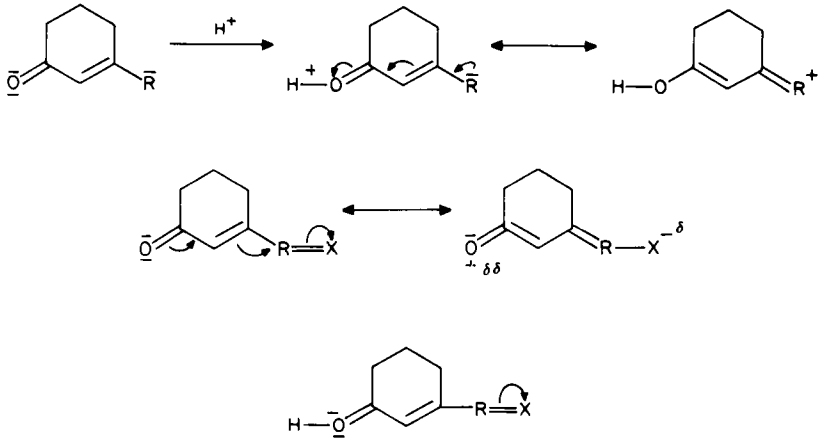
(**B**)

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 pK_{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.

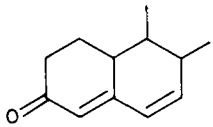
d. β-Substituent effects. The number of various β-substituents in the enones studied is relatively large. Enones substituted by methyl groups in the β-position (e.g. **8,13,14,29**) are stronger than the unsubstituted ones by 0.75 pK_{BH^+} unit. A β-methylene group (or chain) has the same base-strengthening effects, which is seen in numerous bicyclic compounds and steroids (e.g. **53,57,58,59,60**), the pK_{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 pK_{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 pK_{BH^+} unit respectively than the parent compound.

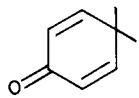


Halogens (**21**, **22**) are moderate base-weakening substituents. Separation of a strong base-weakening substituent from the β-carbon by a methylene group (**23**-CH_2CN, **24**-$CH_2COOC_2H_5$) reduces its influence dramatically.

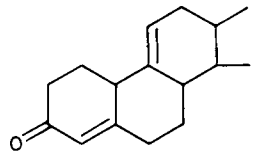
A second conjugated olefinic bond in the molecule will yield a dienone structure. pK_{BH^+} values were reported[109] for three different dienone moieties:



$pK = -2.40$



$pK = -2.80$

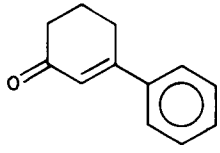


$pK = -2.82$

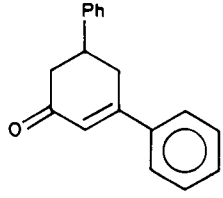
(**80**)

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

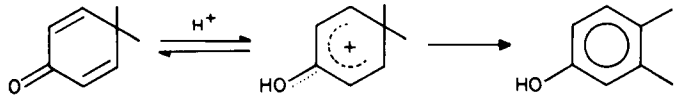
Derivatives of cyclohexa-2, 5-dienone including two and more fused rings (e.g. steroids) form a very interesting class of compounds which undergo dienone-phenol rearrangement in acidic media[117]. This reaction has great practical importance in the synthesis of phenolic steroids and other natural products.

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].

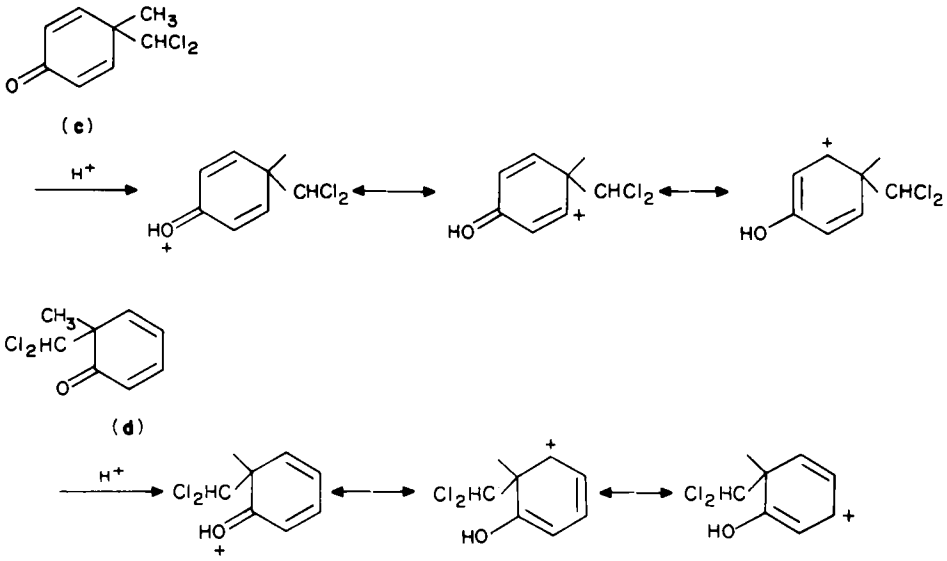
The cross-conjugated dienone (**104**) protonates to its monocation having the carbonyl

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.



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:

$$pK_{BH^+} = -2.80 + \sum \Delta pK_{BH^+} \tag{24}$$

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

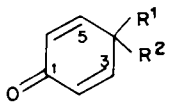
$$pK_{BH^+} = -2.66 \pm 0.12 - 2.32 \sum \sigma^+_{m,p} \tag{25}$$

Statistically calculated $pK^{\circ}_{BH^+}$ values in equations 24 and 25 are in close agreement, within experimental error.

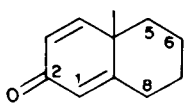
TABLE 3. Basicity data of cross-conjugated dienones

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)



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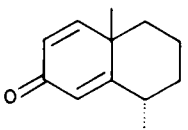
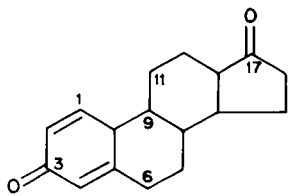


(113)



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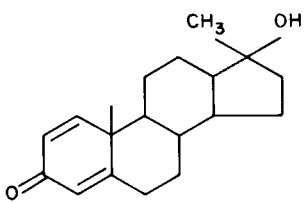

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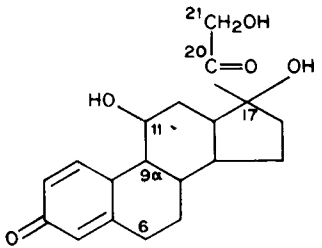

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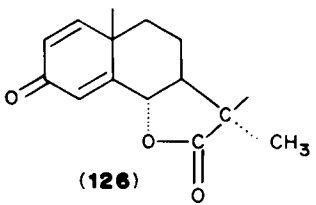
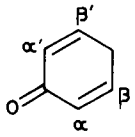


(126)

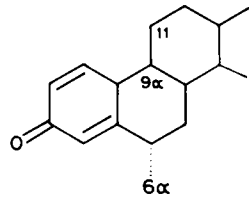
CHART 2

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



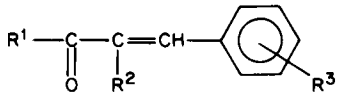
(A)



(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



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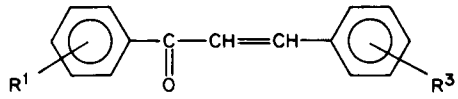

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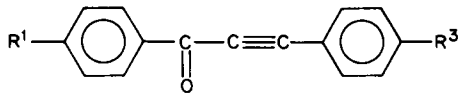
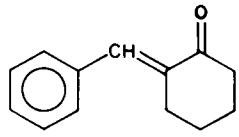


(244–256)



(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 $\mathcal{F}$, $\mathcal{R}$ 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

No.	Substituents R¹	R²	R³	Basicity $-pK_{BH^+}$	Slope	$-H_{A(1/2)}$	Ref.	Relative basicity $\Delta\nu_{OH}$	Ref.	Acidity pK_a	Ref.
Alkyl styryl ketones											
201	Me	H	H	4.83 ± 0.08	1.00 ± 0.05	3.33	133	—		21.09	135
										21.65	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	—	
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_2Ph	H	5.28 ± 0.02			138			
231	*o*-OCH_2Ph	*p*-OH	4.25 ± 0.02			138			
232	*o*-OCH_2Ph	*p*-OMe	4.46 ± 0.02			138			
233	*o*-OCH_2Ph	*p*-NMe_2	5.55 ± 0.02			138			
234	*o*-OCH_2Ph	*p*-F	5.51 ± 0.02			138			
235	*o*-OCH_2Ph	*p*-Cl	5.45 ± 0.02			138			
236	*o*-OCH_2Ph	*p*-Br	5.30 ± 0.02			138			
237	*o*-OCH_2Ph	*p*-COOH	5.75 ± 0.03			138			
238	*o*-OCH_2Ph	*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_6H_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 pK_{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 pK_{BH^+} unit, and its basicity is comparable to acetophenone ($pK_{BH^+} = -6.15$[9a] or -6.26[142] in terms of the H_0 acidity function). The experimental $pK^{\circ}_{BH^+}$ value (-6.51) is in very good agreement with that calculated from Hammett equations:

$$pK_{BH^+} = -6.47 - 2.40\sigma \qquad (r = 0.993) \qquad \text{for various } R^1 \tag{29}$$

$$pK_{BH^+} = -6.48 - 1.69\sigma \qquad (r = 0.995) \qquad \text{for various } R^3 \tag{30}$$

or

$$pK_{BH^+} = 6.473 \pm 0.013 - (2.39 \pm 0.07)\sigma_{R^1} - (1.69 \pm 0.07)\sigma_{R^3} \quad (r = 0.997) \tag{31}$$

The effect of substituents on pK_{BH^+} is additive, as shown by the two-parameter equation 31, where the terms agree with those of equations 29 and 30.

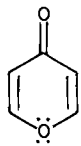
The transmission of the electronic effect of the R^1 substituent is approximately 1.4 times more effective than that of R^3 ($\rho_1/\rho_3 = 2.40/1.69 = 1.42$), and more than reported by Stewart and Yates ($\rho = -2.12$)[9a]. This might be explained by a more effective orbital overlapping between the 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.

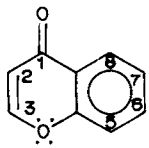
In contrast to the relatively wide interest in the basic properties of alkyl styryl ketones and chalcones, studies of their acidity are very rare[136,137]. Only very few data are available on the acidities of methyl styryl ketones. They are weak acids, as expected. Aromatic ring substituents affect acidity according to their electron accepting or donating ability; however, the relationship between pK_a and σ is not very good. The experimental data are most probably not very precise and accurate.

D. Pyrone Derivatives

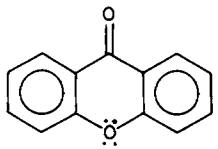
a. γ-Pyrone is a simple compound having a cross-conjugated dienone structure with heterocyclic oxygen (**301**). The heteroatom can be replaced by other atoms such as sulphur or selenium, and the ring may be fused with an aromatic ring to produce chromone (**302**) or



(**301**)

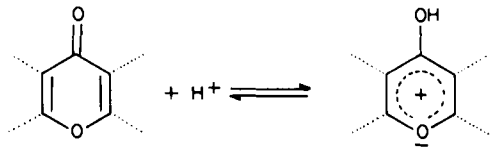


(**302**)



(**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	143
						−2.02 ± 0.02	144,53
303 (Chromones)	H	Ph	H	H	H	−1.46 ± 0.01	144
						−1.53	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	143
						−3.24[b]	43
333 Thioxanthone						−3.95	143
334 Selenoxanthone						−4.36	143
335 Tetralone						−5.40	114

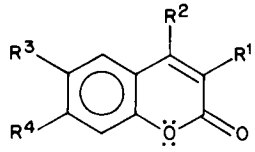
[a] pK_{BH^+} in H_0 units.
[b] pK_{BH^+} in X_0 units (excess acidity).

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	$\overset{+}{N}H_3$	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:

$$pK_{BH^+} = -5.87 - 1.86\sigma_p \tag{32}$$

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]:

$$pK_{BH^+} = -6.77 - 2.809\sigma^+_{R^4} - 1.575\sigma^+_{R^2} \qquad (r = 0.969,\ n = 10) \tag{33}$$

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 (methyl styryl ketone)	−3.33[g]	

[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.

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The Chemistry of Enones
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CHAPTER **10**

Nucleophilic attacks on enones

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*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

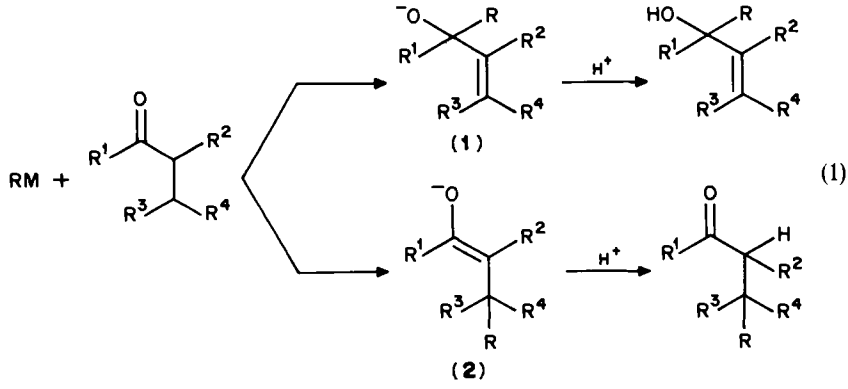
The most frequently met nucleophilic attack, and the synthetically most useful, on α,β-unsaturated aldehydes (enals) and ketones (enones) or quinones, is the addition of organometallic compounds in the widest sense, in which a new carbon–carbon bond is formed.

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.

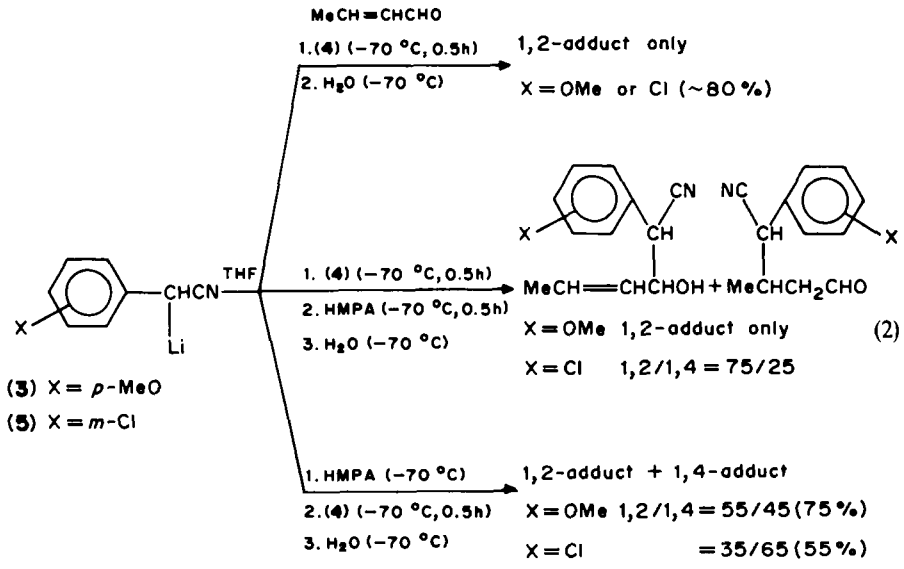
For each class of 'organometallic reagents', we collected typical examples from the large variety of experimental and theoretical results described in the literature in the last 10–15 years and discussed them from the standpoint of the influence of the above factors on the mode of addition.

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).



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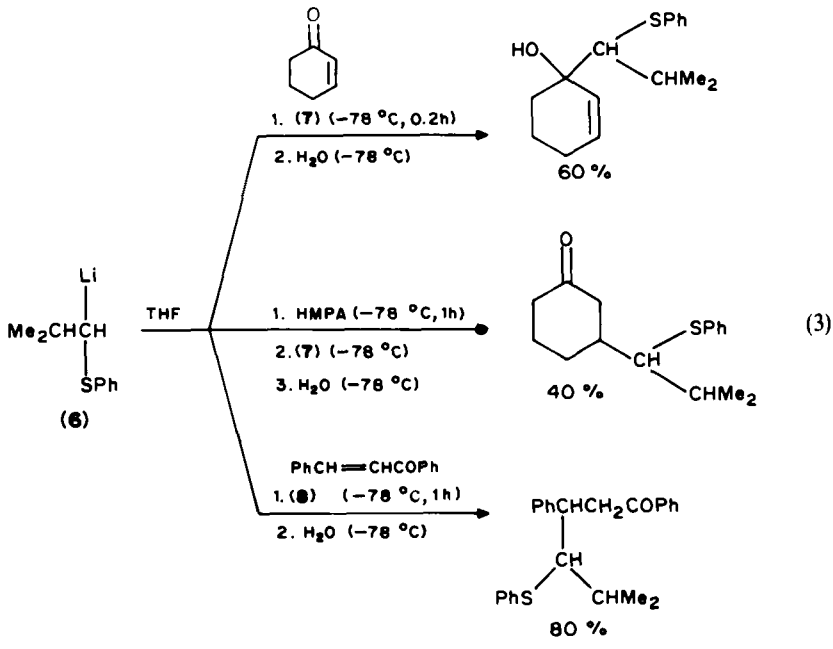


(3)

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) ($H^2_{LU,HO}$) 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.

$R\bar{C}XY$ (**9**) $Ph\bar{C}XY$ (**10**) $X\bar{C}HCO_2R'$ (**11**) $(EtO)_2PO\bar{C}RX$ (**12**)

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 $C_{(1\,3)}$ 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.

$(EtO)_2POCH_2CO_2Et$ (**13**) $(EtO)_2POCH_2CN$ (**14**) Ph_2POCH_2CN (**15**)

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*-$MeOC_6H_4$)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]

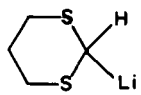
Anion	Geometry[a]	$q_c^{tot\,a}$	E_{HO}(eV)[a]	$C_c^{2p\,a}$	$C_c^{2s\,a}$	$C_{(1)}$ attack	$C_{(3)}$ attack
$[CH_2CN]^-$	pyramidal	−0.398	2.50	0.801	0.403	⩾95	5
	planar	−0.391	2.94	0.823	—		
$[ClCHCN]^-$	pyramidal	−0.240	0.95	0.753	0.471	⩾95	5
	planar	−0.252	1.69	0.814	—		
$[PhCHCN]^-$	planar	−0.251	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 ($\sigma + \pi$) 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].



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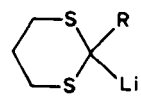


R = Me, $SiMe_3$, Ph

(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

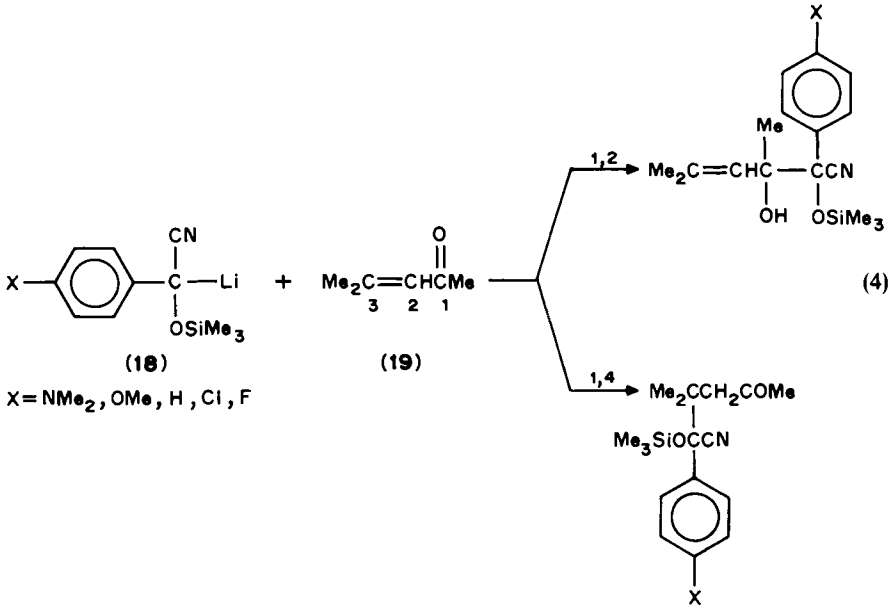
TABLE 4. Addition of 2-lithio-1,3-dithianes to 2-cyclohexenone in various media

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.

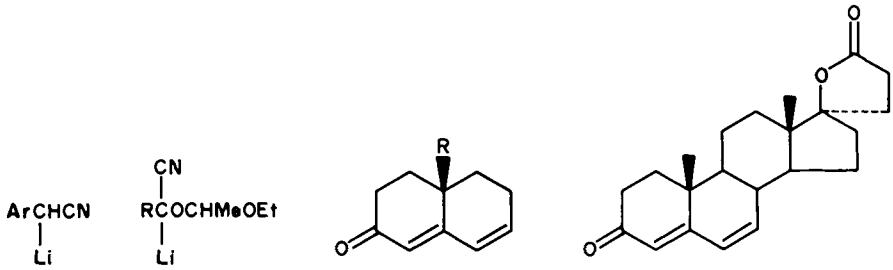
The influence of solvation is strikingly manifested in the reactions between the trimethylsilyl ethers of *para*-substituted benzaldehyde cyanohydrins **18** and mesityl oxide (**19**)[36–38] (equation 4).



(4)

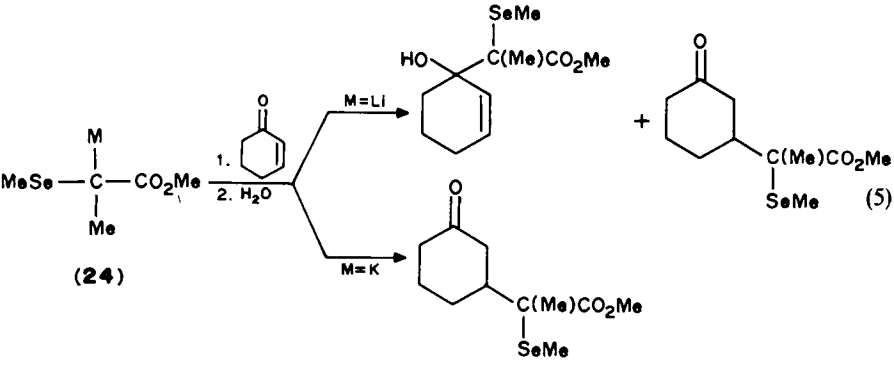
Regioselectivity depends upon the nature of the *para*-substituent and consequently upon the 'hardness' of nucleophiles in a given solvent; it also depends on the solvent. For instance, with **18** (X = H), under conditions of kinetic control a mixture of products of addition to $C_{(1)}$ and $C_{(3)}$ 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].



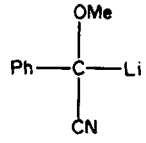
(20) Ar = Ph or *p*-$MeOC_6H_4$ **(21)** R = Ph or CH=CHMe **(22)** R = H or Me **(23)**

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).



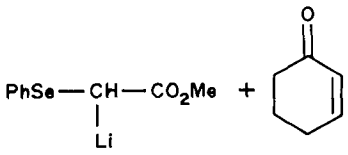
(5)

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].



(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].



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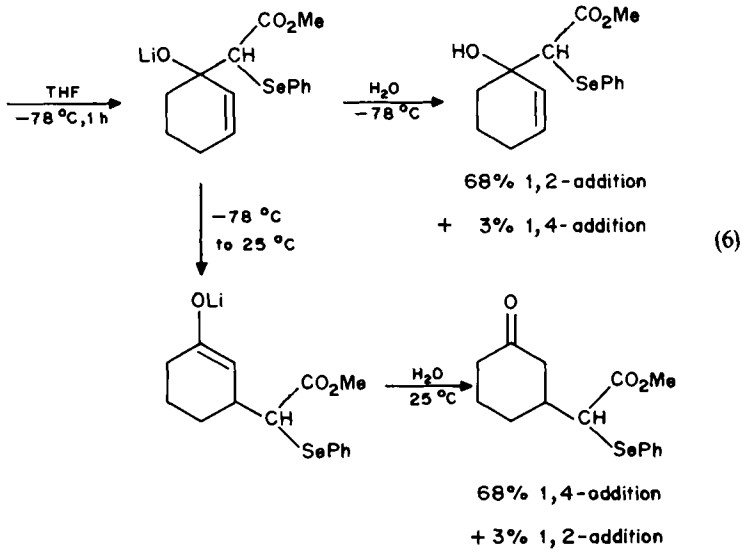


(6)

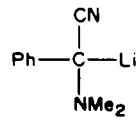
This equilibration, due to the reversibility of the 1,2-adduct formation, is observed with carbanions quite well stabilized and/or delocalized (high HOMO) and can formally occur

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].

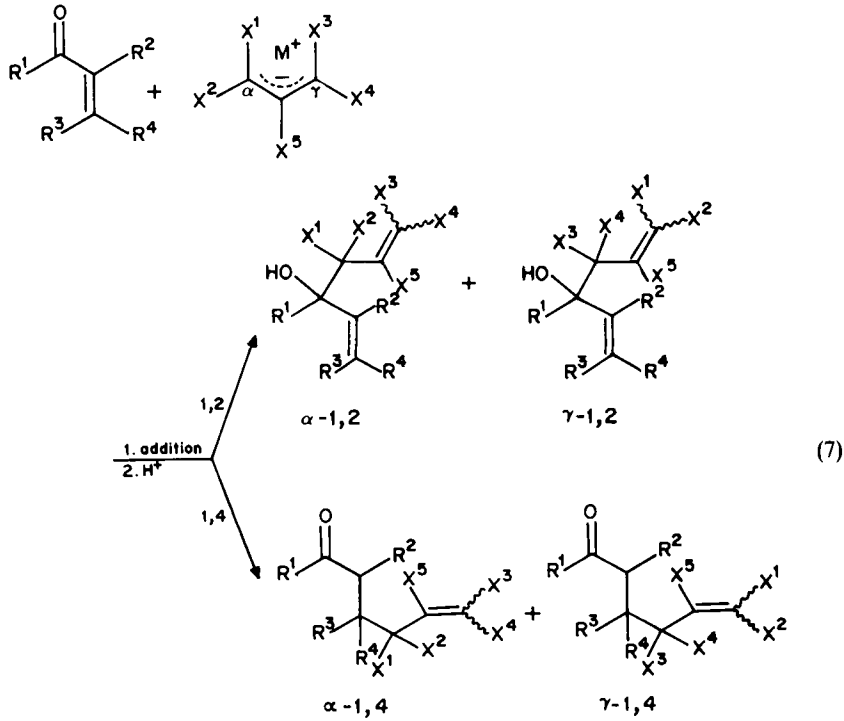
Because the carbonyl-counterion complexation effect can in principle participate in the mode of addition of organoalkali reagents to enones and enals[35], Lewis acids can be used when the nucleophilic additions are very sensitive to the degree of substitution of electrophiles. The changes in the yields 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].



(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

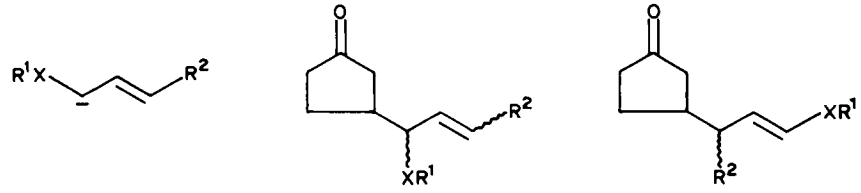
1,2- versus 1,4-reactivity, but also raise the added problem of α versus γ addition (equation 7).



(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

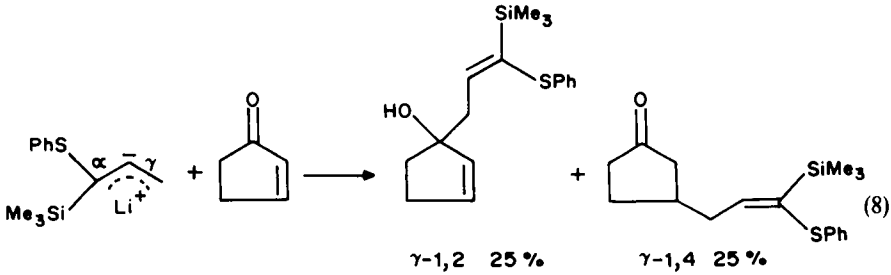
(31) X = S

(32) X = SO_2

γ-1,4

(33) X = SO

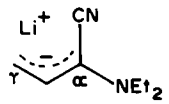
The addition of the 1-phenylthio-1-trimethylsilyl-2-propene lithiated derivative (**34**) to 1-cyclopentenone in THF–HMPA at − 78 °C furnishes a 50:50 mixture of γ-1, 2 and γ-1, 4 adducts, **35** and **36** respectively (equation 8)[75].



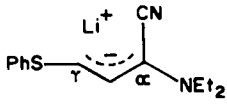
(8)

(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)

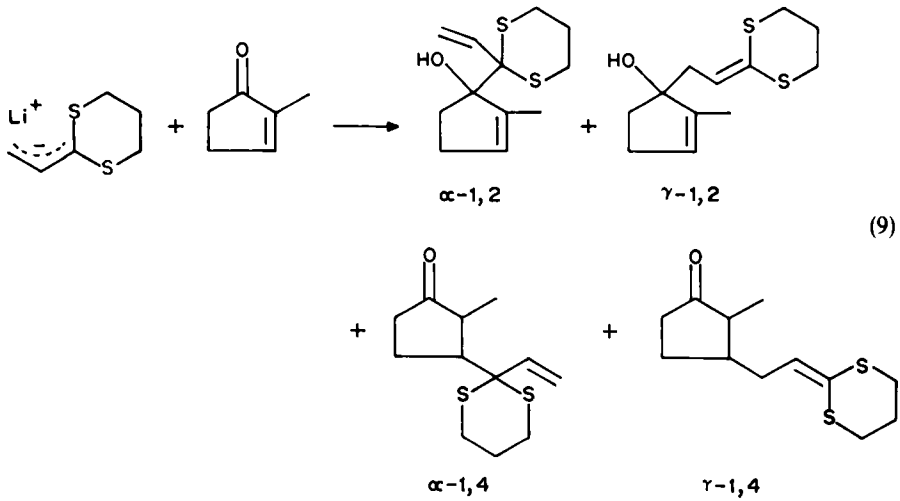
An interesting example of a change in regioselectivity of the reaction as the solvent composition is altered or the counterion modified is provided by the reaction of

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·$(MeO)_3P$[a]	0	98	2	54
THF, HMPA[b]	0	100	0	66

[a] 1.5 equivalent of CuI·$(MeO)_3P$.
[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)

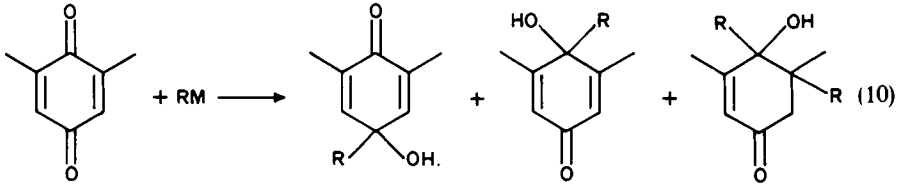
In this example, 1,4-addition predominates over 1,2-addition. Of the 1,4-addition products, γ-addition predominates when the lithium counterion is employed in THF. The increased amount of γ-1,4 adduct formed upon warming (from −78 to 25 °C) arises from an alkoxy-Cope rearrangement[61,80,81]. The preference 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 $CuI \cdot (MeO)_3P$ 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)** (10)

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].

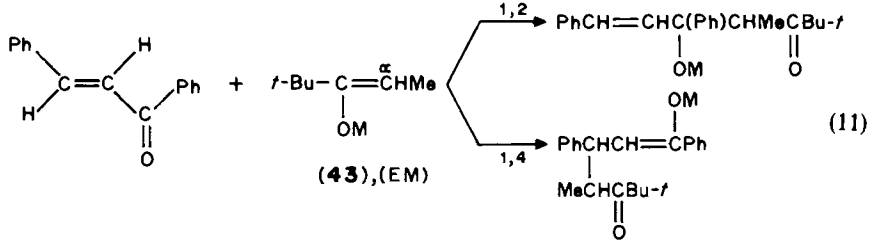
B. Metal Enolates and Related Compounds

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].

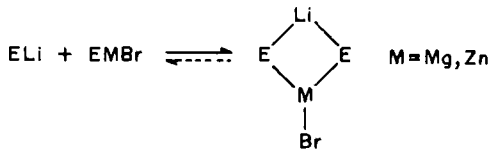
Entry	Enolate formation	Composition of **43**	$\delta^{13}C_{(a)}$[a]	1,2-Adduct	1,4-Adduct	Overall yield (%)
a	*t*-BuCOEt + *i*-Pr_2NLi	ELi	83.1	30	70	55
b	*t*-BuCOEt + *i*-PrMgBr or *t*-BuCOCHBrMe + Mg	EMgBr	95.4	95	5	40
c	*t*-BuCOCHBrMe + Zn	EZnBr	98.7	> 98	< 2	20
d	2 EMgBr + $MgBr_2$	E_2Mg	83.4–95.4	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)

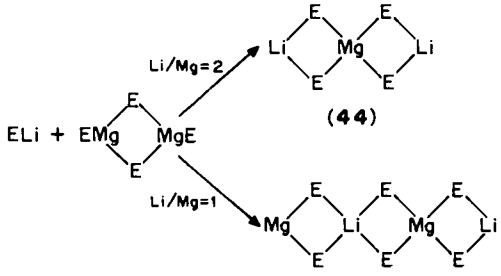
Most surprising are the cases of entries a and d compared to g and h. Metal enolates ELi and E_2Mg lead to a similar 1,2/1,4 ratio (30:70) and should give the same regioselectivity from a mixture of the two metal enolates (entries g and h). In fact, the regioselectivity is reversed (70:30) as the result 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

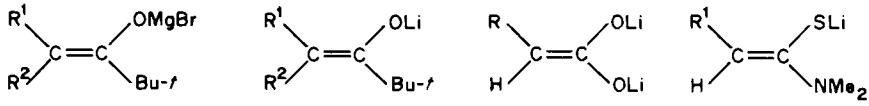
enolate	R^1	R^2	Temperature (°C)	Solvent	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)	Ref.
46	H	H	20	THF	1	100	0	55	96
46	Me	H	−78	Et_2O	1	>95	<5	40	96
46	Me	Me	−78	Et_2O	1	0	100	<30	96
47	H	H	−78	THF	1–60	80	20	40	96
47	Me	H	−78	Et_2O	1	30	70	55	96
47	Me	Me	−78	Et_2O	1	0	100	80	96
48	H		−50	THF	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)

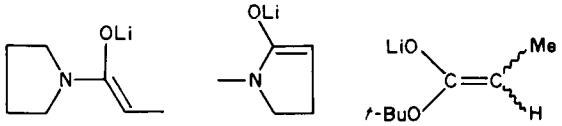
(45)

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_2NC(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_2NNLi)CHMe	0	1	72	28	—	112
p	HC(Me_2NNLi)CMe_2	−78	1	>90	<10	—	112

[a] Reaction performed in Et_2O.
[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.

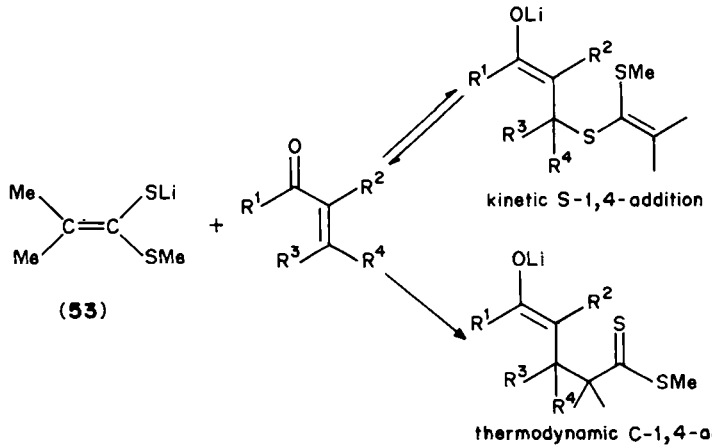
In a homogeneous set of metallated enolates, such as lithiated enolates, it is possible to apply the HSAB concept to predict the preferential orientation of additions according to the nature of the enolates (ketones, thione, amide, thioamide, ester enolates) and of hetero substituent bonded on the carbanionic 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]

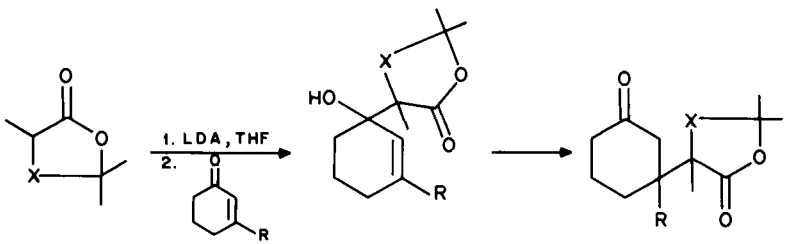
Enone	Temperature (°C)	Time (min)	S-1,4	C-1,4	Overall yield (%)
2-Cyclohexenone	−55	15	86	14	66
2-Cyclohexenone	−55 and then −20	15 15	4	96	82
2-Cyclohexenone	−20	10	1	99	72
3-Penten-2-one	−78	20	85	15	39
3-Penten-2-one	−30	20	5	95	70
2-Cyclopentenone	−126	—	0	100	—
2-Cyclopentenone	−78	10	0	100	45
2-Cyclopentenone	−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)

(**54**) X=O

(**55**) X=S

(**56**) R=H, X=O

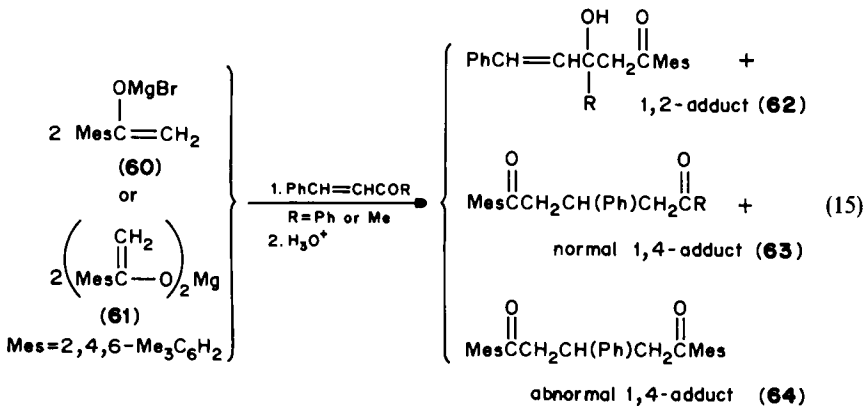
(**57**) R=Me, X=O

(**58**) R=H, X=S

(**59**) R=H, X=S

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).

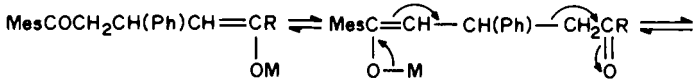


(15)

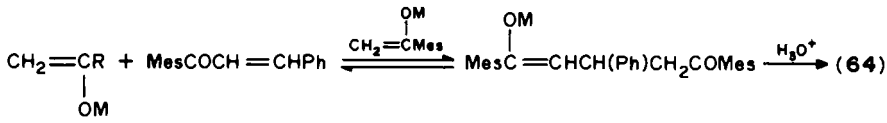
With the reagent **61**, a new 1,4-adduct (**64**) appears that can be explained by the reversibility of the normal 1,4-addition (equation 16) as demonstrated by isolation of acetophenone and 1,3,5-triphenyl-1,5-pentanedione after hydrolysis.

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 (%)			Overall yield (%)
			62	**63**	**64**	
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

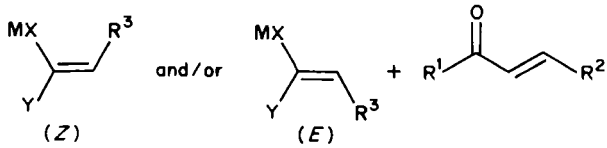


R=Ph or Me, Mes=2,4,6-$Me_3C_6H_2$ M=—MgO— (16)



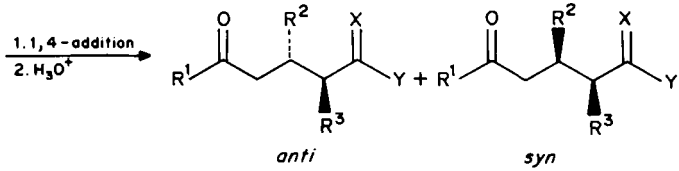
Redistribution reactions arise with **61** and the lithiated derivative of mesityl methyl ketone, but not with **60**. Thus, the phenomenon is joined to the associative states and nucleophilicity of metal enolates[118] and has some importance in the study of the stereochemistry of 1,4-additions.

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

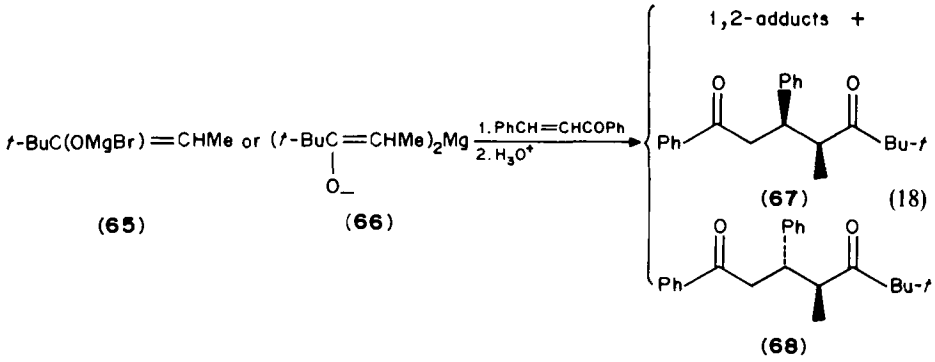
Enones				Temperature	Time	*syn*	*anti*	
R^1	R^2	Enolate	(*E*/*Z* ratio)	(°C)	(min)	(1,4-adduct)		Ref.
t-Bu	Me	*t*-BuOC(OLi)CHMe	(0/100)	−78	15	13	87	105
t-Bu	Ph		(11/89)	−78	15	7	93	105
t-Bu	Ph		(95/5)	−78	15	94	6	105
t-Bu	Ph	PhC(OLi)CHMe	(2/98)	−78	1440[a]	4	96	121
t-Bu	Ph		(87/13)	−20	1440	83	17	121
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).



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).

$$RM + CuX \longrightarrow RCu + MX \tag{19}$$

$$2RM + CuX \longrightarrow R_2CuM + MX \tag{20}$$

$$RM + CuR' \longrightarrow RR'CuM \tag{21}$$

$$RM + CuZ \longrightarrow R(Z)CuM \tag{22}$$

$$M = Li, MgX; \quad Z = OR', SR', CN$$

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

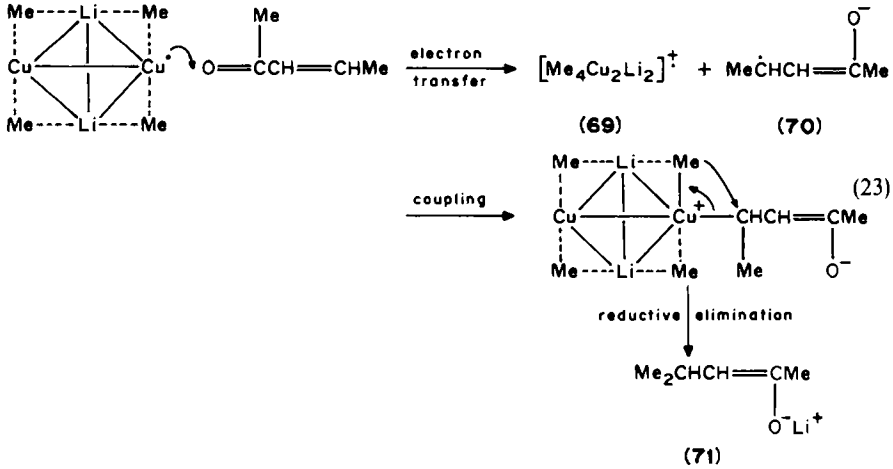
General name	General formula[a]
Copper-catalyzed Grignard reagents	$RMgX/Cu^+$
Organocopper reagent	$RCu \cdot MX$
	$RCu \cdot MX \cdot Ligand$
Organocopper·Lewis acid complex	$RCu \cdot BF_3$
	$RCu \cdot AlCl_3$
	$RCu \cdot Me_3SiCl$
Homocuprates	R_2CuM
	$R_2CuM \cdot Ligand$
Mixed homocuprates	RR'CuM (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].

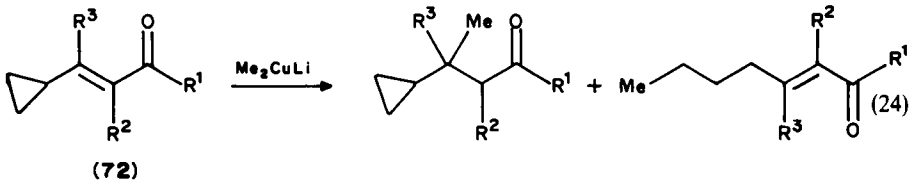
House and coworkers[162,171,180] suggested that the conjugate addition of lithium dimethyl cuprate proceeds by an initial single-electron transfer from the cuprate to the enone to form an electron-deficient metal cluster **69** and an anion radical **70** (equation 23). Rebonding these two species at 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**.



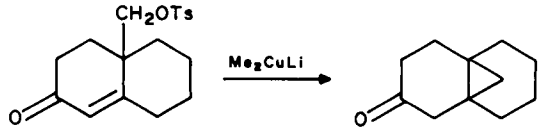
Several reactions which occur concurrently with the conjugate addition of lithium dimethyl cuprate have been cited as evidence for the formation of an intermediate radical anion:

(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],



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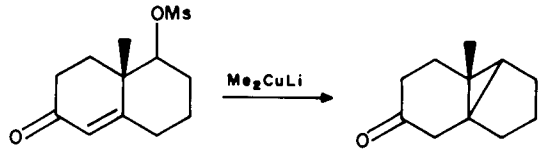
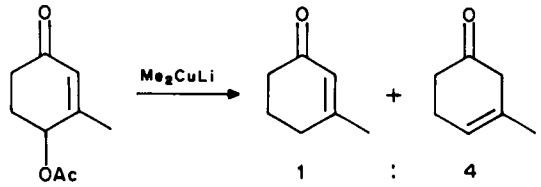


(26)

(iv) reductive cleavage of γ-O-acetoxy-α,β-unsaturated ketones **73** (equation 27)[186–189].

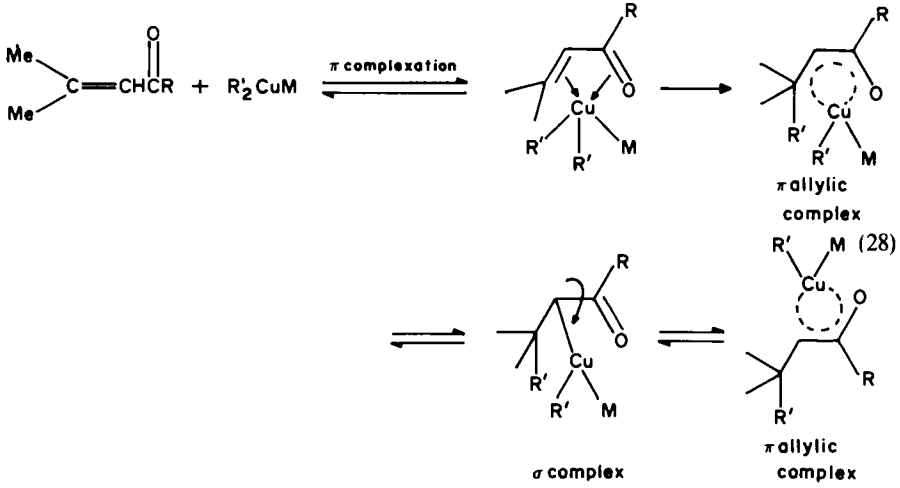


(27)

(73) **(74)** **(75)**

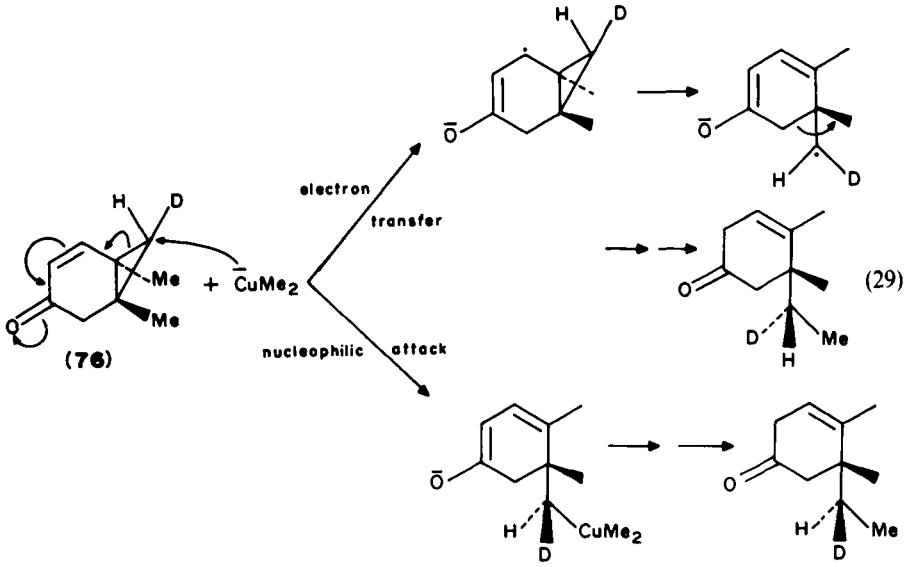
However, no ESR or CINDP signal attributable to an unpaired electron was observed[168,190] and, in the last-named case, when the γ-acetoxy group is replaced by a poorer leaving group, such as alkoxy, the normal addition takes place[191–193].

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)

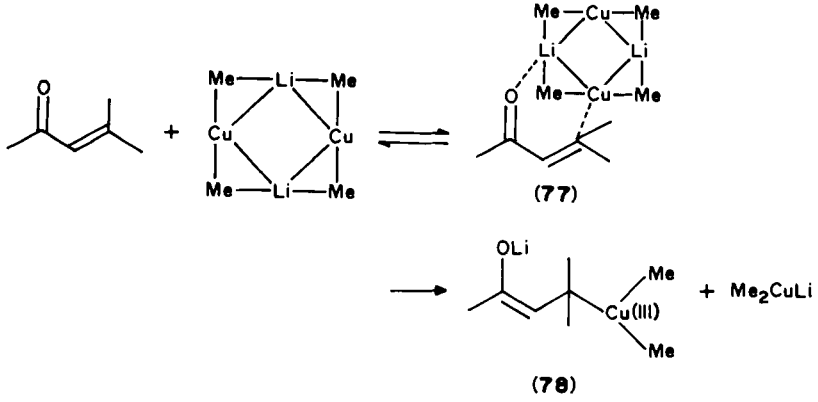
Casey and Cesa showed that the ring opening of the cyclopropyl-α,β-unsaturated ketone **76** is highly stereospecific, providing evidence against an anion radical intermediate and in favour of a direct nucleophilic attack of the cuprate on the cyclopropane ring (equation 29)[199].



(29)

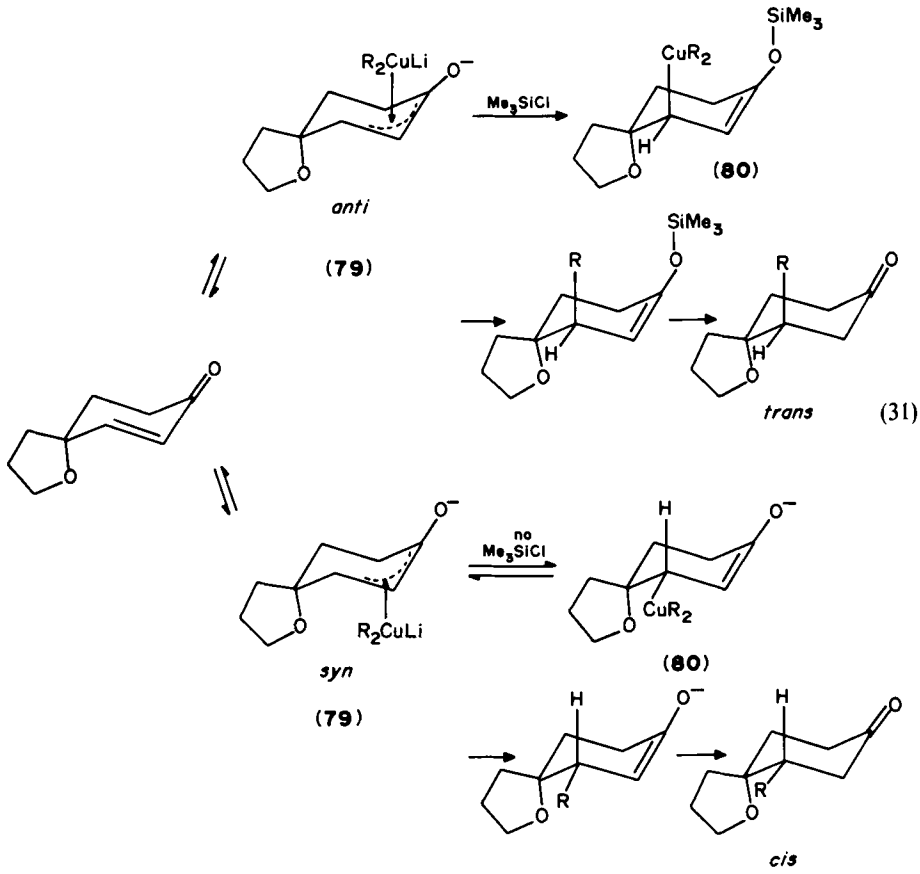
Moreover, on the same type of substrate, Jullien and coworkers[200,201] found no evidence for a correlation between the radical anion half-lives and the formation of ring-opened products. In many cases, the broken bond is different from the bond involved in the reduction by solvated electron in liquid 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 $R^2R^3C{=}CR^1CHO$

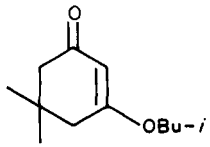
Enal								
R^1	R^2	R^3	Reagent	Solvent	$C_{(1)}$ Attack	$C_{(3)}$ Attack	Overall yield (%)	Ref.
Me	H	Et	Me_2CuLi	Et_2O	18	82	85	206
Me	H	Et	Me_2CuLi	Et_2O/pentane	5	95	75	206
Me	H	Et	Me_2CuLi	Et_2O/THF	60	40	55	206
Me	H	Et	Me_2CuLi, Me_2S	THF	10	90	53	154
Me	H	Et	$Bu_2CuMgCl$	THF	91	9	22	154
Me	H	Et	$Bu_2CuMgCl$	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]

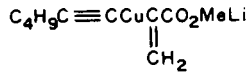
Enone				Reagent	1,4-Addition
R^1	R^2	R^3	E_{red} (V)	R	yield (%)
H	H	Me	−2.08	Me[a]	94
H	Me	Me	−2.21	Me[a]	93
Me	Me	Me	−2.35	Me[a]	21
H	H	Me	−2.08	*s*-Bu[b]	87
H	Me	Me	−2.21	*s*-Bu[b]	77
Me	Me	Me	−2.35	*s*-Bu[b]	17–43

[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)



(82)

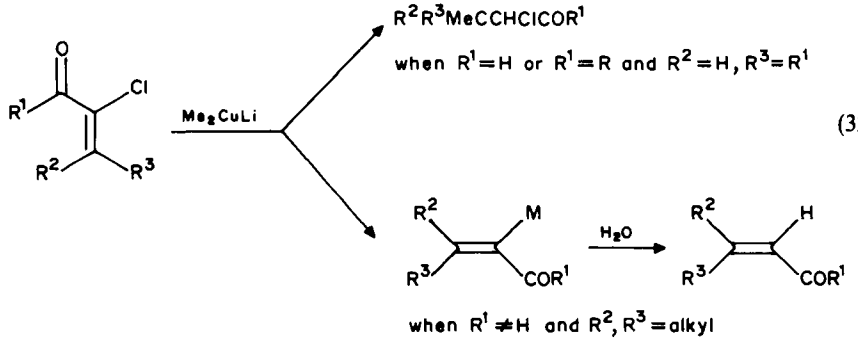
The kind of substituent present on the substrate also affects the course of the reaction. For instance, α-fluoro- and α-chloro-α,β-unsaturated carbonyl compounds whose reduction potentials are greater than −2.4 V react in different ways with lithium dimethyl cuprate[211]. With α-fluoro derivatives, both 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	Time			Overall yield
R^1	R^2	R^3	(°C)	(min)	$C_{(1)}$ attack	$C_{(3)}$ attack	(%)
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



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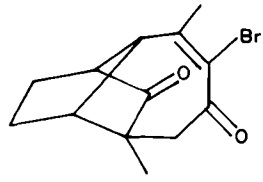
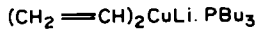


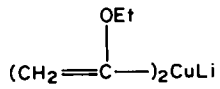
(83)

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).

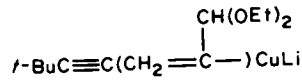


(84)

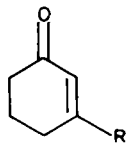
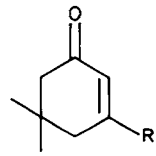
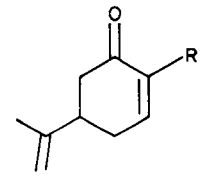
(85)



(86)



(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

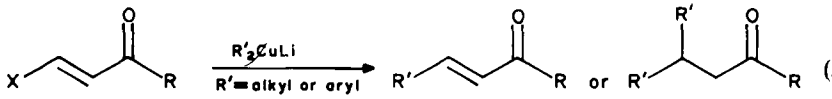
TABLE 24. Influence of substituents on the substrate in the reaction of cuprates with enals $R^3R^2C{=}R^1CHO$

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.

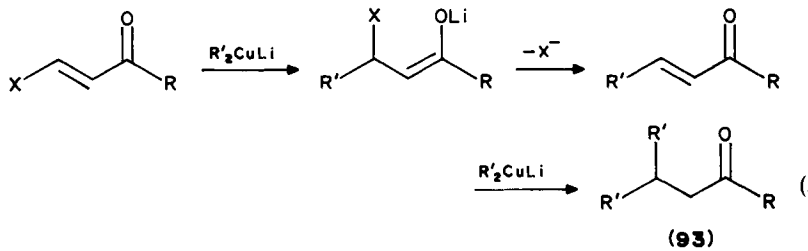
and the yields are improved by quenching the reaction with acetic acid[155] or with trimethylchlorosilane in the presence of triethylamine[153,206].

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)**

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].



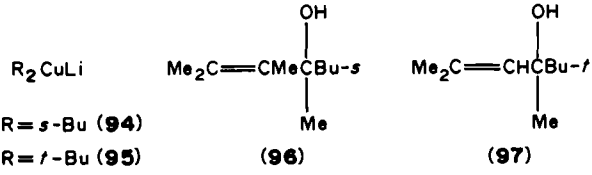
(93)

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≡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].



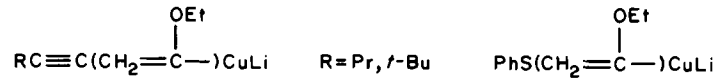
Ashby and Watkins showed that the higher-order species Me_3CuLi_2 exists to an appreciable degree of equilibrium with Me_2CuLi and free MeLi[170]. This complex, which rapidly reacts with ketones[222], delivers the methyl group in a 1, 2 sense upon reaction with the sterically hindered ketone, isophorone, 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.

(98) **(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].

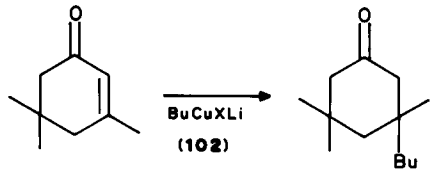


(100) **(101)**

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].

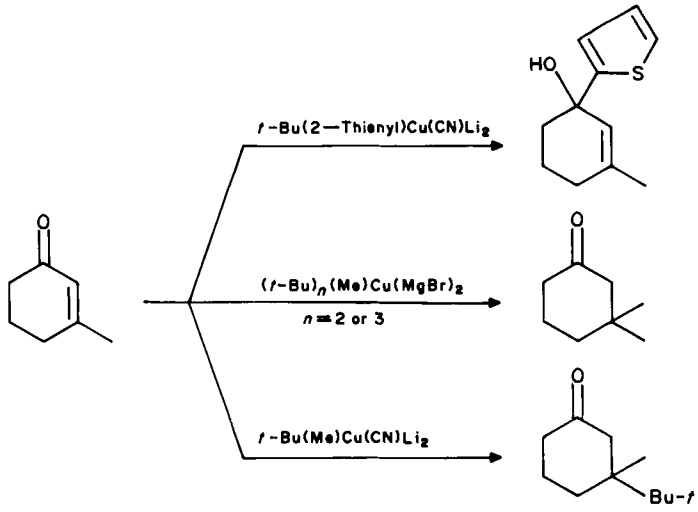
TABLE 27. Conjugate addition of a vinyl group to isophorone using various cuprates

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.

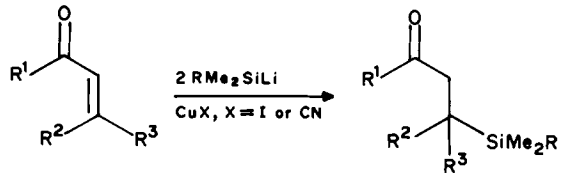
An analogous 1,2-addition of the 2-thienyl group occurs in the reactions of lithium bis(2-thienyl)cuprate with 2-cyclohexenone and benzalacetone[150].

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)

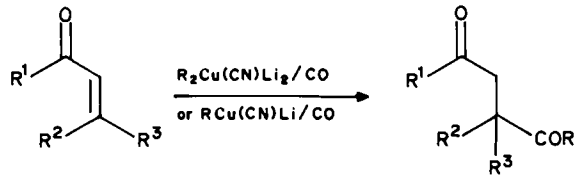
Organocopper reagents proved to be useful in the formation of β-silyl carbonyl compounds **104** (equation 37)[142,229–231].



(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).



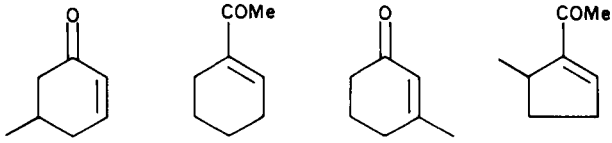
(38)

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 (%) 1,2-adduct	Yield (%) 1,4-adduct	Ref.
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

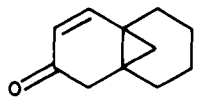
[a] 1,2-adduct is obtained in various amounts depending on the reaction temperature.

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.



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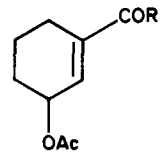


R = Me **(113)**
R = Ph **(114)**

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].

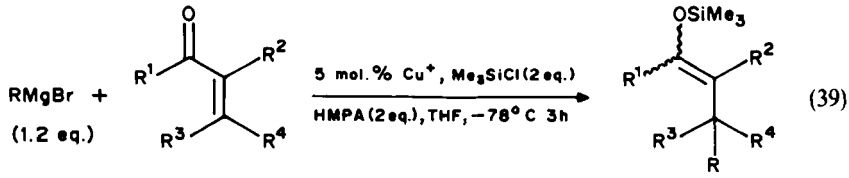
TABLE 31. Reaction of MeCu–$AlCl_3$ and Me_2CuLi with γ-acetoxy-α,β-enones **73**, **113** and **114**

		Yield (%)		
Enone	Reagent	1,4-addition	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

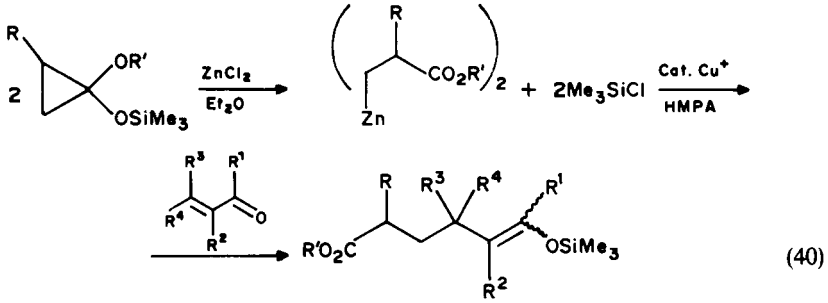
TABLE 32. Chlorosilane-assisted addition of organocopper reagents to α,β-unsaturated carbonyl compounds

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.

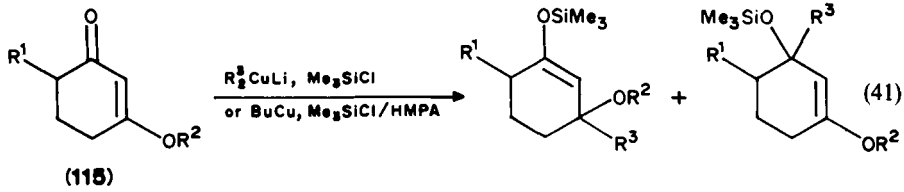


(39)



(40)

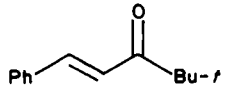
3-alkoxy-2-cyclohexenones **115**, reported to be unreactive towards organocopper species, due to their very low reduction potential ($E_{red} < -2.40$ V), react with R_2CuLi in the presence of TMSCl[244,245] or with BuCu in the presence of TMSCl/HMPA[245], although a mixture of 1,2- and 1,4-adducts is obtained (equation 41).



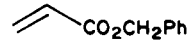
(41)

(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).

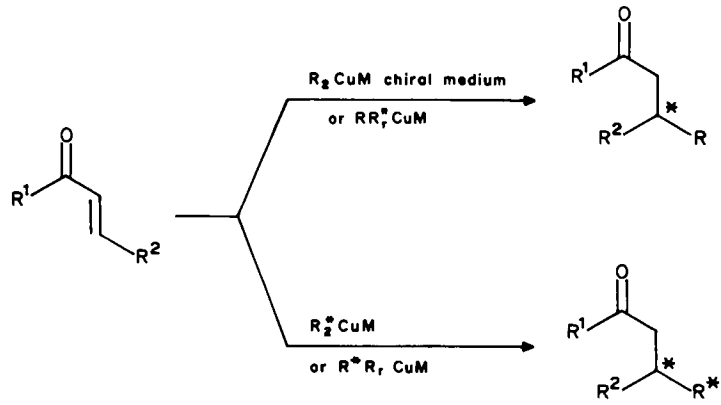


(116)



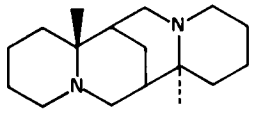
(117)

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 ($R_tR_t^*CuM$) containing a chiral non-transferable group, and (ii) the formation of diastereomeric products using cuprates with a chiral transferable ligand (R_2^*CuM or $R_t^*R_tCuM$) 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)

$Me_2NCH_2CH(OMe)CH(OMe)CH_2NMe_2$

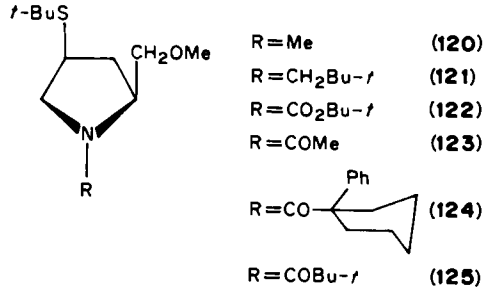
(119) (+)(*S*,*S*)

The use of 4(alkylthio)hydroxyproline derivatives **120**–**125** as bidentate ligands yields

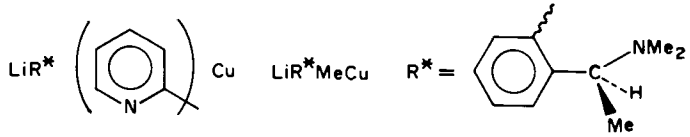
TABLE 33. Asymmetric methylation of chalcone using Me_2CuLi in Et_2O at $-50\,^{\circ}C$ in the presence of chiral ligands **120–125**[252]

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.



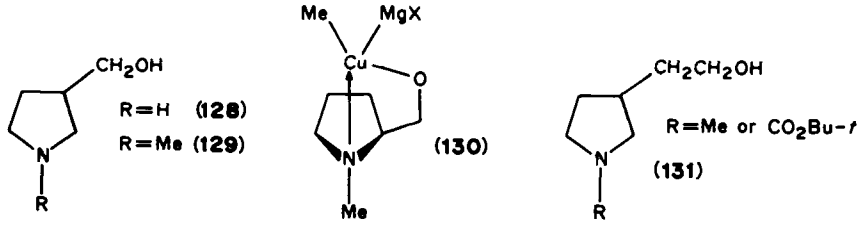
The degree of the asymmetric induction obtained in the reaction of benzalacetone with the mixed cuprate **126** is considerably higher (e.g. 84%)[253] than when a methyl group is transferred (e.e. 5%)[254,255] by cuprate **127** using the same chiral ligand. It seems probable that the pyridine nitrogen atom interacts with the metal atom in a stereodifferentiating step.



(126) (127)

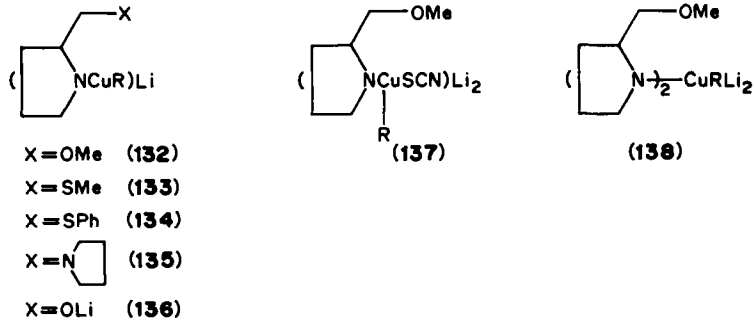
Although the heterocuprates LiR(Het)Cu (Het = R'O, R'S, R'_2N) are valuable reagents for conjugate addition, the methylation of chalcone using reagents generated from various aminoalcohols affords optical yields of 0–31%[256]. Similarly, the alkylation of 2-cyclohexenone with heterocuprates derived from 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].



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.



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.

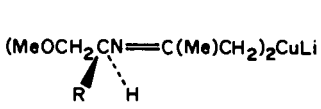
The influence of the substrate structure, the cuprate composition and the solvent upon the induced absolute stereochemistry is more difficult to understand owing to the lack of a thorough knowledge of the structure and aggregation of the cuprate reagent, and the

TABLE 34. Asymmetric induction in methylation of α-enones with $CH_3(R^*O)CuLi$ derived from **128** or **129**[261]

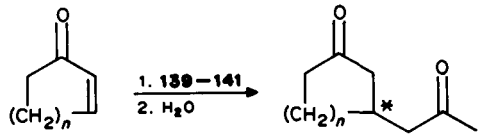
Enone	Alcohol inductor	Solvent	Yield (%)	e.e. (%)	Configuration
2-Cyclohexenone	**129**	PhH	64	1	*R*
2-Cyclohexenone	**129**	THF	70	5	*R*
2-Cyclohexenone	**128**	PhH	36	37	*S*
2-Cyclohexenone	**128**	THF	61	29	*S*
Benzalacetone	**129**	PhMe	80	3	*R*
Benzalacetone	**129**	THF	82	10	*S*
Benzalacetone	**128**	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).



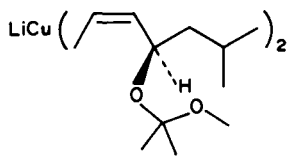
R = CH_2Ph **(139)**
R = *i*-Pr **(140)**
R = *t*-Bu **(141)**



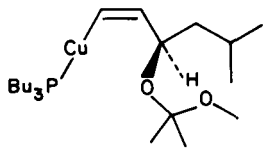
(43)

(142)

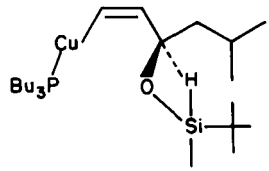
The conjugate addition of chiral organocopper reagents **143–145** to 2-methyl-2-cyclopentenone proceed with a high degree of stereoselectivity (Table 37)[266,267].



(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).

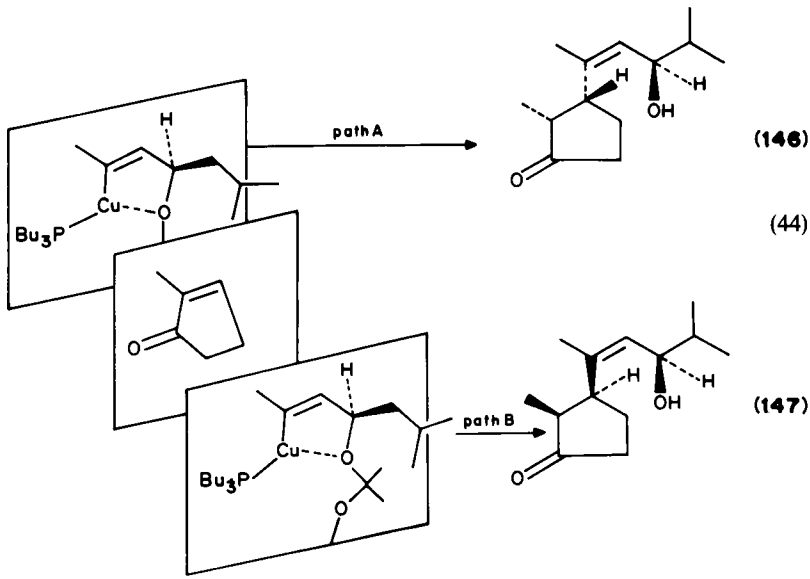
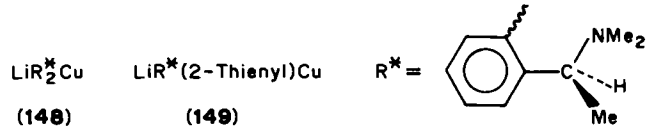


TABLE 38. Diastereomeric excess (d.e.) from conjugate addition of cuprates **148** and **149** to various enones in Et_2O at 0 °C[268]

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

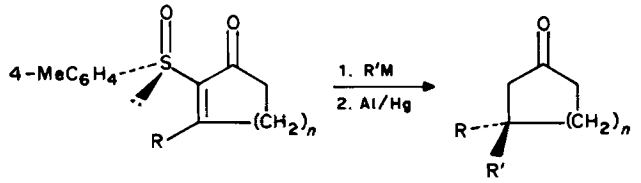
One diastereomer is also formed in large excess (76–98%) on addition of the chiral (*S*)-2-(1-dimethylaminoethyl)phenyl group to various enones (Table 38) using the homocuprate **148** or the mixed 2-thienyl cuprate **149**[268–270].



(148) (149)

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)

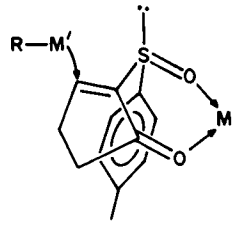
(150) $n = 1, 2$ (151)

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]

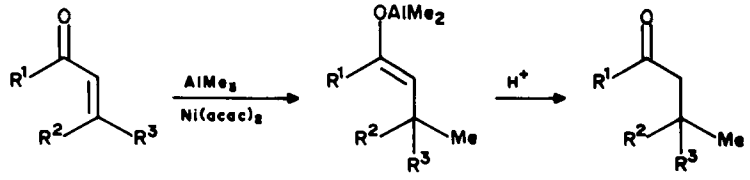
Entry	R in enone **150**	Reagent	e.e. (%)	Yield (%)	Configuration
a	4-MeC_6H_4	Me_2CuLi	78	58	*S*
b	4-MeC_6H_4	Me(PhS)CuMgBr	73	77	*S*
c	4-MeC_6H_4	$Me_5Cu_3Li_2$	65	44	*S*
d	4-MeC_6H_4	Bu_2CuLi	—	0	—
e	4-MeC_6H_4	Bu(PhS)CuMgCl	81	69	—
f	Me	$(4\text{-}MeC_6H_4)_2CuLi$	90–93	53	*R*
g	Me	Bu(PhS)CuMgCl	53	79	—
h	Me	Bu(*t*-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].



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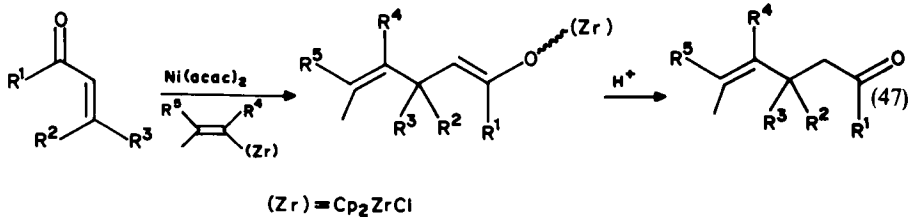
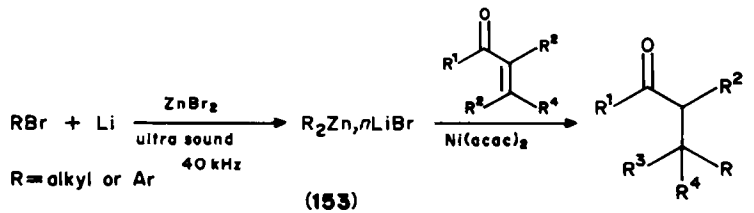


(47)

$(Zr) = Cp_2ZrCl$

Luche and coworkers used $Ni(acac)_2$ for the conjugate addition of diorganozinc reagents **153**, prepared by sonication (equation 48)[283–286].



(48)

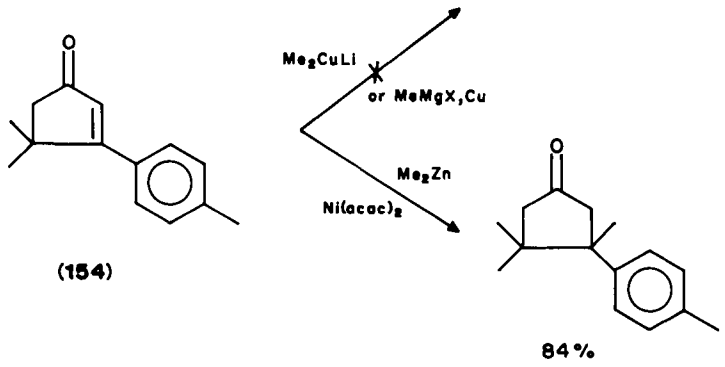
(153)

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).



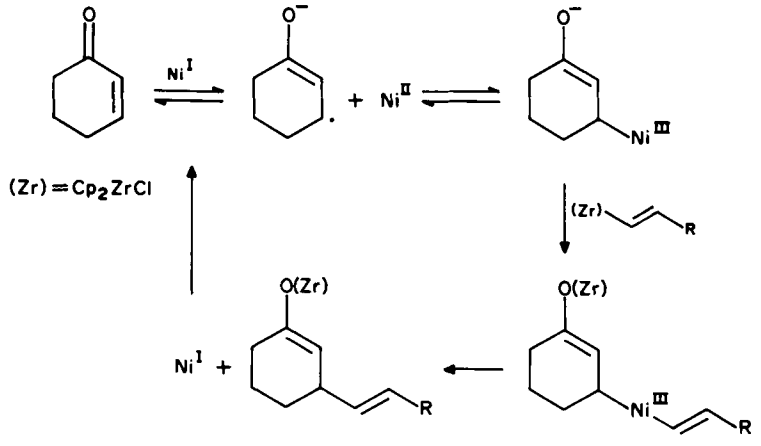
(49)

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-$MeC_6H_4)_2Zn$ 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).

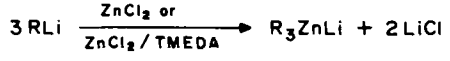
Triorganozincates **155** and **156** are another type of reagent that can be used to add alkyl groups in a 1,4-fashion to α,β-unsaturated ketones. They have not, however, been as extensively studied as cuprates, and the scope of their reactions remains to be established.

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].

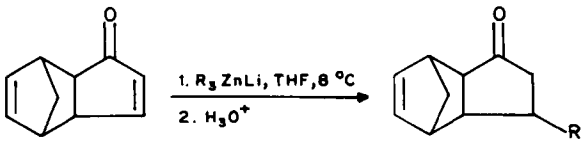


(50)

(155) (156)



(51)



(52)

(157)

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.

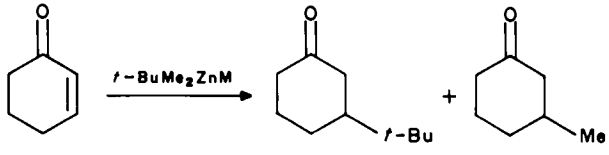
Langer and Seebach have shown that, like cuprates, the 1,4-addition reactions of zincates are enantioselective when carried out in a chiral medium[250]. More recently, Watson and Kjonaas showed that mixed triorganozincates **156** (M = Li, R = Me) selectively transfer the R′ group (R′ = *n*-Bu or *s*-Bu) 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$_2$ZnM in THF at − 78 °C for one hour (equation 53).

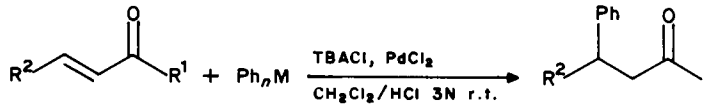


(53)

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].

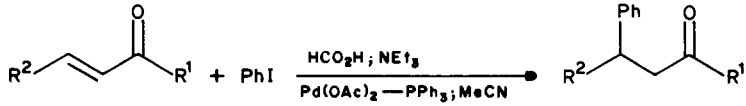


(54)

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)

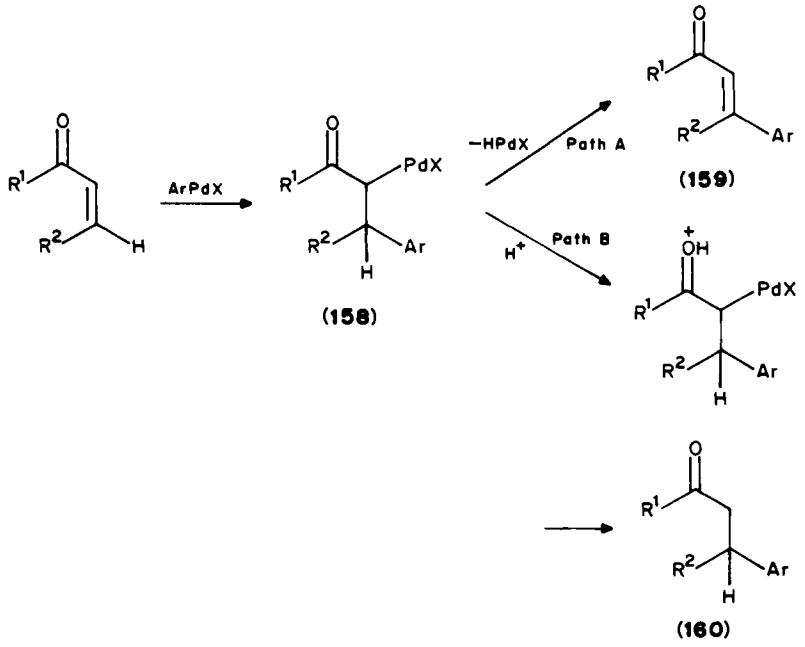
Unhindered α-enones react with these reagents, giving rise to the conjugate addition-type products. The main limitation seems to arise from the steric hindrance in the substrate. Thus, isophorone, cholest-4-ene-3-one and carvone fail to react with phenylmercury or phenyltin compounds under palladium 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].

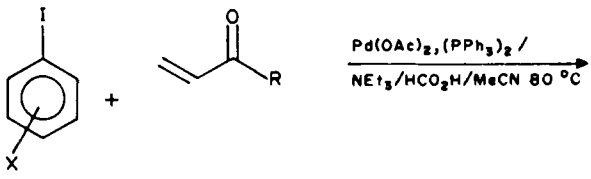
The reaction proceeds through a vinylic substitution followed by an *in situ* conjugate addition to the β-substituted α,β-unsaturated carbonyl compounds **161**. Compounds **163**, derived from a double vinylic-substitution reaction, are also obtained in variable amounts[301].

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].

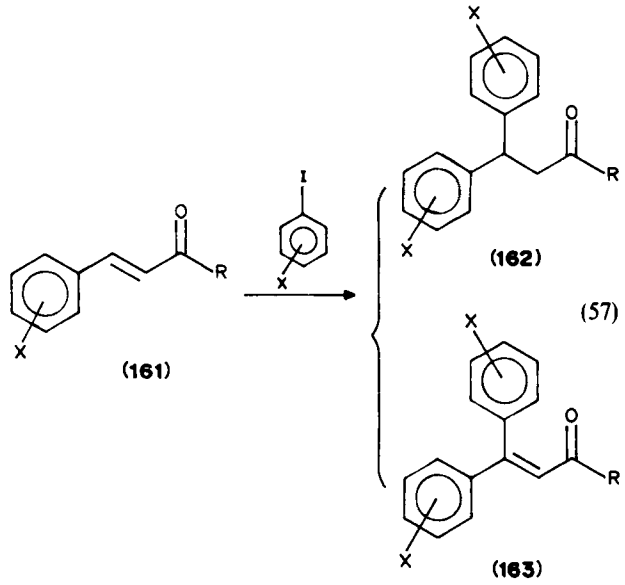
Organometallic compounds involving lanthanides are harder nucleophiles than Grignard reagents[303,304]. Divalent organolanthanide σ-complexes (RLnI with Ln = Ce, Sm, Eu and Yb)[304–306] or organocerium(III) reagents ($RCeCl_2$)[307–310] react with α-enones to afford the 1,2-addition products in higher 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)



R=H or alkyl



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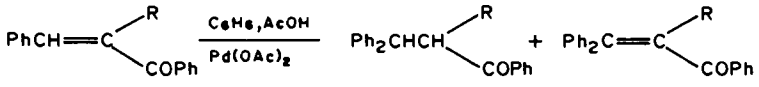


(58)

(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).

$[Li(TMEDA)_2][Lu(Bu\text{-}t)_4]$ (165) $[Li(TMEDA)]_3[LnMe_6]$ (166) Ln = Pr or Sm

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]

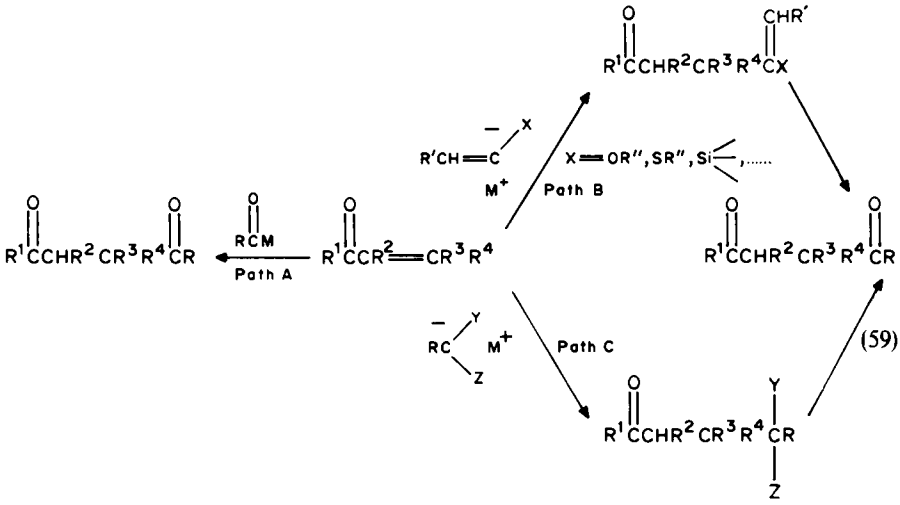
Entry	Enone	Reagent	Solvent	Temperature (°C)	Yield (%) 1,2-adduct	Yield (%) 1,4-adduct
a	CH_2=CHCOMe	**165**	Et_2O	−78	50	50
b	Me_2C=CHCOMe	**165**	Et_2O	−78	> 80	< 20
c	Me_2C=CHCOMe	**166**	THF	−78	> 95	< 5
d	Cyclohexenone	**165**	Et_2O	−78	70	30
e	Cyclohexenone	**166**	THF	−78	> 80	< 20
f	Cyclohexenone	**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.

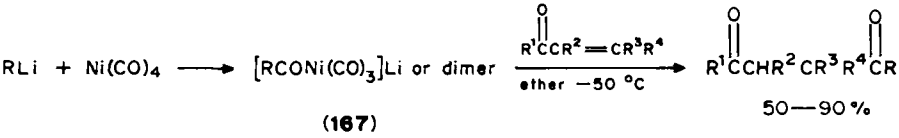
The two pathways to the formation of 1,4-dicarbonyl derivatives from nucleophilic addition to enones and enals use (i) direct nucleophilic 1,4-acylation with acylmetallic compounds (path A in equation 59) and (ii) reagents containing masked functionality to invert carbonyl reactivity of the electrophilic 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



(167)

(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.

$(RC{\equiv}C)_3CuLi_2$ **(168)** $\qquad$ n-$Bu_3SnCH{=}CHCuC{\equiv}CPrLi$ **(169)**

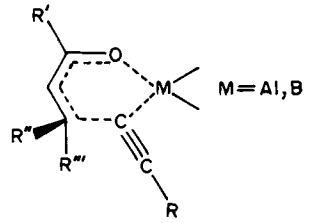
Diethylalkynyl alane **170** undergoes 1,4-addition reactions with α,β-unsaturated ketones to give γ,δ-alkynyl ketones[331,332]. The reaction may be complicated by the concurrent formation of large amounts of 1,2-addition products[332]. It is highly sensitive to the solvent and to β,β-disubstitution 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].

(170) (171)

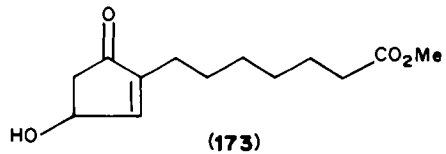
Trialkynyl boron derivatives have been successfully added to methyl vinyl ketone[333]. The use of B-1-alkynyl-9-borobicyclo[3.3.1]nonanes (**171**)[334] avoids the waste of the two residual alkynyl units. A variety of structural modifications on the acetylenic unit, including the presence of a heteroatom, 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].

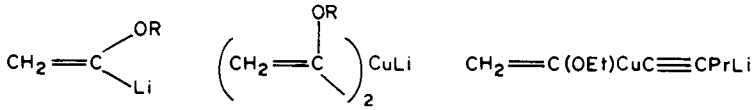
3. *Nitronate anion*

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 con-

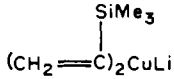
ditions[359,360]. They have been successfully used for conjugate additions of nitroalkanes to enals or enones. Moreover, a variety of mild methods are capable of efficiently converting γ-nitroketones into the corresponding 1,4-diketones[339,351,361-370] with none of the disadvantages that accompany other 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]).



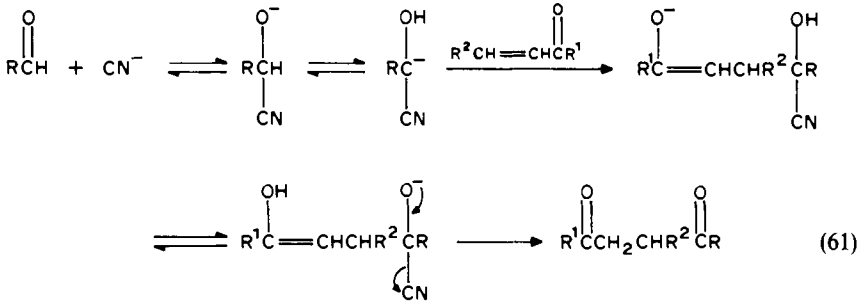
(174) R=Me,Et **(175)** **(176)**



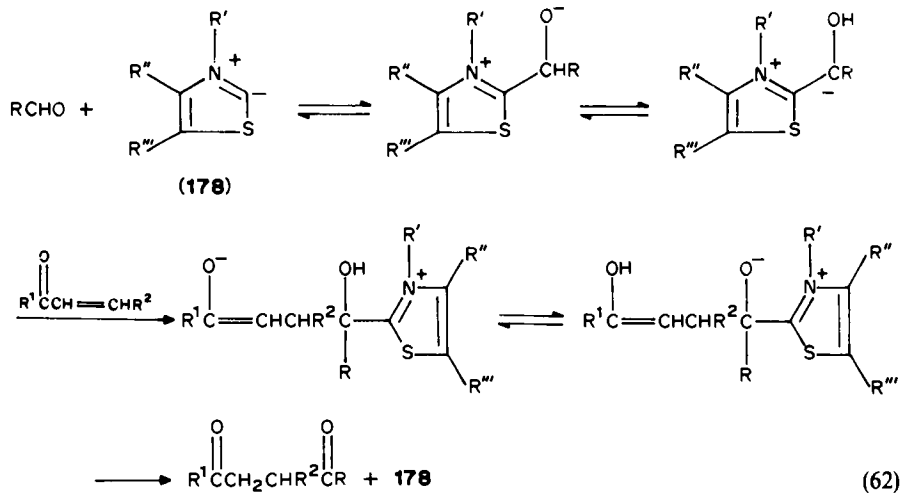
(177)

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)



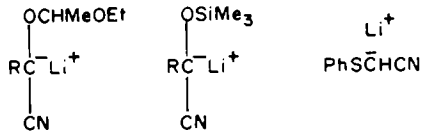
(62)

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].

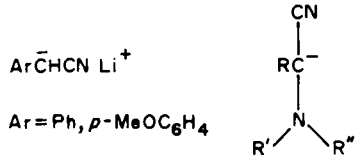


(179) (180) (181)

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].

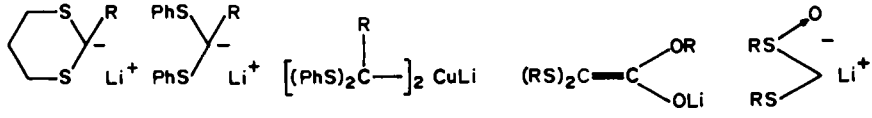


(**182**) (**183**)

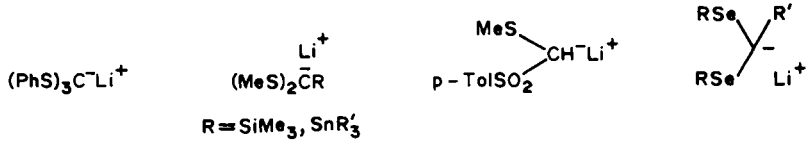
Zervos and Wartski[405] showed that the three lithiated derivatives **179** (R = Ph), **182** (Ar = Ph) and **183** (R = Ph, R′ = R″ = Me) exhibit similar reactivities towards $C_{(3)}$ unsubstituted α-cycloenones, but that **183** and other aminonitriles[12,57,405] do not react with β-disubstituted 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**) (**186**) (**187**) (**188**)



(**189**) (**190**) (**191**) (**192**)

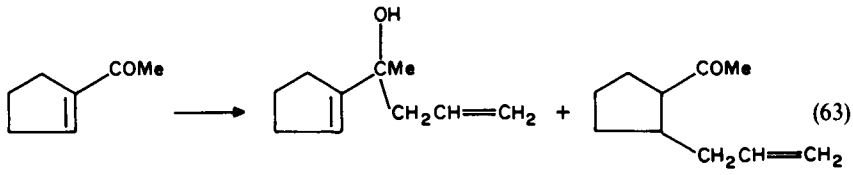
The discovery that polar solvents favour the 1,4-addition of some alkyllithiums has led to the successful reinvestigation of the reaction of the simplest acyl anion equivalents containing sulphur with enals[29,30,429,430] and enones[31,33,34,49,431]. Side by side with lithiothio derivatives, α-lithio 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].



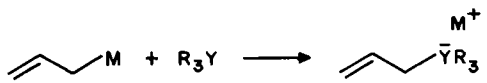
(63)

(193) **(194)** **(195)**

$(CH_2{=}CHCH_2)_2CuLi$ 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]

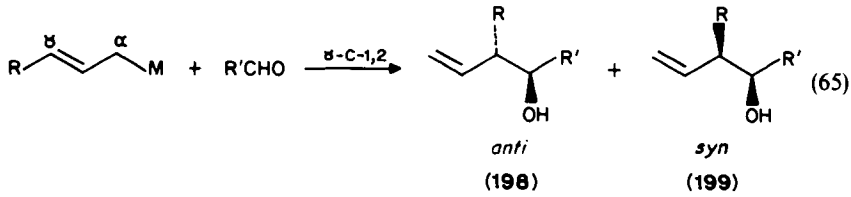
Enone	M in **196**	Additive	$C_{(1)}$ attack	$C_{(3)}$ attack	Overall yield (%)
PhCH=CHCOMe	MgCl	*n*-Bu-9-BBN	95	5	70
PhCH=CHCOMe	Li	*n*-Bu-9-BBN	83	17	72
PhCH=CHCOMe	Cu	*n*-Bu-9-BBN	75	25	62
PhCH=CHCOMe	MgCl	Et_3Al	90	10	85
CH_2=CHCOMe	Li	*n*-Bu-9-BBN	50	50	30

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].

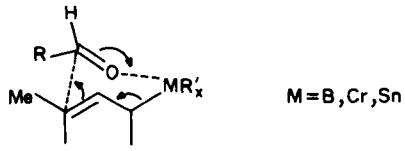
Allylic organometallic derivatives are ambident nucleophiles and, in the case of an unsymmetrical allyl group, both $C_{(\alpha)}$ and $C_{(\gamma)}$ adducts are obtained. Diastereo- and regioselectivities of $C_{(\alpha)}$ or $C_{(\gamma)}$ addition of organometallic reagents have mainly been studied 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).



(65)

anti (**198**) *syn* (**199**)

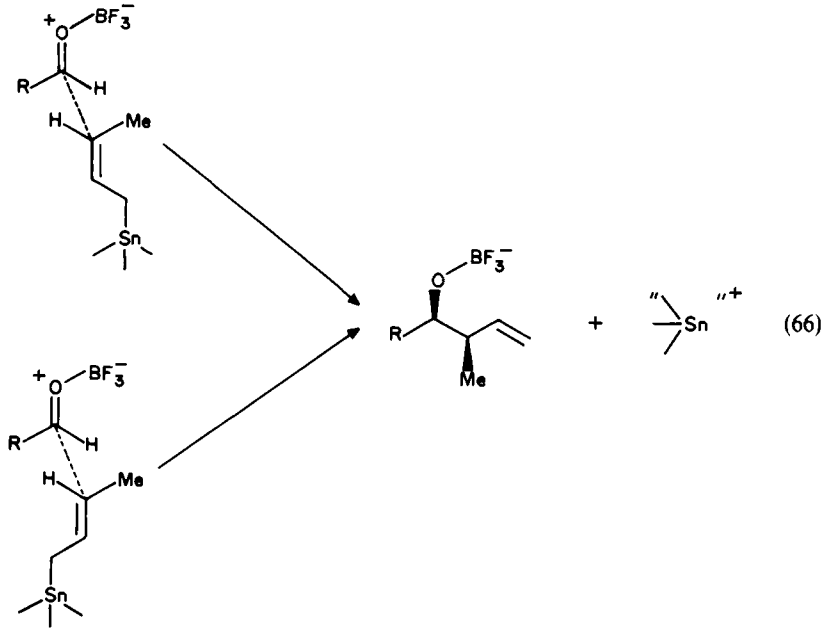
Formation of these rearranged compounds has often been accounted for in terms of a six-membered transition state **200**, owing to the affinity of the metal atom for the carbonyl oxygen[446,449,453-455].



(**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$_2$SnBu$_3$ 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

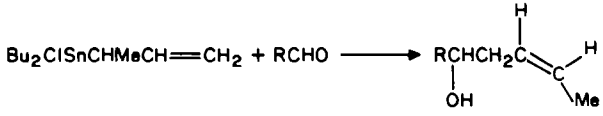
[a]TBS = *t*-Bu(Me)$_2$Si.

$$Z \text{ or } E \quad Bu_3SnCH_2CH{=}CHMe \xrightarrow{Bu_2SnCl_2} Bu_2ClSnCHMeCH{=}CH_2 + Bu_3SnCl \tag{67}$$

$$Bu_2ClSnCHMeCH{=}CH_2 \xrightarrow{Bu_2SnCl_2} (Z + E)Bu_2ClSnCH_2CH{=}CHMe \tag{68}$$

$$Z \quad Bu_2ClSnCH_2CH{=}CHMe \xrightarrow{Bu_2SnCl_2} E\ Bu_2ClSnCH_2CH{=}CHMe \tag{69}$$

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].

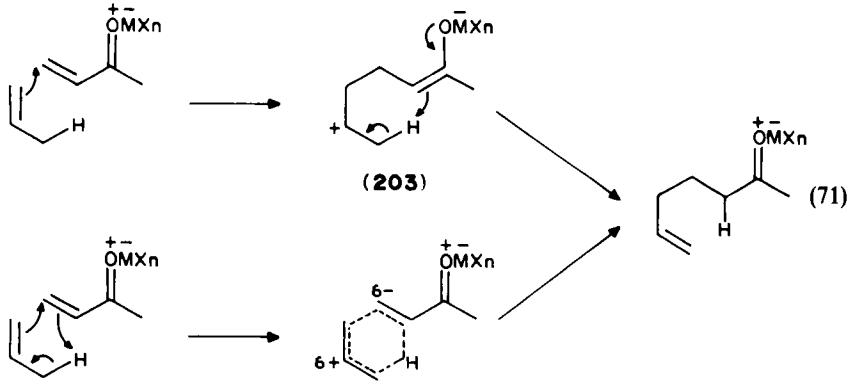


(70)

(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].



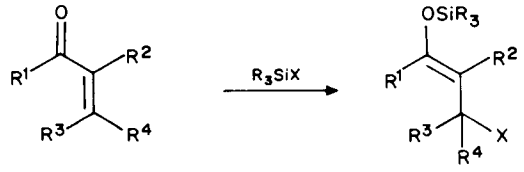
(71)

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].

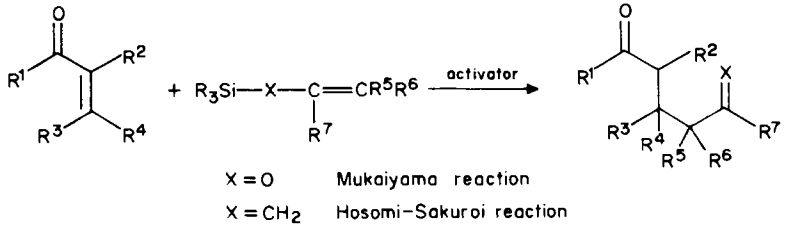
V. CARBON–CARBON BOND FORMATION FROM NUCLEOPHILIC ATTACKS OF ORGANOSILICONS

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 $-78\,^{\circ}C$ 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-$BuMe_2Si$	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]

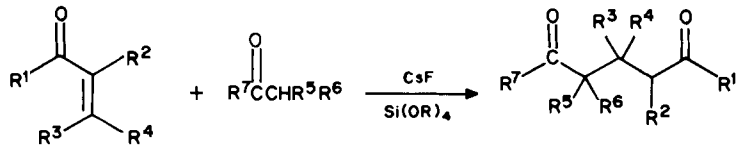
Substrate					Reagent				Time	Temperature			Overall
R^1	R^4	R^2	R^3	(eq)[a]	R_3Si	R^5	R^6	R^7	(h)	(°C)	1,2-attack	1,4-attack	yield (%)
Ph	Ph	H	H	(1)	Me_3Si	H	$-(CH_2)_4-$		0.5	25	0	100	80
Ph	Ph	H	H	(1)	Me_3Si	H	H	Ph	3	25	14	86	84
$-(CH_2)_3-$		H	H	(2)	Me_3Si	H	$-(CH_2)_4-$		1	80	0	100	40
$-(CH_2)_3-$		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)

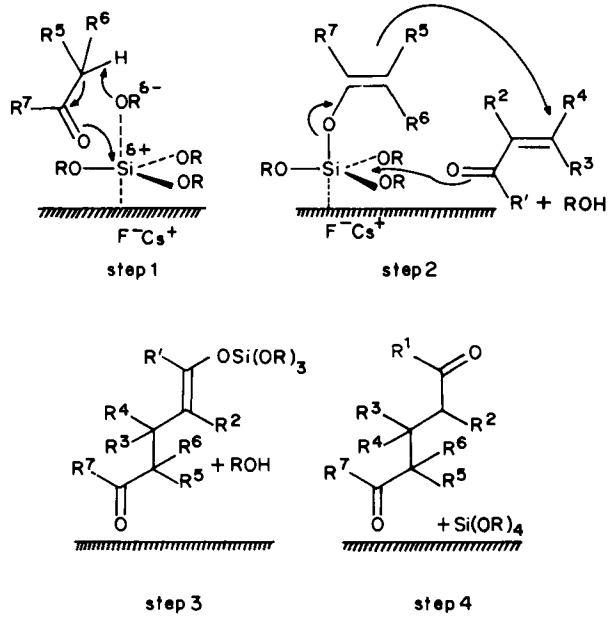
Substrate				Michael donor				Time	Temperature	Yield	
R^1	R^4	R^2	R^3	R^5	R^6	R^7	Method	(h)	(°C)	(%)	Ref.
Ph	Ph	H	H	Me	$-(CH_2)_4-$		A	2	60	65	388
Ph	Ph	H	H	Me	$-(CH_2)_3-$		B	1	20	82	355
$-(CH_2)_3-$		H	H	Me	$-(CH_2)_4-$		A	6	25	65	488
Carvone				Me	$-(CH_2)_4-$		B	4	25	70	489
Carvone				H	$-(CH_2)_3-$		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)

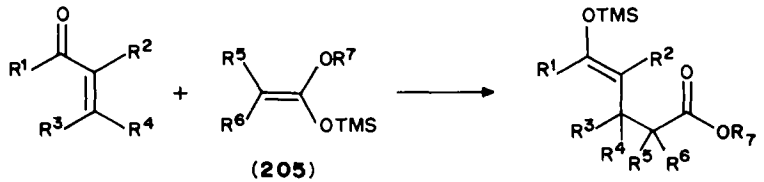
The original Mukaiyama procedure has been used for the preparation of numerous key intermediates in the synthesis of natural products, particularly *via* Robinson-type annelation[491–499]. However, the synthetically valuable silyl enol ethers are not isolated in both $TiCl_4$-promoted Michael reaction 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

Enone	Reagent 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.

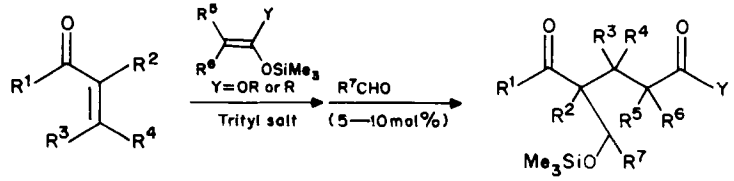
Künzler showed, using a catalytic amount (10 mol%) of TBAF, that the trimethylsilyl enol ether of S-*t*-butyl thioacetate reacts smoothly with an equimolar amount of 2-cyclopentenone in THF at low temperatures, giving the silyl enol ether of the 1,4-addition product in 72% yield[502]. Other appropriate 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

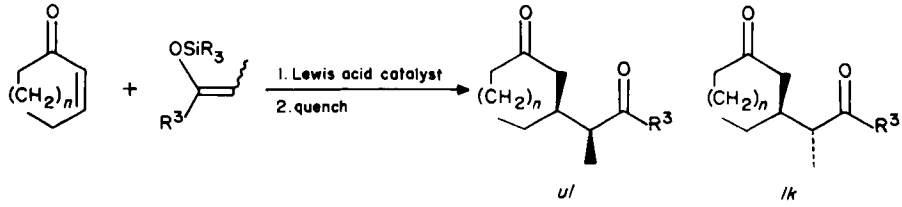
reaction before the quenching, it is possible to obtain the products from further reactions of the intermediate silyl enol ethers with the electrophiles, such as aldol condensation[510,512,513] (equation 77).



(77)

Several papers have been devoted to the interpretation of stereoselective trends of the Lewis and promoted Mukaiyama reactions[492,510,514–516]. 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[514,515] and Mukaiyama and coworkers[510,516].

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[516] explain the *ul* selectivity from the *Z* enolates by assuming the open transition state as shown in Scheme 1.

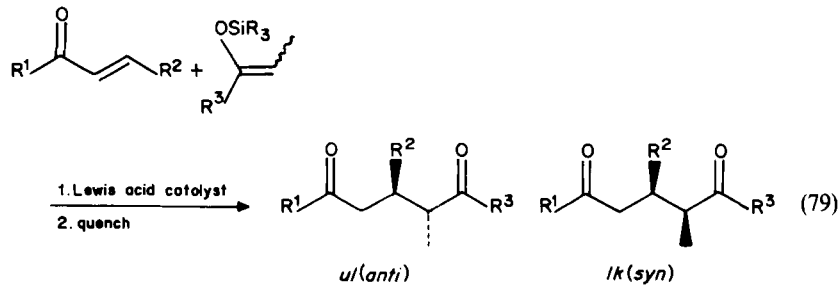


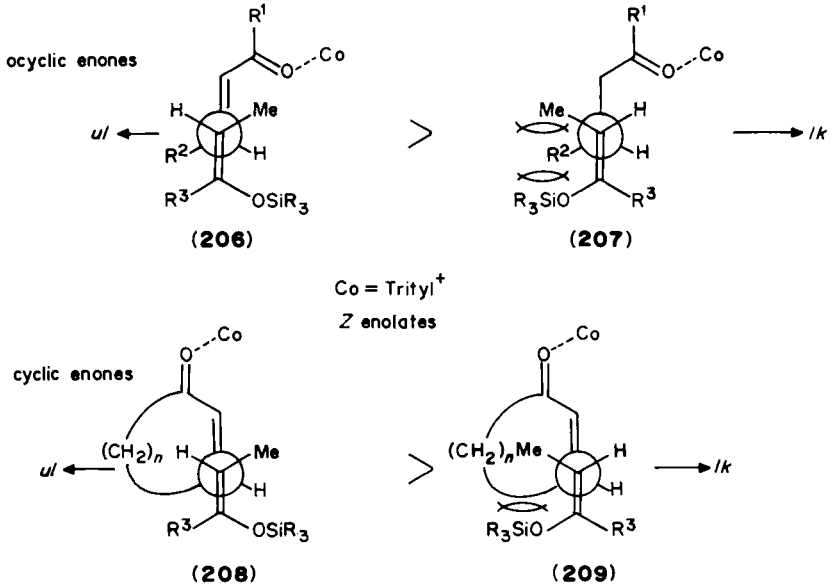
(78)

TABLE 49. Stereochemistry of additions of silyl enol ethers $R^3C(OSiR_3)=CHMe$ 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^3	Configuration	Lewis acid[a]	*ul*	*lk*	Ref.
—$(CH_2)_3$—		*t*-BuMe_2	Ph	*Z*	$TrClO_4$	77	23	516
—$(CH_2)_3$—		*t*-BuMe_2	Ph	*Z*	$TrPF_6$	78	22	516
—$(CH_2)_3$—		*t*-BuMe_2	Ph	*Z*	$TrSnCl_5$	79	21	516
—$(CH_2)_3$—		*t*-BuMe_2	Et	*Z*	$TrClO_4$	54	46	516
Ph	Me	*t*-BuMe_2	Et	*Z*	$TrClO_4$	85	15	516
Ph	Me	*t*-BuMe_2	Et	*E*	$TrClO_4$	77	23	516
Ph	Me	Et_3	Et	*E*	$TrClO_4$	71	29	516
Ph	Me	Me_3	Et	*E*	$TrClO_4$	59	41	516
t-Bu	Me	Me_3	Et	*E*	$SnCl_4$	87	13	514
t-Bu	Me	Me_3	Et	*Z*	$SnCl_4$	89	11	514
t-Bu	Me	Me_3	Et	*Z*	$TiCl_4$	88	12	514

[a]Tr = Trityl.

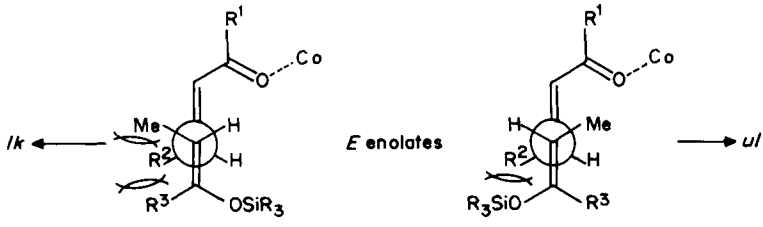




SCHEME 1

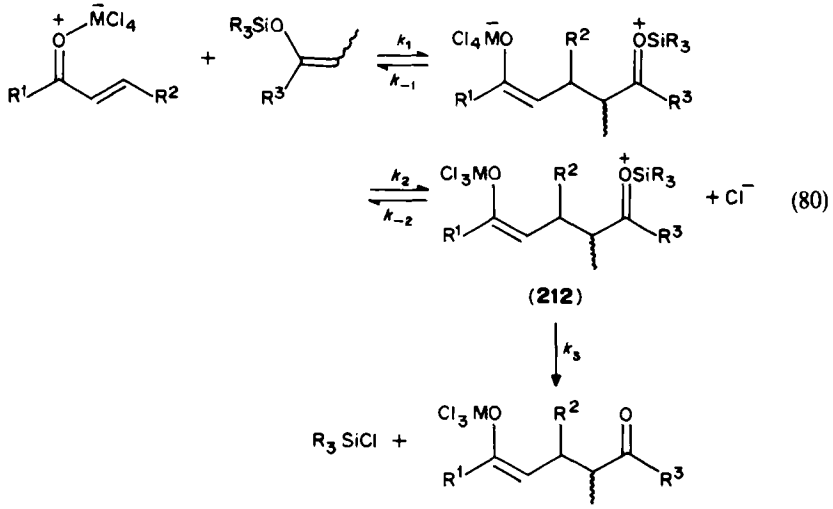
The sterically large trityl cation initially interacts with the enone, and the activated enone is attacked by the silyl enol ether with its bulky siloxy group in such a way that the steric hindrance between trityl cation and the trialkylsiloxy group can be minimized. Transition state **206** is favoured 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



SCHEME 2

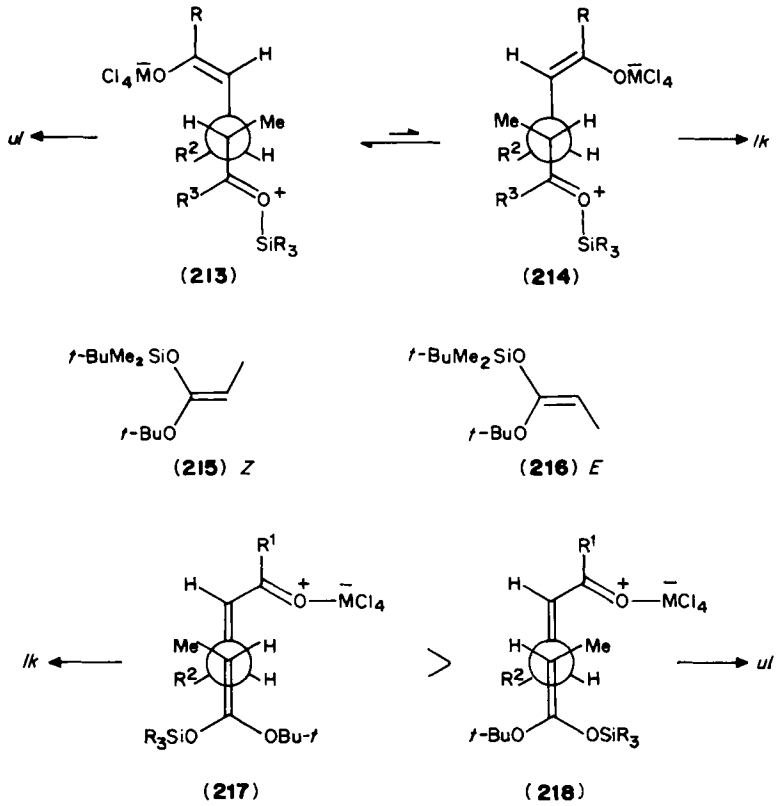
oxygen atom of the new carbonyl group[514] (equation 80). It seems that the initial equilibrium is not very favorable, and the retro-Michael reaction competes with desilylation of **212**. It is possible that *anti* stereochemistry predominates because gauche interactions are minimized in conformation **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 $-78\,^{\circ}C$ 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

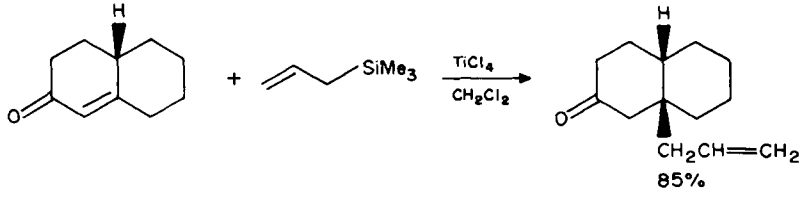
TABLE 51. Stereochemistry of reactions of silyl enol ethers $XC(OSiR_3)=CHMe$ with enones $R^2CH=CHCOR^1$ at $-78\,^{\circ}C$ in dichloromethane in the presence of Trityl perchlorate[510]

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).



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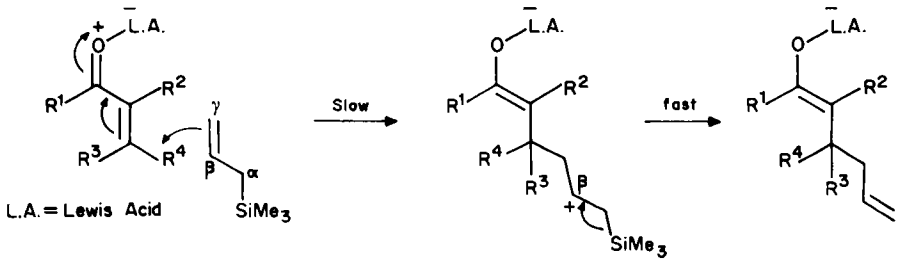


(82)

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].

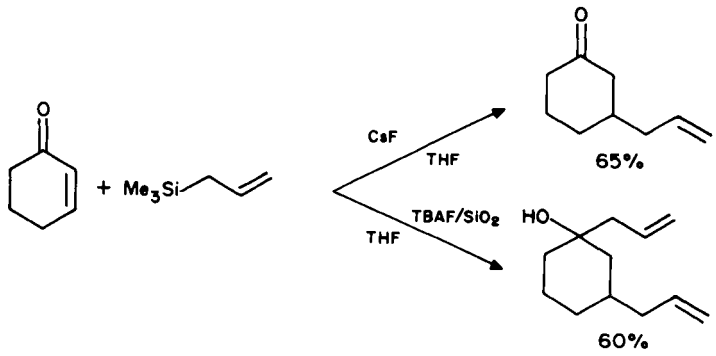
Fluoride ion catalysis can be used as an alternative to the Lewis acid-mediated allylation[536]. Although its mechanism is not clearly established, it seems that addition of a fluoride salt to an allylsilane probably occurs via the rapid formation of a non-basic pentacoordinate organosilicon nucleophile[537].

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]

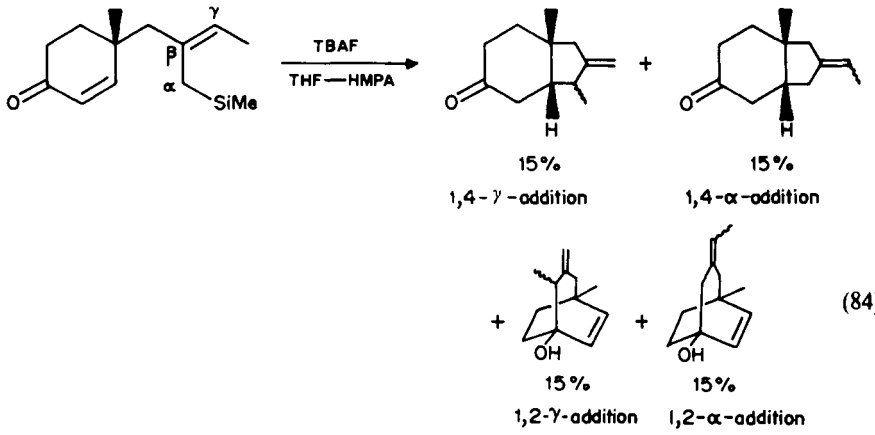
Lewis acid	Temperature (°C)	Time (h)	Yield (%)
$TiCl_4$	−78	1	74
BF_3–Et_2O	−78 to 25	24	< 50
BF_3	−78 to 25	24	no reaction
BCl_3	−78	32	< 20
$ZnCl_2$[a]	−78	72	no reaction

[a]A 1:1 mixture of ether and dichloromethane was used as solvent.

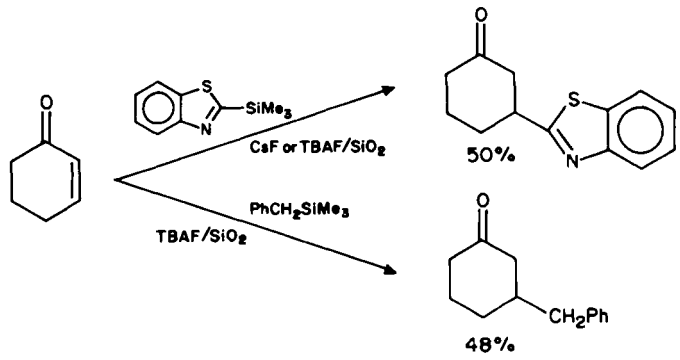


(83)

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)



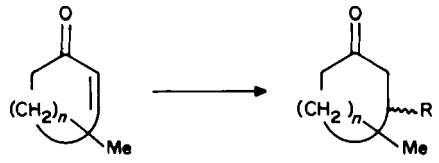
(85)

TABLE 53. Conjugate additions of allyltrimethylsilane and *n*-propylmagnesium bromide to methyl-substituted cyclic enones[521]

Enone	$CH_2{=}CHCH_2SiMe_3$, $TiCl_4$ CH_2Cl_2, −78 °C			*n*-PrMgBr, CuI THF, −20 °C		
	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].



n=3,4 *n*=3,4 R=All or *n*-Pr (86)

VI. CARBON–CARBON DOUBLE BOND FORMATION FROM WITTIG-TYPE REACTIONS

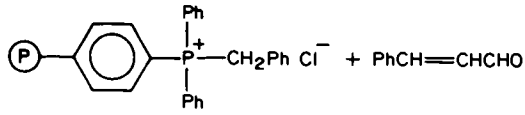
Among the usual approaches to the synthesis of olefins from a carbonyl compound, such as Knoevenagel condensations[544,545] or Peterson olefinations[474,546–548], Wittig-type reactions seem to be the most general and the most easily applicable to α,β-unsaturated aldehydes and ketones. In fact, the papers 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)

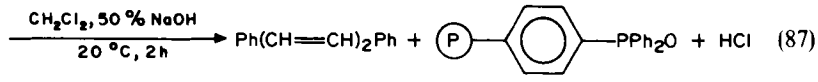
Usually, double or triple bonds conjugated with the carbonyl do not interfer in the Wittig reactions, the attack being at the carbonyl double bond.

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).

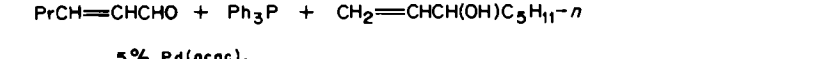


P = linear polystyrene



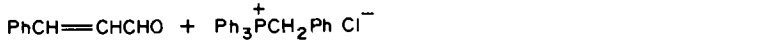
75%

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).



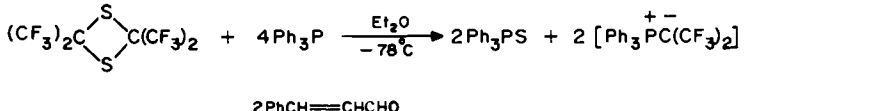
27%

Potassium fluoride supported on alumina also catalyzes Wittig reactions, without any organic solvent (equation 89)[559].



70%

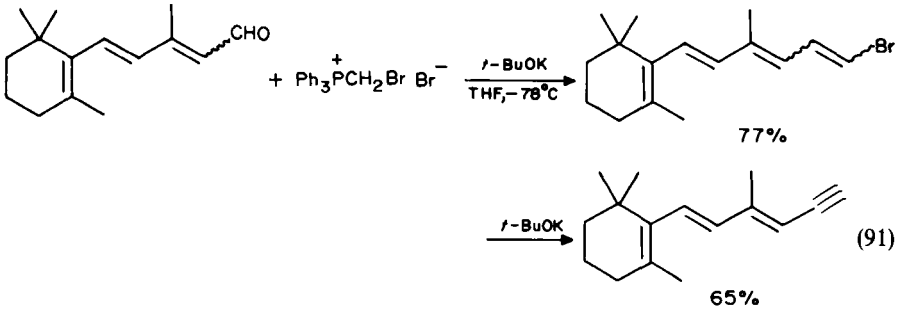
Among the new Wittig reagents, it is noteworthy that a phosphonium analog of Middleton's phosphorane is generated *in situ* from tetrakis(trifluoromethyl)-1,3-dithietane and triphenylphosphine, and reacts with cinnamaldehyde giving the resultant *bis*-trifluoromethyl olefin in 56% isolated yield (equation 90)[560]. Ketones fail to give olefins under these conditions, since decomposition of the ylide occurs faster than olefination of the ketone.



56 %

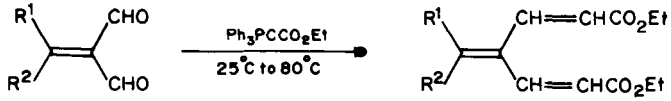
Enals are easily converted to 1-bromoolefins or terminal acetylenes by the use of Wittig

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)

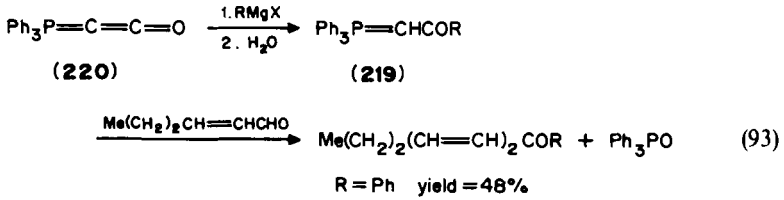
A double Wittig reaction can be performed on 2-ene-1,3-dial[562,563] with functionalized phosphorane in good yields (equation 92)[564].



(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].



(93)

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.

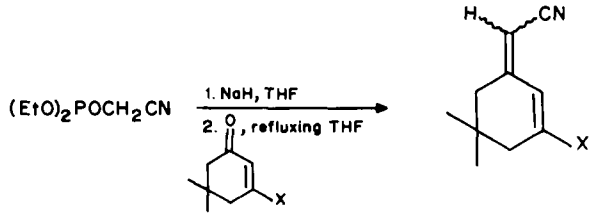
Cinnamaldehyde is converted into the corresponding α,β-γ,δ-dienic ester using triethyl phosphonate and a weaker base such as triethylamine in the presence of lithium bromide

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]

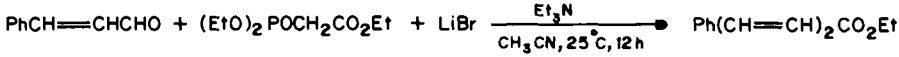
3-X substituent in the ketone	Time (h)	Isolated yield (%)	Product Z	Product E
H	18[a]	28	40	60
Me	24	56	46	54
Ph	24	55	63	37
Cl	24	47	40	60
Br	24	80	50	50
OEt	16	92	62	38
SEt	24	90	35	65
CH_2Ph	48[a]	82	44	56
p-$NO_2C_6H_4$	24	70	47	53

[a]Reactions performed at room temperature.

(equation 95)[581]. Apart from cyclohexanone, simple ketones fail to react under these conditions.



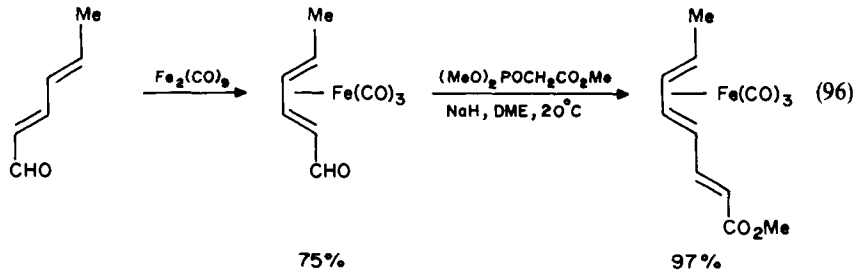
(94)



(95)

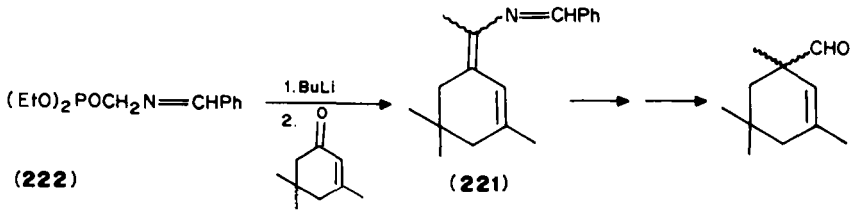
The polymer-supported phosphonate technique has also been successfully used with enals and β-ionone in THF at room temperature[582].

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)

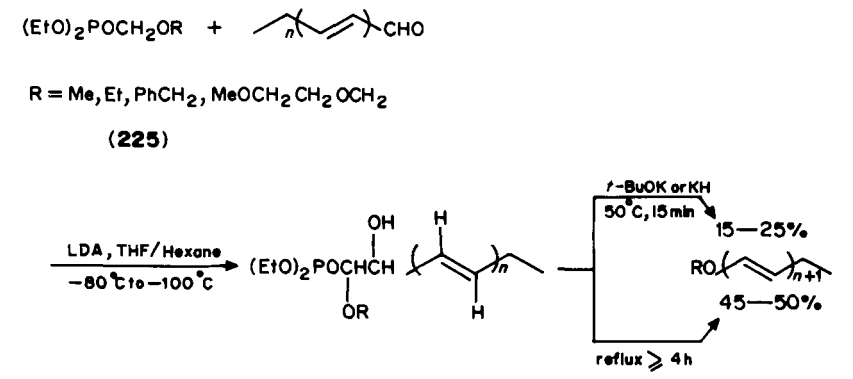
α,β-γ,δ-unsaturated sulphones and sulphoxides can be prepared via the Horner–Emmons reaction of α-enals and α-enones with α-phosphoryl sulphones **223** and sulphoxides **224** (equation 98). Selected results are presented in Table 55[585].

$$RSO_nCH_2PO(OEt)_2 + R^1COCH{=}CHR^2 \xrightarrow[THF]{BuLi} RSO_nCH{=}CR^1CH{=}CHR^2 \quad (98)$$

$n = 2$ (**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].



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].

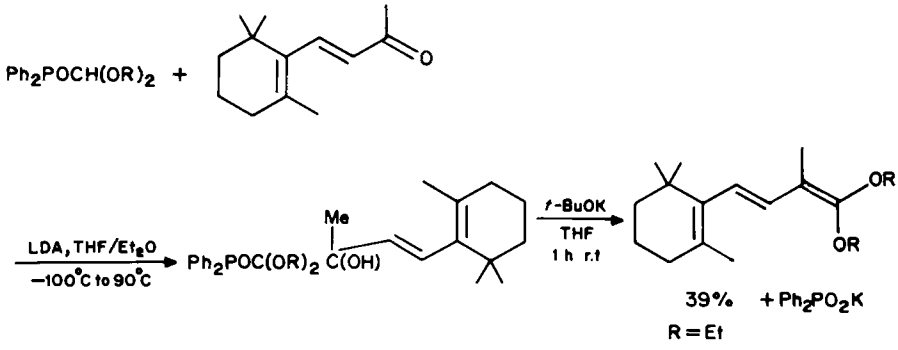
Cyanopolyenes can be prepared in a one-step route based on the Peterson reaction and the Horner–Emmons olefination of diethyl 2-cyano-2-trimethylsilylethanephosphonate **226** as exemplified by reaction with cinnamaldehyde (equation 101)[558].

Olefinations with phosphonates or phosphine oxides are seldom highly stereoselective. However, the stereochemistry with α,β-unsaturated aldehydes tends towards an *E*

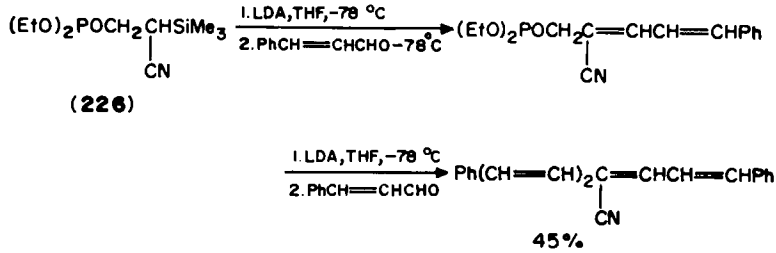
TABLE 55. Reaction of phosphoryl sulphones **223** and phosphoryl sulphoxides **224** with $R^1COCH{=}CHR^2$ at $-78\,^{\circ}C$[585]

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)



(101)

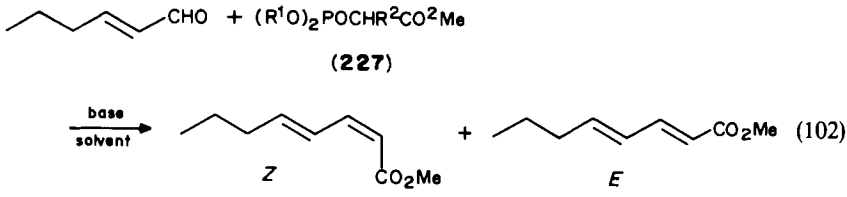
As exemplified in Table 56 with phosphonate **227**, the stereoselectivity depends upon the degree of substitution of the carbon α to phosphorus (entries a and b) as well as upon the nature of alkoxy groups bonded to phosphorus (entries a and c or d, or b and e) (equation 102)[592].

TABLE 56. Reactions between phosphonoesters **227** and 2-hexenal (*E*) under various conditions[592]

Entry	227 R^1	227 R^2	Conditions[a]	Overall yield (%)	Product *Z*	Product *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

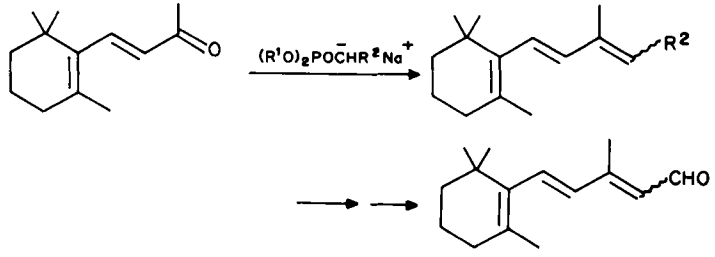
[a]Conditions: (A) KN $(TMS)_2$/18-crown-6/THF; (B) K_2CO_3/18-crown-6/Toluene.

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 counterions 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 (%)	Z	E	**230** Yield (%)	Z	E	**231** Yield (%)	Z	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.

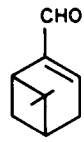
cyanomethylphosphonate (**230**) and diphenyl cyanomethylphosphine oxide (**231**) with enals **232–235** and β-ionone (**236**) in various media[606] (Table 57).

R_2POCH_2CN

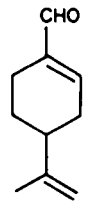
R = EtO (**229**)
R = *i*-PrO (**230**)
R = Ph (**231**)

MeCH=CHCHO (**232**)

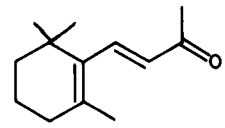
CH_2=CMeCHO (**233**)



(**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

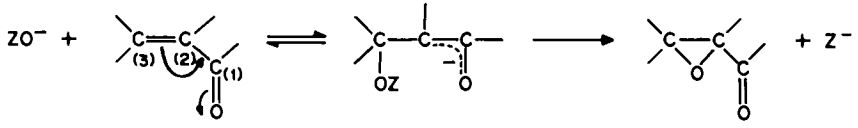
[a]Methods: (A) *n*-BuLi/THF; (B) *t*-BuOK/DMF.

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^-, $t\text{-}BuO^-$ 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].



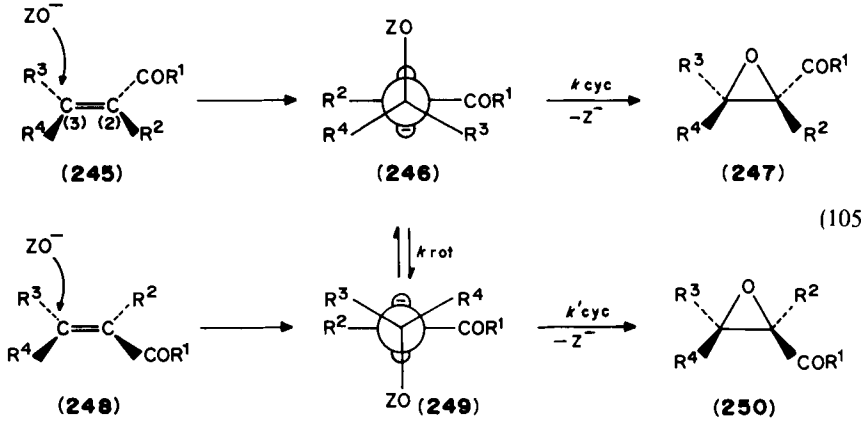
(242) **(243)** **(244)**

(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

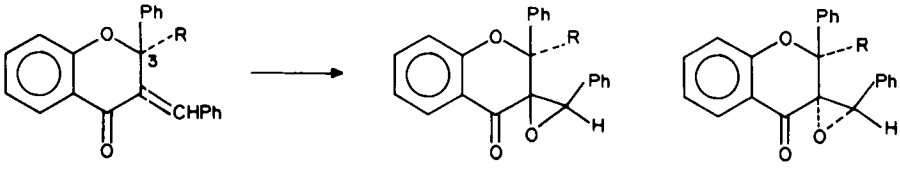
nucleofuge as compared to Cl^-, $k_{rot} > k_{cyc}$ and the product ratio is determined exclusively by the relative energies of the transition states leading to the diastereomeric epoxides. Stereoselectivity but not stereospecificity is often observed[609,621]. If HCA(C—OOBu-*t*) ~ HCA(C—OOH), *t*-BuO^- 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.

cis and *trans*
(251) **(252)** (106)



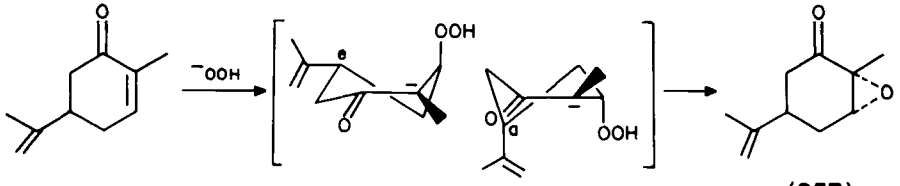
cis and *trans*
(253) R = H
(256) R = Ph
(254) R = H
(255) R = H
(107)

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]

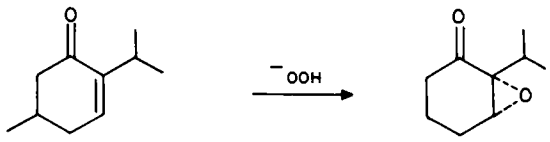
Enone	Product isomers	*trans/cis* ratio
(+)-(1*R*)-Pulegone	(−)-(1*R*:4*R*)-*trans*	64.5
	(+)-(1*R*:4*S*)-*cis*	35.5
(+)-(1*S*:5*R*)-Pinocarvone	(−)-(1*R*:2*S*:5*R*)-*trans*	35.5
	(+)-(1*R*:2*R*:5*R*)-*cis*	64.5
(+)-(1*R*:2*S*)-isopropylidene camphor	(−)-(1*R*:3*S*:4*S*)-*trans*	67
	(+)-(1*R*:3*R*:4*S*)-*cis*	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)



(258)

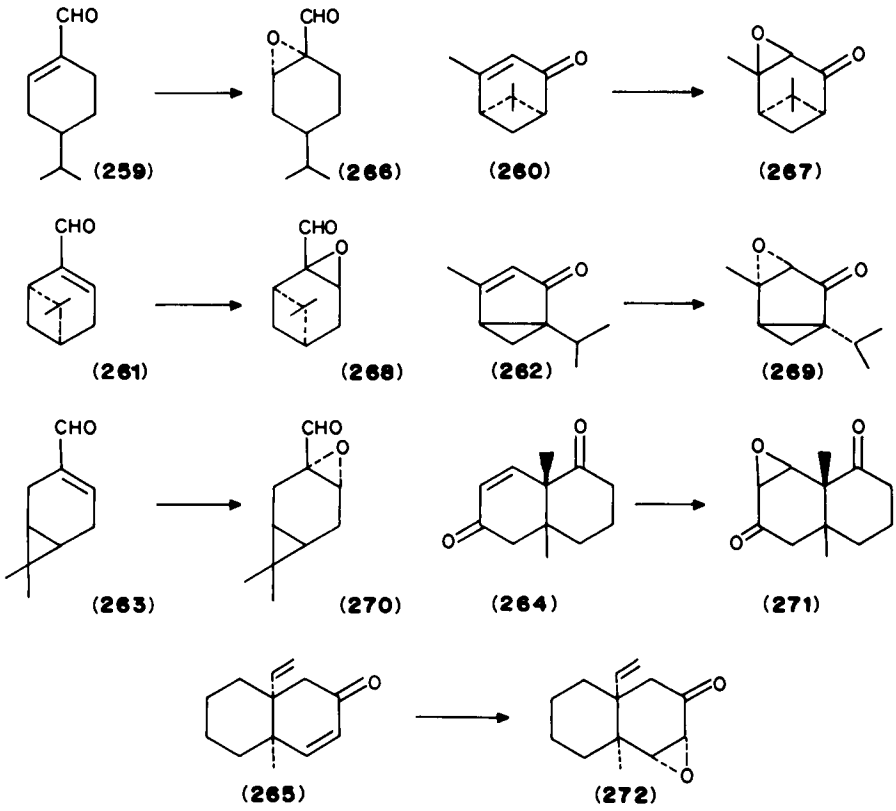
(109)

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).

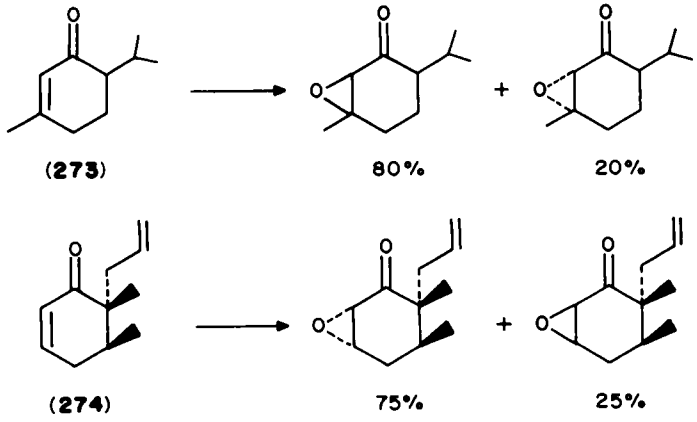
In the case of the epimerizable piperitone **273**[627] and 5,6,6-trisubstituted cyclohexenone **274**[634], a mixture of diastereomeric epoxides is obtained, but the product distributions are in agreement with the relative conformational stabilities of the intermediates (Scheme 5).

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).



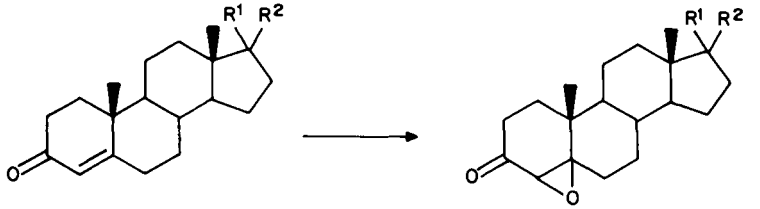
SCHEME 4



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	

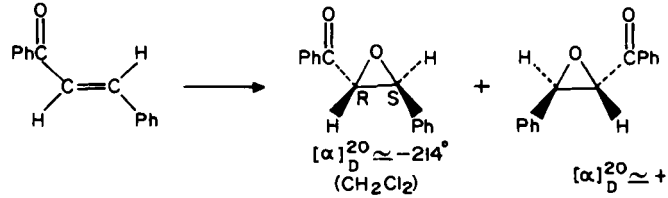


(110)

(275) α or β **(276)**

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)

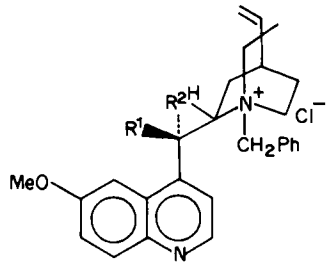
Owing to the many factors involved in the asymmetric epoxidation (structure and amount of the catalyst, solvent, temperature and nature of the oxidant), it is difficult to rationalize the occurrence of asymmetric induction. Nevertheless, some inferences can be made.

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

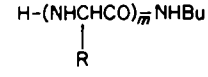
Catalyst	Yield (%)	$[\alpha]_D^{20}$ in CH_2Cl_2 (deg)	e.e. (%)	Ref.
277	99	−51	24	636,637
278	—	+49	23	636,637
279 $m = 10$ (L)	75	−199.5	93	638,639
279 $m = 10$ (D)	53	+193.5	90	638,639
279 $m = 30$ (L)	77	−205.4	96	638,639
280 $m = 10$ (L)	60	−182.2	84	638,639
280 $m = 30$ (L)	44	−189.8	88	638,639
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) $R^1 = OH$, $R^2 = H$

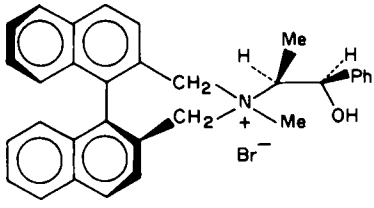
(278) $R^1 = H$, $R^2 = OH$



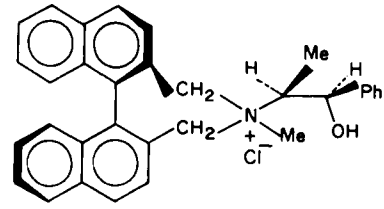
(279) R = Me

(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

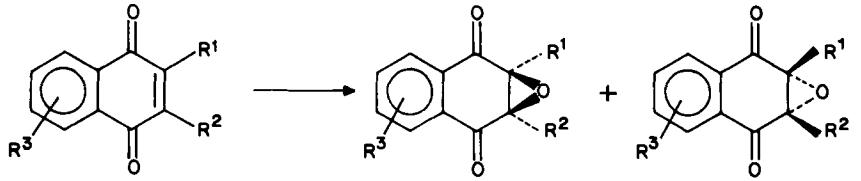
[a]BSA = Bovin Serum Albumin.

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).

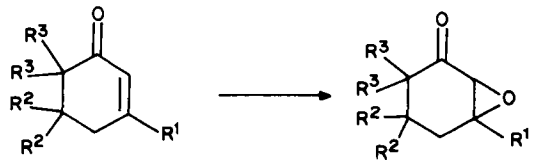
The degree of asymmetric induction in epoxidation of chalcone or substituted chalcones is influenced by the solvent. Toluene or carbon tetrachloride seems to be the solvents of choice when quininium benzyl chloride or poly-α-amino acids are used as catalysts[638,647,648]. However, no direct correlation 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			Oxidizing agent	Catalyst	Chemical yield (%)	$[\alpha]^{RT}$ in CH_2Cl_2	e.e. (%)	Ref.
R^1	R^2	R^3						
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).

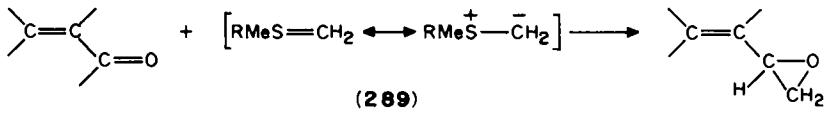
TABLE 65. Epoxidation of α-enones with electrogenerated superoxide and carbon acids[654]

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

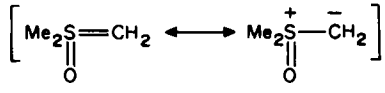


(289)

(114)

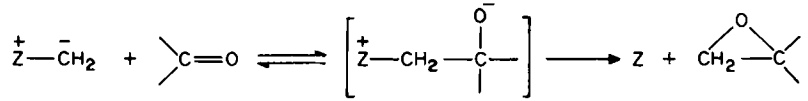
from trimethylsulphonium iodide and sodium hydride in dry dimethyl sulphoxide, are preferred. Thus, several compounds were converted to the corresponding oxiranes by selective addition of methylene to the carbonyl group, for instance benzalacetophenone (87% yield), carvone (89%), eucarvone (93%), pulegone (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).



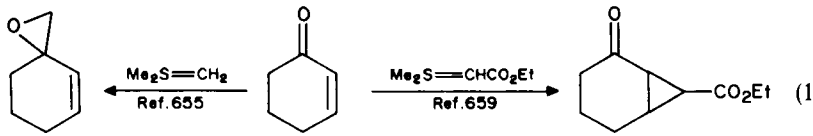
(290)

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)

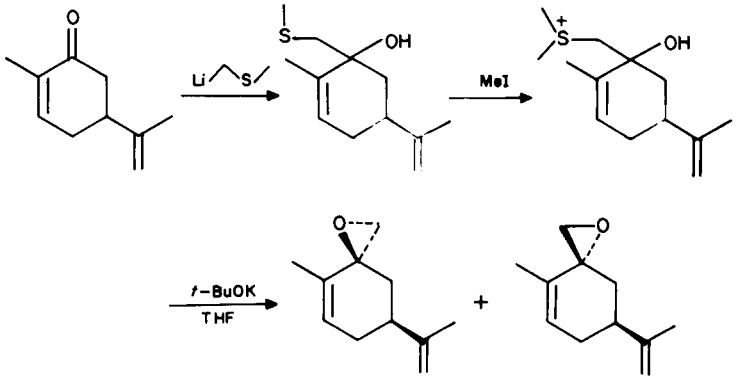


(116)

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].

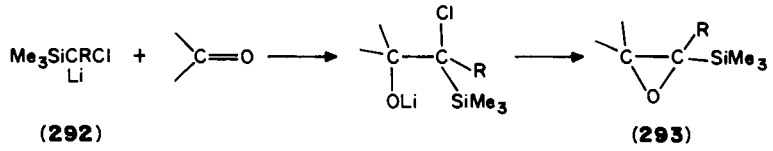
An alternative to the sulphur ylide route for the vinyl spiro epoxide formation from cyclenones, using sulphur compounds as starting materials, is the addition of [(methylthio)methyl] lithium on the carbonyl group, followed by methylation and closure of the hydroxysulphonium salt. Using this method, 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].



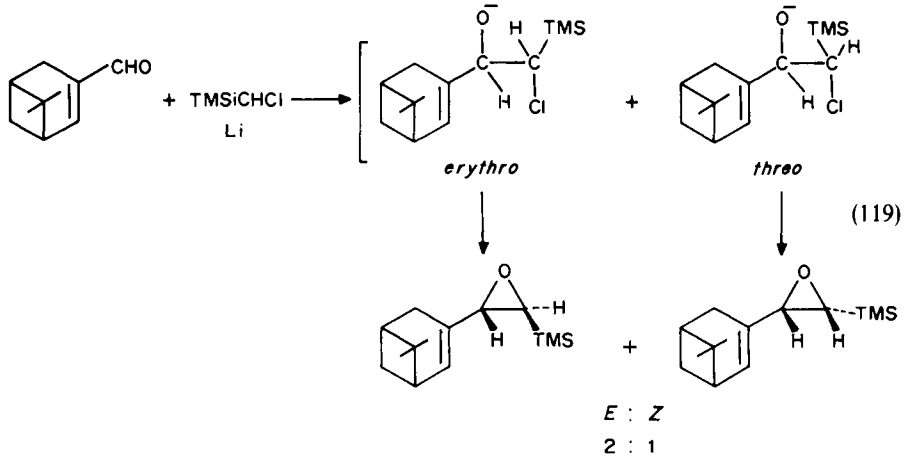
(117)

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].



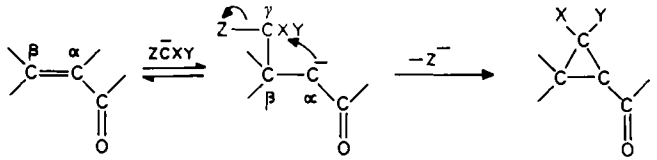
(292) (293) (118)



(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].

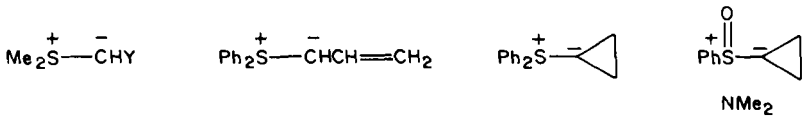


(294) (295)

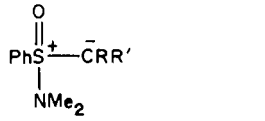
(120)

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.

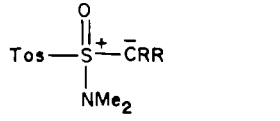
Similar reactions have been performed with nitrogen ylides such as cyanotrimethylammonium methylide[679] and substituted pyridinium phenacylides[680]. Many substituted cyclopropanes can also be made by treatment of α-enones with ZC^-XY in which Z is Cl or



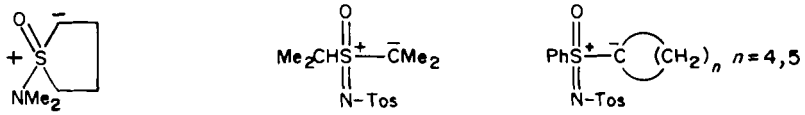
(296) (297) (298) (299)



(300) R = H, R' = Me
R = R' = Me

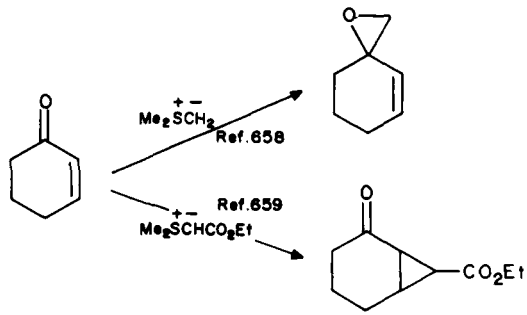


(301) R = H, R' = Me
R = R' = Me

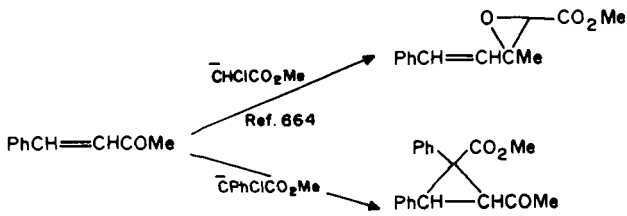


(302) (303) (304)

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).



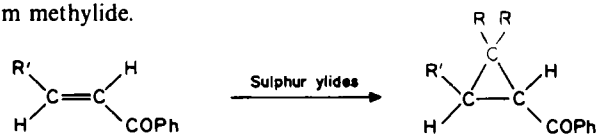
(121)



(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.



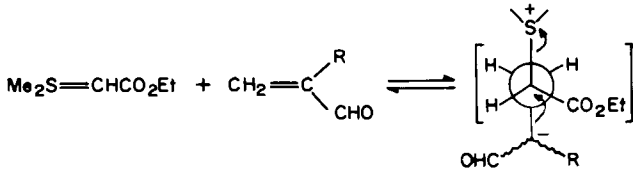
(123)

(**8**) R′ = Ph
(**305**) R′ = COPh

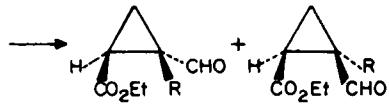
(**306**) R′ = Ph
(**307**) R′ = COPh

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 = CO_2Et (**308**) R = H, Me



trans *cis*

(**309**) R = H, Me

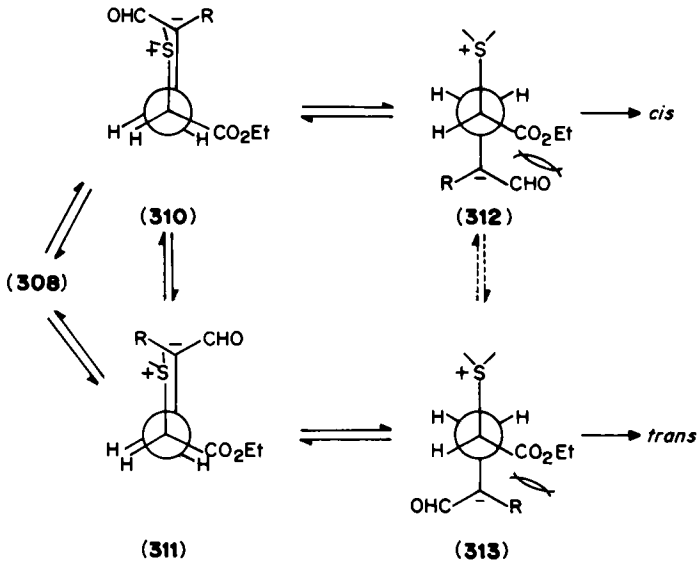
(124)

In all cases, predominant *trans* cyclopropanation to give **309** was observed. Electrosta-

TABLE 66. Stereochemistry of cyclopropanation of **308** by ethyl (dimethysulphuranylidene) acetate

R in **308**	Solvent	Product distribution		Ref.
		cis	*trans*	
H	PhH	8.5	91.5	671
H	Me_2CO	17	83	659
Me	PhH	32	68	671
Me	Me_2CO	45	55	659

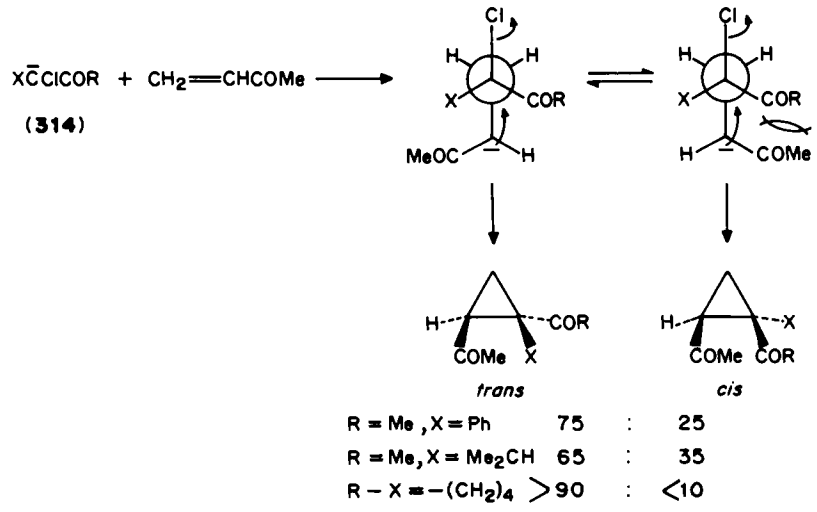
tic interactions favour initial formation of the eclipsed betaines **310** and **311** (equation 125)[550,625].



(125)

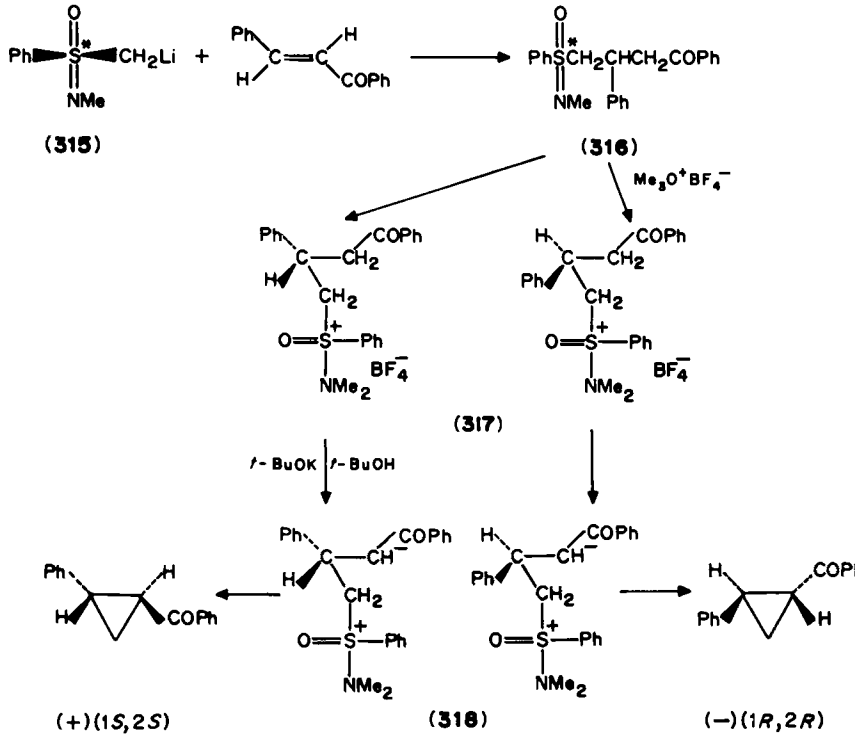
Subsequent collapse to cyclopropanes *via anti* conformers **312** and **313** is retarded in solvents of low dielectric constant such as benzene, that are less capable of solvating the proposed internal ion-pair. These solvents promote the equilibration of **310** and **311**, resulting in preferential 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)

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].

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The Chemistry of Enones
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CHAPTER **11**

Addition of electrons or radicals to α,β-unsaturated ketones

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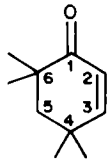
I. RADICAL IONS OF α,β-UNSATURATED KETONES

A. Electron Spin Resonance Studies

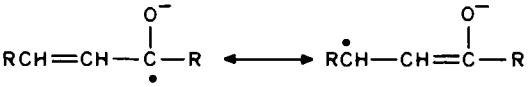
1. General comments

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].

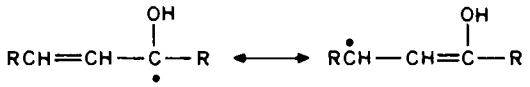
(1)



(2)

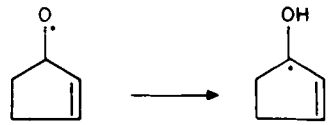


(3)



(4)

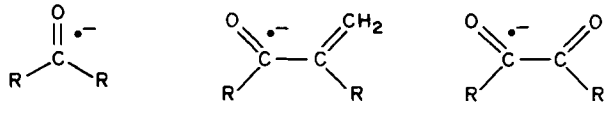
†In ESR spectroscopy the coupling of the electron spin with nuclear spins is measured by the splitting constant (a) which is usually reported in terms of magnetic field (1 gauss = 2.8×10^6 Hz). The coupling constant is a measure of electron density in the s-orbital of the nucleus in question. For protons 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)

$$CH_2{=}CH{-}CH_2OH + O\cdot^- \rightarrow CH_2{=}CH{-}\dot{C}H{-}OH + OH^-$$
$$\rightarrow CH_2{=}CH{-}\dot{C}H{-}O^- + H_2O \qquad (2)$$

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.

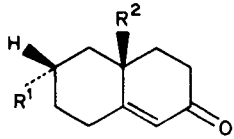


(**5**) (**6**) (**7**)

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].

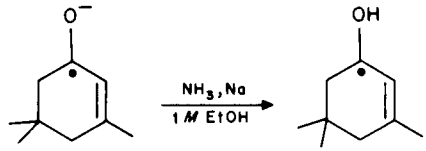
Radical anions of α,β-unsaturated ketones are readily protonated. Although little or no protonation is observed in liquid ammonia, the presence of 1 M ethanol leads to complete protonation of the ketyl (~ 10^{-3} M) in reaction 3 in a continuous-flow ESR experiment[2]; a pK_a of at least 17 is thus indicated. 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*-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*-$Pr_4N^+ClO_4^-$.

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

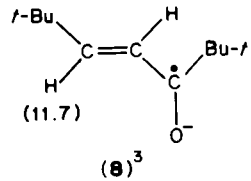
$a^H = 12.1$(1H), C(4), axial; 9.2(1H), C(6) axial; 8.8(3H), C(3), methyl; 4.4(1H), C(4), equat.; 3.0(1H), C(6), equat.; 1.0(1H), C(2), in Gauss

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*

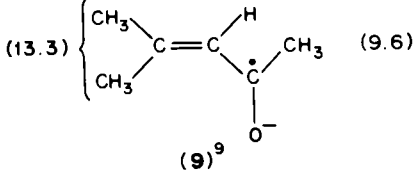
In 1970–71, ketyls **8–11** were reported[3,9,10]. All display a large hfsc (a^H) for the C(β) hydrogen atom because of the value of the electron spin density (ρ_c) at C(β) and the McConnell relationship, $a^H = -23\rho_c$.

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]

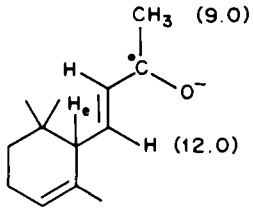
$a^H = 0.35$(9H); 0.27(9H), in Gauss



(**9**)[9]

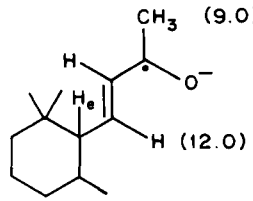
a^H in Gauss

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].



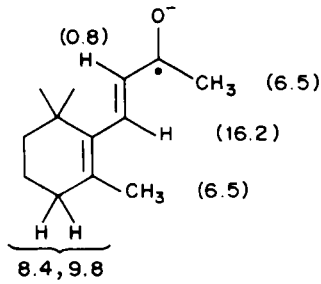
(**10**), α-ionone[10]

a^H for H_e = 3.2 Gauss



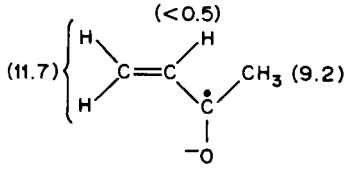
(**11**)[10]

a^H for H_e = 3.2 Gauss



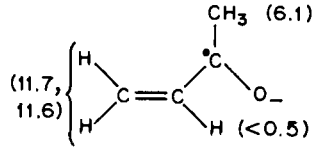
(**12**), β-ionone[7,10]

a^H in Gauss



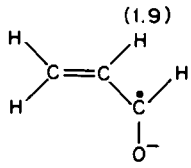
(**13**), *s-cis*

a^H in Gauss



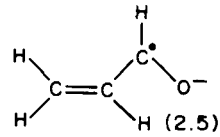
(**14**), *s-trans*

a^H in Gauss



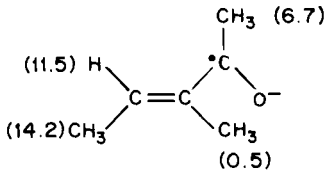
15[6]

a^H = 12.85 (1H), 12.4 (1H), 12.0 (1H), in Gauss



16[6]

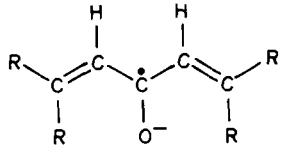
a^H = 13.2 (1H), 12.4 (1H), 11.1 (1H), in Gauss



(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**).

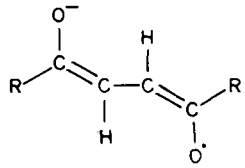


(18)

(**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.

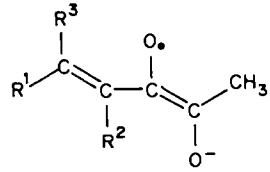


(19)[11]

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) $R^1 = R^3 = CH_3$, $R^2 = H$; $a^H = 4.6(3H), 4.3(3H), 3.6(3H), 2.0(1H)$

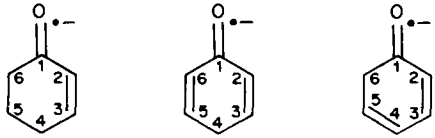
(f) $R^1 = R^2 = CH_3$, $R^3 = H$; $a^H = 4.1(3H), 3.5(1H), 3.3(3H), 1.2(3H)$

(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-



(21) (22) (23)

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

TABLE 2. Hyperfine splitting constants (in Gauss) for ketyls **21–23**

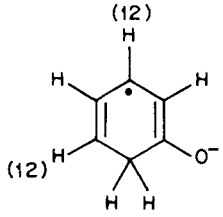
Ketyl	a_2^H	a_3^H	a_{4e}^H	a_{4a}^H	a_{6e}^H	a_{6a}^H	Ref.
21, Unsubstituted	0.8	13.3	6.1	23.5	4.35	12.9	9
21, 3,5-Dimethyl	1.25	14.8[a]	7.5	23.2	4.6	13.8	9
21, 4,4-Dimethyl	< 1	~ 13	< 1[a]	< 1[a]	4.8	13.0	9
21, 5,5-Dimethyl	0.7	13.2	5.8	23.7	4.4	12.9	9
21, 4,4,6-Trimethyl	< 1	~ 13	< 1[a]	< 1[a]	< 1[a]	~ 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	—	~ 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.

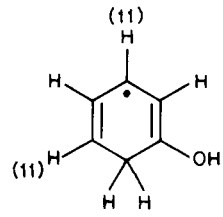
not depend on the sum of the spin densities (i.e. c_2^3 and c_5^3) but upon the square of the sum of the molecular orbital coefficients[20].



(44)

a^H in Gauss

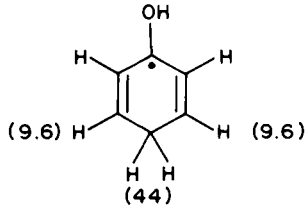
(23a)



(44)

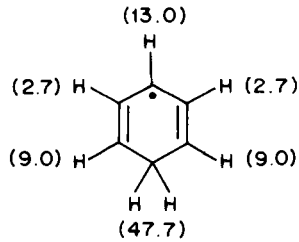
a^H in Gauss

(23b)



a^H in Gauss

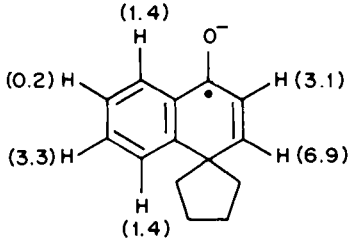
(24)



a^H in Gauss

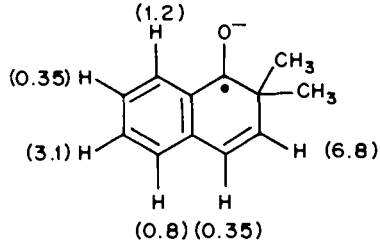
(25)

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

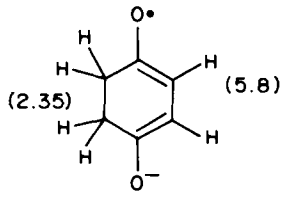
(26)[4]



a^H in Gauss

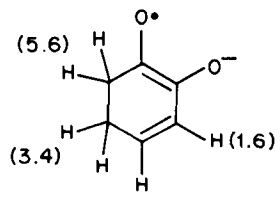
(27)[4]

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].



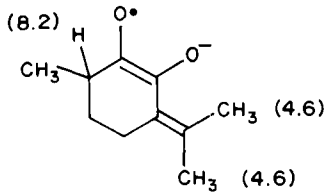
a^H in Gauss

(28)



a^H in Gauss

(29)

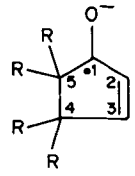


a^H = 1.6, 0.9, 0.8, 0.3, in Gauss

(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].



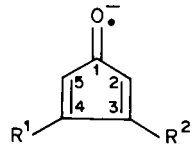
(31)

(**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

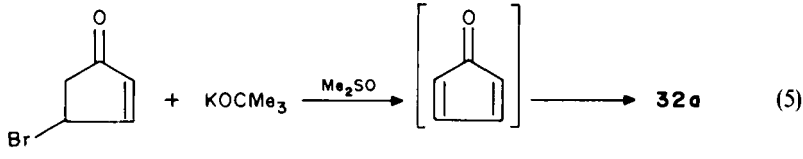
Tetraarylcyclopentadienones readily form a persistent ketyl. For the tetraphenyl derivative the ketyl has hfs by 12 *ortho* and *para* hydrogen atoms (0.56 Gauss) and two sets of *meta* hydrogen atoms [0.28 (4H) and 0.14 (4H) Gauss][22]. The unsubstituted ketyl **32** ($R^1 = R^2 = H$) has a relatively 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 [$\sum a^H/Q^H_{CH} = 16.4/(23–28)$] while for **33** the spin density at C(2)–C(7) approaches 1 ($\sum a^H = 27.6$ Gauss). Ketyl **33** is thus a 7π system (**33a**) while **32** has a large contribution from the 6π resonance hybrid (**32d**).

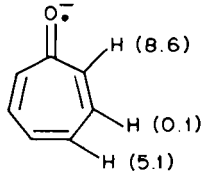


(**32**)

(**a**) $R^1 = R^2 = H$: $a^H = 2.9(2H)$, C(2,5); 5.3(2H), C(3.4), in Gauss
(**b**) $R^1 = H$, $R^2 = CH_3$: $a^H = 2.4(1H)$, 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**) $R^1 = R^2 = CH_3$: $a^H = 2.5(2H)$, C(2,5); 5.9(6H), C(3,4) methyls, in Gauss;

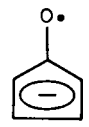


(5)



a^H in Gauss

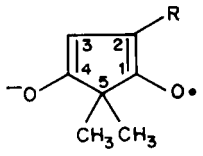
(**33**)[4,24]



(**32d**)

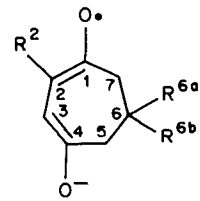
(**33a**)

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].



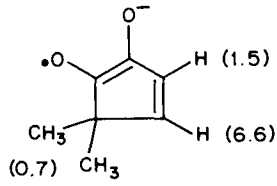
(**34**)

(**a**) R = H: $a^H = 6.4(2H)$, in Gauss
(**b**) $R = CH_3$: $a^H = 6.5(3H)$, C(2); 5.8(1H), C(3), in Gauss



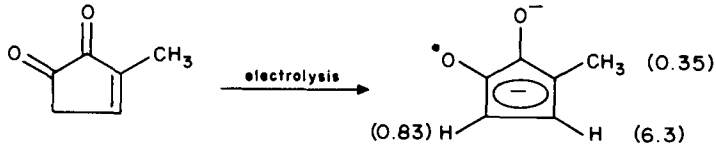
(35)

(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



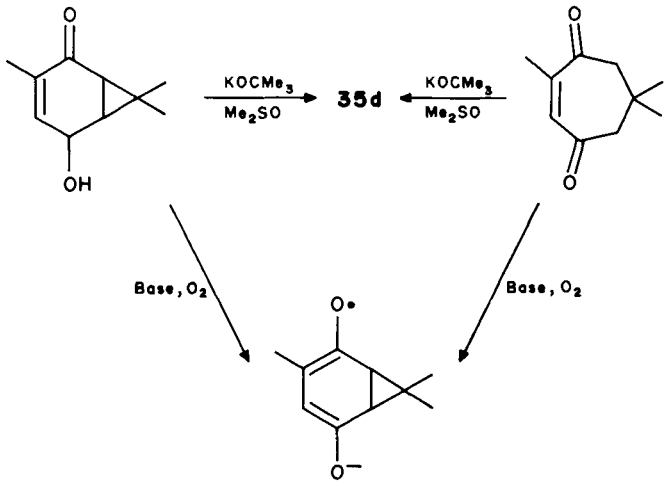
(6)

a^H in Gauss

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].

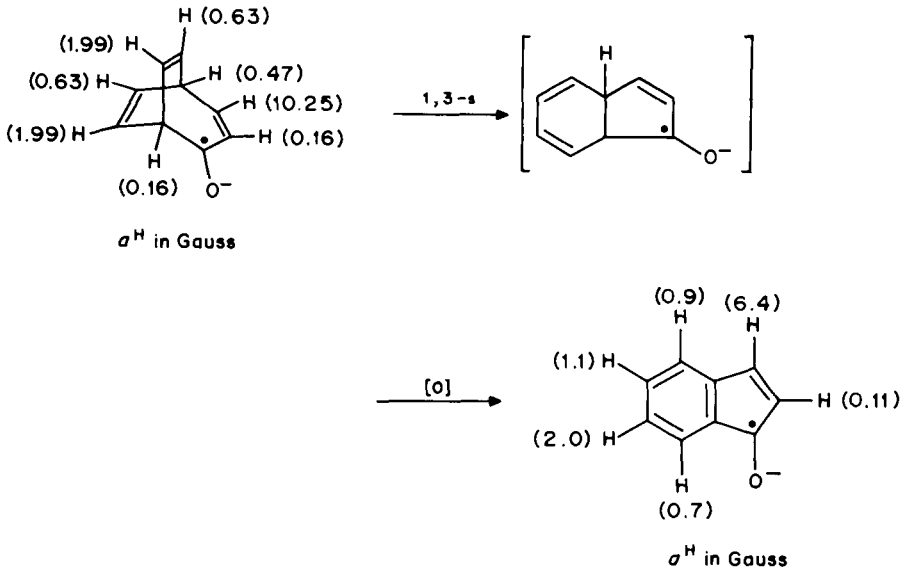
5. *Molecular rearrangement of a bicyclic ketyl of an α,β-unsaturated ketone*

Electrolytic reduction of bicyclo[3.2.2]nona-3,6,8-triene-2-one in DMF or CH_3CN at $-60\,^{\circ}C$ or below yields the expected ketyl[25]. However, above $-60\,^{\circ}C$ 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

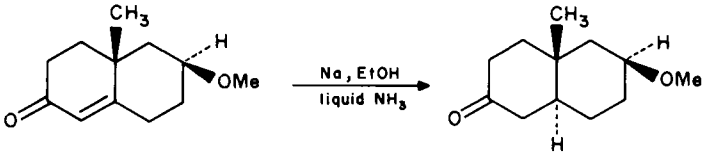
metal, usually lithium or sodium, in liquid ammonia in the presence of a proton donor[28]. The pK_a of $R_2C{=}CH{-}\dot{C}(OH)R$ is too low for $R_2C{=}CH{-}\dot{C}(O^-)R$ to abstract a proton from NH_3; see Section I.A.1. The reactions involve the formation of the enolate anion which can be trapped by MeI to give the C-methylated product[29] (Scheme 2).

$$R_2C{=}CH\dot{C}(O^-)R \xrightarrow[\text{liquid } NH_3,R'OH]{\text{Na or Li}} R_2CH{-}CH{=}C(O^-)R$$

$$R_2CHCH(CH_3)COR \xleftarrow[\text{MeI}]{H_2O} R_2CHCH_2COR$$

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).

$$t\text{-BuCH}{=}\text{CHCOBu-}t \xrightarrow{\text{Na, THF}} t\text{-BuCH}{=}\text{CH}{-}\dot{\text{C}}(\text{ONa})\text{Bu-}t$$

(8a)

$$2\,\mathbf{8a} \longrightarrow t\text{-BuCH}{=}\text{CH}{-}\text{C}(\text{ONa})\text{Bu-}t$$

$$\xrightarrow{H_2O}$$

$$t\text{-BuCH}{=}\text{CH}{-}\text{C}(\text{ONa})\text{Bu-}t$$

$$t\text{-BuCH}{=}\text{CH}{-}\text{C}(\text{OH})\text{Bu-}t$$

$$t\text{-BuCH}{=}\text{CH}{-}\text{C}(\text{OH})\text{Bu-}t$$

SCHEME 3

$$\mathbf{8a} + \text{ROH} \longrightarrow t\text{-BuCH}{=}\text{CH}\dot{\text{C}}(\text{OH})\text{Bu-}t$$

(4a)

$$2\,\mathbf{4a} \longrightarrow [t\text{-BuCH}{=}\text{CH}{-}\text{C}(\text{OH})(t\text{-Bu})\,]_2$$

$$\longrightarrow t\text{-BuCH}_2\text{CH}{=}\text{C}(\text{OH})\text{Bu-}t + t\text{-BuCH}{=}\text{CHCOBu-}t$$

$$\mathbf{8a} + t\text{-BuCH}_2\text{CH}{=}\text{C}(\text{OH})\text{Bu-}t \rightleftharpoons \mathbf{4a} + t\text{-BuCH}_2\text{CH}{=}\text{C}(\text{O}^-)\text{Bu-}t$$

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.

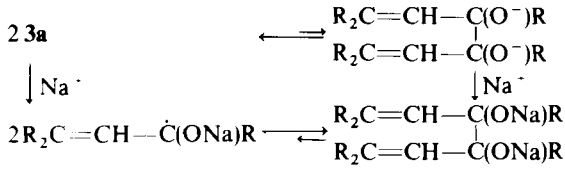
$$R_2C{=}CH{-}COR + M^0 \rightarrow R_2C{=}CH{-}\dot{C}(O^-)R\,M^+$$
$$R_2C{=}CH{-}\dot{C}(O^-)R + H^+ \rightarrow R_2CH{-}CH{=}C(O^{\cdot})R$$
$$R_2CH{-}CH{=}C(O^{\cdot})R + M^0 \rightarrow R_2CH{-}CH{=}C(OM)R$$

SCHEME 5

$$\underset{\textbf{(4b)}}{R_2C{=}CH{-}\dot{C}(OH)R} \rightleftharpoons R_2CH{-}C{=}C(O^{\cdot})R \qquad (8)$$

$$\textbf{3b} + \textbf{4b} \longrightarrow R_2CHCH{=}C(O^-)R + R_2C{=}CHCOR \qquad (9)$$

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.

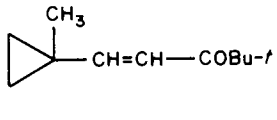


SCHEME 6

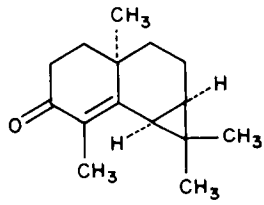
Indirect evidence for radical anions in enone reduction by alkali metals in liquid ammonia include the *cis* to *trans* isomerization observed for unreacted RCH=CHCOBu-*t* (R = Ph or *t*-Bu)[32]. However, although cyclopropylcarbinyl ring opening was observed upon alkali metal reduction of cyclopropyl 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)

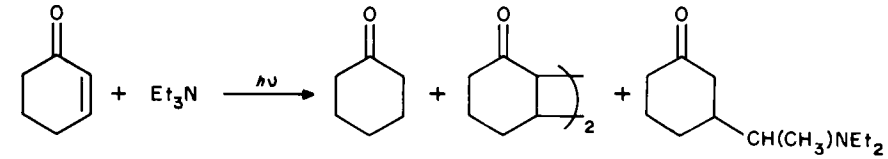
$CH_2{=}CHCH_2CH_2C(CH_3)_2CH{=}CHCOBu\text{-}t$

(40)

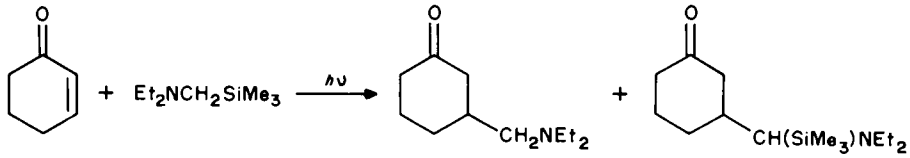
electron transfer will regenerate D: and $R_2C{=}CHCOR$, often with polarization of nuclear spins (CIDNP)[41] (reaction 11). Electron transfer occurs in competition with hydrogen atom abstraction from trialkylamines[38], from alcohols[42] or benzylic positions[43] (leading to the saturated ketone) and 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 $Et_2NCH_2SiMe_3$.

$$R_2C{=}CHCOR^* + D: \longrightarrow R_2C{=}C\dot{C}(O^-)R + D^{\cdot+} \tag{10}$$

$$R_2C{=}C\dot{C}(O^-)R + D^{\cdot+} \longrightarrow R_2C{=}CHCOR + D: \tag{11}$$



(12)



(13)

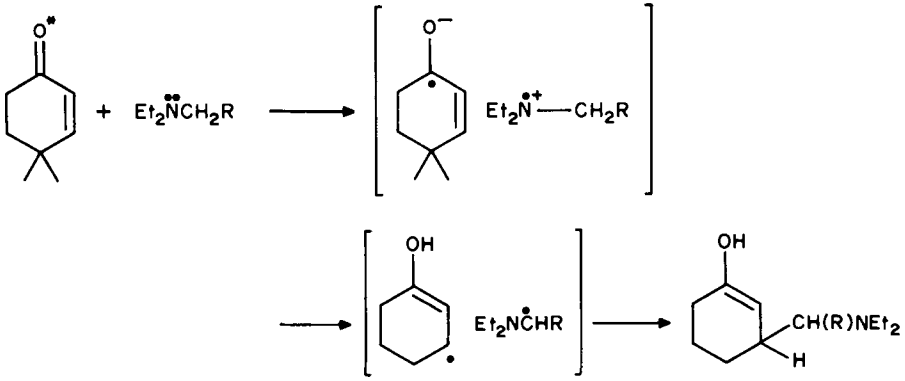
In solvents of low polarity the reaction proceeds via an ion pair in which the enone radical anion serves as the proton acceptor (Scheme 7). With $Et_2NCH_2SiMe_3$ in CH_3CN, or even better in CH_2Cl_2 or $c\text{-}C_6H_{12}$, the contact ion pairs reacts to form the substituted cyclohexanone with $R = Me_3Si$ 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

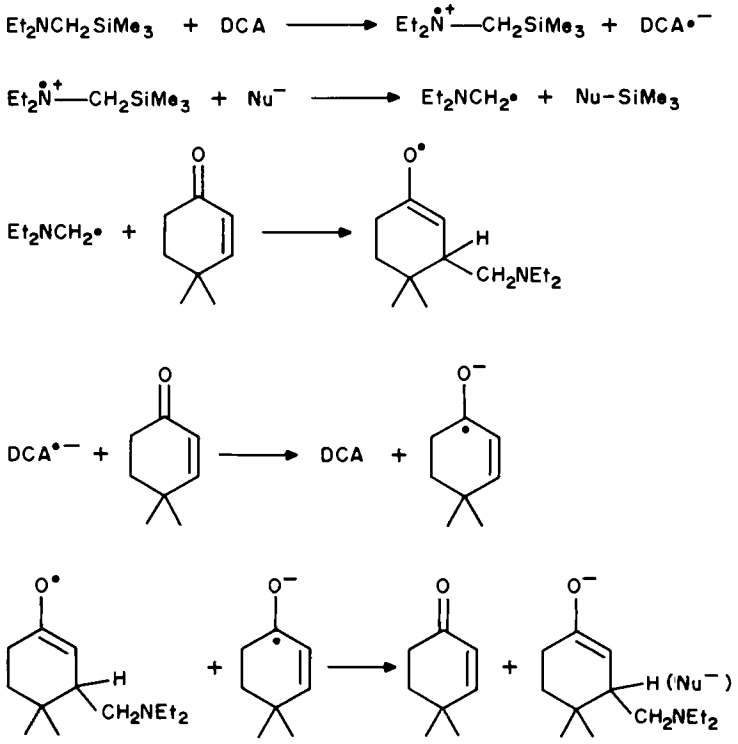
2-Cyclohexenone	Amine	Solvent	Substituted cyclohexenones (%)	Ref.
Unsubstituted	$Et_2NCH_2SiMe_3$	MeCN	3-$CH(NEt_2)SiMe_3$ (30%), 3-CH_2NEt_2 (0%)	44
Unsubstituted	$Et_2NCH_2SiMe_3$	MeOH	3-$CH(NEt_2)SiMe_3$(trace), 3-CH_2NEt_2 (30%)	44
Unsubstituted	Et_3N	Neat	3-$CH(CH_3)NEt_2$ (43%)[a]	40
4,4-Dimethyl	$Et_2NCH_2SiMe_3$	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, $(R_2CuLi)_2$, can occur by the process of Scheme 9[48].

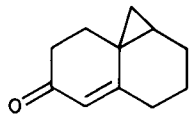
$$(R'_2CuLi)_2 + RCH{=}CH{-}COR \longrightarrow (R'_2CuLi)_2^+ \cdot + RCH{=}CH{-}\dot{C}(O^-)R$$
$$\longrightarrow (R'_2CuLi)_2^+{-}C(H)R{-}CH{=}C(O^-)R$$
$$\longrightarrow R'CH(R){-}CH{=}C(O^-)R + Li^+ + RCu + R_2CuLi$$

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 $E_{red} - E_{ox}$ 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 $((CH_3)_2CuLi)_n$ in Et_2O, conjugate addition is observed for $(CH_3)_2C{=}C(CH_3)COCH_3$ [E_{red} (vs. SCE) $= -2.35$] but not for 5,5-dimethyl-3-butoxy-2-cyclohexen-1-one ($E_{red} = -2.43$), cyclopropyl methyl ketone ($E_{red} = -2.88$) or bicyclo[4.1.0]heptan-2-one ($E_{red} = -2.81$)[39].

Reaction of Ph_3CLi in DME ($E_{ox} = -1.3$ V) with (*E*)-PhCH=CHCOPh ($E_{red} = -1.41$ V) occurs rapidly to form $Ph_3CCH(Ph)CH_2COPh$. On the other hand, reaction with (*E*)-*t*-BuCH=CHCOBu-*t* ($E_{red} = -2.22$ V) occurs slowly[52]. The recovered enone from the reaction of either (*Z*)-PhCH=CHCOBu-*t* ($E_{red} = -1.71$ V) or (*Z*)-*t*-BuCH=CHCOBu-*t* ($E_{red} = -2.21$ V) with $(Me_2CuLi)_2$ in 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 $(Me_2CuLi)_2$ or 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 $(Me_2CuLi)_2$, e.g. reaction 14[51], which could occur by cyclopropylcarbinyl radical ring opening or from nucleophilic attack at a cyclopropyl carbon atom.



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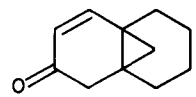

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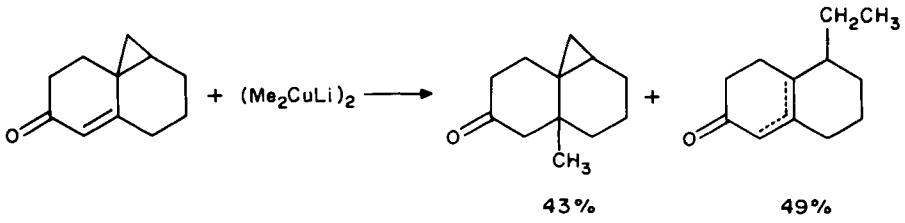
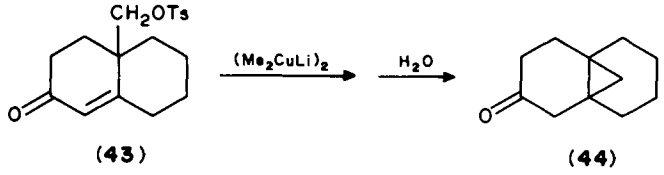


(14)

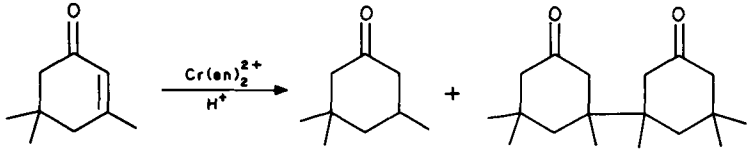
Fragmentations are observed in reactions of some enones with $(Me_2CuLi)_2$ which can be interpreted in terms of a radical anion intermediate. Thus, 4,4-dimethoxycyclohexadienone yields 4-methoxyphenol[49] and the octalone **43** yields the decalone **44** (reaction 15)[50]. (See Note Added in Proof on page 512.)



(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 $R\dot{C}H—CH=C[OCr(en)_2^{2+}]Bu\text{-}t$ is formed reversibly or can dissociate into $RCH=CH—\dot{C}(O^-)Bu\text{-}t$ 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)

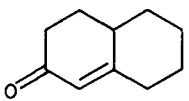
$$RCH=CH—COR + Cr(en)_2^{2+} \longrightarrow R\dot{C}H—CH=C(OCr(en)_2^{2+})R$$

$$\xrightarrow[(-RS\cdot)]{RSH} RCH_2CH=C(OCr(en)_2^{2+})R \xrightarrow{H^+} RCH_2CH_2COR + Cr(en)_2^{3+}$$

$$2RS\cdot \longrightarrow RSSR$$

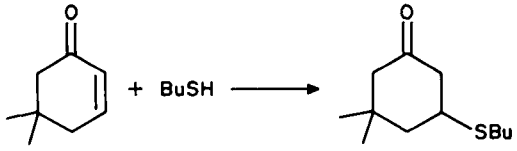
SCHEME 10

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-trimethylcyclo- hexanone (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.



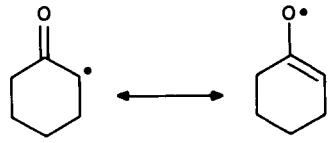
(17)

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

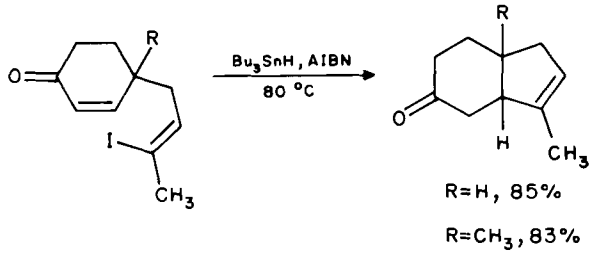
Substrate	Z—H	Product (% yield)	Ref.
PhCH=CHCOPh	$PhCH_2S$—H	$PhCH(CH_2SPh)CH_2COPh$	58
MeCH=CHCHO	MeC(O)S—H	$MeCH(SCOMe)CH_2CHO$ (100)	59
Me_2C=CHCOMe	MeC(O)S—H	$Me_2C(SCOMe)CH_2COMe$ (92)	59
PhCH=$CHCOCH_3$	MeC(O)S—H	$PhCH(SCOMe)CH_2COMe$ (90)	59
PhCH=CHCHO	MeC(O)S—H	$PhCH(SCOMe)CH_2CHO$ (90)	59
HC≡CCHO	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-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-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

$$R\cdot + CH_2{=}CHZ \longrightarrow RCH_2\dot{C}HZ$$
$$RCH_2\dot{C}HZ + CH_2{=}CHZ \longrightarrow RCH_2CH(Z)CH_2\dot{C}HZ$$
$$RCH_2\dot{C}HZ + R'_3MH \longrightarrow RCH_2CH_2Z + R'_3M\cdot$$
$$R'_3M\cdot + RX \longrightarrow R'_3MX + R\cdot$$
$$R\cdot + R'_3MH \longrightarrow RH + R'_3M\cdot$$

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 $c\text{-}C_6H_{11}CH_2CH_2CHO$ of 90% and $c\text{-}C_6H_{11}CH_2CH_2COCH_3$ of 85% have been reported from $c\text{-}C_6H_{11}I$[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].



(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	—
$c\text{-}C_6H_{11}I$	1.25	Ge(1.0)	31	—
$c\text{-}C_6H_{11}I$	1.25	Sn(1.0)	7	—

[a]Reference 70.

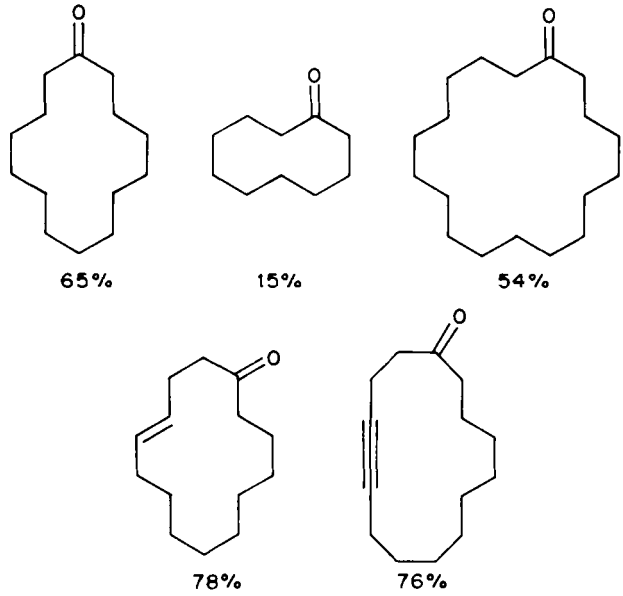
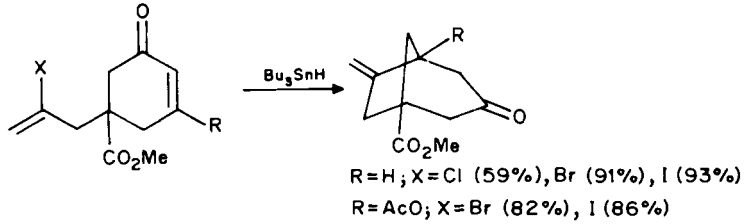


FIGURE 1. Yields of macrocyclic ketones. The 18-membered ring ketone was synthesized under high dilution conditions (after Reference 73)



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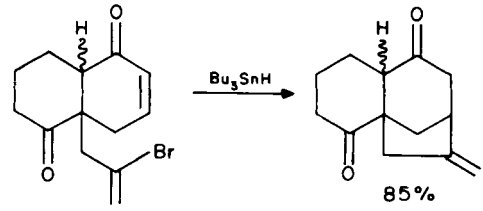

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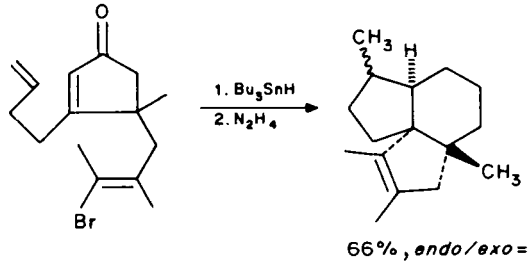


(22)

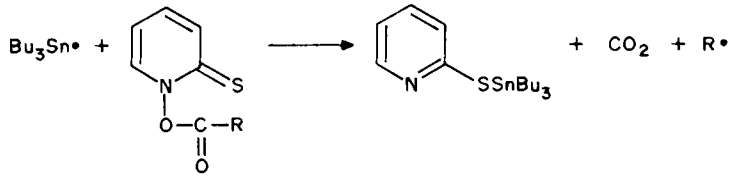
Trialkylstannyl radicals will also generate alkyl radicals by S_H2 displacement on alkyl phenyl selenides (reaction 23)[74], by electron transfer with alkyl mercury halides[75] or *tert*-alkyl nitro compounds (reactions 24 and 25)[76], or by attack at a C=S bond of xanthate esters, thiourethanes (reaction 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].

$$Bu_3Sn\cdot + RSePh \longrightarrow Bu_3SnSePh + R\cdot \tag{23}$$

$$RHgCl + Bu_3Sn\cdot \longrightarrow Bu_3Sn^+Cl^- + Hg^0 + R\cdot \tag{24}$$

$$RNO_2 + Bu_3Sn\cdot \longrightarrow Bu_3Sn^+RNO_2^-\cdot \longrightarrow R\cdot + Bu_3SnNO_2 \tag{25}$$

$$Bu_3Sn\cdot + RO{-}C(=S)X \longrightarrow Bu_3SnSC(=O)X + R\cdot \tag{26}$$



(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.

$$RHgX + CH_2{=}CHZ + NaBH_4 \xrightarrow[CH_2Cl_2]{OH^-} RCH_2CH_2Z + Hg^\circ \tag{28}$$

$$R\cdot + CH_2{=}CHZ \longrightarrow RCH_2\dot{C}HZ$$
$$RCH_2\dot{C}HZ + RHgH \longrightarrow RCH_2CH_2Z + RHg\cdot$$
$$RHg\cdot \longrightarrow R\cdot + Hg^0$$

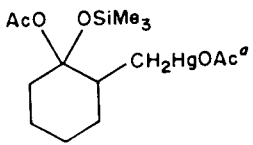
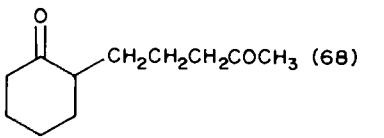
SCHEME 12

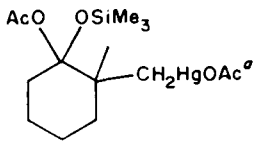
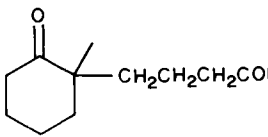
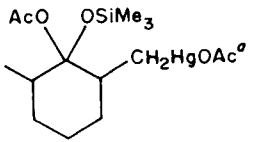
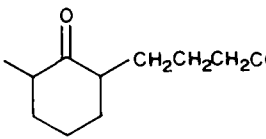
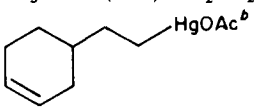
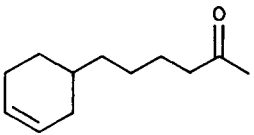
$$R\cdot + CH_2{=}CHZ \longrightarrow RCH_2\dot{C}HZ$$
$$RCH_2\dot{C}HZ + Bu_3SnH \longrightarrow RCH_2CH_2Z + Bu_3Sn\cdot$$
$$Bu_3Sn\cdot + RHgX \longrightarrow Bu_3SnX + Hg^0 + R\cdot$$

SCHEME 13

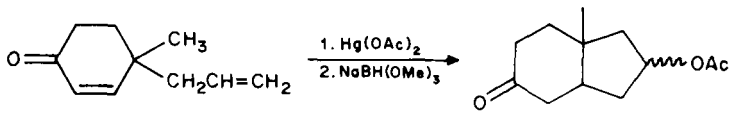
Organomercurials formed by solvomecuration will undergo intramolecular ring closure reactions with appropriate double bonds when treated by $NaBH(OMe)_3$. Thus, reaction 29–31 have been reported[85]. Similar cyclizations have been achieved with N(*o*-allylphenyl)α-methyl acrylamide in which the acrylanilide 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*-$C_6H_{10}HgCl$	$CH_2{=}CHCOCH_3$ ($\sim$ 10)	1-AcO-*c*-C_6H_{10}—$CH_2CH_2COCH_3$ (43)	82
2-AcO-2-norbornyl HgCl	$CH_2{=}CHCOCH_3$ ($\sim$ 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.



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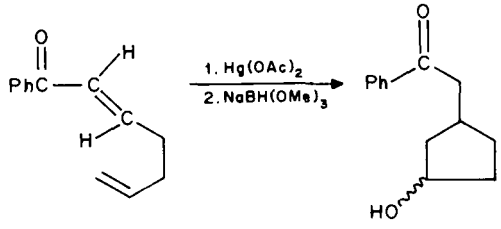

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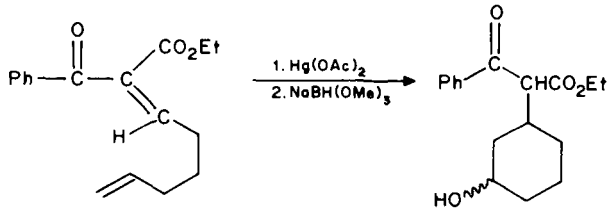


77% (31)

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].

$$R'O{\cdot}(R'OO{\cdot}) + R_3B \longrightarrow R'OBR_2(R'OOBR_2) + R{\cdot} \qquad (32)$$

$$R{\cdot} + CH_2{=}CHCOCH_3 \longrightarrow RCH_2CH{=}C(O{\cdot})CH_3$$
$$RCH_2CH{=}C(O{\cdot})CH_3 + R_3B \longrightarrow RCH_2CH{=}C(OBR_2)CH_3 + R{\cdot}$$
$$RCH_2CH{=}C(OBR_2)CH_3 + H_2O \longrightarrow RCH_2CH_2COCH_3 + R_2BOH$$

SCHEME 14

$$RCH{=}CH_2 + B_2H_6 \longrightarrow R'_3B \xrightarrow[h\nu \text{ or } O_2]{CH_2{=}CHCOCH_3} \xrightarrow{H_2O} R'CH_2CH_2COCH_3 \quad (33)$$

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

$$R_A\cdot + RHgX(\text{or } R) \rightarrow R_AHgX(\text{or } R) + R\cdot \quad (34)$$

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 $p\text{-}O_2NC_6H_4$. 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].

$$R\cdot + CH_2{=}CHZ \longrightarrow RCH_2\dot{C}HZ$$
$$RCH_2\dot{C}HZ + RHgCl \longrightarrow RCH_2CH(Z)HgCl + R\cdot$$

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.

$$t\text{-BuHgX} + CH_2{=}CHZ \xrightarrow{h\nu} \xrightarrow{H_3O^+} t\text{-BuCH}_2CH_2Z \quad (35)$$

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	$Me_2CHCH_2CH_2CH_2$COMe (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	$PhCH_2CH_2CH_2CH_2$COMe (55), PhCH(Me)CH_2CH_2COMe (42)	89
CH_2=CHCOMe	c-C_5H_8	c-$C_5H_9CH_2CH_2$COMe (99)	89
CH_2=CHCOMe	c-C_6H_{10}	c-$C_6H_{11}CH_2CH_2$COMe (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	$Me_2CHCH_2CH_2CH_2$CHO (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-$C_5H_9CH_2CH_2$CHO (88)	90
CH_2=CHCHO	c-C_6H_{10}	c-$C_6H_{11}CH_2CH_2$CHO (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-$C_5H_9CH_2$CH(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

MeCH=CHCOMe	c-C_6H_{10}	c-$C_6H_{11}CH(Me)CH_2COMe$ (96)	92,93
MeCH=CHCOMe	c-C_5H_8	c-$C_5H_9CH(Me)CH_2COMe$ (98)	92
MeCH=CHCHO	$CH_2=CH_2$	$EtCH(Me)CH_2CHO$ (60)	92,93
MeCH=CHCHO	c-C_6H_{10}	c-$C_6H_{11}CH(Me)CH_2CHO$ (100)	92,93
2-cyclohexenone	$CH_2=CH_2$	3-ethylcyclohexanone (95)	92,93
2-cyclohexenone	c-C_6H_{10}	3-cyclohexylcyclohexanone (100)	92,93
2-cyclohexenone	c-C_5H_8	3-cyclopentylcyclohexanone (96)	92,93
2-cyclopentenone	$CH_2=CH_2$	3-ethylcyclopentanone (68)	92
2-cyclopentenone	c-C_5H_8	3-cyclopentylcyclopentanone (85)	92
MeCH=CHCHO	$EtCH=CH_2$	$BuCH(Me)CH_2CHO$ (54), $PrCH(Me)CH(Me)CH_2CHO$ (6)	92
MeCH=CHCHO	MeCH=CHMe	$EtCH(Me)CH(Me)CH_2CHO$ (90)	92
MeCH=CHCHO	$Me_2C=CH_2$	$Me_2CHCH_2CH(Me)CH_2CHO$ (50)	92
$CH_2=C(Br)CHO$	$EtCH=CH_2$	$C_5H_{11}CH(Br)CHO$ (85)	94
$CH_2=C(Br)CHO$	MeCH=CHMe	$EtCH(Me)CH_2CH(Br)CHO$ (81)	94
$CH_2=C(Br)CHO$	$Me_2C=CH_2$	$Me_2CHCH_2CH_2CH(Br)CHO$ (80)	94
$CH_2=C(Br)CHO$	c-C_6H_{10}	c-$C_6H_{11}CH_2CH(Br)CHO$ (65)	94
$CH_2=C(Me)CHO$	MeCH=CHMe	$EtCH(Me)CH_2CH(Me)CHO$ (95)	94
$CH_2=C(Me)CHO$	$Me_2C=CH_2$	$Me_2CHCH_2CH_2CH(Me)CHO$ (95)	94
$CH_2=C(Me)CHO$	c-C_6H_{10}	c-$C_6H_{11}CH_2CH(Me)CHO$ (92)	94
$CH_2=C(Me)CHO$	norbornene	2-methyl-3-(*exo*-2-norbornyl)propanal (97)	94
2-methylenecyclopentanone	$CH_2=CH_2$	2-propylcyclopentanone (90)	95
2-methylenecyclohexanone[a]	$CH_2=CH_2$	2-propylcyclohexanone (85)	95
2-methylenecyclohexanone[a]	MeCH=CHMe	2-(2-methylbutyl)cyclohexanone (61)	95
	c-C_5H_8	2-(cyclopentylmethyl)cyclohexanone (90)	95
3-methylenenorbornane-2-one[a]	$CH_2=CH_2$	3-*n*-propylnorbornan-2-one (94)	95
$HC\equiv CCOCH_3$	$CH_2=CH_2$	$EtCH=CHCOCH_3$ (77)	96
$HC\equiv CCOCH_3$	$EtCH=CH_2$	$BuCH=CHCOCH_3$ (72)	96
$HC\equiv CCOCH_3$	MeCH=CHMe	$EtCH(Me)CH=CHCOCH_3$ (47)	96
$HC\equiv CCOCH_3$	$Me_2C=CH_2$	$Me_2CHCH_2CH=CHCOCH_3$ (34)	96
$HC\equiv CCOCH_3$	c-C_5H_8	c-$C_5H_9CH=CHCOCH_3$ (65)	96
$HC\equiv CCOCH_3$	c-C_6H_{10}	c-$C_6H_{11}CH=CHCOCH_3$ (65)	96
$HC\equiv CCOCH_3$	norbornene	4-(*exo*-2-norbornyl)-3-buten-2-one (67)	96

[a]Formed *in situ* by reaction of MeI and 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%).

$$R\cdot + CH_2{=}CHCOCH_3 \longrightarrow RCH_2\dot{C}HCOCH_3$$
$$RCH_2\dot{C}HCOCH_3 + I^- \longrightarrow RCH_2CH{=}C(O^-)CH_3 + I\cdot$$
$$I\cdot + RHgI \longrightarrow R\cdot + HgI_2$$

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].

$$(R^1CO)_2O + R^3HC{=}CR^2COZ \xrightarrow[DMF,\,B_{12}]{e^-,\,h\nu} R^1C(O)CHR^3CHR^2COZ + R^1CO_2 \quad (36)$$

$$R^1\dot{C}{=}O + R^3CH{=}CR^2C(O)Z \longrightarrow R^1C(=O)CHR^3{-}CR^2{=}C(O\cdot)Z$$
$$\xrightarrow{e^-} R^1C(=O)CHR^3{-}CR^2{=}C(O^-)Z \quad (37)$$

$$RC(=O){-}Co(III) \xrightarrow{h\nu} R\dot{C}{=}O + \cdot Co(II)$$
$$\cdot Co(II) + e^- \longrightarrow :Co(I)^-$$
$$:Co(I)^- + (RCO)_2O \longrightarrow RC(=O){-}Co(III) + RCO_2^-$$

SCHEME 17

TABLE 10. Formation of 1,4-dicarbonyl compounds by acylation of α,β-unsaturated ketones and aldehydes (reaction 36)[a]

Anhydride, R^1	α,β-Unsaturated Compound			Product (% yield)[b]
	R^2	R^3	Z	
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. SCE) 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-8*H*-HDP)cobalt(III)[104].

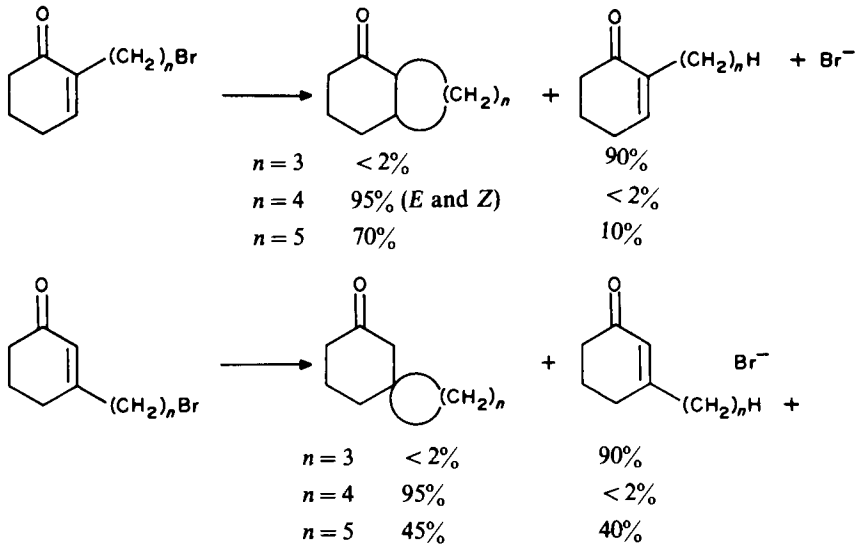
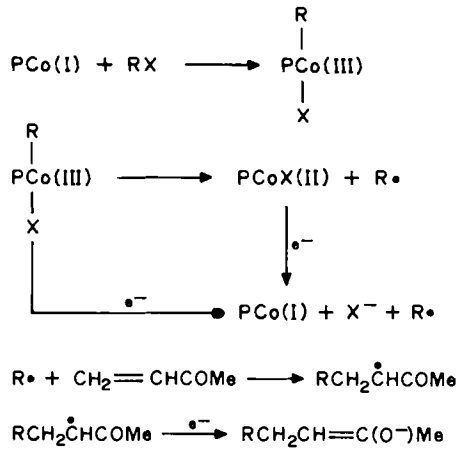


FIGURE 2. Yields of intramolecular cyclization products observed upon electrolysis (NH_4Br in DMF) in the presence of 5 mol% of vitamin B_{12a} (after Reference 104)

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

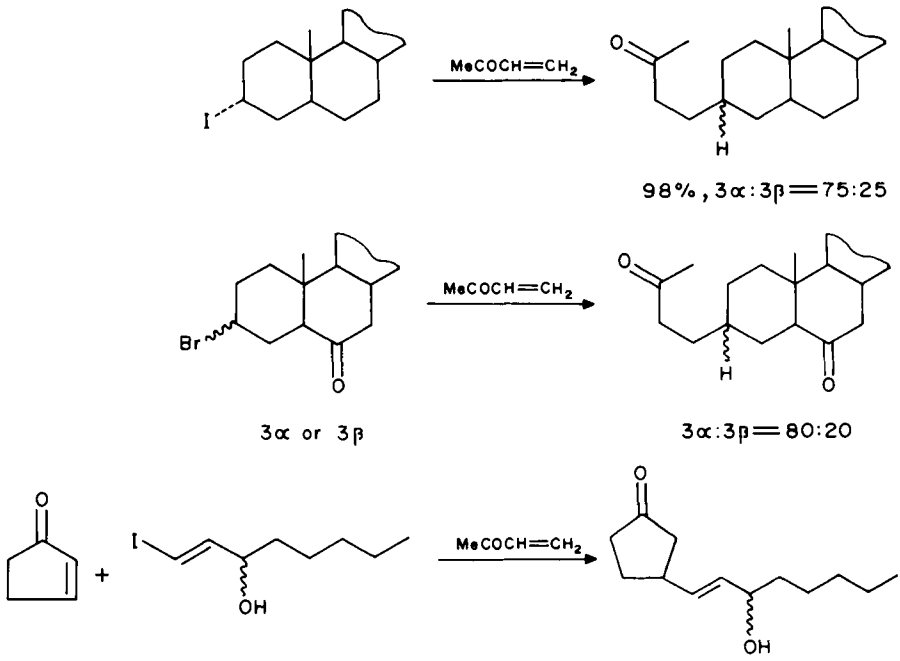
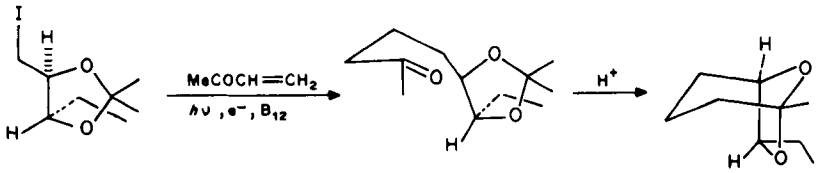


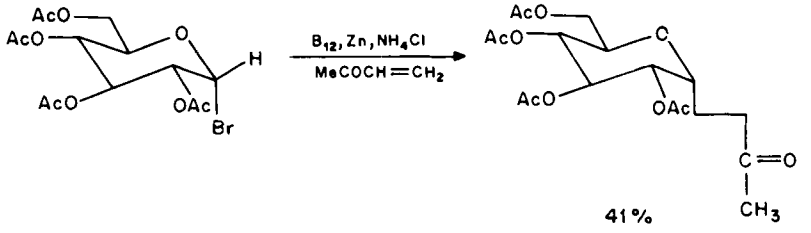
FIGURE 3. Intermolecular alkylation and alkenylation reactions observed upon electrolysis in the presence of vitamin B_{12} in DMF, NH_4Cl

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)

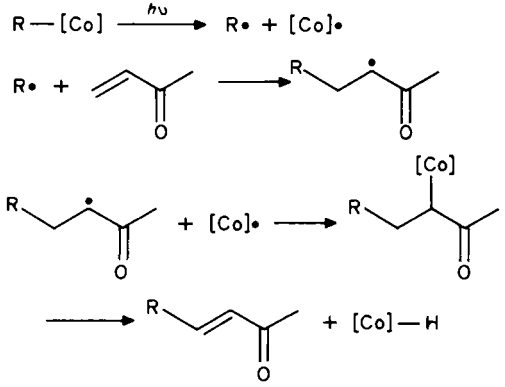
D. Substitutive Alkylations of Vinyl Ketones

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].

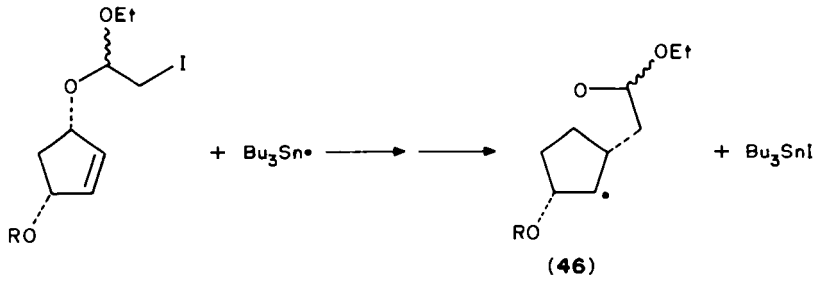
$$R\cdot + R'CH{=}CHX \longrightarrow R'\dot{C}H{-}CH(X)R$$
$$R'CH{-}CH(X)R \longrightarrow R'CH{=}CHR + X\cdot$$
$$X\cdot + RHgCl \longrightarrow R\cdot + XHgCl$$

SCHEME 19 (R′ = Ph, PhCO, EtO_2C, Cl, $PhSO_2$)

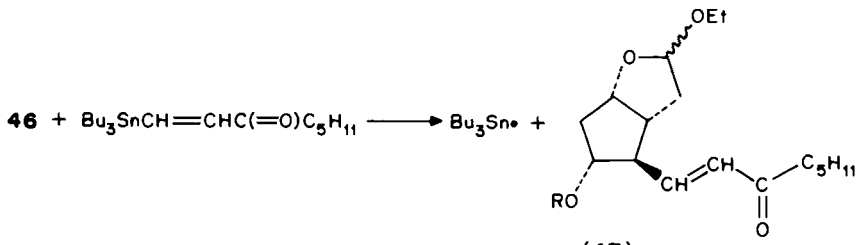
Reaction of (*E*)-PhCOCH=CHCl with *t*-BuHgCl (5 equiv) with sunlamp irradiation in Me_2SO at 35–40 °C gives a 68% yield of (*E*)-PhCOCH=CHBu-*t* in 2 h[110]. The yield is increased to 100% in the presence of 10 equiv of NaI for 1 h. The iodide may increase the efficiency of the reaction by electron 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].



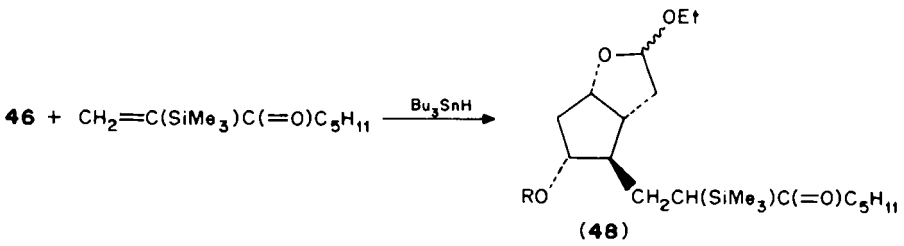
SCHEME 20 ([Co] = pyridine complex of cobalt 'salophen' reagent)



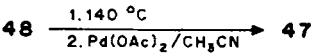
(46)



(47)



(48)



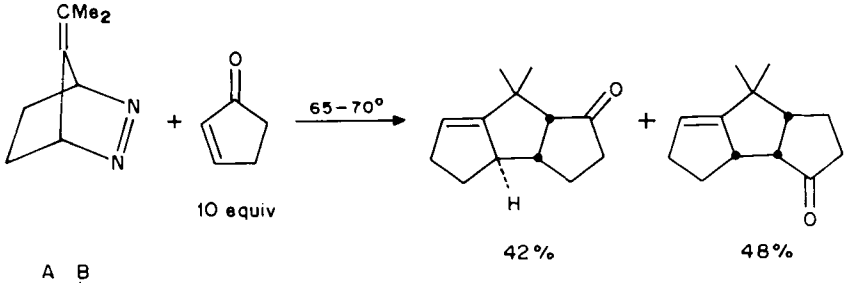
SCHEME 21

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].

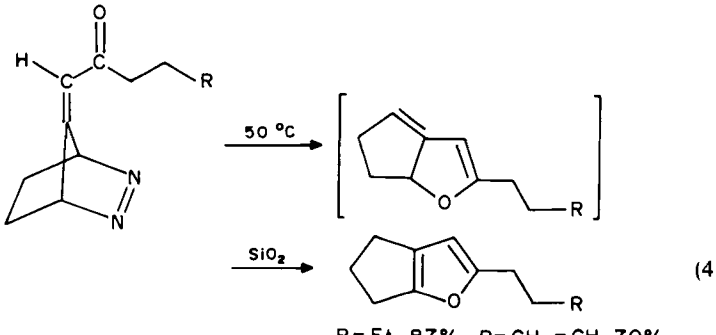
E. Diyl Trapping Reactions

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)



(41)

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111. V. F. Patel and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 871 (1987).
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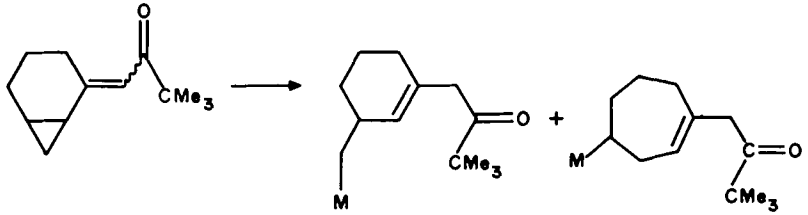
Note Added in Proof (see page 491)

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
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CHAPTER **12**

The reaction of enones with electrophiles

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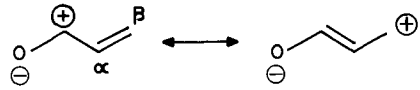
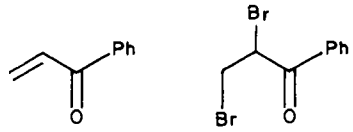
I. INTRODUCTION

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?

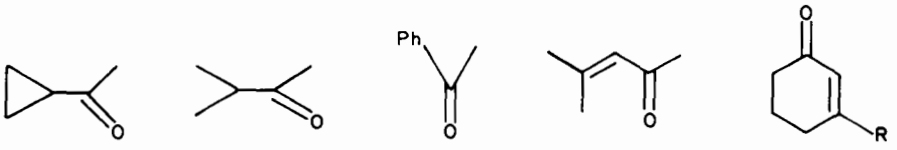
Clearly, the basicity of conjugated enones is of great interest in reactivity studies since, as in the case of saturated ketones and aldehydes, acid-catalyzed reactions of enones could in principle proceed via a preequilibrium protonation of the carbonyl group followed by some sort of nucleophilic attack. 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 ^{1}H 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).

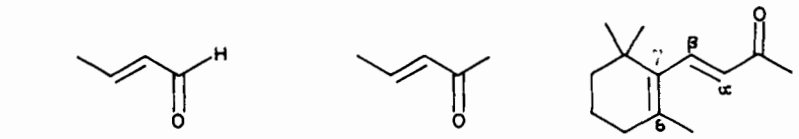


(**4**) (**5**) (**6**) (**7**) (**8**) R=H (**9**) R=CH_3

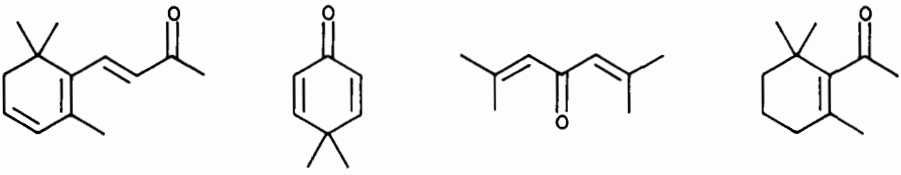
(b) The lower basicity of crotonaldehyde (**10**) relative to mesityl oxide (**7**) is an indication of the lower basicity of aldehydes relative to ketones.

(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].

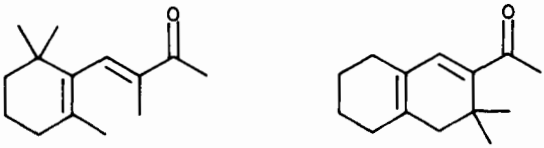
^{13}C NMR studies of a series of unsaturated ketones (**7**, **8** and **11**–**18**)[17] in fluorosulfonic acid/fluorosulfuryl chloride solutions showed that these ketones were quantitatively



(**10**) (**11**) (**12**)



(**13**) (**14**) (**15**) (**16**)



(**17**) (**18**)

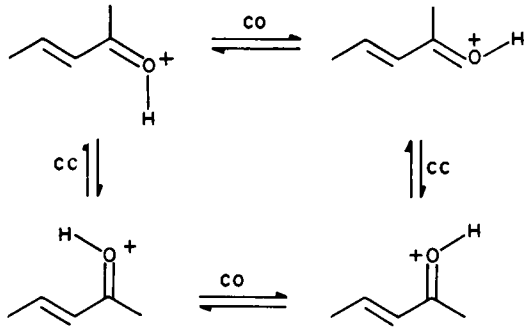
protonated on oxygen. The following results are significant for understanding the bonding in protonated enones and dienones:

(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].

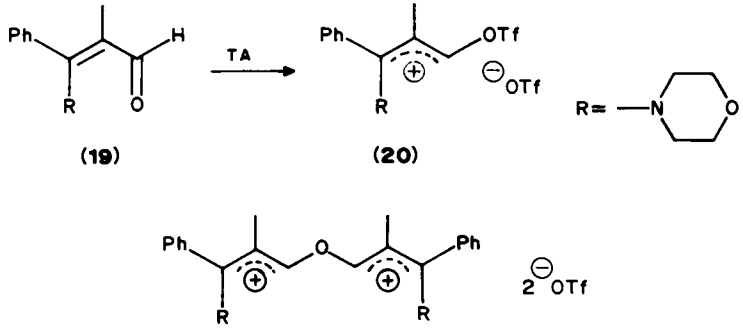
(b) Steric hindrance of the conjugation within a dienone induces a localization of the charge in the enone moiety.

(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).



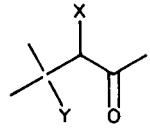
SCHEME 1

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].



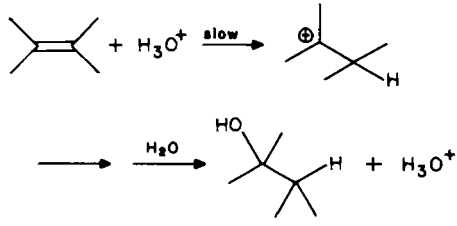
It should be emphasized that under the above reaction conditions the protonated bases do not undergo nucleophilic attack by the counterions (HSO_4^-, FSO_3^-). Therefore, a significant question within the present context is the hydration of enones in aqueous acidic media.

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.

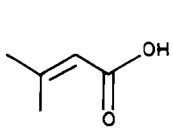


SCHEME 2

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.



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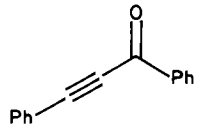

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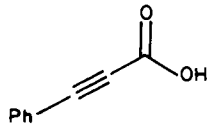
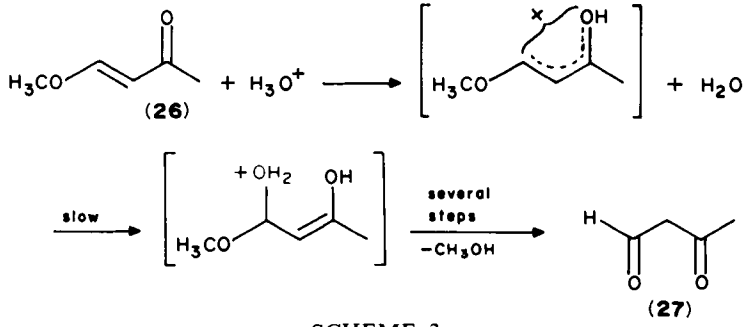


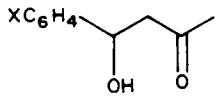
(25)

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].

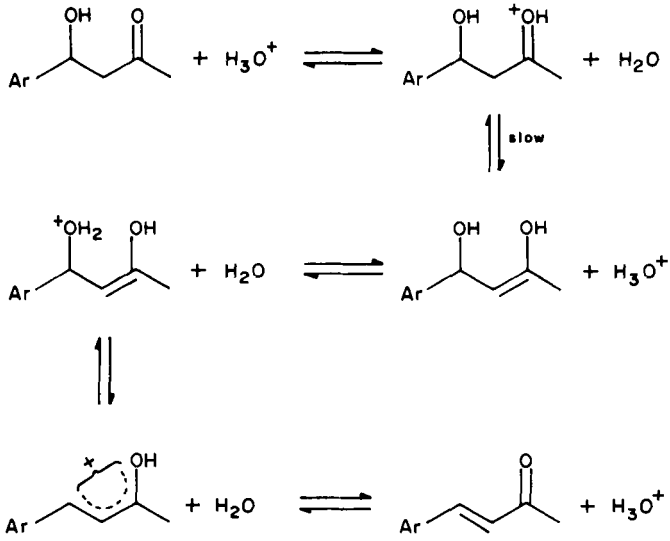


SCHEME 3

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_0, while **28** exhibits a linear correlation with H_0. 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.

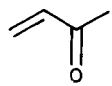


(**28**) X=OCH_3
(**29**) X=H
(**30**) X=NO_2



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.



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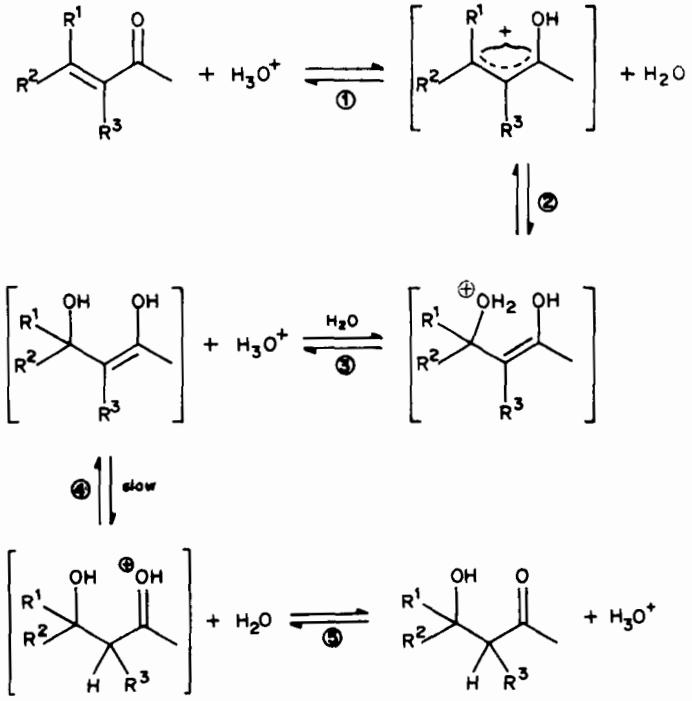
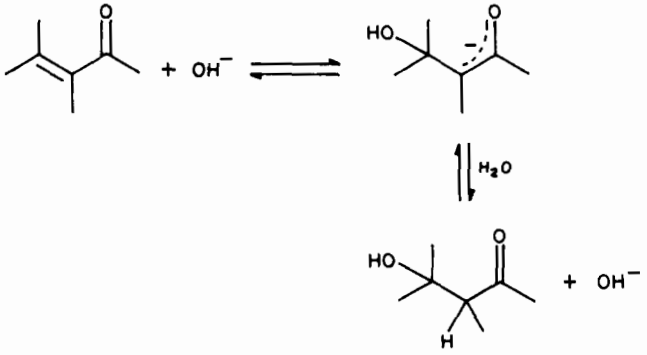


SCHEME 5

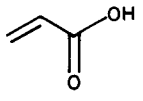
It should be mentioned that, although this reaction type is beyond the scope of the present text, α,β-unsaturated carbonyl compounds can also undergo base-catalyzed hydration. The reaction, kinetically studied for β-oxy-α,β-unsaturated ketones[38], propenals[42] and homologues of 3-buten-2-one[43], proceeds 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



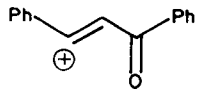
SCHEME 6

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**)

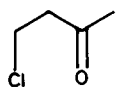


(**33**)

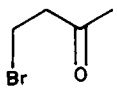
A variety of phosphorus- and/or sulfur-containing acids such as dialkyl phosphites, dialkyl dithiophosphates or ethyl alkylphosphonites add to **7** in high yields[24]. Both the uncatalyzed, base-catalyzed and free-radical catalyzed reactions have been reported, but there are no detailed mechanistic 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.

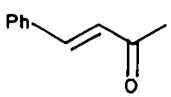
In contrast to the above examples, a β-phenyl substituted enone such as **36** reacts with dry hydroiodic acid (HI) to give the reduction product **37** in 57% yield[52]. One concludes that the primary addition product, the β-iodo species **38**, is susceptible to reduction with HI as indicated in **39**. 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.



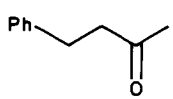
(**34**)



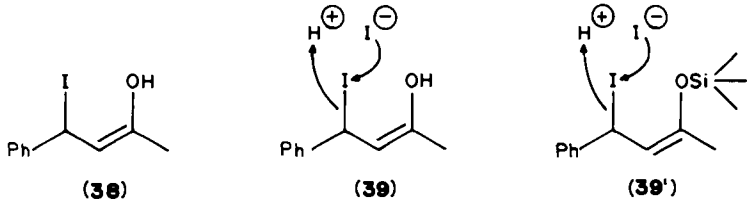
(**35**)



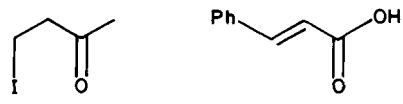
(**36**)



(**37**)

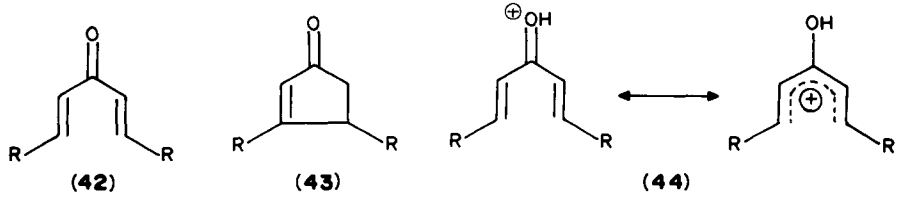


(38) (39) (39')

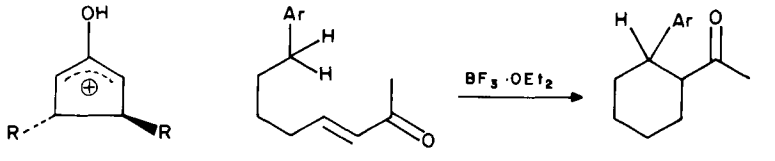


(40) (41)

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**.

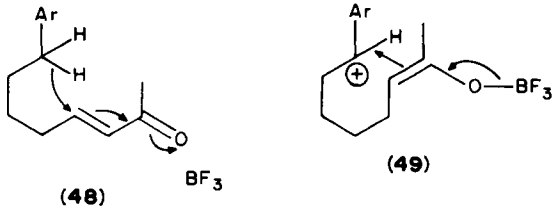


(42) (43) (44)



(45) (46) (47)

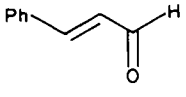
Ar = 4-HOC_6H_4



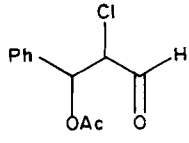
(48) (49)

III. HALOGENATION AND HYDROXYHALOGENATION

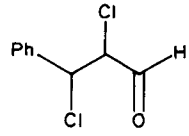
A particularly important question within the present context is whether the halogenation of α,β-unsaturated carbonyl compounds is electrophilic or nucleophilic in nature. The possibility of nucleophilic attack was envisioned as early as 1931[60]. Subsequent studies[61–63] have revealed that the addition 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.



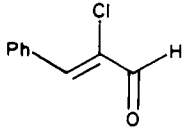
(**50**)



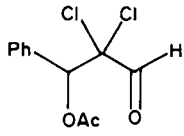
(**51**) *erythro*
(**52**) *threo*



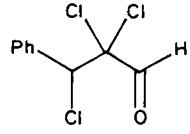
(**53**) *erythro*
(**54**) *threo*



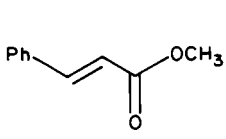
(**55**) *trans*
(**56**) *cis*



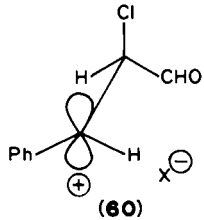
(**57**)



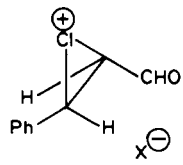
(**58**)



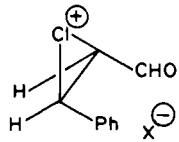
(59)



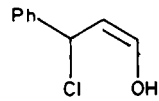
(60)



(61)

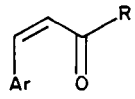


(62)



(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

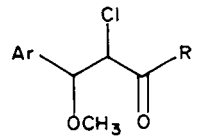
(**64**) Ar = Ph, R = Ph

(**65**) Ar = p-$NO_2C_6H_4$, R = Ph

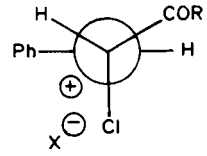
(**66**) Ar = p-$CH_3OC_6H_4$, R = Ph

(**67**) Ar = p-$NO_2C_6H_4$, R = CH_3

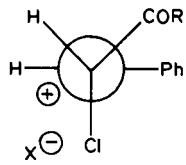
(**68**) Ar = p-$CH_3OC_6H_4$, R = CH_3



(**69**) *erythro, threo*; R = CH_3, Ph

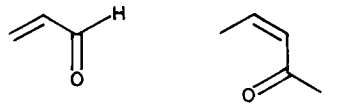


(**70**)

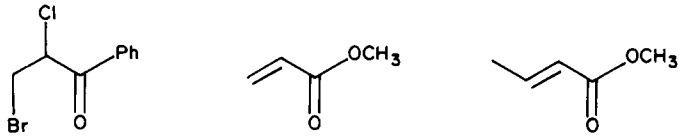


(**71**)

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].

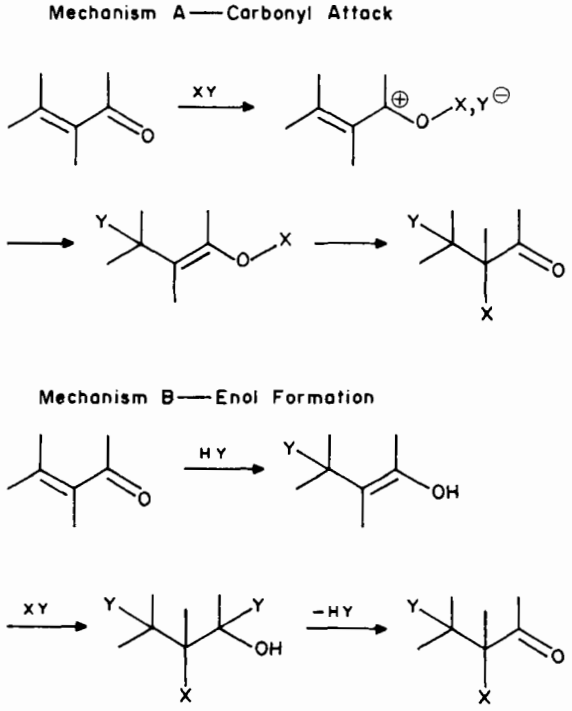


(**72**) (**73**)



(**74**) (**75**) (**76**)

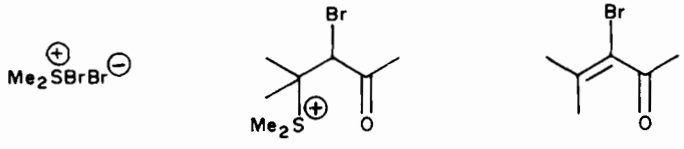
Additional arguments for the above mechanistic picture came from the electrophilic addition of dimethylbromosulfonium bromide (**77**) to conjugated enones which led to an efficient synthesis of α-bromoenones[69]. The preparative significance of such reactions will be discussed in the subsequent section. 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

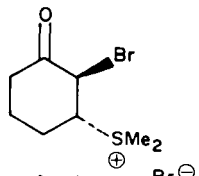
conjugated double bond in a manner very similar to conventional electrophilic reactions. Taking, e.g., **7** as substrate the complete reaction sequence involves the formation of the rather stable addition product **78** followed by base-induced elimination to yield **79**. The characteristic features are the following:

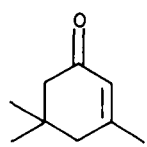
(a) The addition regiospecifically provides α-bromo-β-sulfonium carbonyl compounds.

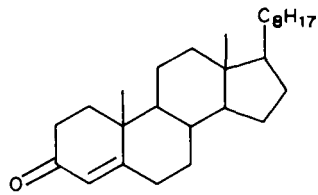


(77) **(78)** **(79)**

(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)

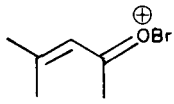

(81)

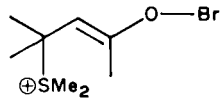

(82)

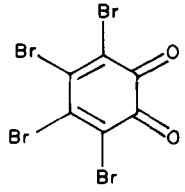
(c) Electronic factors are also operative since addition is relatively slow to conjugated esters[70].

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].

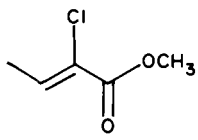

(83)

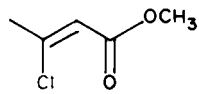

(84)


(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)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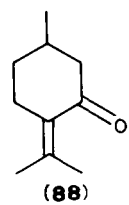
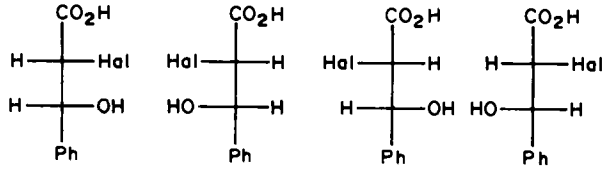
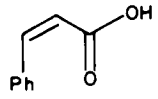

(88)

As in hydration reactions (see Section II) it is illustrative to include other α,β-

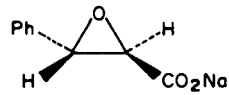
unsaturated carbonyl compounds than enones. The addition of hypochlorous or hypobromous acid to *trans*-cinnamic acid (**41**) could, in principle, afford regioisomers of chloro- or bromohydrins. However, only derivatives of **89** and **90** are obtained when methyl *trans*-cinnamate (**59**) reacts 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_N2-displacement of Br^- by O^- (see Section VI).



(**89**) *erythro* (**90**) *threo*

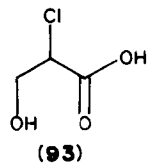


(**91**)

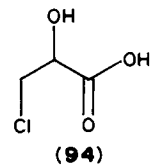


(**92**)

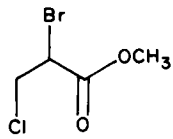
While in the addition of hypochlorous acid and chlorine acetate to cinammic acid (**41**) the intermediate chloronium ion is opened exclusively at the carbon adjacent to the phenyl rings[89-91] the addition of hypochlorous acid to acrylic acid (**32**) is not completely regiospecific since both the 2-chloro-3-hydroxy- (**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].



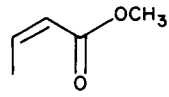
(**93**)



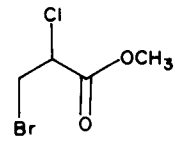
(**94**)



(**95**)



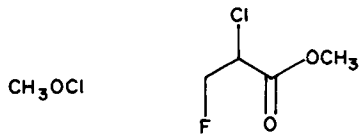
(**96**)



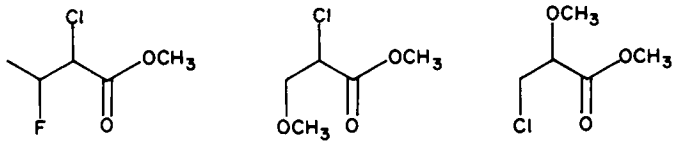
(**97**)

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].

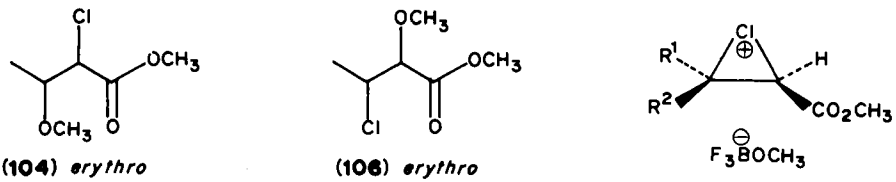
An ion pair formed from a carbonyl-substituted chloronium ion and a BF_3X^- anion has been postulated as an intermediate in the reaction of methyl hypochlorite (CH_3OCl, **98**) (in the presence of BF_3) methyl acrylate (**75**), methyl crotonate (**76**) and methyl isocrotonate (**96**)[96]. In the 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].



(**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

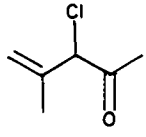
the α-chloro ketones **109**, **110** and **111** (+ **112**), respectively. 2-Phenyl-2-penten-4-one (**113**) affords a 1:1 mixture of the allylic chloride **114** and the vinyl chloride **115**. The following aspects are important:

(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.

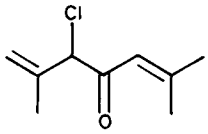
(ii) The reaction can be extended to aldehydes such as β-cyclocitral (**122**).

(iii) The process only succeeds for such conjugated carbonyl *cis*- compounds in which the *s*-conformation of the enone is accessible.

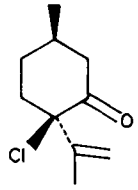
(iv) More highly unsaturated ketones such as α- or β-ionones (**123**), (**12**) provide mixtures of allylic chlorides[100].



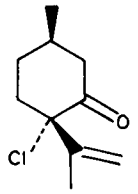
(**109**)



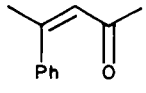
(**110**)



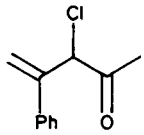
(**111**)



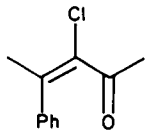
(**112**)



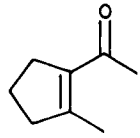
(**113**)



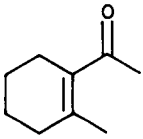
(**114**)



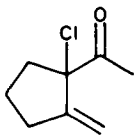
(**115**)



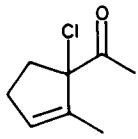
(**116**)



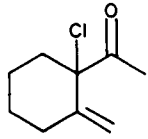
(**117**)



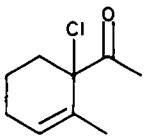
(**118**)



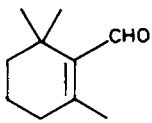
(**119**)



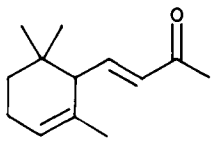
(**120**)



(**121**)



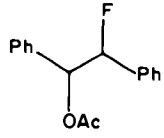
(**122**)



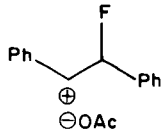
(**123**)

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].



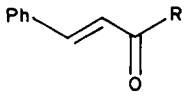
(**124**)



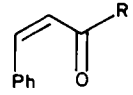
(**125**)

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]:

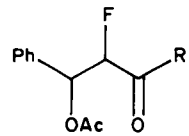
(a) Open-chain aryl-substituted α,β-unsaturated carbonyls give good yields of the expected β-acetoxy-α-fluoro derivatives. Thereby, as anticipated from a *syn* addition, *trans*-ethyl cinnamate (**126**) is converted into the *threo* (**127**), and *cis*-methyl cinnamate (**128**) into the *erythro* 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



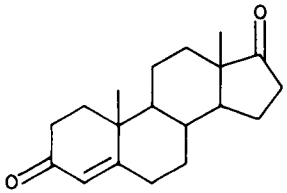
(**127**) *threo*; R=OCH_2CH_3

(**129**) *erythro*; R=OCH_3

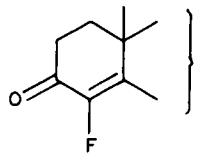
(**130**) *threo*; R=Ph

(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**.

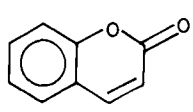
(c) On the other hand, flexible α,β-unsaturated carbonyl compounds without aryl substituents, such as cyclohexenone (**8**), 3-methylcyclohexenone (**9**), ethyl crotonate, diethyl maleinate and diethyl fumarate, do not react even with a large excess of acetyl hypofluorite[101,104].



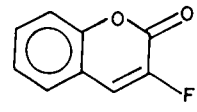
(**131**)



(**132**)

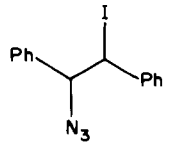


(133)

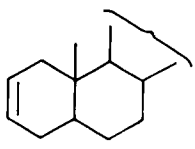


(134)

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*



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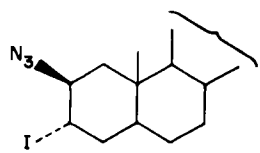

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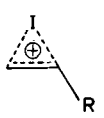

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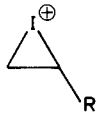
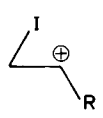
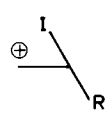


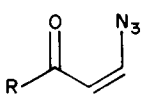
(139a)



(139b)



(139c)



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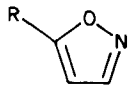

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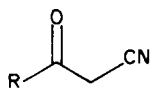
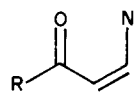


(142)



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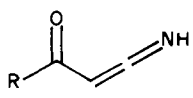

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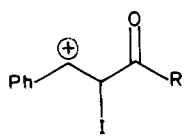
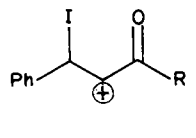
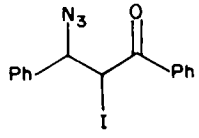


(145a)



(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].



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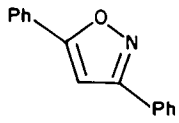
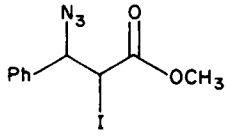
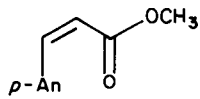


(147)



(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.



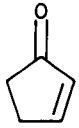
(149)

IV. HALOGENATION AND SUBSEQUENT 1,2-ELIMINATION

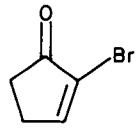
The combination of addition to α,β-unsaturated carbonyl compounds and subsequent elimination reactions which have been mentioned above is important from a mechanistic and also a preparative point of view, since α-haloenone species can be prepared. This reaction shall now be considered in greater detail.

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)



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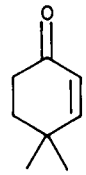

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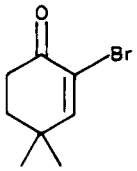
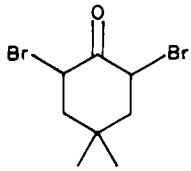
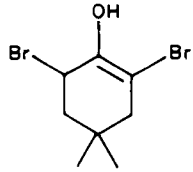


(153)



(154)



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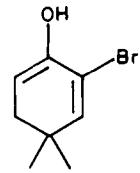
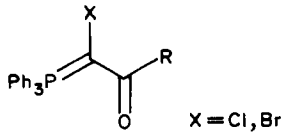


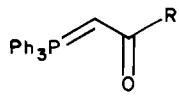
(156)

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].

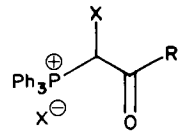


X = Cl, Br

(157) R = Ph
(158) R = CH_3
(159) R = OCH_2CH_3



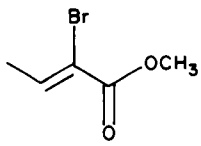
(160) R = Ph
(161) R = CH_3
(162) R = OCH_2CH_3



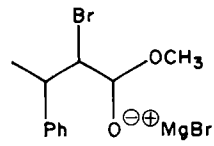
X = Cl, Br

(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.

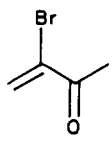


(166)



(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**.



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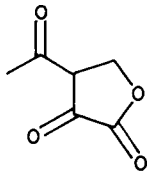

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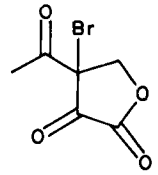

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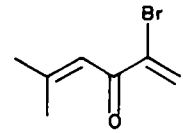
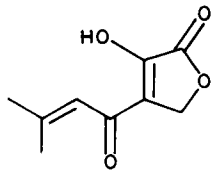


(171)



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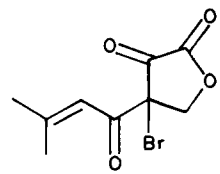
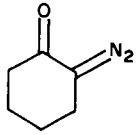


(173)

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].



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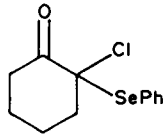

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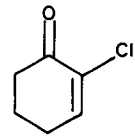

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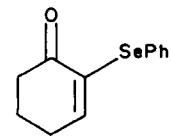

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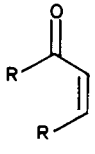

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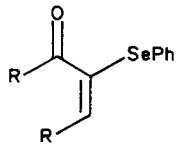

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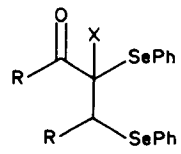

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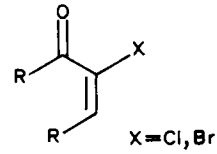
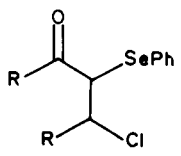


(181)

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].



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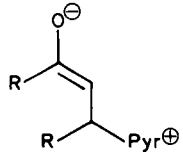

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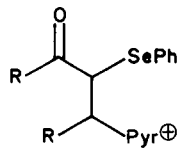
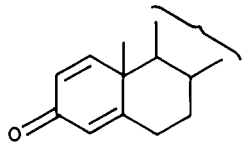


(184)

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

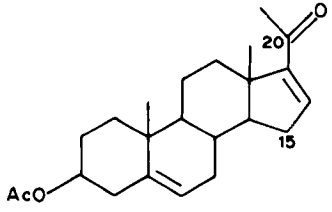
Another question in the bromination of α,β-unsaturated ketones is the attack at the sp^3-hybridized carbons $C_{\alpha'}$ or C_γ. This problem has played an important role in the synthesis of $\Delta^{1,4}$-dien-3-ones of the steroid series, e.g. **185**, which constitute key intermediates in the partial 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



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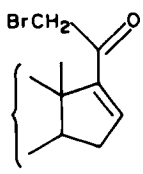

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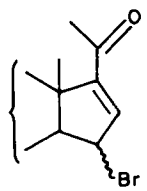
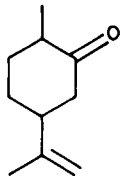


(188)

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.



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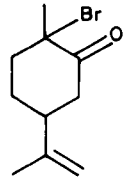

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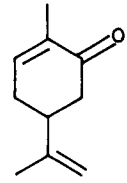

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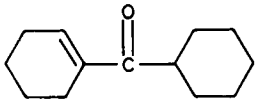

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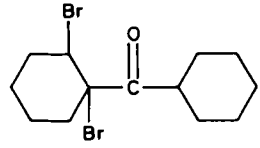

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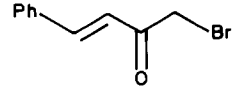
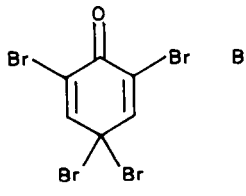


(194)

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**).



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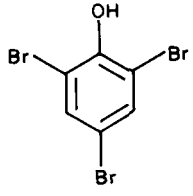

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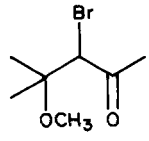

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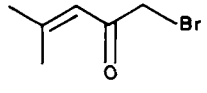

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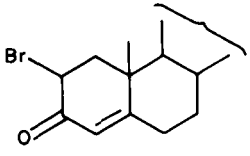

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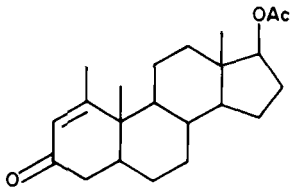

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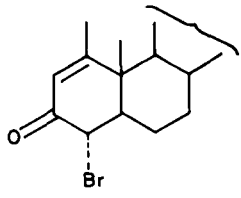
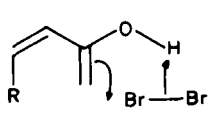


(201)

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).



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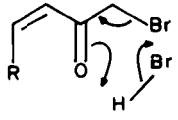
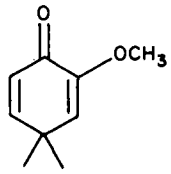


(203)

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 substitu-

ents[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).



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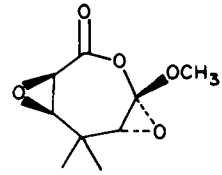
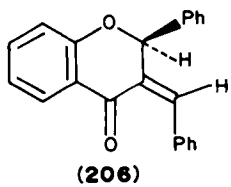


(205)

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.



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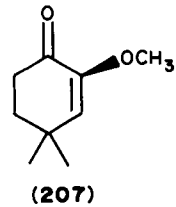


(207)

α,β-Unsaturated esters and acids represent substrates with reduced carbonyl activity. Not surprisingly, therefore, the reaction conditions required for their epoxidation with

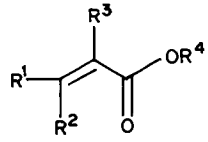
peracids are less severe. These compounds can be converted into the corresponding glycidic esters (respectively acids) by reaction with peracetic acid[144], trifluoroperacetic acid[145], 3,5-dinitroperbenzoic acid[146] or potassium peroxymonosulfate/acetone[151].

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%).



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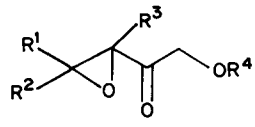


(209)

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

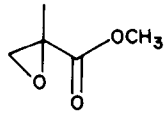
TABLE 2. Epoxidation of α,β-unsaturated esters[146a]

Substrate	Product	Time (h)	Yield (%)
Methylmethacrylate	Methyl-α-methylglycidate	(i) 0.5	(i) 84
		(ii) 7.75	(ii) 80
Ethyl crotonate	Ethyl β-methylglycidate	(i) 0.5	(i) 73
		(ii) 9.5	(ii) 87
Ethyl acrylate	Ethyl glycidate	(i) 0.5	(i) 54
		(ii) 8	(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.



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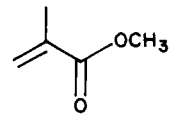

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C. 3,5-Dinitroperbenzoic Acid

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.

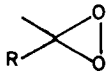
As indicated by kinetic, stereochemical and ^{18}O-labeling experiments[152], the formation of dioxirane intermediates **212** is assumed to be responsible for the higher oxidation activity of this system. This suggestion was confirmed through isolation of some methyldioxiranes (**212**) (R = methyl, 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.



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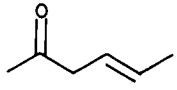

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VII. HYDROXYLATION

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

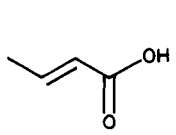
Though the *cis*-hydroxylation of alkenes by osmium tetraoxide has been known since 1912[159], considerable research effort is still focused on this procedure, especially on variations leading to enantioselective product formation.

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].

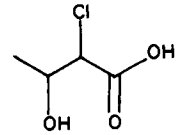
With some metal chlorates, the formation of chlorohydroxy compounds occurs as a side-reaction, presumably due to the intermediate formation of free hypochlorous acid[161]. An example is the reaction of crotonic acid (**214**) with $OsO_4/Ba(ClO_3)_2$ to yield chlorohydroxycrotonic acid (**215**)[161].

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.

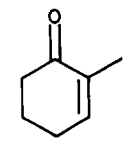
Enones which have been converted[160] into the corresponding keto diols by this method are, e.g., *p*-benzoquinone and 2-methylcyclohexenone (**216**).



(**214**)

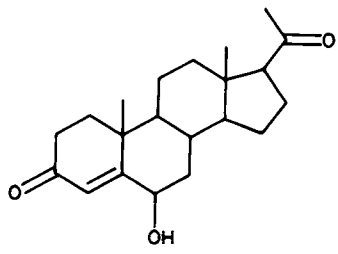


(**215**)

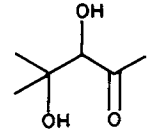


(**216**)

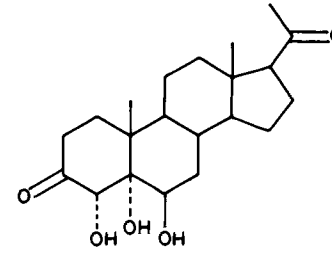
With the more reactive Milas reagent mesityl oxide (**7**) and 6-hydroxyprogesterone (**217**) have been *cis*-hydroxylated to yield **218** and **219**, respectively[162,163]. One major disadvantage of this procedure is that overoxidation sometimes occurs to give rise to carbonyl products thus lowering 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**)



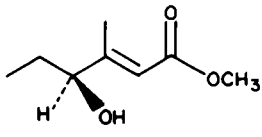
(**218**)



(**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].



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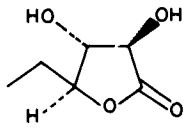

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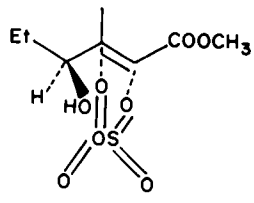

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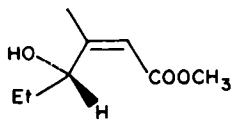

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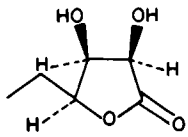

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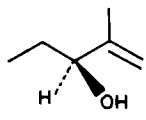

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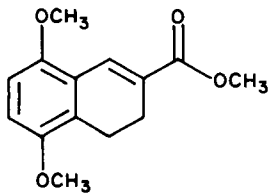
The conversion of olefins into *cis*-diols with OsO_4 can also be conducted enantioselectively by adding a chiral catalyst. The catalytic effect of tertiary amines in the hydroxylation reaction is well known[160]. By choosing optically active tertiary amines it has been possible to generate asymmetric 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**.



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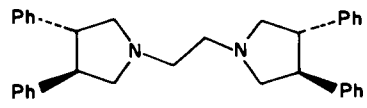

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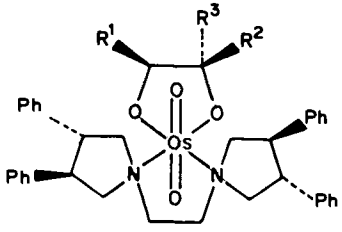

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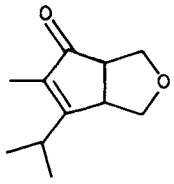

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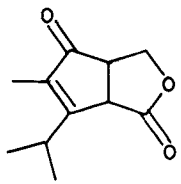

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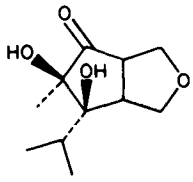

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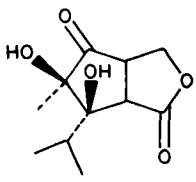

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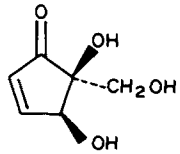

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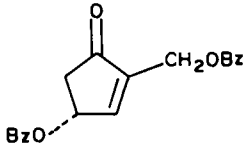

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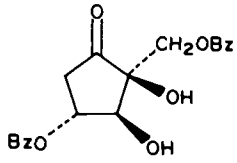


(235)

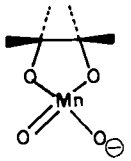
B. Potassium Permanganate

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**.



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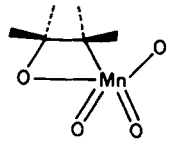
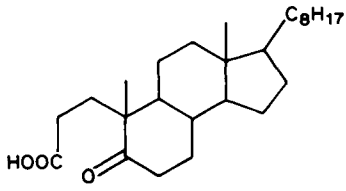


(237)

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.



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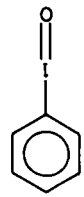

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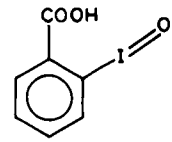
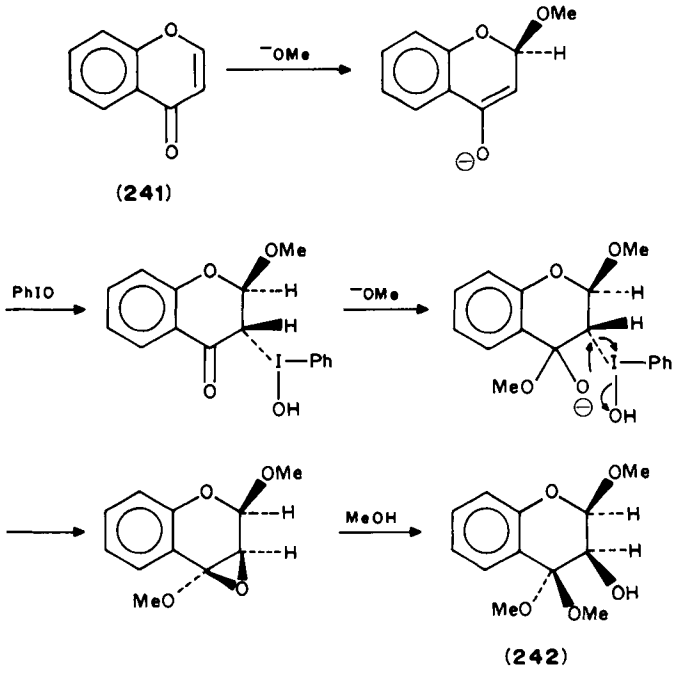


(240)

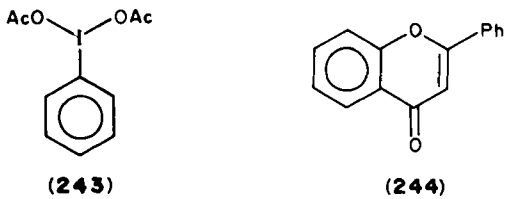
In the case of enones the product is the β-alkoxylated, dimethyl acetal derivative[185]. Though the reaction mechanism does not include an electrophilic attack of the oxidant on the olefinic bond, but rather involves an initial Michael addition of the base at C_β of the unsaturated system, this conversion 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

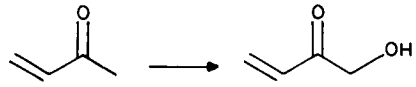
Analogous products have been obtained from the reaction of $PhI(OAc)_2$ (**243**) methanol/KOH with flavone (**244**) and chalcone (**64**)[185], showing its general applicability to the oxidation of α,β-unsaturated ketones.



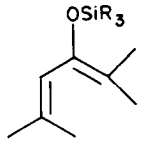
VIII. α′-HYDROXYLATION OF ENOLIZABLE ENONES

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



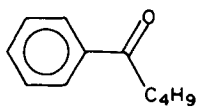
(**245**)

A. Molybdenum Peroxide/Pyridine/HMPA

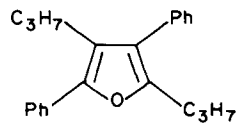
The MoOPH system can easily be prepared[190] from molybdenum trioxide, 30% H_2O_2 and hexamethylphosphoric acid (HMPA). The resulting complex is dehydrated (in a desiccator) and dissolved in THF; addition of pyridine precipitates the oxidant, which is stable over a long period when stored in the dark 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.

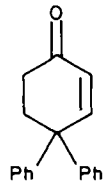
The latter complication becomes especially important in the oxidation of sterically unhindered enolates (e.g. enolates of methyl ketones). Valerophenone (**246**), for instance, yields up to 42% of the furan derivative **247** (formed after cyclization and dehydration of the primary aldol adduct) under 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].



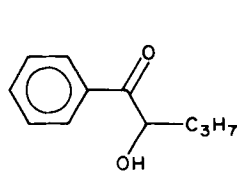
(**246**)



(**247**)



(**248**)



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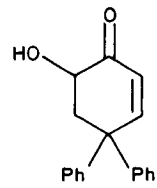

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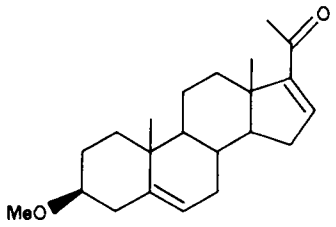

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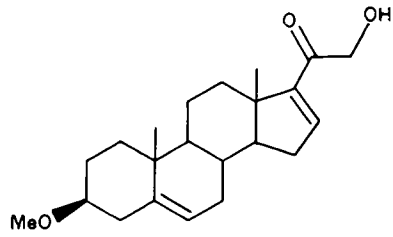
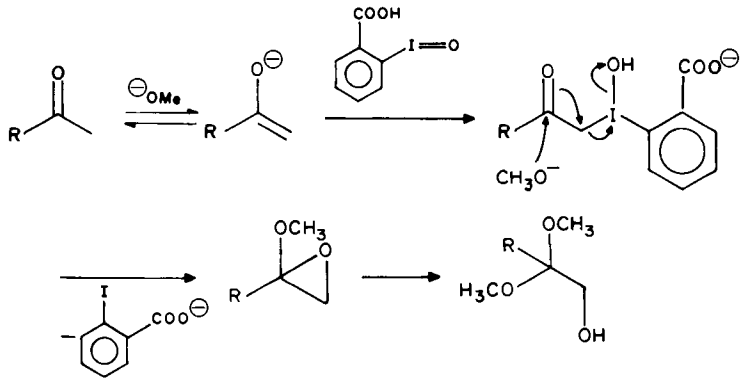


(252)

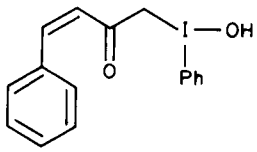
B. Hypervalent Iodine Compounds

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



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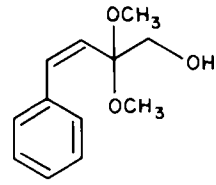

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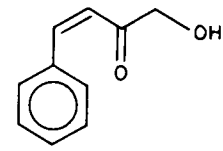
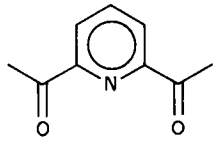


(255)

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.



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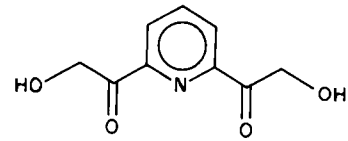
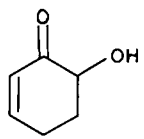


(257)

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].



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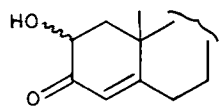


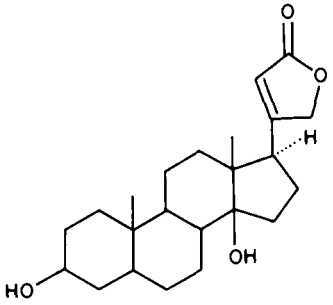
(259)

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].



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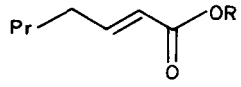

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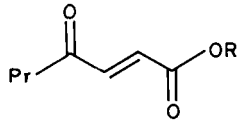

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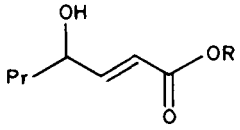

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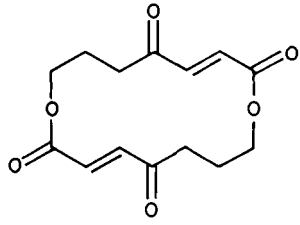
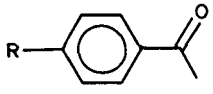


(264)

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**.



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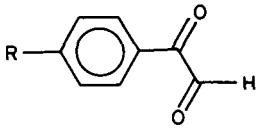
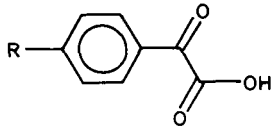


(266)



(267)

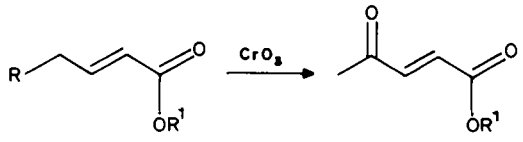
Regioselective γ-hydroxylation of α,β-unsaturated esters has also been described via electrophilic attack at the γ-position of the corresponding enolate anion[157].

X. MISCELLANEOUS

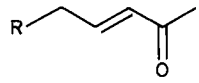
Numerous oxidation reactions of enones which do not follow a general pattern exist in the literature. Some examples have been chosen arbitrarily and are listed below. This list, however, is by no means intended to be comprehensive.

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].



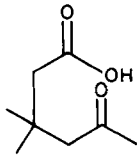
SCHEME 11



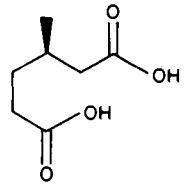
(268)

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**).



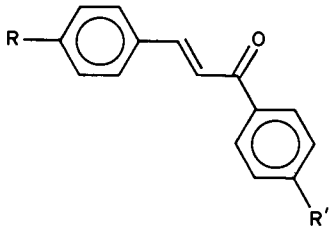
(269)



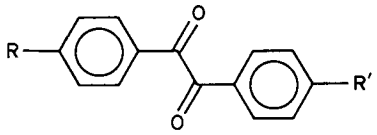
(270)

C. Oxidation with Thallium(III) Compounds

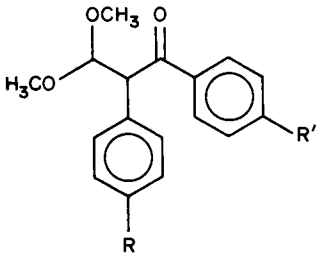
The oxidation of differently substituted chalcones **271** with thallium(III) salts such as $Tl(OAc)_3$ or the more electrophilic $Tl(NO_3)_3$ produces a variety of products dependent on the nature of the substituents and on the reaction conditions. Unsymmetric benzils **272**, for example, are formed 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].



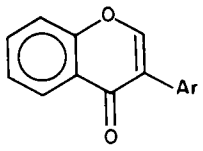
(271)



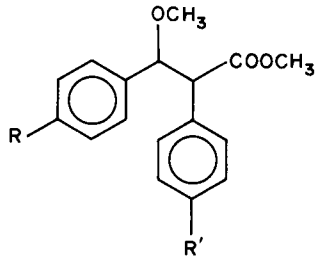
(272)



(273)



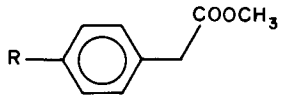
(274)



(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**.

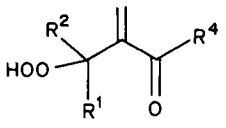
The adsorption of $Tl(NO_3)_3$ on montmorillonite clay enhances the versatility of the reagent[211]. Substituted acetophenones **265** have been converted into methyl arylacetates **276** in excellent yield with this reagent. Oxidations of cinnamic acid esters were successful only with this form of the oxidant[211].



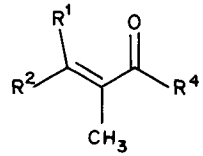
(276)

D. Oxidation with Singlet Oxygen

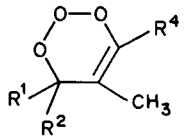
Singlet oxygen has been used to oxidize α,β-unsaturated ketones[210] and esters[212] leading to the formation of the hydroperoxides **277**. A characteristic feature of both classes of compounds is the common regiochemistry encountered in this conversion. In enones of the general structure **278** the 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].



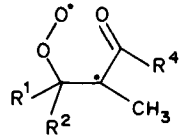
(277)



(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

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CHAPTER 13

Chemical and enzymatic conversion of β,γ-enones to α,β-enones

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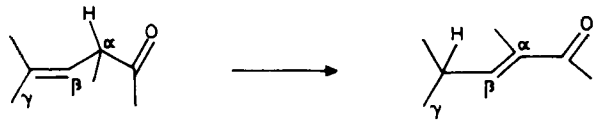
I. INTRODUCTION

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)

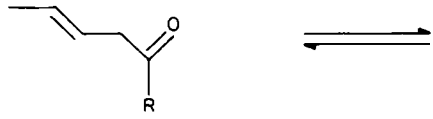
The simplicity of this reaction has made the isomerization an attractive reaction for examining the effect of variation of structure on the rates of protonation and deprotonation at carbon. Studies of the isomerization have provided insight into the nature of a variety of phenomena, including stereoelectronic 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 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%

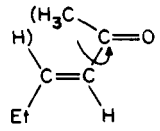
Hine[8,9] has calculated a 'double bond stabilization parameter' (D) for a variety of substituents based on statistical analysis of equilibrium constants for reactions of the type shown in equation 3 over a range of temperatures and in different solvents. Owing to the lack of standardization of temperature 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 ($D = 3.36$ kcal mol^{-1}). The corresponding D value for the formyl substituent is 4.34 kcal mol^{-1}.

$$\textit{trans}\text{-XCH}{=}\text{CHCH}_2\text{Y} \rightleftharpoons \text{XCH}_2\text{CH}{=}\text{CHY} \tag{3}$$

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 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.

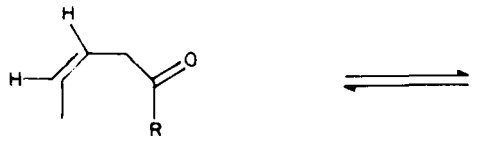
The better stabilizing ability of the formyl group relative to acetyl and carboalkoxy was explained in terms of some destabilizing cross-conjugation in esters and ketones, as well as steric hindrance between the methyl group of the acetyl and the hydrogen *cis* to it in the preferred transoid conformation (**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**).



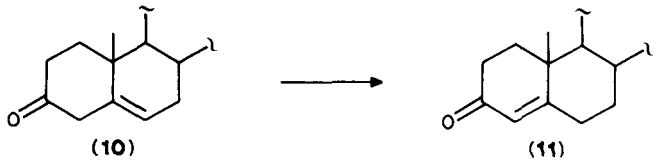
(4)

(**6**) R = Me 100%
(**8**) R = H 52%

(**7**) R = Me 0%
(**9**) R = H 48%

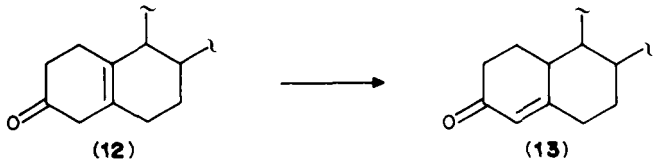
B. Five- and Six-membered Ring Systems

Although substantial amounts of the unconjugated isomer are in equilibrium with the conjugated isomer in simple acyclic systems, $\Delta^5(6)$- and $\Delta^5(10)$-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].



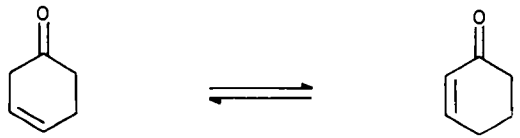
(5)

(**10**) (**11**)



(6)

(**12**) (**13**)



(14) (15) (7)

< 1% >99%

(16) (17) (8)

<0.01% >99.99%

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

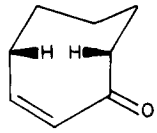
Extension of the series of unsaturated ketones to include seven-, eight- and nine-membered ring 2-cycloalkenones and 3-cycloalkenones shows a dramatic shift in the equilibrium constants with ring size (Table 1). As the ring size increases, the proportion of unconjugated ketone also increases until for 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

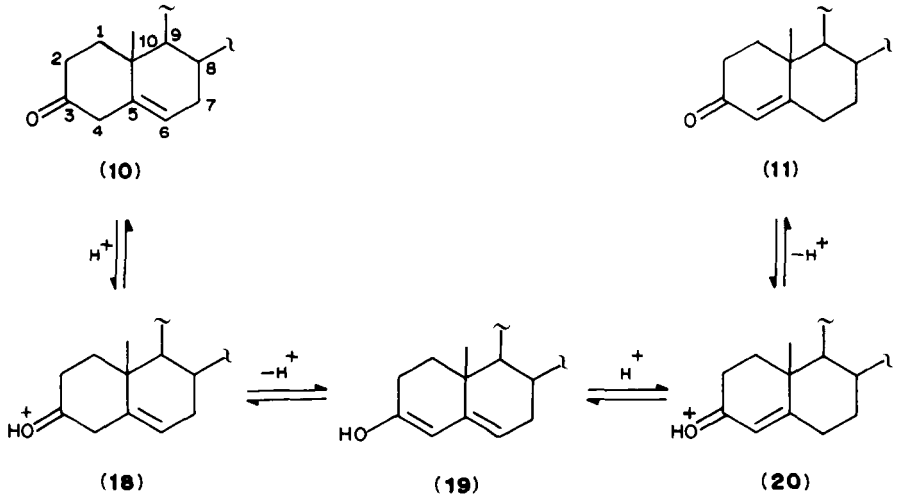
1. General mechanism

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.

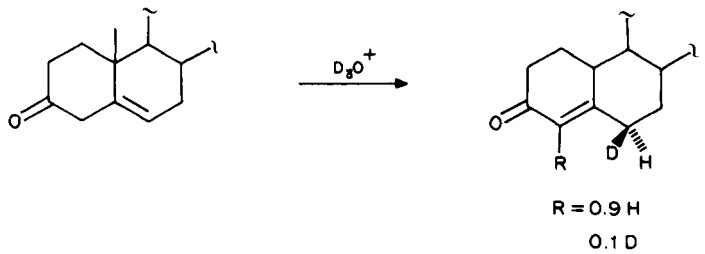
The stereochemical aspects of this reaction were also investigated by Malhotra and Ringold[18]. It was shown that the 4α (equatorial) proton is removed in slight preference to the 4β (axial) proton ($k_{4\alpha}/k_{4\beta} \simeq 1.2$). This small discrimination between axial and equatorial proton loss 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.

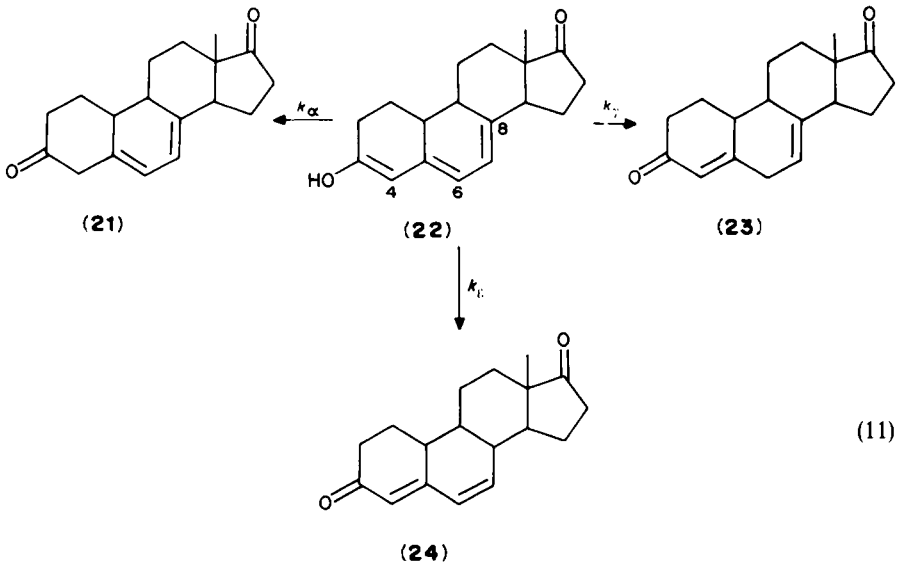
Further evidence that protonation of the dienol intermediate occurs at $C_{(6)}$ much faster than at $C_{(4)}$ came from a determination of the deuterium content of both starting material and product when 5-cholestene-3-one was partially isomerized in deuterated acidic medium (equation 10). The product 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

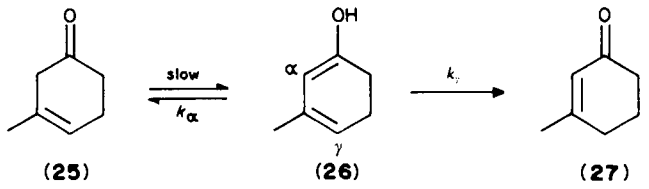
analogous isomerization of 5,7-estradiene-3,17-dione (**21**) to 4,7-estradiene-3,17-dione (**23**). The putative intermediate trienol (**22**) can be isolated[29] and its partitioning has been examined in acidic solutions[30]. This enol can ketonize in three different ways, by protonation at $C_{(4)}$, $C_{(6)}$ 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.



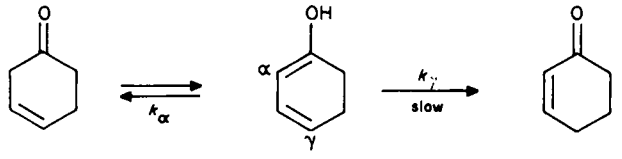
(11)

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) (30)

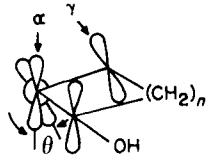
k_α/k_γ 1.9 0.1

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.

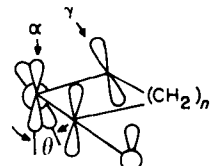
Theoretical considerations are in accord with this model. Molecular orbital calculations by Rogers and Sattar[31] for a series of homoannular methyl-substituted dienol ethers (including compounds **29** and **30**) have yielded satisfactory predictions of $C_{(\gamma)}/C_{(\alpha)}$ protonation rates 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.



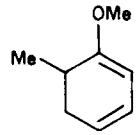
(31a)



(31b)

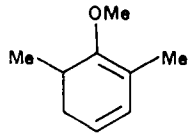
For θ equal to 90°, protonation at $C_{(\gamma)}$ is comparable to protonation of an isolated double bond, whereas protonation at $C_{(\alpha)}$ resembles the much more favorable protonation of an enol ether. This model predicts that the ratio of protonation rates, k_γ/k_α, will be a maximum at $\theta = 0°$ 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.



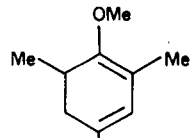
(32)

k_γ/k_α 0.69 (Ref.31)



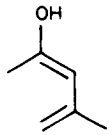
(33)

19 (Ref.31)



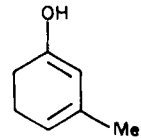
(34)

0.14 (Ref.31)



(35)

v.large (Ref.20)



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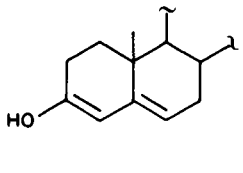
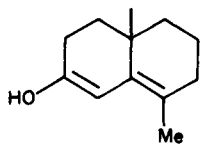
v.large (Ref. 19)



(19)

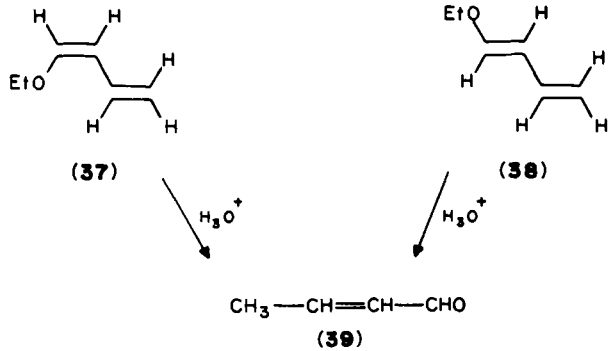
>20 (Ref. 32)



(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.



(14)

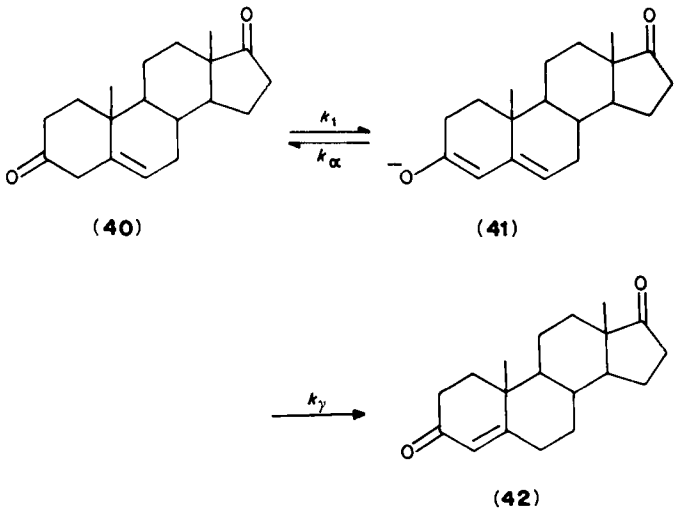
Examination of molecular models reveals that the olefinic proton on $C_{(3)}$ may have an unfavorable steric interaction with the ethoxy group in the *cis* isomer that is more severe than the corresponding proton–proton interaction in the *trans* isomer. The bond between $C_{(2)}$ and $C_{(3)}$ would 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*

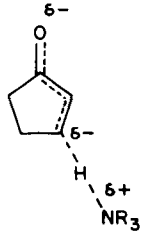
The factors that influence the relative rates of protonation of dienolates at $C_{(\alpha)}$ and $C_{(\gamma)}$ are likely to be similar to those factors that influence the relative protonation rate ratio at these carbons in dienols and dienol ethers. Thus, alkyl substitution at $C_{(\beta)}$, diene 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 $C_{(\alpha)}$.

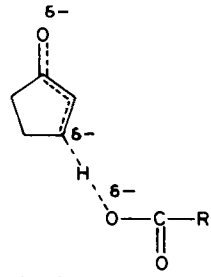
3. *Electrostatic effects in general base catalysis*

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.

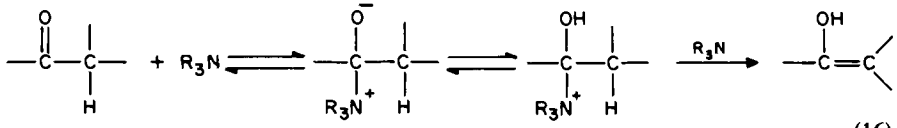


(**43**)



(**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).



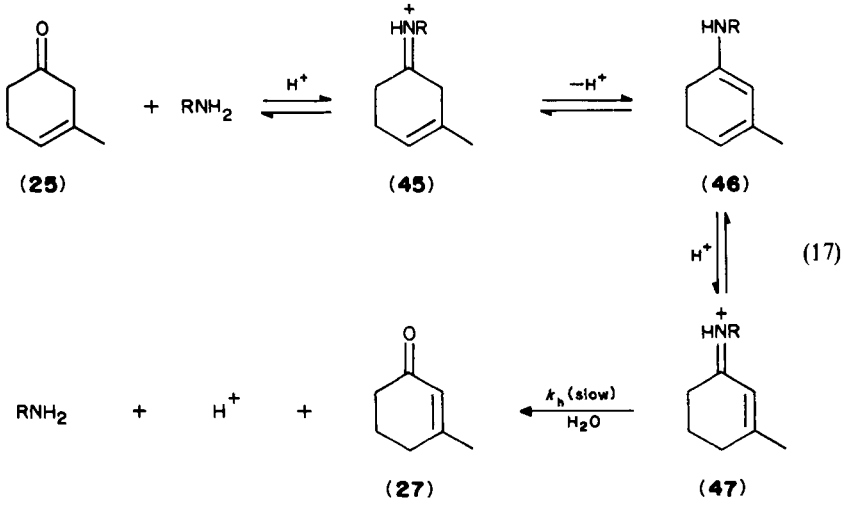
(16)

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 ($pK_a = 10.0$) to 130-fold ($pK_a = 6.2$). 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**, γ_{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.



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* $1 \times 10^{-3}\,s^{-1}$. A comparison of this rate constant with the estimated rate constant for spontaneous isomerization of **25** at neutrality (*ca* $2 \times 10^{-7}\,s^{-1}$) 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.

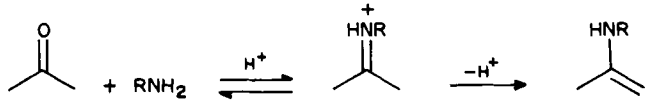
The rate-limiting hydrolysis reaction of the Schiff base has been studied in some detail and two important conclusions can be drawn. (1) The hydrolysis of **47** is subject to general base catalysis[52,53]. Thus, the rate of the hydrolysis reaction (and hence the overall isomerization rate) is increased 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].

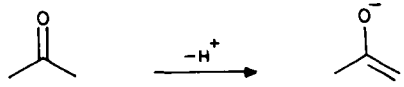
The efficiency by which primary amines catalyze the isomerization of β,γ-unsaturated ketones is attributable to their ability to rapidly and reversibly form Schiff base intermediates in aqueous solution with the carbonyl group of the β,γ-unsaturated ketone[56]. Since simple Schiff bases are somewhat 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:



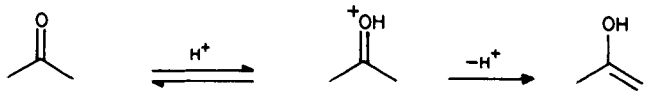
(18)

Base Catalysis:



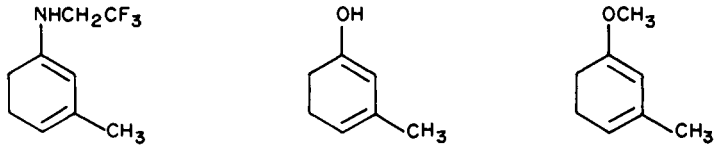
(19)

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**.

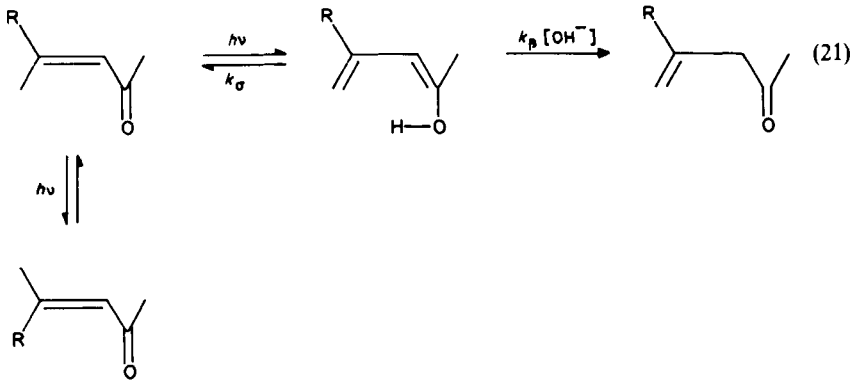


(48) **(26)** **(30)**

k_γ/k_α 0.7 (Ref.31) v. large (Ref.19) 9 (Ref.31)

D. Photochemical Isomerization

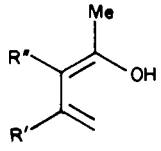
Irradiation of α,β-unsaturated esters and ketones with substituents at the β carbon results in *cis–trans* isomerization through the triplet state[60–67] and slower isomerization to the β,γ-unsaturated isomers through the singlet state. Isomerization to the unconjugated isomer occurs through initial 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.

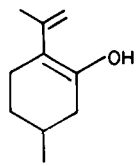


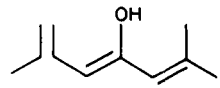
(21)

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.







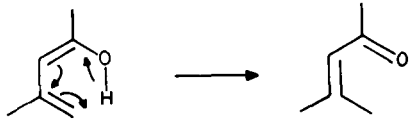
(49) R′ = Me, R″ = H
(50) R′ = *t*-Bu, R″ = H
(51) R′ = R″ = Me

(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 $0.18\,s^{-1}$.

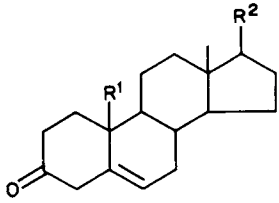
†*Note added in proof*: Recently, it has been concluded that this pathway is not important for the ketonization of the acyclic dienol (*Z*)-1-hydroxy-1,3-butadiene (B. Capon and B. Guo, *J. Am. Chem. Soc.*, **110**, 5144 (1988)).

IV. 3-OXO-Δ^5-STEROID ISOMERASE

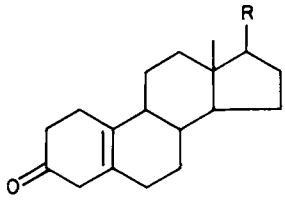
A. Background

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.

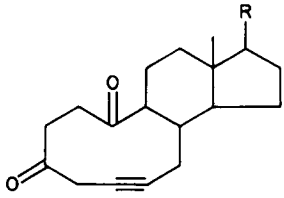
The bacterial isomerase has a rather broad specificity (Table 2). Not only does it catalyze the isomerization of 3-oxo-Δ^5-steroids, such as 5-androstene-3, 17-dione (**40**) and 5-pregnene-3, 20-dione (**54**), but it also isomerizes $\Delta^{5(10)}$ steroids and $\Delta^{5,6}$ acetylenes. In addition, 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 = β–$COCH_3$
(**55**) R^1 = H, R^2 = O



(**56**) R = O
(**57**) R = β–OH
(**58**) R = α–C≡CH, β–OH



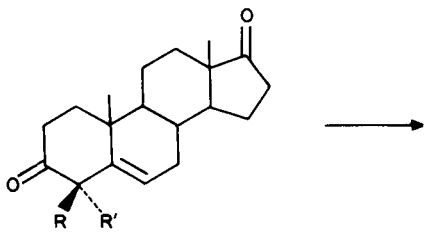
(**59a**) R = O
(**59b**) R = β–$COCH_3$

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]

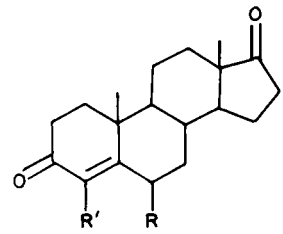
Substrate	$k_{cat}(s^{-1})$	$K_m(M)$	k_{cat}/K_m $(M^{-1}s^{-1})$	References
40	7.0×10^4	3.1×10^{-4}	2.3×10^8	84[b], 115, 137
40[c]	1.2×10^4	3.8×10^{-4}	3.0×10^7	105
54	2.7×10^3	8.2×10^{-6}	3.3×10^8	115
54[c]	3.5×10^3	6.8×10^{-5}	5.1×10^7	115
55	2.7×10^4	8.3×10^{-5}	3.3×10^8	84[b]
56	6.1×10^1	4.8×10^{-5}	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.



(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

(23)

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 pK_E = 4.57 (from k_{cat}/K_m) and pK_{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].

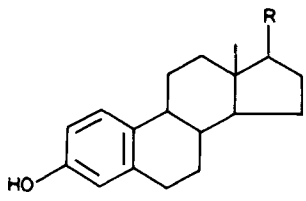
2. Histidine

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.

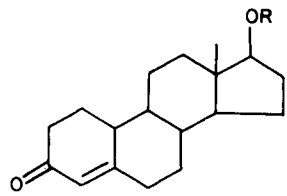
In contrast to the above results implicating histidine in the catalytic mechanism, Benisek and Ogez[97] found that binding of the competitive inhibitor 17β-estradiol produces no significant change in the chemical shifts of the protons of the isomerase histidine residues in the NMR. These results indicate 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



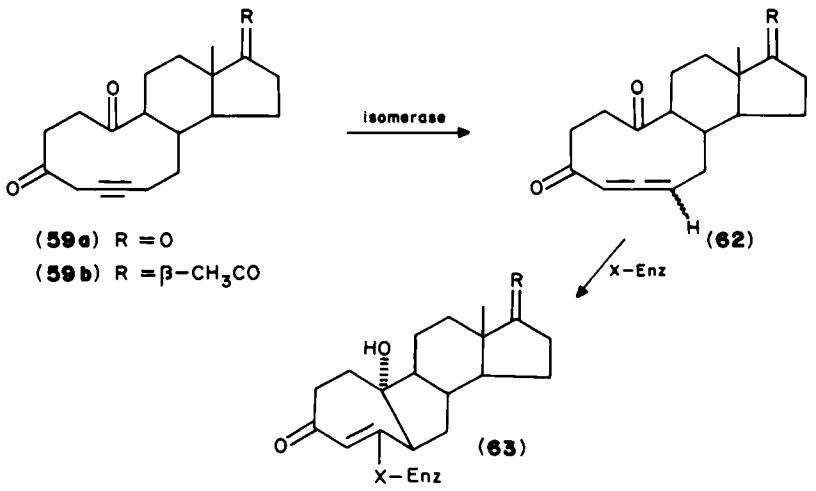
(61a) R = β-OH
(61b) R = β-OAc
(61c) R = O–polymer

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)

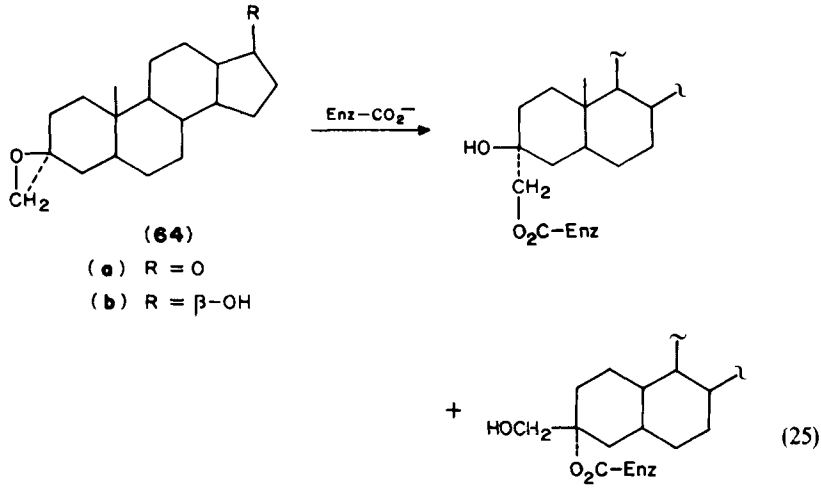
Note added in proof*: Site-directed mutagenesis of the isomerase suggests that Tyr-55 is not catalytically important, but that Tyr-14 is (A. Kuliopulos, A. S. Mildvan, D. Shortle and P. Talalay, *FASEB J.* **2 (Abs. 1704), p. AS89 (1988)).

*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



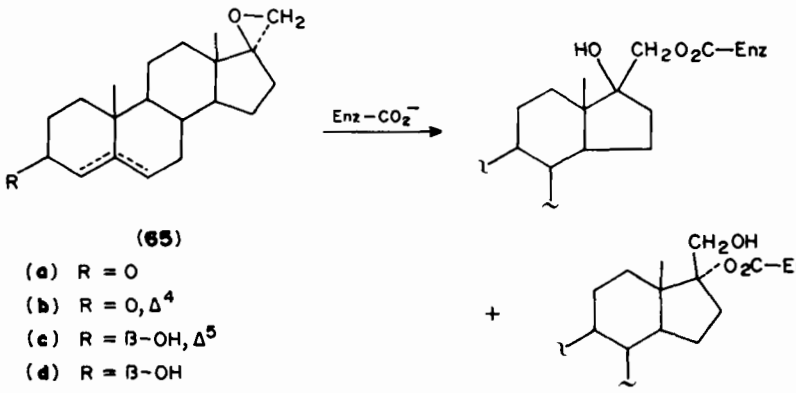
(64)

(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, Δ^4
(c) R = β-OH, Δ^5
(d) R = β-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 3β- and 17β-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).

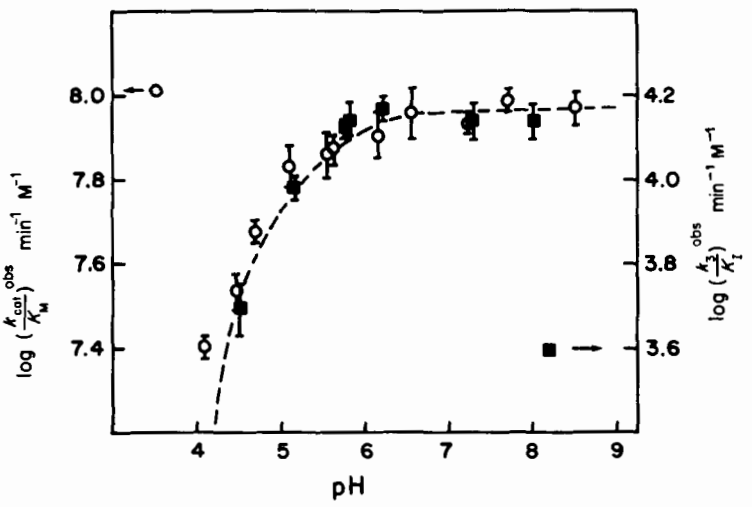
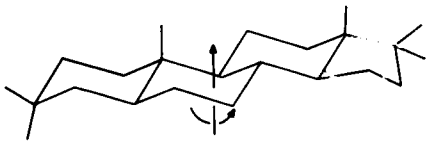


FIGURE 1. Comparison of the pH–rate profiles for log $(k_{cat}/K_M)^{obs}$ for the isomerization of 5(10)-estrene-3,17-dione (○) and log $(k_3/K_I)^{obs}$ for the inactivation by (3*S*)-spiro[5α-androstane-3,2′-oxiran[-17]one (■). The line is theoretical for a simple titration curve with p*K* = 4.75. 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

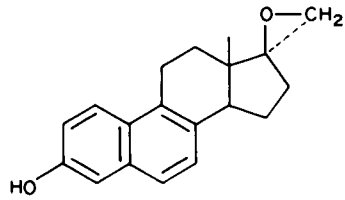
Further evidence that Asp-38 is catalytically important comes from the studies of Linden and Benisek[116]. They reported that, although the amino acid sequence of the 3-oxo-Δ^5-steroid isomerase from *Pseudomonas putida* demonstrates only 34% overall homology with the related *testosteroni* enzyme, 100% 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].



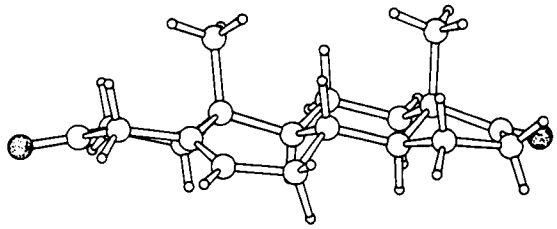
(**66**)



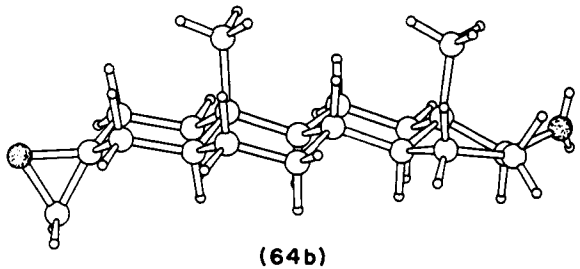
(**67**)

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].

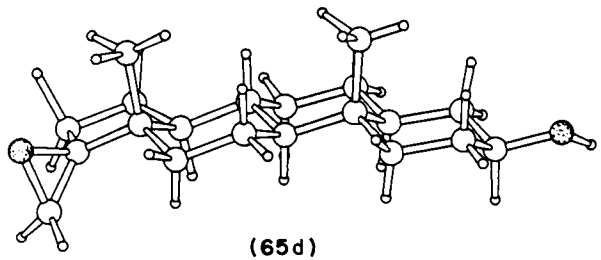
*Backwards refers to a steroid rotated 180° about an axis perpendicular to the plane of the steroid as in **66**.



5-Androstene-3, 17-dione



(64b)



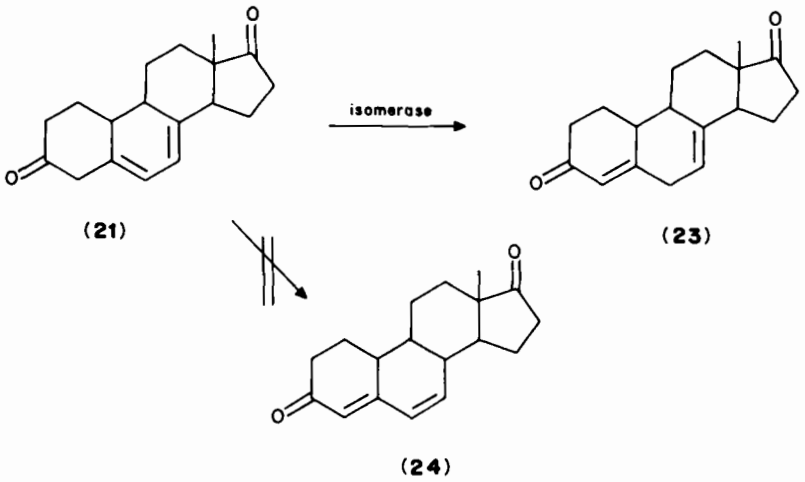
(65d)

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

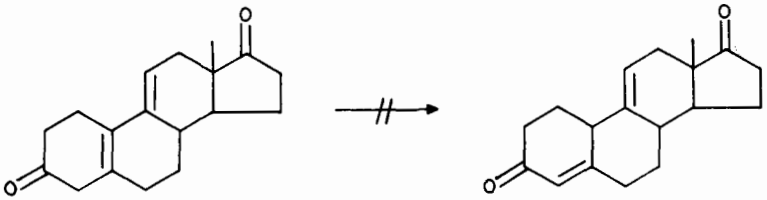
F. Evidence for an Intermediate Enol

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).

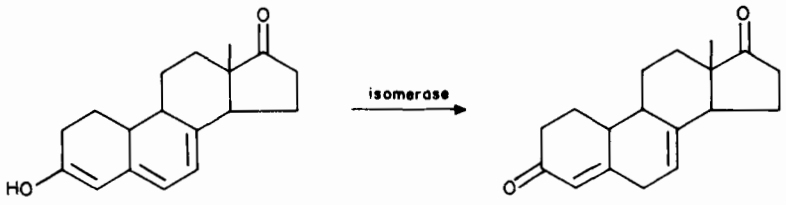


(21) (23) (24) (27)



(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

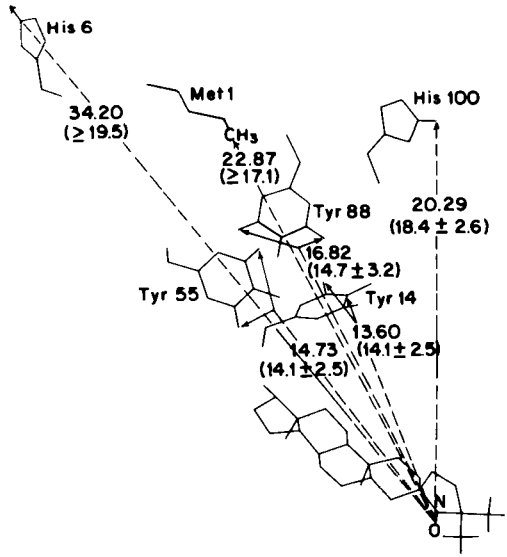
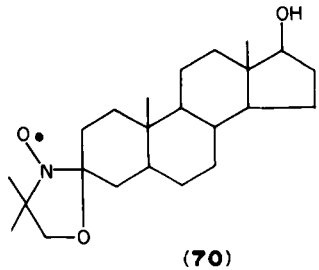


FIGURE 3. Computer-graphics representation showing the location of bound **70** at the active site of 3-oxo-Δ^5-steroid isomerase. Indicated root-mean-sixth average distances in angstroms are those measured by NMR (in parentheses) together with distances derived by positioning the spin label into the 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)

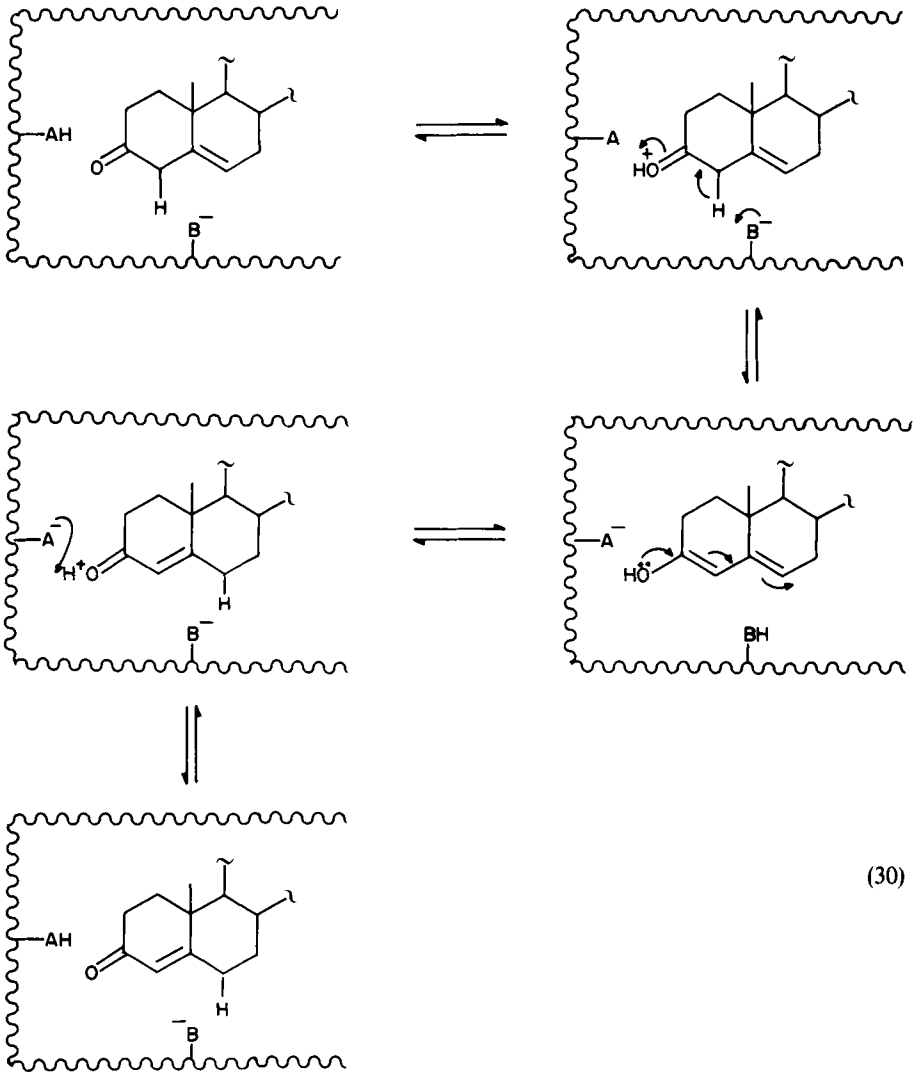
In agreement with previous results, it was found that Asp-38, Asn-57 and Tyr-55 are present at the active site, as well as Thr 35, Tyr 14, Tyr 88, Asp 32 and Glu 37. Binding of steroids seems to be controlled by hydrophobic interactions with three phenylalanine residues (82, 86 and 100) and Val 74 from 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.

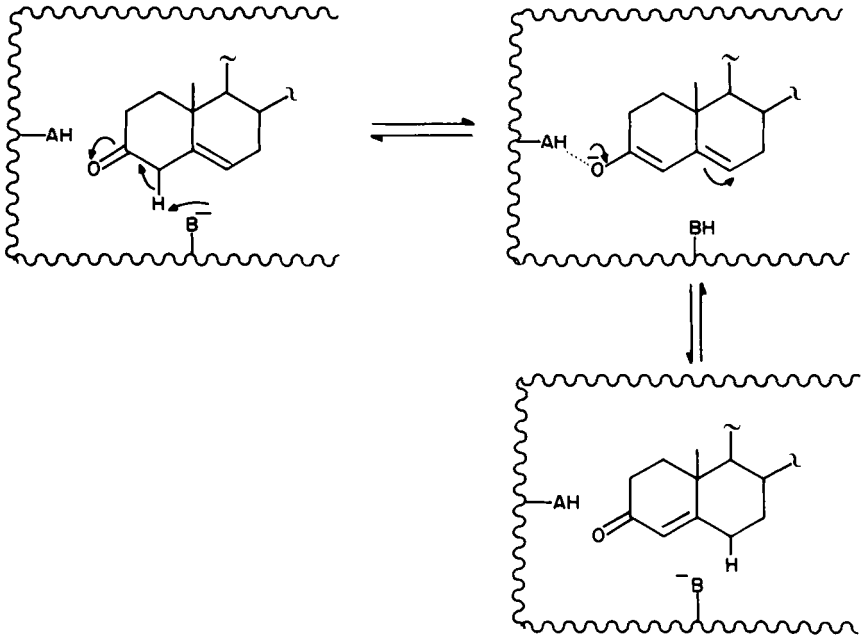
Malhotra and Ringold[18] sought to distinguish between neutral enols and their conjugate enolate anions in terms of the preferred site of protonation during acid-catalyzed interconversion of 3-oxo-Δ^4 and Δ^5 steroids. The neutral enol is preferentially protonated at $C_{(6)}$ to form the conjugated 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



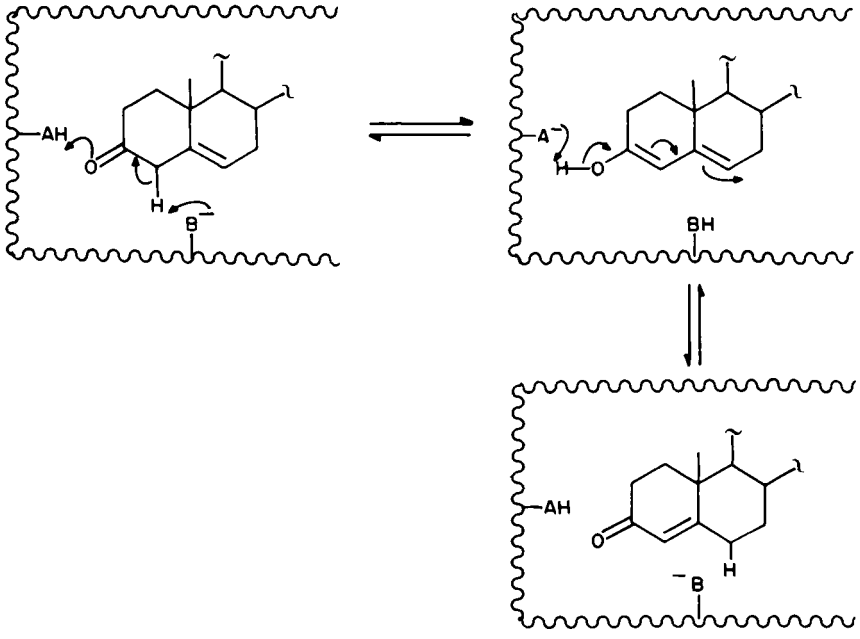
(30)

(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.

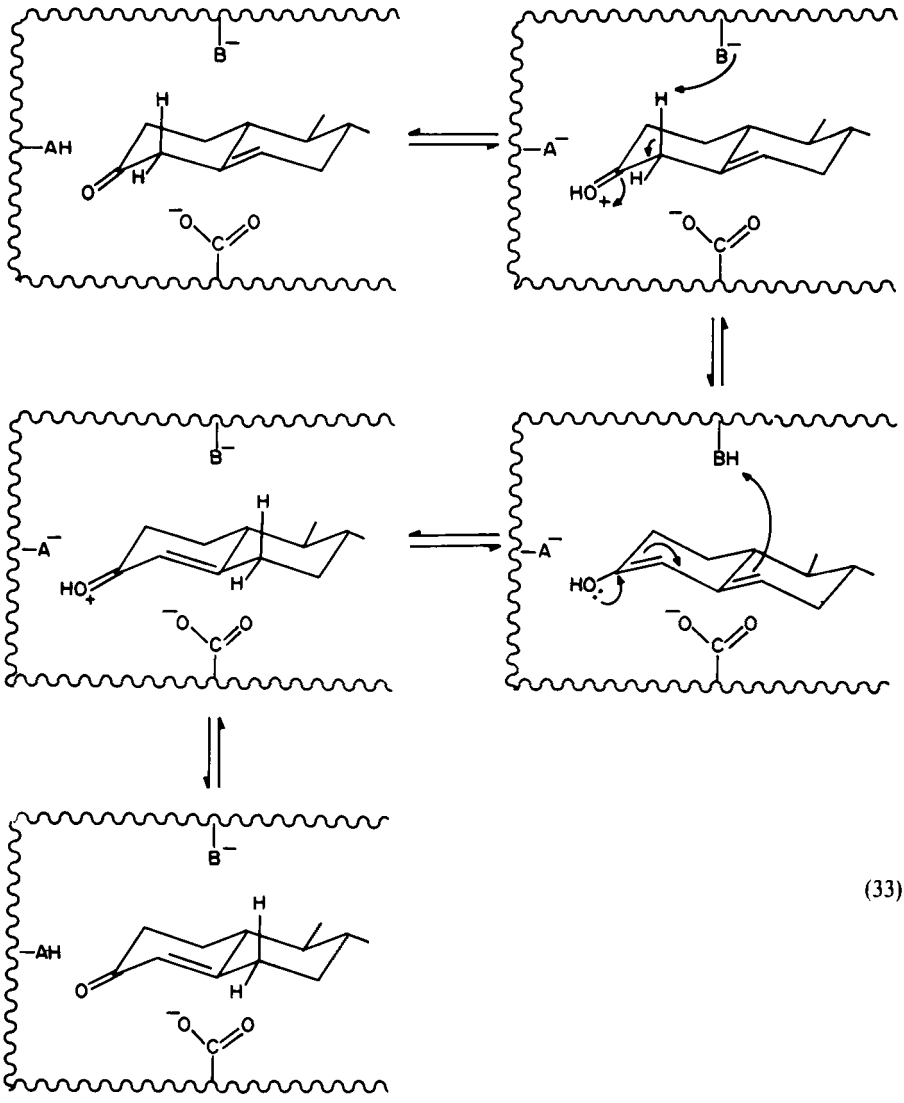
Based on the finding that Asp-38 attacks the oxiranyl steroids from the α-side of the steroid, we proposed that this group may act as an electrostatic catalyst to stabilize protonated ketone intermediates along the reaction pathway to and from a neutral dienol intermediate, analogous to the function 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

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The Chemistry of Enones
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CHAPTER **14**

Enone electrochemistry

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I. INTRODUCTION

The α,β-unsaturated ketone (enone) functional group is undoubtedly one of the most useful in organic chemistry. Each atom of the unit can, under appropriate conditions, function as a site at which a reaction can take place.

Enones have often served as substrates for electrochemical investigations[1-3]. For the most part, focus has been upon the generation and study of radical anions rather than

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radical cations. The reason for this disparity is easy to understand when one realizes that an electronically unperturbed enone possesses both a low-lying highest occupied molecular orbital (HOMO), from which it should be difficult to remove an electron, as well as a low-lying lowest unoccupied molecular orbital (LUMO) into which an electron can easily be added[4].

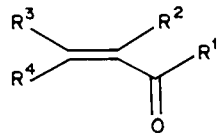
The terms 'difficult' and 'easily' used above are vague and require refinement. A variety of methods have been used to do so, including molecular orbital calculations[4,5], photoelectron spectroscopy[6-8], electron affinity measurements[9], charge transfer and UV spectroscopy[9], polarography and cyclic voltammetry[10-17].

II. PRODUCTION OF THE RADICAL ANION; REDUCTION POTENTIALS

Several compilations of polarographic reduction potentials, in both protic[10,11] and aprotic[12-14] media, are available. Access to this information is invaluable for the mechanistic insight it can provide (*vide infra*). Generally, the potentials measured under aqueous conditions are considerably less negative than those measured under aprotic conditions[12,13].

A detailed investigation and interpretation of the results obtained from a study of the reduction process as a function of pH has been conducted[15-17] and reviewed[2].

From data collected for a wide range of cyclic and acyclic aldehydes, esters and ketones in anhydrous DMF, it has proven possible to derive a very useful set of empirical rules which allow prediction of reduction potentials within $\pm$ 0.1 V as a function of the position and nature of the substituents R^1–R^4[4,14]. As illustrated in Table 1 substitution of an alkyl group at any one of the available positions shifts the reduction potential by -0.1 V from a base value of -1.9 V (vs SCE; $R^1 = R^2 = R^3 = R^4 = H$). An electron-donating alkoxy substituent has a pronounced effect (viz. -0.3 V) when substituted at either the carbonyl or the β-carbon, but has no effect when placed at the α-carbon. In accord with expectation, substitution of a single phenyl group at any position except the α-carbon makes the enone easier to reduce. Inclusion of a second phenyl group has no significant additional effect.



The presence of a phenyl group at either the carbonyl or the β-carbon makes it possible to observe two, rather than as is the case for many enones, one reduction wave[13]. It has been suggested[13] that the second wave corresponds to conversion of the first formed anion to the dianion. Since the potential associated with the second wave is so negative, even for a highly conjugated system (e.g. $E_{1/2}$ for *trans*-PhCH=CHCOBu-*t* is -2.23 V and for

TABLE 1. Empirical rules for estimation of reduction potentials

Substituent	Increment in reduction potential for		
	R^1	R^2	R^3 or R^4
Alkyl group	-0.1	-0.1	-0.1
1st alkoxy group	-0.3	0.0	-0.3
1st phenyl group	$+0.4$	$+0.1$	$+0.4$

trans-PhCH=CHCOCH$_3$ −2.61 V), it has been suggested that dianions may rarely, if ever, be involved in the cathodic chemistry of aliphatic enones[13].

In a few cases, the effect upon reduction potential of substituents placed at various positions on the phenyl group of an aryl ketone has been studied and shown to be correlatable with substituent constants using either Hammett or Yukawa–Tsuno relationships[18–20].

III. ELECTRONIC STRUCTURE OF RADICAL ANIONS; ESR STUDIES

Attempts to generate and study radical anions by electron spin resonance (ESR) spectroscopy are thwarted when the compound being studied contains acidic protons located at either end of the enone[13,21]. Replacement of the hydrogens with alkyl or aryl groups allows observation of well-defined ESR spectra and determination of the electron distribution within the radical anion. Independent studies[13,21] show that 40–50% of the unpaired spin density is located at the β-carbon, while the remainder is divided almost equally between the carbonyl carbon and oxygen atoms. Since the unpaired spin density at the α-carbon is nearly zero, one would anticipate and in fact finds (see Section II) that the reduction potential for an enone should be essentially independent of the nature of the substituent attached to that carbon.

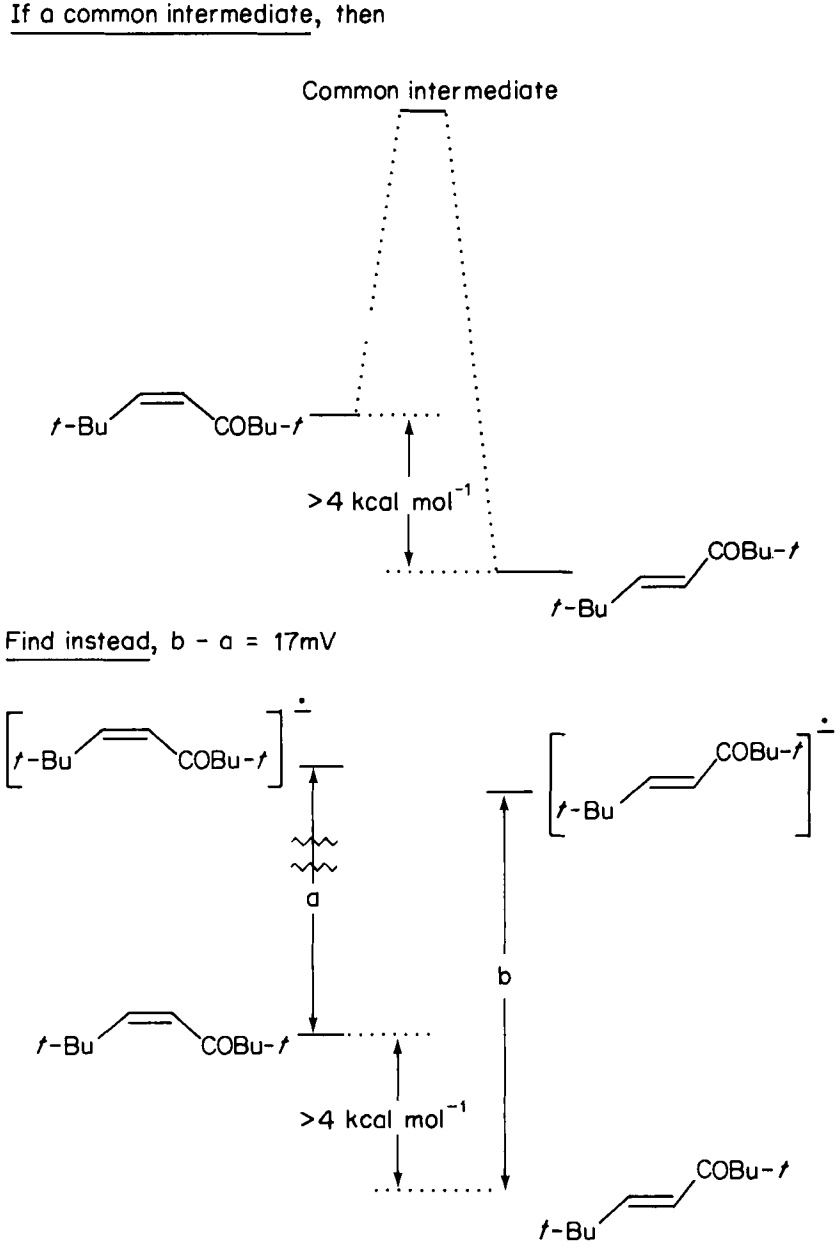
From these observations, it is gratifying to recognize that most of the chemistry of enone radical anions is characterized by reactions occurring at the β-carbon (β,β-coupling, protonation), the carbonyl carbon (pinacolization) and on oxygen (protonation). These and other reactions are discussed in Sections VI–XIII.

IV. LIFETIME OF A RADICAL ANION[13,22,23]

The lifetime of an enone radical anion is critically dependent upon several factors including: (a) The nature of the medium in which it is generated. In general, the presence of even low concentrations (e.g. 10^{-1} to 10^{-3} M) of a proton source (e.g. water, ROH, RCO_2H) or lithium salts leads to a marked decrease in the lifetime. For example, while the half-life for a 10^{-3} M solution of *trans*-*t*-BuCH=CHCOBu-*t* in dry DMF was determined by cyclic voltammetry (CV) to be > 10 s at ambient temperature, the addition of 0.03 M CF_3CO_2H causes a decrease to $< 10^{-3}$. The reason for this behavior is related to the previously mentioned need to replace acidic hydrogens flanking the enone in order to observe an ESR spectrum. That is, in the presence of a proton donor, the radical anion is protonated, leading to a neutral radical which subsequently dimerizes. Lithium, but interestingly not sodium or quaternary ammonium salts, have a similar effect. (b) The temperature at which the measurement is made. As expected, lower temperatures lead to increased lifetimes. (c) The presence of a functional group with which the radical anion can undergo a reaction intramolecularly (e.g. electrohydrocyclization)[1–3].

V. RADICAL ANION GEOMETRY[13]

Enone radical anions can either lose or, if the temperature is sufficiently low, maintain the geometry of the enone precursor for a time long enough to be discerned. For example, while the experimentally determined difference in free energy between the *cis* and *trans* geometric isomers of *t*-BuCH=CHCOBu-*t* is > 4 kcal mol^{-1} at 27 °C, the difference in their reduction potentials is only 17 mV. Since a potential difference of 1.00 V corresponds to an energy difference of 23.06 kcal mol^{-1}, 17 mV corresponds to only 0.017 × 23.06 kcal mol^{-1}, a value at least ten times less than that expected if each enone was reduced to a common, geometry-equilibrated intermediate. This line of reasoning suggests

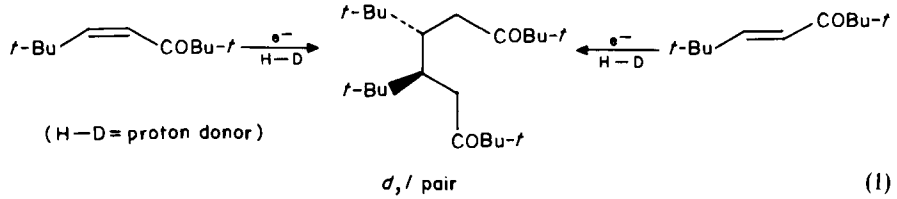

If a common intermediate, then
Common intermediate
t-Bu
COBu-t
>4 kcal mol⁻¹
COBu-t
t-Bu
Find instead, b - a = 17mV
t-Bu
COBu-t
a
b
t-Bu
COBu-t
>4 kcal mol⁻¹
COBu-t
t-Bu

SCHEME 1

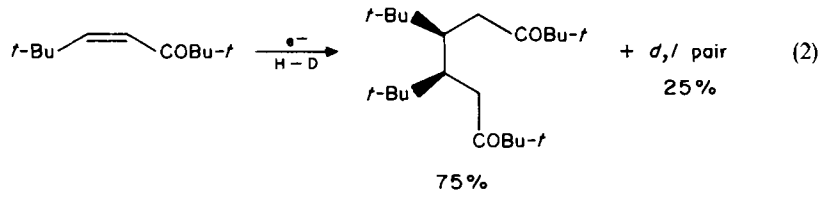
that each enone affords a geometrically distinct radical anion, as demonstrated in Scheme 1.

It must be noted, however, that these radical anions undergo rapid equilibration on the time scale of an ESR experiment at 25–30 °C, because electrolysis of either the *cis*- or the *trans*-enone in the probe of an ESR spectrometer affords the same well-resolved spectrum, undoubtedly that of the equilibrating forms[13]. That is, the barrier to rotation about the α, β-carbon–carbon bond is significantly lower in the radical anion than in the enone.

The rate of equilibration varies with temperature; it is sufficiently fast at temperatures at or above − 35 °C so that no difference in products or product ratio is noted when either the *cis*- or the *trans*-isomer undergoes hydrodimerization[13,24]. However, at − 78 °C, the interconversion is slowed to a value where each enone leads to a different mixture of stereoisomeric products. That is, at $T \geqslant -35$ °C equation 1 applies[13] whereas when $T \leqslant -78$ °C equation 2 applies, while the *trans*-isomer still affords the *d*, *l* pair[13].



(1)



(2)

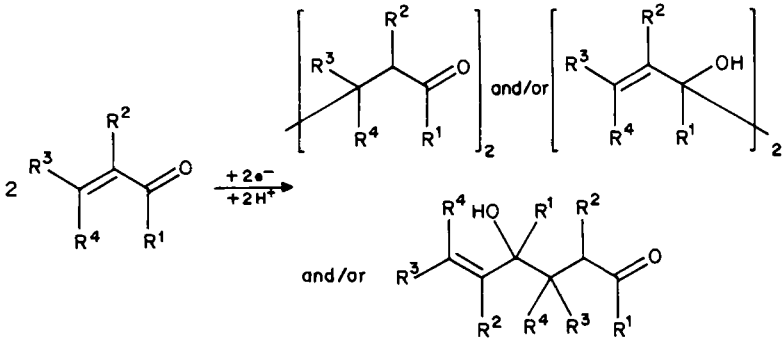
It could be synthetically useful if these observations prove general, that is, if enone radical anions can maintain the geometry of the precursor long enough to express that difference in terms of the stereochemical outcome for subsequent coupling processes.

VI. REDUCTIVE DIMERIZATION OF α, β-UNSATURATED KETONES (HYDRODIMERIZATION)

When reduced, α, β-unsaturated ketones can undergo a variety of transformations; most serve to form a new carbon–carbon bond between two or more enone subunits. As illustrated in equation 3, coupling can occur betwee: (a) β-carbon atoms to generate a 1, 6-diketone; (b) two carbonyl carbons, leading to a 1, 2-diol (a pinacol); or (c) the carbonyl carbon of one unit and the β-carbon of the other, creating a γ-hydroxy ketone.

Note that each product corresponds to a dimer of the starting material plus two hydrogens. Consequently, the reduction should be conducted in the presence of a proton donor. The proton donors span a wide range of acidities ranging, as we shall see, from a mineral acid in an aqueous medium to a carbon acid [e.g. $CH_2(CO_2R)_2$] in an organic solvent, often acetonitrile or DMF.

Appropriately, the intermolecular electrochemically initiated hydrodimerization reactions are referred to as electrohydrodimerization (EHD) reactions[2]. The intramolecular

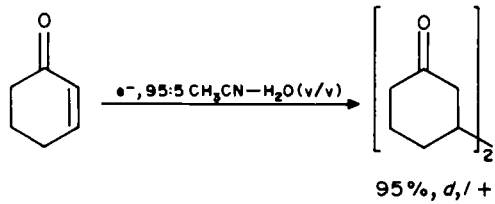


(3)

version of the β,β-coupling process is called electrohydrocyclization (EHC)[2]. In both cases, a wide range of electron-withdrawing groups have served as olefin activators (e.g. CN, CHO, CO_2R, $CONR_2$, etc.)[1-3,25,26]. We will focus attention almost exclusively upon α,β-unsaturated ketones and will attempt to provide an overview of the chemistry rather than an exhaustive survey of the very large amount of work which has been published.

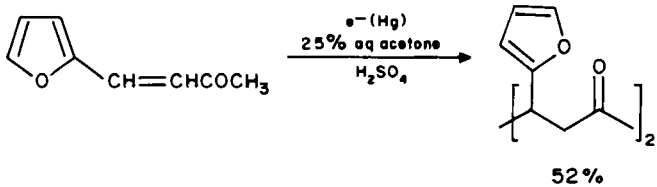
In addition to the modes of coupling listed above, reduction of α,β-unsaturated ketones can also lead to: (1) saturation of the C—C π bond, a process which can become important when dimerization is sterically inhibited; and (2) oligomerization or polymerization, processes which are most likely to occur in an aprotic or basic medium.

The scope and limitations of EHD reactions of monoactivated olefins, mixed (or crossed) reductive coupling among them, and EHC reactions have been discussed[27-38]. Two EHD reactions involving enones are illustrated in equations 4 and 5[39,40]. Others are presented in Section VII.



95%, *d,l* + *meso*

(4)

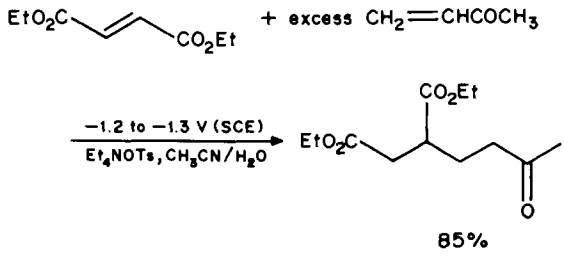


52%

(5)

α,β-Unsaturated ketones are suitable coupling partners in mixed couplings for substances which are reduced at more positive cathode voltages[30]. For example, electrolysis at -1.2 to -1.3 V (vs SCE) of a mixture of diethyl fumarate and a tenfold molar excess of methyl vinyl ketone afforded the keto diester shown in *ca* 85% yield[30] (equation 6).

When the enone is easier to reduce than its partner, then it is desirable to select an enone whose β-carbon is sufficiently encumbered in order to decrease its tendency to undergo self-hydrodimerization, and to couple it with an uncongested acceptor. Examples[30] are



(6)

given in equations 7 and 8. Attempts to couple 9-benzalfluorene with mesityl oxide, each of which is sterically encumbered, failed[30]. Electrolysis of a mixture of methyl vinyl ketone and 9-benzalfluorene afforded mainly the ketone hydrodimer and no coupled product.

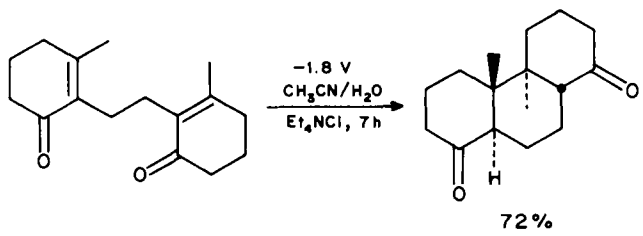
$$\mathrm{PhCH{=}CHCOCH_3 + \text{excess } CH_2{=}CHCN \xrightarrow[Et_4NOTs,\ AcOH]{-1.4 \text{ to } -1.5\ V\ (SCE)}}$$

$$\underset{ca\ 32\%}{\mathrm{CH_3COCH_2CHPhCHPhCH_2COCH_3}} + \underset{<10\%}{\mathrm{CH_3COCH_2CHPhCH_2CH_2CN}} \qquad (7)$$

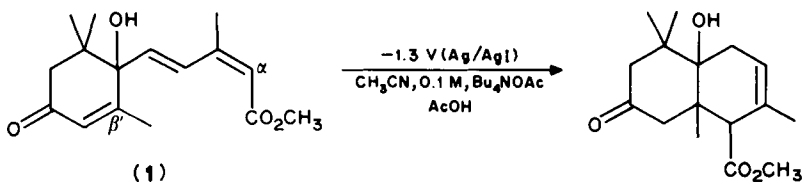
$$\mathrm{(CH_3)_2C{=}CHCOCH_3 + \text{excess } CH_2{=}CHCN \xrightarrow[Et_4NOTs,\ CH_3CN/H_2O]{-1.6 \text{ to } -1.7\ V\ (SCE)}}$$

$$\underset{ca\ 50\%}{\mathrm{CH_3COCH_2C(CH_3)_2CH_2CH_2CN}} \qquad (8)$$

The EHC reaction can provide a powerful means of constructing polycyclic ring systems. Most often, β, β-coupling occurs[41] (equation 9). However, in another example[42], reduction of the dienoate **1**, isomerization of the resulting radical anion, and sigma bond formation between C(α) and C(β') ensues (equation 10). Perhaps β, β'-coupling is simply sterically retarded relative to the alternative pathway. Interestingly, no cleavage of the hydroxyl group was reported.



(9)



(10)

A. Mechanism

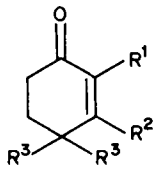
Given the possibilities outlined above, it may not be surprising to discover that a great deal of time and effort has been expended to determine the mechanism for the reactions[1-3,25,26,39,43-51]. A sufficient amount is known about each so that one can choose remarkably well among a host of conditions those most appropriate to achieve selective and efficient conversion to a single product type. Studies have focused upon the effect that variations in (a) cathode material, (b) catholyte, (c) supporting electrolyte, particularly its cation, (d) concentration of the olefin in the catholyte, and (e) type of cell, have upon the various coupling processes[1-3].

B. Mechanistic Overview; Examples

In general, there exist two schools of thought regarding the mechanism for β, β-coupling under neutral or alkaline conditions. In one, dimerization is thought to occur via the combination of two radical anions (an EC process, i.e. an *e*lectrochemical reaction followed by a *c*hemical reaction)[43,45,51]. The other suggests that the process involves coupling between the initially formed radical anion and the starting enone (the ECE mechanism)[23,46,48-50].

Under acidic conditions, it is generally agreed that dimerization occurs between the neutral radicals formed after preprotonation of the enone on oxygen followed by one-electron reduction to generate an allylic radical[13,24].

A comparatively recent study, illustrating the variation in product composition as a function of the amount of proton donor (in this case, water) present in the reaction medium and the way in which the ratio responds to varying degrees of steric hindrance about the enone subunit, has been published[39]. For the enones **2a–c** illustrated below, the solvent was varied from pure acetonitrile to 5% (v/v) water in acetonitrile; tetra-*n*-butylammonium tetrafluoroborate was used as the supporting electrolyte, a stirred mercury pool as the cathode.



(2)

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

(b) $R^1 = R^2 = H$, $R^3 = CH_3$

(c) $R^1 = R^2 = R^3 = CH_3$

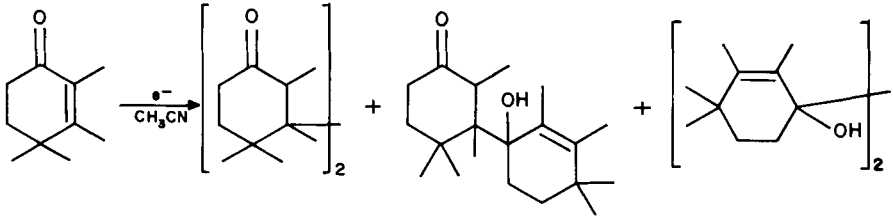
As illustrated in Table 2, regardless of the water content, coupling between β-carbons is preferred when cyclohexenone is used as the substrate. The addition of methyl groups at C(4) leads to a decrease in the amount of β, β-coupling. As the water content increases, the

TABLE 2. Effect of water content on hydrodimer product ratios

Enone	Water content (% H_2O in CH_3CN)	1, 6-Diketone (%)	γ-Hydroxy ketone (%)	Diol (%)
2a	0	97	—	—
	5	95	—	—
2b	0	52	31	16
	5	28	4	64

amount of 1, 2-diol steadily increases until, at 2% water in acetonitrile, equal quantities of diol and diketone are produced. Eventually, the diol-to-diketone ratio inverts and more diol than diketone is formed.

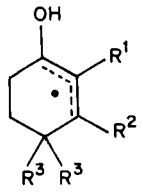
Severe crowding as in enone **2c** causes a substantial drop in the amount of β, β-coupling and a corresponding increase in the quantities of hydroxy ketone and diol[39] (equation 11). This shift toward more diol as steric hindrance about the β-carbon increases is general and has been noted before[24,52,53].



(2c)	No water:	10%	60%	30%
	5% water:	—	45%	50%

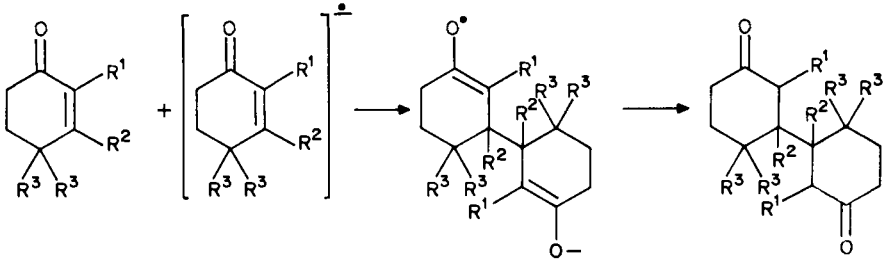
(11)

These results were interpreted in accord with previous analyses[1-3,13,24-26] to indicate that in the presence of a proton donor, protonation occurs on oxygen to form a neutral allylic radical **3** which subsequently dimerizes by coupling between (a) C(1), leading to diol;



(3)

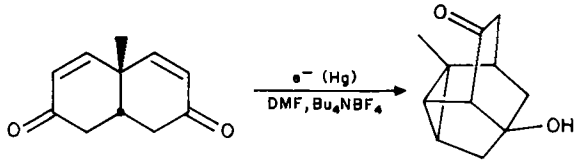
(b) C(1) and C(3), affording hydroxy ketone; and (c) C(3), providing the 1, 6-diketone. In the absence of the water, the enone plus radical anion pathway was suggested to account for the results.



A similar set of cyclohexenones was subjected to a detailed voltammetric study[23]. Using well-established criteria[51], it was again concluded that electrohydrodimerization proceeds via the radical anion plus enone pathway in the absence of a proton donor, despite

evidence accumulated by others based upon voltammetric[43] and chronopotentiometric[45] studies indicating operation of the radical anion dimerization pathway.

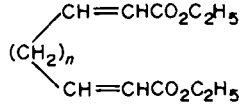
The mechanism of electrohydrocyclization has been studied in great detail and with great care[1-3,46]. Here too it was concluded that cyclization of the bisactivated olefins occurs, at least partially, through the attack of a radical anion upon an unreduced double bond[46]. A more recent study dealing with the symmetrical bisenone **4** (equation 12) led to similar conclusions[50]. Note that the final product **5** corresponds formally to one produced by an intramolecular aldol condensation of the product formed in the EHC reaction. Often the products of EHD and EHC reactions undergo well-known 'secondary' processes[2].



(12)

(4) (5)

The potential associated with conversion of **4** to its radical anion is -2.20 to -2.29 V (vs Ag/Ag^+) depending upon the scan rate associated with the cyclic voltammetry (CV) experiment. This is nearly the value one would have predicted based upon the use of the set of empirical values listed in Table 1 for estimation of reduction potentials[14] and is nearly the same as that of cyclohexenone. These observations would not be noteworthy except for the way in which they stand in marked contrast to the potentials obtained for bis-α,β-unsaturated esters. For example, the polarographic half-wave potentials for a variety of bisenoates **6** are shifted to a value roughly 200 mV (*ca* 4.6 kcal) more positive than that associated with the simple model system possessing only one unsaturated ester unit, ethyl crotonate[31]. That is, even though the two unsaturated esters are insulated from one another by a series of methylene units, the presence of the second influences the potential of the first, making the bisenoate easier to reduce. It is generally accepted that this shift to a more positive potential is correlated with a process wherein the polarizable enoates approach one another with the β-carbons sufficiently close to allow the one-electron reduction and sigma-bond formation to occur in concert[1-3].

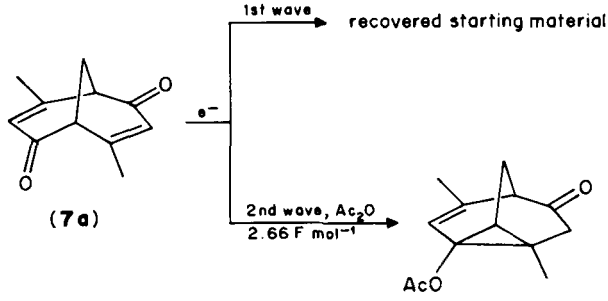


(6)

Based upon precedent of this nature it is curious that a shift to a more positive potential is not observed for the symmetrical bisenone. Perhaps, given the flexibility of the methylene chain linking the α,β-unsaturated ester units to one another, there is a preferred geometry associated with cyclization and attendant potential shift which is unattainable for the comparatively rigid bicyclic enone. It appears as though simply bringing the β-carbons near one another is not sufficient to cause a shift.

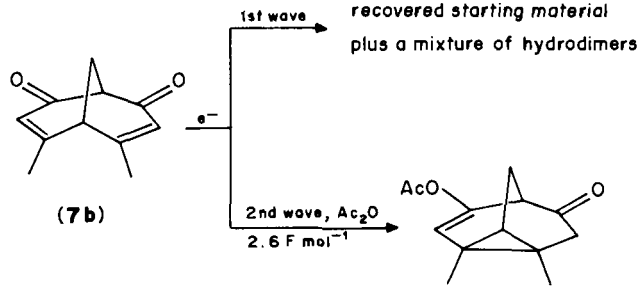
With these observations and comments in mind, it is interesting to note the behavior of the rigid bicyclo(3.3.1)enones (**7**)[54] (equations 13–16). Again, no shift in potential is observed. CV data (Pt, CH_3CN, 0.4 M Bu_4NBF_4, $Ag/AgNO_3$ reference electrode) indicate two one-electron reduction waves, one at -2.0 V, the other at -2.75 V. Preparative scale reduction of **7a** and **7b** illustrates an important and useful feature of controlled potential

electrolysis. That is, different products can sometimes be obtained depending upon whether the reactions are carried out at the first or second wave.



(13)

(14)

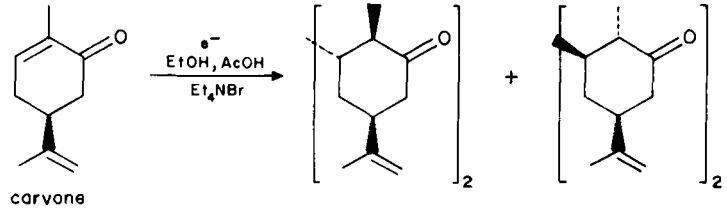


(15)

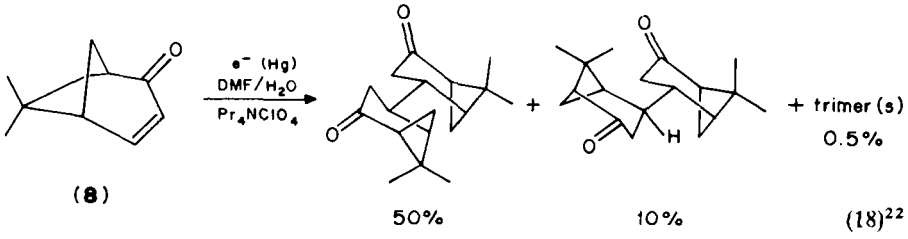
(16)

VII. STEREOCHEMISTRY OF β,β-COUPLING

While the stereochemical outcome of several EHD and EHC reactions has been determined (equations 1, 2, 9, 17 and 18)[13,22,41,55,56] and on occasions there exists a high degree of stereoselectivity[13,22,24,41,55,57,58], the factors leading to and controlling the selectivity have, unfortunately, not been thoroughly investigated.

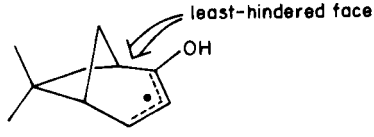


(17)[56]



(18)[22]

In a few cases, such as that of apoverbenone (**8**)[22], it has been suggested that the major product is formed as a result of a least-hindered side approach to the face of the allylic radical **9** opposite the *gem*-methyl group.



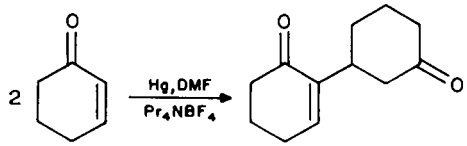
(**9**)

The reaction illustrated in equation 9 is remarkable not only for its stereospecificity, but also for the regiospecificity; only the β,β-coupled hydrodimer is formed[41].

VIII. ELECTROGENERATED BASE (EGB) PROPERTIES OF ENONE RADICAL ANIONS

It was noted previously that the presence of acidic hydrogens at either end of the enone makes it extremely difficult, and in some cases impossible, to obtain an ESR spectrum of the radical anion[13,21]. It was also indicated that even when the hydrogens are replaced by alkyl or aryl groups, the addition of an external proton source greatly diminishes the lifetime of the radical anion[13].

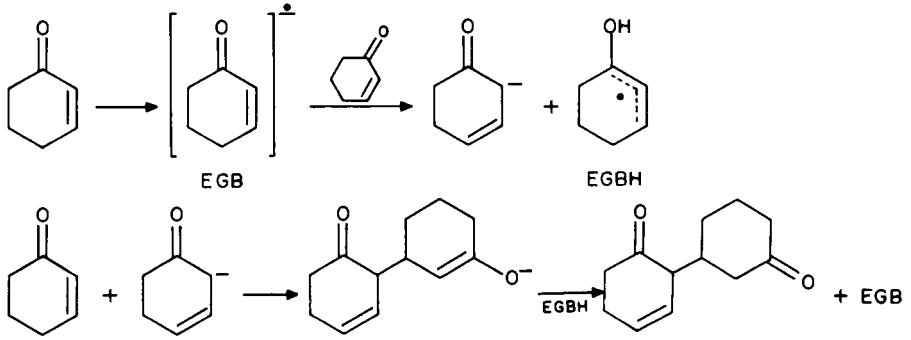
One can use this propensity of radical anions to act as a base, an electrogenerated base (EGB)[59], to affect a variety of transformations. For example, reduction (Hg cathode, -1.90 V, DMF, Pr_4NBF_4) of only a small amount (0.13%) of cyclohexenone leads to the Michael adduct **10**[60] (equation 19).



(**10**) 65%

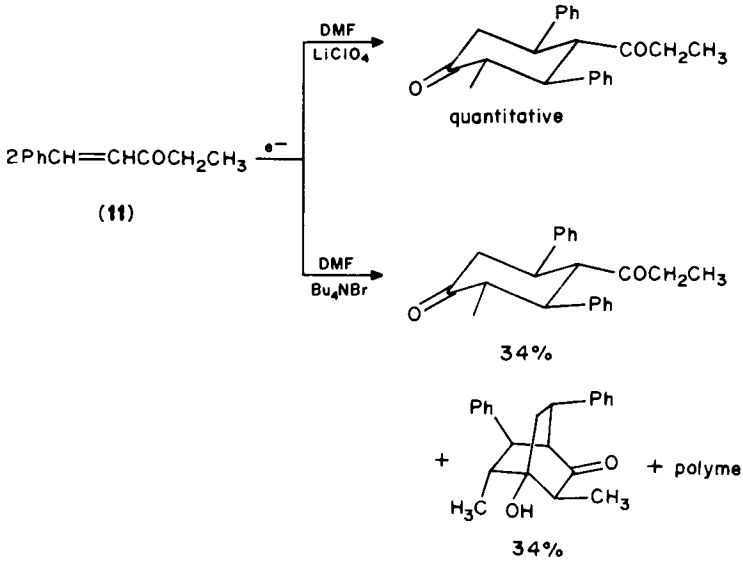
(19)

As illustrated in Scheme 2, only a catalytic amount (often 1–10%) of the enone need be reduced to the radical anion, since the latter is used in a catalytic fashion.



SCHEME 2

Similarly, dimerization of 1-phenyl-1-penten-3-one **11** can be achieved after the passage of less than 0.2 faraday mol^{-1} of electricity. When the reaction is conducted in DMF with lithium perchlorate as the supporting electrolyte, the product is formed stereospecifically and in quantitative yield[61] (equation 20). Interestingly, use of Bu_4NBr in place of lithium perchlorate affords equal amounts of two dimers in addition to polymer[61] (equation 21).



(20)

(21)

Occasionally, radical anions are sufficiently long lived so that they can be trapped by added electrophiles such as acetic anhydride[54,62–65] or carbon dioxide[1–3,66,67]. In the absence of a trapping agent and in the absence of a suitable proton donor, radical anions and dianions can undergo trimerization, oligomerization and polymerization[2,66,68].

IX. SATURATION OF THE C—C π BOND

To accomplish the efficient synthesis of any compound requires that one build into as many steps of a sequence as possible a high degree of selectivity or, preferably, specificity. A classic example of the need for such selectivity stems from efforts to reduce acrylonitrile electrochemically and convert it to the commercially valuable commodity adiponitrile rather than to propionitrile[1–3]. Initial studies, conducted in water, were disappointing and led to propionitrile. However, addition of the hydrotropic salt, Et_4NOTs, to the aqueous solution served to make the region near the cathode sufficiently 'dry' to allow β, β-coupling to occur and saturation to be eliminated[27,28].

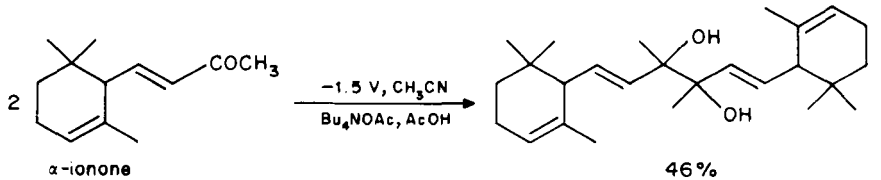
Suppose that one is interested in accomplishing the opposite objective, that being the complete and selective saturation of the C—C π bond with no fear of competing dimerization. One could choose to use nonelectrochemical methods, such as H_2, noble metal catalyst. Recently, however, an elegant solution based upon the design and use of hydrogen-active powder electrodes has been devised[69]. The method consists of using either Raney nickel (R-Ni), Pd—C or Pt—C as cathode materials in the presence of a proton donor, generally chloroacetic acid, pivalic acid, phenol or water, in a solution of THF and water (9:1, v/v) containing $NaClO_4$ as a supporting electrolyte. Reduction of the proton donor serves as a source of adsorbed hydrogen.

Three substrates were examined: 2-cyclohexen-1-one, 4-methyl-3-penten-2-one and *trans*-3-phenyl-2-propenal. For each substrate, all electrode/proton donor combinations were examined. In general, R-Ni and Pd—C afforded high selectivity (up to 100%) for the conversion to cyclohexanone and to 4-methyl-2-pentanone; Pt—C proved less satisfactory. *trans*-3-Phenyl-2-propenal proved to be a difficult case, affording substantial quantities of *trans*-3-phenyl-2-propen-1-ol in addition to the desired product, 3-phenylpropanal.

Prior to this work researchers attempted to use Raney nickel[70-75] and metal blacks[76-80] as cathode materials. However, it has been noted[69] that electrolytic hydrogenation with hydrogen active powder electrodes has several advantages over direct uncatalyzed electrolysis. For example, the large surface area of the electrode leads to an increase in the rate of hydrogenation. Furthermore, hydrodimerization can most often be avoided entirely, since proton discharge to form atomic hydrogen on the catalyst surface can be accomplished at potentials more positive than those required for generation of an enone radical anion. Finally, reactions are conducted under mild conditions at room temperature and atmospheric pressure.

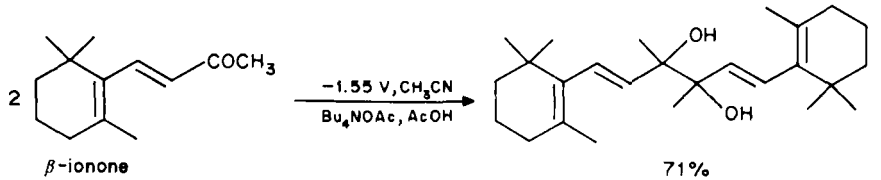
X. PINACOL FORMATION

If the β-carbon of an enone is sterically hindered and the carbonyl carbon is not, then pinacolization can often be carried out in preference to β,β-coupling. Many examples illustrating this characteristic are known[39,81-84] and several are illustrated in equations 22[83], 23[83] and 24[84].



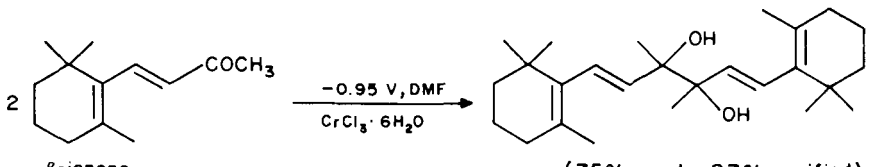
α-ionone 46%

(22)



β-ionone 71%

(23)

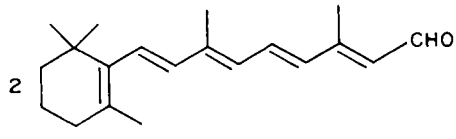


β-ionone (75% crude, 27% purified)

(24)

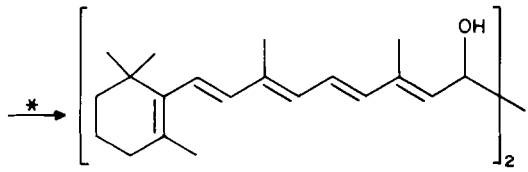
The reduction shown in equation 24[84] is particularly interesting for it is suggested that Cr^{3+} interacts with the carbonyl oxygen of β-ionone to form a Lewis acid–Lewis base complex which is easier to reduce than the enone in its absence, i.e. the Cr^{3+} behaves like a proton.

It is difficult to convert efficiently retinal **12** to its pinacol, unless diethyl malonate is used as the proton donor[85] (equation 25). The reason(s) for this behavior is (are) not well understood.



(12)

*
(a) −1.00V, CH_3CN, Bu_4NOAc, AcOH; 11% product.
(b) −1.4V, CH_3CN, $CH_2(CO_2Et)_2$, Bu_4NClO_4; 50% product

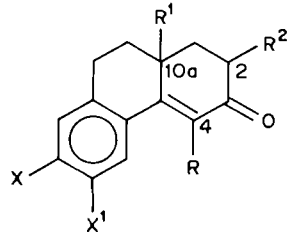


(25)

A. Stereochemistry of Pinacolization

In each of the reactions shown above, a mixture of *d*, *l* and *meso* stereoisomers is formed. For example, the 71% pinacol formed in the dimerization of β-ionone corresponds to a 2:1 mixture of *meso* and *d*, *l* isomers. While the factors controlling these reactions are reasonably well understood[86,87], stereochemical assignments have rarely been made. A glaring exception to this generalization follows.

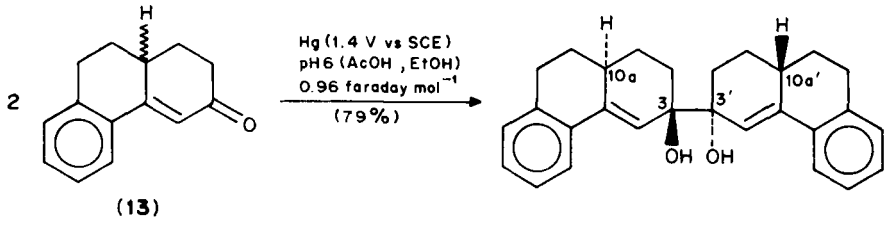
From a remarkable study of the stereochemical outcome of the pinacolization of a series of 1, 9, 10, 10a-tetrahydro-3(2*H*)-phenanthrones **13**, it was possible to obtain detailed information concerning the preferred approach of the reacting partners and the importance of the electrode surface during the reaction[88,89]. Furthermore, an expression of chiral recognition was observed. That is, formation of the new sigma bond was shown to occur preferentially between enones of the same chirality [e.g. (+)- with (+)-, or (−)- with (−)-enone was preferred over the combination of (+)- with (−)-enone].



(13)

Consider the stereoselective conversion illustrated in equation 26. Only the product

with a *trans* relationship between the hydrogen at C(10a) and the hydroxy group at C(3), a *threo* relationship about the new sigma bond and a *trans*-relationship between the hydrogen at C(10a') and the hydroxy group at C(3') was formed[89].

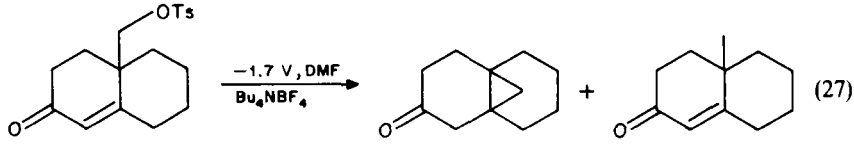


(26)

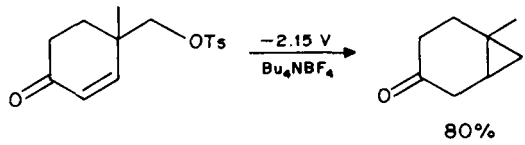
Arguments are presented[89] which lead to the conclusion that in a neutral medium (pH 6), the two reacting ketones are initially adsorbed selectively so that the least hindered face of each is directed toward the surface of the electrode. The unpaired electron is considered to be completely delocalized and the molecule is believed to lie relatively flat. During formation of the new C—C bond, the unpaired electron is presumed to become progressively more localized on the hydroxyl-bearing carbon and the desorption of the aromatic portion of the molecule is thought to occur. Eventually, the two reactive species orient themselves face-to-face leading to formation of the *trans, threo, trans*-diol.

XI. INTRAMOLECULAR CLOSURE ONTO AN sp^3-HYBRIDIZED CARBON

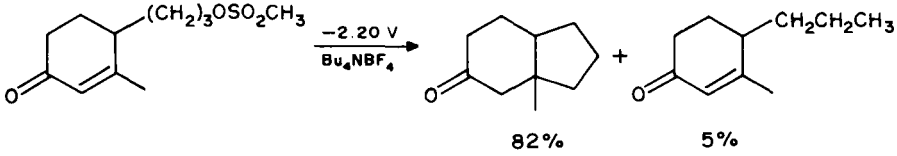
A variety of bicyclic systems can be constructed by capitalizing upon the ability of a suitably positioned radical anion to close onto an sp^3-hybridized carbon bearing a tosylate or mesylate as a leaving group. Examples[90] are given in equations 27–29. It is clear that even the presence of a fully substituted β-carbon does not prevent cyclization from occurring and in high yield.



(27)

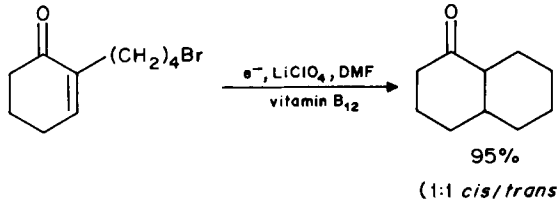


(28)

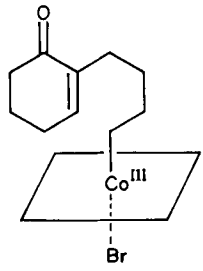


(29)

In these examples, the enone functions as the electrophore, the tosylate or mesylate bearing carbon as the center being attacked (the acceptor). However, when the enone is tethered to an alkyl halide and reduction is carried out in the presence of a cobalt(III) catalyst such as vitamin B_{12} (equation 30)[91], then the role of electrophore and acceptor reverse[91–93]. The initially formed complex between the catalyst and the alkyl halide **14** can be reduced at a potential which is sufficiently negative to cleave the Co^{3+}—C bond but not low enough to reduce the enone[94].



(30)



(14)

XII. NONCONJUGATED ENONES

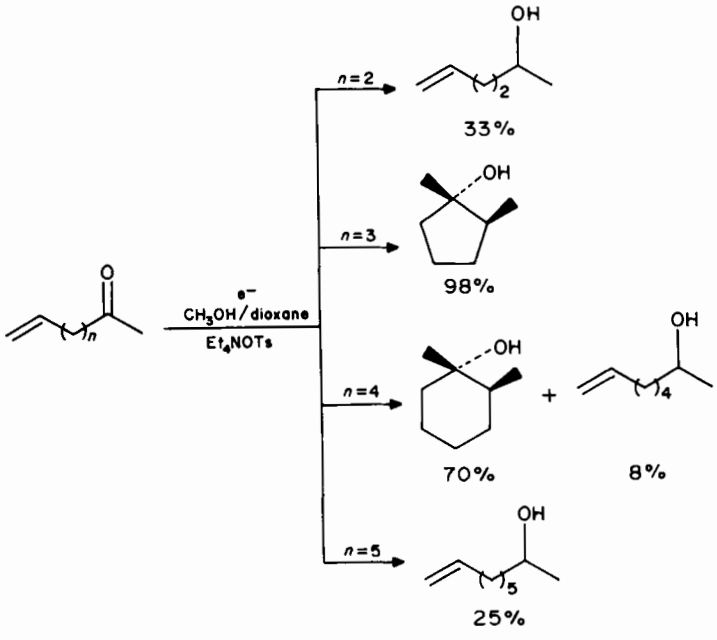
Reduction of a ketone linked to an alkene[95,96], an allene[97,98] or an alkyne[98,99] by a chain of variable length and composition leads to formation of a C—C bond between that unit and the carbonyl carbon. The reactions are often conducted at constant current either in DMF or in a 1:9 (v/v) mixture of methanol and dioxane containing Et_4NOTs as a supporting electrolyte[95,96]. Five- and six-membered rings are formed efficiently, but four- and seven-membered rings are not (equations 31–34)[96].

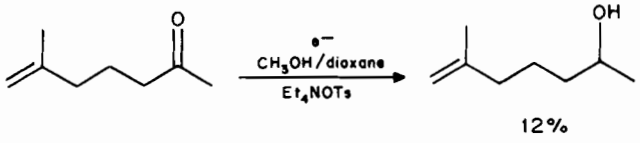
Cyclization proceeds regioselectively; given the choice between forming a five- or a six-membered ring, five is preferred. However, even formation of a five-membered ring is thwarted when the internal carbon of the olefinic linkage bears an alkyl group as shown in equation 35[96].

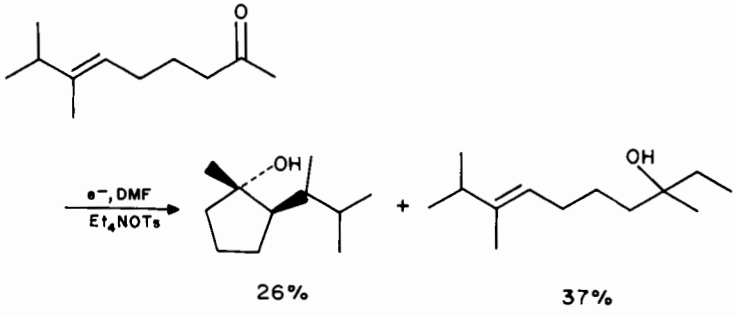
Substitution of two alkyl groups on the terminal olefinic carbon apparently slows the rate of closure sufficiently so that formation of an acyclic tertiary alcohol becomes a competitive process. The supporting electrolyte serves as a source of the new alkyl group, in this case an ethyl group, which becomes attached to the carbonyl carbon[96] (equation 36).

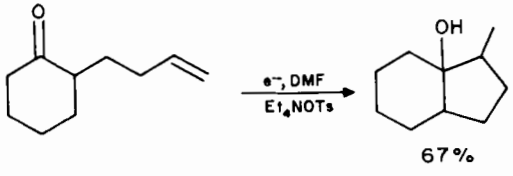
Bicyclic compounds containing a bridgehead hydroxyl group can also be constructed[96,98] (equations 37 and 38).

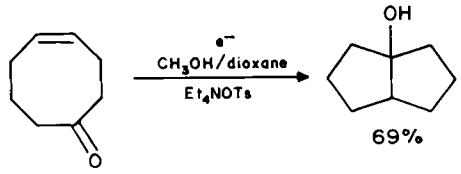
The methodology has been extended to the preparation of both endo- and exocyclic bridgehead allylic alcohols[98] (equations 39 and 40). Unfortunately, attempts to use this capability to synthesize ene-diol-containing natural products such as isoamijiol[100] (**15**)


n=2
33%
(31)
n=3
98%
(32)
e⁻
CH₃OH/dioxane
Et₄NOTs
n=4
70%
8%
(33)
n=5
25%
(34)

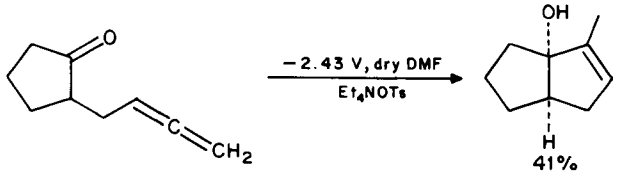

e⁻
CH₃OH/dioxane
Et₄NOTs
12%
(35)


e⁻, DMF
Et₄NOTs
26%
37%
(36)

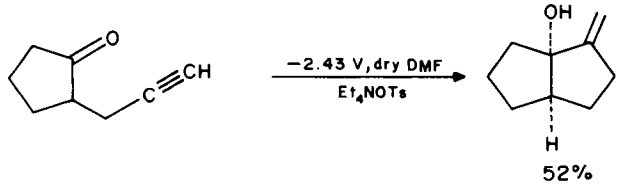

e⁻, DMF
Et₄NOTs
67%
(37)



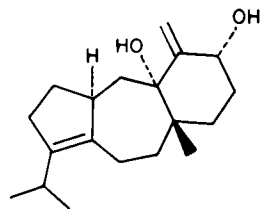
(38)



(39)

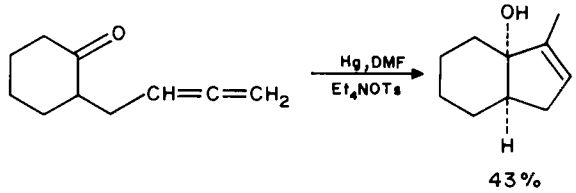


(40)



(15)

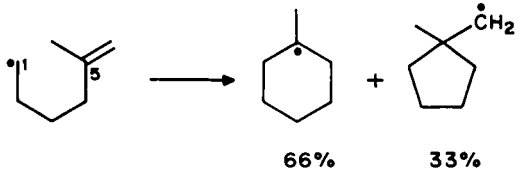
were thwarted by the tendency to form endo- in preference to the required exocyclic π bond in the product[98] (equation 41). Again, closure to form a five-membered ring is preferred to generating the six-membered alternative.



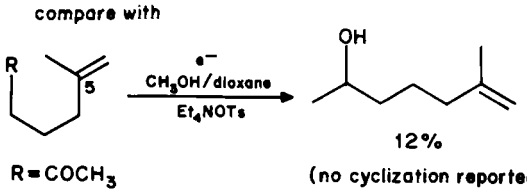
(41)

Both the regio- and stereochemical outcome of the reactions illustrated in this section are reminiscent of that associated with 5-hexen-1-yl radical cyclization[101]. However, the similarity is at best qualitative. For example, substitution of an alkyl group at C(5) of the 5-hexenyl radical leads to a decrease in the rate of cyclization to form a five-membered ring

to a point where formation of the six-membered ring counterpart occurs at a faster rate and is preferred (equation 42). On the other hand, reduction of 6-methyl-6-hepten-2-one leads neither to a five- nor to a six-membered ring[96], but only to a carbonyl reduction product (equation 43).



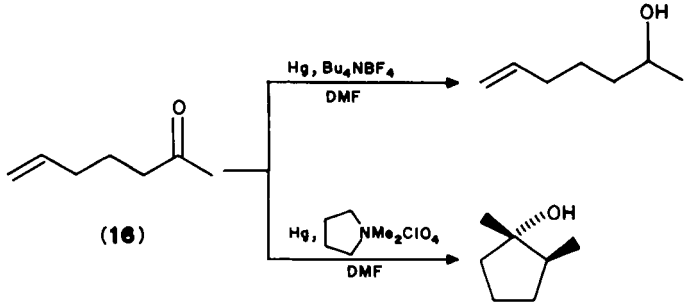
(42)



(43)

Remarkably, it is possible to form selectively either an acyclic alcohol or a cyclized product through a judicious choice of reactions. For example, reduction of hept-6-en-2-one (**16**) at -3.1 V (vs SCE) using a mercury cathode and Bu_4NBF_4 as a supporting electrolyte affords hept-6-en-2-ol in 85% yield[102] (equation 44). A similar result is obtained using a graphite electrode, though far more current must be passed to consume starting material[102].

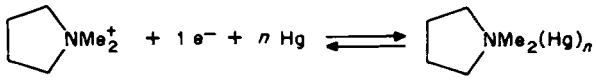
The addition of either a 0.01 M solution of *N*, *N*-dimethylpyrrolidinium or tetraethylammonium perchlorate causes the reduction potentials to shift to a value some 300 to 400 mV more positive than in their absence. Now, the major product (90–94%) corresponds to *cis*-1, 2-dimethylcyclopentanol[102] (equation 45).



(44)

(45)

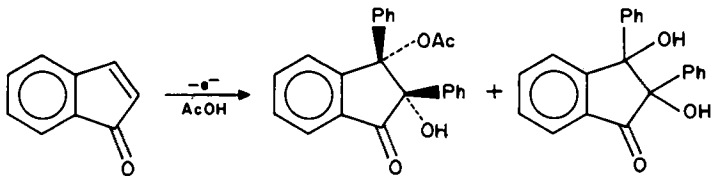
From cyclic voltammetry, it was possible to conclude that the role of the pyrrolidinium salt is to function as a catalyst in the formation of an amalgam, the actual reducing agent[102] (equation 46).



(46)

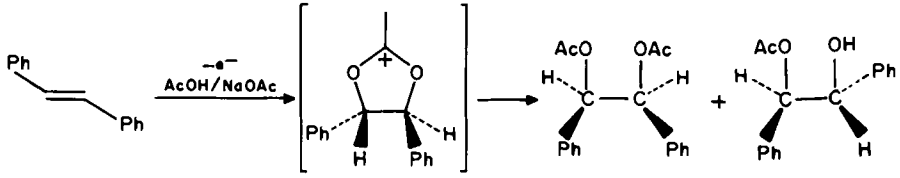
XIII. OXIDATION OF ENONES

It was indicated in the introductory portion of this chapter that very little of what is known about the electrochemistry of enones involves, as a primary step, oxidation of the functional group. Once again, the reason for this behavior stems from the fact that most enones have low-lying HOMOs, thereby making it difficult to remove an electron at those potentials which are accessible electrochemically. One noteworthy *apparent* counter-example to these generalizations[103,104] is illustrated in equation 47.



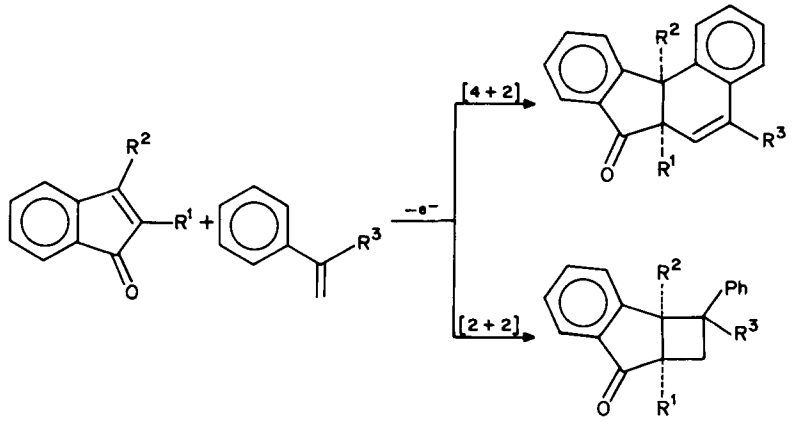
(47)

It should be noted, however, that the indenone behaves more like an aryl olefin than an enone. That is, the net effect of appending three aromatic groups to the olefin dominates any effect(s) due to the presence of the carbonyl and the chemistry which is observed is much like that of an aryl-substituted olefin as demonstrated for *trans*-stilbene[105] (equation 48).



(48)

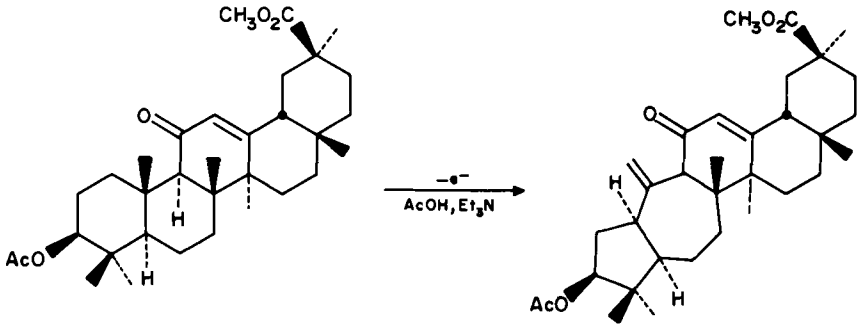
In the absence of a nucleophile, the indenone radical cation can be trapped by an anodically electroinactive species such as styrene. In this way, [4 + 2] and [2 + 2] cycloadditions have been carried out at room temperature[104] (equations 49 and 50). Yields of cycloadduct as high as 70% have been reported, even when electricity consumption is less than 1 faraday mol^{-1}.



(49)

(50)

Finally, the interesting and potentially synthetically useful rearrangement pictured in equation 51 is initiated by oxidation at a Pt anode[106]. It is suggested, though it seems unlikely on energetic grounds, that the first step involves a one-electron oxidation of the enone found in ring C. Whatever the case may be, it is likely, and it has been suggested[106], that a carbocation is formed adjacent to C(10) and that it triggers the skeletal rearrangement.



(51)

XIV. ACKNOWLEDGEMENTS

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The Chemistry of Enones
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CHAPTER **15**

The photochemistry of enones

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I. GENERAL INTRODUCTION

Organic compounds containing a ketonic or aldehydic carbonyl group as well as a carbon–carbon double bond undergo a wide variety of reactions on exposure to ultraviolet radiation which are not observed in compounds containing only one of these functional groups. Enones have a very rich photochemistry, depending on the relative proximity of the C=O and C=C moieties. The discussion below will therefore deal in turn with α,β-unsaturated ketones in which the two moieties are conjugated, then with homoconjugated β,γ-unsaturated ketones, and finally with intramolecular interactions between C=O and C=C moieties that are sufficiently separated such that there is no direct chromophoric interaction between them as judged from UV absorption spectroscopy.

Since the photochemistry of enones and their spectroscopy is discussed extensively in textbooks[1–4] and in recent literature reviews[5–9], the discussion below will attempt to

summarize and categorize the types of reactions that are observed on UV excitation of enones, with emphasis on recent findings reported in the literature.

For those not familiar with terms and concepts commonly used in photochemistry[10], it is useful to first consider the orbital description of ground and excited states given in Figure 1 and the modified Jablonski diagram given in Figure 2. The ground electronic state of the molecule is designated S_0. Promotion of an electron from the highest occupied molecular orbital (HOMO) of the molecule in its ground electronic state to the lowest unoccupied molecular orbital (LUMO) will occur on absorption of a single photon of UV light of frequency ν, light whose energy is $h\nu = E_{LUMO} - E_{HOMO}$ (h is Planck's constant). The first law of photochemistry is that a substance undergoing photochemical change does so through the absorption of a single quantum of light. In solution, the absorption of light by a molecule at a given wavelength λ or frequency ν, where $\nu = hc/\lambda$, depends directly on the concentration of the absorber c (in mol l^{-1}), the path length l (in cm), and the decadic molar extinction coefficient ε (in units of 1 mol^{-1} cm^{-1}) which is characteristic of the molecule and changes with wavelength. In order for light absorption to occur with high probability (corresponding to a large value of ε and of the related oscillator strength f), there has to be a change in symmetry of the total electronic wave function in proceeding from the ground to the excited state. Thus, certain electronic transitions are highly allowed according to quantum mechanics, while others are strongly forbidden. We will discuss specific types of transitions a little later. Electronic excitation takes place in *ca* 10^{-15} s and gives an electronic state of the molecule in which the electron in the HOMO and the remaining electron in the LUMO are still spin-paired, one with spin state $+\frac{1}{2}$ and the other with spin $-\frac{1}{2}$. This singlet excited state is designated S_1. Excitation at shorter wavelengths (higher energy) allows direct population of higher singlet excited states (S_2, S_3, etc.) by promotion of an electron from the HOMO to an MO of higher energy than the LUMO, or from an MO of lower energy than the HOMO to one of the unoccupied MOs. Each such transition corresponds to a different UV absorption band of the molecule, and has its own particular transition probability and corresponding extinction coefficient ε. Each electronic excited state has its own characteristic electron distribution, reactivity and lifetime.

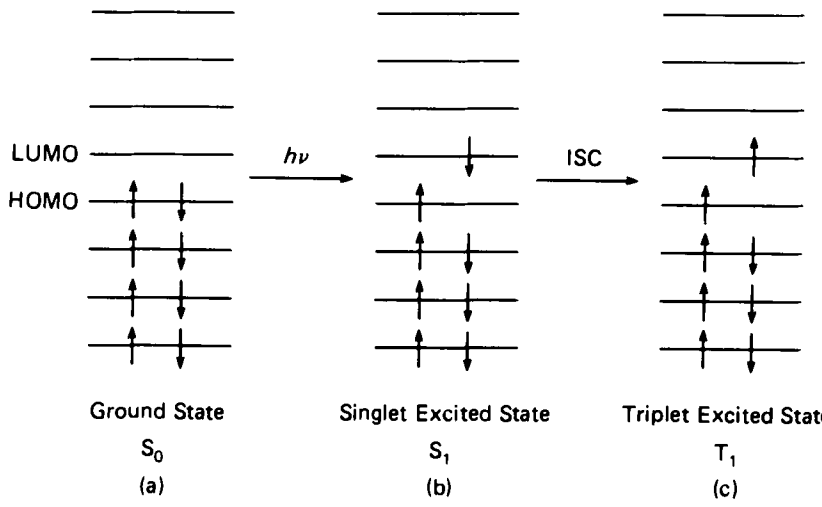


FIGURE 1. Orbital description of ground state and singlet and triplet electronic excited states. Reproduced by permission of Academic Press, Inc. from Ref. 10

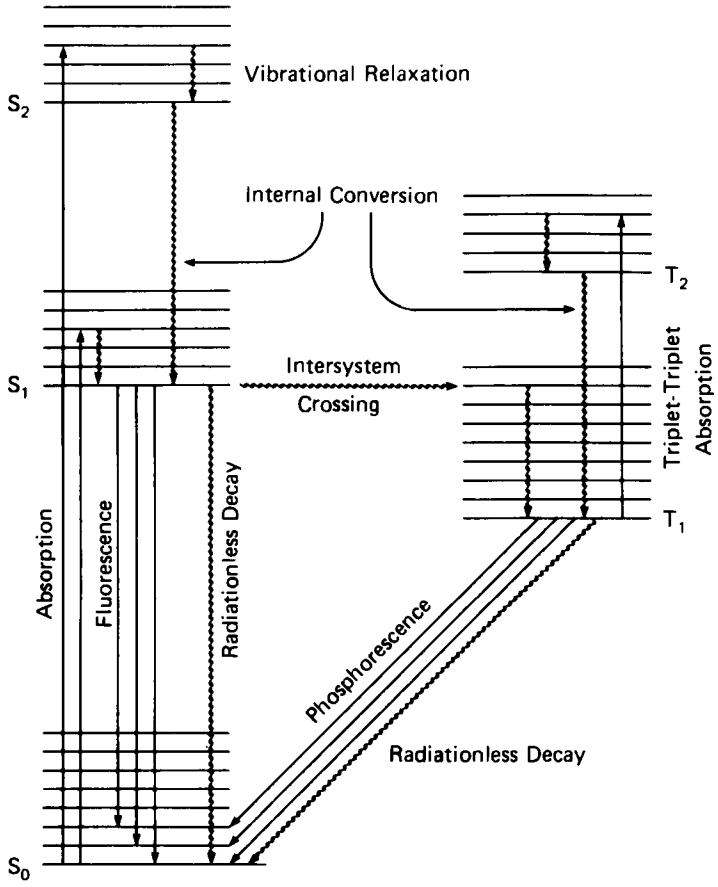


FIGURE 2. Modified Jablonski diagram. Reproduced by permission of Academic Press, Inc. from Ref. 10

Using standard, relatively low-intensity UV light sources, the probability that a molecule might simultaneously absorb two quanta of light of a given frequency is remote. However, with the increasing use of powerful lasers as excitation sources, such an event has become much more likely. In this event, an excited singlet state can be reached by absorption of two quanta of a frequency that otherwise would not be absorbed, such that $2h\nu = E_{exc} - E_0$. Although this possibility should be kept in mind, the discussion below will assume that the excited state is reached by absorption of a single photon.

In general, radiationless decay from higher-energy excited states S_n ($n > 1$) to the S_1 state (internal conversion; see Figure 2) is very fast, particularly in condensed phases. Thus, lifetimes of upper singlet states are usually less than 10^{-12} s (1 ps). Under these circumstances, the opportunity for upper singlet states to participate in chemical processes, especially involving collisional interactions with another molecule, is very limited. Also, vibrational relaxation within a given excited state is also so fast (rate *ca* $10^{13}\,s^{-1}$) that population by light absorption of upper vibrational levels of a given

electronic excited state, such as S_1, results in rapid radiationless decay to the lowest vibrational level of that state, which therefore is the origin of all the processes which result in depopulation of that electronic state. The lifetime of the S_1 state τ_s is limited primarily by the rate at which a quantum of light is emitted as fluorescence to regenerate the ground state. The greater the transition moment or oscillator strength associated with light absorption, the greater is the probability and rate of fluorescence emission. First-order rate constants for fluorescence emission, measured using pulse techniques (specifically single photon counting) by the exponential decrease in fluorescence intensity following excitation, are of the order of 10^7–$10^{10}\,s^{-1}$, corresponding to singlet lifetimes of 10^{-7}–10^{-10} s. Thus, for any photochemical change to occur directly from a singlet excited state, the rate must be very fast in order to compete with rapid radiative decay to the ground state. Since fluorescence decay originates almost entirely from the lowest vibrational level of the S_1 state, fluorescence spectra are red-shifted compared to absorption spectra, and the spectra have a mirror-image appearance in cases where the excited state undergoes no appreciable geometric changes prior to light emission.

As can be seen in Figures 1 and 2, an electronic spin flip can occur to generate an excited state in which the two odd electrons (usually one in the formerly HOMO and the other in the formerly LUMO) are no longer spin correlated. This state is a triplet excited state, since the total spin of two unpaired electrons can be either $+1, 0$ or -1. The process in which a triplet excited state is generated from a singlet state is known as intersystem crossing. Radiative (phosphorescence) and nonradiative decay from the triplet manifold to regenerate the ground state S_0 can occur, but since these processes involve coupling of states of different spin parity, they are quantum mechanically spin-forbidden, and have rate constants which are several orders of magnitude less than for corresponding decay from S_1 to S_0. The lifetimes of triplet excited states, particularly the lowest triplet state T_1, are usually much longer than corresponding singlet excited states, often by several orders of magnitude. These triplets are therefore much more likely to undergo chemical reactions than the corresponding singlets particularly bimolecular reactions with an added reagent or the solvent. Thus it is not surprising that most of the photochemical reactions of enones to be discussed later occur via triplet and not singlet excited states. Those in which singlet excited states have been implicated are exclusively unimolecular processes (rearrangements and fragmentations) whose rates can be competitive with those of singlet decay processes.

Mechanisms exist which allow quantum-mechanical coupling of excited singlet and triplet states of ketones, the most important of which is spin–orbit coupling[11], so that intersystem crossing in these systems is generally very rapid (rate constants 10^8–$10^{11}\,s^{-1}$) and efficient (quantum efficiencies often of the order of unity). Thus, fluorescence of enones is rarely observed. Triplet states of enones as well as other types of systems can also be generated efficiently by transfer of triplet excitation from an electronically excited donor (sensitizer) by the following scheme (equations 1 and 2)[12],

$$\mathrm{Sens}_0 + h\nu \longrightarrow {}^1\mathrm{Sens}^* \longrightarrow {}^3\mathrm{Sens}^* \tag{1}$$

$$^3\mathrm{Sens}^* + E \xrightarrow{k_q} \mathrm{Sens}_0 + {}^3E^* \tag{2}$$

where E is an enone and k_q is the second-order rate constant for transfer of triplet excitation. The ideal situation is shown schematically in Figure 3, in which the S_1 and T_1 states of the donor (sensitizer) are, respectively, lower and higher in energy than the corresponding states of the acceptor (enone). In this case, use of appropriate excitation wavelengths (controlled by the choice of lamps and filters) allows direct excitation exclusively of the donor, and triplet transfer to the acceptor will occur at or close to a diffusion-controlled rate, depending primarily on the frequency of encounters of excited

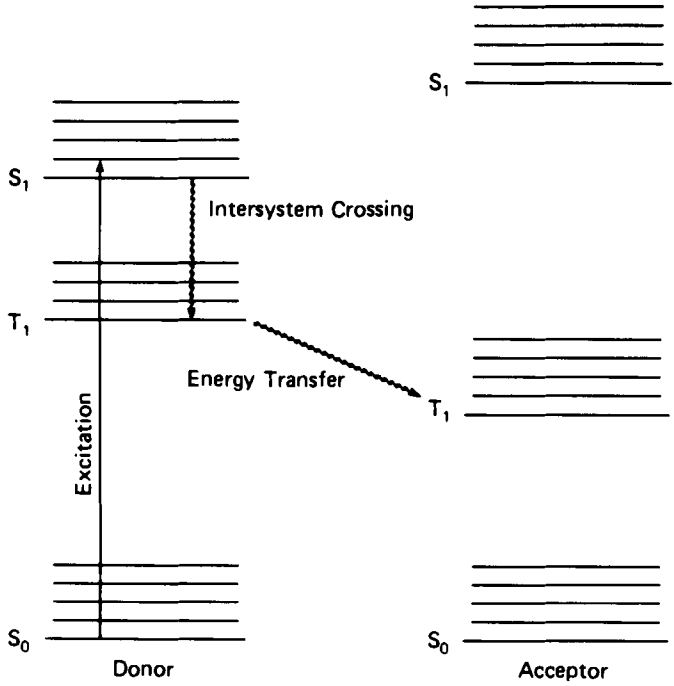


FIGURE 3. Schematic description of triplet excitation transfer, Reproduced by permission of Academic Press, Inc. from Ref. 10

donor and ground-state acceptor. The main advantage of generation of acceptor triplets by the triplet sensitization route is that the acceptor singlets are bypassed; for mechanistic purposes, this permits characterization of the reactivity of triplet states uncontaminated by singlet contributions. In some systems, most notably certain classes of hydrocarbons, triplets can be efficiently generated only by the sensitization route.

Triplet energy transfer can also be used to get information about dynamics of reactive triplet states. Thus, the yield of product derived from chemical reaction of a donor triplet will be reduced in the presence of an appropriate acceptor. In this case, the enone can serve as the donor and any of a series of appropriate triplet quenchers (e.g. naphthalene, conjugated dienes, oxygen, etc.) can be utilized. In the simplest case, the quenching follows the Stern–Volmer relationship given in equation 3

$$\phi_i^0/\phi_i^Q = 1 + k_q\tau_D[Q] \tag{3}$$

where ϕ_i^0 and ϕ_i^Q are the respective quantum efficiencies for process i in the presence and absence of quencher Q, and k_q is the bimolecular rate constant for quenching of the donor triplet excited state whose lifetime is τ_D in the absence of the quencher. The quantum efficiency ϕ_i is defined as the number of molecules undergoing process i divided by the number of quanta of light absorbed in a given period of time. Thus, for a chemical reaction, the relative quantum efficiencies given in equation 3 are equal to the relative yields of the

product(s) formed in the presence and absence of the added quencher, which can be conveniently measured using appropriate spectroscopic or chromatographic techniques following co-irradiation of samples with and without known concentrations of quencher Q. Plots of relative product yields vs. quencher concentration should be linear according to equation 3 if there are no kinetic complications, with an intercept of 1.0 and a slope equal to $k_q\tau_D$. If a value for k_q is known or can be estimated (a value equal to the diffusion-controlled rate is often assumed), this technique allows estimation of triplet lifetimes τ_D. If more than one chemical transformation occurs via a common triplet excited state, the Stern–Volmer quenching slopes corresponding to each reaction should have identical slopes. Conversely, if Stern–Volmer quenching plots for formation of different products resulting from excitation of a given compound have experimentally distinguishable slopes, the reactions must occur via different triplet excited states or conceivably via some other quenchable intermediates.

The quenching relationship of equation 3 will be observed when a triplet state is intercepted by any added reagent, and is not limited to triplet energy transfer. As an example, we shall consider later the interaction of triplet states of cyclic conjugated enones with alkenes to give cycloaddition products. Furthermore, sensitizers function not only as agents for transfer of electronic excitation, but also in electron transfer processes in appropriate situations, according to equations 4 and 5[13]:

$$D^* + A_0 \longrightarrow D^{\cdot+} + A^{\cdot-} \tag{4}$$

$$A^* + D_0 \longrightarrow D^{\cdot+} + A^{\cdot-} \tag{5}$$

Thus, either the donor or the acceptor can serve as the excited component, which is usually in a singlet excited state. The free-energy change for a photoinduced electron-transfer process is given by equation 6, known as the Weller equation[14],

$$\Delta G_{et} = E(D/D^+) - E(A^-/A) - E_{0,0} - e_0^2 a\varepsilon \tag{6}$$

where the first term is the oxidation potential of the donor, the second is the reduction potential of the acceptor, the third is the excitation energy of the sensitizer, and the last term is the energy gained by bringing the two radical ions to the encounter distance a in a solvent of dielectric constant ε; in polar solvents the last term is negligibly small, but it can be significant in nonpolar media. We shall encounter cases in which enone radical ions generated by sensitized electron transfer undergo reactions not characteristic of singlet or triplet excited states. Interesting developments in this rapidly growing area of organic photochemistry can be expected in the next few years.

II. ULTRAVIOLET SPECTROSCOPY AND ENERGIES OF ELECTRONIC EXCITED STATES OF ENONES

Before discussing the photochemistry of enones, it is necessary to review the UV spectroscopy of these compounds[15]. The lowest energy electronic transition in formaldehyde and simple aldehydes and ketones is the promotion of an electron from the nonbonding orbital on oxygen into the vacant antibonding π orbital of the carbonyl group ($n \rightarrow \pi^*$). Since these orbitals are formally orthogonal for a planar carbonyl group, this transition is quantum mechanically forbidden; it is observed, but the extinction coefficient ε is very small (10^1–10^2 l mol^{-1} cm^{-1}). The lowest energy excited singlet state, S_1, is therefore a $^1n,\pi^*$ state. For simple aldehydes and ketones and nonconjugated enones, this transition is usually observed in the range of 290–330 nm, corresponding to an excitation

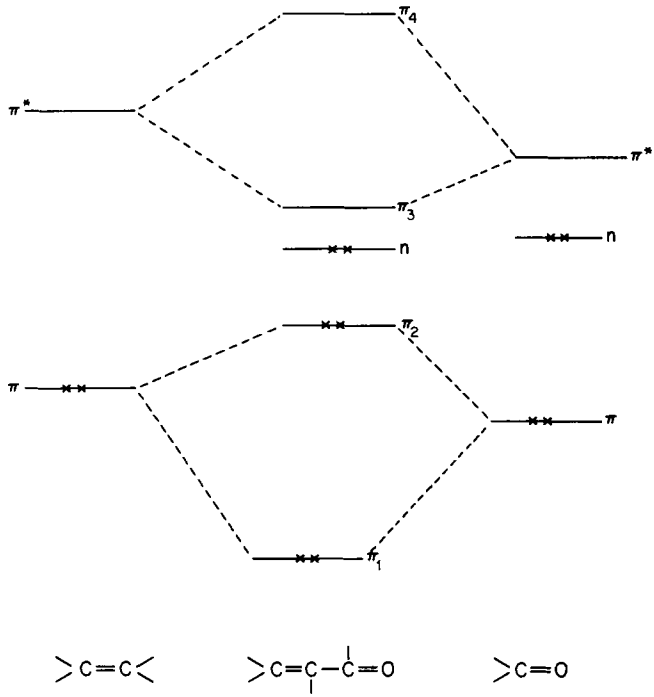


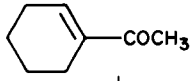
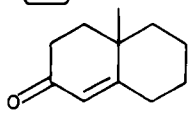
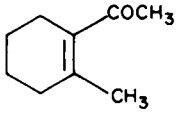
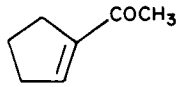
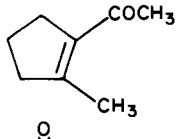
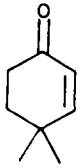
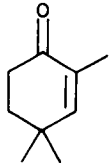
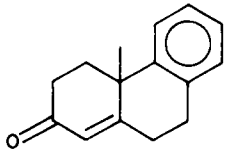
FIGURE 4. Qualitative energy-level diagram for α,β-unsaturated ketones (adapted from Reference 16)

energy of the ^{1}n, π^* state (the difference in energy of the lowest vibrational levels of the S_1 and S_0 states) of 80–85 kcal mol^{-1}. For formaldehyde, λ_{max} is 304 nm in the vapor phase, and ε_{max} is only 181 mol^{-1} cm^{-1}. The next higher-energy electronic transition is promotion of an electron from the bonding carbonyl π_{CO}-MO to the corresponding antibonding π^*_{CO}-MO. For simple carbonyl compounds, this transition occurs at *ca* 180–220 nm with ε of the order of 10^4 l mol^{-1} cm^{-1}, corresponding to an excitation energy of the S_2 state ($^1\pi,\pi^*$) 140–150 kcal mol^{-1} above the ground state. This energy is similar to that required for excitation of a nobonding electron on oxygen into the σ^*-MO (the antibonding MO for the C—O sigma bond), and in some cases (formaldehyde in particular) it is not clear whether the $n \rightarrow \sigma^*$ or $\pi \rightarrow \pi^*$ transition is of the lower energy; in most cases, it is generally assumed that the second UV absorption band (going from lower to higher energy) is the $\pi \rightarrow \pi^*$ transition.

For simple alkenes, the lowest energy UV absorption corresponds to a $\pi \rightarrow \pi^*$ transition, and generally occurs between 170 and 210 nm, depending on the substitution pattern on the C=C chromophore, corresponding to an S_1 excitation energy of the order of 140–150 kcal mol^{-1}.

For α,β-unsaturated ketones, interaction of the C=O and C=C molecular orbitals leads to the qualitative energy-level diagram shown in Figure 4[16]. The lowest energy π-MO (π_1) is considerably lower in energy than either the isolated C=C or C=O π—MOs, while the highest occupied π-MO (π_2) is higher in energy than in the isolated chromophores. There is also substantial energy lowering of the LUMO (π_3^*) and a corresponding increase in energy of π_4^*. The energy of the nonbonding (n) orbital on oxygen is not significantly affected by bringing the C=C and C=O moieties into

TABLE 1. UV absorption spectra of selected α,β-unsaturated ketones in ethanol

Ketone	λ_{max} (mm)	ε_{max}
$CH_2=C(C_2H_5)-COCH_3$	221	6450
$CH_3-CH=CH-COCH_3$	224	9750
	234 306(CH_3CN)	13,000 42
	237 312	15,800 56
	249	6890
	239	13,000
	253	10,010
	224 318	15,600 35
	235 321	9500 37.6
	234(2-PrOH) 315(2-PrOH)	18,620 62

conjugation. The result of conjugation is that the energies of both the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions in the C=C—C=O chromophore are lowered in energy relative to the isolated chromophores, i.e. they are shifted to higher wavelength. Typically, the $\pi \rightarrow \pi^*$ absorption band (S_0–S_2) occurs with λ_{max} 220–250 nm and $\varepsilon_{max} > 10^4\,l\,mol^{-1}\,cm^{-1}$. The location of the absorption maximum for such compounds can be estimated very closely

using a set of rules proposed by Woodward, depending on the location of substituents, orientation relative to other carbocyclic rings and ring size (e.g. cyclopentenone absorbs at slightly lower wavelength than cyclohexenone, 218 vs. 225 nm). Table 1 gives values for the $\pi \rightarrow \pi^*$ transitions and the corresponding singlet excitation energies for some typical conjugated enones in ethanol. The corresponding $n \rightarrow \pi^*$ transitions for enones are in the 300–350 nm region, corresponding to S_1 excitation energies of 75–85 kcal mol^{-1} relative to the lowest vibrational level of S_0. The band intensities are slightly higher ($\varepsilon \sim 50$–$100\,l\,mol^{-1}\,cm^{-1}$) than for simple aliphatic aldehydes and ketones. The $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ absorption bands of enones (and indeed of simple ketones) are shifted in opposite directions by an increase in solvent polarity. A red (bathochromic) shift is observed for $\pi \rightarrow \pi^*$ absorption bands and a blue (hypsochromic) shift is observed for the $n \rightarrow \pi^*$ absorption. The latter effect is rationalized in terms of greater stabilization (energy lowering) of the n electrons in hydrogen bonding solvents than the antibonding π-MO (π_3^* in Figure 5), which in turn is stabilized (presumably due to greater contributions of structures involving polarization of charge) relative to the bonding MO (π_2 in Figure 4) by an increase in solvent polarity.

When the C=C and C=O chromophores are separated by a single tetrahedral carbon atom in β,γ-unsaturated ketones, interaction of the π systems still occurs, but to a much lesser extent than in α,β-enones because of the restrictions placed by the molecular geometry on the overlap of p orbitals between the chromophores, as shown in Figure 5. The result is that the energies of the MOs are not affected to nearly as great an extent as

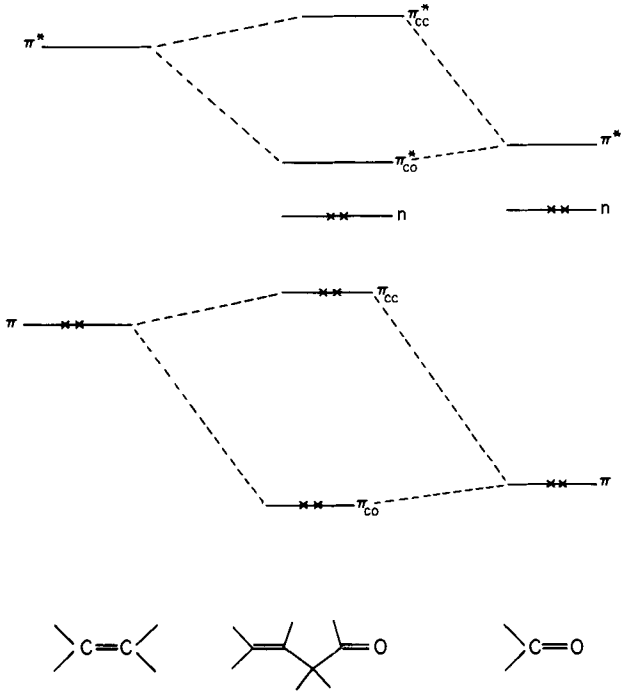


FIGURE 5. Qualitative energy-level diagram for β,γ-unsaturated ketones.

depicted in Figure 4 for the α,β-enones. The $\pi \rightarrow \pi^*$ absorption for typical β,γ-enones without conjugating substituents is centred at *ca* 220 nm and the $n \rightarrow \pi^*$ absorption typically has λ_{max} 290–310 nm. What is notable is the intensification of the $n \rightarrow \pi^*$ absorption for many (but not all) β,γ-enones, with values of ε 3–10 times as large as for α,β-enones (see Table 2 for representative examples). This effect has received a great deal of attention from spectroscopists, and is discussed at length in a review by Houk[6] on the spectroscopy and photochemistry of β,γ-enones. Labhart and Wagniere[17] suggested that this intensification results from overlap of the n orbital on oxygen with the alkene p orbitals, so that the $n \rightarrow \pi^*$ transition in effect borrows intensity from the $\pi \rightarrow \pi^*$ transition. That is, in this situation, the $n \rightarrow \pi^*$ transition can be viewed as promotion of an electron from an n orbital mixed to some extent with the $\pi_{C=C}$ orbital to a π^*_{CO} orbital which is mixed with the $\pi^*_{C=C}$ orbital, conferring 'allowedness' to this transition, calculated as about 1% of that of a fully allowed transition. It has also been noted that those β,γ-enones which show large intensification of the $n \rightarrow \pi^*$ transition also show large optical rotations and Cotton effects, due to the inherent dissymmetry of the chromophore. For β,γ-enones in which the p orbitals of the carbonyl carbon and the C=C bond are not directed at each other, such as 3-cyclopentenone and 3-cyclohexenone, $n \rightarrow \pi^*$ intensification is not observed. These spectral properties are of relevance to the photochemical behaviour of β,γ-enones, as is well recognized[6].

The nature of the triplet excited states of enones is of particular significance in understanding the photochemistry of these systems. Triplet states are always of lower energy than the corresponding singlet excited states, but the energy gap is a function of the electronic configuration. Thus, the singlet–triplet energy gap is much larger for π,π^* states than for n,π^* states. The large difference in energy between the S_1 and S_2 ($^1\pi,\pi^*$ and $^1n,\pi^*$)

Table 2. UV absorption spectra of typical β,γ-unsaturated ketones

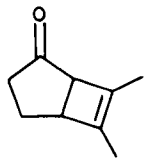
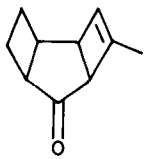
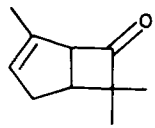
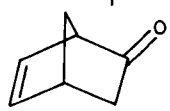
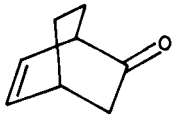
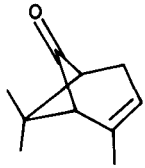
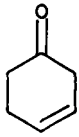
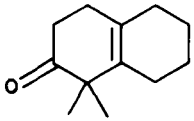
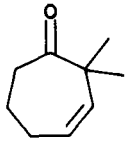
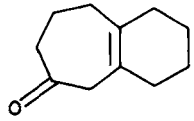
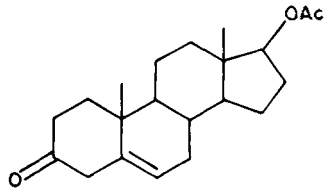
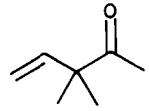
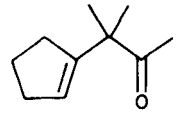
Compound	λ_{max}	ε_{max}	Solvent
	304	327	EtOH
	309	301	95% EtOH
	307	289	$CHCl_3$
	210 308	3000 290	EtOH

TABLE 2. (*continued*)

Compound	λ_{max}	ε_{max}	Solvent
	202 298	3000 110	95% EtOH
	290	120	EtOH
	277	108	C_6H_{12}
	278	55	Not given
	282	41	MeOH
	292	252	MeOH
	222 295	931 121	*t*-BuOH
	290	78	C_6H_{14}
	298	118	C_6H_{14}

states of simple carbonyl compounds guarantees that the lowest-energy triplet state T_1 is indeed the $^3n,\pi^*$ state, as is borne out by phosphorescence and $S_0 \rightarrow T_1$ absorption measurements at low temperatures. For conjugated α,β-enones, the energies of the triplet n,π^* and π,π^* states are very similar, so that either one may become the T_1 state, depending on substituents and the solvent. Interesting inversions in the ordering of the states have been observed, since increasing solvent polarity stabilizes $^3\pi,\pi^*$ states and destabilizes $^3n,\pi^*$ states. For β,γ-enones, calculations indicate that in general the T_1 state is a π,π^* state, which is consistent with the observed photochemistry[5,6].

III. TYPICAL PHOTOCHEMISTRY OF COMPARATIVE MODEL SYSTEMS

In order to put the photochemistry of enones into proper perspective, it is useful to summarize the photochemical behaviour of model monochromophoric alkene and carbonyl compounds in order to see what changes in the photochemistry ensue in when both chromophores are present in the same molecule. Since these model reactions are discussed at length in photochemistry texts which can be consulted for details[1-4], they will be presented here only briefly.

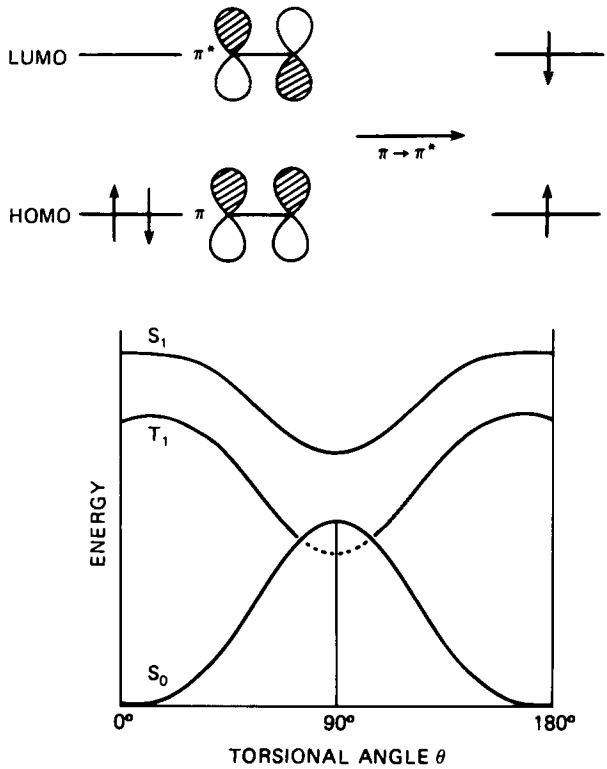


FIGURE 6. Dependence of energies of S_0, S_1 and T_1 states of alkenes on the torsional angle. Reproduced by permission of Academic Press, Inc. from Ref. 10

A. Photochemistry of Alkenes

This brief discussion will concern compounds containing only a single C=C moiety, for comparison with the photochemistry of enones. For discussions of the very rich and interesting photochemistry of dienes, trienes and more extended polyenes, which is not directly relevant to the main subject of this chapter, the reader should consult any of a number of reviews of the literature.

1. Cis-trans isomerization of alkenes

The prototypical reaction which ensues on electronic excitation of acyclic alkenes is isomerization around the C=C bond (*cis–trans* or *Z–E* isomerization). If no other reactions occur which interfere with the isomerization process, a photostationary mixture of isomers results from excitation of either the *Z* or *E* alkene. It is generally agreed that this reaction takes place via singlet excited states, since intersystem crossing is slow in most alkenes compared with the rate of relaxation of the planar excited singlet to a more stable perpendicular geometry, at which point rapid radiationless decay takes place to the ground-state potential surface at or near its energy maximum (see Figure 6).

Triplet-sensitized isomerization of alkenes via alkene triplets is also well known, particularly in the case of stilbenes and conjugated dienes whose triplet excitation energies lie below those of typical triplet sensitizers [acetone, aromatic ketones (particularly benzophenone) and aromatic hydrocarbons]. In this case the ratio of isomers at the photostationary state depends on the triplet excitation energy of the sensitizer, which has been examined in detail in a classic series of studies by Hammond and coworkers[18] (see Figure 7). A second mechanism for triplet-sensitized photoisomerization of alkenes was proposed by Schenck and coworkers[19], involving covalent bonding between the sensitizer

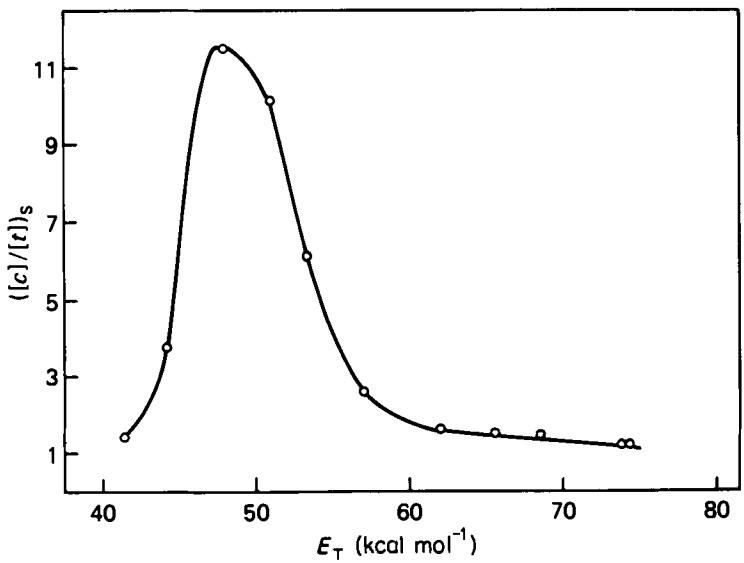
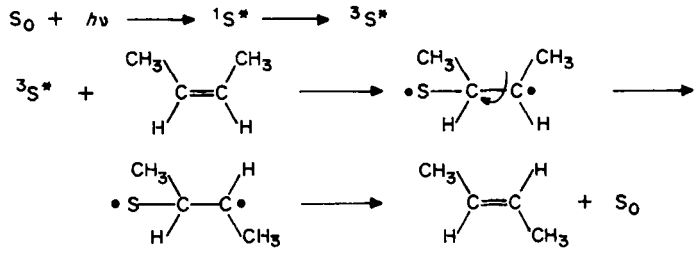


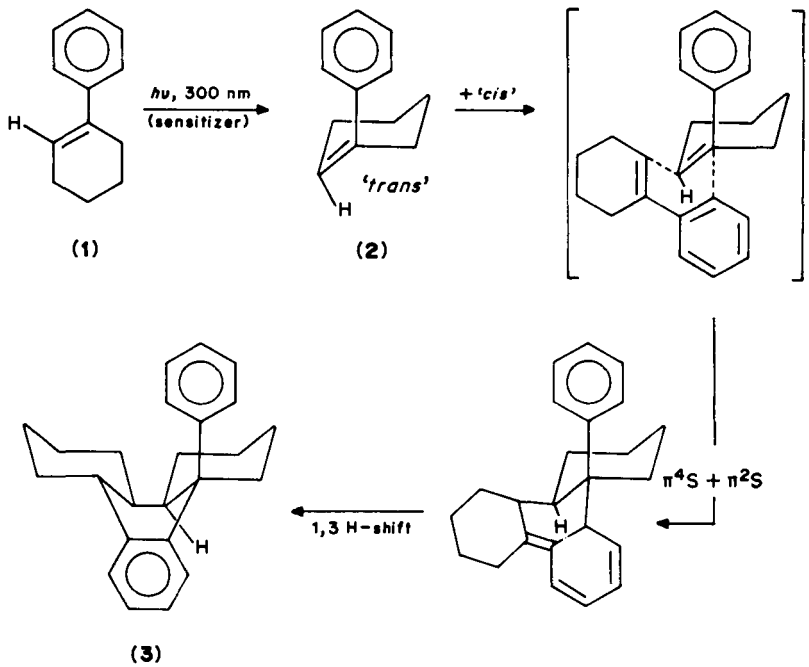
FIGURE 7. Dependence of the ratio of *cis*-stilbene/*trans*-stilbene at the photostationary state on the triplet excitation energy of the sensitizer. Reprinted from Ref. 18 by courtesy of Marcel Dekker, Inc

and the alkene to give a triplet 1,4-biradical, rotation around the former C=C bond and fragmentation (see Scheme 1). Although the Schenck mechanism has been discarded in favor of the Hammond triplet energy-transfer mechanism in the case of stilbenes and dienes, the mechanism has been invoked for photosensitized isomerization of alkenes in cases where the energetics of triplet energy transfer are unfavorable, i.e. with low-energy sensitizers and/or alkenes with high triplet excitation energies, as in sensitized isomerization of 2-butene ($E_T \sim 80$ kcal mol^{-1}).



SCHEME 1

Photoisomerization of medium ring cycloalkenes is of particular interest with respect to corresponding reactions of analogous cycloalkenones. Not surprisingly, photosensitized excitation of *cis* cyclooctenes leads to isolable *trans* cyclooctenes[20], and *trans* cycloheptenes have been implicated in sensitized photoaddition reactions (see below) of *cis* cycloheptenes and have been directly detected using nanosecond flash photolysis techniques[21]. Direct or triplet-sensitized excitation of 1-phenylcyclohexene **1** yields *trans*-

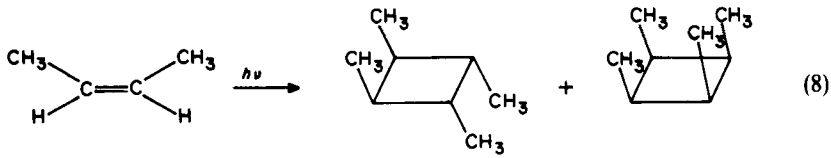


(7)

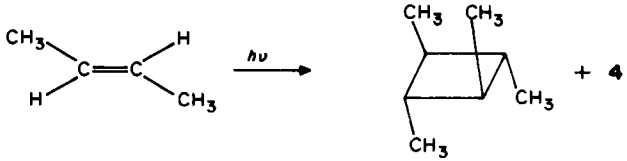
1-phenylcyclohexene **2**, which has been directly detected as a transient intermediate using nanosecond flash photolysis[22]. It has also been trapped chemically by reaction with acidic methanol[23] and by stereospecific [4 + 2] addition to *cis*-1-phenylcyclohexene to give **3** (equation 7)[24]. The lifetime of 9 μs for **2** in methanol obtained by flash techniques has been confirmed using time-resolved photoacoustic calorimetry[25], and the strain energy of **2** vs. **1** is 44.7 $\pm$ 5 kcal mol^{-1}. The barriers for thermal reversion of **2** to **1** in methanol and benzene are $\sim$ 7 kcal mol^{-1} and 10.6 kcal mol^{-1} respectively, which accounts for the relative kinetic stability of **2**. It is of interest that photoacoustic calorimetric data indicate that the triplet excitation energy of the twisted triplet state of **1** (56 $\pm$ 3.4 kcal mol^{-1}) is only slightly lower than the value of $\sim$ 60 kcal mol^{-1} for the planar spectroscopic triplet estimated from appropriate model compounds[25]. Thus, the triplet potential surface of **1** is quite flat. Bonneau has recently reported spectral and kinetic properties of eight '*trans*' cyclohexenes prepared by xanthone-sensitized excitation of the corresponding *cis* cyclohexenes in benzene[26]; in some cases, the same species could be prepared by direct excitation at 266 nm in cyclohexane or acetonitrile. In all cases, the UV absorption of the '*trans*' isomer is considerably red-shifted with respect to the *cis*, and the barriers to thermal isomerization of '*trans*' to *cis* are all *ca* 10 kcal mol^{-1}, with frequency factors in the range 10^{12}–10^{13} s^{-1} [26].

2. *Photodimerization of alkenes*

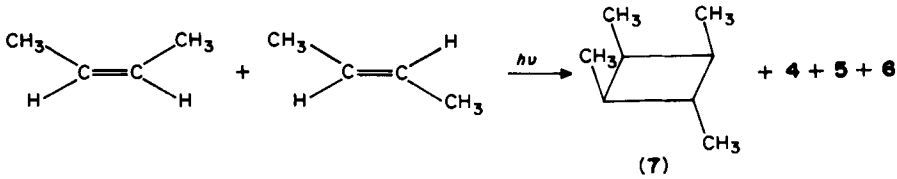
Intermolecular photodimerization of alkenes to give cyclobutanes is a well-known reaction that can be brought about on either direct or triplet-sensitized excitation. Thus, direct irradiation of liquid *cis*-2-butene gives dimers **4** and **5** (equation 8) while irradiation of *trans*-2-butene gives **4** and **6** (equation 9); isomerization to 1-butene competed with dimerization[27]. Irradiation of a mixture of *cis*- and *trans*-2-butene gave dimer **7** in addition to **4**–**6** (equation 10). These stereospecific photodimerizations, necessarily observed only



(4) (5) (8)



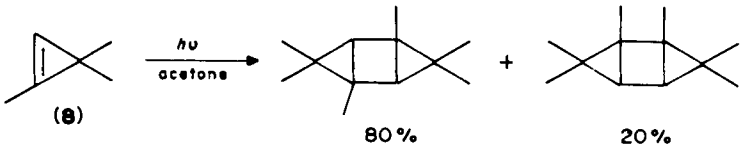
(6) (9)



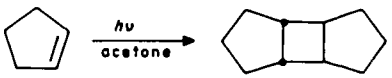
(7) (10)

at low alkene conversion because of competitive *cis–trans* isomerization, indicate that the excited alkene undergoing dimerization does not also undergo isomerization, which was rationalized in terms of rapid formation of excited state–ground state complexes en route to dimers. Dilution with neopentane decreased dimer yields drastically. Tetramethylethylene also photodimerizes on direct excitation.

Triplet-sensitized photodimerization of simple alkenes, such as ethylene, can be brought about in the vapour phase using mercury, while small and medium ring cycloalkenes photodimerize in solution using typical organic sensitizers. Thus cyclopropene **8** dimerizes (equation 11) in acetone (in the presence of benzophenone, which may or may not play a role)[28] and cyclopentene also photodimerizes in acetone (equation 12)[29]. An instructive example is provided by norbornene **9**[30]. Dimerization can be sensitized by acetophenone ($E_T = 74\,kcal\,mol^{-1}$) but not by benzophenone ($E_T = 69\,kcal\,mol^{-1}$); in the latter case cycloaddition occurs to give the oxetane **10** (equation 13). Both reactions occur using xanthone ($E_T = 72\,kcal\,mol^{-1}$). Thus, there is a competition between triplet energy transfer and cycloaddition to alkenes, depending on the relative triplet excitation energies of the sensitizer and the alkene.



(11)



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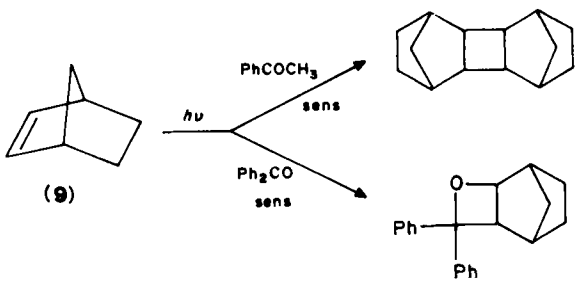
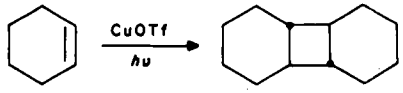


(13)

Copper salts also can be used to catalyze photodimerization of cyclic but not acyclic alkenes, via a Cu(I)–olefin complex[31]. With cyclohexene or cycloheptene, the major products are the *trans*-fused dimers **11** and **12** (equations 14 and 15). It was suggested that these products arise by Cu(I)-catalyzed photoisomerization to the *trans* cycloalkenes, perhaps still complexed to Cu(I), which then undergo stereoelectronically controlled $[\pi^2_s + \pi^2_a]$ addition to the respective *cis* cycloalkenes. The fact that cyclooctene and acyclic dienes do not undergo Cu(I)-catalyzed photodimerization can be ascribed to reduced reactivity of twisted alkene–Cu intermediates in these cases, Cu(I)-catalyzed photodimerization of cyclopentene and norbornene gives exclusively *cis*-fused dimers (equations 16 and 17). In the latter case, quantum yield measurements suggest that the

reaction proceeds via a 2:1 norbornene–Cu(I) triflate complex in which the Cu is simultaneously bonded to the π systems of both alkenes.



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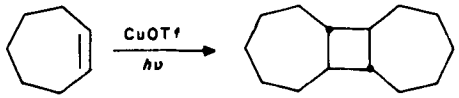
(14)



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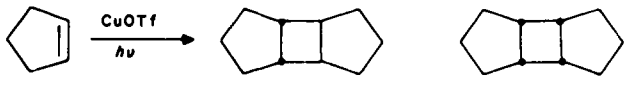

30% 3%

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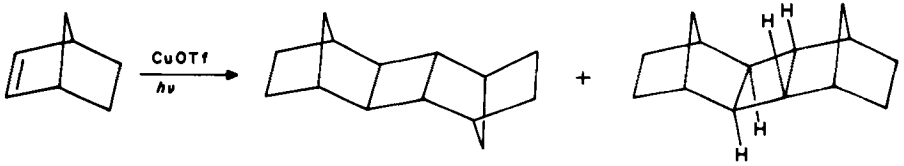
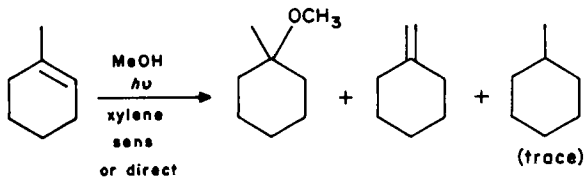


(major) (minor)

(17)

3. *Photoaddition of nucleophiles*

Photoaddition of methanol to cyclohexenes and cycloheptenes to give ethers occurs in the presence of high-energy sensitizers, such as benzene, toluene and xylene (the latter is used most frequently)[23a,32,33]. Typical examples are shown in equations 18–20. Such photoaddition reactions are not observed using acyclic or cyclooctenes. The addition reaction is usually accompanied by alkene isomerization. It has been proposed that the reaction involves triplet-sensitized isomerization to a trans cyclohexene or trans cycloheptene, which on protonation gives a carbocation, which is either captured by the nucleophile or loses a proton to give the rearranged alkene (see Scheme 2). It is proposed that unstrained *trans* or acyclic alkenes do not possess sufficient



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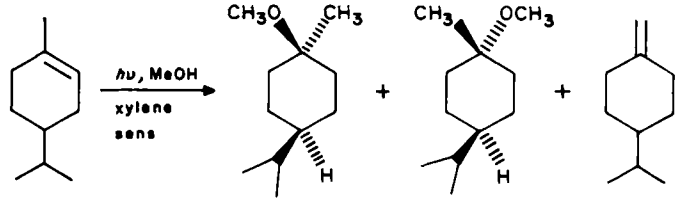

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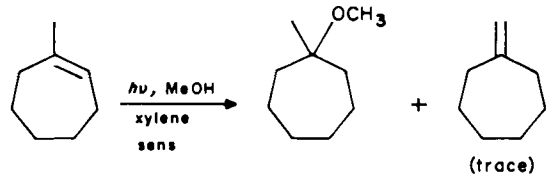

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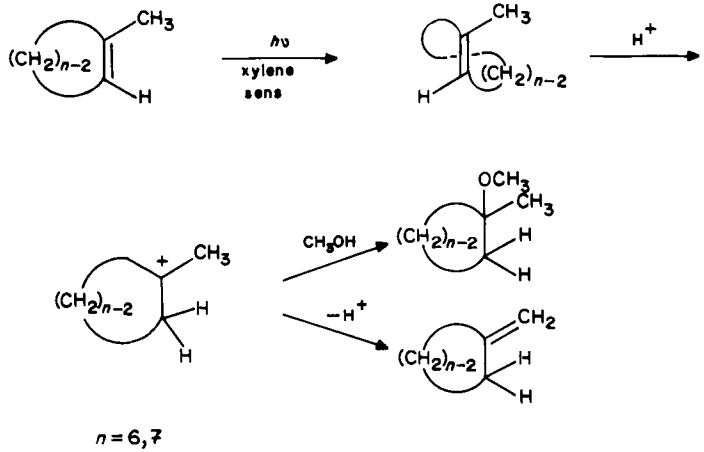
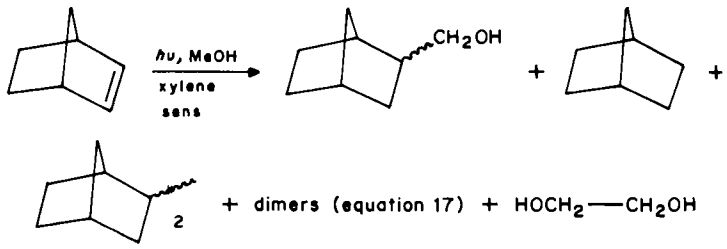


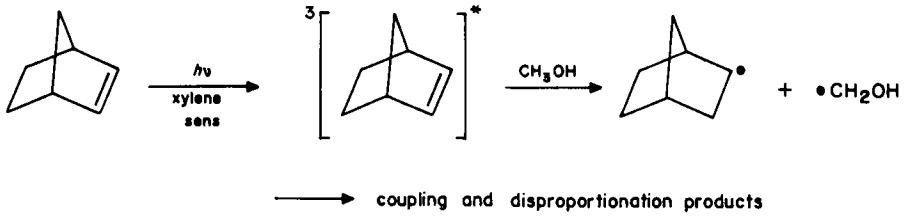
SCHEME 2

driving force toward protonation under these conditions. The proposed mechanism is supported by the observation of completely different behavior with norbornene under identical conditions (equation 21)[23a,32,33]. In this case, products resulting from typical free radical reactions (addition, coupling and disproportionation) are observed, which clearly



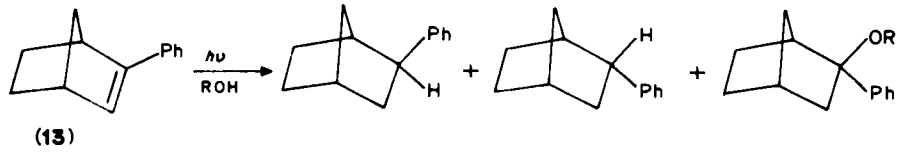
(21)

arise as a result of hydrogen abstraction by planar (or nearly planar) norbornene triplets from the methyl group of CH_3OH (Scheme 3). Thus, it would appear that ionic reactions are observed with cyclic alkenes capable of forming strained *trans* isomers, while free radical chemistry is characteristic of planar alkene triplets under similar conditions[34].



SCHEME 3

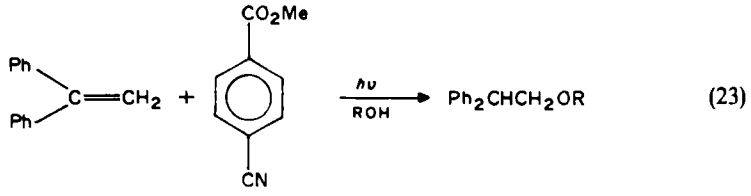
Curiously, direct excitation of 2-phenylnorbornene **13** in methanol efficiently gives a tertiary ether (with Markownikoff regiochemistry) and other products resulting from initial formation of a carbocation intermediate (equation 22)[35]. This behavior of **13** is



(13)

(22)

ascribed to reaction via a singlet excited state or perhaps a high-energy triplet state, since no such reactions are seen on triplet sensitization using acetophenone (E_T = 74 kcal mol^{-1}) in CH_3OD, which causes slow disappearance of **13** and formation of reduction products containing only traces of deuterium. Photoprotonation of 1-phenylcyclohexene and 1-phenylcycloheptene occurs on direct as well as triplet-sensitized excitation, suggesting (but not requiring) that in these systems photoprotonation occurs via a triplet state formed on either direct or sensitized excitation. Completely different behavior is observed on irradiation of both acyclic and cyclic alkenes in the presence of nucleophilic reagents (a variety of alcohols, acetic acid, potassium cyanide) using methyl *p*-cyanobenzoate, *p*-dicyanobenzene or 1-cyanonaphthalene as sensitizers[36]. As shown in equations 23–25, anti-Markownikoff addition products are formed in moderate to excellent yields to the complete exclusion of Markownikoff addition of the nucleophiles. A general mechanism for these addition reactions is shown in Scheme 4. The key step is electron transfer from the alkene to the sensitizer singlet excited state to give the alkene radical cation ($Alk^{+\cdot}$) and the sensitizer radical anion ($Sens^{-\cdot}$)[13]. Quenching of sensitizer



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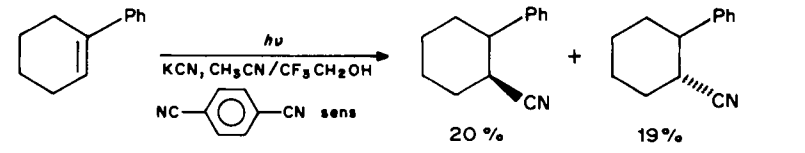

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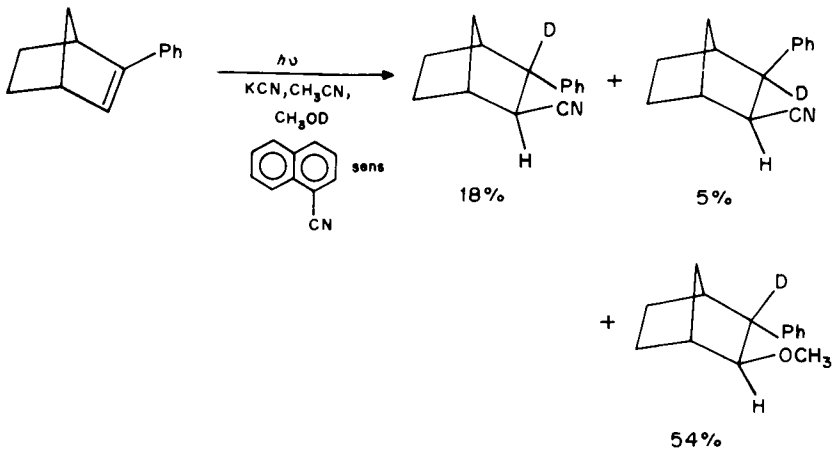
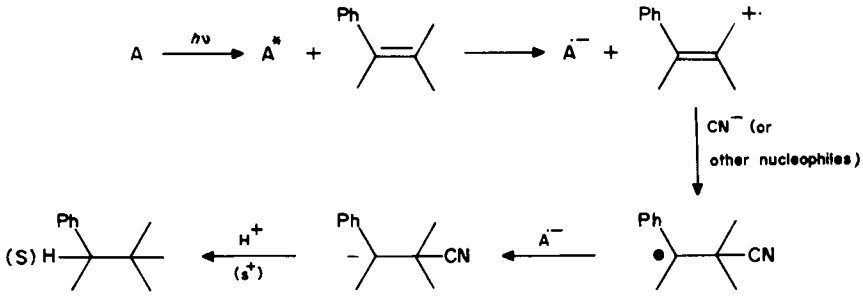


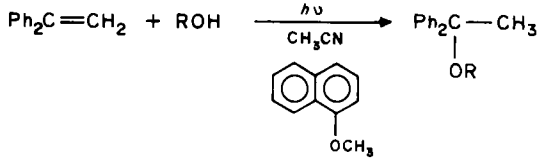
(25)

fluorescence by alkenes which undergo photoaddition supports an electron transfer mechanism. Nucleophilic addition to $Alk^{+\cdot}$ occurs in an anti-Markownikoff sense to generate the more stable free radical, which is then reduced to an anion by back electron transfer from $Sens^{-\cdot}$, followed finally by protonation. If the reaction is run using a deuteriated solvent ROD, the product incorporates one deuterium at the position predicted by this mechanism.



SCHEME 4

Nucleophilic addition in the Markownikoff sense can be brought about using electron donor sensitizers such as 1-methoxy- and 1,4-dimethoxynaphthalene, as illustrated in equations 26 and 27[37]. In these systems, the mechanism is the reverse of that shown in Scheme 4. As shown in Scheme 5, electron transfer gives initially an alkene radical anion which gives the more stable radical upon protonation by the solvent; loss of an electron to the sensitizer radical cation gives a carbocation which is finally captured by the nucleophilic reagent. The facile preparation of 2, 2, 2-trifluoroethyl ethers by this route (see equation 27) is notable owing to the difficulty of preparing such compounds by conventional ground-state nucleophilic addition reactions.



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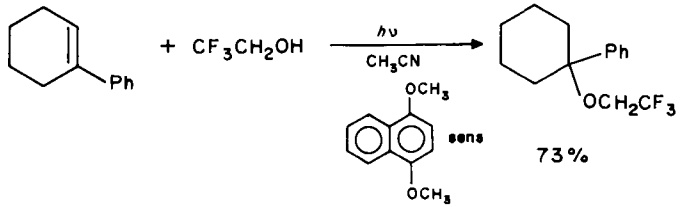

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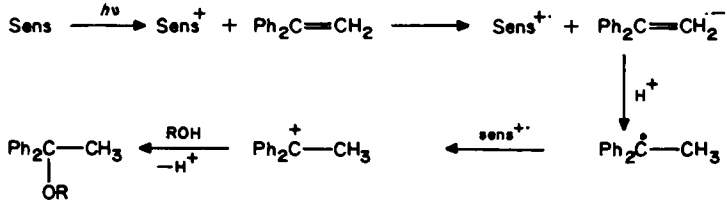
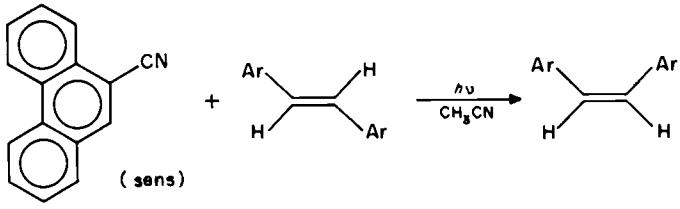
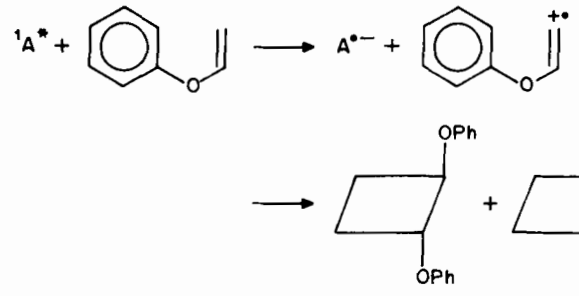


SCHEME 5

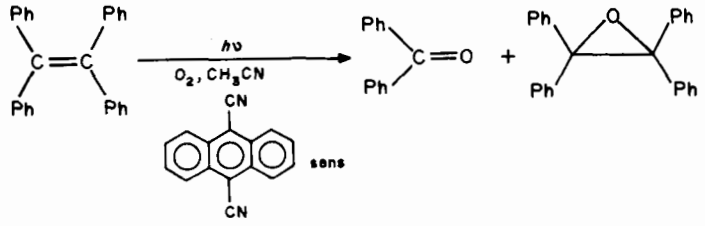
A number of other types of reactions of alkenes can also be induced by electron transfer from electron-deficient sensitizers. These include isomerization, dimerization and oxygenation, which are illustrated in equations 28–30. Many of these electron transfer reactions have been found to be preparatively useful, although they have yet to be exploited by synthetic organic chemists. The interested reader is directed to several excellent recent reviews in this area[13,38].



(28)



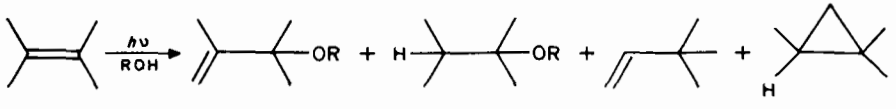
(29)



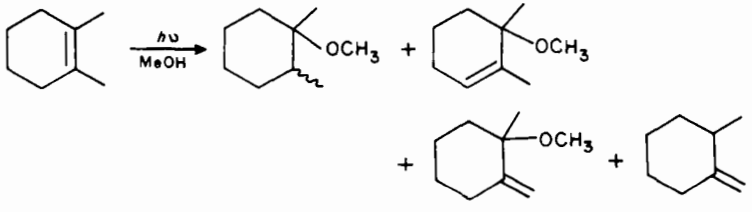
(30)

4. Photorearrangements and related reactions

Unusual photochemical rearrangements of tetrasubstituted alkenes have been observed on direct excitation[23b,34,39]. Thus, direct excitation of tetramethylethylene and 1,2-dimethylcyclohexene in nonhydroxylic solvents (ether, hydrocarbons) gives a mixture of structurally rearranged alkenes and cyclopropanes while, in hydroxylic media, the formation of these products is accompanied by the formation of a mixture of saturated and unsaturated ethers (equations 31 and 32). Kropp and coworkers[23b,34,39] have suggested that these reactions occur by initial formation of a π, R(3s) Rydberg excited state of the



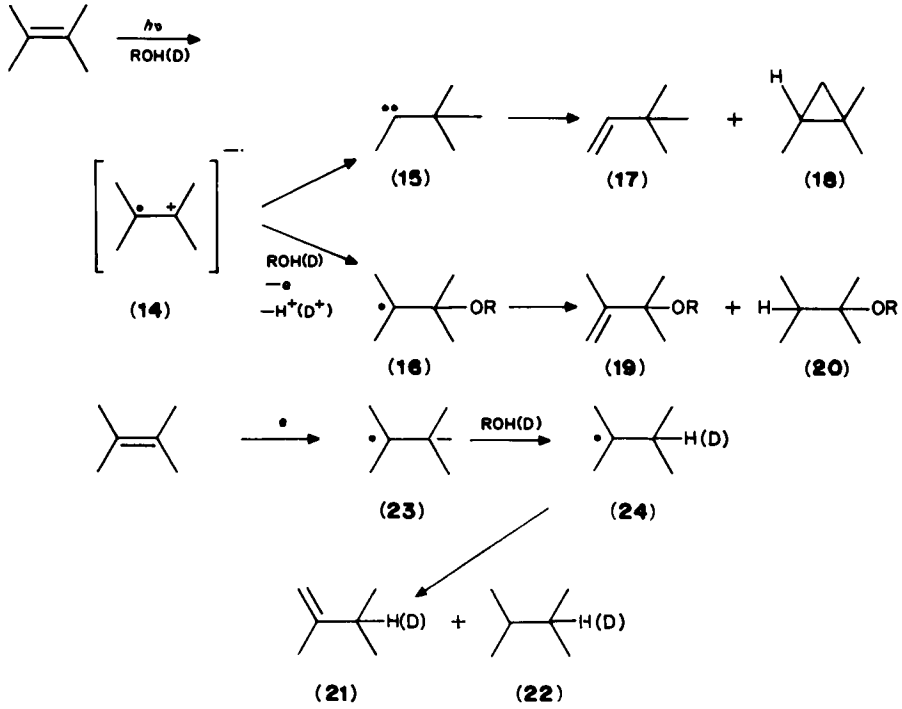
(31)



(32)

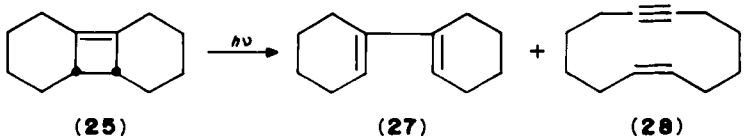
alkene (R ← N transition in spectroscopic terms), in which the orbital containing the excited electron is much larger than the molecular core which, in effect, becomes positively charged. As Kropp puts it, 'the (excited) electron has been placed in a sort of holding pattern; it has been removed from the core and yet not completely separated from the core's influence'. Structure **14** in Scheme 6 is Kropp's pictorial designation for the π, R(3s) Rydberg state for tetramethylethylene. The energy for this UV transition decreases with the degree of substitution on the C=C bond, from 7.12 eV (174 nm) for $CH_2{=}CH_2$ to 5.40 eV (230 nm) for $(CH_3)_2C{=}C(CH_3)_2$; for tetrasubstituted alkenes, the $\pi \rightarrow R$ transition may well be the lowest energy transition in solution, but in any event the Rydberg character of the S_1 state will increase with alkyl substitution. This is consistent with the marked changes in photochemistry observed as a function of degree of substitution on C=C. It should be noted that the π, π^* and Rydberg states remain widely separated in the triplet manifold, so that only the $^3\pi, \pi^*$ state need be considered in discussion of triplet reactivity of alkenes.

Kropp proposed that a Rydberg state undergoes two key reactions, as illustrated in Scheme 6: rearrangement to carbenes **15** (path A) and nucleophilic trapping to give alkoxy radical **16** and solvated electrons (path B). Products **17** and **18** arise from carbene **15** by a 1,2-H shift and C—H insertion, respectively, while ethers **19** and **20** arise by disproportionation of radical **16**. The two hydrocarbon products **21** and **22** are proposed to arise by capture of an electron by the starting olefin to give radical anion **23**, and protonation by the solvent to give radical **24** which undergoes disproportionation to give the isolated products. Related observations with a variety of tri- and tetrasubstituted alkenes are presented and discussed in Kropp's excellent review article[34].

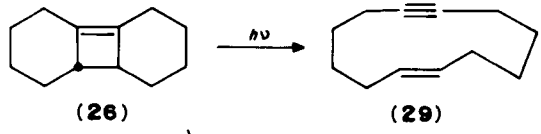


SCHEME 6

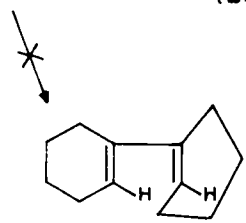
Ring opening of cyclobutenes to give dienes and the reverse process are classic electrocyclic reactions, which are predicted by one or another version of orbital symmetry theory to occur photochemically by a disrotatory path[40]. Although photochemical formation of cyclobutenes from 1,3-dienes is well known and indeed occurs stereospecifically in accord with theoretical predictions, the reverse ring opening is not well known. The problem is that 1,3-dienes absorb at longer wavelengths and with greater intensity than cyclobutenes, so that under the conditions required to effect ring opening of cyclobutenes, the reverse photochemical ring closure of dienes should be a facile process. One of the few reported studies of cyclobutene ring opening involves compounds **25** and **26** (equations 33 and 34)[41]. The former indeed affords *cis,cis*-1,1′-bicyclohexenyl **27** and the fragmentation product **28**, while the latter gives only the isomeric fragmentation product **29**; disrotatory ring opening of **26** would afford the highly strained *cis,trans* isomer of **27** (i.e. **30**). Compound **30** was proposed as the intermediate in the photosensitized conversion of **27** to **25** and has indeed been detected and characterized by laser flash techniques[26].



(25) (27) (28) (33)



(26) (29)



(30) (34)

5. Hydrogen-atom abstraction

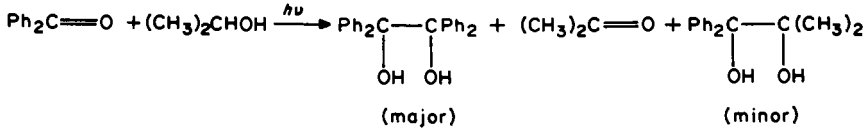
Abstraction of hydrogen from solvents or added reagents is a relatively rare mode of reaction of electronically excited alkenes, since the other types of reactions previously mentioned are usually much faster and therefore dominate. H-atom abstraction from 2-propanol and methanol has been reported for 1,1-diphenylethylene and 1,1-di-*t*-butylethylene. It is likely that the reactive excited states in these systems are $^3\pi,\pi^*$ states[42].

B. Photochemistry of Ketones

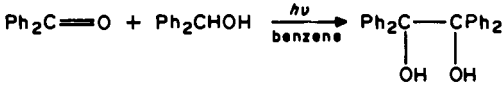
Simple carbonyl compounds (aldehydes and ketones) undergo several prototypical reactions whose mechanisms are reasonably well understood at the present time. These are inter- and intramolecular hydrogen abstraction, cleavage of C—C bonds α- to the carbonyl group, and intermolecular addition to olefins to give oxetanes. These processes are discussed at length in basic texts, so they will be only briefly reviewed here.

1. Photoreduction as a consequence of hydrogen abstraction

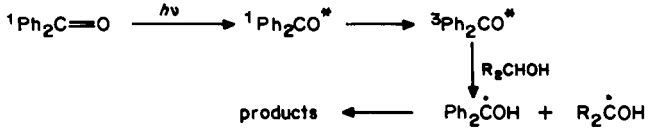
Photoreduction of ketones in hydrogen-donor solvents or in the presence of added reagents has been known ever since the pioneering studies of Ciamician and Silber at the turn of the century[43]. Thus, irradiation of benzophenone in 2-propanol or in benzene containing benzhydrol efficiently produces benzpinacol (equations 35 and 36). In classic mechanistic investigations, Hammond and coworkers established that this reaction proceeds via triplet n, π^* excited states according to the mechanism shown in Scheme 7[44].



(35)

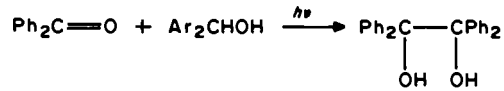


(36)



SCHEME 7

The key step is abstraction of the hydrogen attached to the carbinol carbon by benzophenone triplet, for which a kinetic isotope effect k_H/k_D of 2.8 has been determined. The quantum efficiency for disappearance of benzophenone is *ca* unity using benzhydrol as the reductant, indicating that triplets are formed with 100% efficiency (the rate constant for intersystem crossing has been determined to be *ca* $10^{11}\,l\,mol^{-1}\,s^{-1}$). In 2-propanol, the QE for disappearance of ketone approaches 2.0 at high ketone concentrations because of hydrogen atom transfer from $Me_2\dot{C}OH$ to ketone[45]; the rate constant for this process, which Steel and coworkers view as a simultaneous electron/proton transfer, to be differentiated from transfer of a hydrogen atom as such, has recently been determined to be $3.5 \pm 1.5 \times 10^4\,l\,mol^{-1}\,s^{-1}$ [46]. The pinacol product is formed by combination of two $Ph_2\dot{C}OH$ radicals. When the aryl group in the ketone is different from that in the corresponding hydrol, as a result of either incorporation of a substituent or an isotopic label, it is found that the initial products are as shown in equation 37, i.e. the pinacol is derived only from the ketone[47]. This result indicates that proton/electron transfer occurs as shown in equation 38, in which the initial ketyl radical is converted to ketone and a



(37)

(38)

second molecule of ketone is reduced; the rate constant for this reaction has been determined by Steel and coworkers to be $1.3 \pm 0.2 \times 10^4$ l mol^{-1} s^{-1} [46]. Thus, in the classic Hammond mechanism of Scheme 7 the two initially formed ketyl radicals do not directly combine, undoubtedly because of spin restrictions arising from the fact that they are produced as a triplet radical pair.

Photoreduction is general for ketones whose lowest triplet is an n,π^* state, which includes all aliphatic ketones and aromatic ketones with electron-withdrawing substituents on the aromatic ring. Benzophenones with electron-donor substituents undergo such reaction much less efficiently or not at all, attributed to low-lying π,π^* or charge-transfer triplet states[48]. This unreactive group of ketones also includes carbonyl derivatives of naphthalene and anthracene.

Photoreduction of ketones by amines is a well-known process, illustrated in equation 39 for benzophenone in the presence of triethylamine[49]. In this case, electron transfer occurs from the amine to the ketone triplet to give a radical ion pair, followed by proton transfer to give the ketyl radical $Ph_2\dot{C}OH$, which then either dimerizes to pinacol or abstracts a second hydrogen atom to give the secondary alcohol. The efficiency of the electron transfer process is governed by the factors discussed previously in Section I, the most critical factor being the ionization potential of the amine.

$$^3Ph_2C{=}O^* + Et_3N: \longrightarrow Ph_2\dot{C}{-}\,^- + Et_3N^{+\cdot} \longrightarrow$$

$$Ph_2\dot{C}OH + CH_3\dot{C}H{-}NEt_2 \longrightarrow$$

coupling and disproportionation products (39)

The Norrish Type II reaction, illustrated in Scheme 8 for γ-methylvalerophenone (MVP), is the intramolecular counterpart of the intermolecular hydrogen-abstraction process discussed above[50]. This is a general process for ketones possessing a lowest n,π^* triplet with accessible γ-hydrogens on the side-chain. Aromatic ketones undergo this reaction exclusively from triplet states because of rapid intersystem crossing, while aliphatic ketones (which have values of k_{isc} of the order of 10^8–10^9 s^{-1}) generally react from both singlet and triplet n,π^* states[51]. Studies of appropriately substituted compounds show that the singlet component of the reaction is largely stereospecific, while the triplet component gives alkenes with mixed stereochemistry. In cases where the γ-carbon of the side-chain is fully substituted, H abstraction from the next (δ) position is sometimes observed[52]. The Norrish Type II fragmentation to alkenes and ketones is usually accompanied by the formation of low yields of cyclobutanols, as shown in Scheme 8.

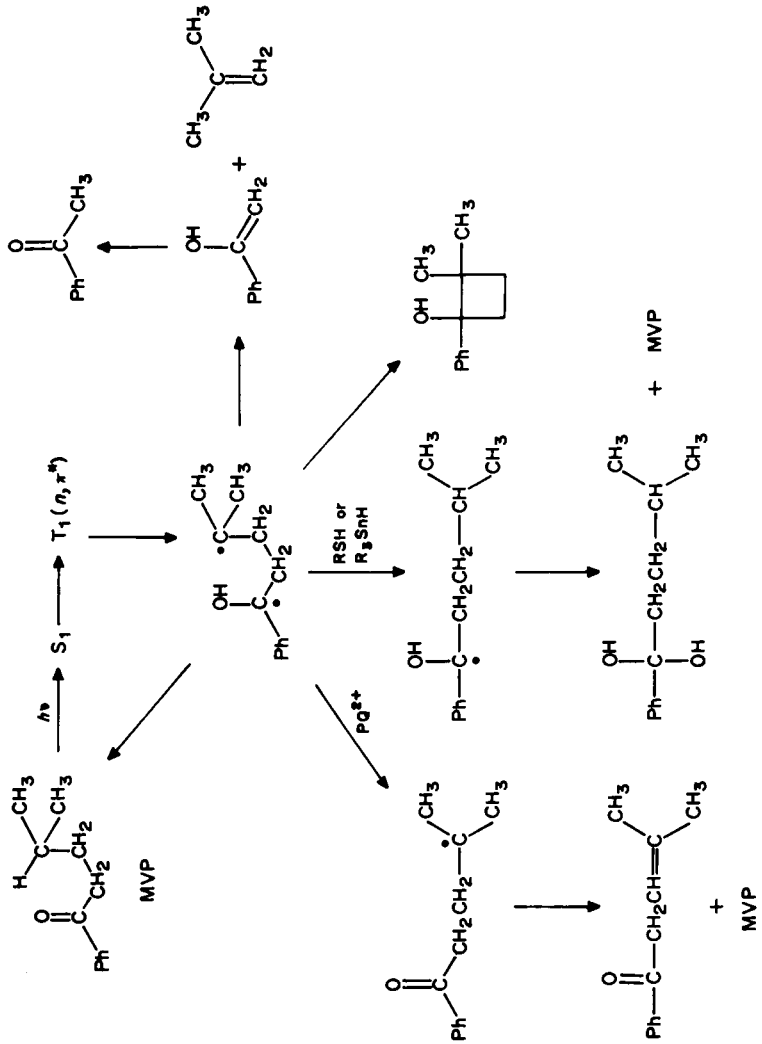
2. *Norrish Type I cleavage of ketones*

Irradiation of aliphatic ketones in the vapor phase usually leads to formation of an acyl–alkyl radical pair by homolytic cleavage of one of the C—C bonds to the carbonyl carbon, illustrated in equation 40[53]. The acyl radical usually loses CO to give a second alkyl radical. The products arise by combination and disproportionation of the various radicals. Many acyclic and alicyclic ketones undergo similar reactions in solution[54]. Intermediate

$$R^1{-}\overset{O}{\overset{\|}{C}}{-}R^2 \xrightarrow{h\nu} R^1\overset{O}{\overset{\|}{C}}\cdot + R^2\cdot + R^1\cdot + R^2\overset{O}{\overset{\|}{C}}\cdot \qquad (40)$$

$$\downarrow$$

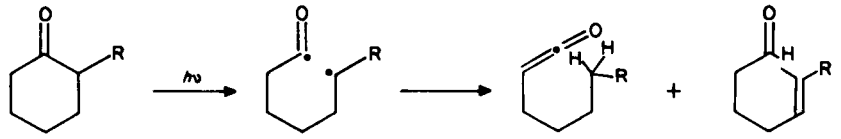
products



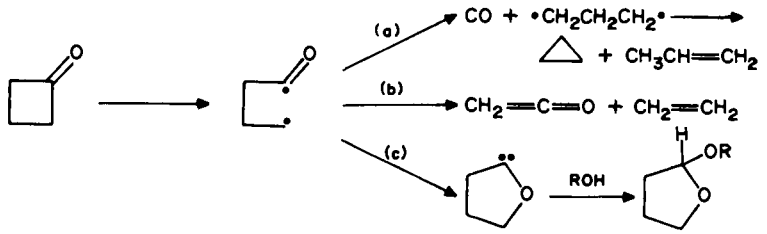
SCHEME 8

radicals have been directly detected by electron spin resonance (ESR) techniques, and observations of nuclear polarization under these conditions also provide evidence for radical intermediates[55].

Norrish I cleavage of aliphatic ketones can occur from both singlet and triplet n,π^* states, and sometimes competes directly with Norrish Type II reactions when there is a side-chain with γ-hydrogens[54]. In the case of cyclohexanone, cleavage affords a 1,6-acyl-alkyl diradical that gives a ketene and an unsaturated aldehyde by competitive intramolecular 1,5-H migrations (see Scheme 9)[56]. In the case of cyclobutanone, the initial 1,4-acyl–alkyl diradical has a choice of (a) cleavage to CO and a trimethylene diradical, (b) fragmentation to ketene and ethylene, or (c) rearrangement to an oxacarbene that can be trapped in alcohol solvents (see Scheme 10)[57].



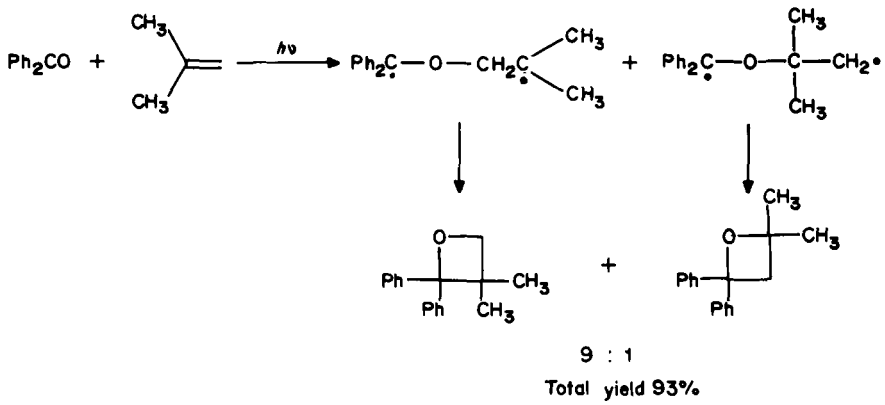
SCHEME 9



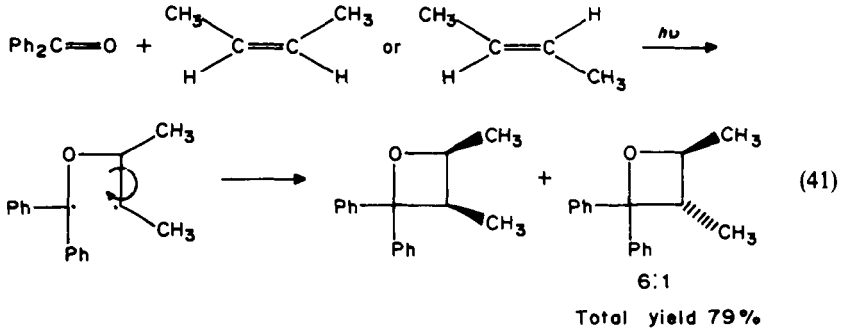
SCHEME 10

3. *Photoaddition to alkenes—oxetane formation*

Another reaction of ketone triplet n,π^* states is addition to alkenes to give oxetanes, known as the Paterno–Büchi reaction, due to its discovery by Paterno and Chieffi in 1909[58] and the fundamental contributions made nearly fifty years later by Büchi and coworkers[59]. The reaction is illustrated in Scheme 11 for the case of photoaddition of benzophenone to isobutene. As is seen in this system, the relative yield of isomeric products can be nicely rationalized in terms of the relative stability of the corresponding 1,4-diradical intermediates. The same mixture of isomeric products is obtained on reaction with either of a pair of (*Z*)- and (*E*)-alkene isomers, consistent with the intermediacy of a triplet biradical in which rotation around a single C—C bond is competitive with ring closure (equation 41)[60]. Since simple alkenes with alkyl or alkoxy substituents have triplet excitation energies $\geqslant 74$ kcal mol^{-1}, addition to ketone triplets occurs to the exclusion of triplet energy transfer from the ketone to the alkene. Since triplet energies of alkenes with electron-withdrawing substituents, such as acrylonitrile and fumaronitrile, are much lower (recent photoacoustic calorimetric measurements give values of 58 ± 4 and 48 ± 3 kcal mol^{-1} for CH_2=CHCN and NC—CH=CH—CN, respectively)[61], triplet transfer from benzophenone and other sensitizers is possible, leading to dimerization (quantum efficiency only 0.06)[62] and *cis–trans* isomerization, respectively.

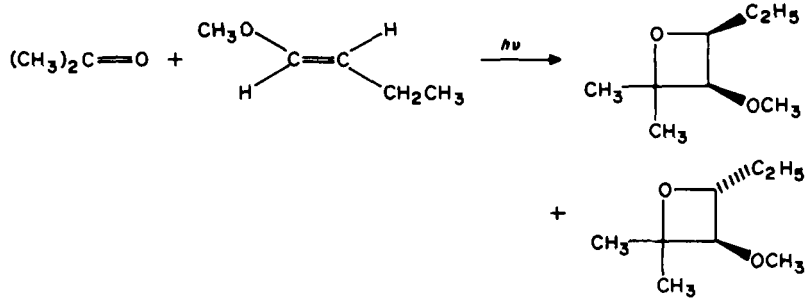


SCHEME 11



(41)

In contrast to aromatic ketones, aliphatic ketones add to alkenes via either singlet or triplet n, π^* states for reasons already discussed. Indeed, reaction of acetone with electron-rich olefins appears to involve both states, and the ratio of products in equation 42 depends on the alkene concentration, consistent with competition between stereospecific trapping by alkene of the singlet and intersystem crossing to give triplets which react non-stereospecifically[63,64]. Photocycloaddition of acetone to *cis* or *trans* NC—CH=CH—CN is completely stereospecific, suggesting the reaction occurs exclusively via the ketone



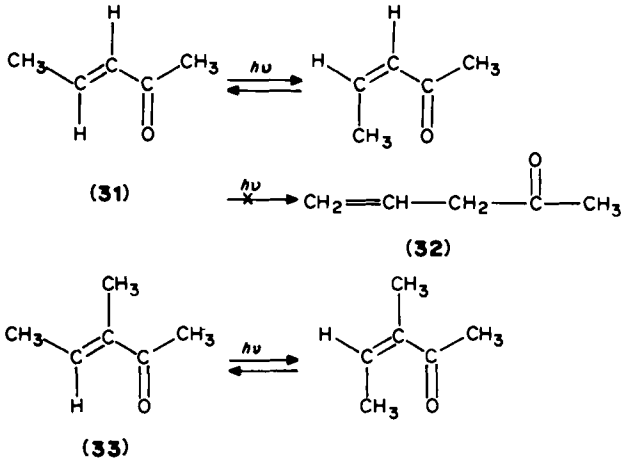
(42)

S_1 state. This is supported by the fact that acetone fluorescence is not quenched by electron-deficient alkenes, and that the cycloaddition is not affected by typical triplet quenchers. This reaction is suggested to involve interaction between the electron-poor π system of the alkene and the electron-rich π system of the ketone S_1 state. The course of oxetane formation has been rationalized in terms of perturbational molecular orbital theory[65].

IV. PHOTOCHEMISTRY OF α,β-UNSATURATED KETONES

A. Acyclic Systems

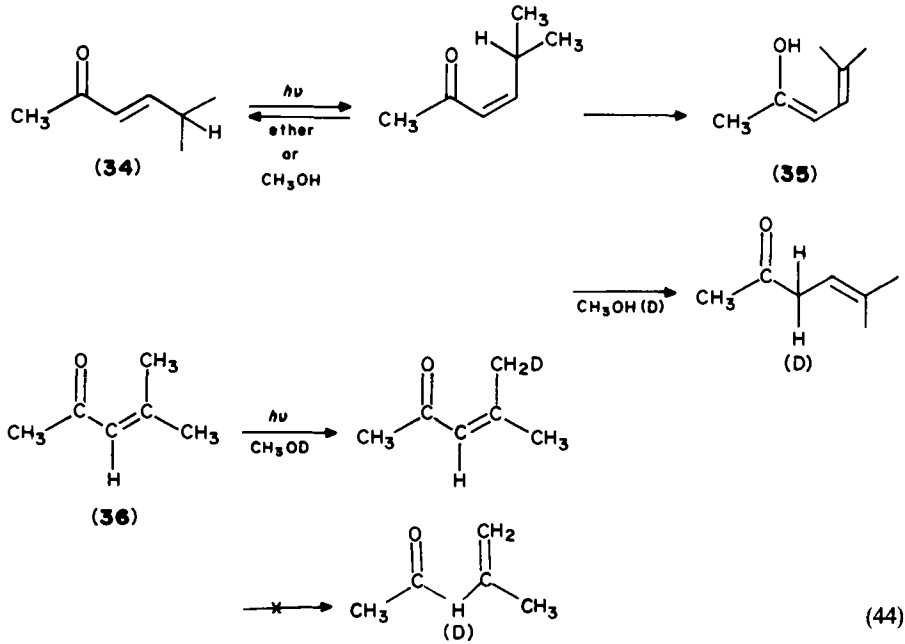
In early studies of acyclic conjugated enones three general types of behavior were observed, depending on the enone structure. A large group of enones, typified by 3-penten-2-one (**31**), were initially reported to be resistant to change on UV excitation[66], although later studies clearly showed that **31** undergoes efficient E–Z isomerization when irradiated at 313 or 238 nm in the vapor phase or at 254 or 313 nm in hexane or ether solution (equation 43)[67]. None of the deconjugation product 4-penten-2-one **32** was detected in the solution studies. The sum of the quantum efficiencies for $Z \rightarrow E$ and $E \rightarrow Z$ isomerization for **31** as well as for enone **33** was significantly less than 1.0, indicating that a twisted excited state common to both E and Z isomers cannot be an intermediate in the isomerization, if it is formed with unit efficiency from both isomers[67]. The photoisomerization on direct irradiation could not be quenched by piperylene (1, 3-pentadiene), stilbene or oxygen, and the quantum yields are significantly greater than for sensitized photoisomerization using propiophenone and acetophenone ($E_T = 74.6$ and 73.6 kcal mol^{-1}, respectively); no sensitization is observed using benzophenone ($E_T = 68.5$ kcal mol^{-1}). No fluorescence or phosphorescence of this or other simple acyclic enones has been observed. Thus, it is concluded that the photoisomerization on direct excitation involves singlet excited states which apparently are not sufficiently twisted that they are common to both isomers. The sensitization studies indicate an excitation energy of *ca* 70 ± 1 kcal mol^{-1} for the enone triplet.



(43)

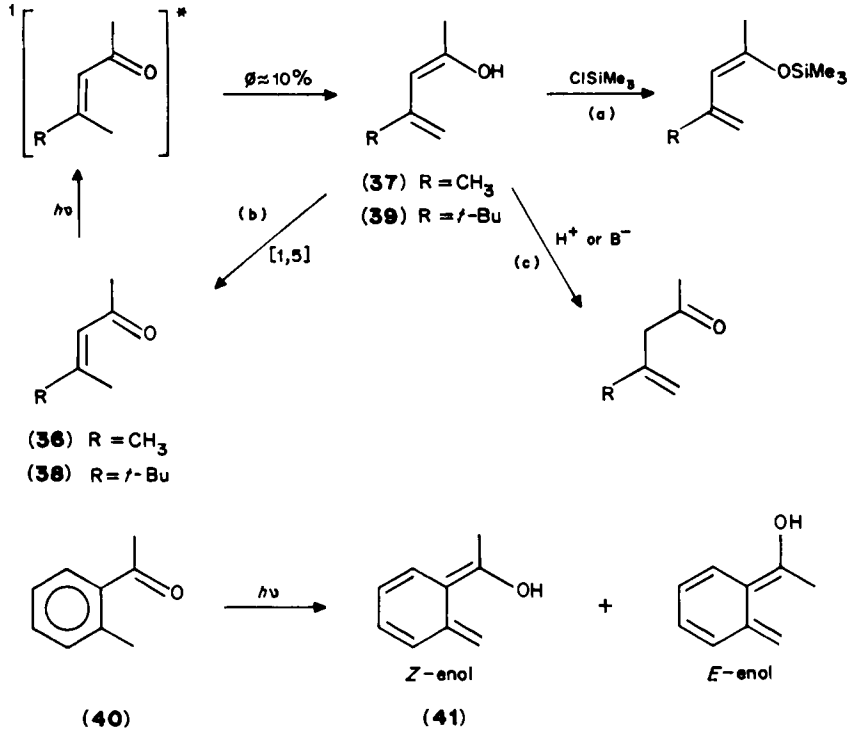
Conjugated enones possessing a γ-hydrogen as well as at least one γ-alkyl group additionally undergo isomerization to a β,γ-unsaturated ketone, presumably via a dienol intermediate, as illustrated for 5-methyl-3-hexan-2-one (**34**) in equation 44[66]. In accord with this suggestion (equation 44), irradiation of **34** in CH_3OD led to 95% D-

incorporation at C_3, presumably upon ketonization of dienol **35** (later studies to be discussed below establish this mechanism with virtual certainty). Certain enones such as **36** are not converted to their deconjugated isomers on direct excitation, although they do incorporate deuterium on irradiation in CH_3OD, indicating formation of a dienol isomer which gives exclusively the conjugated enone on ketonization[66].



(44)

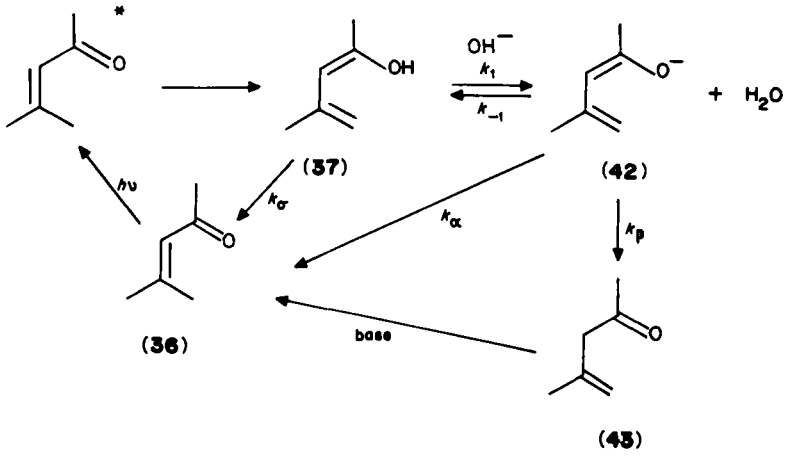
Weedon and coworkers have recently reported a series of studies of dienol formation on irradiation of a large number of acyclic conjugated enones[68]. A clear pattern of photochemical reactivity in these systems has emerged from these studies. Thus, virtually all acyclic γ-alkyl-α,β-unsaturated ketones undergo intramolecular H transfer from the γ-carbon to the carbonyl oxygen (analogous to the Norrish Type II reaction); this singlet excited state process proceeds stereoselectively to give a (*Z*)-dienol (illustrated for enone **36** in Scheme 12). Quantum yields for this process are of the order of 10%. The (*Z*)-dienols can (a) be trapped as their trimethylsilyl ethers, (b) undergo a noncatalyzed 1, 5-sigmatropic H shift to regenerate the starting enone or (c) reketonize under acid or base catalysis to give a β,γ-unsaturated ketone[65]. ^{1}H-NMR spectra taken at $-76\,^\circ C$ of solutions of enone **36** in MeOH-d_4 irradiated in NMR tubes in an acetone/dry ice slurry show a new set of signals belonging to (*Z*)-dienol **37**; similar results were found for the photoconversion of **38** to **39** (Scheme 12)[69]. Conversion of enone to dienol is generally incomplete under these conditions, probably owing to overlap of UV absorption spectra of the tautomers. The dienols are cleanly reconverted to the starting enones when the solutions are brought from $-76^\circ C$ to ambient temperatures; no deconjugation products are formed under these conditions, supporting Weedon's proposal that reketonization occurs via an uncatalyzed 1, 5-hydrogen shift. The reversion process follows clean first-order kinetics whose temperature dependence yields the following activation parameters: for **37**, $A = 4 \times 10^8\,s^{-1}$ and $E_a = 15 \pm 1$ kcal mol^{-1}; for **39**, $A = 1 \times 10^6\,s^{-1}$ and $E_a = 11 \pm 1$ kcal mol^{-1}. These parameters should be compared with those for the (*Z*)-enol **41** derived from *o*-methylacetophenone **40**; E_a for reversion to **40** is 8.9 kcal mol^{-1}, very close



SCHEME 12

to that for **37** and **39**, but the pre-exponential factor in the case of **41** is much greater, $3 \times 10^{12}\,s^{-1}$. Weedon speculates that this may reflect the constrained cisoid geometry of **41** which optimizes the suprafacial orbital overlap required for the 1, 5-hydrogen shift. Thus, the *Z*-dienols derived from acyclic enones are much longer-lived than their aromatic analogs, or even than simple enols which are relatively stable in the absence of acid and base catalysts. The latter situation can be ascribed to the difficulty of ketonization via a symmetry-allowed antarafacial 1, 3-hydrogen shift, which is the only available mechanism in the absence of acids and bases. Attempts to trap dienols using reactive dienophiles in Diels–Alder reactions have thus far been unsuccessful. Such reactions have been successful for the relatively long-lived (*E*)-dienols derived from *o*-alkyl aromatic ketones such as **40**[70], but the corresponding (*Z*)-dienols (e.g. **41**) are too short-lived to permit interception by dienophiles.

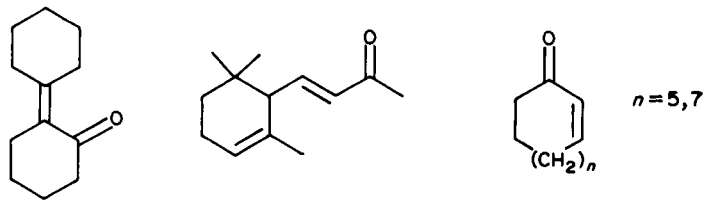
When enones such as **36** are excited with a 20-μs UV pulse in aqueous basic solution, transients are produced with UV absorption maxima at *ca* 290 nm[71]. The transient absorption, which Weedon assigns to dienolate anions (**42** in Scheme 13), decays by clean first-order kinetics with a rate depending on the enone and the pH of the solution. The data indicate that equilibration of the dienol and dienolate is rapid compared with rates of ketonization (k_α and k_β in Scheme 13) which vary with pH depending on the proportions of dienol and dienolate. Indeed, the variation of the first-order decay rate constant with pH resembles a titration curve, and these data can be used to obtain pK_as of the dienols. Thus, for **37** the pK_a is 10.42 ± 0.01. Protonation of the dienolate can give either the starting α,β-



SCHEME 13

enone or the rearranged β,γ-enone **43**; however, it is found that protonation of **42** at C-3 to give the deconjugated ketone **43** occurs *ca* ten times faster than protonation at C-5 (k_α) which would regenerate **36**. The quantum efficiency for base-catalyzed photodeconjugation of **36** (excitation at 254 nm) in aqueous solution varies (as expected from Scheme 13) as a function of added base (1,2-dimethylimidazole), and has a limiting value of 0.033 ± 0.001. The deconjugation reaction is much less efficient in solvents of lower polarity (hexane, ether) at comparable base concentrations, indicating that solvation and consequent stabilization of the dienolate anion is an important factor; the uncatalyzed 1,5-hydrogen shift dominates in nonpolar solvents. If the strength of the added base is decreased, deconjugation is inhibited since the equilibrium between dienol and dienolate is shifted toward the dienol, which ketonizes via the 1,5-hydrogen shift. If the strength of the base is increased too much, the efficiency of photodeconjugation (e.g. in the presence of triethylamine) drops to zero. This is attributed to thermal base-catalyzed conversion of **43** to **36**; indeed, rapid reconjugation of **43** occurs in the dark in the presence of triethylamine in methanol at a rate much faster than that of photodeconjugation under comparable conditions[71].

The reactions described for enone **36** are general, as Weedon and coworkers have demonstrated for a large series of acyclic and cyclic enones[68]. Some general conclusions regarding the effect of enone structure on the efficiency of deconjugation can be drawn from the data. Thus, a substituent in the γ-position to the carbonyl (as in **34**, **44**, **45** and **46**) interferes with adoption of the cisoid (skewed or planar) conformation of the dienol required for the suprafacial 1,5-hydrogen shift, thus increasing the opportunity for

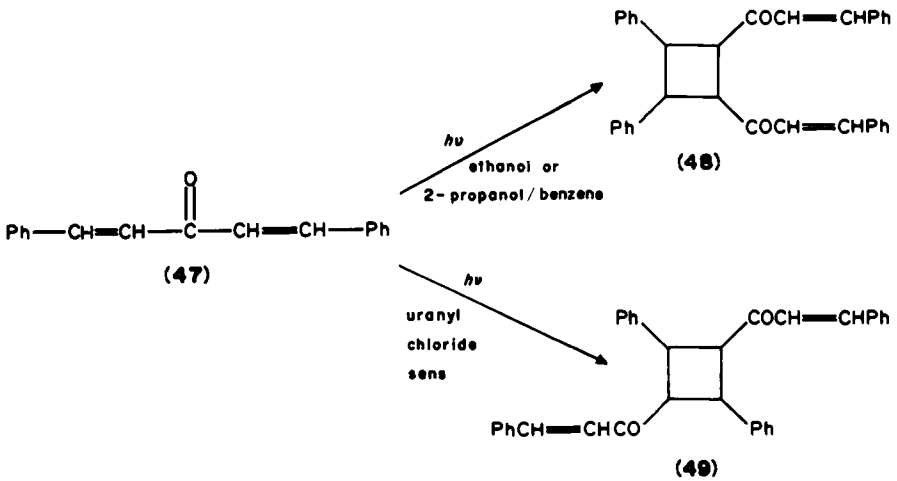


(44) (45) (46)

conversion to the dienolate by added base or the solvent itself; protonation of the dienolate can then give the deconjugated enone. When there is no substituent at the γ-carbon (as with **31**, **34** and **36**) there is no structural inhibition for formation of the (*Z*)-dienol, which (in the absence of added base) reverts exclusively to the conjugated enone by the 1,5-hydrogen shift. Such enones are therefore inert to photodeconjugation in the absence of added base, although D-incorporation in deuteriated solvents indicates that dienols are indeed formed. The few exceptions to these generalizations can be rationalized on consideration of pertinent structural features in each system[68].

Photodeconjugation of α,β-unsaturated esters on irradiation at 254 nm in the presence of a weak base such as 1,2-dimethylimidazole has also been reported by Weedon and coworkers[72]. This reaction, although technically outside the scope of this review, shows structural effects similar to those of the α,β-enones discussed above, and the mechanism is entirely analogous. Deconjugation again appears to involve intramolecular hydrogen abstraction by singlet excited states to give the corresponding (*Z*)-dienol, competitive with *Z*–*E* isomerization. Formation of the dienolate followed by protonation gives a mixture of the conjugated and unconjugated esters. For esters which are constrained with respect to *Z*–*E* isomerization, quantum yields for deconjugation approach 0.3.

Photodimerization of acyclic α,β-enones generally does not compete with the reactions discussed above, but there are a few exceptions. Ciamician and Silber reported photodimerization of dibenzylideneacetone **47** in solution to give the cyclobutane **48**[73], while later studies showed that uranyl chloride sensitized dimerization gave **49** (equation 45)[74]. There are several reports of photodimerization of chalcones Ar—CH=CH—CO—Ar′ in solution as well as in the solid state; the former reactions have been assigned a triplet mechanism in accord with the extensive studies involving photodimerization of cyclic enones, to be discussed later[75].



(45)

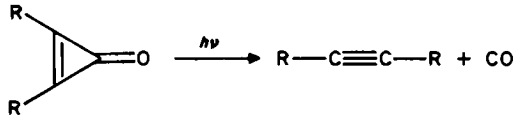
B. Cyclic Systems

Perhaps the most important reaction of cyclic α,β-unsaturated ketones is photocycloaddition to alkenes. This reaction, which has received a great deal of attention recently with respect to mechanistic studies and synthetic applications, will be discussed separately

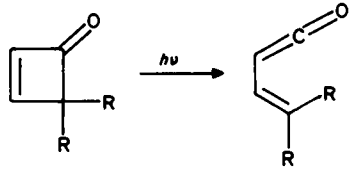
below. The following discussion will first focus on other types of photoreactions of cyclic α,β-enones, grouped according to ring size.

1. Cyclopropenones and cyclobutenones

There are very few reports concerning the photochemistry of cyclopropenones and cyclobutenones. As shown in equation 46, cyclopropenones undergo fragmentation to give acetylenes and carbon monoxide[76], while cyclobutenones undergo ring opening to vinyl ketenes (equation 47), which can be detected by infrared spectroscopy when the irradiation is carried out at 77 K or lower temperatures[77].



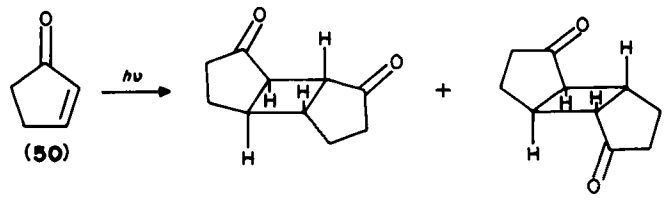
(46)



(47)

2. Cyclopentenones

a. Photodimerization. Photodimerization of cyclopentenone (CP) **50** gives a mixture of the *cis*-fused head-to-head and head-to-tail dimers **51** and **52** (equation 48)[78]. The reaction can be quenched by piperylene ($E_T = 57$–59 kcal mol^{-1}) and sensitized by xanthone ($E_T = 74.2$ kcal mol^{-1}) without affecting the ratio of the dimers, indicating they arise from a common triplet state precursor. The product ratio depends on solvent polarity, with the proportion of **51** increasing as solvent polarity or the concentration of enone (which is interpreted as a solvent effect) is increased, although **52** remains the major product under all conditions examined to date. The quantum efficiency for dimerization of 1.0 M **50** in acetonitrile is 0.34, and sensitization studies indicate that the inefficiency arises after triplet formation, i.e. $\phi_{isc} = 1.0$[79]. Wagner and Bucheck[79] argue that the reactive excited state of **50** is more likely a π,π^* than an n,π^* triplet state, and that the inefficiency arises from competitive decay to two ground-state enones from unidentified intermediates (collision complexes, π complexes, triplet 1,4-biradicals) en route to dimers. This question will be considered later in more detail in connection with enone–alkene photocycloadditions.



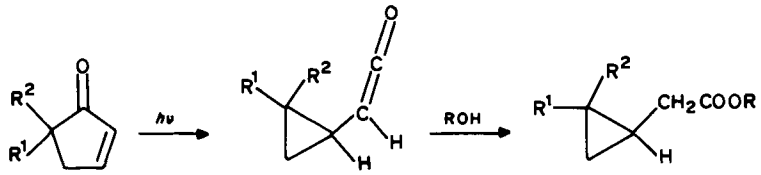
(48)

(51) (minor) (52) (major)

From quenching studies, Wagner and Bucheck[79] estimated lifetimes for CP triplets assuming quenching by piperylene is diffusion-controlled (a rate constant of $1.0 \times 10^{10}\,l\,mol^{-1}\,s^{-1}$ was assumed), from which they could obtain values for rate constants for capture of CP triplets by ground state CP ($6.6 \times 10^{8}\,l\,mol^{-1}\,s^{-1}$) and for unassisted radiationless decay of the triplet ($4 \times 10^{7}\,s^{-1}$), corresponding to a limiting triplet lifetime of 25 ns. Direct measurement of these quantities using nanosecond flash techniques by Heibel and Schuster[80] indicate that Wagner's rate constants are too high. The triplet lifetime (τ_T) of CP (**50**) is 130 ns in acetonitrile at 0.008 M, a concentration at which dimerization is insignificant, upon excitation at 355 nm using a Nd: YAG laser; the transient triplet decay was monitored at 300 nm (a full discussion of laser flash excitation of cyclic enones will be given below). This directly measured value of τ_T is significantly greater than Wagner's estimates[79] or Bonneau's earlier measurement of 30 ns at higher enone concentrations[81]. The plot of $(\tau_T)^{-1}$ vs. [CP] is linear (see equation 49)[80], where τ_0 is the triplet lifetime of CP at infinite dilution and k_a is the rate constant for interception of the triplet by ground state CP, which is found to be $1.2 \times 10^{8}\,l\,mol^{-1}\,s^{-1}$, a factor of five less than Wagner's estimated value. The rate constant for quenching of CP triplets by 1-methylnaphthalene ($E_T = 61$ kcal mol^{-1}) in acetonitrile is $3.8 \times 10^{9}\,l\,mol^{-1}\,s^{-1}$, considerably lower than the diffusion-controlled limit assumed by Wagner[79].

$$(\tau_T)^{-1} = (\tau_0)^{-1} + k_a[CP] \tag{49}$$

b. Photorearrangements. Irradiation of 5-substituted cyclopentenones **53** results in ring contraction to cyclopropylketenes **54**, which are usually isolated as the esters **55** (equation 50)[82,83]. This transformation has been observed for a variety of compounds. The ketene can be directly detected by its characteristic IR absorption at 2110 cm^{-1} when reaction is carried out in pentane; addition of methanol gives the ester. The occurrence of α-cleavage in these systems is to be contrasted with the absence of such a pathway in the photochemistry of structurally analogous 6,6-disubstituted cyclohexenones. It is likely that this is a triplet state reaction.



(**53**) (**54**) (**55**) (50)

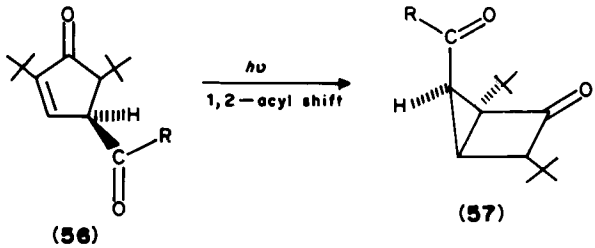
$R^1 = R^2 = CH_3$ or Ph

$R^1 = H$, R^2 = Et, Pr, OEt

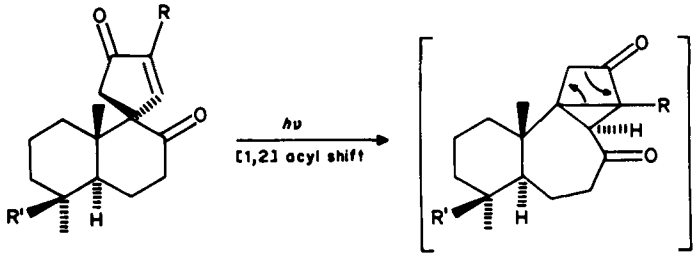
4-Acyl-2,5-di-*t*-butylcyclopentenones **56** rearrange to bicyclo[2.1.0]pentanones **57** (equation 51) on UV irradiation[84]. Isotopic labelling indicates that the reaction occurs by migration of the acyl group from C-4 to C-3 and formation of a new bond between C-2 and C-4. Mechanistically, this is an oxa-di-π-methane photorearrangement which is characteristic of β,γ-enones[5,6]. A related rearrangement involves acylcyclopentenone **58** which rearranges to the butenolide **59**, presumably via the bicyclo[2.1.0]pentanone **60** and ketene **61** (equation 52)[85]. By analogy with the photo-chemistry of β,γ-enones, it is likely that these reactions proceed via triplet excited states, although this has not been demonstrated.

A related photorearrangement occurs with **62**. In this case, a phenyl shift would give the bicyclo[2.1.0]pentanone **63**, which on ring opening would give ketene **64**, the source of the

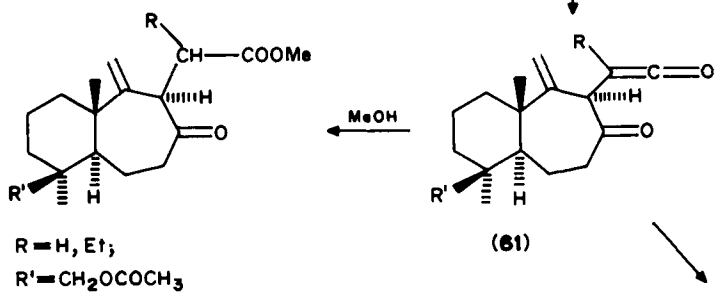
isolated product **65** (equation 53)[86,87]. This reaction is structurally analogous to the chemistry of 4-arylcyclohexenones discussed later. As in that case, triplet intermediates are implicated by sensitization and quenching studies.



(56) (57) (51)

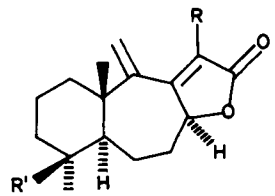


(58) (60)



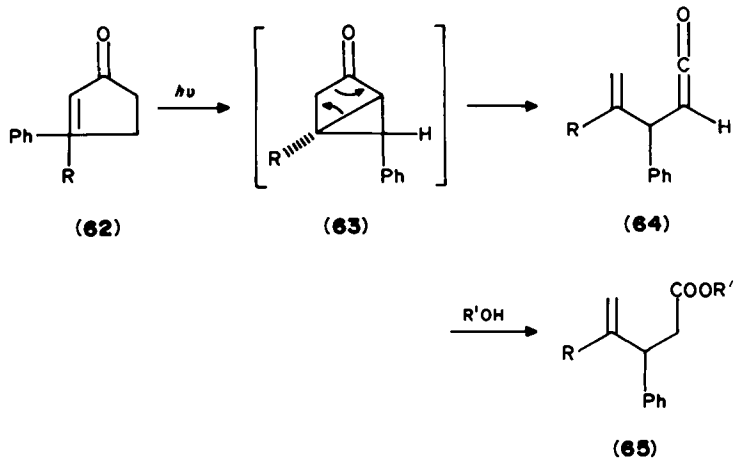
R = H, Et;
R' = CH_2OCOCH_3

(61)



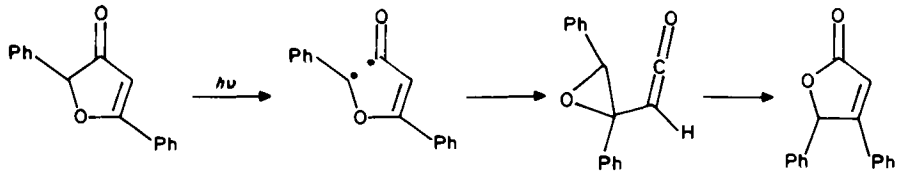
(59)

(52)



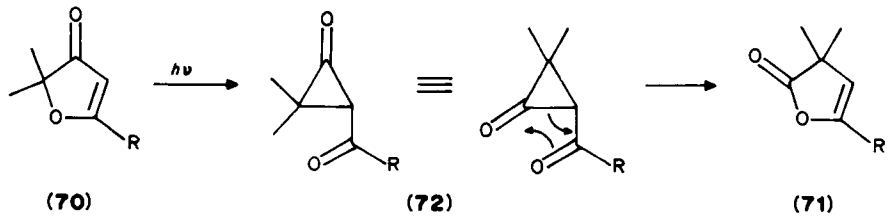
(53)

The photochemistry of simple derivatives of 3(2*H*)-furanones shows some analogies to the above reactions[88]. Thus, the 2,5-diphenyl derivative **66** rearranges to **67** by the proposed route shown in equation 54, involving α-cleavage to **68**, ring closure to **69** and finally a ring expansion analogous to the well-known vinylcyclopropane–cyclopentene thermal interconversion. However, completely different behavior is seen with alkyl-substituted furanones such as **70** which photorearrange cleanly to lactones **71**. The proposed mechanism, shown in equation 55, involves initial isomerization to cyclopropanone **72**, which can give **71** directly on ring expansion; each step represents a vinylcyclopropane–cyclopentene interconversion. Supporting evidence derives from **73**, which photodecarbonylates to give **74**, a reaction which is believed to result from fragmentation of the sterically crowded cyclopropanone **75**. These reactions are efficiently quenched by 2,3-dimethyl-1,3-butadiene, suggesting that they proceed via enone triplets.



(54)

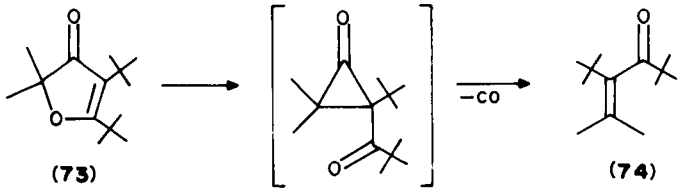
c. Inter- and intramolecular hydrogen abstraction. Irradiation of dilute solutions of cyclopentenone **50** in 2-propanol gives an adduct **76** in addition to the usual dimers[89]. The same adduct **76** is formed on benzophenone sensitization, although benzophenone sensitizes neither dimerization of **50** nor cycloaddition of **50** to alkenes. Moreover, CP efficiently quenches photoreduction of benzophenone in 2-propanol. Based on these data, de Mayo and coworkers originally proposed that CP reacts via two triplet excited states, a T_1 state whose energy is below that of benzophenone (68.5 kcal mol^{-1}) which gives only reduction, and an upper T_2 state which is responsible for cycloaddition and dimerization. However, phosphorescence data on cyclopentenones **77** and **78**[90] show that it is unlikely that T_1 of **50** is in fact low enough to allow energy transfer from Ph_2CO to be as rapid as



(70) (72) (71)

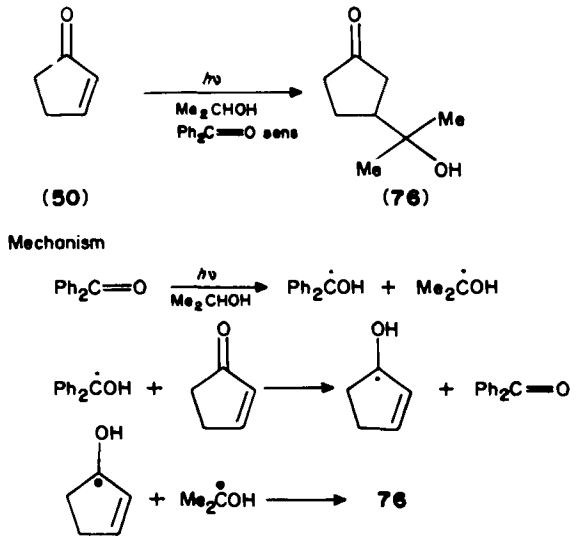
R=Et, *t*-Bu

(55)



(73) (75) (74)

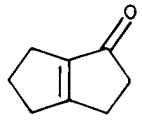
required by de Mayo's data[89]. This anomaly was resolved by invoking the mechanism shown in Scheme 14 involving so-called 'chemical sensitization', in which the species quenched by CP is not benzophenone triplet excited state but rather the diphenylketyl radical. As indicated earlier, hydrogen transfer from ketyl radicals to ground-state ketones is a well-documented reaction. This type of 'sensitization' has to be considered in situations where triplet energy transfer is unlikely for energetic reasons.



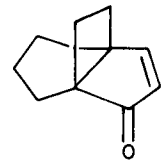
(50) (76)

Mechanism

SCHEME 14

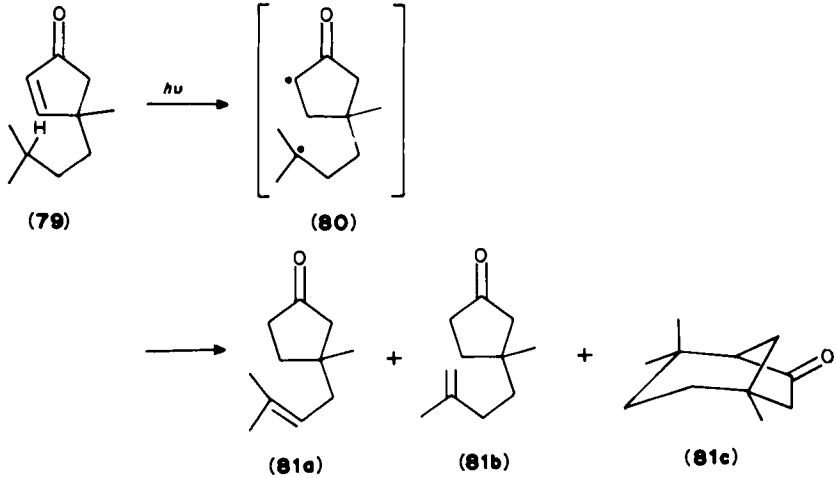


(77)



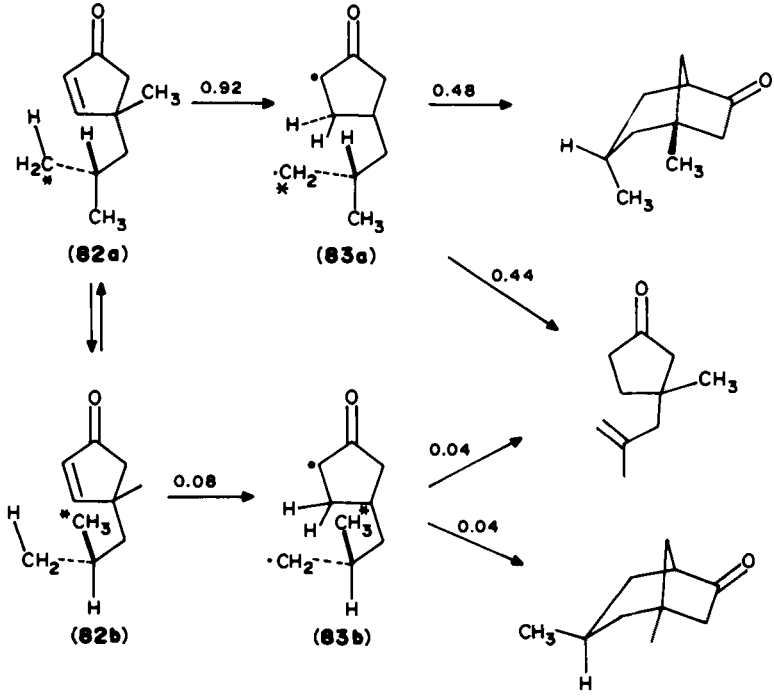
(78)

Irradiation of the 4-substituted cyclopentenone **79** in benzene gives ketones **81a**, **81b** and **81c**, which are logically derived from the diradical **80** formed by hydrogen transfer from the side-chain to the β-carbon of the enone (equation 56)[91]. Agosta and coworkers used deuterium-labeled compounds to demonstrate that 1, 5-hydrogen transfer via a six-membered transition state is preferred over 1, 6-hydrogen transfer; no evidence for 1, 4-hydrogen transfer was obtained. Using **82** in which the diastereotopic methyl groups were distinguished by isotopic labeling, it was possible to discriminate between hydrogen abstraction via conformation **82a** and **82b** to give diradical **83a** and **83b**, respectively[92]. It was found that 92% of the reaction to give the indicated products proceeds via **82a** and **83a** (equation 57). However, it was not possible to assess the degree of reversion to starting materials from the diradicals, nor the extent to which nonvolatile products (totaling 35%) derive from one or the other biradical.



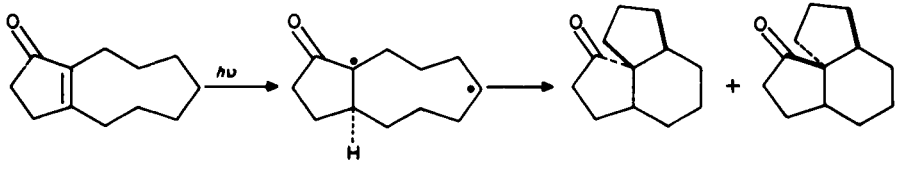
(56)

In these and related systems, no hydrogen transfer to the α-carbon is observed, and all the data are consistent with exclusive hydrogen transfer to the β-carbon of the enone. Irradiation of 4, 4-dimethylcyclopentenone in *t*-butyl alcohol gives exclusively the 2-*t*-butoxy adduct, again indicating hydrogen abstraction at the β-carbon followed by radical coupling (a Michael-type nucleophilic photoaddition should occur at the β-carbon, as is observed with some substituted cyclohexenones)[82]. The intramolecular hydrogen abstractions are efficiently quenched by 2, 3-dimethyl-1, 3-butadiene ($E_T \sim 60\,kcal\,mol^{-1}$) and sensitized by propiophenone ($E_T = 74\,kcal\,mol^{-1}$), pointing to a triplet excited intermediate. The course of reaction suggests a π, π^* rather than an n, π^* triplet; the latter should abstract hydrogen at the carbonyl oxygen (see above) leading to radical coupling at the β-carbon, which is not observed.



(57)

A recent study concerns cyclopentenone **84**, which is converted on UV excitation into the fused tricyclic ketones **85a** and **85b** as shown in equation 57a. Once again, this is consistent with initial hydrogen abstraction at the β-carbon of the enone to give biradical **85** which, on coupling, gives the observed products[93].



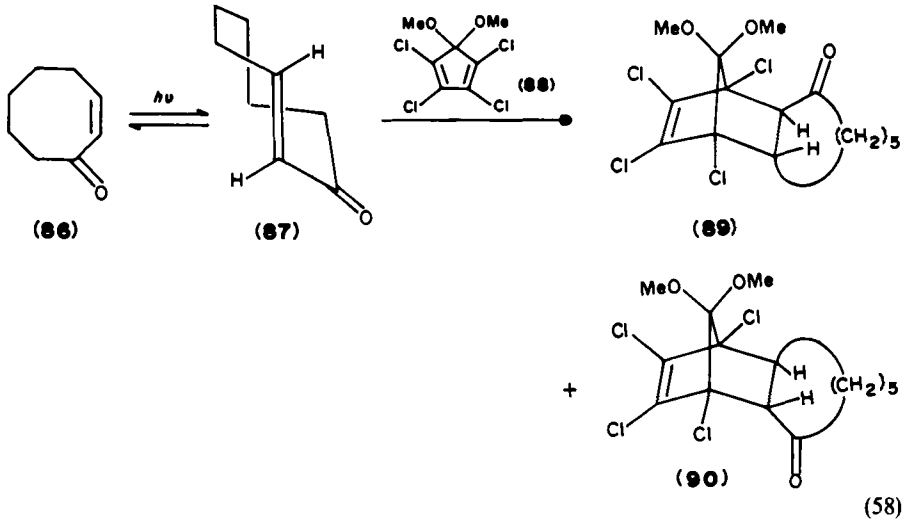
(57a)

That hydrogen abstraction by cyclopentenones does not always occur at the β-carbon is shown by the fact that direct excitation of CP in cyclohexane gives both 2- and 3-cyclohexylcyclopentanones, perhaps due to reaction via both n,π^* and π,π^* triplets which, as mentioned previously, should have similar excitation energies[78b,79,91,92,94].

3. 2-Cycloheptenones and 2-cyclooctenones

Before discussing the complex photochemistry of cyclohexenones, it is useful to first consider the photochemical behavior of medium ring cyclic enones, particularly cycloheptenones and cyclooctenones, which illustrate the possibilities for reaction of electronic excited states in flexible as opposed to rigid ring systems.

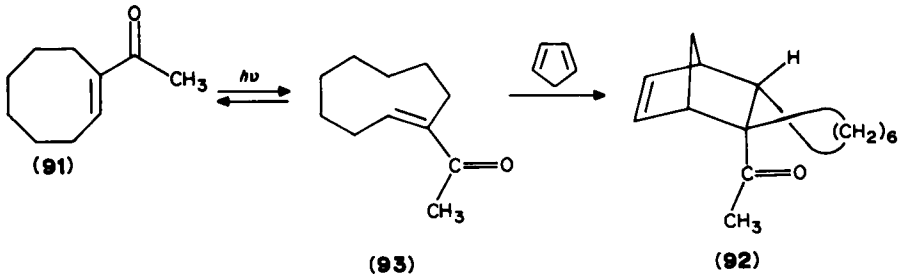
a. Cis–trans isomerization. Based upon the fact that simple alkenes, medium and large ring cycloalkenes ($n \geqslant 8$) and acyclic enones all undergo *Z–E* (*cis–trans*) isomerization, it was reasonable to investigate whether medium ring cyclic α,β-enones also undergo this reaction. Eaton and Lin first reported the conversion of *cis* cyclooctenone **86** to the *trans* isomer **87** on UV (>300 nm) irradiation in cyclohexane (see equation 58), as detected by loss of the UV absorption of **86** at 223 nm, shift of the $n \rightarrow \pi^*$ absorption λ_{max} from 321 to 283 nm, and appearance of a new IR band for C=O absorption at 1727 cm^{-1} in place of the original band at 1675 cm^{-1}[95]. Other new IR bands observed are similar to those found in *trans* but not *cis* cyclooctene. Since only *ca* 80% conversion of **86** was observed, Eaton and Lin concluded that under the conditions of the experiment photoequilibration of **86** and **87** was achieved. Evidence in support of photochemical formation of **87** was obtained by isolation of *trans*-fused Diels–Alder adducts **89** and **90** upon reaction of the product of irradiation of **86** with diene **88** (equation 58), and the fact that dienes that react sluggishly with **86** (such as cyclopentadiene and furan) react readily with the presumed *trans* enone **87**. Furthermore, the *trans* enone **87** dimerizes in the dark at room temperature, although the structures of the dimers have never been reported.



(58)

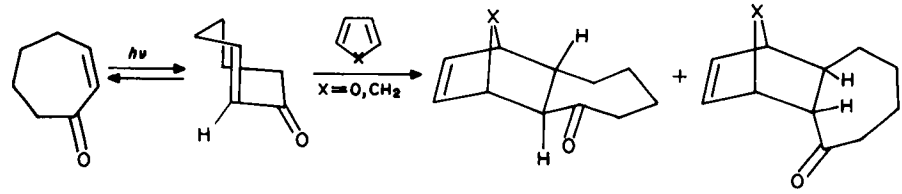
Related to the above results is the observation that irradiation of acetylcyclooctene **91** in the presence of cyclopentadiene (CPD) gives the *trans*-fused [4 + 2] adduct **92**, and the fact that the same product is isolated upon addition of CPD (in the dark) to a solution of **91** after UV irradiation[96]. Thus, the adduct **92** would appear to arise from thermal addition of CPD to the *trans* enone **93** (equation 59). Eaton indeed detected a new material assumed to be **93** on excitation of **91** at room temperature as well as dry ice temperatures, but details of this study were never reported.

Shortly thereafter the Corey and Eaton groups both reported the detection of *trans*-2-cycloheptenone **95** from irradiation of the *cis* isomer **94** at low temperatures (−160 °C to −195 °C) using either a thin film of **94** or a dilute solution in 95:5 cyclohexane–isopentane[97,98]. The main evidence in support of the structure of **95** was the characteristic low-temperature IR spectrum, featuring C=O absorption at 1715 cm^{-1} (vs. 1664 cm^{-1} for **94**) and other spectral shifts consistent with conversion of **94** to **95**. The new absorption bands persisted if the samples were kept at temperatures below −160 °C. However, if the frozen samples were warmed slowly to −120 °C or higher, the IR absorption bands



(59)

assigned to **95** completely disappeared, and the bands characteristic of **94** reappeared with reduced intensity, superimposed on absorption bands of cycloheptenone dimers (see below). If **94** is irradiated in the presence of CPD or furan, *trans*-fused Diels–Alder adducts **96–99** are formed in good yield (equation 60). The adduct **96** was also obtained on irradiation of **94** in glassy methylcyclohexane at $-190\,^{\circ}C$ followed by treatment in the dark with a cold solution of CPD in pentane, and subsequent warming. These results support the contention that the reactive intermediate produced on irradiation of **94** is indeed a ground-state *trans* cycloheptenone **95** in which conjugation between the C=O and C=C moieties is sharply reduced vis-à-vis the corresponding *cis* isomer **94**.



(60)

The formation of a *trans* cycloheptenone was confirmed using laser flash techniques[99]. Flash photolysis of **94** produced a transient species with λ_{max} 265 nm with a lifetime of 45 s in cyclohexane but much shorter lifetimes in alcoholic solvents (74 ms in EtOH, 33 ms in MeOH). The reduced transient lifetime in alcohol solutions reflects nucleophilic attack by alcohols on **95** (see below), analogous to reaction of alcohols with *trans* cycloalkenes discussed in Section III.A.3. The transient decay in cyclohexane is first order at low excitation energies, but at higher energies corresponding to larger concentrations of the transient the decay is mixed first and second order, which suggests that at least a component of photodimerization (at least at high excitation energies) involves interaction of two *trans* cycloheptenones. In polar and protic solvents, the transient decay is mainly first order, due to reaction with the solvent (see below). From the temperature dependence of the rate of decay of the transient in cyclohexane solution, an activation energy of $15.2 \pm 0.5\,kcal\,mol^{-1}$ and a pre-exponential factor of $2 \times 10^9\,s^{-1}$ were determined by Bonneau and coworkers[99]. The much lower value of the activation energy for thermal isomerization of **95** to **94** determined by Goldfarb[100] was rationalized by Bonneau[99] as a reflection of photoinduced *trans* → *cis* isomerization caused by the analyzing light source. Figure 8 shows the approximate potential surfaces for the ground and excited states of 2-cycloheptenone proposed by Bonneau and coworkers[99].

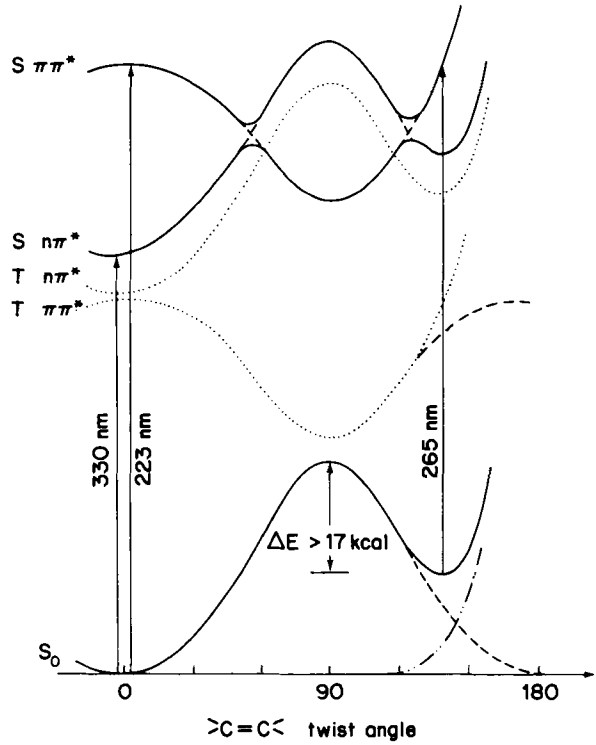


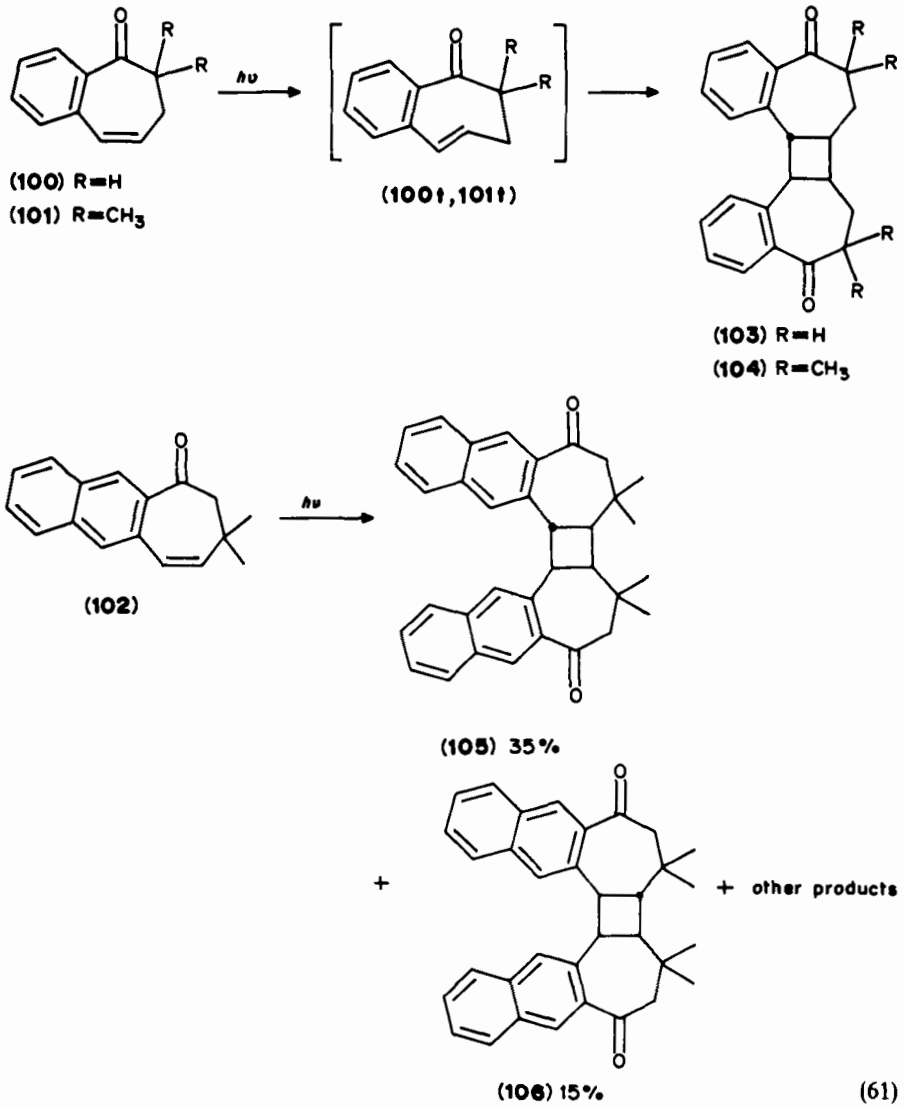
FIGURE 8. Approximate potential surfaces of the ground and excited states of 2-cycloheptenone. Reproduced by permission of Gantier Villars from Ref. 99

By analogy with the mechanism of Z–E photoisomerization of acyclic α,β-enones, it has been assumed that the isomerizations of **86** to **87** and **94** to **95** proceed via triplet excited states. Bonneau[81] observed a very short-lived (11 ns) transient on flash excitation of **94** in cyclohexane at 353 nm, the absorption spectrum of which was similar to that of **95**. The 11 ns transient can be quenched by oxygen but not (at least not efficiently) by piperylene. Bonneau speculates that this species is a highly twisted π,π^* triplet excited state of **94**, represented by the minimum in the $T_{\pi\pi^*}$ potential curve shown in Figure 8, whose very short lifetime can be understood in terms of the small energy difference between the triplet excited state and ground-state potential-energy surfaces at (or close to) a C=C twist angle of 90°[81]. The closer the approach of these two surfaces, the better the coupling of the ground and excited states, resulting in more rapid radiationless decay. The dynamics associated with the surface crossing and considerations of momentum of the molecule as it passes through the 'funnel' on the triplet surface[101] suggest that formation of the ground-state *trans* enone may be facilitated over return to the ground-state *cis* enone.

b. Photodimerization. In all the papers on the photochemistry of cycloheptenone **94** from the earliest until the present, formation of enone dimers has been observed under almost all reaction conditions in a wide variety of solvents. In their 1965 paper on *trans* cycloheptenone, Eaton and Lin[98] indicate that the structures of the dimers were

determined, but the details have never been published. This is of some interest, since dimers could arise from coupling in a head-to-head or head-to-tail fashion of two *trans* enones and/or from one *cis* and one *trans* enone, so that a large number of regio- and stereoisomers are theoretically possible. Bonneau and coworkers' kinetic studies[99] indicate that *trans–trans* coupling may be important under certain conditions, while Caldwell and coworkers[102] find that photodimerization of 1-phenylcyclohexene mainly involves coupling of two *trans* isomers (**2**).

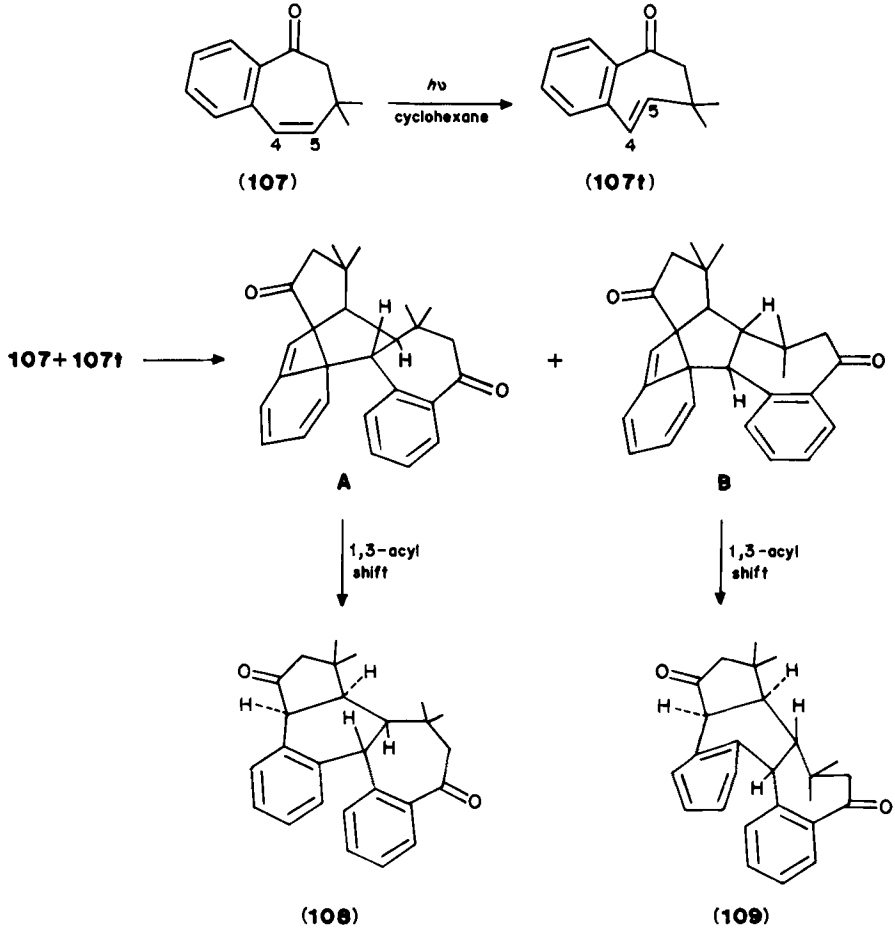
Hart and coworkers have determined that irradiation of benzocycloheptadienones **100** and **101** and the naphtho analog **102** give stereoselectively cyclobutane photodimers **103**, **104**, **105** and **106**, respectively (equation 61)[103]. The observed stereochemistry is consistent



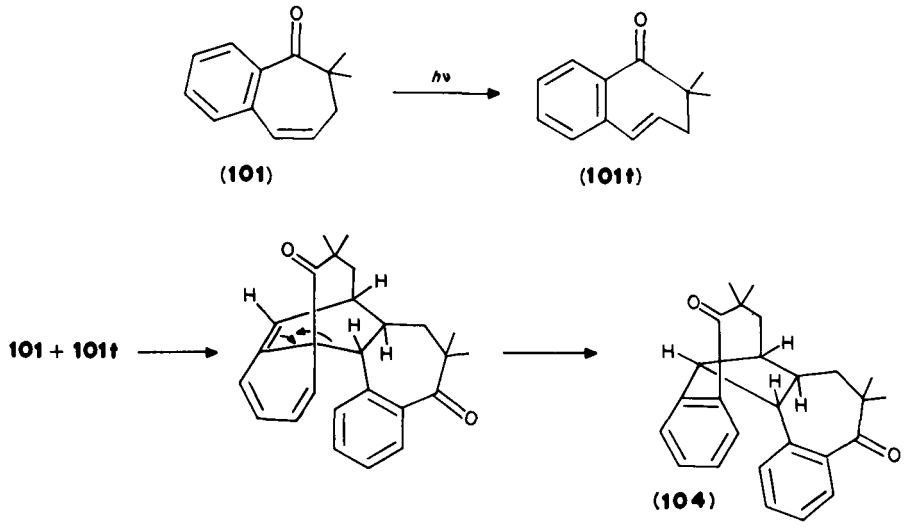
(61)

with concerted ground-state dimerization of two *trans* cycloalkenones in a symmetry-allowed $_{\pi}2_s + _{\pi}2_a$ manner. Support for photogeneration of *trans* cycloalkenones is provided by the formation of *trans*-fused [4 + 2] adducts of these and several other cycloheptadienones upon irradiation in furan. A different mode of photodimerization is seen with **107** which gives **108** and **109**. This reaction course is rationalized as seen in Scheme 15 by addition of the *trans* isomer of **107** (**107 t**) to the styrene moiety of the starting enone, followed by suprafacial 1, 3-acyl shifts to give the isolated products. Hart suggests that even the cyclobutane-type photodimers as in the case of **101** may arise by initial cycloaddition of the *trans* enone (**101t**) to the styryl moiety, followed by a 1, 3-shift (see Scheme 16), in which case it would not be necessary to postulate two completely different reaction mechanisms for photodimerization of structurally similar molecules.

c. Photoaddition of nucleophiles. Noyori and Kato[104] found that irradiation of cycloheptenone **94** in protic solvents (alcohols, acetic acid, aqueous acetonitrile, diethy-

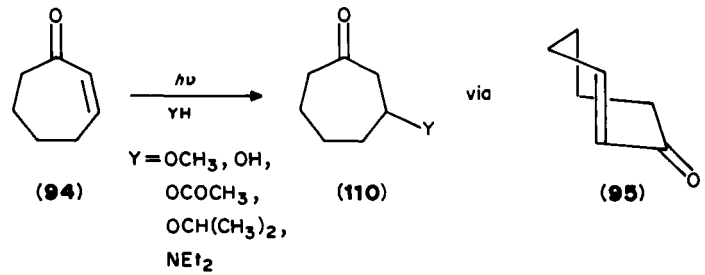


SCHEME 15



SCHEME 16

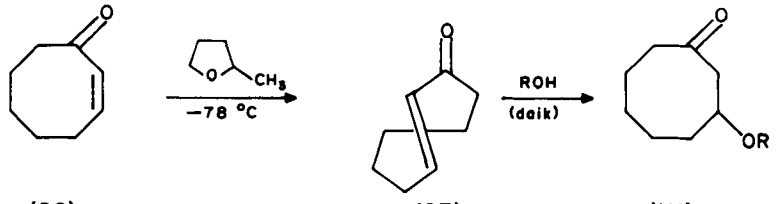
lamine) at room temperature leads to polar-type adducts **110** in which the nucleophilic center becomes attached to the β-carbon of the enone (equation 62). This mode of addition is to be distinguished from the type of reaction seen with cyclopentenone (Scheme 14) which clearly involves free radical intermediates. The yields of adducts **110** on irradiation of a 1% enone solution at room temperature, based on consumed enone, are 55% for diethylamine, 73% for EtOH and 86% for MeOH, making these reactions preparatively useful. Yields are somewhat lower using *i*-PrOH, *t*-BuOH, MeCOOH and H_2O—MeCN; under these conditions the ubiquitous enone dimers are also obtained.



(62)

Analogous transformations were observed using 2-cyclooctenone (**86**). With the suspicion that these reactions might involve *trans* cycloalkenones as reactive intermediates, Noyori and Kato[104] irradiated **86** in 2-methyltetrahydrofuran at −78 °C for 15 min, after which the light source was extinguished, the cold photolysate was poured into an excess of cold MeOH kept at −78 °C, and the mixture was allowed to warm to room temperature in the dark, giving adduct **111a** in 43% yield (equation 63) and 41% recovered **86**. When the same procedure was repeated using *i*-PrOH, the corresponding adduct **111b** was obtained in only 27% yield; however, irradiation of **86** in *i*-PrOH at low temperature followed by treatment with a large excess of MeOH gave almost exclusively **111a** and only

a trace of **111b**, demonstrating that these alcohols are not reacting with an excited state of **86**, but rather with a long-lived reaction intermediate, probably *trans* cyclooctenone **87**.



(**86**) (**87**) (**111**)

(a) R=CH_3

(b) R=$(CH_3)_2CH$

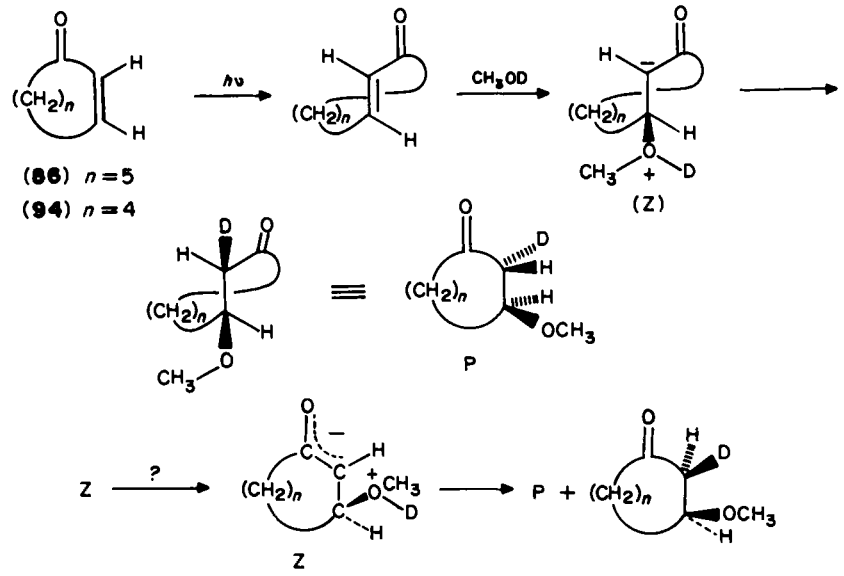
(63)

Not surprisingly, using the same approach it was more difficult to demonstrate the intermediacy of *trans* cycloheptenone **95** in the photoadditions of nucleophiles to *cis* cycloheptenone **94**, due to the much shorter lifetime of **95** vis-à-vis **87**. Thus, irradiation of **94** at −78 °C in liquid nitrogen in EPA (ether–pentane–alcohol glass), addition of cold MeOH in the dark and gradual warming to room temperature gave only enone dimers and no MeOH adducts. Irradiation of **94** at −196 °C in MeOH followed by warming also failed to produce MeOH adducts. However, substitution of diethylamine for methanol in the former experiment led to formation of adduct **110** (Y = NEt_2) in 25% yield; no thermal reaction of **94** and Et_2NH was observed under similar conditions[104].

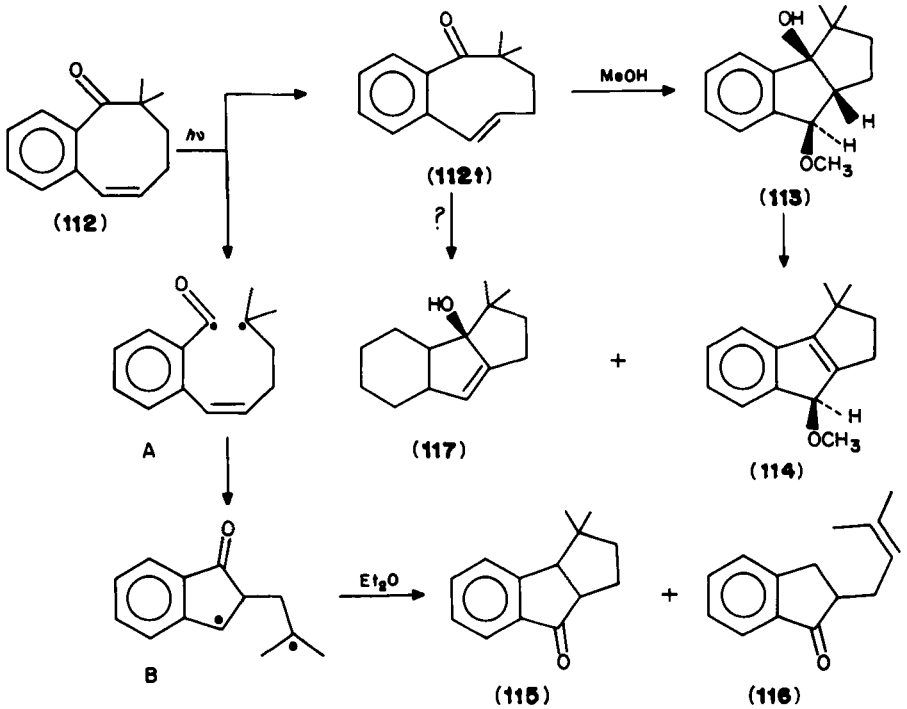
When the ring size is expanded to nine (*cis*-2-cyclononenone), the *trans* enone is stable enough to be isolated and survives treatment with MeOH at 0 °C, although addition occurs when the solution is heated at 100° C. However, neither *cis*- nor *trans*-2-cyclododecenone show any reactivity toward nucleophiles even under these forcing conditions.

Hart and coworkers have determined the stereochemistry of photoinduced addition of methanol to **86**, **94** and a number of fused benzo analogs using CH_3OD[105]. Photoaddition places the methoxy and deuterium stereospecifically *trans*, a reaction course observed with benzo analogs as well. A large deuterium isotope effect is observed in 1:1 MeOH/MeOD, favoring the light solvent by a factor of 4.4 for **94** and 6.0 for **86** at room temperature. Thus, proton transfer is clearly important in the rate-determining step. The results require a regio- as well as stereospecific reaction mechanism involving the respective *trans* cycloalkenones as key reaction intermediates, as shown in Scheme 17. Basically, the authors postulate *syn* addition of MeOH(D) to the ground-state *trans* enone, involving either stepwise addition via the dipolar ion Z or a concerted process in which Z or a similar structure is the transition state. Note that in this highly twisted structure, one face of the twisted C=C bond is completely shielded from attack. Hart considers the possibility that Z might relax conformationally to Z′ to permit charge delocalization prior to protonation, which might be expected to lead to nonstereospecific protonation (or deuteriation). It was determined that base-catalyzed Michael addition to these enones in fact also proceeds in a stereospecifically *trans* manner, presumably via an anion analogous to Z′. Thus, reaction via Z′ cannot be ruled out, although the *syn* addition mechanism of Scheme 17 is clearly very attractive.

A somewhat different course of reaction is taken by benzocyclooctadienones such as **112**[106]. Irradiation in methanol results in transannular reaction to give **113** and its dehydration product **114**. Hart again envisages initial formation of a *trans* isomer of **112** (i.e. **112t**), which then reacts as shown in Scheme 18; the formation of only one



SCHEME 17



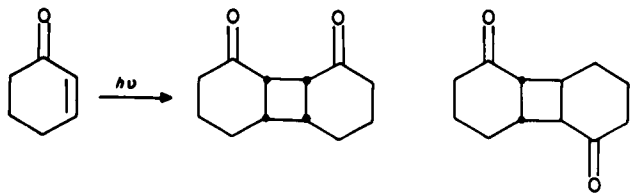
SCHEME 18

stereoisomer suggests that nucleophilic attack and ring closure may be synchronous. Products **115** and **116**, which are also formed along with **117** on irradiation in ether, are attributed to competitive α-cleavage to biradical A, cyclization to B, and formation of **115** and **116** by ring closure and hydrogen transfer, respectively. Product **117** most likely arises by addition of water to *trans*-**112** and dehydration, although the mechanism was not established.

4. 2-Cyclohexenones

The photochemistry of cyclohexenones, particularly substituted systems, is especially rich and complicated compared with the photochemistry of acyclic enones and cyclic enones with larger and smaller rings. Nonetheless, the similarities as well as the differences can often be understood as effects of ring size as opposed to fundamental differences in the electronic structure of the chromophore itself. Extensive recent investigations reveal mechanistic complexity which does not appear to exist in the photochemistry of the α,β-enones previously discussed.

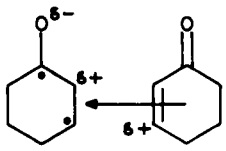
a. Photodimerization. Photodimerization of cyclohexenone itself (**118**) to give the head-to-head (HH) and head-to-tail (HT) dimers **119** and **120** has been known for many years (equation 64)[107]. Most substituted cyclohexenones also undergo this reaction in solution at relatively high concentrations (≥ 0.2 M). Classic sensitization and quenching studies demonstrated that the reaction involves a triplet state of **118** lying *ca* 70 kcal mol^{-1} above the ground state, which was concluded to be the lowest-energy triplet state of the enone[79,107]. The configuration of the triplet was assigned as $^3\pi,\pi^*$ by analogy to photodimerizations of alkenes (see above), on the basis of calculations by Zimmerman and coworkers of differences in electron densities on the C=C bond in n,π^* vis-à-vis π,π^* triplets[108], and the likelihood that twisting around the C=C bond would lower the energy of the π,π^* vs. the n,π^* triplet. Particularly in polar solvents, it was proposed that the energetic separation of the two states would be at least a few kcal mol^{-1}, although the gap was expected to narrow in nonpolar solvents where reactions via the n,π^* triplet might be expected (see below)[79]. From Wagner and Bucheck's studies of the kinetics of photo-dimerization of **118** in acetonitrile, assuming diffusion-controlled triplet quenching by 1,3-pentadiene (piperylene) and 1,3-cyclohexadiene, the triplet lifetime of **118** at infinite dilution was concluded to be *ca* 2 ns, and the rate constant for capture of ^{3}CH* by ground-state CH (CH = cyclohexenone) was found to be 1.1×10^8 l mol^{-1} s^{-1} [79].



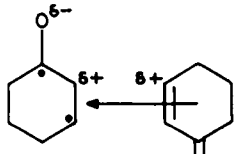
(**118**) (**119**) (**120**) (64)

As in the case of photodimerization of cyclopentenone, there is an effect of solvent polarity on the ratio of dimers **119** and **120**. The lack of regiospecificity led Wagner and Bucheck[79] to reject the idea of an intermediate charge transfer complex, since complex **121** ought to be more stable than **122**, leading to the prediction that formation of HH dimers should be favored substantially over HT dimers, contrary to the facts. They conclude that intermediate π complexes or charge-transfer complexes, with differing dipole moments, probably precede the triplet 1,4-biradicals which are direct precursors of the products.

The quantum yields (0.20 at 1 M CH in acetonitrile) indicate that significant percentages of these biradicals fragment to regenerate ground-state enone[79].

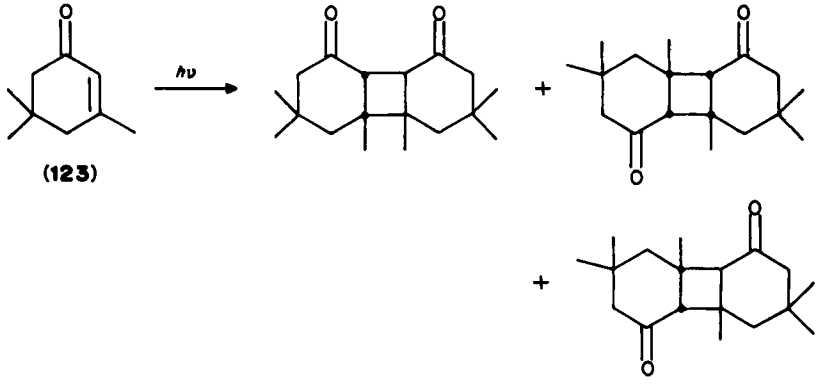


(121)



(122)

As mentioned above, photodimerization of cyclohexenones is quite general. Isophorone **123** yields three photodimers (equation 65), and once again the ratio of the HH dimer to the two stereoisomeric HT dimers varies as a function of solvent polarity[109]. Mechanistic

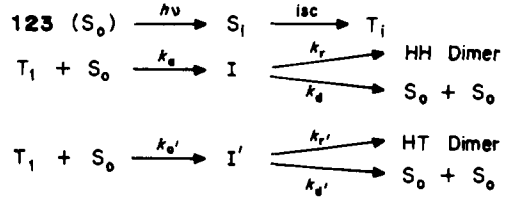


(123)

(65)

complexities are suggested by the following observations of Chapman and coworkers: (a) plots of $(\phi_{dim})^{-1}$ vs. [isophorone]$^{-1}$ in acetic acid give straight lines with significantly different slopes and intercepts for HH and HT dimerization; (b) identical linear Stern–Volmer plots for quenching of both modes of dimerization by isoprene or ferric acetylacetonate are obtained, but differential quenching is observed using di-*t*-butyl nitroxide; (c) the ratio of HH vs. HT dimerization is different on benzophenone sensitization (benzophenone absorbed *ca* 32% of the incident light) than on direct irradiation of **123**. The last observation in particular led Chapman to propose that two different triplet states of **123** are responsible for HH vs. HT photodimerization; if only one triplet were involved, the reaction course ought to be the same on direct or triplet-sensitized excitation, unless there was some anomaly associated with benzophenone photosensitization. The latter might be a possibility if the triplet excitation energy of benzophenone ($E_T = 68.5$ kcal mol^{-1}) were less than that of **123**. As indicated above, Wagner concluded that for CH itself E_T is probably > 70 kcal mol^{-1} [79], so that triplet energy transfer from benzophenone to **123** might be uphill, which could introduce other mechanisms for sensitization (e.g. Schenck-type processes as discussed earlier). In other studies of cyclohexenones to be described below, higher-energy triplet sensitizers were used and product ratios were the same as on direct enone excitation. Results (a) and (b) above are compatible with a single triplet precursor for both HH and HT dimers assuming the kinetic scheme given in Scheme 19[109]. The key point is that distinctly different double

reciprocal plots of quantum yield vs. enone concentration, as in (a) above, will be observed if there are distinctly different rate constants k_a and k_a' for formation of metastable intermediates (whether they be π complexes or biradicals) en route to HH and HT dimers, and different factors ϕ_p and ϕ_p' for the fractions of these adducts which proceed on to dimers in competition with reversion to enone ground states. If HH and HT dimers arose from a common enone triplet, triplet quenching should alter the yield but not the ratio of the dimers, as indeed seen in (b)[109].

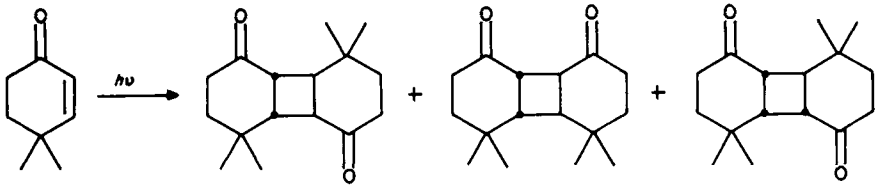


$$\phi_p = \frac{k_r}{k_r + k_d}$$

$$\phi_p' = \frac{k_r'}{k_r' + k_d'}$$

SCHEME 19

Photodimerization of 4,4-dimethylcyclohex-2-en-1-one **124** has been studied by Nuñez and Schuster[110]. Three dimers are formed upon irradiation of neat enone, two of which were formed in sufficient quantity to allow structure determination as the HH dimer **125** and the HT dimer **126**; the third (trace) dimer appeared to isomerize to **126** upon prolonged standing at room temperature and was therefore tentatively assigned structure **127** (equation 66). As with isophorone (**123**), plots of ϕ_{HH}^{-1} and ϕ_{HT}^{-1} vs. [enone]$^{-1}$ were



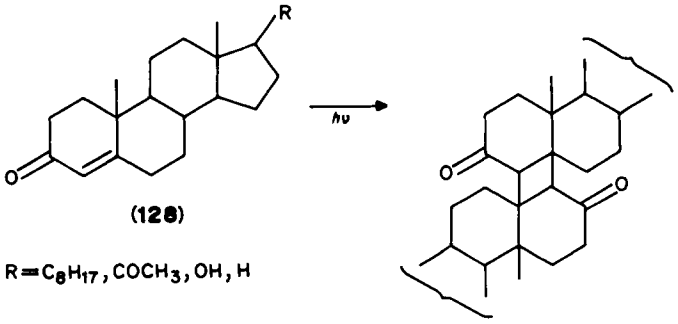
(124) **(126)** **(125)** **(127)**

(66)

linear but with distinctly different slopes and intercepts, consistent with Scheme 19 but also compatible with dimerization via two different triplets. Photosensitized excitation of **124** in 2-propanol was carried out using *p*-methoxyacetophenone (MAP), not only because of its relatively high triplet energy (71.7 kcal mol^{-1}) but also since photoreduction of MAP in 2-propanol is very inefficient, ϕ_{isc} is high and self-quenching is unimportant. It was found that the yields of all the photoproducts of **124** (concentration 0.5 M) including dimers **125** and **126** were the same as on direct excitation under the same conditions. Tucker[111] later found that formation of the two dimers **125** and **126** from **124** in 2-propanol was quenched to the same extent by 1-methylnaphthalene (E_T = 60 kcal mol^{-1}), indicating they indeed arise from a common triplet. On the other hand, Nuñez[110] found

that the ratio of **126** to **125** changed as a function of enone concentration in 2-propanol, from 6.4 at 0.10 M to 2.1 at 1.5 M, which could be considered as evidence for their formation from two different triplets. However, CH shows the same behavior in benzene but not in acetonitrile, which was attributed by Hammond and coworkers[107] to changes in the polarity of the medium as a result of increasing enone concentration. It is concluded that the same explanation holds for **124** in 2-propanol[110]; analogous experiments in other solvents were not undertaken.

Even steroidal enones undergo photodimerization, as shown with compounds **128** and **129** in equation 67[112]. A very important example involves photodimerization of thymine **130**, which is technically an enone in its principal tautomeric form. One of the most important reactions which occurs on exposure of DNA to UV light is formation of a dimeric structure between neighboring thymine residues[113]. Although other pyrimidine bases undergo photodimerization, they tend to preferentially undergo photohydration, which is a relatively unimportant reaction for thymine. In frozen solution, thymine reacts on exposure to 254 nm excitation to give exclusively the *cis–syn–cis* dimer **131** (equation 68), which is also the mode of photodimerization in DNA[114]. Using photosensitizers, the other regio- and stereoisomeric *cis*-fused thymine dimers are formed[115]. The dimers can be split by shorter wavelength excitation or by a natural photoreactivating enzyme which serves in nature to repair radiation-damaged DNA. Details of the nature and mechanism of operation of this enzyme can be found in photobiology texts[116].

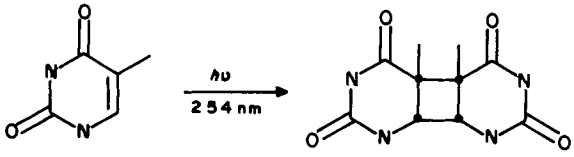


(128)

$R = C_8H_{17}, COCH_3, OH, H$

(129)

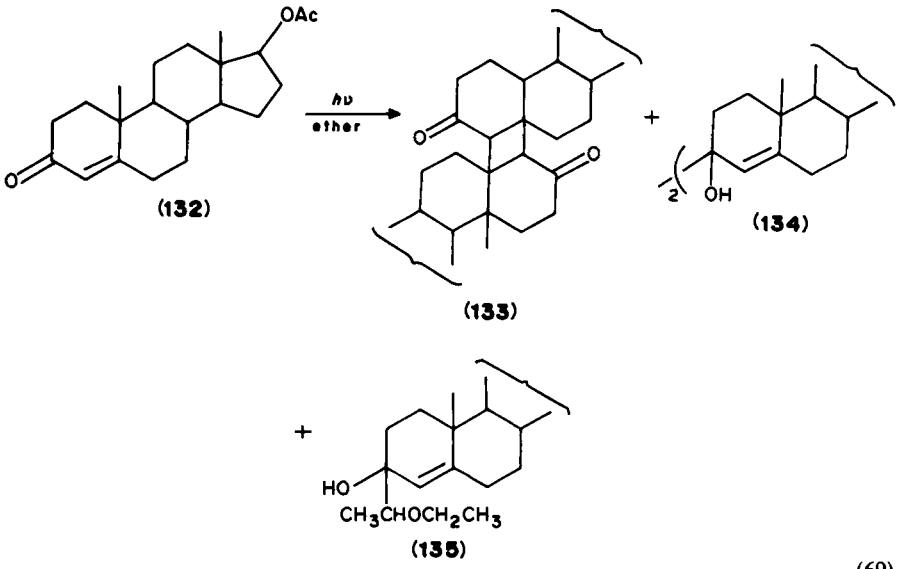
(67)



(130) (131)

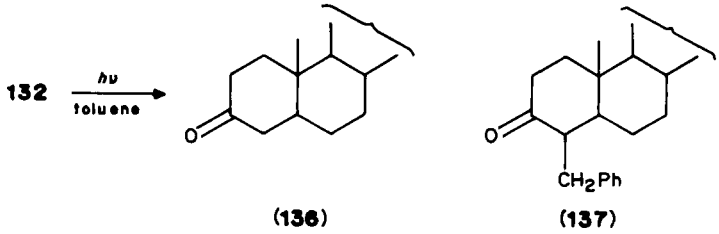
(68)

b. Photoreduction. Photoreduction of enones could involve in principle either the n,π^* or π,π^* triplet states, and in fact both states have been invoked to rationalize the course of reactions of these systems. Irradiation of testosterone acetate **132** in ether gives 2% of cyclobutane dimer **133**, 30% of pinacol **134** and 15% of a mixture of diastereomeric adducts **135** (equation 69)[117]. The latter two products are clearly attributable to initial hydrogen abstraction from the solvent by the oxygen atom of a triplet n,π^* state of the enone. Irradiation of **132** in toluene gives the saturated ketone **136** and the toluene adduct **137**



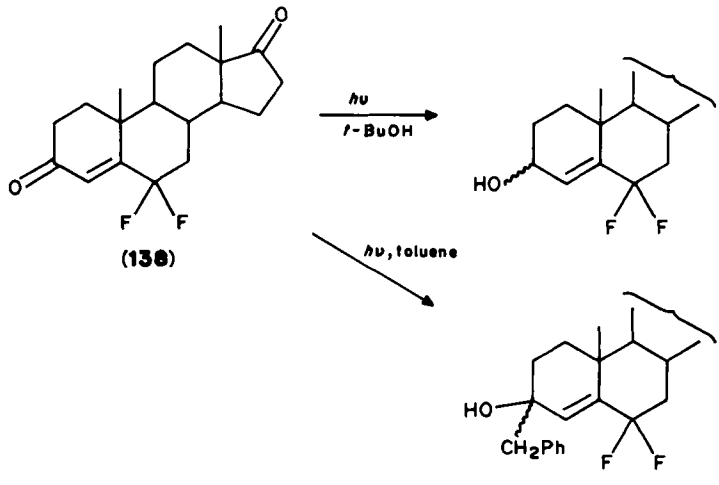
(69)

with an α-benzyl group (equation 70)[118]. In ethanol, **136** was again formed in 20% yield in addition to rearrangement products to be discussed later. Thus, in these solvents the course of photoreduction seems to be most readily rationalized in terms of reaction via $^3\pi,\pi^*$ states. In contrast, as shown in equation 71, the difluoro-substituted steroid enone **138** undergoes reduction to an allylic alcohol in *t*-BuOH (a solvent in which photoreduction is rarely observed) and to a carbonyl adduct in toluene, again implicating an n,π^* triplet[119]. Since γ-fluorine substitution in cyclohexenones has been found to stabilize the n,π^* vis-à-vis the π,π^* triplet[120], this result is not very surprising.

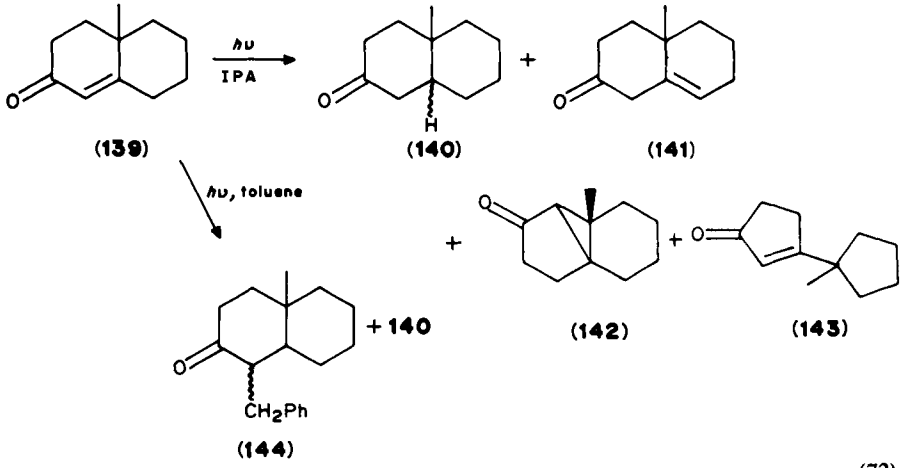


(70)

The octalone **139** upon irradiation in 2-propanol (IPA) was reported[121] to give the saturated ketone **140** (31%), the deconjugated ketone **141** and rearrangement products **142** and **143** to be discussed later (equation 72); no dimers or products of reduction of the C=O group were reported. On irradiation of **139** in toluene, the main products were again **140** and the α-adduct **144** (equation 72). Later studies by Chan and Schuster[122] showed that the original assignment of stereochemistry to the ring junction in **140** was incorrect, as the rings are *cis*- and not *trans*-fused, which has mechanistic implications that will be clear shortly. Photoreduction of the C=C and not the C=O bond of isophorone **123** to give **145** was reported to take place in nonpolar solvents such as cyclohexane, but photoreduction did not compete with photodimerization in 2-propanol at the enone concentrations utilized[109]. These reactions of **123** and **139** fit the pattern of reactivity

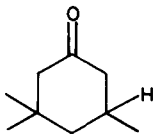


(71)



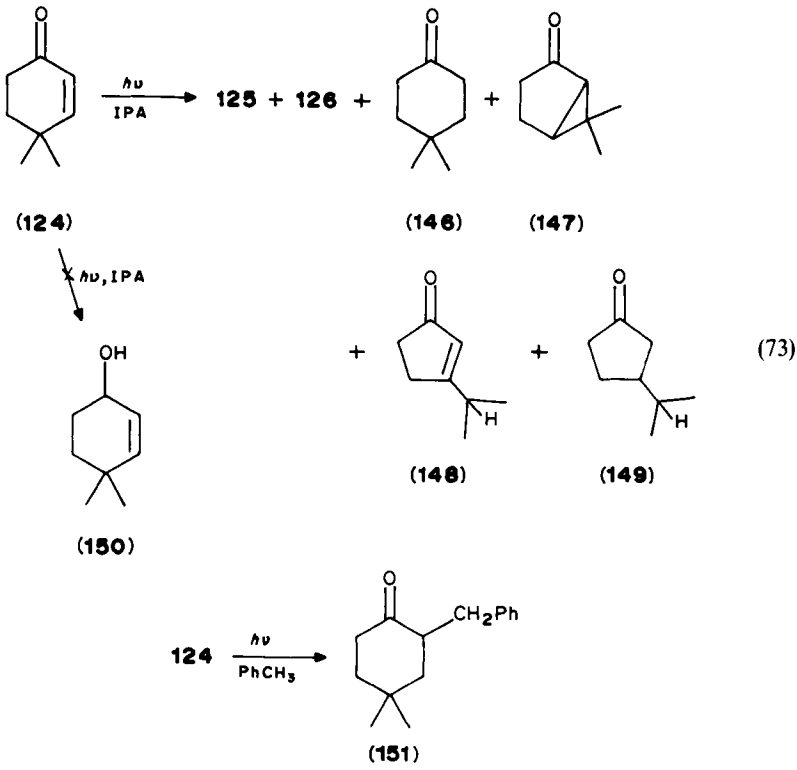
(72)

expected of a $^3\pi,\pi^*$ state in which initial hydrogen abstraction occurs at the β-carbon of the enone, followed by abstraction of a second hydrogen or combination (as in toluene) with solvent-derived radicals.



(145)

A detailed study of photoreduction of enone **124** in IPA was undertaken by Nuñez and Schuster[110]. Irradiation of a 0.3 M solution gave the saturated ketone **146** (16%), dimers **126** (12%) and **125** (2%), the rearrangement products **147** (36%) and **148** (34%), and traces of 3-isopropylcyclopentan-1-one (**149**) (equation 73). The yields were the same in two runs

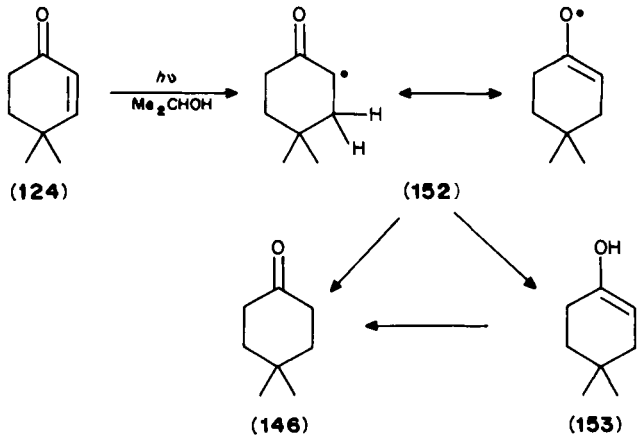


(73)

corresponding to 16% and 29% conversion of **124**, and the mass balance under these conditions is excellent, indicating that the formation of other products (such as pinacols and solvent adducts) is unimportant under these conditions. The allylic alcohol **150** was independently prepared and shown not to be present in the above photolysis mixture. Irradiations were carried out in IPA-*O*-d, IPA-d_8 and $(CD)_3)_2CHOH$ in the hope of determining the site on the enone of initial H (or D) abstraction from IPA[123]. Neither the starting enone **124** nor the reduction product **147** underwent H–D exchange in these media after 24 h in the dark; a slight reduction in the NMR signal of the α-protons in **146** was detected after the solution was kept for 96 h in the dark. Using IPA-*O*-d as the solvent, significant D-incorporation into **146** was observed after 24 h irradiation (using mass spectroscopic analysis), but there was no significant incorporation of deuterium into the rearrangement products. Base treatment of the photolysate led to *ca* 50% loss of deuterium in labeled **147**, indicating that the principal (if not exclusive) site of labeling was at C-2. When irradiation of **124** was carried out in $(CD_3)_2CHOH$, there was no significant incorporation of deuterium into any of the products, indicating that hydrogen transfer from methyl groups in the solvent-derived radical $(CH(D)_3)_2COH$ to starting enone or radical intermediates (e.g. as occurs with benzophenone; see above) is unimportant. The

yield of **146** when **124** was irradiated in IPA-d_8 was sharply reduced compared to the yield in unlabeled IPA, to the point where insufficient quantities of product could be isolated to determine the site of deuterium incorporation. The kinetic isotope effect $k_r(H)/k_r(D)$ was determined to be 9.6 ± 0.8 based upon the yields of **146** produced by simultaneous irradiation of **124** (0.3 M) in *t*-BuOH solutions containing an equal amount of IPA or IPA-d_8; the yield of the photorearrangement product **147** was the same in the two solutions[110,123]. Finally, irradiation of **124** in toluene gives the reduction product **146** and the α-benzyl adduct **151**, identified by comparison of chromatographic and spectral properties with a sample synthesized independently[110].

The mechanism shown in Scheme 20 accounts for all the experimental observations[123]. Thus, photoreduction of **124** is initiated by hydrogen abstraction at the β-carbon of an enone $^3\pi,\pi^*$ state, as is the case with most (but not all) of the cyclohexenones previously discussed, as well as cyclopentenones (see above). The enoxyl radical **152** can abstract a second hydrogen from the solvent (*not* from the solvent-derived radical) to give either **146** directly or the enol **153**. Deuterium incorporation from IPA-*O*-d takes place upon ketonization of **153**, suggesting that most of **146** is formed via the enol. The very large kinetic isotope effect (KIE) indicates that hydrogen transfer is well developed at the transition state for hydrogen abstraction, consistent with a symmetric C—H—C transition state; hydrogen transfer from C to O is characterized by a much smaller KIE, indicating an early transition state in which the extent of formation of the O—H bond is much less. The effect of temperature (43–71 °C) on photoreduction vis-à-vis photorearrangement of **124** was measured in IPA, from which a rough estimate of E_{act} for hydrogen abstraction of 5.2 ± 0.3 kcal mol^{-1} could be obtained; there was virtually no effect of temperature on the yields (relative quantum efficiencies) of the photorearrangement products **147** and **148**[110]. This value for E_{act} is also consistent with hydrogen abstraction by a π,π^* triplet excited state[124].

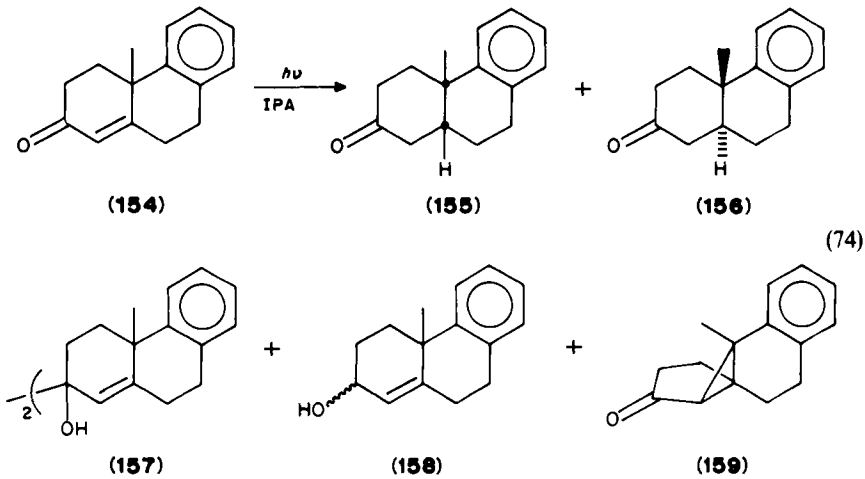


SCHEME 20

The quantum yield for photoreduction of **124** by IPA is, as expected, linearly proportional to the concentration of IPA using *t*-BuOH as the cosolvent[110]; the limiting value for ϕ_{red} in neat IPA is only 0.0037[125]. The slope of the plot, $2.8 \pm 0.4 \times 10^{-4}$ l mol^{-1}, is equal to $\phi_{isc} k_r \tau_T$, where k_r is the rate constant for hydrogen abstraction and τ_T is the enone triplet lifetime in the absence of IPA. Sensitization experiments indicate that intersystem

crossing for **124** is totally efficient (i.e. $\phi_{isc} \sim 1.0$). Stern–Volmer plots for quenching of formation of **124** by naphthalene in neat IPA are linear, with slopes ranging from 11.6–14.9 l mol^{-1} corresponding to an enone triplet lifetime of *ca* 2.6 ns in neat IPA, assuming triplet energy transfer is diffusion-controlled with $k_g = 5 \times 10^9$ l mol^{-1} s^{-1} [110]. Using this value for τ_T, the quantum yield data give a value for k_r of 1.0×10^5 l mol^{-1} s^{-1}. Problems associated with direct determination using laser flash techniques of the lifetime of the triplet state of **124** responsible for photoreduction will be discussed later.

The photochemistry of 4a-methyl-4, 4a, 9, 10-tetrahydro-2(3*H*)-phenanthrone **154** provides a clear example of simultaneous reaction via both ^{3}n, π^* and $^3\pi, \pi^*$ triplet states. As shown by Chan and Schuster[122], irradiation of **154** in IPA gives the five products shown in equation 74: the *cis*- and *trans*-fused reduced ketones **155** and **156**, pinacol **157**, allylic alcohol **158** and the rearranged ketone (lumiketone) **159**. Quenching by napthalene shows



(154) (155) (156) (74)

(157) (158) (159)

that these products fall into two distinct groups according to the Stern–Volmer plot in Figure 9: **155** and **159** on the one hand, and **156**, **157** and **158** on the other. The data clearly demonstrate that these products arise from two different triplet states of **154** which are quenched differentially by naphthalene. The nature of the products clearly indicates that the latter group arises from an n, π^* triplet, while the former group arises from a π, π^* triplet. The most interesting point is that each of the stereoisomeric dihydroketones **155** and **156** is produced stereospecifically from a different enone triplet, and do not arise from a common triplet precursor by a stereorandom reaction. The selective formation of the *cis* dihydroketone **155** from the same triplet responsible for photorearrangement (see below) is consistent with the proposal that the geometry of the π, π^* triplet is twisted to the point that the hydrogen donor is able to approach the β-carbon only from the same side of the molecule as the angular methyl (see Scheme 21)[122]. In contrast, a more or less planar n, π^* state should undergo hydrogen abstraction on oxygen to give the ketyl radical **160**, which is the precursor for **156**, **157** and **158** (Scheme 21). The stereoselective formation of **156** can be rationalized if the hydrogen donor approaches the planar ketyl radical **160** exclusively on the least-hindered face of the molecule, i.e. opposite to the angular methyl group. On this basis, it seemed surprising that photoreduction of octalone **139** via a twisted $^3\pi, \pi^*$ state should give a *trans*-fused dihydroketone **140**[121]. Restudy of this reaction showed that the structure of the dihydroketone was originally misassigned and that, as predicted, it is actually the *cis*-fused ketone **161**. Mechanistically, this supports the proposal that in

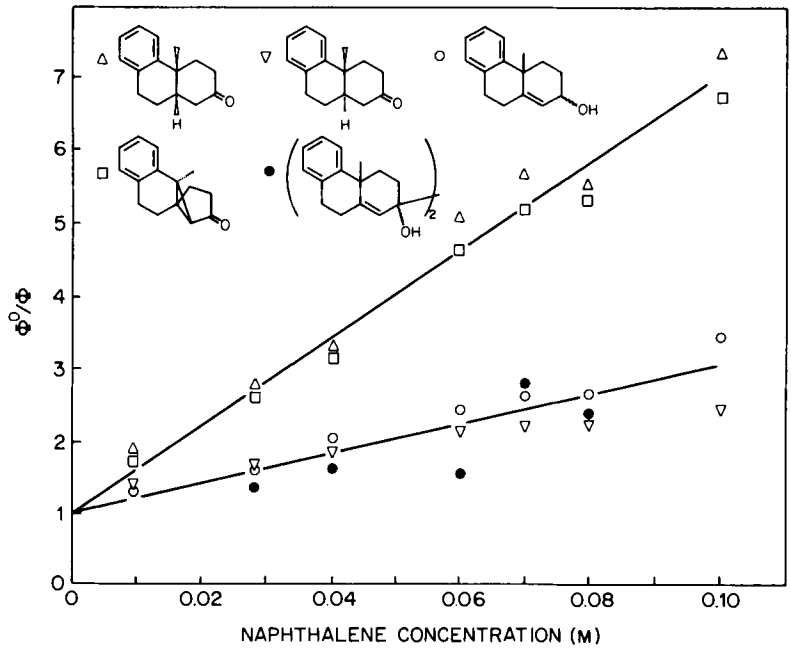
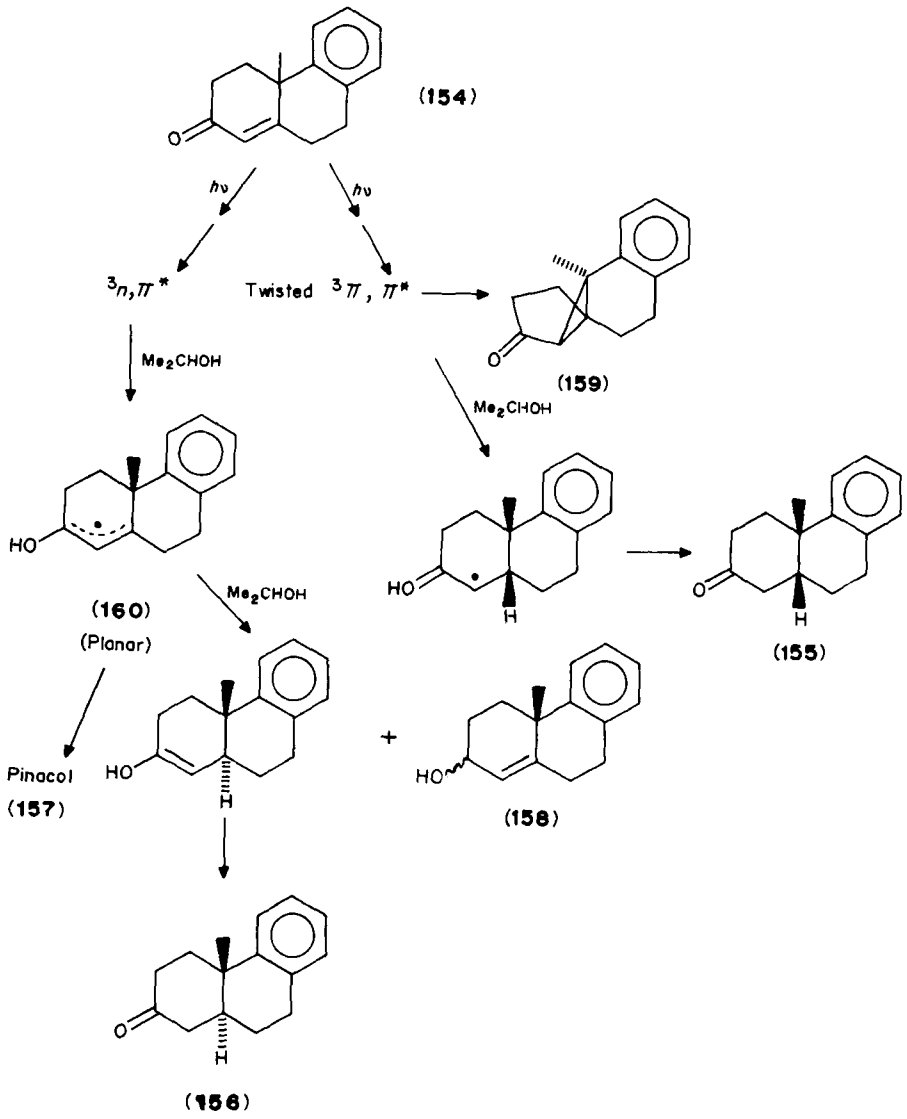


FIGURE 9. Stern–Volmer plots for naphthalene quenching of the photochemistry of 4a-methyl-4, 4a, 9, 10-tetrahydro-2(3H)-phenanthrone **154** in isopropyl alcohol[122]. Reprinted with permission from *J. Am. Chem. Soc.*, **108**, 4561 (1986). Copyright (1986) American Chemical Society

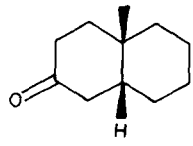
sufficiently flexible cyclohexenones, including compound **139**, the lowest π,π^* triplet assumes a twisted conformation whose geometry controls the course of both photoreduction and photorearrangement processes.

c. Photorearrangements of cyclohexenones. (i) General considerations. The molecular rearrangements of 4, 4-disubstituted cyclohexenones have been the subject of great deal of attention for almost thirty years, and several reviews on this subject have appeared[109b,126–129], including one by the present author in 1980[5]. The subject has also been well covered in basic texts on organic photochemistry[1–4]. This article will attempt to briefly summarize the basic features of these classic photorearrangements, and then to indicate the important contributions in this area made in the last several years.

4, 4-Dialkylcyclohex-2-en-1-ones undergo unimolecular photorearrangement to bicyclo[3.1.0]hexan-2-ones (so-called lumiketones) usually accompanied by ring contraction to 3-substituted cyclopent-2-en-1-ones, upon irradiation in a variety of polar and nonpolar solvents. These transformations are illustrated by the photorearrangements of 4, 4-dimethylcyclohexenone **124** and testosterone acetate **132**, two of the first systems investigated, shown in equations 75 and 76[130,131]. As indicated earlier, these reactions are competitive with photodimerization and photoreduction of the enones, depending on the enone concentration and the nature of the solvent. Formation of deconjugated ketones also occurs in some systems, such as octalone **139** (see equation 72)[121]. As will be seen later, this competition between photochemical pathways can be put to advantage in mechanistic studies. Chemical yields of lumiketone are usually optimal in polar solvents such as *t*-BuOH in which photoreduction and deconjugation are minimized. In acetic acid, enone

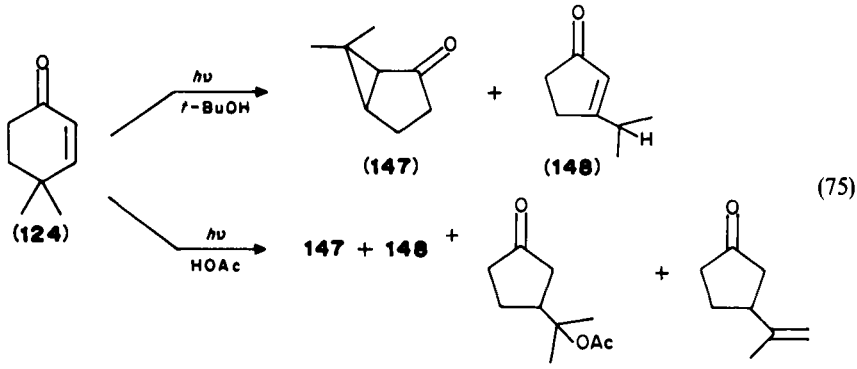


SCHEME 21



(161)

124 gives high yields of a ketoacetate, which may or may not be a primary photoproduct[131]. Quantum efficiencies for these photorearrangements on direct or triplet-sensitized excitation are generally very small, $\leqslant 0.01$[5]. Possible explanations will be discussed later.



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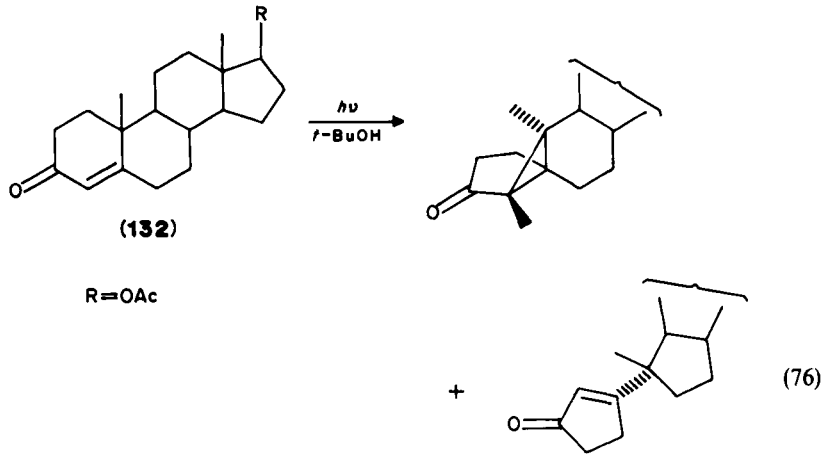
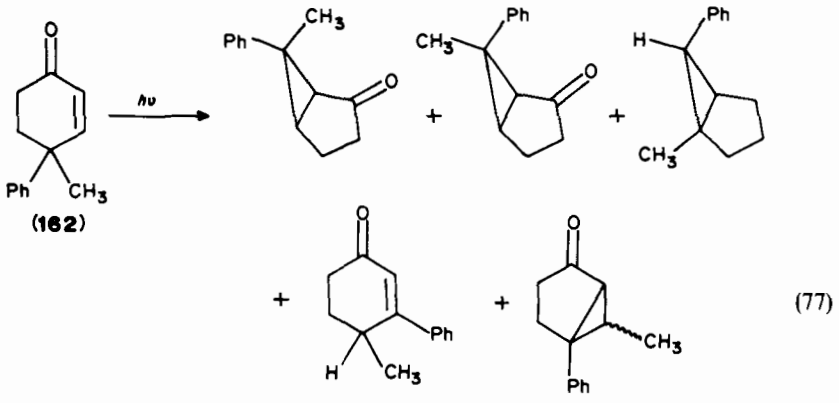


(76)

From a survey of the photochemical behavior of a large number of cyclohexenones, Dauben and coworkers[132] concluded that a necessary condition for the cyclohexenone–lumiketone photorearrangement was the presence of two substituents at C-4, at least one of which must be alkyl. With 4-alkyl-4-arylcyclohexenones such as **162**, the lumiketone rearrangement competes with phenyl migration, as shown in equation 77, with the former more prominent in more polar protic and aprotic solvents (such as MeCN, DMF, 30% MeOH) while phenyl migration products are the exclusive products in benzene and ether[133]. 4,4-Diarylcyclohexenones such as **163** give only products of phenyl migration on direct or sensitized excitation, as seen in equation 78[134]. Irradiation of 4-alkyl-4-vinylcyclohexenones such as **164** leads to vinyl migration (see equation 79)[135,136]. These reactions are structurally analogous to the well-known di-π-methane photorearrangements[137].

Although they are related, it is useful to separate discussions of the two types of rearrangements of cyclohexenones, the lumiketone photorearrangement (also known as the Type A rearrangement)[126] and the 1,2-aryl and 1,2-vinyl migrations.



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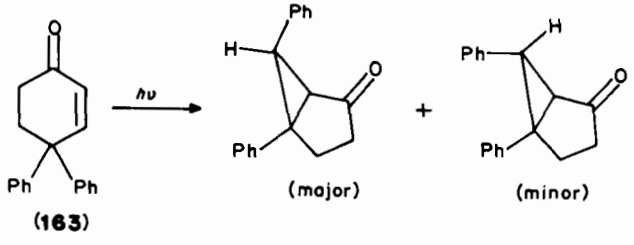

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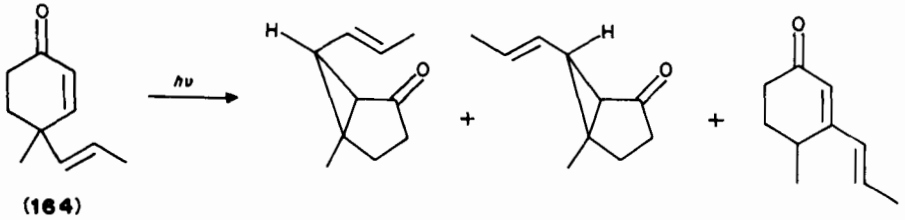
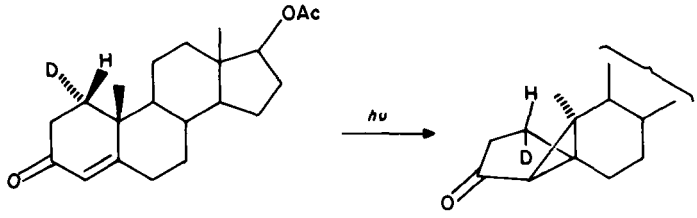


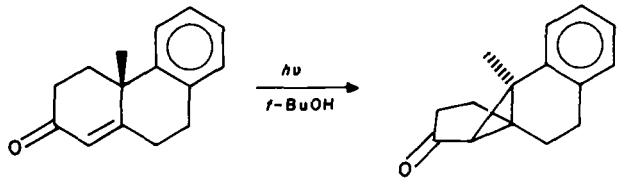
(79)

(ii) Stereochemistry and mechanism of the lumiketone photorearrangement. Several key studies have served to define the stereochemistry associated with the rearrangement of cyclohexenones to bicyclo[3.1.0]hexanones (lumiketones). First, Jeger and coworkers established that the stereochemistry of the rearrangement products of testosterone is as shown in equation 76 with H in place of OAc, and that other possible diastereomeric products are not formed[138]. Secondly, Schaffner and coworkers demonstrated that 1α-deuteriotestosterone acetate **165** rearranged stereospecifically to **166** with retention of configuration at C-1 and inversion of configuration at C-10 (analogous respectively to C-5 and C-4 of a simple cyclohexenone), as shown in equation 80[118]. Chapman and coworkers demonstrated that photorearrangement of optically active phenanthrone **154** to its lumiketone **159** proceeded stereospecifically (equation 81) with inversion of configuration at C-10 and loss of less than 5% optical purity (enantiomeric excess)[139]. These results were interpreted in terms of a more or less concerted bond-switching process as opposed to

rearrangement via biradical intermediates that could result in loss of stereochemical integrity.

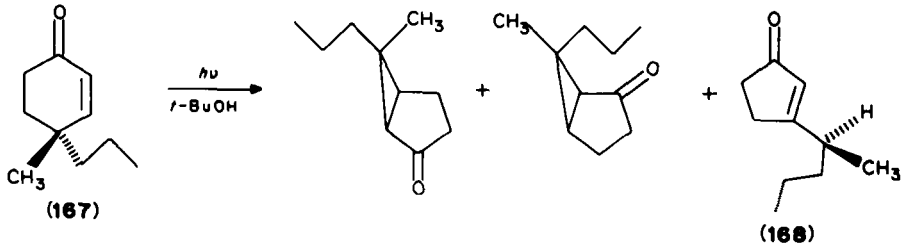


(165) (166) (80)

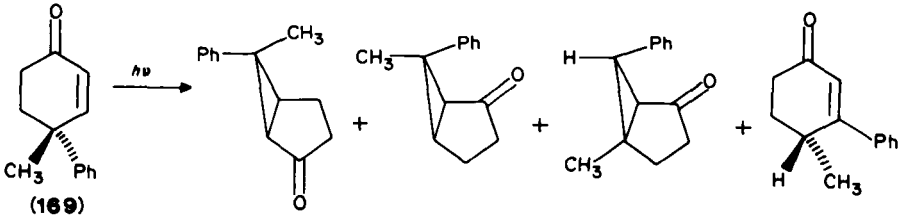


(154) (159) (81)

The possibility that the fused ring systems of the above cyclohexenones might obscure the 'true' stereochemistry of the photorearrangement was addressed by Schuster and coworkers in their studies of simple chiral cyclohexenones, *R*-(+)-4-methyl-4-propylcyclohexenone **167** and *R*-(+)-4-methyl-4-phenylcyclohexenone **169**[140]. The photoproducts with their stereochemical assignments are shown in equations 82 and 83, respectively, with the latter including products of phenyl migration. In both systems, it was found that there was no loss in optical purity in formation of the



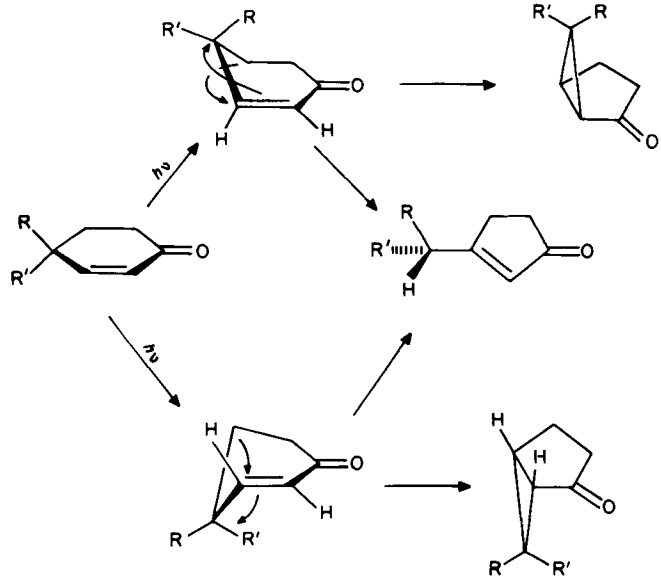
(167) (168) (82)



(169) (83)

lumiketones nor in the recovered enones, even after 325 h continuous irradiation in the case of **167**. These data, coupled with those above, establish with certainty that cleavage of the bond between C-4 and C-5 in cyclohexenones must be concerted with formation of the new bond between C-5 and C-3. In other words, no triplet diradical intermediate which is sufficiently long-lived to allow stereorandomization at either radical site as a result of rotations around C—C single bonds can intervene in formation of lumiketone as well as reversion to starting material (recall that quantum efficiencies for photorearrangement are notoriously small). Furthermore, reactions proceed stereospecifically with inversion of absolute configuration at C-4 (C-10 in steroids)[140].

The stereochemical course of reaction in simple cyclohexenones is summarized in Scheme 22. The reaction is stereospecific on each face of the cyclohexenone ring system, with retention of absolute configuration at C-5 and inversion at C-4, leading to formation of diastereomeric lumiketones (with respect to *exo–endo* configuration of the substituents) in which the bicyclo[3.1.0]hexanone ring systems have opposite chirality. Thus, despite the fact that it originates from an enone triplet state (see discussion below), the cyclohexenone–lumiketone photorearrangement has the appearance of a concerted reaction, with a stereochemical course corresponding to a $_{\pi}2_a + _{\sigma}2_a$ process, in Woodward–Hoffmann terminology[141], involving antarafacial addition to both the C_2—C_3 π bond and the C_4—C_5 σ bond. In steroids and analogous fused-ring enones, such as **132** and **154**, reaction can occur only on one face of the enone because of steric constraints, necessarily affording only a single lumiketone.

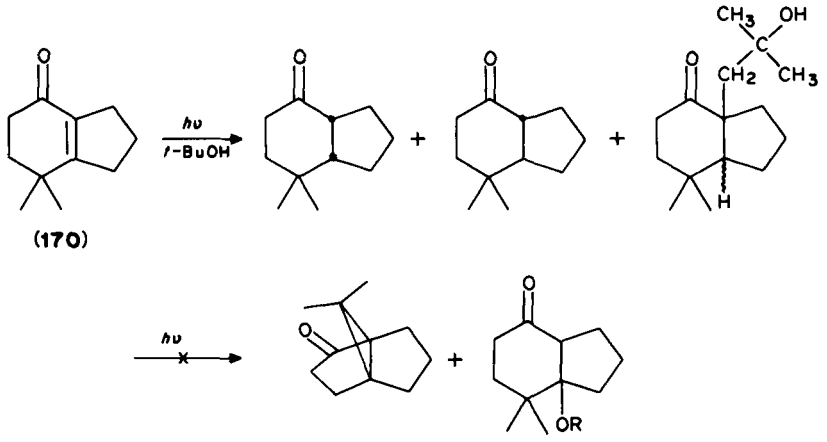


SCHEME 22

The potential inconsistency of a symmetry-allowed process proceeding from a triplet-excited state in which electrons are unpaired has been addressed by Shaik[142], who concludes that in certain situations spin inversion and product formation may occur concomitantly. This is possible when both spin inversion and orbital symmetry

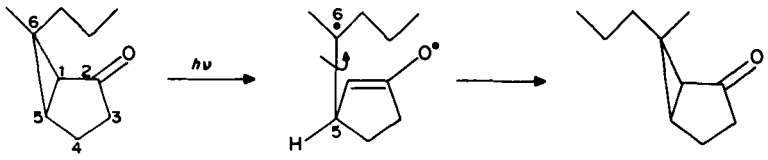
requirements are met along the same reaction coordinate, which is precisely the case with the twisting motion required in order in achieve the geometry corresponding to a concerted ${}_{\pi}2_a + {}_{\sigma}2_a$ intramolecular cycloaddition, as discussed above. Shaik raises the interesting possibility that such a process might be triplet sublevel specific, i.e. that the x, y and z sublevels of the triplet state might react with differing efficiencies. No studies along these lines have been reported.

It is clear from Scheme 22 that the reactive triplet-excited state of the enone (see below) must undergo substantial twisting around the C=C bond in order for the bond-switching process corresponding to a ${}_{\pi}2_a + {}_{\sigma}2_a$ cycloaddition to occur as shown. It was predicted that structurally analogous cyclohexenones whose structures preclude significant twisting around the C=C bond would not undergo the lumiketone photorearrangement[140]. This was verified by Schuster and Hussain[143] with enone **170** which undergoes photoreduction and radical-type solvent photoaddition, but neither rearrangement nor polar-type addition reactions (equation 84).



(84)

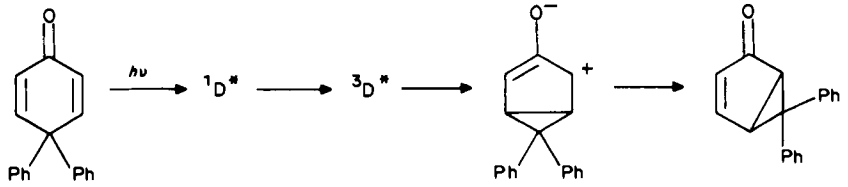
An additional point is that photoexcitation of one of the lumiketones **171** from optically active enone **167** causes isomerization to its diastereomer **172** by a process that must involve cleavage of the exocyclic C_1—C_6 cyclopropane bond, rotation around C_5—C_6 in biradical **173**, and ring closure on the opposite face of the trigonal center at C_6 to give **172** (see equation 85)[140]. Since photoexcitation of **167** stereospecifically afforded the enantiomer of the product obtained upon excitation of $R-(+)-$ **167** (see equation 82), intermediate **173** is necessarily excluded from the pathway leading to lumiketones from cyclohexenone **167** and related systems.



(85)

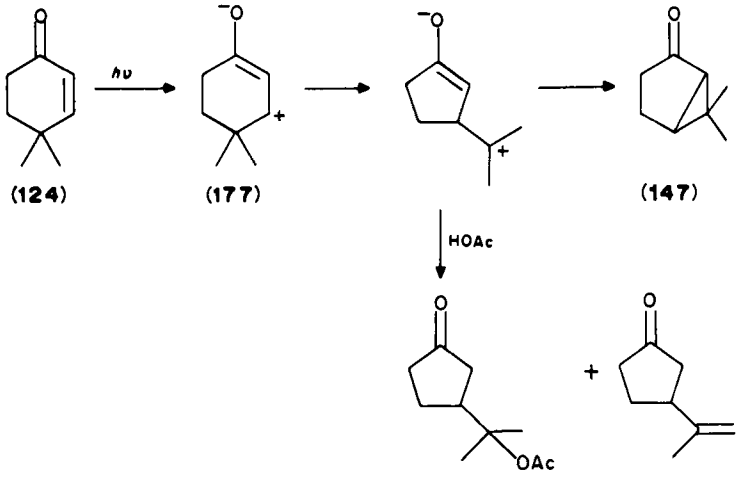
The Type A photorearrangement of cyclohexenones is formally analogous to the photorearrangement of cyclohexadienones to bicyclo[3.1.0]hex-3-en-2-ones, also called a lumiketone rearrangement, typified by the conversion of **174** to **175** shown in equation

86[144,145]. This reaction, which proceeds via dienone triplets, has been shown in suitable systems to be stereospecific with inversion of configuration at C_4 [146]; thus, in a formal sense it is also an intramolecular $_{\pi}2_a + _{\sigma}2_a$ cycloaddition. However, it has been demonstrated unequivocally that the photorearrangement of cyclohexadienones proceeds stepwise via zwitterion intermediates (**176**)[126,144,145], which can be trapped in certain cases[145,147,148], and is therefore not a concerted intramolecular cycloaddition. Furthermore, the quantum efficiencies (QE) for the cyclohexadienone photorearrangements are quite high (generally 0.8–1.0), indicating that the second C=C bond plays a key mechanistic role[144,145]. Note also that lumiketones are formed in high yield from cyclohexadienones such as **174**[144], while corresponding 4,4-diphenylcyclohexenones react exclusively by phenyl migration[134].



(86)

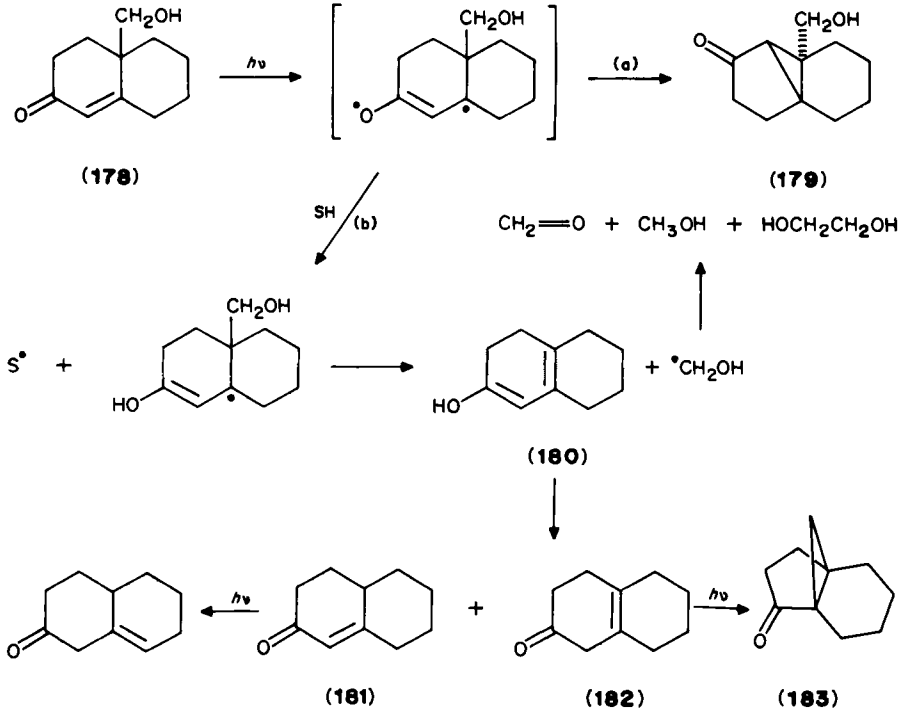
In an attempt to link the cyclohexenone and cyclohexadienone photorearrangements mechanistically, as well as to account for the formation of polar addition products (see equation 75) Chapman[127,128,131] proposed that the cyclohexenone photorearrangements proceed via a 'polar state' **177** (equation 86a) although it was never specified whether **177** represents an excited or ground-state species. Such a species did provide a convenient way of accounting for the formation of bicyclo[3.1.0]hexanones by mechanistic analogy with carbocation rearrangements, as shown in equation 86a, although the subsequently observed stereospecificity would be hard to rationalize on the basis of stepwise reaction of a dipolar intermediate. It is even less obvious how to rationalize the direct formation of ring-contracted cyclopentenones as shown in equations 75 and 76 via a dipolar species without invoking one or more hydride shifts. Irradiation of optically active **167** gives



(86a)

optically active cyclopentenone **168** (see equation 82) with the absolute configuration as shown, although it is not known whether this rearrangement is totally or only partially stereospecific[140]. The predominant course of reaction is as depicted in Scheme 22 involving a formal ${}_{\sigma}2_{a} + {}_{\sigma}2_{a}$ cycloaddition of the $C_4—C_5$ σ bond to the $C_3—H$ bond, i.e. the hydrogen migration from C_3 to C_4 results in inversion of configuration at C_4. This certainly is not the stereochemical course of reaction expected if **168** arose via ring contraction of a dipolar species such as **177**.

A study of 10-hydroxymethyloctalone **178** was undertaken by Schuster and Brizzolara[149] specifically to test Chapman's 'polar state' theory[127,128]. It was anticipated that irradiation of **178** would produce a CH_2OH fragment, either as a radical or a carbocation, depending on whether the precursor was a dipolar or diradical species. The products and reaction course of **178** are shown in Scheme 23. It is clear that there are two competitive pathways for **178**: (a) rearrangement to lumiketone **179**, and (b) hydrogen abstraction–fragmentation to give hydroxymethyl radical and dienol **180**, which is the precursor to octalones **181** and **182**. Path (a) was the sole reaction course in *t*-BuOH, while reaction via (b) as well as (a) occurred on irradiation of **178** in $CHCl_3$, toluene, cumene and (curiously) benzene. Triplet quenching experiments showed that both pathways occur from a common triplet excited state of **178** which must have diradical and not dipolar character, in order to account for the nature of the fragmentation products and the effect of solvent on the reaction course[149].



SCHEME 23

Based on the observations summarized above, Schuster and coworkers[140] suggested that the mechanism of the cyclohexenone–lumiketone photorearrangement involves

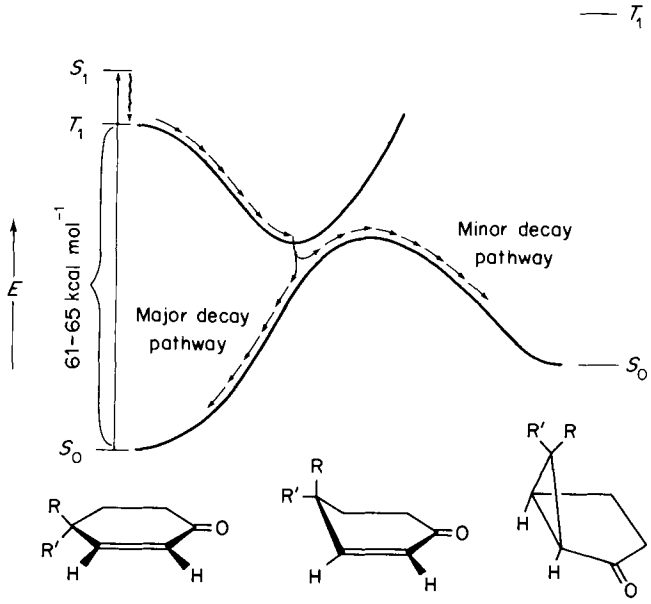


FIGURE 10. Proposed topology of the triplet and ground-state potential surfaces along the reaction coordinate for conversion of 2-cyclohexenones to bicyclo[3.1.0]hexan-2-ones (lumiketones). Reprinted with permission from *J. Am. Chem. Soc.*, **100**, 4504 (1978). Copyright (1978) American Chemical Society

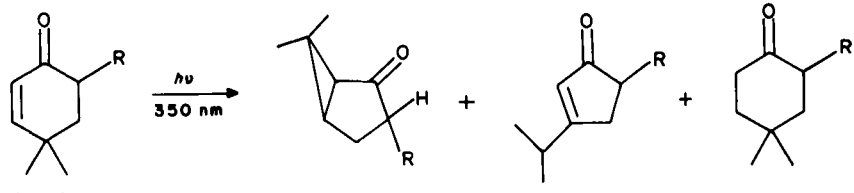
rapid intersystem crossing from the enone S_1 to the T_1 state ($^3\pi,\pi^*$), which then relaxes energetically by twisting around the C=C bond as shown in Figure 10. Intersystem crossing by spin inversion back to S_0 at the twisted geometry should be favored because of the energetic proximity of the S_0 and T_1 surfaces at, or close to, the 90° geometry, as in the case of 2-cycloheptenone (Figure 8). The diagram in Figure 10 is based on the assumption that a twisted cyclohexenone ground state partitions between formation of lumiketone (minor pathway) and reversion to starting enone (major pathway). The existence of a small energy barrier leading to lumiketone on the ground-state surface from the point corresponding to the minimum on the triplet surface, as shown in Figure 10, would provide a convenient way of rationalizing the low quantum efficiency for the rearrangement. The precise location of the minima and maxima in Figure 10 should depend on the substituents at or near the enone chromophore, accounting for structural variations on the quantum efficiency for rearrangement. If the course of reaction is indeed as depicted in Figure 10, it is meaningless to talk about rate constants for triplet decay and reaction as derived from quantum yields and triplet lifetimes, as if these processes competed directly from T_1, as in other types of systems. Thus, the rate of decay of cyclohexenone triplets according to Figure 10 depends only on the energy difference between T_1 at its potential minimum and S_0 at the same geometry, while the reaction efficiency depends on the topology of the ground-state surface, i.e. the fraction of twisted ground-state molecules that make it over the top. However, the possibility that formation of lumiketone is concerted with spin inversion as suggested by Shaik[142] is by no means excluded.

According to the above picture, the efficiency of photorearrangment ought to be temperature dependent, but this has yet to be studied. The observation[143] that enone **170** does not undergo photorearrangement is consistent with this description of the

reaction. One of the more intriguing observations is that **170** is weakly fluorescent at room temperature (λ_{max} 385 in cyclohexane and acetonitrile), which is not the case for simple acyclic or cyclic enones. Exceptions are the structurally rigid cyclopentenones **77** and **78**; it was proposed that for these enones there is an unusually large energy gap between S_1 and T_1, which inhibits intersystem crossing[90]. An implication of these findings is that intersystem crossing in cyclohexenones may occur preferentially in a twisted rather than a planar geometry, which is reasonable since twisting should enhance spin–orbit coupling. Thus, Figure 10 may require modification to incorporate energetic stabilization of singlets as well as triplets by twisting around the C=C bond.

An alternative mechanism for the photorearrangement, which would explain why this mode of reaction is seen with cyclohexenones and not with smaller and larger cycloalkenones, is that it involves the intermediacy of highly reactive *trans* cyclohexenones. That is, it is possible that the fundamental photochemical act upon photoexcitation of cyclohexenones is isomerization (via a twisted triplet-excited state) to a high-energy ground-state *trans* isomer, analogous to the photoisomerizations of cycloheptenone and cyclooctenone discussed earlier; the *trans* isomer might then partition between rebonding to generate lumiketone and reversion to ground-state *cis* enone. Evidence in support of such a mechanism will be discussed following a discussion of recent studies involving generation and detection of triplet states of cyclohexenones using laser flash techniques, and the competition between rearrangement and other processes on steady-state excitation of cyclohexenones.

Cruciani and Margaretha[150] reported that irradiation of **184a**, an analog of **124** with a CF_3 group at C-6, and the corresponding enone **184b** with a 6-methyl group, affords the usual rearrangement products, as shown in equation 87; however, in these systems the cyclopentenones are formed in higher yields than the lumiketone, in contrast to the behavior seen with the unsubstituted enone **184c** (= **124**). They also noted that the



(184)

(a) R=CF_3

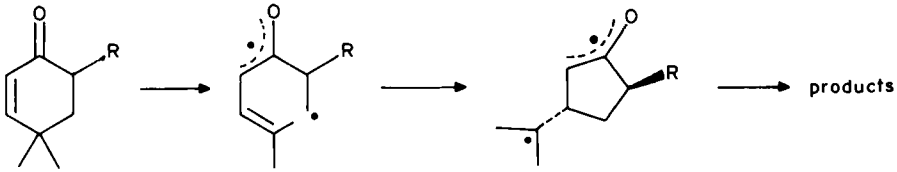
(b) R=CH_3

(c) R=H (=124)

(87)

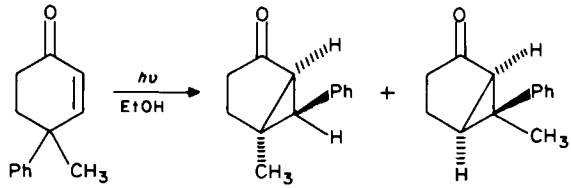
reduction of **184a** to the saturated ketone occurred to a significant extent in *t*-BuOH and CH_3CH, which is not the case with analogous enones, which was not explained. The relative quantum yields for rearrangement of these enones at 350 nm are **184a** < **184b** < **184c**. They suggest that the lowering of the quantum yield is probably due to conformational changes in the enone excited states; if so, there ought to be substantial enhancement of triplet lifetimes, as discussed in section IV.B.4.d. The authors interpret the shift of the ratio of rearrangement products toward ring contraction as evidence that these products arise by the route shown in equation 88, i.e. ring opening to a substituted 5-hexenyl radical, ring closure selectively to the *trans*-disubstituted five-membered ring, which then either undergoes ring closure to the lumiketone or a 1,2-hydrogen shift to give the cyclopentenone. Such a photorearrangment mechanism was previously considered and discarded based upon stereochemical data for model cyclohexenones, as discussed

earlier. Thus, in the interests of mechanistic simplicity and in accord with Occam's Razor[151], it seems best at present to interpret these findings in terms of the rearrangement mechanisms discussed above, in the absence of compelling reasons to assign a special mechanism to this set of enones. For reasons which are far from clear at this time, the formation of lumiketone from the twisted enone triplet state of **184a** and **184b** by essentially a $_{\pi}2_a + _{\sigma}2_a$ route is slower than the $_{\sigma}2_a + _{\sigma}2_a$ route which leads to cyclopentenones.



(88)

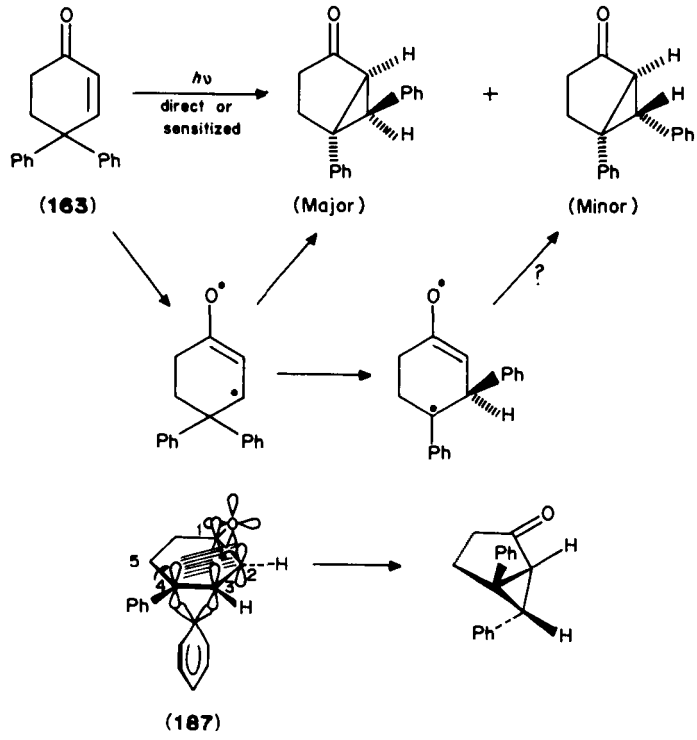
(iii) Di-π-methane rearrangements: 1,2-aryl and 1,2-vinyl migrations. As shown in equation 77, when an aryl group is present at C_4 as in enone **162**, an aryl migration pathway competes with the lumiketone rearrangement[133]. With two aryl groups at C_4, only aryl migration is observed, which gives a mixture of stereoisomers in which the isomer with a 6-endo aryl group dominates. From the work of Zimmerman and coworkers, the mechanism of this transformation is well understood[134,152]. Migratory aptitudes have been determined from studies using enones with two different 4-aryl substituents, and they establish that aryl migration occurs to a carbon center (C_3) with odd electron character. Once again, the results are inconsistent with the 'polar state hypothesis'[127]. Sensitization and quenching studies establish that the rearrangement occurs via triplet-excited states which are formed with close to unit efficiency. From the dependence of product ratios on solvent polarity in the case of enone **162** Dauben and coworkers[133] proposed that it is the enone $^3n,\pi^*$ state which is the intermediate in the aryl migration pathway, while the $^3\pi,\pi^*$ state is the species responsible for the lumiketone rearrangement, in agreement with the assignments made earlier. Differential quenching of formation of **185** and **186** by naphthalene on irradiation of **162** in ethanol (equation 88a) supports the proposal that these products indeed arise via two different triplet excited states which are not in thermal equilibrium.



(162) **(185)** **(186)**

via $^3n,\pi^*$ via $^3\pi,\pi^*$

Except for the fact that these aryl migrations proceed from $^3n,\pi^*$ states, the rearrangement is analogous to the di-π-methane rearrangements extensively studied by Zimmerman and his coworkers[136]. The formation of the major rearrangement product with a 6-endo-aryl group in the reaction of **163** can be rationalized in terms of a bridged intermediate **187**[153]. However, the fact that the 6-exo-aryl product is also formed suggests that this reaction is not concerted, and that it occurs at least in part via the open diradical intermediate shown in Scheme 24. Quantum yields for aryl migration as high as 0.18 have

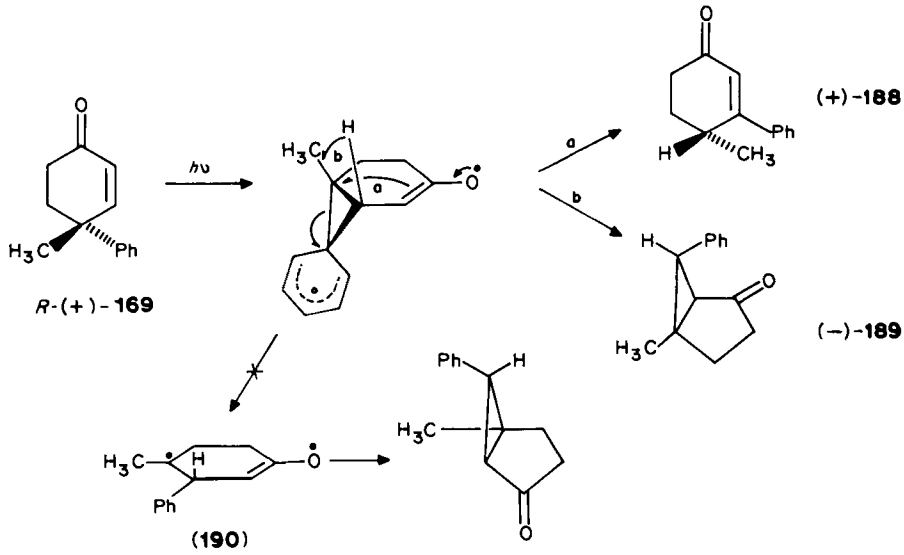


SCHEME 24

been measured[153], but they vary with the nature of the migrating and nonmigrating groups. Assuming that decay to the ground state and rearrangement are competitive processes of the triplet state, rate constants for these processes (k_d and k_r, respectively) can be determined from quantum yields and triplet lifetimes; the latter are determined from Stern–Volmer triplet quenching plots, assuming that triplet energy transfer is diffusion controlled. (No studies involving direct determination using laser flash techniques of triplet lifetimes for enones **162**, **163** or similar enones have been reported, so the validity of this assumption has yet to be tested experimentally.) Values of k_r determined on this basis depend on the nature of the migrating and nonmigrating groups, while k_d values show little variation, and are *ca* $10^9\ s^{-1}$. Zimmerman concludes that the 'decay to product seems to have little in common with the decay back to reactant'.

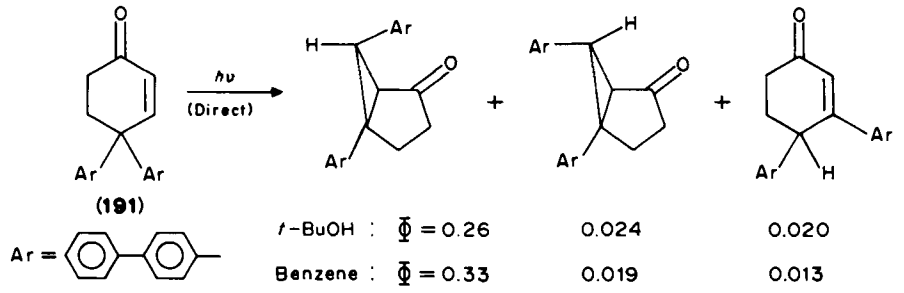
The stereochemistry of the phenyl shift in **162** was determined for the chiral system by Schuster and coworkers[140]. Both **188** and **189** were formed stereospecifically without any loss of optical purity. By relating the absolute configurations of the products and the starting materials, it was shown that both rearrangements occurred as shown in Scheme 25 with complete inversion of configuration at C_4. Thus, it appears that phenyl bridging and ring contraction are synchronous in this system, since the epimer of **189** with a 6-exo-phenyl is not formed; reaction via the open diradical **190**, on the other hand, should lead to both epimers.

Zimmerman and coworkers have recently reported interesting studies on 4,4-biphenylylcyclohexenone **191**, to determine the effect of incorporating in the molecule a



SCHEME 25

moiety whose triplet energy should be approximately the same as that of the enone moiety[154]. The course of reaction of this system, shown in equation 89, is similar to that for the 4,4-diphenylenone, except that the quantum yields shown are considerably larger.

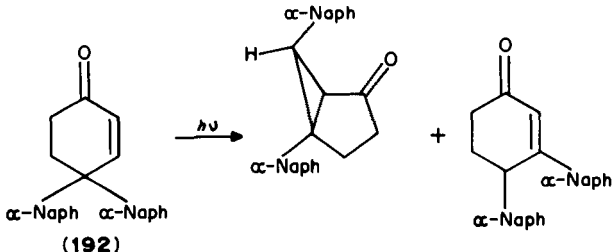


(89)

Triplet sensitization by either xanthone (E_T 74 kcal mol^{-1}) or benzophenone (E_T 69 kcal mol^{-1}) gave the same products with undiminished quantum yields, while the quantum yields on sensitization by thioxanthone (E_T = 65 kcal mol^{-1}) were much lower, indicating uphill triplet energy transfer. They assigned a triplet energy of *ca* 69 kcal mol^{-1} to enone **191**. The reaction was quenched by 1,3-cyclohexadiene; from the Stern–Volmer slopes, Zimmerman and coworkers calculated a triplet lifetime for **191** of 3.1 ns in *t*-BuOH and 2.9 ns in benzene. They suggest that equilibration of the triplet excitation between the enone and biphenyl moieties is faster than the rate of rearrangement in this system, with excitation initially localized in the enone moiety on direct excitation and in either moiety on triplet sensitization. From the data, they calculated a k_d value in benzene which is about

one-half that of **163**, which they suggested may be due to energy storage in the longer-lived biphenyl moiety. The rate of rearrangement k_r is about 5 times greater in **191**, probably owing to better delocalization of the odd electron density in the bridged intermediate when biphenyl is the bridging group. The net result is an increase in quantum efficiency for rearrangement by about a factor of 10.

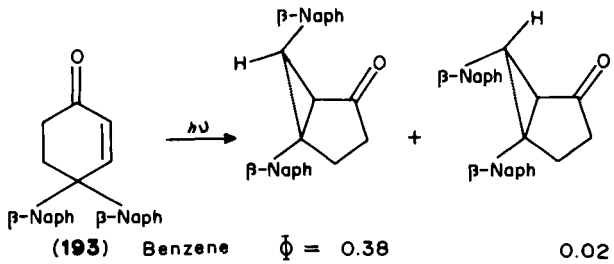
To determine the effect of incorporating a triplet quencher at C_4 of a cyclohexenone, Zimmerman and Solomon studied the photochemistry of 4,4-di(α-naphthyl)- and 4,4-di(β-naphthyl)-cyclohexenone, **192** and **193**[155]. The course of reaction together with the quantum yields is shown in equations 90 and 91 respectively. The reaction not only took place in the presence of these internal triplet quenchers, but with a marked improvement in quantum efficiency, especially with **192**. In this system, totally efficient sensitization was observed using both xanthone and thioxanthone. Triplet intermediates were implicated by quenching studies using cyclohexadiene and di-*t*-butylnitroxyl. Triplet lifetimes in benzene, estimated as above, were 6.0 ns for **192** and 7.3 ns for **193**. Zimmerman and Solomon propose that intramolecular triplet energy transfer from the enone triplet (T_2) to the lower-energy naphthyl moiety (T_1) is faster than any other competitive process. The values for k_d calculated are slightly lower than for the diphenyl enone **163**, while the rates of rearrangement are again enhanced. They visualize a spectrum of reactivity from the diphenyl enone, in which the excitation (in the reactive $^3n,\pi^*$ state) is localized in the enone portion of the molecule, to the present example which is akin to classic di-π-methane rearrangements of $^3\pi,\pi^*$ states of aromatic hydrocarbons[136].



(90)

(192)

Benzene	Φ =	0.46	0.54
t-BuOH	Φ =	0.43	0.57



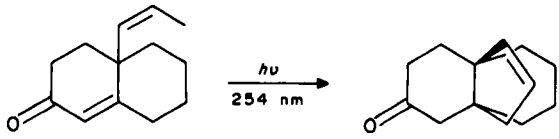
(91)

(193)

Benzene	Φ =	0.38	0.02
t-BuOH	Φ =	0.40	0.02

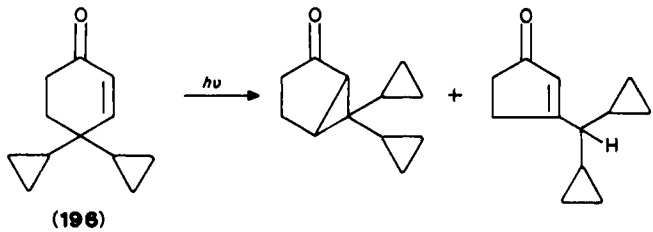
A mechanistically analogous rearrangement of enone **164** has been observed involving migration of a 4-vinyl substituent (equation 79)[135]; *E*–*Z* isomerization of the starting material competed with the rearrangement. No lumiketone product was observed in this study. It is likely that the reaction occurs via triplet states, but this was not established. It is also interesting that **164** does not undergo a cyclization reaction analogus to that seen with

194 (equation 92), even on excitation into S_2 (see discussion in Section IV.B.4.c.vi), which the authors attribute to conformational problems in **194** preventing the intramolecular hydrogen abstraction required for the cyclization.



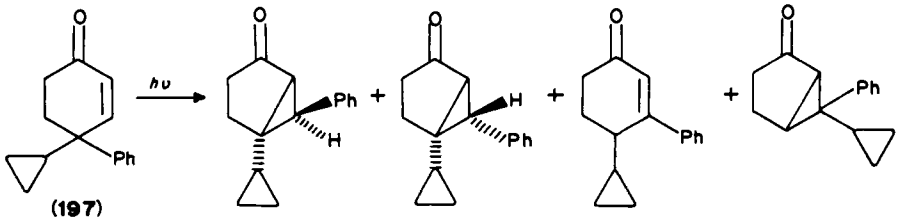
(194) (195) (92)

The possibility that cyclopropyl substituents might undergo 1,2-shifts analogous to those seen for aryl and vinyl substituents was investigated by Hahn and coworkers[156]. Irradiation of the 4,4-dicyclopropyl-2-cyclohexenone **196** gave only lumiketones, as shown in equation 93. The reactions seen on irradiation of 4-cyclopropyl-4-phenyl-2-cyclohexenone **197** followed the pattern seen previously with enone **162**, namely 1,2-phenyl migration in nonpolar solvents, and lumiketone formation in addition in polar solvents. Again, competitive reaction via $^3\pi,\pi^*$ and $^3n,\pi^*$ states was invoked.



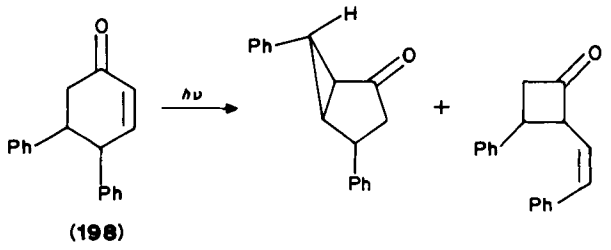
(198)

(93)

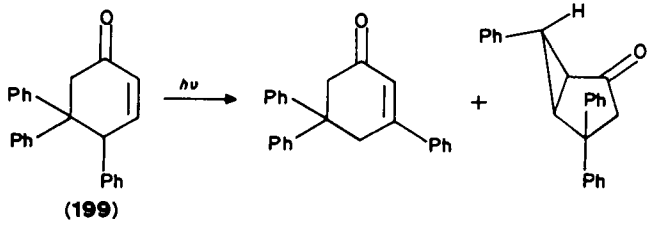


(197)

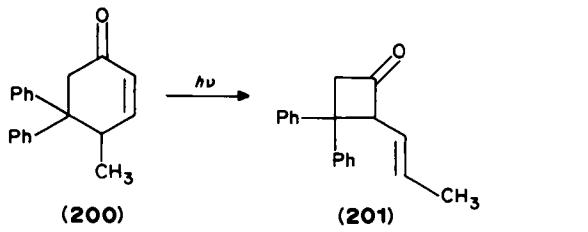
(iv) Ring contraction to cyclobutanones. Some time ago, Zimmerman and Sam[157,158] reported that ring contraction to a cyclobutanone competed with phenyl migration on irradiation of 4,5-diphenyl-2-cyclohexenone **198**, as shown in equation 94. Recent studies by Zimmerman and Solomon[159] extend the earlier investigations and go a long way to establishing the mechanism of this interesting rearrangement as well as its relationship to the photochemical rearrangements discussed above. Thus, 4,5,5-triphenyl-2-cyclohexenone **199** gives a variety of irradiation products, shown in equation 95, involving both phenyl migration and ring contraction, while 4-methyl-5,5-diphenyl-2-cyclohexenone **200** gives only ring contraction to **201** (equation 96). On acetophenone sensitization the same products are formed with identical quantum yields as upon direct excitation, and both reactions are quenched by 1,3-cyclohexadiene. This establishes that these reactions occur via enone triplets, whose lifetimes (assuming diffusion-controlled quenching) are 7.4 and 8.1 ns, respectively.



(198) (94)



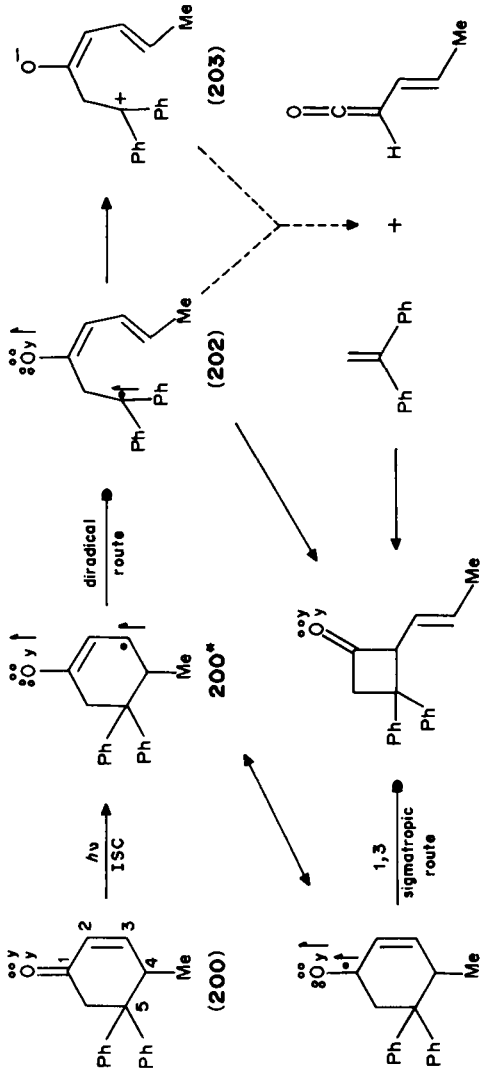
(199) (95)



(200) (201) (96)

Since cleavage to ketenes and 1, 1-diphenylethylene, followed by recyclization, is a possible route to the cyclobutanones, irradiations were carried out in the presence of potential ketene traps, namely in ethanol and in benzene containing cyclohexylamine. No ester or amide products were detected. A further test was to carry out the irradiation of **200** in the presence of 1, 1-di(*p*-tolyl)ethylene and to look for crossover products; none were observed. These experiments strongly suggest that these ring contractions occur intramolecularly by cleavage of only one C—C bond.

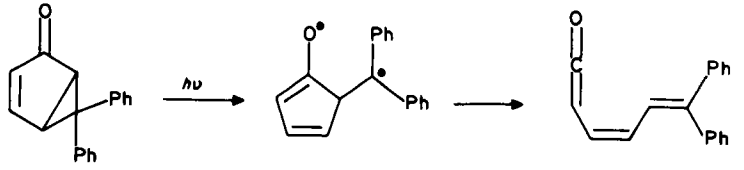
Stereochemical studies clarify the picture. Irradiation of optically active enone **200** gave nearly racemic cyclobutanone **201**, with $6.7 \pm 2.0\%$ residual enantiomeric excess. Recovered starting material had not undergone any racemization. Zimmerman and Solomon[159] discuss these results within the mechanistic framework shown in Scheme 26, using the model for n, π^* triplet states originally proposed many years ago[126,144,160]. It is proposed that the key reaction of this triplet is 4, 5-bond fission to give diradical **202**. In principle, as shown in Scheme 26, this triplet could cleave to 1, 1-diphenylethylene and a


(200)
hν
ISC
200*
diradical
route
(202)
(203)
1,3
sigmatropic
route
(201)
(200")

SCHEME 26

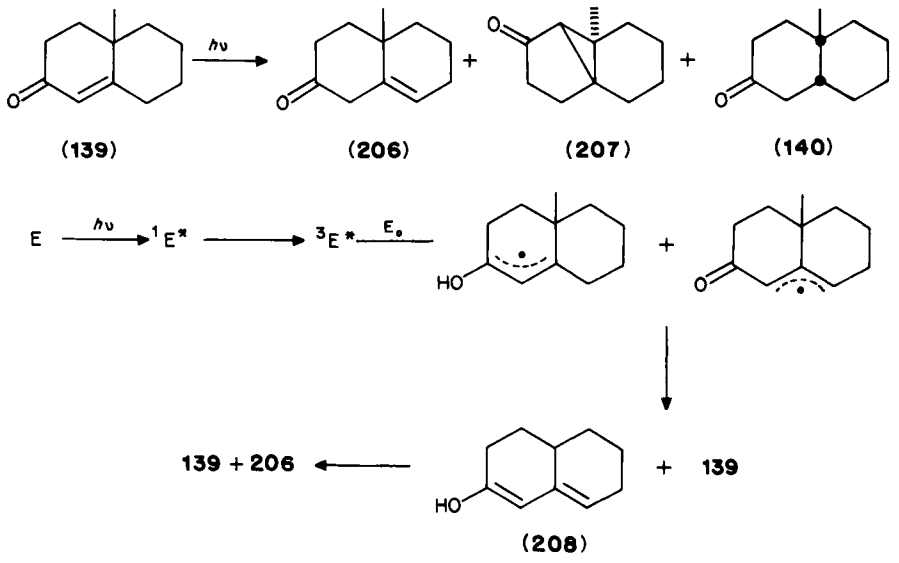
ketene, but this process does not appear to take place, as indicated above, supporting the suggestion that the spins in **202** are unpaired. Instead, diradical **202** closes to **201**, with a spin flip occurring at some point during this process. Indeed, Zimmerman suggests that spin relaxation to give zwitterion **203** occurs prior to ring closure, analogous to the reaction course in cyclohexadienone rearrangements[126,144,160], and supported by theoretical calculations. The residual enantiomeric excess in **201** probably arises from incomplete conformational equilibration of **202** prior to ring closure. The data establish that **202** does not revert to the starting enone **201**, at least not after conformational equilibration. Although the reaction efficiency is low, of the order of 0.01–0.03, the reaction in the case of **200** is nonetheless synthetically useful.

It is of interest that the 4, 5-bond cleavage to generate an intermediate triplet diradical which occurs in these rearrangements does *not* occur in the course of the lumiketone (Type A) rearrangement on the basis of the stereochemical results[139,140] although it was a distinct mechanistic possibility. Thus, the presence of two phenyl substituents at C_5 clearly tips the balance in favor of the cleavage process, providing stabilization of diradical **202**. Another case where similar diradical stabilization undoubtedly plays an important role is cleavage of the bicyclic enone **204** to ketene **205**, shown in equation 97[144,161], and the cleavage of 5, 5-disubstituted cyclopentenones **53** discussed earlier (see equation 50)[82,83]. It is also noteworthy that when a phenyl group is present at C_4, as in enone **199**, the phenyl migration pathway (established by deuterium labeling) remains competitive with 4, 5-bond cleavage despite the fact that this phenyl group can also help to stabilize the open-chain biradical analogous to **202**.



(204) (205) (97)

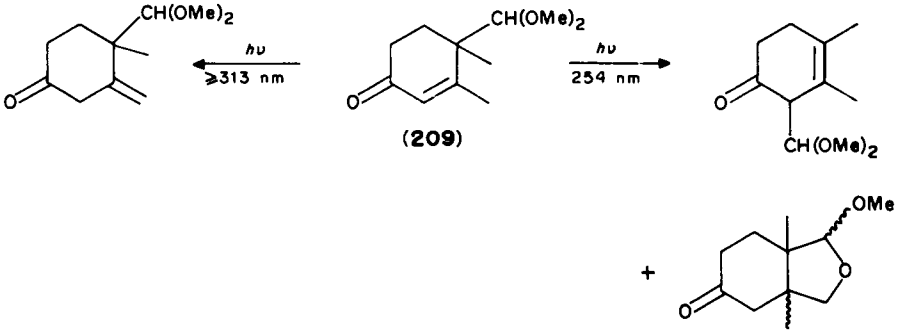
(v) Rearrangement to β,γ-unsaturated ketones. The photorearrangement of acyclic α,β-enones to β,γ-enones was discussed in Section IV.B.4.c.v. The corresponding rearrangement in cyclic systems is much less common, and is still not understood. The best known case involves octalone **139**, which rearranges to **206** competitive with formation of lumiketone **207** and dihydroketone **140**[121,122]. It was initially reported[121] that the efficiency of formation of **206** depended on the enone concentration, indicating reaction between an octalone triplet and ground-state enone E was involved, which was supported by studies using labeled compounds. On this basis, the mechanism in Scheme 27 was proposed, involving hydrogen abstraction from ground-state enone by the octalone triplet (presumably an n, π^* triplet, if reaction indeed occurs on oxygen) to give a pair of allylic radicals, which then disproportionate to a mixture of starting enone **139** and dienol **208**. The latter on ketonization gives the product **206** and the starting enone depending on the site of protonation (see discussion in Section IV.1)[121]. In accord with this mechanism, quenching of formation of **206** by 2, 5-dimethyl-2, 4-hexadiene was much less than of formation of lumiketone **207**, which makes sense since, as discussed earlier, **207** should arise from a $^3\pi,\pi^*$ state. However, later studies[162] revealed analytical problems connected with the thermal stability of **206** which raised doubts as to the validity of the two triplet mechanism in this system. This problem appears not to have been resolved.



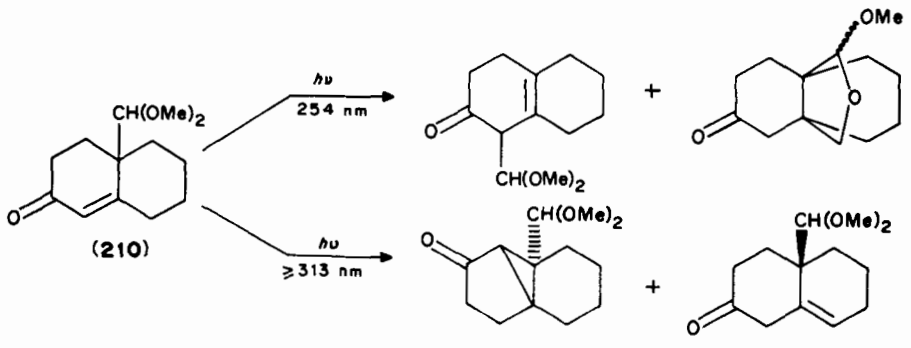
SCHEME 27

(vi) Allylic rearrangements and cyclizations: wavelength-dependent photochemistry. As discussed in the earlier review of enone rearrangements by this author[5], enones **209**, **210** and **211** give different sets of reactions on excitation at 254 nm into the $\pi \rightarrow \pi^*$ absorption band, and at $\geqslant 313$ or $\geqslant 340$ nm on excitation into the $n \rightarrow \pi^*$ absorption band[163]. These are shown in equations 98 and 99. It can be seen that $n \rightarrow \pi^*$ excitation of **209** and **210** leads to deconjugation (see above) and lumiketone formation, while $\pi \rightarrow \pi^*$ excitation results in allylic rearrangements ([1, 3]-sigmatropic shifts)[164] along with cyclization of the ether moiety to the β-carbon of these enones. Enone **211** is dead on long-wavelength excitation, but at short wavelengths cyclization is observed.

The allylic rearrangements are definitely intramolecular, while stereochemical studies show that the migrating group loses stereochemistry in the course of reaction, suggesting that the [1, 3]-shift is not concerted, but involves as the major pathway formation of

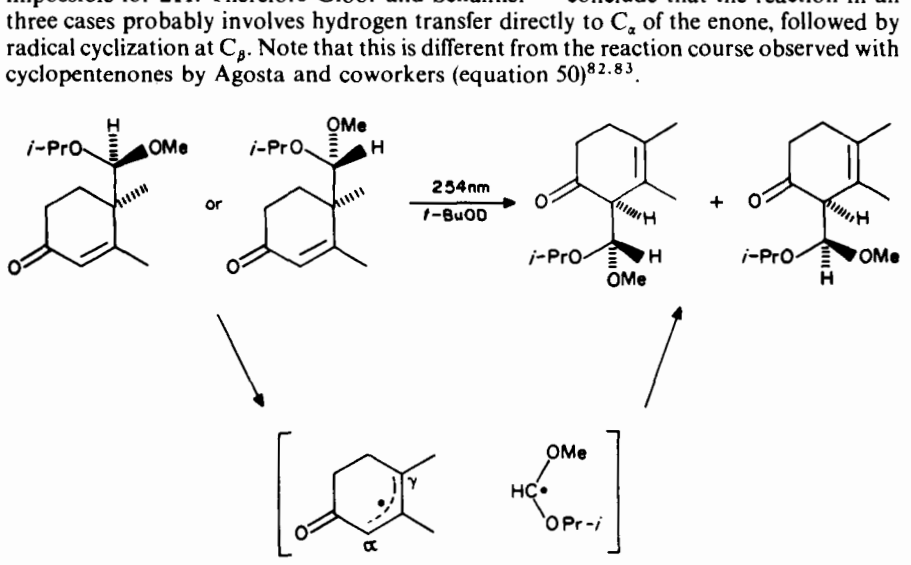


(98)

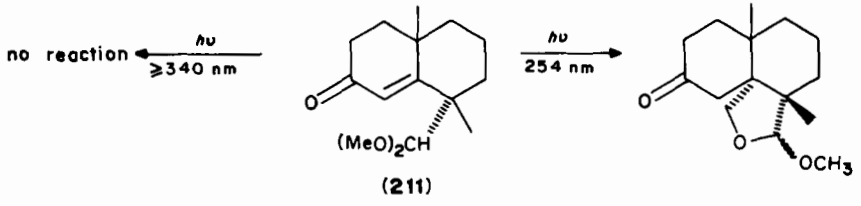


(99)

an intermediate radical pair as shown in Scheme 28. The starting enones in these studies did not lose stereochemistry under the irradiation conditions. The cyclization of **209** and **210** were originally proposed to occur by an intramolecular hydrogen abstraction from a methoxy group by the carbonyl oxygen, but such a mechanism is sterically impossible for **211**. Therefore Gloor and Schaffner[165] conclude that the reaction in all three cases probably involves hydrogen transfer directly to C_α of the enone, followed by radical cyclization at C_β. Note that this is different from the reaction course observed with cyclopentenones by Agosta and coworkers (equation 50)[82,83].



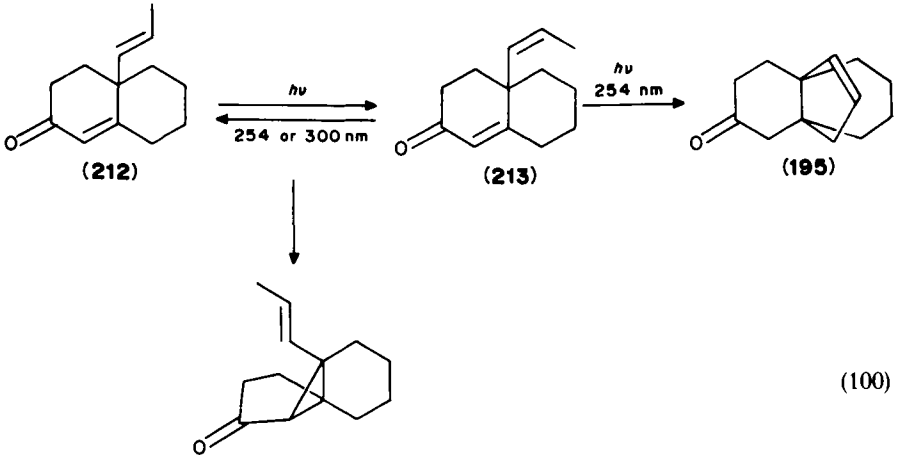
SCHEME 28



(211)

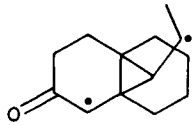
The excited state responsible for the [1, 3]-shifts and radical cyclization is not accessible upon excitation into the enone S_1 state, but rather requires excitation into S_2. Thus, the reactive state is either S_2 or the triplet state T_3, since both T_1 and T_2 lie below S_1 in these systems[163,165]. The authors prefer an interpretation in which S_2 undergoes reaction competitive with radiationless decay to S_1, but this matter remains experimentally unresolved.

Excitation of either the (*E*)- or (*Z*)-propenyl enones **212** and **213** in the $n \rightarrow \pi^*$ absorption bands results in *E*–*Z* isomerization, deconjugation and lumiketone formation, as shown in equation 100; only the lumiketone with the (*E*) configuration in the side-chain was formed starting with either **212** or **213**[135]. On irradiation into S_2 the tricyclic ketone **195** was also



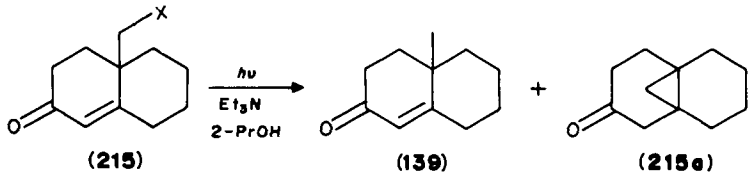
(100)

formed. The cyclization efficiency was surprisingly not much higher starting with the enone with the (*Z*) configuration in the side-chain. The product distributions on acetophenone sensitization in benzene or *t*-BuOH were similar to those on direct excitation of the enones at long wavelengths, i.e. excitation into S_1. The cyclization to **195** could not be sensitized using acetophenone under any conditions. Mechanistically, these transformations are analogous to those discussed above, except for the observation that only one lumiketone stereoisomer is obtained starting with either of the isomeric enones. There could be factors operating in this system which are different from those in systems discussed earlier which allow isomerization in the side-chain concomitant with the Type A rearrangement. Another possibility is that the lumiketone is formed by a di-π-methane rearrangement via diradical **214**. The two routes can be distinguished by appropriate labeling, but the results of such experiments have not been reported.



(214)

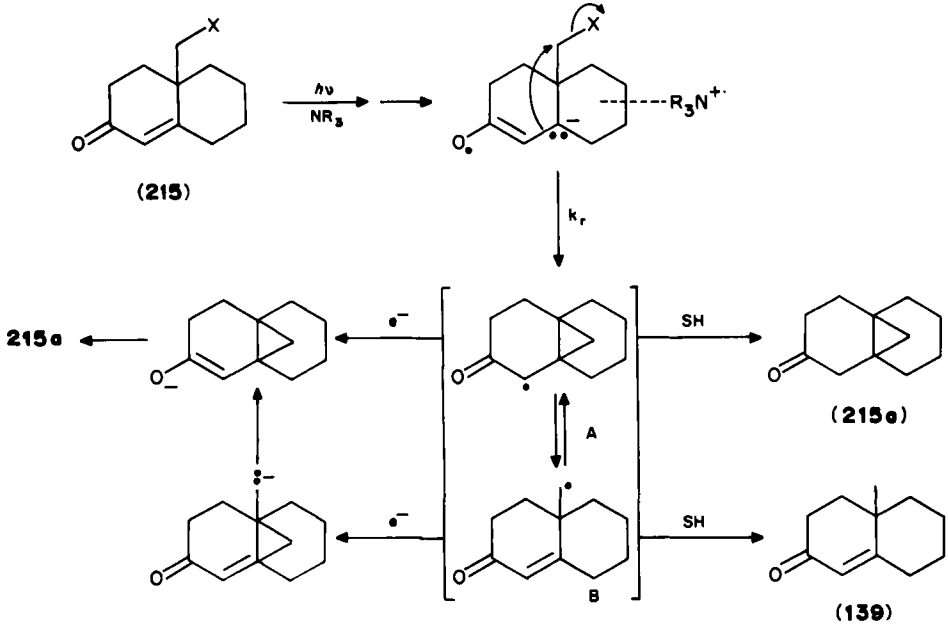
(vii) Rearrangements of photogenerated enone radical anions. Givens and Atwater[166] recently reported the reaction of octalones **215** upon irradiation in 2-propanol in the presence of triethylamine (equation 101). The process was shown to involve electron



(215) (139) (215a) (101)

X=OTs, OMs, O_2CCF_3, Br

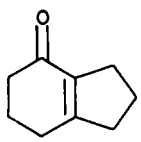
transfer from the amine to the excited octalone by the appropriate inverse dependence of quantum efficiency on the inverse of the amine concentration, and piperylene quenching indicated that it was a triplet process. The surprising finding is that the major product is octalone **139** (> 95%) rather than the cyclopropyl ketone **215a**, which is the major product from reduction of **215** by lithium in liquid ammonia, a process that is also supposed to proceed via a radical anion of **215**[167]. Scheme 29 shows the mechanism proposed by Givens and Atwater, involving internal nucleophilic displacement to give a cyclopropylcarbinyl radical A which should undergo facile reversible ring opening to the more stable homoallyl-neopentyl radical B. The ratio of products would then depend critically on the nature and concentration of the hydrogen donor, which in this case could be the solvent or $Et_3N^{+\cdot}$. Under reductive conditions, such as Na/NH_3, it is proposed that the intermediate radicals are first reduced to the corresponding anions, which are probably also in equilibrium, to give the two final products on protonation. It is clear that the main pathway in the photochemical system involves free radical ring opening and hydrogen abstraction to give octalone **139**.



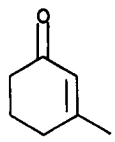
SCHEME 29

d. Direct observation of triplet states of cyclohexenones by nanosecond laser flash techniques. On laser flash excitation of 1-acetylcyclohexene **168** and cycloheptenone **94**[81], two transient intermediates are observed, one very short-lived (16 and 11 ns, respectively, in cyclohexane) and the other relatively long-lived (15 and 45 μs, respectively). The long-lived species B have been identified as the ground-state *trans* enones, as previously discussed. The short-lived transient A from acetylcyclohexene which has a very different UV spectrum (λ_{max} 285 nm) from that of the *trans* enone *B* (λ_{max} 345 nm), was shown to be a direct precursor of B since the rate of decay of A was equal to the rate of growth of B. Since transient A is quenched by oxygen (see Table 3), Bonneau and Fornier de Violet[168] conclude that A is a twisted (orthogonal) triplet state of acetylcyclohexene. The similarity of the absorption spectrum for transient A from cycloheptenone (λ_{max} 280 nm), coupled with its short lifetime, lead Bonneau to conclude that this species was also a twisted triplet, as previously discussed[81].

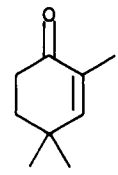
Using the same technique, Bonneau[81] observed short-lived transients from cyclohexenone and cyclopentenone (τ 25 and 30 ns, respectively, in cyclohexane) which absorbed in the same region as transients A above, and which were quenchable by oxygen; he concluded that these were also triplet π,π^* states of these enones[81]. In these cases, no transient absorption was observed that could be assigned to a ground-state *trans* enone. Subsequently, a number of other cyclohexenones have been examined using the laser flash technique by Schuster and coworkers in collaboration with Bonneau, Scaiano and Turro[80,169-174] using different laser excitation wavelengths (Nd:Yag laser at 353 or 265 nm; nitrogen laser at 337 nm) in a variety of solvents. The data are summarized in Table 3. In addition to the parent system, the cyclohexenones studied to date include 4,4-dimethylcyclohexenone **124**, testosterone as well as testosterone acetate **132**, octalone **139**, phenanthrone **154**, bicyclo[4.3.0]nonenones **170** and **216**, 3-methylcyclohexenone **217**, 2,4,4-trimethylcyclohexenone **218** and 4,4,6,6-tetramethylcyclohexenone **219**. All of these enones produce transients that show strong UV absorption in the range 270–350 nm with maxima in most cases at *ca* 280 nm; in all cases, these transients are quenched by oxygen. The remote possibility that the '280 nm transients' of the cyclohexenones might be triplets of cyclohexadienols produced by photoenolization is countered by the fact that enone **219**, which cannot photoenolize, produces a transient with similar absorption spectrum and lifetime as **124**. By analogy with the systems reported previously and on the basis of other considerations (see below), it has been concluded that these transients are relaxed twisted cyclohexenone triplet π,π^* states.



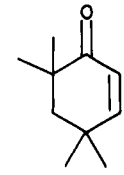
(216)



(217)



(218)



(219)

There is a clear trend in the transient lifetimes given in Table 3, in that they become increasingly long as the structural constraints to twisting around the C=C bond increase. Thus, the monocyclic enones give transient lifetimes of 25–40 ns except for **217** which is 70 ns; the lifetimes for octalone **139**, the tricyclic phenanthrone **154** and the steroid enone **132** increase in the order **139** < **154** < **132**; the conformationally rigid bicyclononenones **170** and **216** have very long lifetimes, > 1500 ns. This order is precisely as predicted for energetically relaxed twisted enone triplets, based on Bonneau's proposal[81] that the lifetime of such triplets is determined principally by the energy gap between the minimum in the π,π^* triplet surface and the energy of the ground-state enone at that same geometry.

TABLE 3. Triplet lifetimes of enones and quenching rate constants measured by laser flash techniques

Enone	Solvent	τ_{dir}	τ_{ext}	k_q, NA(MN) $mol^{-1} s^{-1}$	k_q, Piperylene $l\,mol^{-1} s^{-1}$	k_q, O_2 $l\,mol^{-1} s^{-1}$	Ref.
2-Cycloheptenone **94**	Cyclohexane (CH)	11			$\leqslant 10^7$		81, 99
1-Acetylcyclohexene **91**	CH	16			$\leqslant 10^7$	3.5×10^9	81, 168
2-Cyclohexenone **118**	CH	25(28)	29	7.5×10^8	4×10^7	7×10^9	169(174)
	Acetonitrile (AN)	23(40)	24	1.0×10^9	$< 10^8$		169, 172(174)
	MeOH	27					174
4,4-Dimethylcyclohexenone **124**	*t*-BuOH	32	29	4.5×10^8	$< 10^8$ (nonlinear)		169
	i-PrOH (IPA)	21	28	8.5×10^8			169
	CH	24(28)				7.5×10^9	169
	AN	23	28	1.0×10^9		7.1×10^9	169, 172
	MeOH	40					174
4,4,6,6-tetramethylcyclohexenone **219**	AN	34					174
3-Methylcyclohexenone **217**	AN	72	69	(4.6×10^9)			80
	CH	72		(10×10^{10})			80
Octalone 139	AN	57	58	(1.3×10^9)			173
	CH	47					173
Cyclopentenone **50**	AN (0.006 M)	125					80
	AN (0.06 M)	43	48	4.1×10^9			80
	CH (0.016 M)	68	80	1.3×10^{10}			80
	CH	30			$< 10^8$	5×10^9	81
Phenanthrone **154**	AN	131				3.8×10^9	169
	IPA	150	145	4.0×10^8	2×10^8 (nonlinear)	2.5×10^9	169
Testosterone acetate **132**	AN	385	413	(4.4×10^9)			173
	AN	380	295	5.0×10^9			172
	CH	292					173
Testosterone	AN	330			10^9	2.2×10^9	81
	CH	440					169
Bicyclononenone **170**	IPA	1,400	1,500	4.5×10^9	$\sim 10^9$		169, 172
	t-BuOH	2,300				3.0×10^9	172
Bicyclononenoal **216**	AN	1,700		$(\geqslant 10^{10})$			173
	CH	1,850					173

The monocyclic enones have sufficient flexibility to allow close approach of the two surfaces at something near to an orthogonal triplet geometry, as in the case of cycloheptenone (Figure 8), while the T_1–S_0 energy gap for the bicyclononenones should be much larger, corresponding to a planar enone chromophore. Thus, based on the structural dependence of the transient lifetime data, the assignment of the transient absorption centered at *ca* 280 nm to energetically relaxed π,π^* triplets seems secure. Supporting evidence from quenching data is given below. This assignment for the lowest triplet excited state, at least for cyclohexenone, cyclopentenone and 1-acetylcyclohexene, has recently received confirmation by direct observation of these enone triplets at 77 K using time-resolved electron paramagnetic resonance[174a].

The ability of dienes to quench the '280 nm transients' has been determined in several cases from the dependence of transient lifetime on quencher concentration, with often confusing results. The more rigid enones are quenched linearly by dienes such as piperylene and 1, 3-cyclohexadiene at close to diffusion-controlled rates, suggesting that triplet energy transfer is energetically favorable. However, plots of $(\tau_{obs})^{-1}$ or optical density (ΔOD) vs. [piperylene] curve downward at higher diene concentrations for the more flexible systems, such as cyclohexenone itself, enone **124** and to a lesser extent phenanthrone **154**[81,172]. It is known that cyclohexenones undergo photoaddition to conjugated dienes[110,175], which would gradually deplete the diene concentration, accounting at least in part for the observed nonlinear quenching behavior. Quenching rate constants k_q, estimated from the linear portion of these plots at low diene concentrations, are given in Table 3. It is obvious that these are much below the diffusion-controlled limit, indicating (a) that the triplet excitation energies of these enones is less than or equal to that of piperylene (58–59 kcal mol^{-1}) and/or (b) that there is a geometric inhibition of triplet energy transfer from the nonplanar enone triplets. In any event, the contrast between the linear and efficient quenching by piperylene of transient triplets derived from testosterone and enone **170** and the inefficient nonlinear quenching of transient triplets derived from the more flexible cyclohexenones strongly supports the proposal that the triplet energies of the more rigid enones are in the range of 67–70 kcal mol^{-1}, while the latter are highly twisted species with energies closer to 60 kcal mol^{-1}.

These conclusions are supported by studies using naphthalene (NA, $E_T = 60.9$ kcal mol^{-1}) and 1-methylnaphthalene (MN, $E_T = 59.6$ kcal mol^{-1}) as triplet quenchers[80,169,170,172]. Because ground-state UV absorption by naphthalenes obscures the transient absorption of the enones, it is not possible to directly measure transient quenching by naphthalenes. However, the growth of NA/MN triplet absorption at 413/420 nm can be easily observed, and in general gives an excellent fit to a simple first-order rate law. The rise time for NA or MN triplet absorption depends on quencher concentration as shown in equation 102, where τ_0 is the lifetime of the donor (enone) triplet

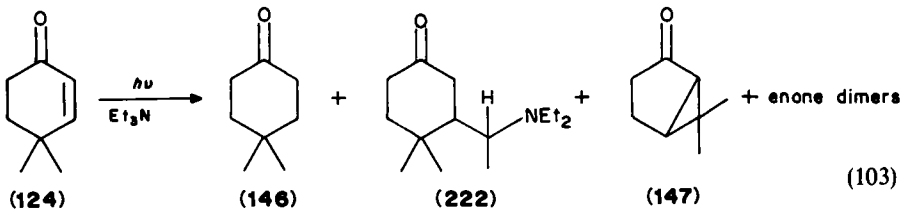
$$k_{obs} = 1/\tau_{obs} = 1/\tau_0 + + k_q[Q] \qquad (102)$$

in the absence of quencher and k_q is the quenching rate constant corresponding to transfer of triplet excitation from the enone triplet to NA or MN. Values of k_q and τ_0 obtained from the slope and reciprocal of the intercept of plots of $(\tau_{growth})^{-1}$ vs. [NA] or [MN] are given in Table 3; given the relatively large error in estimating intercepts from these plots, the agreement between these extrapolated values of τ_0 and the triplet lifetimes τ_T determined by measurement of triplet decay at 280–350 nm is excellent. There can be little doubt that the species transferring triplet excitation energy to NA and MN is indeed the species responsible for UV absorption at 280–350 nm[170]. The variation in k_q is again consistent with the argument that the donor is an energetically relaxed enone triplet: triplet transfer is effectively diffusion controlled for the more rigid cyclohexenones, especially **170** and **216**, slightly less so for the steroid enones, even less for octalone **139** and substantially lower for

the monocyclic enones. This trend is exactly as expected if the cyclohexenone triplet energy is gradually being reduced by the increasing ability to twist around the C=C bond. Thus, the rigid enones must have triplet excitation energies well above 65 kcal mol^{-1}, probably closer to 70 kcal mol^{-1}, while the energies of the twisted triplets of simple cyclohexenones must be near 60 kcal mol^{-1}, as previously concluded on the basis of other experimental evidence. The energies of several enone triplets have recently been determined by time-resolved photoacoustic calorimetry, and are completely consistent with these proposals[241].

The variation of rate constants for oxygen quenching $k_q(O_2)$ with enone structure also makes sense on this basis. Bonneau and coworkers[176] have observed differing rates of quenching of planar vis-à-vis perpendicular styrene and α-naphthylethylene triplets by oxygen. This was attributed to changes in spin statistics associated with different mechanisms of oxygen quenching, a spin-exchange mechanism ($k_q \sim k_{diff}/3 = 9 \times 10^9\,l\,mol^{-1}\,s^{-1}$) for quenching of perpendicular triplets, and an energy transfer mechanism ($k_q \sim k_{diff}/9 = 3 \times 10^9\,l\,mol^{-1}\,s^{-1}$) for quenching of planar triplets[177]. The same trend is seen with the cyclohexenones in Table 3, as higher values of $k_q(O_2)$ are consistently observed for the more twisted cyclohexenone triplets compared with the enone triplets constrained to planarity. This effect should be associated with variations in yields of singlet oxygen with enone structure, but this has yet to be studied.

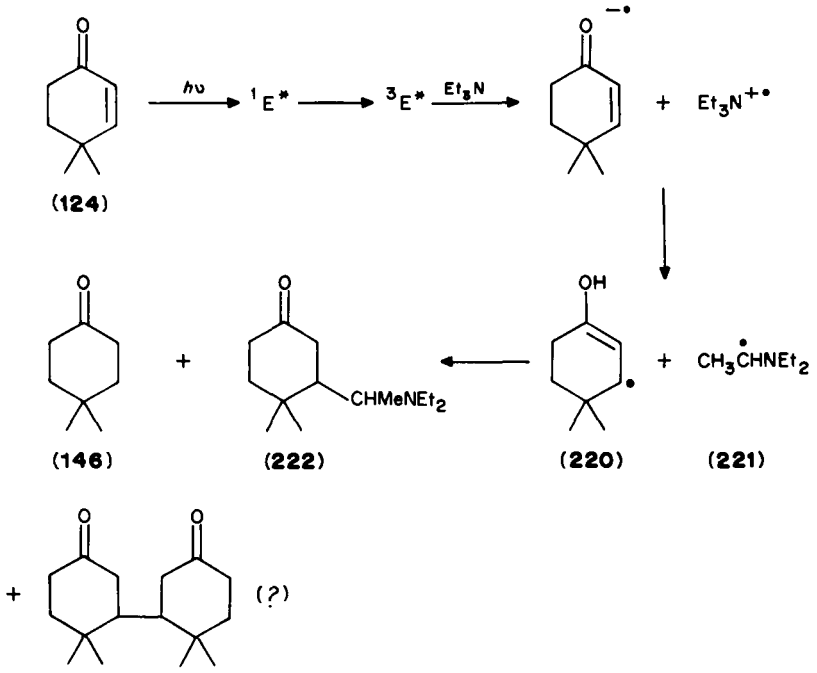
e. Competition between various reaction pathways of photoexcited cyclohexenones. As indicated above, cyclohexenones can undergo [$_\pi 2 + _\pi 2$] dimerization, reduction and rearrangement on direct or triplet-sensitized excitation. In addition, as will be discussed in detail below, they undergo photoaddition to alkenes to give cyclobutanes and (less often) oxetanes. In the presence of amines, photoexcited cyclohexenones give a mixture of dimers, reduction (**146**) and addition (**222**) products, as shown in equation 103 for enone **124** and triethylamine[111,172,178]. The simplest mechanism for this reaction involves electron



(124) (146) (222) (147) (103)

transfer from amines to enone triplets to generate a radical ion pair which, after proton transfer, gives the pair of free radicals **220** and **221**; radical combination would give the β-adducts **222** as a pair of diastereomers, while a second hydrogen abstraction would give the saturated ketone **146** (Scheme 30). Pienta and McKimmey[178] reported that the ratio of (**222** + **146**) to photodimers was linear with Et_3N concentration (from 1 to 7 M), and that the same ratio was independent of the enone concentration (from 0.006 to 1.6 M). On this basis, they proposed that all of these products arose from a dimeric excited species (or excimer). However, this mechanism is inconsistent with a number of observations of Schuster and coworkers, to be described below. An attempt to replicate Pienta's data[178] was unsuccessful. Insogna and Schuster[179] found that with an enone concentration of 0.3 M and amine concentrations above 0.5 M, the [2 + 2] photodimers formed from **124** in the absence of amine (see above) were no longer formed; in addition to adduct **222** and ketone **146**, two new products were observed whose mass indicates they are stereoisomeric dimers of radical **220** or (less likely) the corresponding species with the odd electron at C_2. It is possible that these products of reductive dimerization were mistaken for [2 + 2]

photodimers in the earlier study[178]. The product distribution is in fact totally consistent with Scheme 30 and it is therefore not necessary to postulate reaction via a triplet excimer.

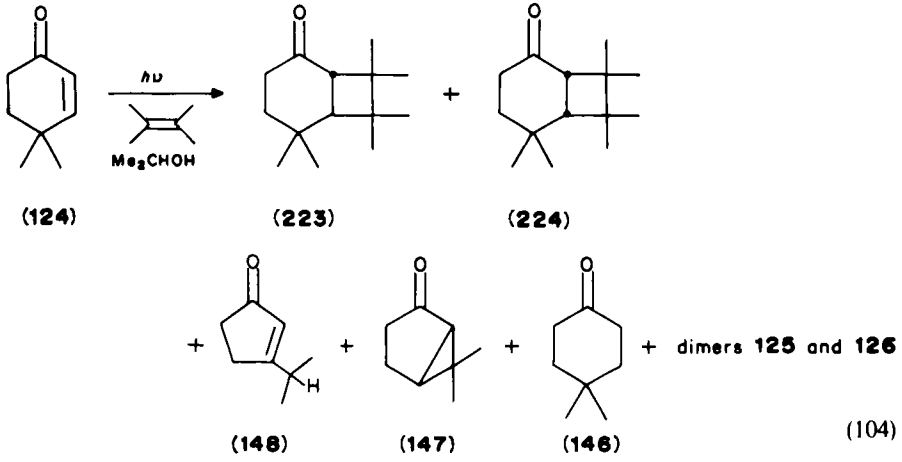


SCHEME 30

A series of studies have been undertaken to determine the competition between the various reaction pathways of photoexcited **124** and, to a lesser extent, other cyclohexenones, as a function of (a) enone concentration, (b) triplet quenchers, (c) amines as quenchers and (d) alkenes as quenchers. These will be summarized below, with details to be given elsewhere.

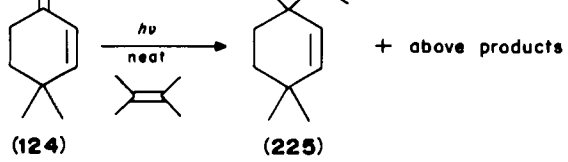
(i) Variation of enone concentration. Quantum yields of photodimers of cyclohexenones depend on the enone concentration, as originally reported by Wagner and Bucheck[79]. What was surprising was that, upon increasing the concentration of **124** from 0.23 to 1.64 M in 2-propanol, there was no effect within experimental error on the quantum yields of photoreduction product **146** and lumiketone **147**[172]; over this concentration range, the optical densities at $\geqslant 300$ nm were all > 2.0, so the results could not be explained by differential light absorption. Furthermore, a linear double reciprocal plot of $(\phi_{dim})^{-1}$ vs. $[enone]^{-1}$ was observed, with different slopes for the two dimers, as in Wagner's earlier study of cyclohexenone itself[79]. In a second experiment involving **124** in 2-propanol in the presence of tetramethylethylene (TME), it was found that increasing enone concentration from 0.93 to 1.86 M caused only a very slight reduction (overall $< 12\%$) in the yields of the cycloadducts **223** and **224** (equation 104) while there was a very large increase ($> 173\%$) in dimer yields. In the inverse experiment, a negligible effect of increasing the concentration of alkene (cyclohexene) on the yields of photodimers of **124** was observed[111]. These data indicate: (1) photodimerization of **124** occurs from a different

triplet state of **124** than is responsible for rearrangement, reduction or cycloaddition to alkenes. This conclusion is confirmed by both flash and steady-state quenching studies as indicated below.



(104)

(ii) Effect of triplet quenchers. As indicated earlier, quenching studies using piperylene have given confusing results, such as nonlinear Stern–Volmer plots, due at least in part to the formation of enone–diene photoadducts competitive with triplet excitation transfer[110]. Cleaner results have been obtained using MN and NA as triplet quenchers. As seen in Figure 11, Stern–Volmer slopes are identical for quenching by NA of the formation of lumiketone **147** and cycloadducts **223** and **224** in 2-propanol[111,170], indicating these three products arise from one and the same triplet (or, much less likely, two thermally equilibrated triplets). When **124** is irradiated in neat TME, oxetane **225** is obtained in addition to [2 + 2] cycloadducts **223** and **224**[180]. The Stern–Volmer slope for quenching of formation of **225** is experimentally different from that for the other two adducts[111], supporting the proposal that the oxetane arises from a $^3n,\pi^*$ state and the other adducts from a $^3\pi,\pi^*$ state.



A series of studies of the effect of naphthalene on the products of irradiation of **124** were carried out by Schuster and Nuñez[110]. They observed that Stern–Volmer slopes for formation of the photoreduction product **146** in 2-propanol were consistently 15–20% lower than for the photorearrangement products **147** and **148** (which gave the same slopes within experimental error). The same effect was seen using 1:1 *i*-PrOH benzene. However, in *t*-BuOH–toluene (1:1) NA had virtually no effect on the formation of **146** while it quenched formation of **147** and **148** with efficiency similar to that in the other solvents.

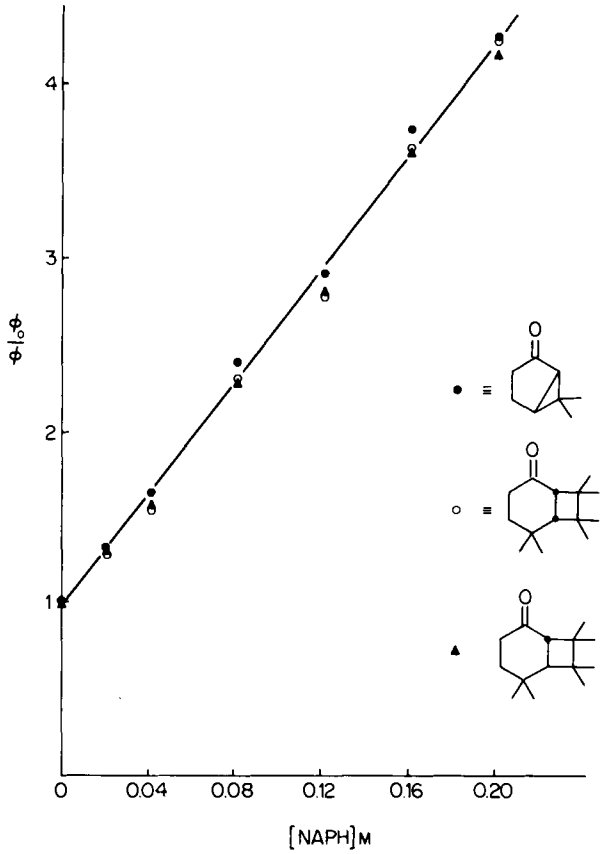
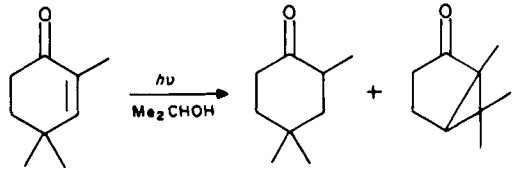


FIGURE 11. Quenching by naphthalene [Naph] of concomitant photorearrangement of enone **124** and its photoaddition to tetramethylethylene in 2-propanol (from Reference 111)

Based upon these data, it is concluded that photoreduction and photorearrangement of enone **124** occur via different triplet states of the enone. This conclusion is supported by similar observations using acenaphthene ($E_T = 59.2$ kcal mol^{-1}) as triplet quencher, and by the finding of very pronounced differential quenching by naphthalene of photoreduction vs. photorearrangement of the related enone **226** in 2-propanol (equation 105). Photorearrangement of **226** is much less efficient than for **124**, and sensitization studies with *p*-methoxyacetophenone indicate ϕ_{isc} is ~ 0.75 for **226** compared with 1.0 for **124**.



(226) (105)

Otherwise, the course of the reaction is similar for the two systems. The conclusion that different enone triplets are responsible for photorearrangement and photoreduction is supported by results using amines and alkenes as triplet quenchers, as discussed below. The effect of the solvent on the magnitude of the differential quenching effect is tentatively attributed to relative stabilization of the two reactive triplet states.

Differential quenching by naphthalene of the photochemical reactions of phenanthrone **154** in 2-propanol was discussed earlier in Section IV.B.4.6, and was taken as evidence for simultaneous reaction via both $^3n,\pi^*$ and $^3\pi,\pi^*$ states[122]. In that case, unlike **124**, the triplet leading to lumiketone **159** also was the source of the *cis*-fused reduction product **155**. By analogy, photoreduction of **124** to give **146** may also occur from both $^3n,\pi^*$ and $^3\pi,\pi^*$ states by different mechanisms and to extents that vary with the nature of the solvent, although there are as yet no data to support such an interpretation.

(iii) Effect of amines as quenchers. The reactions of enone **124** that occur in the presence of triethylamine as well as other amines was discussed above. The effect of amines on the other photoreactions of enone **124** has been studied. Dunn[172] showed that triethylamine strongly quenches rearrangement to lumiketone **147** but has virtually no effect on photoreduction to **146** in 2-propanol, while Tucker[111] showed that both photorearrangement and cycloaddition of **124** to TME in 2-propanol are quenched to the same extent by triethylamine, although neither reaction was quenched by *t*-butylamine[172]. DABCO (1,4-diazabicyclo[2.2.2]octane) strongly quenches lumiketone formation in 2-propanol and acetonitrile, but uniquely in this case Stern–Volmer plots of the data have distinctly upward curvature; while DABCO has a noticeably smaller but nonetheless significant effect on both dimerization of **124** and photocycloaddition to TME, with nicely linear Stern–Volmer behavior, it has no measurable effect on photoreduction[111].

These data clearly demonstrate the separation of the reaction pathways leading to photorearrangement and photoreduction of enone **124**. The relative ability of amines (DABCO > Et_3N > *t*-$BuNH_2$) to quench photorearrangement of **124** to **147** is inversely related to their ionization potentials (7.10, 7.50 and 8.64 eV, respectively), strongly suggesting that the triplet-quenching process involves electron transfer, as has been shown for other ketone–amine systems[181], and in accord with the nature of the products in the case of Et_3N (see above). DABCO does not afford enone–amine adducts nor induce photoreduction of the enone[172], consistent with the known reluctance of $DABCO^{+\cdot}$ to lose a proton. The pronounced curvature seen in the Stern–Volmer plots for quenching by DABCO of photorearrangement of **124**, and the diversion of these curves from the linear plots for quenching by DABCO of photocycloaddition to TME, are puzzling[111]. The quenching data discussed previously as well as the effect of alkenes on photorearrangement (see below) all strongly indicate that these reactions occur from a common triplet. The relatively long lifetime of the DABCO radical cation compared with radical cations derived from the other amines studied may be a factor. One possibility is that DABCO or $DABCO^{+\cdot}$ may intercept an intermediate, not evident from other studies, on the way to lumiketone from the reactive triplet.

The effect of DABCO on the photochemistry of phenanthrone **154** in 2-propanol was also investigated[172]. A clear distinction between quenching of formation of **156** as opposed to **155** and **159** (which showed the same Stern–Volmer slope) was observed, consistent with earlier evidence that these products arise from different triplets.

(iv) Effect of alkenes as triplet quenchers. Photorearrangement of **124** and photocycloaddition to alkenes apparently take place via a common triplet-excited state, according to the naphthalene quenching data[111,170]. If so, one would expect that alkenes ought to inhibit lumiketone formation. Since the enone triplet implicated in the lumiketone rearrangement is apparently highly twisted, the observation that photoaddition of enones such as **124** to electron-rich alkenes affords *trans*-fused cycloadducts as major products

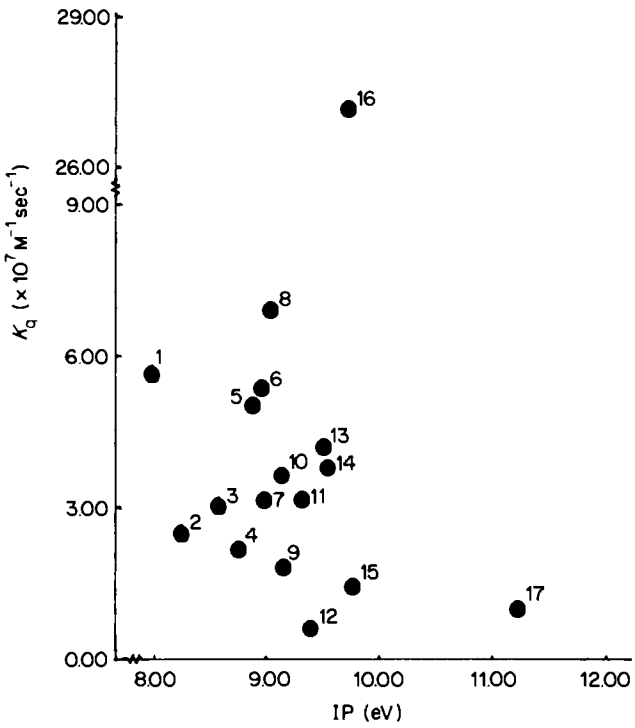


FIGURE 12. Rate constants for quenching of photorearrangement of enone **124** by alkenes and alkynes as a function of alkene ionization potential. Quencher: 1. 2,3-dimethyl-2-octene; 2. tetramethylethylene; 3. 2-methyl-2-butene; 4. norbornene; 5. 2,4,4-trimethyl-1-pentene; 6. cyclohexene; 7. *trans*-3-hexene; 8. cyclopentene; 9. *trans*-2-pentene; 10. *cis*-2-pentene; 11. 2-methyl-1-butene; 12. 4-octyne; 36. 1-heptene; 14. 3,3-dimethyl-1-butene; 15. 3,3-dimethyl-1-butyne; 16. *cis*-1,2-dichloroethylene; 17. maleic anhydride; 18. bicyclo[2.2.2]-2-octene; 19. dimethyl acetylenedicarboxylate

Studies by Schuster and coworkers[182,183] established that alkenes which undergo photocycloaddition to cyclic enones such as **124**, cyclopentenone and cyclohexenone quench the lumiketone rearrangement of **124** in 2-propanol and acetonitrile. The efficiency of this quenching, measured by the slopes ($K_q = k_q\tau$) of the linear Stern–Volmer plots of the quenching data, was studied as a function of the ionization potential (IP) of twenty alkenes and alkynes by Rhodes and Schuster[183], where k_q is the second-order rate constant for interaction of the alkene with the reaction intermediate of lifetime τ. A linear inverse correlation of $\log k_q^{rel}$ vs. alkene IP was anticipated, because it has been widely accepted since the pioneering studies of Corey and coworkers[184] that the initial alkene–enone interaction involves formation of a π complex (exciplex) with the alkene acting as donor and the enone triplet as acceptor. In fact, no such correlation of the quenching data with IP was observed (see Figure 12). As an example, tetramethylethylene (TME) has the second lowest IP of the alkenes used in Rhodes' study, but was one of the poorest quenchers of the photorearrangement[183]. In two cases in which pairs of *cis–trans* alkene isomers were utilized, the *cis* alkene was the better quencher. The data suggest that steric effects dominate over electronic effects in this system, and raise serious questions about the

donor–acceptor mechanism for the photocycloaddition process. Recent laser flash data to be discussed later lead to the same conclusion.

One other important observation is that alkenes do not inhibit photoreduction of **124** to **146** in 2-propanol. This supports the conclusion reached earlier on the basis of other quenching data that photorearrangement and photoreduction of **124** do not occur via a common triplet-excited state.

f. Correlation of flash data and quenching data from continuous irradiations. Given the multitude of enone triplet-excited states implicated above in the photochemical reactions of **124** and **154** and, by implication, other cyclohexenones, an obvious problem concerns the relationship between the steady-state quenching data and the flash data. That is, are the transient triplets observed in the laser flash experiments intermediates in the photochemical reactions of these cyclohexenones, and if so, which reactions?

The answer to these questions can be obtained from a comparison of the Stern–Volmer slopes ($k_q \tau_T$) for quenching of the photorearrangement of enones **124**, **154** and **226** by naphthalene (NA) or 1-methylnaphthalene (MN) with the absolute values of the rate constants for triplet-excitation transfer k_q (as obtained from the kinetics of growth of NA and MN triplet absorption) and the directly measured lifetimes τ_T for transient triplet decay[172]. For a number of systems, this agreement is excellent, and cannot be simply fortuitous. Thus, the relaxed triplet-excited states observed upon laser flash excitation of these cyclohexenones are indeed intermediates in the photorearrangements of these systems. From the data previously presented, they must also be intermediates in the photocycloadditions of these (and by implication other) cyclohexenones to alkenes.

However, these triplets appear not to be intermediates in enone photodimerizations. Bonneau originally reported that the lifetimes and optical densities of the '280 nm' transient derived from cyclohexenone did not change as a function of enone concentration[81], an observation that was extended to enone **124** (at concentrations up to 0.99 M) by Dunn and Schuster[172]. From the dependence of the quantum efficiency of photodimerization on enone concentration, a pronounced reduction in the lifetime of the enone triplet undergoing photodimerization should be seen; however, no such effect on the '280 nm transient' is observed. Also, the triplet lifetimes observed in the flash experiments are much longer than those estimated in Wagner's study of photodimerization[79]. Thus, it appears that photodimerization proceeds via a short-lived higher-energy triplet, perhaps a planar π,π^* triplet, rather than the relaxed (twisted) species observed in the flash studies. The triplet which leads to the enone dimers cannot be a precursor of the triplet observed by laser flash techniques, since the optical density of the latter is not reduced as the enone concentration is increased, up to 0.99 M in the case of **124**. This, perhaps surprising, conclusion requires that the twisted triplet is formed independently, perhaps via a twisted singlet excited state of the enone.

Flash excitation of cyclohexenones in the presence of amines has provided controversial data. New long-lived transient absorption is observed in the region of the triplet absorption (270–350 nm) which quickly obscures the triplet decay and makes lifetime measurements difficult[185,186]. However, Pienta has reported that at low amine concentrations, the enone triplet lifetimes appear to increase, which he associates with a rapid equilibrium between the enone triplet and an enone–amine exciplex, as in Scheme 31. Equilibrium constants for formation of the exciplex could be calculated from these data[186]. However, Dunn, Schuster and Bonneau performed similar experiments, and were unable to see the effect of amines on enone triplet lifetimes reported by Pienta[185]. Recently, Weir, Scaiano and Schuster studied the effect of several amines on the triplet decay of several cyclohexenones[174]. After correction for light emission following the flash (by subtracting the photomultiplier response after the flash with the analyzing beam off), they find that the amines definitely quench the enone triplets. The second-order rate constants determined in their study are given in Table 4. From the dependence of the initial optical

$$EN \longrightarrow {}^1EN^* \longrightarrow {}^3EN^* \overset{K_{eq}}{\underset{Amine}{\rightleftharpoons}} (EN \cdots Amine)^*$$

$$k_{obs} = \frac{k_1 + k_2 K_{eq}[Amine]}{1 + K_{eq}[Amine]}$$

Where $k_1 = (\tau_T)^{-1}$ and $k_2 = (\tau_{EN\cdots Amine}^*)$

SCHEME 31

density of the long-lived absorption on amine concentration, the lifetimes of the enone triplets intercepted by the amines were determined, which allows their identification as the '280 nm' transients, i.e. as relaxed $^3\pi,\pi^*$ enone triplets. The quenching rate constants, taken with values of τ_T, agree with Stern–Volmer slopes for quenching by amines of photorearrangement in the case of **124**[111,172].

Dunn, Schuster and Bonneau[185] have observed new transient absorption centered at 450 nm when enones are excited at 353 nm in the presence of DABCO. They established that this absorption is due to $DABCO^{+\cdot}$. From the rate of growth of this absorption, rate constants for the interaction of DABCO with the relevant enone triplet, and the lifetime of the enone triplet which is intercepted by DABCO were determined. It is clear that DABCO is intercepting the '280 nm transient', i.e. the twisted enone π,π^* triplet, in an electron transfer process which generates amine radical cations. Once again, excellent agreement was found between the directly measured quenching rate constants and the initial slopes for quenching by DABCO of enone photorearrangement. There can be little doubt from these data that the twisted enone π,π^* state which leads to lumiketone and alkene addition products is the species which is intercepted by amines. The shorter-lived triplet responsible for photodimerization is also quenched by amines, but with much lower efficiency according to the steady-state data[172].

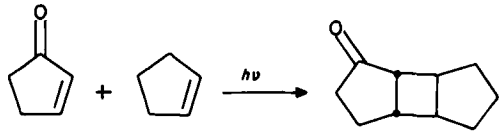
The effect of alkenes on the rate of decay of the transient enone triplets will be discussed below in the section dealing with the enone–alkene photocycloaddition process.

g. Intermolecular photocycloaddition of cyclic enones to alkenes. (i) Introduction. Eaton and Hurt[78a] originally discovered the photodimerization of cyclopentenone, and shortly afterward Eaton reported that 2-cyclopentenone reacts similarly with cyclopentene to give cycloadduct **227** (equation 106)[187]. Corey and coworkers studied analogous $[_\pi 2 + _\pi 2]$ photocycloaddition of cyclohexenone to a variety of alkenes, and established many of the basic features of this reaction, as discussed below[184]. Corey first recognized the potential of the enone–alkene photocycloaddition reaction as a key element of a scheme for synthesis of natural products, as demonstrated in his synthesis of caryophyllene[188]. Since

TABLE 4. Triethylamine quenching of cyclohexenone triplets

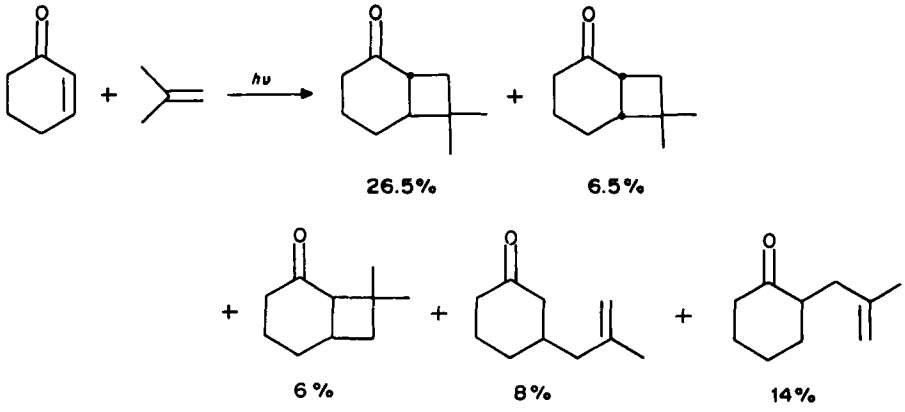
Compound	Solvent	k_q ($l\,mol^{-1}\,s^{-1}$)
118	acetonitrile	$(9.0 \pm 0.8) \times 10^7$
	cyclohexane	$(9.2 \pm 4.6) \times 10^7$
124	methanol	$(1.1 \pm 0.4) \times 10^8$
	acetonitrile	$(3.7 \pm 0.5) \times 10^7$
192	cyclohexane	$(1.3 \pm 0.5) \times 10^8$
154	acetonitrile	$(2.0 \pm 0.6) \times 10^6$

these pioneering studies, inter- and intramolecular photocycloadditions of cyclic enones (cyclopentenones and cyclohexenones for the most part) to alkenes (also called photoannelations) have become probably the most frequently utilized photochemical reaction in the arsenal of synthetic organic chemists. Several excellent reviews of the applications of this methodology have been recently published, so that there is no need here to review this large literature in detail[7-9,189]. This discussion will be concerned with the basic features of the intermolecular reaction, and recent studies relating to its mechanism. The synthetically important intramolecular enone–alkene photocycloaddition possesses several other features which will be discussed separately.

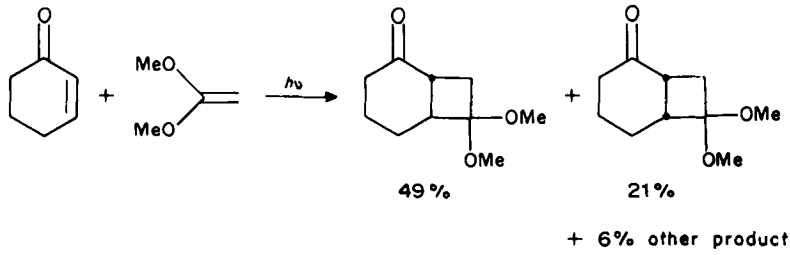


(227) (106)

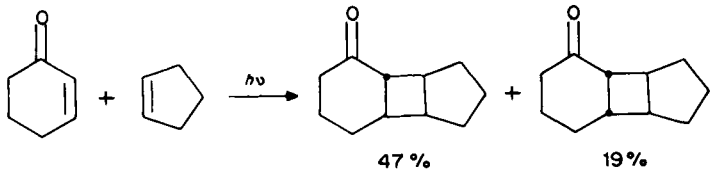
(ii) Scope, regiochemistry and stereochemistry of the [2 + 2] photocycloaddition of cyclic enones to alkenes. Corey and coworkers[184] originally established that cyclohexenone undergoes photocycloaddition to a variety of alkenes, including isobutylene (equation 107), 1,1-dimethoxyethylene (DME) (equation 108), cyclopentene (equation 109), allene (equation 110), vinyl acetate (equation 111), methyl vinyl ether



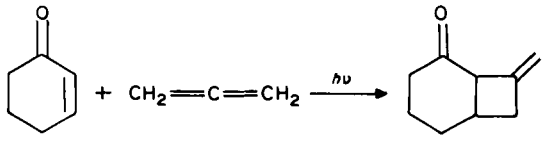
(107)



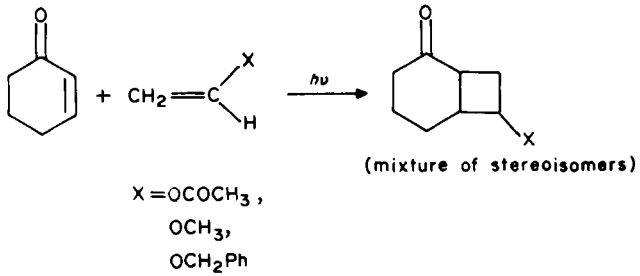
(108)



(109)

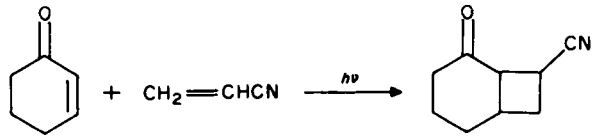


(110)



(111)

(equation 111) and benzyl vinyl ether (equation 111). As can be seen from equations 107–109, the major cycloadduct in these systems has a *trans* fusion of the four- and six-membered rings, which was a feature that Corey immediately recognized as having potential value in the synthesis of complex ring systems. The stereochemistry of the adducts in the other cases was not established. In the case of isobutylene, the cycloadducts were accompanied by olefinic ketones which Corey suggested were formed via disproportionation of 1,4-diradical intermediates (see below). Orientational specificity was clear in all these cases. A much 'slower' reactions was observed between cyclohexenone and acrylonitrile, which gave four adducts whose structures and stereochemistry were not established, although it was suggested that they have the regiochemistry shown in equation 112, opposite to that seen above.

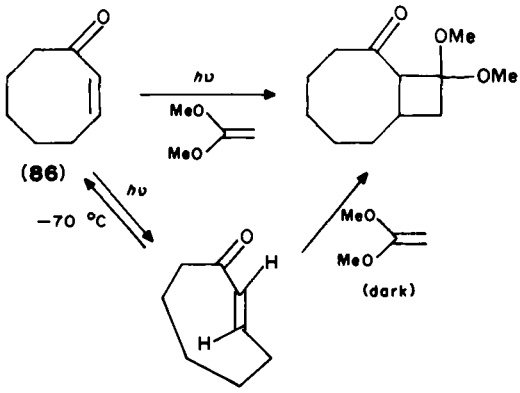


(112)

A mixture of identical cycloadducts was obtained from photoaddition of cyclohexenone to either *cis*- or *trans*-2-butene, suggesting that the stereochemistry of the alkene reactant is lost in the course of the reaction. Recovery and IR analysis of the starting materials after various reaction times established that $< 1\%$ isomerization of the alkene had occurred[184].

Utilizing DME as his model alkene, Corey and coworkers established that photoad-

dition occurred to cyclopentenone and cyclooctenone (**86**) but not to cycloheptenone **94** (equation 113). A special pathway for 2-cyclooctenone was established by the fact that the same cycloadduct could be obtained by irradiation of **86** at dry ice temperatures until a photostationary state with the *trans* isomer **87** was achieved, discontinuation of irradiation, followed by addition of DME and warming to room temperature in the dark. Thus, at least in this system, the alkene appears to react with the ground-state *trans* enone, and not with an excited state of the *cis* enone[184].



(113)

Methyl-substituted cyclohexenones were shown to react with isobutylene in a manner analgous to that shown in equation 107. The 'rate' of reaction was considerably reduced by the presence of a 2-methyl substituent (2-methylcyclohexenone) but a methyl at C_3 (enone **217**) had no effect on the 'rate'.

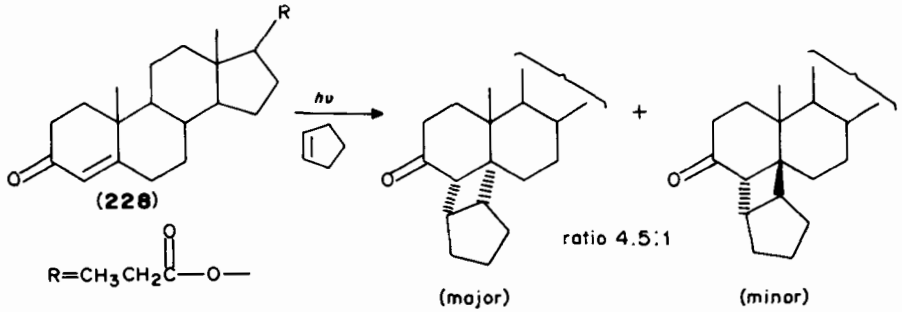
Corey and coworkers[184] determined 'relative rate factors' for reaction of five alkenes with cyclohexenone from irradiation of the enone in the presence of pairs of alkenes in large molar excess, with cyclopentene as the reference alkene. The numbers (corrected for statistical factors) were as follows: DME, 4.66; methoxyethylene, 1.57; cyclopentene, 1.00; isobutylene, 0.13–0.40; allene, 0.23. These 'rate factors' were of key importance in Corey's mechanistic proposals, as will be seen shortly.

Since it will be a matter of considerable importance latter in this discussion, it should be pointed out that the relative 'rates' frequently mentioned in Corey's paper[184] are of course not really rates at all but rather relative quantum efficiencies for disapperance of starting material and/or appearance of products. The relationship of relative or even absolute quantum efficiencies of product formation to rates of particular steps in a multistep photochemical reaction scheme is always ambiguous, as was recognized many years ago for the Norrish Type II reaction of aromatic ketones[50]. This important distinction, which has important mechanistic implications, does not appear to have been recognized in prior discussions of the enone–alkene cycloaddition process.

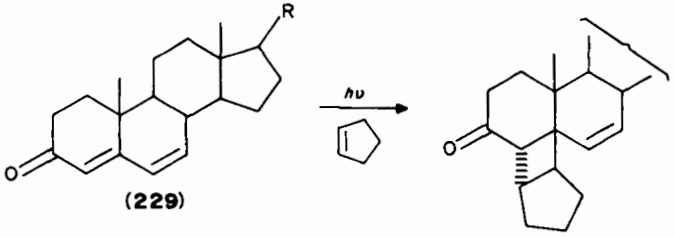
A number of other studies have been reported since Corey's seminal contributions to this area which basically reproduce and extend his findings. Under certain circumstances, oxetane formation via $^3n, \pi^*$ states can compete with the [2 + 2] mode of cycloaddition. Thus, as mentioned earlier, when enone **124** is irradiated in neat TME[180] oxetane **225** is obtained in addition to *trans*- and *cis*-fused cycloadducts and open-chain adducts, but no trace of **225** can be detected when the reaction is carried out in acetonitrile as solvent[111,172]. Earlier observations of differential quenching of formation of the two cycloadducts using di-*t*-butylnitroxyl[180] were interpreted in terms of two different triplet precursors for the stereoisomeric adducts; more recent studies using naphthalene as

quencher demonstrate clearly that both [2 + 2] adducts arise from a common triplet state[111], and that $(t\text{-Bu})_2NO$ is probably intercepting triplet 1,4-biradical intermediates.

Steroid enones also give a mixture of *cis*- and *trans*-fused cycloadducts with simple alkenes. Thus, Rubin and coworkers[190] found that testosterone propionate **228** reacts with cyclopentene to give a 4.5:1 mixture of *cis*- and *trans*-fused adducts as shown in equation 114, while the corresponding dienone **229** gives only a single *trans*-fused adduct (equation 115). Rubin compared the ratio of *cis*- to *trans*-fused adducts in equation 114 and in addition of 2-cyclohexenone to cyclopentene in ethyl acetate solvent at room temperature and in dry ice–acetone (−78 °C). The *cis*–*trans* ratio of adducts in equation 114 decreased as the temperature was lowered and also varied with the alkene concentration; the product ratio in the cyclohexenone–cyclopentene reaction appeared to be relatively insensitive to temperature changes. No quantum yield data were reported.

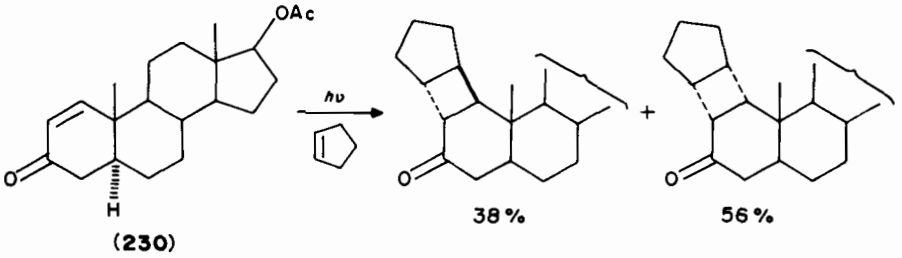


(114)

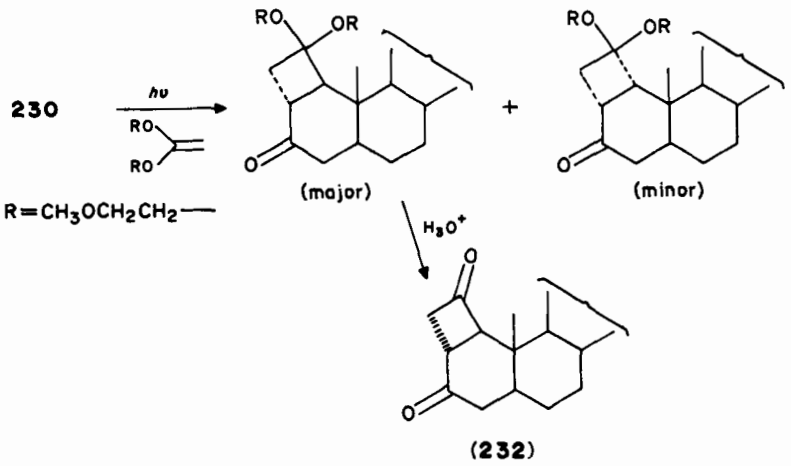


(115)

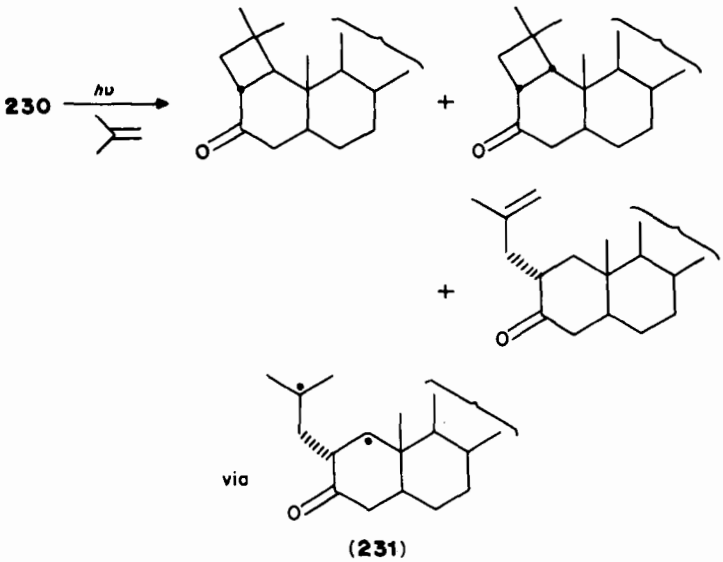
Lenz[191] has studied photocycloaddition of the Δ^1-steroid enone **230** to cyclopentene, a ketene acetal and isobutene. In all cases, *trans*-fused adducts are formed as major products. The products in each case are shown in equations 116–118; note the formation of disproportionation product in the last equation as in Corey's original study



(116)



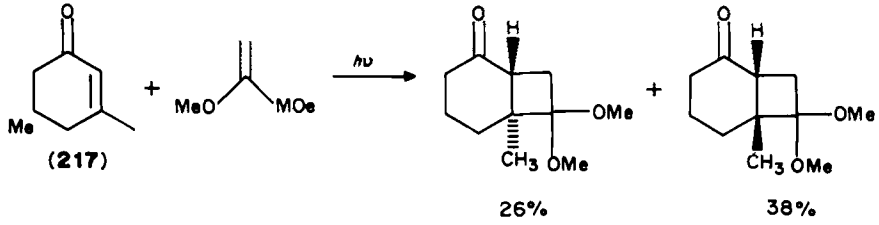
(117)



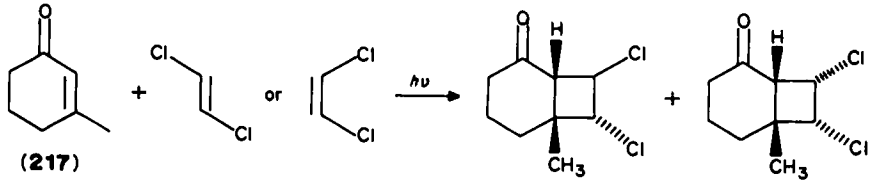
(118)

(equation 107). Lenz notes that all the products in equation 118 can be derived from the same intermediate 1,4-diradical **231** formed by bonding between the alkene and the β-carbon of the enone. The addition to cyclopentene was readily quenched by piperylene implicating a triplet state process. The *trans*-fused cyclopentene and isobutene adducts are remarkably stable to both strong acid and base at room temperature, probably due to steric shielding of the enolizable proton. This is significant since base-catalyzed epimerization has been used in many cases to distinguish between *cis*- and *trans*-fused adducts[7,8,184]; thus, such assignments must be made with care. By hydrolysis of the *trans*-fused adduct in equation 117, Lenz was able to isolate the first *trans*-fused cyclobutanone **232**.

Cantrell and coworkers[192] studied photocycloaddition reactions of 3-R-cyclohexenones, with R = methyl, phenyl and acetoxy, to several alkenes. The course of reaction of the 3-methyl enone (**217**) with DME is shown in equation 119 as an example of the behavior observed. The regiochemistry is similar to that observed by Corey[184] for the parent system, and again a mixture of *cis*-and *trans*-fused isomers is obtained. Irradiation of **217** in the presence of *cis*- or *trans*-1,2-dichloroethylene gave the same two major adducts in slightly different yields (equation 120) plus three unidentified minor products. Once again, one sees loss of alkene stereochemistry en route to the photoadducts. The photoadducts of 3-phenylcyclohexenone are all presumed to be *cis*-fused, since they are stable to base (see below).



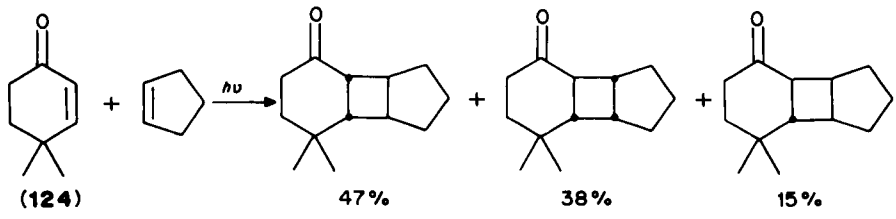
(119)



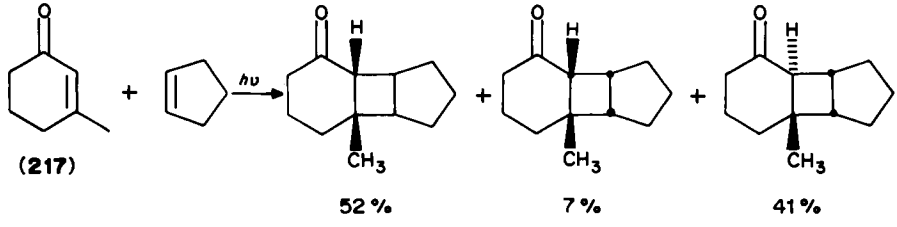
(120)

An important observation[192] was that photocycloaddition of **217** to acrylonitrile 'proceeded surprisingly rapidly'. The structures and stereochemistry of the adducts were not rigorously determined, but it appears that the predominant regiochemistry is analogous to that for the parent system (equation 112). In fact, acrylonitrile was the 'most reactive' of the olefins used with **217**, contrary to Corey's results with cyclohexenone itself[184]. The 'relative rates' found by Cantrell and coworkers[192] for photoaddition to **217** are: acrylonitrile, 7.68; ethoxyethylene, 1.96; DME, 1.27; cyclopentene, 1.00; isobutene, 0.59; *trans*-1,2-dichloroethylene, 0.40. Except for acrylonitrile, the trend is similar but not identical to that seen by Corey (note the inversion of DME and ethoxyethylene). Again, one must be reminded that these data represent not 'rates' but relative quantum yields, which may or may not have any relationship to the rate of the initial interaction of the reactive excited state of the enone with the alkene, as will be clear in the later discussion. Cantrell and coworkers tried to rationalize the apparently 'abnormal' reactivity of acrylonitrile by invoking some rather *ad hoc* mechanistic alternatives. It is significant that the other enones studied did not react especially 'fast' with acrylonitrile.

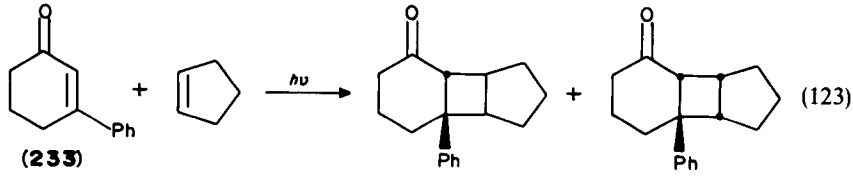
McCullough and coworkers[193] isolated three cycloadducts from photoaddition of 4,4-dimethylcyclohexenone **124** to cyclopentene (CP), whose structures are given in equation 121. The major adduct has the *cis–anti–cis* stereochemistry, and the other two adducts have *trans*-fused cyclobutane rings. Similar behavior is observed on photoaddition of CP to 3-methylcyclohexenone **217** as seen in equation 120, in agreement with findings from Cantrell's laboratory[192]. However, photoaddition of CP to 3-phenylcyclohexenone (**233**) gives only *cis*-fused cycloadducts, as shown in equation 123.



(121)



(122)

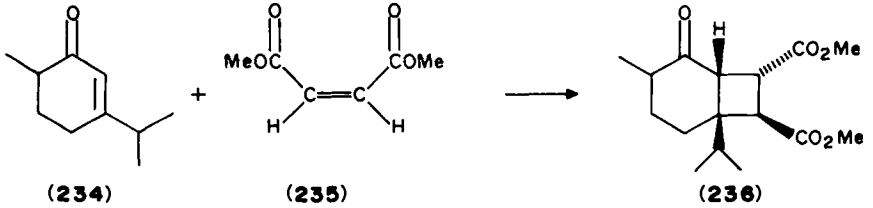


(123)

McCullough and coworkers also showed[193] that the ratio of rearrangement products to CP adducts of enone **124** in methanol was unchanged in the presence of 0.05 M naphthalene, although the efficiency of reaction was reduced by a factor of 3. These data are in agreement with results of the more extensive quenching studies of Tucker discussed earlier, which demonstrated conclusively that photoaddition of **124** to tetramethylethylene and photorearrangement to **147** in 2-propanol are quenched to exactly the same extent by naphthalene[170,172]. McCullough and coworkers[193] propose that formation of *trans*-fused adducts in major amounts from **124** and **217** with CP can be rationalized by attack of a nonplanar triplet state of the enone on ground-state alkene, with initial bonding at C_2 of the enone, and rapid formation of the second bond of the cyclobutane before the enone moiety can relax to its equilibrium configuration. Since it is likely that these reactions proceed via 1,4-biradicals[194] (see below), the second step must be fast, since it is otherwise difficult to understand why an equilibrated biradical would give highly strained adducts with *trans*-fused four- and six-membered rings. The fact that neither Cantrell[192] nor McCullough[193] found evidence for *trans*-fused adducts from 3-phenylcyclohexenone and a variety of alkenes implies that (a) this enone does not twist about the C=C bond and/or (b) the intermediate biradical is stabilized by the phenyl group, enhancing the probability that it will assume a relaxed geometry prior to ring closure. These arguments will be considered later in the detailed discussion of the mechanism of the photocycloaddition reaction.

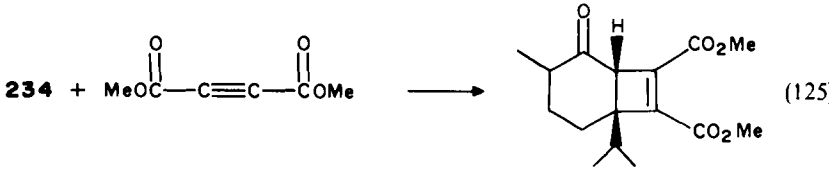
The effect of incorporating large alkyl groups at C_3 of the enone on the stereochemical course of photoaddition was examined by Singh[195] with carvenone **234** and 3-*tert*-butyl-2-cyclohexenone. From addition of **234** to ethoxyethylene and DME, both *cis*- and *trans*-fused cycloadducts were isolated, the latter as minor products. In all other reactions of

these two enones, only *cis*- fused adducts were formed. Photocycloaddition of **234** to dimethyl maleate **235** was sluggish, but one adduct identified as **236** could be isolated in low yield (equation 124). Loss of stereochemical integrity of the alkene moiety is again apparent in this reaction. Photoaddition of **234** to dimethyl acetylenedicarboxylate to give **237** was also observed (equation 125).



(234) **(235)** **(236)**

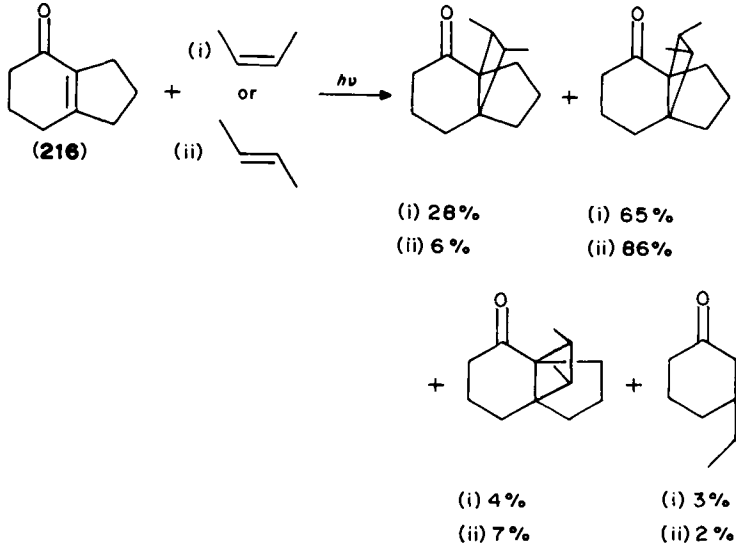
(124)



(125)

(237)

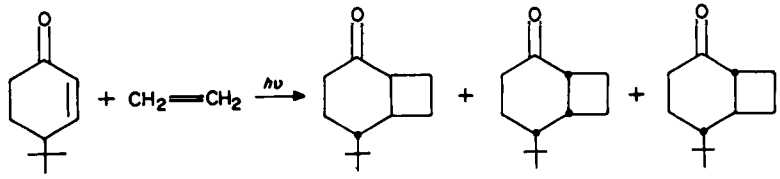
Three cycloadducts were observed by Cargill and coworkers[196] on photoaddition of $\Delta^{1,6}$-bicyclo[4.3.0]nonen-2-one **216** to either *cis*- or *trans*-2-butene, as shown in equation 126. As seen previously, stereochemical integrity of the alkene is lost. The product distribution from each alkene isomer could be rationalized in terms of preferential



(126)

formation of 1, 4-biradicals by bonding to the β-carbon and not the α-carbon of the enone, and by rotational equilibration of the biradicals prior to ring closure. The same conclusion was reached by Dilling and coworkers[197] from studies of addition of cyclopentenone to *cis*- and *trans*-1, 2-dichloroethylene. In both studies, however, no provision is made for possible reversion of biradical intermediates to ground-state enone and alkene (quantum yields were not measured in either study) which can seriously affect this type of mechanistic model. Neither Cargill nor Dilling found it necessary to invoke π complexes in their mechanisms.

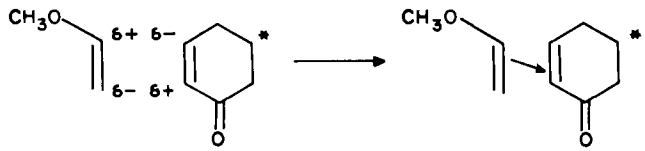
Cargill and coworkers[198] also found that photoaddition of 4-*tert*-butylcyclohexenone **238** to ethylene gave the adducts shown in equation 127, which bears directly on models for the cycloaddition reaction proposed by Wiesner[199] that will be discussed below.



(127)

Various models suggested to rationalize of the stereochemistry and regiochemistry observed in enone–alkene photocycloadditions, as illustrated above using representative examples from the literature, will be discussed within the context of proposed photocycloaddition reaction mechanisms.

(iii) The Corey–de Mayo mechanism for photocycloaddition of enones to alkenes. On the basis of the regiochemistry and the 'relative rate factors' associated with addition of alkene to photoexcited cyclohexenone, Corey suggested in 1964[184] that the first step of the reaction involved interaction of an enone excited state, which most likely was a triplet state (whether n, π^* or π, π^* was not clear at that time), to a ground-state alkene to give an 'oriented π-complex'. For the case of addition of methoxyethylene, Corey suggested that the preferred orientation was as shown in Scheme 32. The charge polarization in the enone

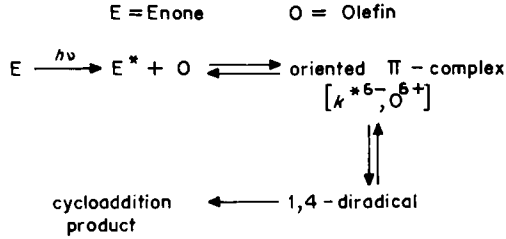


SCHEME 32

component was based on the assumption that the reactive excited state of the enone was an n, π^* state whose charge distribution, according to calculations made by the extended Hückel method, was such that C_β is negative relative to C_α. The π complex was proposed to be of the donor-acceptor type in which the alkene acted as donor and the excited enone as acceptor, the two held together by coulombic attraction. Corey notes that the face that differences in 'reactivity' of allene, methoxyethylene and cyclopentene are modest despite large differences in their ionization potentials argues against a highly polar donor–acceptor complex. There is no doubt, however, that alkene reactivity ought to correlate with ionization potential according to this model. It was also noted that this π-complex model cannot be extended to photodimerization of enones, and possibly not to reaction of

enones with olefins possessing electron-withdrawing substituents such as CN or COOR. The importance of steric effects could not be assessed at the time the π-complex model was introduced. No evidence for ground-state π complexation of cyclohexenone and ethoxyethylene was observed.

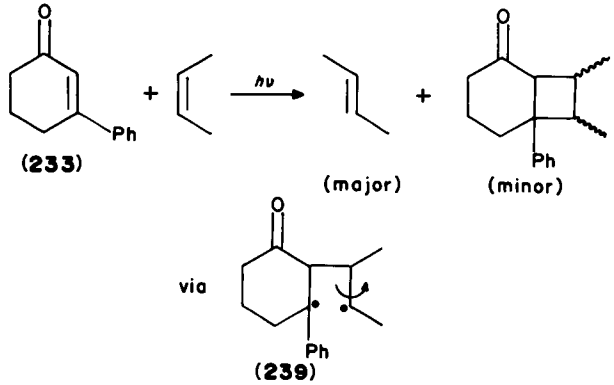
Corey rejects the alternative hypothesis that the orientation in photocycloaddition is controlled by preferences in diradical formation, since it does not predict the correct regiochemistry in photoaddition of cyclohexenone to DME. Also, it was not in accord with the 'relative rate factors' determined earlier. However, it was necessary to invoke 1, 4-diradicals in order to rationalize the formation of disproportionation products as in equation 107, and the loss of stereochemistry upon photoaddition of cyclohexenone to the 2-butenes. The overall scheme proposed by Corey and coworkers[184] is as shown in Scheme 33.



SCHEME 33

Before citing recent evidence bearing directly on the mechanism of photocycloaddition of enones to alkenes, some criticism of Corey's proposed mechanism[184] can be made in hindsight. First of all, without quantum yield data, it is impossible to say very much about the nature of the intermediates involved in this reaction. Any and all of the intermediates proposed by Corey (enone triplet, π complex, biradicals) can in principle revert to ground-state enone and alkene in competition with progress forward to cycloadduct. The importance of such reversion was not at all apparent until the first quantitative studies of this reaction were made by Loutfy and de Mayo[200] (see below). Without such information, it is not possible to relate the orientational specificity to preferred formation of one or another π complex, since the partitioning factors for progress vs. reversion may be very different for isomeric π complexes and biradicals. That is, the quantum yield ratio (or product yields) obtained in competition experiments, whether involving formation of adducts of two different olefins or isomers from a single olefin, is not related in a simple way to the rate of the initial enone–alkene association. That biradical reversion may well be the most important factor leading to quantum inefficiency in cycloadditions is suggested by McCullough and coworkers' observation[201] that irradiation of 3-phenyl-2-cyclohexenone **233** and *cis*-2-butene gave a much higher yield of *trans*-2-butene than of addition products, which he attributes to preferred reversion vs. cyclization of the intermediate 1, 4-biradical (**239**) in this system (see equation 128). They demonstrated by sensitization and quenching studies that this reaction proceeds via a relatively long-lived (1.59 μs) triplet state of **233**; recent flash data[80] demonstrate that indeed the 3-phenylcyclohexenone T_1 state is very long-lived, as is T_1 of 3-phenylcyclopentenone[202].

Secondly, Corey's model[184] for the oriented π complex is based upon the assumption that the reactive excited state of the enone is a triplet n, π^* state. Corey diligently but unsuccessfully searched for phosphorescence from cyclohexenones in order to directly identify the lowest triplet state as n, π^* or π, π^*. Studies by Kearns, Marsh and Schaffner[203] of phosphorescence emission from steroidal enones at 77 K and 4.2 K published only a few

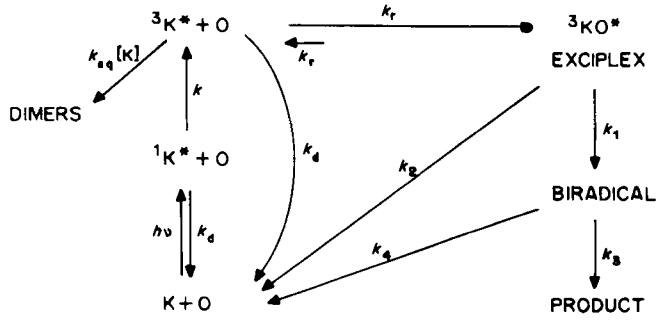


(128)

years later established that the lowest triplet in these cases is a π,π^* triplet, with the lowest n, π^* triplet only a few kcal mol^{-1} higher in energy. The assignment was based upon the diffuseness of the spectra, lack of spectral overlap with $S_0 \rightarrow T_{n,\pi}$, absorption, lifetime data, heavy atom effects and polarization measurements. Jones and Kearns concluded sometime later[204] that for these enones at low temperatures the enone chromophore is essentially planar, although this of course does not preclude twisting around the C=C bond in these enones at higher temperature, or even at very low temperatures for conformational unconstrained cyclohexenones. The closeness of n, π^* and π,π^* states of 2-cyclopentenones is evident from phosphorescence studies on rigid systems carried out by Cargill, Saltiel and coworkers[90]. Those compounds without substituents on the C=C bond appeared to emit from ^{3}n, π^* states whereas those with substituents on the C=C bond showed emission from π,π^* triplets. The emission from the former group could be changed to that of the second group simply by adsorption on silica gel, which stabilizes $^3\pi,\pi^*$ states relative to n, π^* states. They suggest that the lowest relaxed triplet of simple cyclopentenones and cyclohexenones in solution is probably $^3\pi,\pi^*$ due to stabilization by torsion around the C=C bond. It is now known with virtual certainty from the studies summarized in Section IV.B.4.e. that the reactive excited state in enone–alkene photocycloadditions is the lowest π,π^* state of the enone, whose charge distribution is not predicted to be as shown in Scheme 32.

There are therefore very good grounds for challenging Corey's assignment of the nature of the reactive triplet state of cyclohexenone in photocycloaddition to alkenes, and the structure for the 'oriented π-complex' shown in Scheme 32, despite the fact that this model has been very successful in correlating regiochemical data in a large number of examples[7,8,189].

In his review of the 'enone photoannelation' reaction in 1971[205], de Mayo pointed out the kinetic deficiencies of Corey's original mechanism, and explicitly considered reversion of all possible reaction intermediates to ground-state enone and alkene (see Scheme 34). He and his coworkers measured quantum yields for photoaddition of cyclopentenone and in no case were they greater than 0.50 in neat olefin. Representative data (all at 334 nm) are: cyclohexene, 0.50; cyclopentene, 0.32; tetramethylethylene, 0.12; DME, 0.34 (at 313 nm). The effect of triplet quenchers (piperylene, acenaphthene) on the addition of cyclopentenone to cyclohexene in benzene and cyclohexane was determined. From the slopes of Stern–Volmer plots, assuming diffusion-controlled quenching, rate constants k_r for interaction of cyclohexene with cyclopentenone were calculated to be $2.3–5.0 \times 10^8$ l mol^{-1} s^{-1} and the rate constant k_d for unimolecular decay of the enone triplet was found to be $9–46 \times 10^8$ s^{-1}, depending on the quencher and the solvent. De Mayo recognized that these values of k_d were unreasonably large, indicating some deficiency in



SCHEME 34

the reaction scheme, but it was unclear what the problem was. A temperature dependence of the quantum yield for photoannelation of cyclopentenone with several different olefins was observed; in some systems, these values increase as the temperature is lowered (cyclohexene, cyclopentene, *cis*-dichloroethylene) while in others (3-hexene) it decreases. For cyclopentenone–cyclohexene, the value increased from 0.46 at 27 °C to 0.72 at − 102 °C, while for cyclopentenone–cyclopentene it more than doubled from 0.23 at 27 °C to 0.61 at − 71 °C. It was concluded that the large changes in ϕ_{add} with temperature result from changes in the fraction of intermediate that gives product rather than from changes in the fraction of enone triplets trapped by alkene.

Loutfy and de Mayo[200] carried out the most extensive quantitative studies of enone photoannelation published to date. They studied the dependence of quantum yields for additions to cyclopentenone and cyclohexenone on temperature and on the alkene concentration at varying temperatures, as well as quenching of photoaddition at various temperatures with 2, 5-dimethyl-2, 4-hexadiene. To get rate constants, they assumed as before that quenching by the diene is diffusion controlled. From their data, values of k_d of $1.1 \pm 0.1 \times 10^8\,s^{-1}$ and $3.3 \pm 0.3 \times 10^9\,s^{-1}$ were found for cyclopentenone and cyclohexenone at concentrations of 0.10 and 0.14 M, respectively, corresponding to triplet lifetimes of *ca* 10 and 3 ns under these conditions. These lifetimes are much shorter than the lifetimes of these triplets measured by flash techniques (see Section IV.B.4.d), indicating that the values for the quenching rate constants assumed by Loutfy and de Mayo are too high by about an order of magnitude. Thus, their values for k_r are also too high by an order of magnitude. However, this problem does not significantly affect the results of their study which were: (a) a triplet exciplex (Corey's π complex) is formed irreversibly and is short-lived; (b) the exciplex collapses to a 1,4-biradical which cyclizes or reverts to starting materials; (c) biradical reversion is the main source of inefficiency in the cycloaddition; (d) there is insufficient evidence from this or prior work to indicate whether the first bond is formed α or β to the carbonyl group. However, their data do not *require* reaction via an exciplex, since direct formation of a triplet 1,4-biradical would be in accord with their data and other data in the literature.

In Corey's and de Mayo's studies, as well as in subsequent reviews, it is taken for granted that enone dimerization is a special case of enone photoannelation. This assumption, while structurally reasonable, is surprising in the context of the exciplex hypothesis, since the rate constant for self-quenching of the triplet k_{sq} is larger than the rate constant for triplet capture (k_r) by most electron-rich alkenes. However, the kinetic evidence given earlier (Section IV.B.4.e.i.) suggests that at least in the case of simple cyclohexenones, such as the 4,4-dimethyl enone **124**, annelation and dimerization occur via different enone triplet excited states. The generality of this finding for other enones remains to be established.

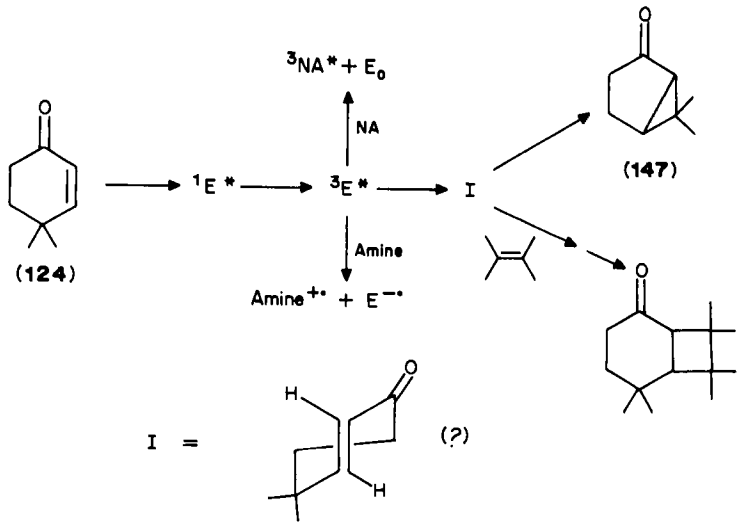
(iv) Recent kinetic studies and alternative mechanisms for enone–alkene photocycloadditions. Several recent studies by Schuster and coworkers cast serious doubt on the Corey–de Mayo exciplex mechanism[200] for photoaddition of enones to alkenes, which has been widely adopted by investigators in this field[7–9].

As discussed earlier (Section IV.B.4.e.iv), an investigation was undertaken of the effect of alkenes on the lumiketone photorearrangement of 4,4-dimethylcyclohexenone **124**, since it seemed likely that both photorearrangement and photocycloaddition originated from a common triplet state of the enone. Indeed, linear Stern–Volmer plots for quenching by a variety of alkenes of the photorearrangement of **124** to **147** were observed[182,183]. However, as previously mentioned, the slopes of these plots showed absolutely no correlation with the ionization potential of the alkenes (see Figure 12)[183]. For formation of a π complex in which the alkenes were acting as donors, a linear relationship of log k_q with ionization potential would be expected. The failure to observe such a correlation means that the Corey–de Mayo mechanism is wrong in at least one of two regards: (1) the triplet of **124** reacts with alkene to give 1,4-diradicals directly without the involvement of a discrete exciplex intermediate; (2) the alkenes may intercept some other intermediate on the pathway to lumiketone **147**.

The direct observation of enone triplet-excited states using laser flash techniques made it possible to directly measure the rates of interaction of alkenes with these triplets. Results of such a study involving 4,4-dimethylcyclohexenone **124** have recently been reported[170]. In this case, the congruity of steady-state quenching data with the lifetime and rate constants for quenching measured by flash techniques made it clear that the triplet observed in the flash was indeed the species responsible for both photorearrangement and photocycloaddition to alkenes. However, it came as a surprise that alkenes (TME, DME, cyclopentene, cyclohexene) which form photocycloadducts with **124** with moderate to good quantum efficiency (up to 0.44) do not appear to directly quench this enone triplet, according to studies of the effect of alkene in high concentrations (e.g. up to 3.8 M in the case of TME) on both the rate of decay of the enone triplet at 280 nm and[170,172], in solutions containing methylnaphthalene (MN), the rate of growth of MN triplet absorption at 420 nm[170]. Thus, the extrapolated enone triplet lifetime in acetonitrile (AN) solution obtained from the MN growth kinetics, monitored at 420 nm, was 26 ns in AN alone and 29 ns in AN containing 30% TME; for comparison, the triplet lifetime for **124** in AN measured by transient decay at 280 nm is 27 $\pm$ 2 ns. Thus, TME had no effect on either the rate of radiationless decay of the relaxed enone π,π^* triplet or on triplet transfer to MN. In another comparison, τ_T for **124** in neat cyclopentene (23 ns) is indistinguishable from the value of τ_T in isooctane[170]. These data are in complete agreement with earlier results of Dunn[172] on enone **124** and phenanthrone **154** with cyclohexene and DME obtained using a different laser flash apparatus.

These flash data are in marked contrast with the effect of the same alkenes as quenchers of the rearrangement of **124** to lumiketone **147**[182,183]. There is a clear mismatch between values of $k_q\tau_T$ obtained from the quenching experiments and upper limits to $k_q\tau_T$ calculated from the flash data[170]. These data require that at least in this system these alkenes must be intercepting an intermediate I formed from the relaxed (twisted) enone triplet but not the triplet itself, as indicated in Scheme 35. The nature of this intermediate is not precisely defined by any of the studies carried out to date, but an intriguing possibility is that I is a ground-state *trans* isomer of **124**, that is, a *trans* cyclohexenone[170]. Similar experiments have not yet been carried out using the parent compound, so it is not clear whether these results can be generalized. The consequences of photocycloaddition via a *trans* cyclohexenone will be discussed after first considering cases in which the enone triplet is definitely intercepted by alkenes.

It was anticipated that enones which were structurally constrained from formation of a ground-state *trans* isomer would react directly with alkenes. This indeed is the case for



SCHEME 35

cyclopentenone (**50**)[80], 3-methylcyclohexenone (**217**)[80], testosterone acetate (**132**)[173] and $\Delta^{1,6}$-bicyclo[4.3.0]nonen-2-one (**216**)[173]. In these cases, the rate of decay of the '280 nm' transient triplet was enhanced in the presence of added alkenes in both acetonitrile and cyclohexane solutions. The quenching rate constants given in Table 5, determined from slopes of plots of $(\tau_{obs})^{-1}$ vs. alkene concentration, represent the first absolute values of rate constants determined for interaction of enone triplets with alkenes. For several of these systems absolute or relative quantum yield data have been obtained, which are also given in Table 5.[242]

Two important conclusions can be drawn from these data[242]. One is that there is no correlation between the quantum efficiency for adduct formation and the rate of reaction of the enone triplet with alkenes, which is hardly surprising given the example of the Norrish Type II reaction of aromatic ketones in which triplet 1,4-biradicals also play a crucial role[50]. Secondly, and perhaps more surprising, in all cases studied thus far the rates of interaction of enone triplets with electron-deficient alkenes are much larger than for electron-rich alkenes, which is completely contrary to expectations based on Corey's π-complex hypothesis[184]. Moreover, for some enones (such as **216**) photoadducts with electron-deficient olefins are formed in good yields. Thus, Cantrell's observation[192] of enhanced reactivity of acrylonitrile toward photoexcited enone **217** was not anomalous.

The possibility that the primary interaction of enone triplets with electron-deficient alkenes such as acrylonitrile (AN) might involve triplet energy transfer must be considered. Liu and Gale[206] and, independently, Hosaka and Wakamatsu[207] discovered many years ago that dimerization of AN to give *cis*- and *trans*-1,2-dicyanocyclobutane can be sensitized by benzophenone and a number of other triplet sensitizers. The triplet energy of AN was estimated to be *ca* 62 kcal mol^{-1}, and a recent measurement by photoacoustic calorimetry indeed places it at 58 ± 4 kcal mol^{-1} and that of fumaronitrile at 48 ± 3 kcal mol^{-1}[61]. It was therefore necessary to determine if enones could also sensitize dimerization of AN and α-chloroacrylonitrile (CAN). Authentic AN and CAN dimers were first prepared by benzophenone sensitization as per the literature[206,207]. Using cyclopentenone, 3-methylcyclohexenone **217** and bicyclononenone **216**, whose triplets had

TABLE 5. Rate constants for quenching of enone triplets by alkenes[a] and relative quantum yield for adduct formation[b]

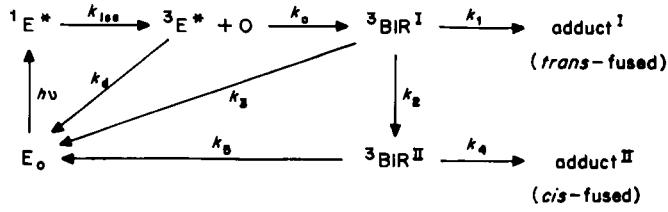
Ketone	Alkene[c]	$k_q \times 10^{-7}$ (l mol^{-1} s^{-1})		$\Phi^d(\phi_{tc})^g$	
		MeCN	C_6H_{12}	MeCN	C_6H_{12}
50	CAN	200	520	0.04(0.99)	0.05(0.99)
	AN	63	180	0.08(0.97)	0.03(0.99)
	fumaronitrile	160	460	0.00(0.99)	(0.99)
	cyclohexene	33	42	0.64(0.94)	0.42(0.96)
	$Cl_2C{=}CCl_2$	65		0.00(0.97)	0.00
	CP	15	40	0.56(0.85)	0.26(0.95)
	TME		99	0.71	0.29(0.99)
	$CH_2{=}CCl_2$	78		0.18(0.98)	0.15
217	CAN	46	35	0.10(0.95)	0.07(0.91)
	AN	15	11	0.14(0.84)	0.08(0.87)
	fumaronitrile		67	0.20	(0.95)
	cyclohexene	5.2	0.5	0.16(0.66)	0.07(0.12)
	$Cl_2C{=}CCl_2$	1.2	2.0	0.00(0.31)	0.00(0.41)
	CP	<0.1	0.5	0.21	0.10(0.14)
	TME	<0.1		0.08	0.03
	DME	0.7			
	$CH_2{=}CCl_2$			0.07	0.04
132	AN	24			
	CP	6		0.21[e]	
216	AN	130		1.60[f]	
	cyclohexene	27		4.16[f]	
	CP	3.8		1.00[f]	(0.048)[g](0.91)
	DME	26		0.62[f]	

[a]Determined from lifetimes of enone triplets of flash excitation of 355 nm as a function of alkene concentration.
[b]Adducts determined by GC/MS. Conversion $<10\%$.
[c]CAN = α-chloroacrylonitrile. AN = acrylonitrile. CP = cyclopentene. TME = tetramethylethylene. DME = 1,1-dimethylethylene.
[d]Quantum yield at 313 nm at 0.50 M alkene.
[e]Quantum yield at 313 nm in neat cyclopentene.
[f]Relative quantum yield at 0.75 M alkene.
[g]Quantum yield for triplet capture (see text).

been shown to be highly reactive toward both AN and CAN, it was found that only trace quantities of AN or CAN dimers could be detected upon irradiation of these enones in neat alkene. It was also possible that enone–AN adducts could arise by triplet transfer to AN followed by attack of AN triplets on ground-state enone. However, when a mixture of benzophenone (1.0 M) and cyclopentenone (0.2 M) was irradiated in neat AN under conditions where more than 97% of the light was absorbed by benzophenone, with the enone at a concentration greater than that needed to furnish AN adducts in good yield, only AN dimers were produced and no enone–AN adducts could be detected[80,242]. Thus, it is concluded that triplet transfer from cyclopentenone to AN is very inefficient compared to formation of triplet 1,4-biradicals en route to cycloadducts.

On the basis of these new data, and the criticisms of the π-complex hypothesis made earlier, one can speculate that these enonetriplets may react with alkenes to give 1,4-biradicals directly without the intervention of exciplexes as discrete intermediates.

Inefficiency in adduct formation would then result from a combination of two factors: decay of the enone triplet to ground-state enone competitive with formation of triplet 1,4-biradicals (^{3}BIR), and reversion to enone and alkene ground states from each of the sequentially formed biradicals ^{3}BIR I and ^{3}BIR II competitive with cyclization and disproportionation (Scheme 36); the importance of each process will vary with each specific enone–alkene system depending on the rate constants of the competitive processes. The analogy to other photochemical reactions proceeding via triplet 1,4-biradicals, most significantly the Norrish II reaction[50], should be obvious.

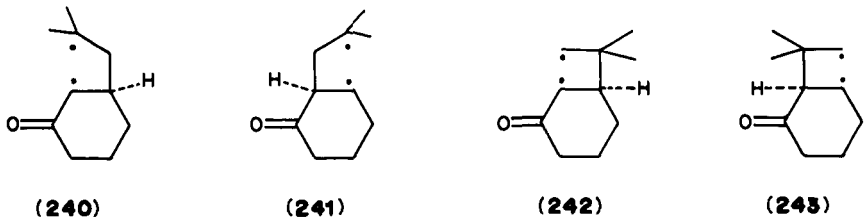


SCHEME 36

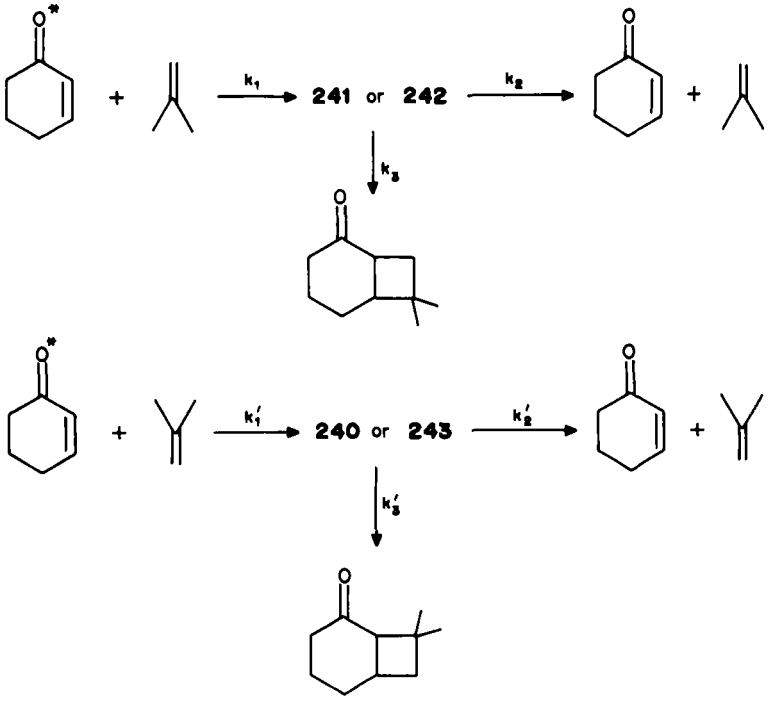
The quantum efficiency for triplet capture ϕ_{tc} by the alkene can be calculated from the flash data according to the expression $\phi_{tc} = 1 - \tau_{obs}/\tau_0 = k_q[\text{alkene}]\tau_{obs}$. Comparison with quantum yields for adduct formation reveals the extent to which reversion to ground state enone occurs before and after enone triplet interception by alkene[242] (see Table 5). Thus, ϕ_{tc} for capture of enone triplets in neat cyclopentene at room temperature is 0.82 and 0.91 for testosterone acetate and bicyclononenone **216**, respectively, while ϕ_{prod} for these systems is 0.21 and 0.049[173]. Thus, most (but not all) of the reaction inefficiency in these systems is due to biradical reversion, which is especially important in the latter case, probably for steric resons. In general, enone triplet decay will play a more important role for shorter- than for longer-lived triplets.

The photocycloaddition of cyclic enones to electron-deficient alkenes has received little attention from organic photochemists and synthetic chemists probably owing to the strong influence of Corey's 'oriented π-complex' mechanism[184], despite its problematic basis. There will undoubtedly be important applications of such photoaddition reactions in organic synthesis in the future. For example, Stoute, Shimonov and Schuster[209] have found that electron-deficient alkenes such as AN, CAN, maleic anhydride and chloroalkenes form adducts with cycloheptenone **94** at the expense of formation of photodimers of **94**. In contrast, electron-rich alkenes such as DME and TME do not form adducts, as originally observed by Corey and coworkers[184]. The structures of these new adducts and the mechanism of their formation are currently being elucidated. Thus, it is not yet known whether such alkenes react with triplets of **94** or with the *trans* enone. The reactions of electron-deficient alkenes with other cyclic enones is currently under study.

(v) Regiochemistry and stereochemistry of photocycloadditions to cyclohexenones—alternative explanations. Bauslaugh[210] proposed many years ago that the regiochemistry observed by Corey and coworkers[184] could be explained without invoking exciplexes, as a consequence of the competition between cyclization and reversion to ketone and olefin ground states from intermediate biradicals. On the basis of the arguments and data given above, this explanation seems to be sufficient to rationalize the experimental facts. Thus, Bauslaugh[210] analyzes the addition of cyclohexenone to isobutylene in terms of the formation of the four 1,4-biradicals **240–243** shown in Scheme 37. On the basis of radical stabilization, the rate (and efficiency) of formation of **240** should be the greatest, and of **243**

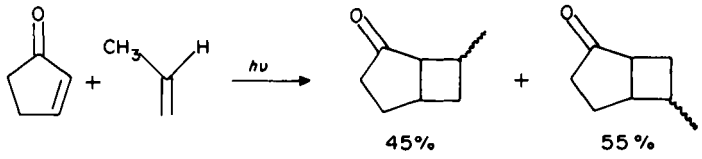


(240) (241) (242) (243)



SCHEME 37

the least. The latter probably plays little role in the reaction. Since **240** is the most stable, it is not unreasonable that it would show the most reversion to ground states of starting materials (k_2 in Scheme 37) of any of the biradicals. Thus, if cyclization occurred mainly from **241** and **242** ($k_3/k_2 > k'_3/k'_2$) the predominant product would be the head-to-tail adduct shown in equation 107. As Eaton noted in his 1968 review[96], this preference is in any event 'really rather small'. The fact that analogous addition of cyclopentenone to propene gives about an even distribution of head-to-head and head-to-tail adducts (see equation 129) is rationalized by Bauslaugh in terms of the reduced importance of the k_2 process in this case because of reduced tendency to regenerate a cyclopentenone vs. a cyclohexenone system due to strain; the result would be an increase in the formation of head-to-head adducts via the k_3 path. This experimental result is inconsistent in any event with the exciplex hypothesis.

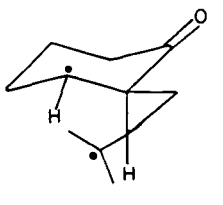


(129)

As far as the regiospecificity of the addition of cyclohexenone to DME (equation 108) is concerned, Bauslaugh[210] proposes that the diradical which would lead to head-to-head adducts would require superimposing the polar groups before ring closure can be achieved. It is therefore not surprising that this mode of addition is not observed relative to the alternative process.

Admittedly, the above explanations of Bauslaugh[210] have a definite *ad hoc* flavor, and are not subject to a precise kinetic analysis. The same argument could in fact be made about Corey's original exciplex hypothesis[184]. In order to really assess the validity of this type of analysis, it would be necessary to know the quantum yields of formation of the isomeric biradicals (i.e. the magnitude of k_1 vis-à-vis k'_1 in Scheme 37 and the efficiency of triplet capture ϕ_{1c}) and the quantum yields for formation of the regioisomeric products. Since no one has yet devised a way of obtaining all these data, Bauslaugh's type of analysis in terms of biradical reversion vs. cyclization/disproportionation is as good an approach as any for discussing the regiospecificity of these photocycloadditions.

Bauslaugh[210] also proposes a simple steric argument to account for the formation of *trans*-fused cycloadducts from cyclohexenones as major products. Considering again the addition of cyclohexenone to isobutylene, he proposes three staggered conformations for the diradical **241**, the principal if not exclusive source of the head-to-tail adduct which is the predominant product in equation 107. These are shown in structures **241a**, **241b** and **241c**. Diradical **241a** would give the *trans*-fused adduct with a diequatorial linkage, **241c** would give the *cis*-fused adduct (axial–equatorial linkage) while **241b** is unable to give either adduct. According to Bauslaugh, examination of models suggests that reaction via **241a** is more favored than via **241c**, since **241a** is conformationally more stable than **241c**, and because **241c** encounters more severe steric problems when it closes to form a cyclobutane than does **241a**. Similarly, the head-to-head adducts formed from cyclohexenone and isobutylene arise from three likely conformations **240a, b** and **240c** of the



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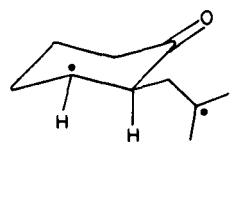

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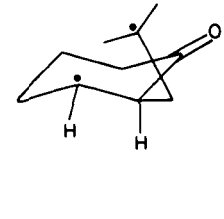
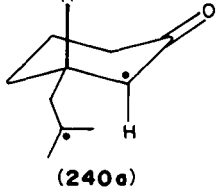
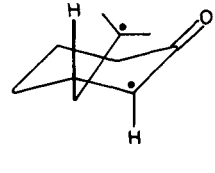


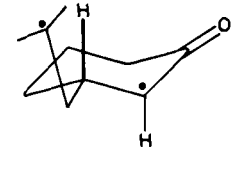
(241c)



(240a)



(240b)



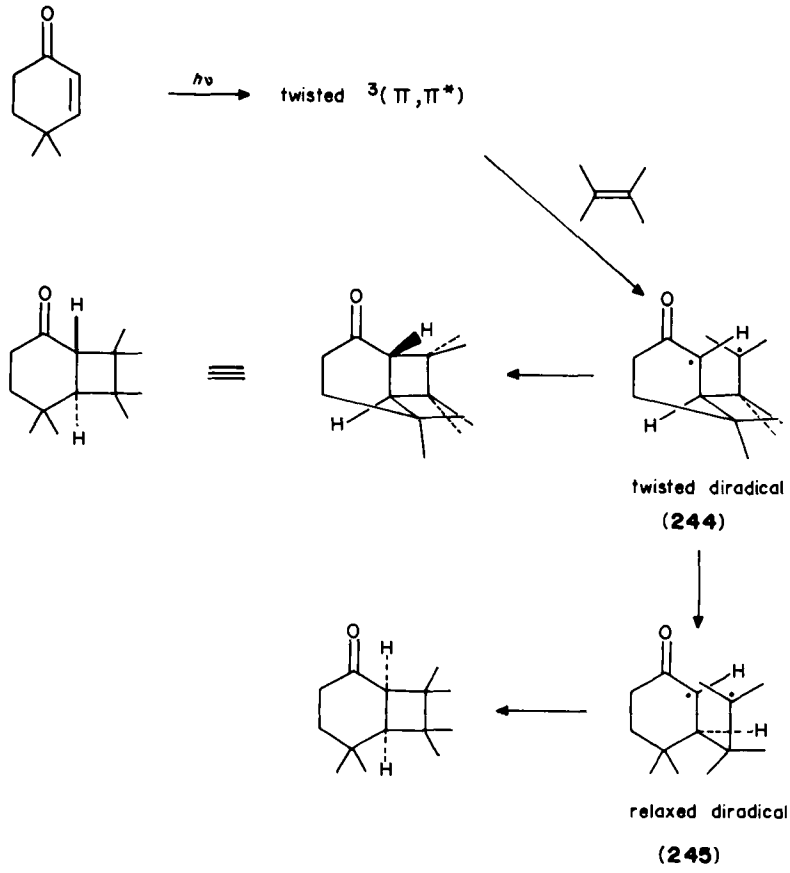
(240c)

diradical **240**; of these, **240a** is clearly the one best suited for ring closure. In this case, Bauslaugh sees no compelling preference for closure of conformer **240a** in a *trans* vs. a *cis* fashion, so that the amount of *trans*-fused adduct should diminish. In fact, Corey and coworkers observed only *cis*-fused head-to-head adduct in this reaction (equation 107). Other reactions which also give head-to-head adducts, as in addition to allene and acrylonitrile, apparently give only *cis*-fused adducts, consistent with this analysis.

Wiesner[199] proposed a model to explain the facial stereoselectivity associated with photoaddition of steroid enones to allene, which he suggested might have generality. Application of principles of conformational analysis, along with the suggestion that the β-carbon of the enone excited state is pyramidal, allowed Wiesner to rationalize why allene adds to one or the other face of the steroid molecule. His argument was basically that the configuration at C_β of the excited enone will be the one which is preferred thermodynamically on the basis of ring strain and nonbonded interactions. However, this model gives the wrong prediction with respect to the direction of addition of ethylene to enone **238** studied by Cargill and coworkers[198] as demonstrated by the two *cis*-fused isomers in equation 127. Moreover, since this model does not take into account competition between reversion to starting materials and ring closure of diradical intermediates, it will not be considered further.

Returning to the Bauslaugh stereochemical analysis[210], it is not obvious how this theory can explain why addition of unsubstituted ethylene to enone **238** gives 24% of a *trans*-fused isomer (equation 127), and why addition of cyclopentene to Δ^1- as well as Δ^4-steroidal enones gives major amounts of *trans*-fused adducts. It seems clear from the kinetic studies discussed earlier that the excited state of cyclohexenones which lead to cycloadducts is a highly twisted $^3\pi,\pi^*$ state. If such a species were to interact directly with alkenes, *trans*-fused adducts would be produced if the twisted geometry could be preserved, as pointed out many years ago by McCullough and coworkers[193]. One could then envisage a scheme such as that shown in Scheme 38 in which the interaction of enone triplet with alkene leads to a geometrically distorted 1,4-biradical **244** which would give *trans*-fused cycloadducts if cyclization occurred competitively with relaxation of the biradical to the more stable geometry shown in structure **245**, which would be expected to give only *cis*-fused cycloadducts on ring closure[182]. According to this scheme, the biradicals leading to *trans*- and *cis*-fused cycloadducts are formed sequentially rather than concomitantly as in Bauslaugh's scheme[210]. One would therefore expect that any structural feature which would prolong the lifetime of the first-formed biradical or inhibit ring closure would enhance the probability of forming *cis*-fused adducts via the conformationally relaxed biradical **245** as well as return to ground-state enone and alkene. Some of the conformational effects discussed by Bauslaugh might indeed play a role in this regard. Again, it is not possible to discuss this scheme in quantitative terms unless one knew (a) the quantum yield for formation of the first-formed biradical, and (b) the extent of reversion from both **244** and **245**. While the first parameter can be obtained from flash data (see equation 128), there is still no good way of obtaining (b); the best one can do at present is to calculate the total extent of reversion from the difference between ϕ_{tc} and ϕ_{prod}. In order to obtain rate constants for cyclization and reversion, and to understand the dependence of these kinetic parameters on structural features of the reactants, one would need to determine lifetimes of the triplet biradicals; at present these are unknown, but in principle they could be determined by methods analogous to those used by Wagner and Scaiano in their studies of the triplet 1,4-biradicals involved in the Norrish Type II reaction[211,212].

The observation that steroid enones give good yields of *trans*-fused cycloadducts, under conditions where the enone triplet is directly quenched by alkenes, suggests that the mechanism of Scheme 38 is operative. Thus, testosterone acetate reacts with cyclopentene to give two adducts in *ca* 1:1 ratio, one *cis*-fused and one *trans*-fused[173]. In neat

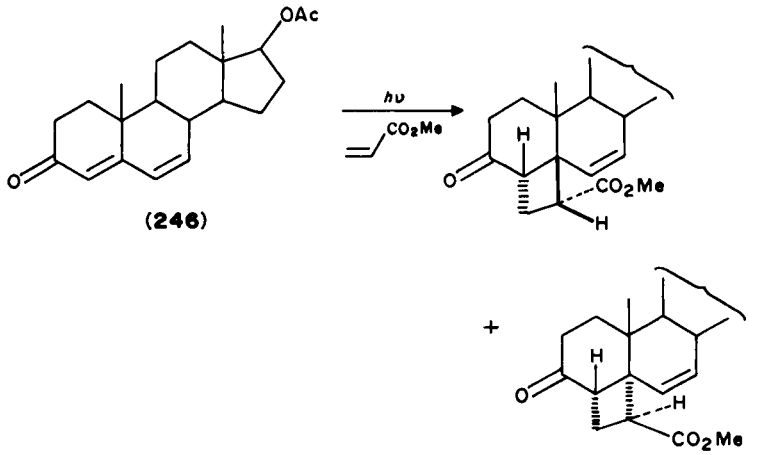


SCHEME 38

cyclopentene, the quantum efficiency of adduct formation is 0.21 while flash data show that 82% of the enone triplets are captured by cyclopentene. Thus, 75% of the initially formed radicals revert to starting materials. However, no conclusion can be drawn as to the extent of reversion to starting materials from twisted biradicals of type **244** vis-à-vis relaxed biradicals of type **245**, although it is likely that reversion from the latter is more important. These data, as well as the findings of Lenz on Δ^1-steroid enones discussed earlier[191], suggest that even in these relatively rigid systems the enone chromophore is significantly twisted in the excited state.

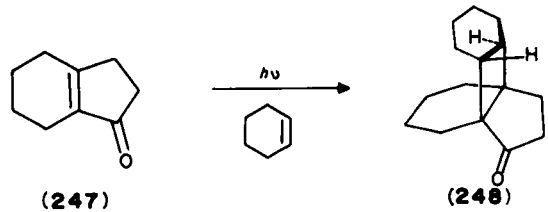
Lenz has extensively investigated photocycloaddition reactions of linear steroid dienones[213] which, in general, are beyond the scope of this review. However, the results of the studies of Lenz and Swenton on photoadditions of dienone **246** to electron-deficient alkenes[213] are of direct relevance to present considerations. Photocycloaddition of **246** to methyl acrylate gave a mixture of *cis*-and *trans*-fused adducts, as shown in equation 130; this represents the first example of isolation of *trans*-fused cycloadducts using an electron-deficient alkene. The cycloaddition could be quenched by a low-energy triplet quencher, 3,3,4,4-tetramethyldiazetidine 1,2-dioxide, suggesting that reaction occurs via a π,π^*

triplet of **246** with an energy of *ca* 50 kcal mol^{-1}. Schuster, Dunn and Bonneau concluded that the triplet state of the parent alcohol has an energy of 42–43 kcal mol^{-1} based on quenching data in laser flash experiments[171]. The fact that **246** gives a mixture of *cis*- and *trans*-fused adducts with methyl acrylate while addition to electron-rich alkenes such as DME gives only *trans*-fused adducts was taken by Lenz and Swenton[214] as support for the proposal by Shaik and Epiotis that there should be a change in the mode of photocycloaddition from [2s + 2a] (leading to *trans*-fused adducts) to [2s + 2s] (leading to *cis*-fused adducts) as the ionization potential of the olefin is increased[215]. They proposed that good donor–acceptor interactions promoted the non-Woodward–Hoffmann [2s + 2a] process, whereas the [2s + 2s] process would be seen when this was not the case. Although this is an interesting proposal, the absence of quantum yield data for any of these reaction weakens the strength of the argument, and reaction via 1,4-biradicals can not be excluded. The regiochemistry suggests that if the reaction in equation 130 is stepwise, the first bond must be formed to the α- and not the β-carbon of the enone.



(130)

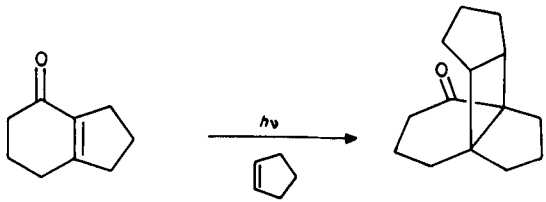
One of the more unusual observations in the photocycloaddition literature is the report by Tobe and coworkers that photoaddition of enone **247** to cyclohexene gives the *cis–anti–trans* adduct **248** in 84% yield and a quantum yield of 0.69 (equation 131)[216].



(131)

Quenching studies with piperylene implicated a triplet state of the enone as the reactive excited state. Analogous systems with smaller ($n = 5$) and larger ($n = 7$ or 8) cycloalkene rings fused to cyclopentenone give mixtures of stereoisomeric adducts. The formation of only one product in equation 131 is rationalized by the authors in terms of more severe nonbonded interactions of the hydrogens in the other possible adducts vis-à-vis **248**, i.e. the mode of ring closure of the intermediate triplet biradical is governed by conform-

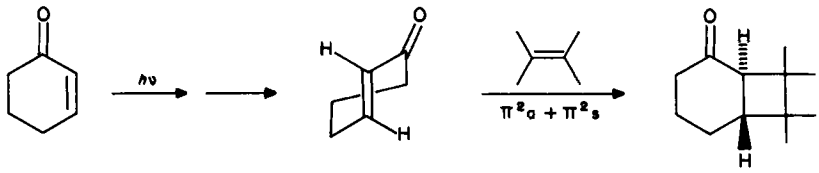
ational energetics, as in Bauslaugh's original proposal[210]. This same effect is seen in addition of cyclopentene to enone **216** (equation 132), where the efficiency of triplet capture in neat alkene is 91% but the efficiency of formation of the adduct **248** is only 0.05[173]; nonbonded interactions between hydrogens in **248** are severe, whether the cyclopentane ring is oriented above either the five- or six-membered ring of the enone, which is not yet known. Thus, 95% of the intermediate biradicals in this case revert to starting materials. It would be of interest in this connection to see if the quantum efficiency of adduct formation increases as the ring size of the olefinic reactant is systematically enlarged, as predicted by this mechanism.



(132)

(216) (stereochemistry not determined)

It was suggested earlier on the basis of the incompatibility of the flash and steady-state kinetic data on enone **124** that in this system the alkene does not directly intercept the triplet state but rather reacts with an intermediate derived from the triplet, perhaps a *trans* cyclohexenone[170]. If this is indeed the correct mechanism, which is by no means certain, one would have to provide an alternative mechanism for formation of *trans*- and *cis*-fused cycloadducts in this system and other systems which show similar kinetic behavior. (As mentioned earlier, corresponding studies of cyclohexenone itself have yet to be done.) One might anticipate that addition of ground-state *trans* cyclohexenones to alkenes ought to be a rapid process, due to the great strain and consequent high reactivity of the enones. If it were concerted, orbital symmetry rules predict it should be a $_{\pi}2_a + {}_{\pi}2_s$ process[40]. Addition to the *trans* enone is expected to occur only suprafacially since one face of the enone moiety is shielded by the ring atoms. Therefore, addition to acyclic alkenes should give only cycloadducts in which the cyclobutane and cyclohexanone rings are *trans* fused (Scheme 39). Similarly concerted photocycloaddition of a *trans* cyclohexenone to



SCHEME 39

cyclopentene should give adducts in which both the five- and six-membered rings are *trans* fused to the cyclobutane ring, which is not observed. Similarly, concerted formation of *cis*-fused cycloadducts on photoaddition of **124** to acyclic alkenes is difficult to rationalize on the basis of a *trans*-cyclohexenone intermediate, since it would require antarafacial addition to the enone component. Therefore, it seems likely that photoadditions of **124** to alkenes are nonconcerted and may proceed via triplet biradical intermediates, although there is no definitive evidence in this connection (e.g. reactions with *cis–trans*

pairs of alkenes have not yet been investigated). Since the ground-state and triplet potential surfaces are energetically close at the geometry corresponding to the *trans* cyclohexenone (see below), it is conceivable that intersystem crossing back to a triplet surface may take place when the *trans* enone reacts with alkenes. Although this discussion must be considered to be highly speculative due to the lack of conclusive supporting data, alternative mechanisms should be seriously considered in the case of cyclohexenones which are capable of undergoing severe molecular distortion by twisting around the C=C bonds.

h. trans-*2-Cyclohexenones as intermediates in photochemical reactions of* cis-2-*cyclohexenones. Theoretical and experimental studies (i) Introduction.* There has been speculation for some time that *trans*-2-cyclohexenones might be formed on photoexcitation of the *cis* enones[96,193,205], analogous to the formation of *trans*-2-cycloheptenone and *trans*-2-cyclooctenone from the corresponding *cis* enones. As discussed earlier, ground-state *trans* cyclohexenes have been directly detected using flash techniques in a number of cases[25,26], but no case has been reported of a *trans* cyclohexene with a third trigonal center in the six-membered ring. Probably the closest example is *trans*-1-acetylcyclohexene in which a trigonal center (the carbonyl carbon) is directly attached to the twisted C=C bond[168].

Schuster, Scaiano and coworkers have reported kinetic data which require that in photocycloaddition of enone **124** to electron rich alkenes the reaction intermediate intercepted by the alkenes is not the enone triplet, which is directly observable in flash experiments, but some species I derived from that triplet (see Scheme 35, Section IV.B.4.g.iv)[170]. The identity of I is by no means established, but one possibility that must be considered is that I is a *trans* cyclohexenone. In the following discussion, theoretical predictions concerning the viability of *trans* cyclohexenones as photochemical reaction intermediates will be discussed followed by experimental findings which bear directly on this question.

(ii) Theoretical treatments of trans-*2-cyclohexenone.* Verbeek and coworkers have published the results of theoretical *ab initio* calculations relating to the existence of *trans* cyclohexene[217]. To obtain a zeroth-order description of this system, at least a two-configuration wave function is required. They used an equivalent GVB formalism, in which the geometries of *cis* and *trans* cyclohexene were optimized using a minimal STO-3G basis set, assuming C_2 symmetry throughout. Single-point GVB calculations at the optimized geometries were then carried out using the split-valence 6-31G basis set, and the effect of adding polarization functions to the carbon basis set was checked using Pople's 6-31G* basis set.

The results are that *trans* cyclohexene with the geometry shown in structure **249** in Figure 13 is predicted to lie in a potential minimum located 56 kcal mol^{-1} above the *cis* isomer, with an estimated barrier of 15 kcal mol^{-1} for conversion of the *trans* to the *cis* isomer[217]. The distortion in the calculated minimum energy structure for *trans* cyclohexene lies mainly in the C_1—C_2 'double bond'. The π overlap in this compound is poor, reflected in the long C_1—C_2 bond of 1.421 Å and the C_3—C_2—C_1—C_6 torsional angle of 81°. The dihedral angle between the p orbitals is estimated to be about 46°, corresponding to considerable diradical character in **249**, *ca* 30% compared to *ca* 10% for *cis* cyclohexene. The strain in the molecule is also reflected by unusually long C—C single bonds, e.g. 1.564 Å for C_4—C_5 in **249** compared to 1.542 Å for the corresponding bond in *cis* cyclohexene. The transition state for conversion of *trans* to *cis* cyclohexene is nearly a pure (*ca* 90%) biradical, with perpendicular p orbitals[217].

The authors conclude that *trans* cyclohexene corresponds to a local minimum, and that it might be possible to generate and observe it in an inert matrix, as had indeed been

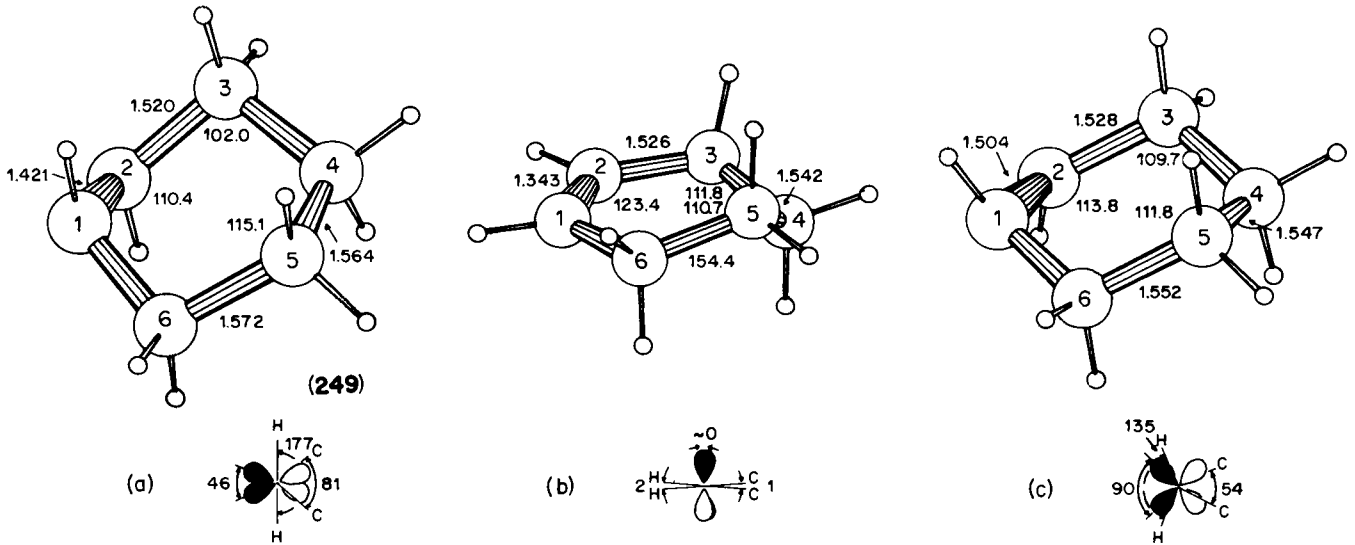
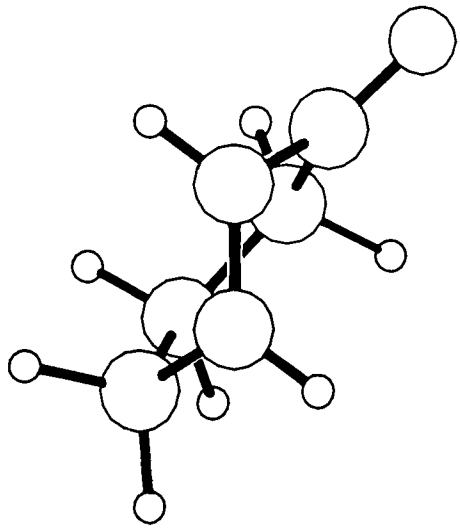


FIGURE 13. Optimized structures for (a) *trans* cyclohexene (**249**) (b) *cis* cyclohexene and (c) the transition state for isomerization of (a) to (b). Reprinted with permission from *J. Org. Chem.*, **52**, 2955 (1987). Copyright (1987) American Chemical Society



(250)

FIGURE 14. Optimized structure for *trans* cyclohexenone from MNDO and AM1 calculations (from Reference 218)

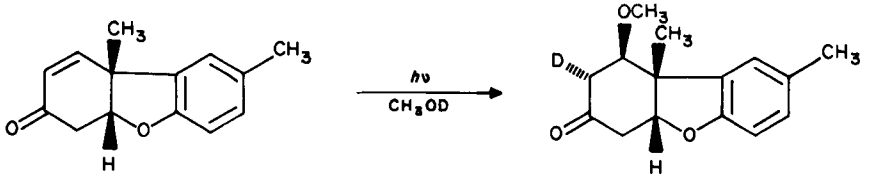
accomplished in recent flash studies[25,26] of which the authors were apparently unaware. They also noted that considerable stabilization of the strained alkene by coordination to transition metals is likely, and that they may indeed have observed such species in metal-catalyzed photochemical reactions of *cis* cyclohexene[217].

Johnson[218] has carried out preliminary calculations on *trans* cyclohexenone using MNDO and AM1 techniques, and found a local minimum corresponding to the twisted geometry shown in structure **250** (Figure 14) located *ca* 60 kcal mol^{-1} above *cis* cyclohexenone. Unfortunately, it has not yet been possible to calculate the barrier for thermal isomerization of this structure back to *cis* cyclohexenone, which is critical with respect to the anticipated lifetime of *trrans* cyclohexenone and the possibility of directly observing it in flash experiments or trapping it chemically. Using his recently reported two-body force field followed by the MM2 force field[219], Saunders[220] explored the potential surface of 2-cyclohexenone and independently found a local minimum located *ca* 60 kcal mol^{-1} above the ground-state *cis* enone with a geometry close to that found in Johnson's calculations. Again, Saunders did not determine the potential barrier for isomerization of the *trans* cyclohexenone to the lower-energy *cis* enone.

These calculations, while clearly preliminary and in need of considerable refinement, suggest that *trans* cyclohexenone is at least a theoretically possible reaction intermediate, and should fuel attempts to directly detect *trans* cyclohexenones using flash techniques at ambient temperatures and matrix isolation techniques at low temperatures.

(iii) trans-*Cyclohexenones as intermediates in photoaddition of nucleophiles to cyclohexenones.* As an extension of his investigations of photoinduced addition of methanol to cycloheptenones and cyclooctenones, which appeared to occur via ground-

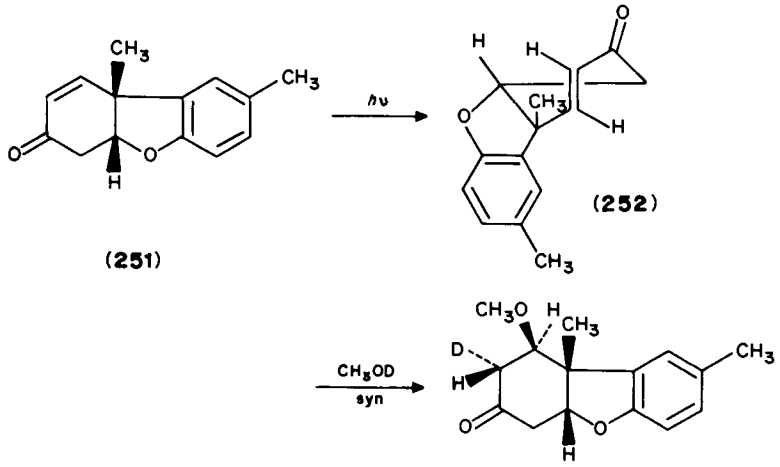
state *trans*-cycloalkenone intermediates[105], Hart and coworkers studied analogous additions to cyclohexenones[221]. Noyori and Kato[104] had previously reported that irradiation of 2-cyclohexenone in methanol solvent gave only a 0.7% yield of 3-methoxycyclohexanone, while other simple cyclohexenones also gave disappointingly low yields of alcohol or water adducts. However, Matsuura and Ogura had reported that a crystalline methanol adduct was formed from Pummerer's ketone, **251**[222]. To obtain further information about the mechanism of this unique photoreaction, Hart and coworkers studied the stereochemistry of the photoaddition using CH_3OD[221]. Using NMR spectroscopy, they determined that the product had the structure shown in equation 133, indicating that the reaction had proceeded in a stereospecific *trans* manner,



(251)

(133)

completely analogous to the findings on additions of MeOH(D) to seven- and eight-membered cyclic enones[105]. Hart proposed the mechanism shown in Scheme 40 in which irradiation of **251** 'results in an excited state or intermediate (depicted as **252**) in which the carbon–carbon double bond is twisted more than 90°'[221]. Only *syn* addition of methanol to the '*trans*' double bond is possible, since one face is completely blocked by the ring itself. Therefore, the methoxyl group attached to the β-carbon of the enone must end up *cis* to the angular methyl group, as was shown in Matsuura and Ogura's original study[222] and

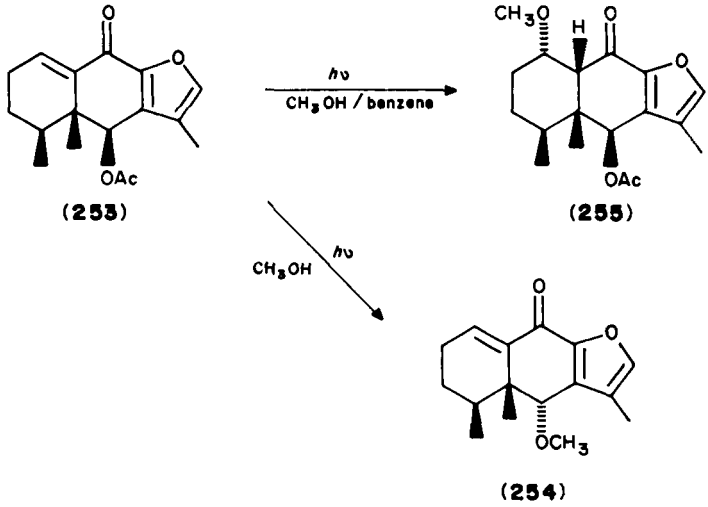


(251) **(252)**

SCHEME 40

confirmed by Hart and coworkers[221]. After the former enone ring untwists, the deuterium ends up *trans* to the methoxy group, i.e. *trans* stereochemistry arises from *syn* addition to a twisted *trans* enone. The isotope effect of 4.3 ± 0.5 found using mixtures of MeOH/MeOD is comparable to that found in additions of methanol to *trans* cycloheptenone and *trans* cyclooctenone[105], although a smaller effect was anticipated for addition of MeOH to the much more reactive and hence less selective *trans* cyclohexenone **252**.

Very few other examples of photoadditions of methanol to cyclohexenones have been reported. Thus, Rodriguez-Hahn and coworkers[223] reported that irradiation of decompostin **253** in methanol gave only the 6-epi-methoxy substitution product **254**; however, irradiation of **253** in benzene in the presence of methanol gave the methyl ether **255** whose structure was determined by X-ray crystallography. These transformations are shown in equation 134. Analogous addition reactions to **253** occurred using water and isopropyl alcohol. The mechanism of the MeOH photoaddition reaction was not investigated, but the authors speculate that it involves 'initial isomerization to the *trans*-alkenone followed by *syn* addition of methanol to the highly strained 1, 10 double bond', following Hart's lead[221]. The fact that the addition did not occur in neat methanol but worked well when benzene was used as the solvent is very interesting, and remains unexplained.



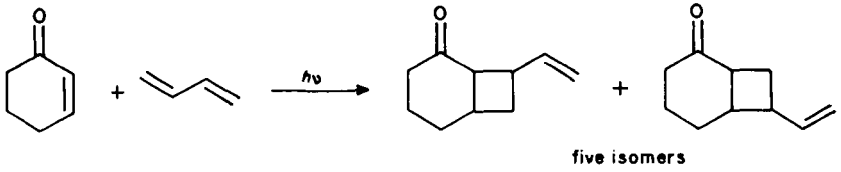
(253) (255) (254)

(134)

Brown[173] irradiated octalone **139** in methanol in the hope of obtaining addition products analogous to those obtained by Hart using **251**, but without success. Analysis of the photolysate by GC/MS indicated that trace amounts of adducts were formed, but attempts to isolate them were completely fruitless. Experiments in progress at the time of writing suggest that methanol adducts are not formed in detectable yields even upon irradiation of **139** in benzene in the presence of methanol, following the example of Rodriguez-Hahn and coworkers[223].

(iv) Photoaddition of cyclohexenones to conjugated dienes. Cantrell[175] originally reported that cyclohexenone and cyclopentenone undergo both [2 + 2] and [4 + 2] addition to conjugated dienes. Using acyclic dienes, such as 1, 3-butadiene and 2, 4-hexadiene, as well as cyclic dienes such as 1, 3-cyclohexadiene and spiro[2, 4]hepta-2, 5-diene, only [2 + 2] adducts were formed, as illustrated in equation 135. However, both

types of adducts were formed from cyclohexenone and cyclopentadiene (equation 136) and from both enones with furan (equations 137 and 138). The quantum efficiencies for addition were somewhat larger with cyclohexenone than with cyclopentenone. Unfortunately, the nature of the ring fusion in the [4 + 2] adducts in equations 136 and 137, which relates to the possible capture of *trans* cyclohexenone by the cyclic dienes, was not established. An interesting mechanistic observation was made with the cyclohexenone–butadiene system[175]. Along with the adducts shown in equation 135, dimers of the diene are formed; the latter were attributed to triplet energy transfer from the enone to the diene based on studies by Hammond and coworkers[224]. Curiously, while the efficiencies of both processes increased as the diene concentration was increased, the ratio of diene dimers to adducts increased as a function of diene concentration. No explanation was offered, but one possibility is that the triplet excitation transfer may be taking place from a different (higher-energy) enone triplet than the triplet state (twisted π,π^*) that is implicated in the cycloaddition process.



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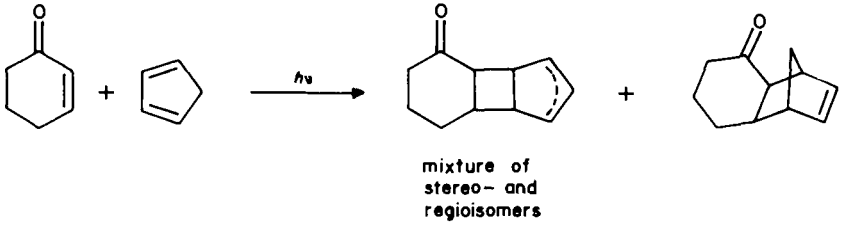

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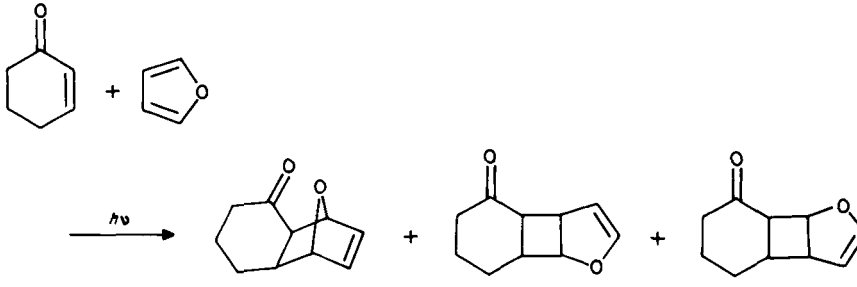

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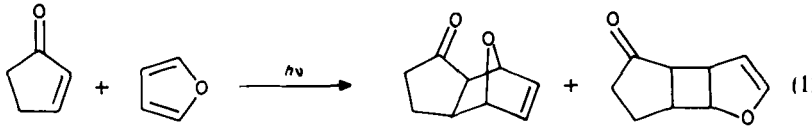
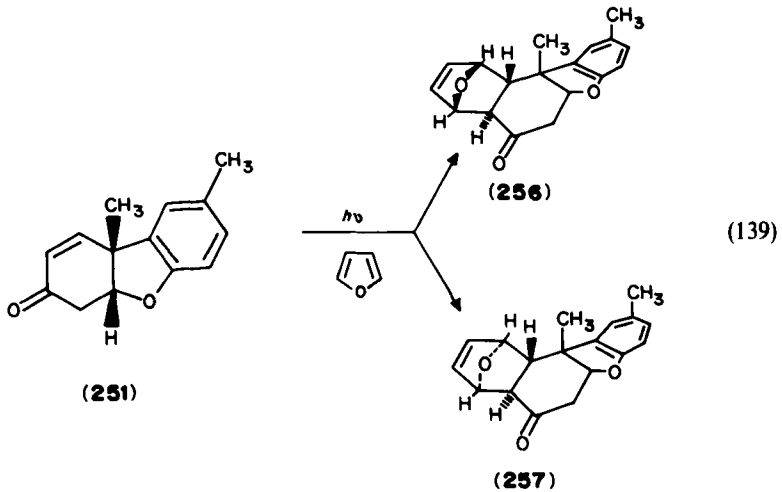


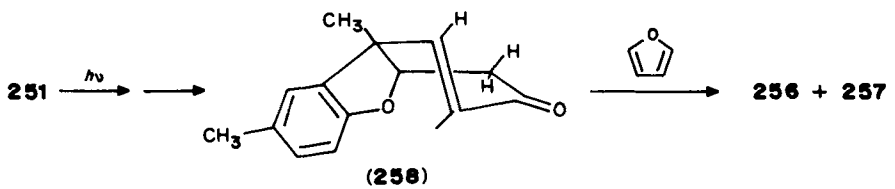
(138)

At the very least, as pointed out by Cantrell[175], these findings indicate why erratic results are often observed in kinetic studies in which dienes are used as potential quenchers of enone triplets, both in flash and steady-state studies. Enone triplets whose energies are substantially reduced by twisting around the C=C bond may be quenched very inefficiently by dienes by triplet energy transfer, which was not appreciated until recently[81]. Under these conditions, cycloaddition processes may dominate. However, it is interesting that even 2-cyclopentenone, whose triplet is not anticipated to undergo substantial distortion due to twisting, forms [2 + 2] adducts relatively efficiently with cyclopentadiene, although absolute quantum yields for this process have not been reported[175].

Since dienes were used effectively as reagents for trapping of *trans* cycloheptenone and *trans* cyclooctenone, the possibility that *trans* cyclohexenones as generated from Pummerer's ketone **251** (see above) might also be capturable using cyclic dienes was investigated by Mintas, Schuster and Williard[225,229]. Indeed, irradiation of **251** in neat furan led to the isolation of two furan adducts assigned structures **256** and **257** on the basis of NMR spectral analysis and X-ray crystallography (equation 139). In both adducts, a *trans* fusion of the furan moiety to the cyclohexanone ring was observed, consistent with interception of a *trans* cyclohexenone in a ground-state Diels–Alder reaction. However, the fact that the hydrogen on the β-carbon of the enone ended up *cis* to the angular methyl group in both adducts is inconsistent with addition of furan to the *trans* cyclohexenone structure **252** proposed by Hart. If the adducts indeed arose by addition of furan to a *trans* isomer of Pummerer's ketone, the latter must have the structure **258** resulting from twisting in the opposite direction, as shown in equation 140, a structure which Hart and coworkers had originally dismissed as untenable because of nonbonded interactions[221].

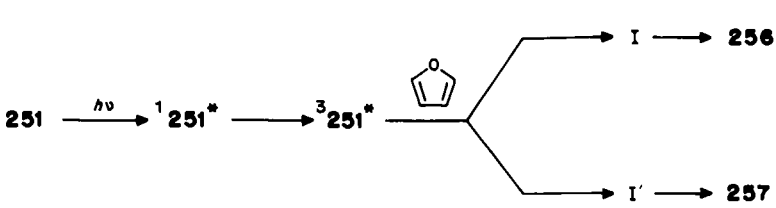


(139)



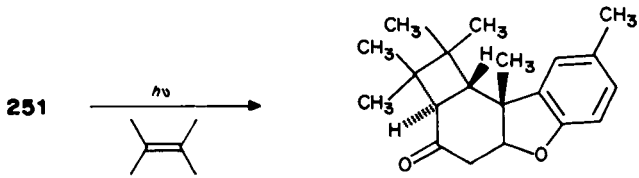
(140)

However, further experiments raise doubts about formation of adducts **256** and **257** via a *trans* cyclohexenone. Methylnaphthalene ($E_T = 61$ kcal mol^{-1}) does not quench adduct formation, which is consistent with the finding that the triplet of lifetime of **251** in acetonitrile is only *ca* 15 ns on laser flash excitation at 308 nm[226]; this finding, in turn, suggests that the π,π^* triplet state of **251** is indeed highly twisted, according to the data and interpretation given in Section IV.B.4.d. However, the free radical tetramethyl-1-piperidinyloxy (TEMPO) as well as oxygen quench formation of the adducts, but to very different extents, demonstrating that these reagents are not intercepting a common precursor of **256** and **257**. This finding was interpreted in terms of the mechanism indicated in Scheme 41, in which it is proposed that a highly twisted triplet state of **251** reacts with furan to give stereoisomeric triplet biradical intermediates I and I′, which are the species intercepted by the paramagnetic reagents TEMPO and O_2[225]. Since a ground-state Diels–Alder reaction between **258** and furan should be concerted, even if not entirely synchronous[227], quenching of such a process by TEMPO or O_2 would be unprecedented. The observed stereochemistry suggests that reaction occurs on only one face of the twisted triplet of **251**, but indiscriminately with respect to the oxy bridge in furan. Furthermore, the low quantum yields for formation of **256** (0.062) and **257** (0.065) suggest that reversion to ground state reactants probably occurs predominantly from the relatively long-lived triplet biradicals I and I′ rather than from the short-lived triplet state of **251**. These observations raise doubts about the role of highly strained *trans* ground states in other cases where *trans*-fused Diels–Alder adducts have been isolated[96,228].

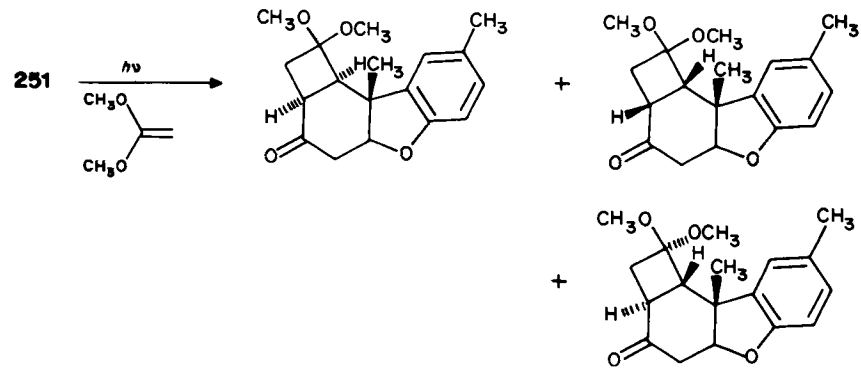


SCHEME 41

Photocycloaddition of Pummerer's ketone **251** to several alkenes has also been investigated by Mintas, Schuster and Williard[229]. The predominant cycloadduct formed from **251** and tetramethylethylene (TME) has the *trans*-fused structure **259** (*cis*-fused adducts are formed in at best trace amounts) (equation 141) reminiscent of the course of reaction of enone **124** with TME, while addition to 1, 1-dimethoxyethylene (DME) gives a mixture of *cis*- and *trans*-fused adducts (equation 142). The structures of these adducts were determined by X-ray crystallography. It is worth noting that the *cis*-fused DME adducts are formed by attack on opposite faces of the reactive intermediate derived from **251**, whether it be a triplet-state or a ground-state *trans* enone. The short triplet lifetime of **251** precludes studies of triplet quenching by alkenes or dienes using nanosecond flash photolysis; such studies will require the use of picosecond flash techniques.



(259) (141)

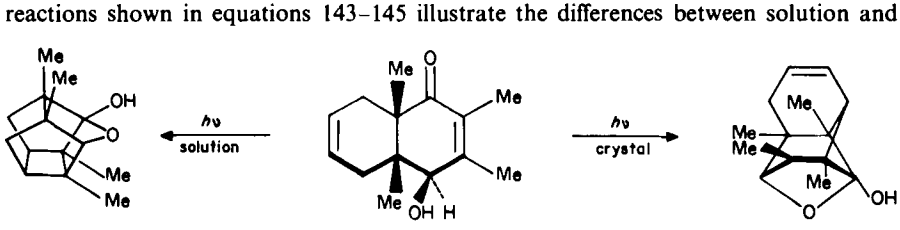


(142)

In summary, there is as yet no compelling evidence for the formation of ground state *trans* cyclohexenones on photoirradiation of *cis* cyclohexenones, although such intermediates provide an attractive way of rationalizing a number of experimental observations. Further studies directed toward observation and trapping of such species will be awaited with keen interest.

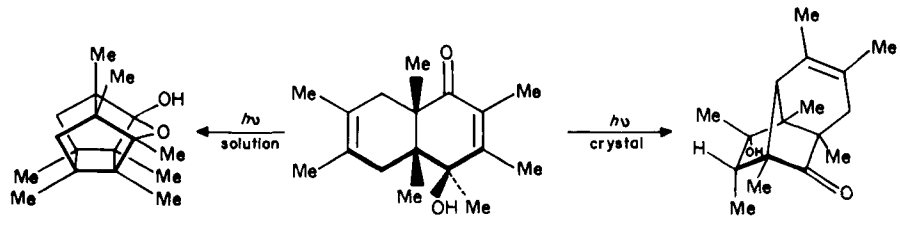
i. Photochemical reactions of cyclohexenones in the solid state. With the development of modern techniques of X-ray crystallography, interest in photochemical reactions of organic compounds in the solid state grew apace. The work of Schmidt in particular established that photodimerization of cinnamic acids and related compounds in the solid state were mainly governed by the distance between molecules in the crystal lattice[230]. Under these conditions, bonding occurs only between molecules when both intermolecular distances and molecular orientation are favorable, i.e. reactions are governed basically by the principle of least motion. However, different forces govern the course of unimolecular reactions in the solid state, as shown by the beautiful work of Scheffer and his colleagues in recent years[231]. Here, the reaction course is determined mainly by molecular conformation. In the solid state, only one molecular conformation is involved, and that is nearly always the lowest-energy conformation of the molecule[232]. In contrast, reactions in solution may proceed via minor populations of more reactive higher-energy conformations if the rate constant for reaction is sufficiently large. Thus, Scheffer and his coworkers have observed many cases in which different products are formed upon irradiation of organic compounds in solution vs. the solid state[231]. The understanding of such differences depends critically on knowledge of the X-ray crystal structures of the systems of interest, which will be assumed in the discussion below.

Some of the most interesting findings in Scheffer's studies concern cyclohexenones. The reactions shown in equations 143–145 illustrate the differences between solution and



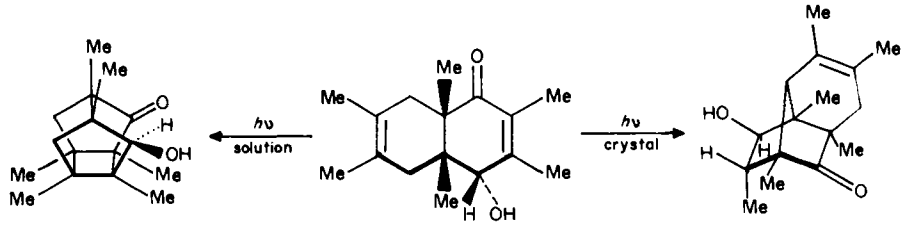
(260) (265)

(143)



(261) (263)

(144)



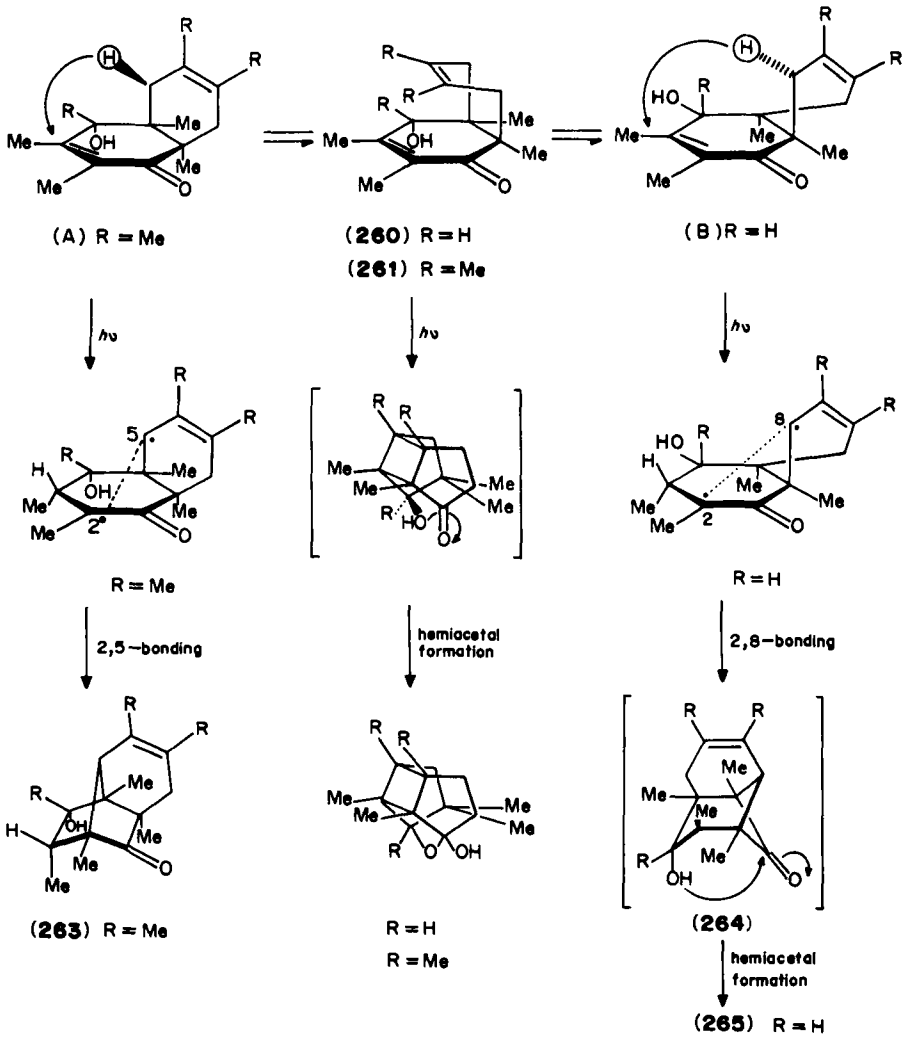
(262)

(145)

solid-state photochemistry of three representative cyclohexenones, **260**, **261** and **262**[233]. In solution, the only reaction observed is intramolecular [2 + 2] photocycloaddition, while irradiation of crystals of these systems leads to rearrangements and only traces of the cage compounds. In the crystalline state, these compounds adopt one of the twist conformations A or B shown in Scheme 42, depending on the nature of the substituents at C_4 of the enone moiety; the bulkier substituent prefers to adopt the pseudoequatorial position. In solution, the two conformations are in rapid equilibrium at room temperature.

Thus, as shown in Scheme **42** enone **261** crystallizes in conformation A with an equatorial methyl group. Irradiation leads to intramolecular hydrogen transfer from the allylic position at C_5 to the β-carbon of the enone moiety, establishing the stereochemistry at this center. The resulting biradical cyclizes to give the observed product **263**. Enone **260**, however, with an H in place of methyl at C_4, adopts conformation B in the solid state with an equatorial hydroxyl group. In this case, intramolecular hydrogen transfer to the β-carbon of the enone can occur only from the other allylic position C_8, giving a biradical which closes to ketone **264**; this then cyclizes to the hemiacetal **265**, the isolated product[233].

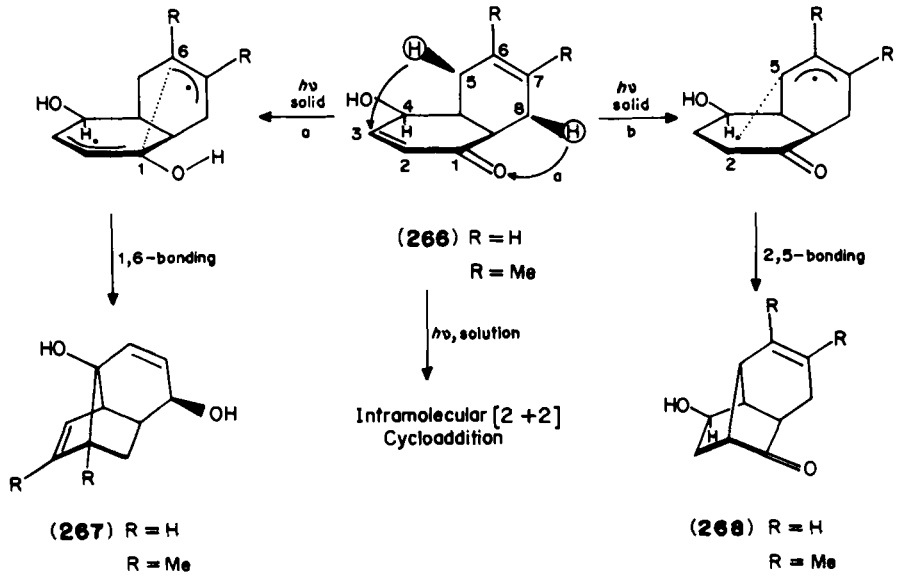
Other features are illustrated by the photochemistry of enones **266** (R = H or CH_3) shown in Scheme 43[234], in which methyl groups on the enone double bond are missing. In solution, as above, only intramolecular [2 + 2] cycloaddition to give a cage compound is observed. In the solid state, Irradiation gives both **267** and **268**, in a ratio that is temperature dependent (2.25:1 at 13 °C, 0.5:1 at −40 °C), corresponding to a difference in activation energy of 4 kcal mol^{-1}. Path a involves allylic hydrogen transfer to the carbonyl oxygen followed by bonding between the radical centers at C_1 and C_6, while path b involves hydrogen transfer from the other allylic carbon to the β-carbon of the enone, and bonding between C_2 and C_5 of the intermediate diradical. Scheffer and coworkers argue that path a involves reaction of a $^3n,\pi^*$ state and path b reaction of a $^3\pi,\pi^*$ state, with the former having the larger activation energy. Substitution of methyl



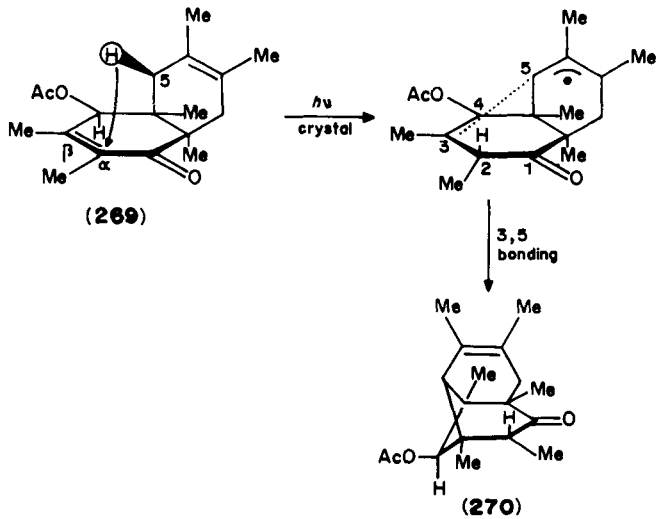
SCHEME 42

groups on the enone C=C bond should stabilize the π,π^* triplet, so it is not surprising that carbonyl abstraction reactions are not seen with enones such as **260–262**[234].

Unusual reactivity was observed for enone **269** in the solid state, in that hydrogen transfer in this case occurs exclusively to the α-carbon of the enone moiety, as shown in Scheme 44, the reverse of the selectivity usually observed. In solution, once again caged products as a result of [2 + 2] cycloadditions are observed. The explanation proposed by Scheffer and coworkers[235,236] involves a crystal-lattice steric effect, or what he calls 'steric compression control'. Since pyramidalization occurs at the carbon that is the migration terminus, the methyl group at this position is forced downward, into close contact with atoms on neighboring molecules in the crystal lattice. In most examples studied



SCHEME 43



SCHEME 44

previously, this effect was comparable at both the α- and β-carbons of the enone moiety, affording no special selectivity. However, in the case of **269** computer simulation studies reveal that steric compression results only from hydrogen transfer to the β-carbon, since a void space surrounds the α-carbon. In the absence of such effects, hydrogen transfer to the α-carbon of the π,π^* triplet is preferred electronically, and is the lower-energy pathway, in solution as well as in the solid state. Scheffer argues that steric compression in

the unique case of **269** raises the activation energy for hydrogen transfer to the β-carbon significantly, so that the lowest-energy path is hydrogen transfer to the α-carbon to ultimately yield **270**.

V. FINAL COMMENTS

Owing to the extensive coverage of the recent literature in the area of enone photochemistry discussed above, it has not been possible for reasons of space and time to cover two other important subjects originally planned for inclusion in this chapter. These are (a) intramolecular enone–alkene photoadditions and (b) the photochemistry of β, γ-enones. Fortunately, reviews on both of these topics are available to interested readers. For (a), the reader can consult References 7, 8 and 189, as well as a recent chapter by Wender on cycloaddition of alkenes[237] and an extensive review by Crimmins[238] on synthetic applications of intramolecular enone–olefin cycloadditions. There are some differences with regard to mechanistic interpretation between these authors and the present author along lines discussed in this chapter, but otherwise the coverage of the literature is rather complete and up to date. With respect to (b), the reviews in References 5 and 6, although somewhat dated, still give a fairly accurate picture of this subject, in which activity appears to have waned somewhat in recent years. For some interesting new findings, the reader is referred to recent work of Koppes and Cerfontain[239] and of Schaffner and coworkers[240].

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The Chemistry of Enones
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CHAPTER **16**

Radiation chemistry of enones

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I. INTRODUCTION

Radiation chemistry deals with the chemical effects of ionizing radiation, such as X-rays, gamma rays, high energy electrons, or other energetic particles. Ionizing radiation is absorbed in organic materials somewhat indiscriminately and causes ionizations and excitations which may result in bond scission. In discussing the radiation chemistry of an organic compound, we should distinguish between the radiation chemistry of the neat compound, where the energy is absorbed totally by the compound itself, and the radiation chemistry of its solutions, where the energy is absorbed predominantly by the solvent. In the latter case, the solute undergoes chemical changes only via reactions with the primary radicals formed from the solvent. The radiation chemistry of enones was studied mainly in solution, as will become clear from this review, and most often it involved aqueous solutions.

Radiolytic studies have been carried out with only a limited number of enones. Several studies have dealt with the simple enones such as acrolein or crotonaldehyde and with the polyene retinal. A number of papers have been published on ascorbic acid and related compounds. Among the heterocyclic enones, we find a study on pyridones but a very large number of papers on pyrimidine and purine bases. In fact, the amount of research carried out on these bases is orders of magnitude higher than that on all other enones, obviously because of the importance of understanding the basic radiation chemistry of DNA. As a result, many reviews and books dealing with the radiation chemistry of DNA components

have been published. In order to keep this chapter on enones somewhat balanced, we shall discuss the DNA bases only briefly and refer the interested reader to the main literature on the topic.

To facilitate discussion of the radiation chemistry of individual compounds in solution, we shall describe here briefly the primary reactions that take place in typical irradiated solvents. The most important and best understood of the solvents is water.

Radiolysis of water results in the production of hydrated electrons, hydrogen atoms, hydroxyl radicals and molecular products (hydrogen and hydrogen peroxide). The yields (G values) of these species in neutral water are approximately 2.8 e_{aq}^-, 2.8 OH, 0.6 H, 0.8 H_2O_2 and 0.4 H_2 (molecules per 100 eV absorbed in solution). In most cases, the molecular products do not interfere with the reactions of the radicals.

Hydrated electrons react with aldehydes and ketones and with conjugated double bonds very rapidly ($k = 10^9$–10^{10} $M^{-1} s^{-1}$) to form radical anions, which subsequently may protonate to yield neutral radicals. Hydroxyl radicals react with enones very rapidly ($k = 10^9$–10^{10} $M^{-1} s^{-1}$) by addition to the double bond and more slowly ($k = 10^8$–10^9 $M^{-1} s^{-1}$) by hydrogen abstraction from C—H bonds. Hydrogen atoms also add to double bonds rapidly but they abstract hydrogen much more slowly ($k = 10^5$–10^7 $M^{-1} s^{-1}$) and also may add slowly to the carbonyl group. These reactions will be discussed in more detail in conjunction with each group of compounds. It is clear, however, that if all the primary radicals are allowed to react with the solute, the system will be very complex and the ensuing chemistry may not be meaningful. To simplify the system under study and to direct the reaction toward a desired product one has to manipulate the primary radicals by addition of proper scavengers.

To study one-electron reduction without interference by OH and H one may add a scavenger for these radicals, commonly an alcohol or formate ions, which react with H and OH rapidly and thus prevent their reaction with the solute under study. Moreover, the radicals produced by reactions of H and OH with alcohols and formate may be reducing in nature and thus the net result is one-electron reduction of the solute by e_{aq}^- and by the organic radical, i.e. a system with one radical produced from the solute under study, with no other side-reactions, e.g.

$$\dot{O}H + HCO_2^- \rightarrow H_2O + \dot{C}O_2^- \qquad (k = 3 \times 10^9\ M^{-1} s^{-1}) \tag{1}$$

$$\dot{H} + HCO_2^- \rightarrow H_2 + \dot{C}O_2^- \qquad (k = 2 \times 10^8\ M^{-1} s^{-1}) \tag{2}$$

$$e_{aq}^- + S \rightarrow S^{\cdot -} \tag{3}$$

$$\dot{C}O_2^- + S \rightarrow CO_2 + S^{\cdot -} \tag{4}$$

To study the reactions of OH without interference by e_{aq}^- the solution is saturated with N_2O, which converts the hydrated electron into OH radical.

$$e_{aq}^- + N_2O \rightarrow N_2 + OH^- + \dot{O}H \qquad (k = 9 \times 10^9\ M^{-1} s^{-1}) \tag{5}$$

In this case the yield of H atoms amounts only to 10% of that of OH radicals and thus no significant interference by H is experienced. Moreover, H and OH often react with a solute by the same mechanism, i.e. hydrogen abstraction to give the same radical or addition to a double bond to give similar radicals.

To study specifically the reactions of H atoms one uses acidic solutions where the hydrated electron is protonated to give H.

$$e_{aq}^- + H^+ \rightarrow \dot{H} \qquad (k = 2.3 \times 10^{10}\ M^{-1} s^{-1}) \tag{6}$$

The interfering OH reaction may be eliminated by using t-butyl alcohol as a scavenger. This alcohol reacts rapidly with OH ($k = 5 \times 10^8$ $M^{-1} s^{-1}$) but much more slowly with H ($k = 1.7 \times 10^5$ $M^{-1} s^{-1}$) and, furthermore, the radical produced by its reaction with OH is

relatively unreactive and is not likely to interfere with the study of the reaction of H with the solute.

$$\dot{O}H + (CH_3)_3COH \rightarrow H_2O + \dot{C}H_2C(CH_3)_2OH \quad (7)$$

The above manipulations allow the study of each of the three primary radicals with little interference by the others. Further, they allow the study of one-electron reduction of solutes. To carry out one-electron oxidation of a solute one may attempt to use OH radicals in N_2O saturated solutions. The OH radicals, however, although they are strong oxidants, generally react by addition or abstraction rather than by a one-electron transfer mechanism. Addition of OH may be followed by water elimination to result in a net oxidation process, but for many compounds this is not the case. Therefore, to carry out one-electron oxidation it is advantageous to convert the OH into strict one-electron oxidizing radicals by the intermediacy of halides, thiocyanate, azide or ethylene glycol. For example, bromide ions form Br_2^- radicals

$$Br^- + \dot{O}H \rightarrow \dot{B}r + OH^- \qquad (k = 1.1 \times 10^{10}\,M^{-1}\,s^{-1}) \quad (8)$$

$$\dot{B}r + Br^- \leftrightarrows \dot{B}r_2^- \qquad (K = 2 \times 10^5\,M^{-1}) \quad (9)$$

azide ions form the azidyl radical

$$N_3^- + \dot{O}H \rightarrow \dot{N}_3 + OH^- \qquad (k = 1.2 \times 10^{10}\,M^{-1}\,s^{-1}) \quad (10)$$

and ethylene glycol undergoes hydrogen abstraction followed by acid- or base-catalyzed water elimination to yield the oxidizing formylmethyl radical.

$$HOCH_2CH_2OH + \dot{O}H \rightarrow HOCH_2\dot{C}HOH + H_2O \qquad (k = 1.8 \times 10^9\,M^{-1}\,s^{-1}) \quad (11)$$

$$HOCH_2\dot{C}HOH \rightarrow \dot{C}H_2CHO + H_2O \quad (12)$$

The radicals $Cl_2^{\bullet-}$, $Br_2^{\bullet-}$, $I_2^{\bullet-}$, $(SCN)_2^{\bullet-}$, $N_3^{\bullet}$, and $\dot{C}H_2CHO$ are strict one-electron oxidants of different redox potentials and may serve to oxidize a variety of enones. Other oxidants may be produced from metal ions or from organic compounds to serve the same purpose.

Radiolysis of a solute in non-aqueous solutions also may lead to oxidation or reduction products and certain solvents are sufficiently well understood to be useful for specific purposes. For example, radiolysis of a solute dissolved in alcohols or ethers results in the formation of its radical anion, and radiolysis in carbon tetrachloride or methylene chloride results in the formation of the radical cation. In both cases the radiolysis produces initially an electron and a positive hole. However, in alcohols the hole is converted into a reducing radical while in halogenated hydrocarbons the hole oxidizes the solute and the electron reacts with the solvent to form an inert halide ion. Further details on the various solvents and the experimental techniques are found in a number of reviews[1,2] and books[3-6].

II. SIMPLE UNSATURATED KETONES AND ALDEHYDES

Irradiation of neat enones, like the irradiation of many olefins, may result in polymerization. Thus gamma radiolysis of frozen acrolein produces a polymer. The rate of polymerization and the structure of the resulting polymer were determined as a function of the irradiation temperature[7], and the results suggested that the polymerization was anionic.

Irradiation of acrolein, methyl vinyl ketone, crotonaldehyde, 3-hexene-2, 5-dione and 2,4,6-octatrienal in aqueous solutions containing an alcohol as OH scavenger and deoxygenated by bubbling with Ar led to the formation of the radical anions of these enones[8].

$$RCH{=}CHCO{-}R + e_{aq} \rightarrow RCH{=}CH\dot{C}O^-{-}R \quad (13)$$

The rate constants for reaction 13 must be close to the diffusion-controlled limit ($\sim 10^{10}\ M^{-1}\ s^{-1}$) since acetaldehyde and acetone react with e_{aq}^- very rapidly ($k = 3.5 \times 10^9$ and $6 \times 10^9\ M^{-1}\ s^{-1}$, respectively)[9]. The optical absorption spectra of the radical anions formed in reaction 13 are in the UV range, the maxima are at 270–280 nm for the radicals with one carbonyl and one double bond, but shift to 350–370 nm when a second carbonyl or a second double bond is conjugated with the basic enone[8]. These ketyl radical anions undergo protonation in neutral or acid solution to form the ketyl radicals.

$$RCH{=}CH\dot{C}O^-R + H^+ \leftrightarrows RCH{=}CH\dot{C}OH{-}R \qquad (14)$$

The absorption spectra of the neutral forms are shifted to lower wavelengths, about 250 nm for the simple enones and 320 nm for the more highly conjugated ones. The difference in spectra permits determination of the pK_a values for these radicals. They were found to be 9.6–10.1 for the simple enone radicals, 9.0 for the radical derived from 2, 4, 6-octatrienal and 5.2 for the radical derived from 3-hexene-2, 5-dione[8]. Clearly, an additional conjugated double bond lowers the pK_a somewhat but an additional carbonyl group exerts a very strong effect by withdrawing electrons from the radical site. In the case of the latter radical (from 3-hexene-2, 5-dione) the spin density and the negative charge are divided between the two carbonyl groups equally, so that protonation is greatly facilitated. Both the pK_a values of the radicals and the wave numbers of their absorption maxima gave linear correlation with the transition energies calculated by LCAO methods[8].

Acrolein, crotonaldehyde and methyl vinyl ketone also react with OH radicals. This reaction was studied in N_2O saturated solutions and found to take place with very high rate constants, $3.5\text{–}5.1 \times 10^9\ M^{-1}\ s^{-1}$, and to form the corresponding OH adducts[10].

$$RCH{=}CHCOR + \dot{O}H \rightarrow RCH(OH){-}\dot{C}HCOR \qquad (15)$$

These radicals absorb light in the UV region and the absorption maxima are below 240 nm. The spectra were found to change with time due to the second-order decay of the radicals, and the product spectra were pH dependent. The decay may take place by radical–radical combination or disproportionation.

$$2RCH(OH){-}\dot{C}HCOR \nearrow RCH(OH)CH(COR)CH(COR)CH(OH)R \qquad (16)$$

$$2RCH(OH){-}\dot{C}HCOR \searrow RC(OH){=}CHCOR + RCH(OH)CH_2COR \qquad (17)$$

The contribution of disproportionation was determined to be 30% for acrolein and methyl vinyl ketone and 86% for crotonaldehyde[10]. The reaction of OH with the hydrated form of crotonaldehyde follows a similar mechanism and produces the hydrated enol $CH_3C(OH){=}CHCH(OH)_2$, which undergoes spontaneous dehydration ($k = 54\ s^{-1}$) to $CH_3C(OH){=}CHCHO$. It also dehydrates in a base catalyzed process by deprotonating to $CH_3C(O^-){=}CHCH(OH)_2$ ($pK_a = 11.6$) and then losing water very rapidly ($k = 1 \times 10^4\ s^{-1}$)[10].

2, 3-Dihydroxy-2-propenal (triose reductone, TR) reacts with OH radicals ($k = 10^{10}\ M^{-1}\ s^{-1}$) to form adducts, which absorb mainly in the UV region[11].

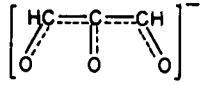
$$CH(OH){=}C(OH)CH{=}O + \dot{O}H \nearrow CH(OH)_2{-}\dot{C}(OH)CH{=}O \qquad (18)$$

$$CH(OH){=}C(OH)CH{=}O + \dot{O}H \searrow \dot{C}H(OH)C(OH)_2CH{=}O \qquad (19)$$

When the substrate is present in its anionic forms ($pK_1 = 5$, $pK_2 = 13$),

$$\underset{(TRH_2)}{CH(OH){=}C(OH)CHO} \leftrightarrows \underset{(TRH^-)}{CH(O^-){=}C(OH)CHO} + H^+ \leftrightarrows \underset{(TR^{2-})}{CH(O^-){=}C(O^-)CHO} + 2H^+ \qquad (20)$$

the reaction of OH leads partially to the oxidation product, $(OCHCOCHO)^{\cdot -}$, which exhibits intense absorption at 398 nm due to its highly delocalized π system[11].

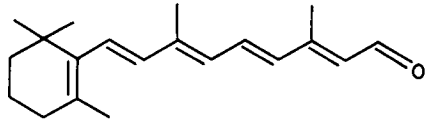


This radical is formed quantitatively by one-electron oxidation of 2,3-dihydroxy-2-propenal with Cl_2^- [$k(TRH_2) = 1.1 \times 10^9$], Br_2^- [$k(TRH_2) = 2.2 \times 10^8$, $k(TRH^-) = 1.8 \times 10^9$], $(SCN)_2^-$ [$k(TRH_2) = 2.7 \times 10^7$, $k(TRH^-) = 9 \times 10^8$], I_2^- [$k(TRH_2) < 10^6$, $k(TRH^-) = 3.4 \times 10^8$] and N_3 [$k(TRH^-) = 4 \times 10^9\ M^{-1}\ s^{-1}$][12]. Its absorption at 398 nm is perfectly symmetric with 71 nm width at half maximum and with molar absorptivity of $5500\ M^{-1}\ cm^{-1}$. This radical resembles that formed by oxidation of ascorbate in that both are conjugated tricarbonyl anions which absorb at similar wavelengths and protonate only at very low pH. The pK_a for protonation of $TR^{\bullet -}$ was found to be 1.4. Both $TR^{\bullet -}$ and $TRH^{\bullet}$ decay by second-order processes, the neutral form more rapidly than the anion, to yield TRH_2 and TR.

Radical anions of enones were formed also by radiolysis in frozen (77 K) methyltetrahydrofuran glasses and their absorption spectra reported[13].

III. RETINAL AND RELATED COMPOUNDS

Retinal is the chromophore of rhodopsin, the visual pigment, and of bacteriorhodopsin. Therefore, many studies have been carried out on the excited state of retinal, including some by pulse radiolysis. The latter technique was used also to investigate the properties of the radical anions and radical cations of retinal and other related polyenes.

all-trans-retinal 

Das and Becker[14] studied the photophysical properties of the triplet state of retinal and of shorter and longer homologues having 3–7 conjugated double bonds next to the aldehyde group. In this series, the peak of the triplet–triplet absorption band was found to change from ca 400 to 500 nm with increase in chain length, and the molar absorptivity increases in the same series by about a factor of four. Some solvent effects were observed on both of the above parameters as well as on the rate of decay of the triplet. The nature of solvent also affected the quantum yield of the lowest triplet state; the effect was minimal for the short homologues, moderate for retinal and considerably higher for the longer homologues, where a decrease by a factor of 5–18 was found on changing from cyclohexane to acetonitrile, benzene and methanol.

Wilbrandt and Jensen[15] produced the lowest triplet state of retinal by pulse radiolysis in benzene or toluene solutions containing naphthalene as a sensitizer. Similarly, Bensasson and coworkers[16] prepared the triplet states of retinal homologues by radiolysis in hexane solutions containing biphenyl. Radiolysis of these solvents results in the formation of the triplet states of naphthalene or biphenyl which then transfer the energy to retinal and its homologues very rapidly (for naphthalene triplet reacting with retinal $k = 5.5 \times 10^9\ M^{-1}\ s^{-1}$). The resulting triplet retinal is short-lived and was found to decay with a second-order rate constant of $2k = 6 \times 10^9\ M^{-1}\ s^{-1}$. Using time-resolved resonance Raman spectroscopy, they recorded the Raman spectrum of the triplet state of retinal and found strong bands at 1550 and 1186 cm^{-1} and weaker bands at 1137, 1212, 1253, 1305 and 1339 cm^{-1}[15]. By comparing these bands with those of retinal in the ground state they concluded that the triplet state has a higher delocalization of π electrons. They also found similarity between the Raman spectrum of triplet retinal and that of an intermediate

observed in the photochemical cycle of bacteriorhodopsin. Later, they compared the absorption and Raman spectra of the triplet state of *all-trans*-retinal with those of the 9-*cis*-, 11-*cis*- and 13-*cis*-isomers[17]. They concluded that each isomer forms a different triplet state or a different mixture of triplet states.

Land and collaborators[18] investigated the radical anions and radical cations of retinal and of shorter (2–3 double bonds) and longer (9 and 13 double bonds) homologues. Pulse radiolysis in deoxygenated hexane solutions produced a mixture of the radical anion and cation, but in the presence of N_2O the anion was absent. The absorption spectra of the radical-anion and -cation of the same polyenal were found to be similar, the maxima differing usually by only 10 nm. However, for the different homologues the maxima changed from 380 nm (for the compound with 3 conjugated double bonds) to 1130 nm (14 double bonds). Pulse radiolysis in methanol solutions gave only the radical anions. These underwent rapid protonation to form species which absorb at much lower wavelengths. Raghavan and colleagues[19] repeated the experiments in methanol and determined the rate of protonation of the radical anion by the solvent to be $7 \times 10^5\ s^{-1}$. The rate of protonation in 2-propanol was found to be considerably lower, $8.1 \times 10^3\ s^{-1}$.

$$Ret^{\cdot -} + ROH \leftrightarrows RetH^{\cdot} + RO^- \tag{21}$$

For homologues of retinal, these rates were dependent on the chain length[20]. They increased by a factor of > 25 in going from a C_{30} to a C_{10} polyene, i.e. an increase in the number of conjugated double bonds stabilizes the radical anion against protonation.

Bobrowski and Das[21] utilized the radiolysis of 2-propanol/acetone/CCl_4 as a source of protons in order to measure the rate of protonation of the radical anions of retinal and other polyenes. For the retinal anion they considered the equilibrium

$$Ret^{\cdot -} + ROH_2^+ \leftrightarrows RetH^{\cdot} + ROH \tag{22}$$

where ROH_2^+ represents the proton in 2-propanol, and determined k(forward) = $9.6 \times 10^6\ M^{-1}\ s^{-1}$ and k(reverse) = $3.5 \times 10^4\ s^{-1}$, and hence an equilibrium constant of $270\ M^{-1}$.

The same authors also determined the spectra of the radical anion and radical cation of retinal in a wide variety of solvents[22]. They found only small shifts for the radical cation, the peak being between 580 and 600 nm, but large shifts for the radical anion, between 440 and 580 nm. The shifts are hypsochromic on going from non-polar to polar solvents and from aprotic to protic solvents.

The retinal radical cation, but not the anion, forms a complex with a molecule of retinal.

$$Ret^{\cdot +} + Ret \leftrightarrows (Ret)_2^{\cdot +} \tag{23}$$

This complexation results in a small change in the spectrum which permits determination of the rate and equilibrium constants[23]. The results were solvent dependent. In acetone k(forward) = $1 \times 10^9\ M^{-1}\ s^{-1}$ and k(reverse) = $2.4 \times 10^6\ s^{-1}$, hence the equilibrium constant is $K = 430\ M^{-1}$. In 1,2-dichloroethane $k_f = 1.3 \times 10^9$, $k_r = 8 \times 10^5$ and K = 1600, in the same units.

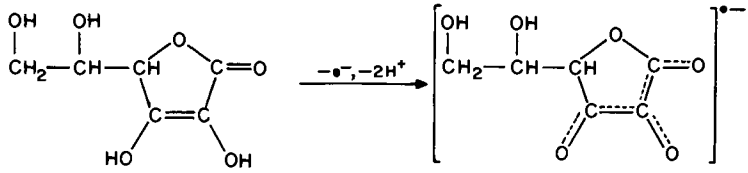
The radical cations of polyenals also react with nucleophiles such as water, triethylamine or Br^-[20]. The rate constants for these reactions increase with decreasing chain length due to increased stabilization of the more highly conjugated radicals. The rate constants were found to be in the range of 10^8–$10^{10}\ M^{-1}\ s^{-1}$ for Br^-, 10^6–$10^9\ M^{-1}\ s^{-1}$ for triethylamine and 10^3–$10^5\ M^{-1}\ s^{-1}$ for water.

IV. ASCORBIC ACID AND RELATED COMPOUNDS

Ascorbic acid is an important component of many biological systems and there are indications that some of its biochemical reactions lead to the formation of the ascorbate

radical. Radiolytic techniques, in conjunction with optical and ESR detection, have been used extensively to study the properties of ascorbic acid and its radical and thus shed some light on their biochemical role. Although the radiolysis of ascorbic acid in aqueous solutions has been suggested[24] to produce the ascorbate radical, Bielski and Allen[25] were the first to provide conclusive evidence by recording the optical absorption spectrum of the radical. Subsequent studies dealt with the rate and mechanism of reaction of ascorbic acid with various radicals and with the properties of the ascorbate radical.

The reaction of OH radicals with ascorbic acid or ascorbate ion leads to the formation of a mixture of radicals[26,27] because OH may add to the double bond on either end or abstract hydrogen and some of the OH adducts may lose a water molecule. To avoid these complications, the ascorbate radical can be produced by one-electron oxidation of ascorbate with a wide variety of oxidizing radicals.



(24)

The rate constants for oxidation increase in going from ascorbic acid to its monoanion ($pK_1 = 4.2$) and dianion ($pK_2 = 11.5$). The values for various radicals are summarized in Table 1. It is seen from the Table that the rate constants vary over many orders of magnitude, depending on the oxidation potential of the radical and its self-exchange rate (i.e., the rate of electron transfer between the radical and its reduction product, e.g., $CO^{3-\cdot} + CO_3^{2-} = CO_3^{2-} + CO_3^{\cdot}$). Nevertheless, all these radicals produce the ascorbate radical as formulated in reaction 24 with no side-reactions.

Ascorbic acid (AH_2) and ascorbate ions (AH^-) are also oxidized by HO_2 and O_2^- radicals, but the pH dependence of the rate constant is somewhat complex because both the compound and the radical undergo acid–base equilibria[38]. The rate constant for $AH_2 + HO_2$ is 1.6×10^4 and for $AH^- + O_2^-$ it is $5 \times 10^4\ M^{-1}\ s^{-1}$. However, the reaction of AH^- with HO_2 is much faster and the pH profile shows a maximum at pH 4.5, where the overall rate constant is $1 \times 10^7\ M^{-1}\ s^{-1}$.

Ascorbate ions react also by hydrogen abstraction with carbon-centered radicals such as $(CH_3)_2\dot{C}OH$ ($k = 1.2 \times 10^6$) and $\dot{C}H(CO_2^-)_2$ ($k = 1.3 \times 10^7\ M^{-1}\ s^{-1}$) and these reactions lead to formation of the same ascorbate radical[39].

The ascorbate radical exhibits an optical absorption spectrum with a maximum at 360 nm and molar absorptivity of $3300\ M^{-1}\ cm^{-1}$[30]. The radical is very long lived in alkaline solutions but decays more rapidly in acidic solutions. The mechanism of decay was suggested to involve an equilibrium between the radical and its dimer, where the dimer may undergo protonation to yield the disproportionation products, ascorbate (HA^-) and dehydroascorbic acid (A)[40].

$$A^{\cdot -} + A^{\cdot -} \leftrightarrows (A)_2^{2-} \tag{25}$$

$$(A)_2^{2-} + H^+ \rightarrow HA^- + A \tag{26}$$

The ascorbate radical is unreactive toward O_2 and most simple organic compounds but can reduce cytochrome c (Fe^{3+}) slowly ($k = 6.6 \times 10^3\ M^{-1}\ s^{-1}$)[41]. The low reactivity of the radical is an important factor in the antioxidant activity of ascorbate. As seen from Table 1, ascorbate reduces peroxyl radicals and thus serves as an antioxidant. But ascorbate reduces also the radicals from other antioxidants, such as phenols and tocopherol, and thus may serve as the ultimate antioxidant. One of the factors that

TABLE 1. Rate constants for one-electron oxidation of ascorbic acid

Radical	pH	k^{*}_{acid} ($M^{-1}s^{-1}$)	pH	k^{**}_{ions} ($M^{-1}s^{-1}$)	Reference
$CO_3^{\cdot -}$			11	1.1×10^9	28
O_3	2	6.9×10^5	4.8	5.6×10^7	28
$N_3^{\cdot}$			7	2.9×10^9	28
NH_2			11.3	7.3×10^8	28
NO_2			6.5	1.8×10^7	28
$SO_3^{\cdot -}$	< 3	$< 1 \times 10^6$	5–10	9×10^6	28
			> 12	3×10^8	28
$SO_5^{\cdot -}$	2	2×10^6	7	1×10^8	28
$(SCN)_2^{\cdot -}$	1.8	1×10^7	7	5×10^8	28
$Cl_2^{\cdot -}$	2	6×10^8			28
$Br_2^{\cdot -}$	2	1.1×10^8	7	1×10^9	28
$I_2^{\cdot -}$	2	5×10^6	7	1.4×10^8	28
CH_2CHO			7	8.8×10^7	29
C_6H_5O			11	6.9×10^8	30
4-CNC_6H_4O			11	2×10^9	30
4-$NH_2C_6H_4O$			11	5×10^7	30
3-$^-OC_6H_4O$			11	1.1×10^8	30
2-$^-OC_6H_4O$			11	5×10^5	31
Tryptophanyl radical			7	7.3×10^7	32
α-Tocopheryl (Vit. E radical)			7	1.6×10^6	33
$CH_3O_2^{\cdot}$			7	2×10^6	34, 35
$HOCH_2O_2^{\cdot}$			7	4.7×10^6	34
$^-O_2CCH_2O_2^{\cdot}$			7	2.2×10^6	34
$(CH_3)_2C(OH)CH_2O_2^{\cdot}$			7	2.1×10^6	35
$CH_2ClO_2^{\cdot}$			7	9.2×10^7	35
$CHCl_2O_2^{\cdot}$			7	2×10^8	35
$CCl_3O_2^{\cdot}$			7	2×10^8	35
$CBr_3O_2^{\cdot}$			7	2×10^8	36
$CF_3O_2^{\cdot}$			7	7×10^8	36
$SCH_2CH_2NH_2$			6.5	1.3×10^9	37
$SCH_2CH(NH_3^+)CO_2^-$			6.5	1.2×10^9	37
GS (Glutathione radical)			6.5	6.0×10^8	37

*This is the rate constant for ascorbic acid (AH_2).
**This is the rate constant for the ascorbate ions, AH^- and A^{2-} (depending on pH).

determine the activity of an antioxidant is the potential for its one-electron oxidation to the corresponding radical. For ascorbate and many phenols, these potentials were determined by pulse radiolysis by establishing equilibrium between radicals before they decay and measuring the equilibrium constant[31]. The potential for ascorbate was determined from equilibrium against catechol:

$$A^{2-} + {}^-OC_6H_4O^{\cdot} \leftrightarrows A^{\cdot -} + {}^-OC_6H_4O^- \qquad (27)$$

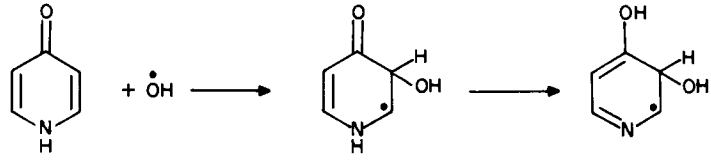
This electron-transfer equilibrium was established at high pH where the reaction is relatively rapid and the radicals more stable[31]. The one-electron oxidation potential of ascorbate was calculated from the equilibrium constant based on the value for catechol. The potential for neutral solutions was then calculated using the known pK_a values of the compound and the radical. The value was found to be 0.30 V vs NHE, (normal hydrogen electrode) indicating that ascorbate is a stronger one-electron reductant at pH 7 than hydroquinone or catechol[31].

The long lifetime and low reactivity of the ascorbate radical as well as its intense absorption spectrum are ascribed to the highly conjugated system of the tricarbonyl anion, which is inferred from its ESR spectrum. *In situ* radiolysis ESR experiments have demonstrated that the ascorbate radical is present in the anionic form throughout most of the pH range and that it protonates only in strongly acidic solutions ($pK_a = -0.45$)[42]. In the anionic form the three CO bonds form a conjugated system such that the unpaired electron is distributed among all of them. This conclusion was supported also by studies on model compounds such as reductic acid [$\underline{CH_2CH_2C(OH)=C(OH)C}=O$] and hydroxytetronic acid [$\underline{OCH_2C(OH)=C(OH)C}=O$]. Other models for the ascorbate radical were that derived from γ-methyl-α-hydroxytetronic acid[43], and the nitrogen analogue 2,3,4-trioxopyrrolidine radical anion[44]. In all the above cases the radicals were long lived and accumulated in the *in situ* radiolysis experiments in sufficiently high concentrations to permit determination of the ^{13}C hyperfine constants at the natural abundance level. These parameters provided further insight into the electronic structure of the radicals, beyond that obtained from the easily determined proton hyperfine constants. They provided an estimate of the spin density on the various carbon atoms and suggested that a considerable portion of the unpaired spin density is on the three carbonyl oxygens. The ring oxygen was suggested to have a very small portion of the spin density as well.

V. PYRIDONES

Although pyridones are the tautomeric forms of hydroxypyridines, they exist mainly as the enone forms. In aqueous solutions the enone form predominates by a factor of 340 for 2-pyridone and 2200 for 4-pyridone. This justifies the inclusion of their radiation chemistry in this chapter, although in some respects they may behave in parallel with phenols.

The reaction of OH radicals with 4-pyridone takes place via addition to the 3-position but the adduct undergoes rapid keto-enol tautomerization to the hydroxypyridine form[45].



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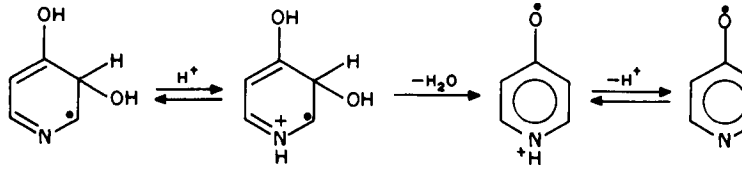
This radical undergoes acid- and base-catalyzed water elimination to form the pyridine-4-oxyl radical[45]. Acid catalysis is by protonation of the radical on the ring nitrogen ($pK_a = 2.5$).



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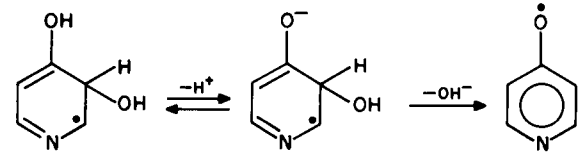
Base catalysis is by deprotonation of the 4-OH group ($pK_a = 10$) followed by loss of OH^- (reaction 30). The rate of the latter process is $1.8 \times 10^4\ s^{-1}$[45], at least two orders of magnitude lower than the parallel reaction with phenol, due to electron-withdrawing by the ring nitrogen.

The reaction of OH with 2-pyridone yields two isomeric adducts; the OH adds to the 3- and 5-positions, where the electron density is the highest (reactions 31, 32). These adducts also revert to the hydroxypyridine tautomer, but in contrast with the case of the 4-pyridone, they do not eliminate water[45].



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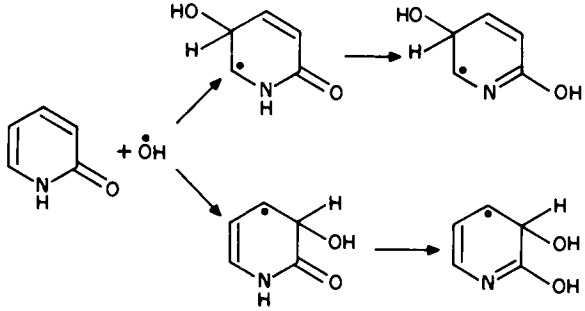


(31)

(32)

The OH adduct of 2, 6-dicarboxypyridone-4 was suggested to remain in the pyridone form and to isomerize to the pyridol tautomer only in alkaline solutions, i.e. after deprotonation of the NH^+ group[45].

VI. PYRIMIDINE AND PURINE BASES

The radiation chemistry of pyrimidine and purine bases has been studied very extensively because of its importance in understanding the mechanism of radiation damage to DNA and all living cells. Radiation damage occurs by two pathways, i.e. by direct effect of radiation on the DNA molecule and by the indirect effect resulting from the reaction of DNA with radicals produced in the radiolysis of water. Therefore, the radiation chemistry of the bases was investigated both in the solid phase and in solution. Studies in the solid phase involved single crystals and powders, as well as glasses and frozen solutions, and concentrated on identifying the radicals by ESR spectroscopy. Studies in aqueous solutions applied ESR to determine the structure of transient species, optical pulse radiolysis to determine their kinetic behavior and product analysis to learn their ultimate fate.

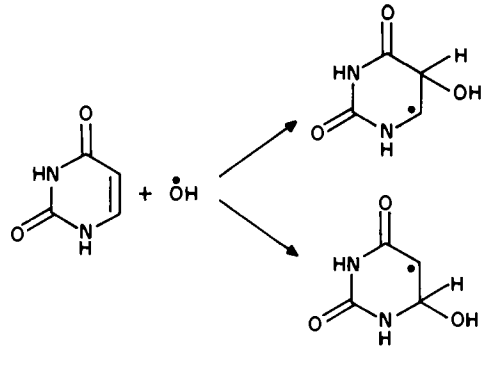
The direct effect of radiation on DNA is likely to result in ionization of one of the bases to produce a radical cation ($B^{\bullet +}$) and an electron. The electron is captured by another base moiety to yield a radical anion ($B^{\bullet -}$). This may protonate, most likely on carbon 6, to yield a neutral 5-yl radical equivalent to an H atom adduct. The radical cation may deprotonate, probably losing the NH proton, to form a neutral radical. Alternatively, it may hydroxylate at carbon 6 to give the neutral 5-yl radical. All the above species have been identified by ESR in the solid phase. One of the main conclusions of those studies is that the effect of radiation on DNA is likely to result in the oxidation of guanine and reduction of thymine. It is beyond the scope of this chapter to review all the literature on this subject, but the interested reader is referred to several representative examples[46–54].

When the radiolysis was carried out in frozen alkaline solutions, an additional reaction was observed, that of $O^{\bullet -}$ radicals with thymine leading to hydrogen abstraction from the methyl group[50]. The formation of this radical was confirmed also by irradiating polycrystalline thymine and then dissolving it in an aqueous solution of a spin trapping material, 2-methyl-2-nitrosopropane[55]. The radicals formed in the solid were trapped and identified by ESR; they were found to include also the C5 and C6 H-adducts.

Spin-trapping ESR studies have been carried out also with aqueous solutions irradiated at room temperature. Here the irradiation is done in the presence of the spin trap so that the short-lived radicals are trapped to form very long lived or persistent radicals which are easily identified by ESR[56–58]. Thus the OH adducts to C5 and C6 of several pyrimidine bases and the radicals formed by oxidation of these bases with SO_4^- have been observed. In certain cases, the spin-trap radicals are sufficiently persistent to be separated by chromatography before ESR analysis[59]. This method identified the 5-OH adduct of uracil and distinguished between the *cis* and *trans* isomers. However, the ESR spectra of spin-trapped radicals do not provide as much information on the structure of the initial radicals as is obtained by direct observation of these radicals.

Direct ESR measurements on short-lived radicals in irradiated solutions was achieved by *in situ* radiolysis within the ESR spectrometer. Studies were carried out using pulse or continuous radiolysis. In the pulse radiolysis experiments the radicals produced by the reactions of OH and of e_{aq}^- with pyrimidine bases have been identified and the rate constants for their reactions with oxygen and with thiols were measured[60]. The sensitivity of this technique, however, was lower than that of the steady-state method and thus only the major hyperfine constants were determined with accuracy. The steady-state method provided detailed hyperfine constants but, because of the lack of the time resolution, secondary radicals were observed along with, or instead of, the primary ones[61–65]. These studies identified the radical formed upon H-abstraction from the methyl group of thymine by O^- radicals, but the C5 and C6 OH-adducts were not observed in their initial form, only the products of dehydration or secondary oxidation were identified. In the case of 5-halo- and 5-nitrouracil the OH-adducts underwent rapid loss of HX or HNO_2 to form the 5-oxo-6-yl radicals[62,63].

The main reactions occurring in the irradiated solutions discussed above are shown in equations 33–37. Further details on these reactions were obtained from pulse radiolysis experiments utilizing optical and conductometric detection.



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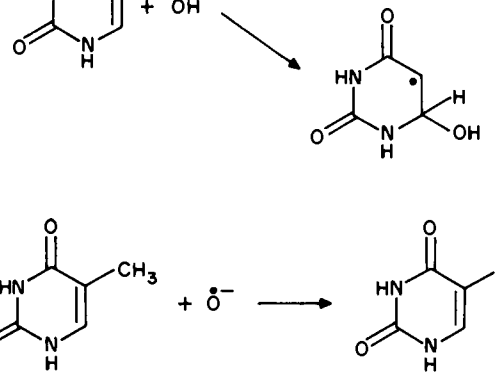

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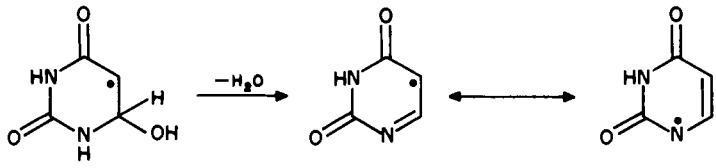
The rate constants for the reactions of representative bases with the primary radicals of water radiolysis and with certain secondary radicals are summarized in Table 2. The



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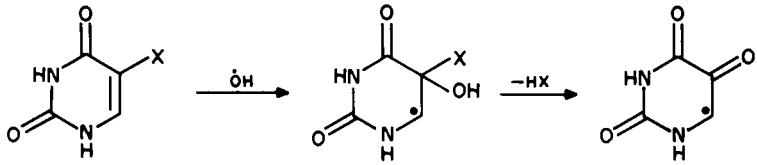


(37)

purine and pyrimidine bases react with OH radicals at nearly diffusion-controlled rates, k approaching $10^{10}\ M^{-1}\ s^{-1}$. They react with H atoms somewhat more slowly, $k \sim 10^8$–$10^9\ M^{-1}\ s^{-1}$. Both reactions lead mainly to addition to the 5,6-double bond as in reactions 33 and 34. In purine bases addition to the 8-position is also possible[66,67]. These adduct radicals have similar absorption spectra[68–72] but can be distinguished through differences in their redox behavior. In general, the 6-yl radicals are reducing while the 5-yl are oxidizing. Table 3 shows that the 5-OH adducts, i.e. 6-yl radicals, reduce tetranitromethane, quinones, riboflavin and hemin very rapidly while the 6-OH adducts oxidize *N*, *N*, *N'*, *N'*-tetramethyl-*p*-phenylenediamine (TMPD), also rapidly. This difference permitted determination of the relative yields of the two types of radicals. In all pyrimidine bases, the OH addition was found to take place preferentially at C5 (uracil—82%,

TABLE 2. Rate constants for selected reactions of DNA bases with radicals

Base	Radical	pH	$k(M^{-1}\ s^{-1})$	Reference
Uracil	$\dot{O}H$	7	6×10^9	73
Thymine	$\dot{O}H$	7	6×10^9	73
Thymine	$\dot{O}^-$	> 13	4×10^8	73
Uracil	H	1,7	3×10^8	73
Thymine	H	1	7×10^8	73
Uracil	e^-_{aq}	7	$\sim 1 \times 10^{10}$	73
Thymine	e^-_{aq}	7	1.7×10^{10}	73
Uracil	$CO_3^{\cdot -}$	7	$< 1 \times 10^4$	28
Uracil	$HPO_4^{\cdot 2-}$	9	1×10^8	28
Uracil	$H_2PO_4^{\cdot}$	4.5	6×10^8	28
Uracil	$SO_4^{\cdot -}$	7	1×10^9	28
Thymine	$(SCN)_2^{\cdot -}$	7	1×10^6	28
Thymine	$(SCN)_2^{\cdot -}$	12	3×10^7	28
Uracil	$Cl_2^{\cdot -}$	2,6	4×10^7	28
Uracil	$Br_2^{\cdot -}$	7	$< 1 \times 10^7$	28
Uracil	$Br_2^{\cdot -}$	12	2×10^8	28
Thymine	$\dot{C}O_2^-$	7	$\sim 5 \times 10^4$	28
5-Bromouracil	$(CH_3)_2\dot{C}OH$	7	2×10^7	74
Adenosine	$(CH_3)_2\dot{C}OH$	7	$< 10^6$	74
Adenosine	$(CH_3)_2\dot{C}OH$	2	5×10^7	74
Isobarbiturate	$\dot{C}H_2CHO$	13.5	1.6×10^9	75

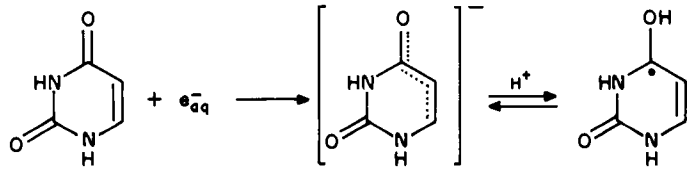
TABLE 3. Rate constants for representative reactions of DNA base radicals[84]

Radical	Reactant	k ($M^{-1}s^{-1}$)
Thymine-5-OH adduct	O_2	2×10^9
	menaquinone	4×10^9
	tetranitromethane	1.5×10^9
	cysteine	$< 1 \times 10^6$
Thymine-6-OH adduct	TMPD	1.3×10^9
Cytosine-5-OH adduct	riboflavin	1.6×10^9
	hemin c	1.1×10^9
	tetranitromethane	1.1×10^9
Cytosine-6-OH adduct	TMPD	1.1×10^9
Deoxyguanosine-OH adduct	ascorbate ion	1.4×10^9
	NADH	4.0×10^8
	cysteine	8×10^7
Thymine radical anion	O_2	6×10^9
	menaquinone	4×10^9
	orotic acid	1.5×10^9
Uracil radical (ox., pH 13)	adenine	9×10^7
	guanine	7×10^8
	xanthine	8×10^8
	tryptophan	1.4×10^9

thymine—60%, cytosine—87%)[76-79]. Hydrogen abstraction by OH from the methyl group of thymine amounts to 10% contribution. However, at high pH, when OH is converted to O^-, hydrogen abstraction becomes predominant (reaction 35). In the case of 5-halouracils, the contribution of OH addition to C5 was estimated from the extent of dehalogenation (reaction 37)[80].

The 6-OH adduct eliminates a water molecule at high pH (reaction 36)[76,77]. The radical formed in this reaction can be produced directly by one-electron oxidation of the pyrimidine base with an oxidizing radical such as $SO_4^{\bullet -}$. Table 2 shows that the rate constant for oxidation with $SO_4^{\bullet -}$ is very high but weaker oxidants, such as the dihalide radicals, react much more slowly. The rate of oxidation depends also on pH; the ionized forms of the pyrimidine bases are oxidized more rapidly than the neutral forms. The radicals produced in these reactions may behave as oxidants toward other molecules. Table 3 lists several examples for the radical of uracil. In general, such radicals oxidize pyrimidine or purine bases of lower redox potential as well as tryptophan, 5-hydroxytryptophan, vitamin E and certain phenols. These reactions were observed in alkaline solutions but are slow in neutral solutions[81].

The reactions of pyrimidine and purine bases with hydrated electrons take place with diffusion-controlled rate constants[82] but electron transfer to these bases from other reducing radicals is a slow process (Table 2). The initial electron adducts have pK_a values near 7[83]. Both forms are strongly reducing and may transfer an electron to oxygen, quinones, nitro compounds, and to other pyrimidines with higher electron affinity, such as orotic acid (Table 3)[85,86]. The electron adducts also protonate slowly on carbon to yield 6-H-adducts, which are oxidizing radicals[87].



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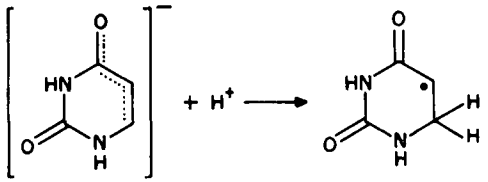
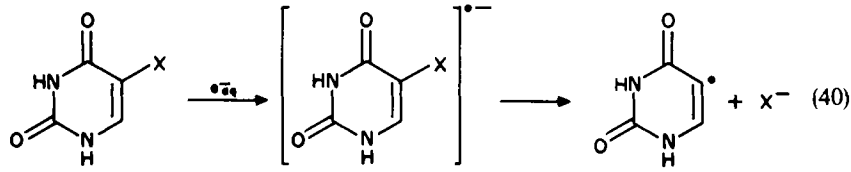


(39)

The electron adducts of 5-halouracils undergo rapid dehalogenation[88-90]. This process predominates in the case of bromo and iodo derivatives but with chlorouracil it is in competition with the protonation reaction[91,92]. The uracilyl radical produced in reaction 40 is very reactive and can add to another molecule of halouracil or abstract hydrogen from 2-propanol, in the latter case propagating a chain reaction[88-90].



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Radicals produced by addition of H and OH to pyrimidine and purine bases undergo dimerization or disproportionation reactions to form the final products. When oxygen is present in solution, they react with it very rapidly to give peroxyl radicals, which then decay to stable products. These products have been determined over the past three decades by various analytical techniques and under different experimental conditions[79]. Before we discuss the mechanism of formation of final products we briefly summarize the main findings.

Thymine. Monomeric products of thymine radicals have been identified by a number of laboratories[93-97]. Table 4 presents a list of thymine products and their yields from three different sources. The main product is thymine glycol (*cis*- and *trans*-5, 6-dihydro-5, 6-dihydroxythymine). Other OH radical-induced products of thymine are 5-hydroxy-5, 6-dihydrothymine, 6-hydroxy-5, 6-dihydrothymine and 5-hydroxymethyluracil. 5, 6-Dihydrothymine results from H-atom reactions with thymine. The nature of OH radical-induced dimers of thymine has recently been elucidated[97]. The structures of the dimers have been obtained from mass spectral data, which suggested that combination reactions of OH-adduct radicals of thymine lead to dimers. Some of the dimers have been shown to dehydrate presumably during the derivatization process prior to analysis. In the case of

TABLE 4. Products and their yields from γ-radiolysis of thymine in N_2O-saturated aqueous solution

Product	*G* value		
	Ref. 95	Ref. 96	Ref. 97
Thymine consumption	3.9	2.7	5.5
cis- and *trans*-Thymine glycol	2.26	0.32	1.4
5-Hydroxy-5, 6-dihydrothymine	—	0.08	0.5
6-Hydroxy-5, 6-dihydrothymine	0.13	0.1	
5, 6-Dihydrothymine	0.1	0.17	0.04
5-Hydroxymethyluracil	0.22	0.27	0.2
Dimers	0.26	—	3.1

TABLE 5. Products and their yields from γ-radiolysis of thymine in aerated aqueous solution[101]

Product	*G* value
Thymine consumption	2.6
cis- and *trans*-Thymine glycol	0.248
5-Hydroxy-5,6-dihydrothymine	0.016
6-Hydroxy-5,6-dihydrothymine	0.008
5-Hydroxymethyluracil	0.017
5-Hydroxy-5-methylbarbituric acid 5-Hydroxy-5-methylhydantoin	0.149
Formylurea	0.065
Formylpyruvylurea	0.460
cis- and *trans*-5-Hydroperoxy-6-hydroxydihydrothymine	1.144
cis-6-Hydroperoxy-5-hydroxydihydrothymine	0.081
5-Hydroperoxymethyluracil	0.047
5-Hydroperoxydihydrothymine	0.062
cis- and *trans*-Hydroperoxydihydrothymine	0.055
5-Hydroperoxy-5-methylhydantoin	0.005
5-Hydroperoxy-5-methylbarbituric acid	0.011
trans-5,6-Dihydroperoxydihydrothymine	0.009

thymine oligo- and polynucleotides, the dimers resulting from combination reactions of OH-adduct and H-adduct radicals of thymine have also been identified[98,99]. The combination of electron-adduct radicals of thymidine has been demonstrated to yield a dihydrodimer in deareated aqueous solutions of thymidine in the presence of formate ions[100]. The same dimer has also been found to be formed by reaction of formate ions with thymine in N_2O-saturated solution.

In the presence of oxygen, a large number of thymine products have been observed[101–106]. The major products observed in aerated aqueous solution and their yields are listed in Table 5. Some of these products might have been secondary products because large radiation doses have been used. The dominant products are the hydroperoxides, which are formed from the interaction of the HO_2/O_2^- radicals with thymine peroxyl radicals. No dimers have been found in the presence of oxygen.

Uracil. The main monomeric products of uracil in the absence of oxygen are *cis*- and *trans*-uracil glycols and isobarbituric acid[107–111]. The latter one presumably results from dehydration of uracil glycols, and thus it is not a primary product. The yields of the products have been measured under different conditions and pH values. Table 6 shows the

TABLE 6. Products and their yields from γ-radiolysis of uracil in deoxygenated aqueous solution at neutral pH[108]

Product	*G* value
Uracil consumption	3.75
cis-Uracil glycol	0.81
trans-Uracil glycol	0.92
Isobarbituric acid	0.38
6-Hydroxy-5,6-dihydrouracil	0.13
Formylurea	0.34
Alloxan	0.25
Dialuric acid	0.15
Dimers	0.21

TABLE 7. Products and yields from the γ-radiolysis of 1,3-dimethyluracil in N_2O-saturated aqueous solution[113]

Product	G value		
	pH 3	pH 6.5	pH 10.4
1,3-Dimethyluracil consumption	3.9	5.7	5.1
1,3-Dimethyluracil glycol	1.5	0.85	0.8
1,3-Dimethylisobarbituric acid	0.15	0.1	0.1
5-Hydroxy-5,6-dihydro-1,3-dimethyluracil	0.4	0.75	0.6
6-Hydroxy-5,6-dihydro-1,3-dimethyluracil	0.1	0.2	0.1
Dimers	1.7	3.6	3.2

uracil products and their yields in deoxygenated aqueous solution from one source. There appears to be a disagreement on the yields of products among different laboratories[108–111]. Dimers have also been observed; however, no definite structure could be assigned to dimeric products[109,111,112]. In the case of 1,3-dimethyluracil, structure of dimeric products of OH-adduct radicals in N_2O-saturated aqueous solution could be assigned with certainty because this compound was more suitable to analysis than uracil[113]. Mass spectral data suggested that dimers were formed exclusively by combination of a C(5)-OH adduct radical with an identical radical or with a C(5)-H adduct radical. Monomeric products and their yields have also been determined at different pH values (Table 7).

The formation of unstable hydroxyhydroperoxides of uracil in aerated aqueous solution has been observed in earlier studies[114,115]. A number of products have been isolated and identified[108,116,117]. Recently, the radiolysis of uracil has been reinvestigated in N_2O/O_2-saturated aqueous solution by product analysis and pulse radiolysis[118]. The yields of the products observed (Table 8) are strongly pH dependent and the mechanisms of product formation have been discussed in detail[118]. No dimers have been observed in the presence of oxygen.

Cytosine. Products of cytosine radicals in the absence and presence of oxygen have been identified, and their yields have been measured[119–125]. Tables 9 and 10 summarize the findings in the presence and absence of oxygen, respectively. 5-Hydroxycytosine, which

TABLE 8. Products and their yields from γ-radiolysis of uracil in N_2O/O_2-saturated aqueous solution[118]

Product	G value		
	pH 3.0	pH 6.5	pH 10.0
Uracil consumption	4.9	5.3	5.2
cis-Uracil glycol	0.6	0.9	1.4
trans-Uracil glycol	0.5	1.1	1.0
Isobarbituric acid	0	0.2	1.2
Formylhydroxyhydantoin	1.6	1.4	0.2
Dialuric acid	0.9	0.4	0.2
Isodialuric acid	0.1	0.2	0.1
5-Hydroxyhydantoin	0.4	0.4	0.3
Unidentified products	0.9	0.6	0.9

TABLE 9. Products and their yields from the γ-radiolysis of cytosine in aerated aqueous solution[120]

Product	G value
Cytosine consumption	2.5
trans-1-Carbamoylimidazolidone-4, 5-diol	0.6
4-Amino-1-formyl-5-hydroxy-2-oxo-3-imidazoline	0.2
cis-Uracil glycol	0.03
trans-Uracil glycol	0.1
5-Hydroxyhydantoin	0.1
Oxaluric acid and ureides	0.2
Parabanic acid	0.03
Biuret	0.06
Formylurea	0.06

TABLE 10. Products and their yields from the γ-radiolysis of cytosine in N_2O-saturated aqueous solution[125]

Product	G value
Cytosine consumption	5.6
Uracil	0.02
Uracil glycol	0.15
5-Hydroxycytosine	1.4
6-Hydroxycytosine	0.07
Cytosine glycol	0.05
5, 6-Dihydroxycytosine	0.20
Dimers	3.2

was observed with a high yield in the absence of oxygen (Table 10), is not a primary product and results from dehydration of cytosine glycol. Dimers have been found only in the absence of oxygen and their structures have been elucidated from mass spectral data[125].

Adenine and Guanine. The radiation chemistry of purine bases is less well understood than that of pyrimidines. The site of attack of the species from the water radiolysis has not been determined definitely. The yield of oxidizing and reducing radicals of some purine nucleotides, which were produced upon OH radical attack, has been determined recently and three sites of OH radical attack for guanine derivatives have been proposed[66]. Several products of adenine have been identified in earlier studies[126–129]. Table 11 lists the products and their yields. The formation of these products may be accounted for by the

TABLE 11. Products and their yields from the γ-radiolysis of adenine in N_2O-saturated aqueous solution[129]

Product	G value
Adenine consumption	1.0
8-Hydroxyadenine	0.35
4, 6-Diamino-5-formamidopyrimidine	0.2
6-Amino-8-hydroxy-7, 8-dihydropurine	0.1

TABLE 12. Products and their yields from the γ-radiolysis of 2′-deoxyguanosine in N_2 and N_2O-saturated aqueous solutions[130]

Product	G value	
	N_2	N_2O
2′-Deoxyguanosine consumption	0.81	1.50
9-(2-Deoxy-β-D-erythropentopyranosyl)-2, 4-diamino-5-formamidopyrimid-6-one	0.08	0.09
9-(2-Deoxy-α-D-erythropentopyranosyl)-2, 4-diamino-5-formamidopyrimid-6-one	0.26	0.25
9-(2-Deoxy-α-D-erythropentopyranosyl)guanine	0.02	0.03
9-(2-Deoxy-β-D-erythropentopyranosyl)guanine	0.01	0.02
9-(2-Deoxy-α-D-erythropentofuranosyl)guanine	0.02	0.02
9-(2-Deoxy-α-L-threopentofuranosyl)guanine	0.02	0.03
9-(2-Deoxy-β-D-erythropento-1, 5-dialdo-1, 4-furanosyl)guanine	0.07	0.08
5′, 8-Cyclo-2′, 5′-dideoxyguanosine	0.05	0.06
8-Hydroxy-2′-deoxyguanosine	—	0.24
Guanine	0.19	0.38

OH radical attack at the C(8)-position of adenine. The low product yields and the low adenine consumption in N_2O-saturated aqueous solution have been suggested to result from reconstitution reactions of adenine radicals[129].

The radiation chemistry of guanine has been investigated using guanine nucleosides or nucleotides because of the insufficient solubility of guanine in water. Table 12 summarizes the products identified in deareated and N_2O-saturated aqueous solutions of 2′-deoxyguanosine[130]. Similar to the adenine system, the yields of the products and the consumption of 2′-deoxyguanosine have been found to be low.

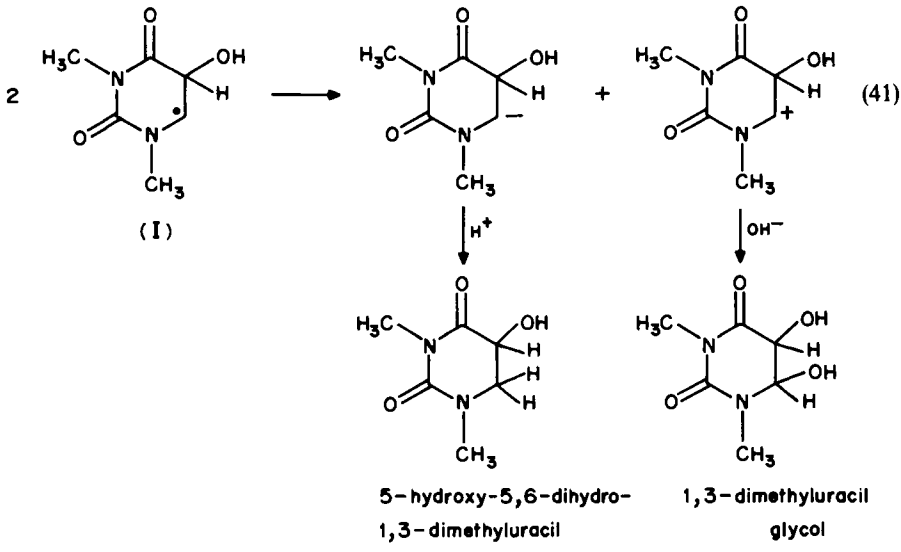
In the presence of oxygen, addition of the OH radical to the C(4)-position of adenine and peroxidation of the resultant radical has been suggested to account for the degradation of adenine; however, no peroxides have been detected[131]. In aerated aqueous solution, 8-hydroxyadenine has been found as the major product of adenine[127,129]. Some other degradation products of adenine have also been identified; however, their formation has been suggested to result from the decomposition of 8-hydroxyadenine[132]. The knowledge of the radiation chemistry of purines in the presence of oxygen is very limited at present.

Mechanistic Aspects. In the absence of oxygen, disproportionation and combination reactions of the adduct radicals of pyrimidines lead to final products. Some of the major pathways are illustrated in reactions 41–44 using the 1, 3-dimethyluracil system as an example[113]. Combination reactions take place between the C(5)-OH adduct radicals and another C(5)-OH adduct or an H-adduct to give the observed dimers (reactions 43 and 44)[113]. Analogous mechanisms for dimer formation have been described for thymine, its oligo- and polynucleotides, and cytosine[97–99,125].

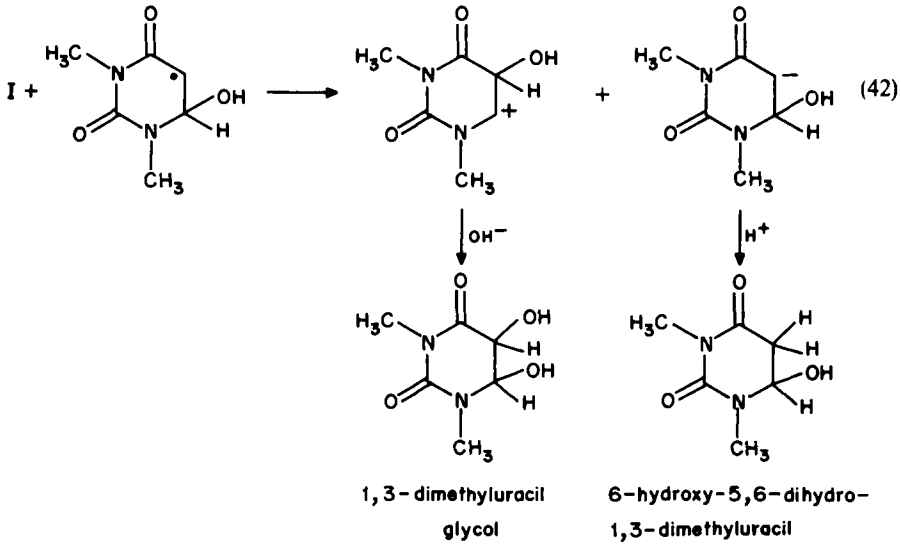
The electron adducts of thymine also undergo dimerization after protonation as illustrated in reaction 45[100].

In the presence of oxygen, peroxyl radicals, which are formed by addition of oxygen to the adduct radicals of pyrimidines, disproportionate to give the final products. The major pathways are illustrated in reactions 46–48 using the uracil system[118].

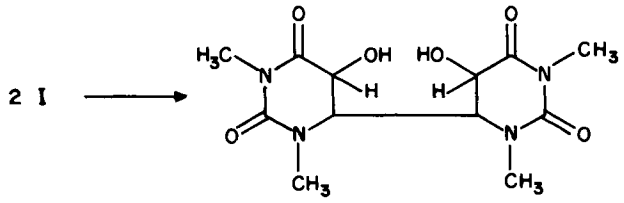
The pathways in equation 49 have been suggested for the formation of the products of adenine[129]. In the case of guanylic acid (dGMP), reaction with OH radicals was suggested to lead to formation of a radical cation or a protonated OH-adduct (reactions 50–52)[133,134]. Recently, three OH-adduct radicals of guanylic acid have been postulated[66].


2
(I)
5-hydroxy-5,6-dihydro-
1,3-dimethyluracil
1,3-dimethyluracil
glycol

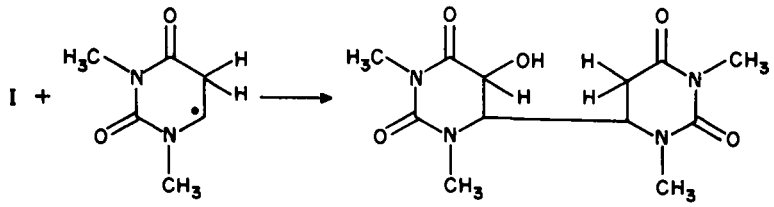
(41)


I +
1,3-dimethyluracil
glycol
6-hydroxy-5,6-dihydro-
1,3-dimethyluracil

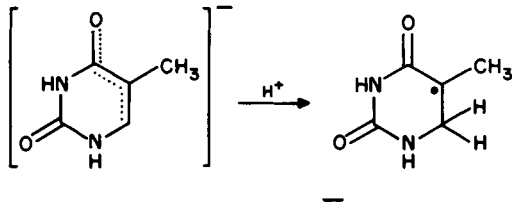
(42)


2 I

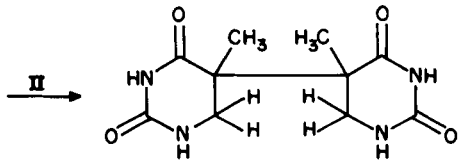
(43)



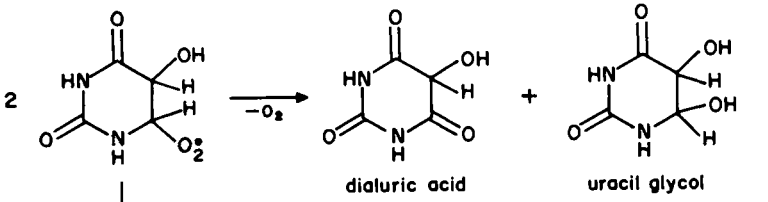
(44)



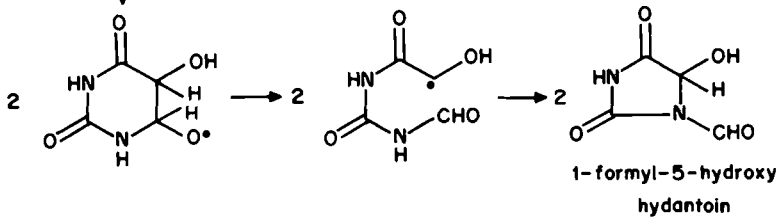
II



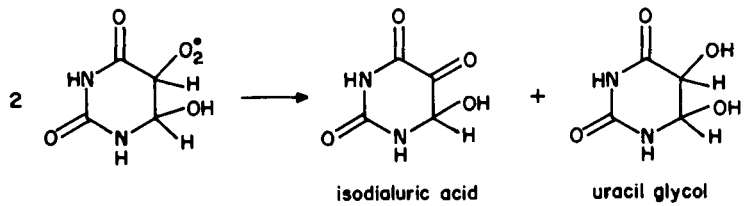
(45)



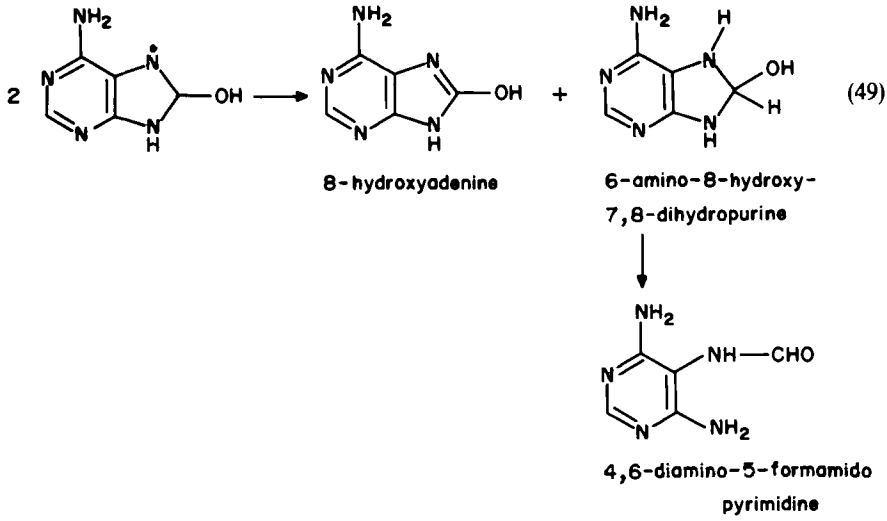
(46)



(47)



(48)



(49)

At present, there is no satisfactory mechanism for the formation of the products of adenine and guanine.

$$dGMP + OH \rightarrow dGMP^{\cdot +} + OH^- \quad (50)$$

$$dGMP + OH \rightarrow dGMP(OH)^{\cdot} \quad (51)$$

$$dGMP(OH)^{\cdot} + H^+ \rightarrow dGMP(OH)H^{\cdot +} \quad (52)$$

VII. CONCLUSION

The enones discussed in this chapter belong to various groups of compounds which exhibit diverse behavior in radiation chemistry, in terms of the properties of transient radicals and nature of final products. The main feature that is common to most enones is that they react rapidly with all three radicals of water radiolysis, OH, H and e_{aq}^-. The reactions of OH and H involve addition of these radicals to the C=C double bond. On the other hand, e_{aq}^- adds to the carbonyl group and may form a radical anion in which the electron is delocalized over the carbonyl and the conjugated double bonds. All the above radicals decay by combination or disproportionation or by reaction with O_2, if present in solution. In general, OH and H adducts react with O_2 by addition to form peroxyl radicals while electron adducts transfer an electron to O_2. These and subsequent reactions lead to a wide variety of products, as discussed for the pyrimidine bases. However, many experiments with other enones were carried out under conditions specifically designed to produce one predominant radical and subsequently only one or two products. Again, the final outcome is very much dependent on the presence or absence of oxygen in solution.

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The Chemistry of Enones
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CHAPTER 17

The oxygenation of enones

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I. INTRODUCTION

The discovery of oxygen over 200 years ago can be attributed to three people: Lavoisier, Priestly, and Scheele[1]. The continuing fascination of the scientific community with this element stems from the complicated role molecular oxygen (dioxygen) and its derivatives play not only in the 'breath of life' but more interestingly in oxygen toxicity[2,3]—what might be poetically called 'the breath of death'[4]. This review will focus on the interaction of various active oxygen species with enones, one of the most fascinating and useful organic moieties.

For the purpose of this review, we have surveyed the literature through January 1988 and have discussed variously substituted α,β- and β,γ-unsaturated carbonyl compounds (including keto enols and aci-reductones) as well as ketenes. While we have tried to present a complete picture, no attempt has been made to be encyclopedic and exhaustive.

II. THEORETICAL DESCRIPTION OF ACTIVE OXYGEN SPECIES

Ever since the discovery of oxygen over two centuries ago, mankind has invested a good deal of time and resources in attempting to understand the exact role this life-supporting molecule plays in autoxidative, photooxidative and metabolic processes. Since the electronic makeup of a molecule determines its reactivity, it was to molecular orbital theory and electronic excitation spectroscopy that scientists turned in order to get an exact description of the configuration of the various electronic states of molecular oxygen[5]. We shall limit our discussion to the structure of the lowest three electronic states of dioxygen (O_2) which differ primarily in the manner in which the two electrons of highest energy occupy the two degenerate π^*_{2p} orbitals. Following Hund's rule, in the ground state of O_2, these two electrons will have parallel spins and be located one each in the two degenerate π^*_{2p} orbitals (Figure 1). Such an electronic configuration corresponds to a triplet $^3\Sigma_g^-$ state and we shall henceforth refer to ground-state molecular oxygen as triplet oxygen, $^3O_2$.

This triplet character is responsible for the paramagnetism and diradical-like properties of $^3O_2$. More importantly, this triplet electronic configuration only permits reactions involving one-electron steps. Thus, despite the exothermicity of oxygenation reactions, a spin barrier prevents $^3O_2$ from reacting indiscriminately with the plethora of singlet ground-state organic compounds surrounding it. One could well argue that it is this spin barrier that permits life to be maintained.

The two lowest excited states are both singlets in which the two highest-energy electrons have antiparallel spins. Thus, no spin barrier should exist for their reaction with organic substrates. In the first ($^1\Delta_g$) state, which lies 22.5 kcal mol^{-1} above the ground state, both of

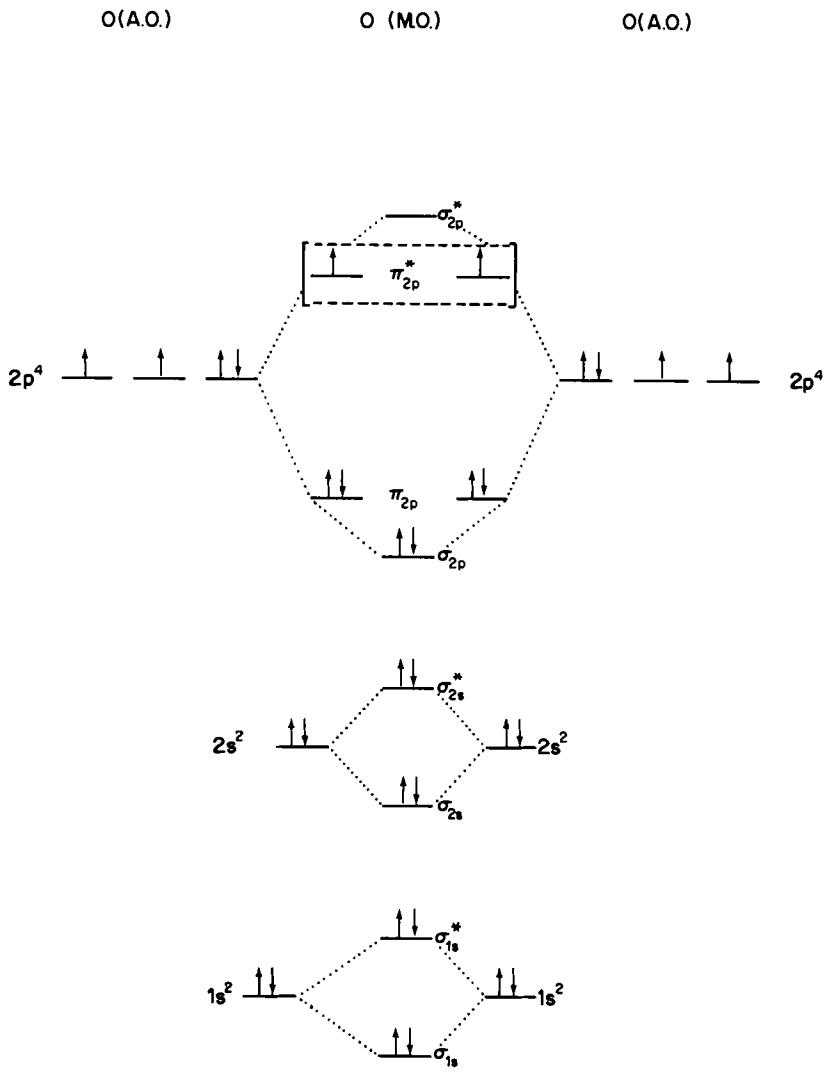
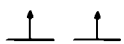


FIGURE 1. Schematic energy-level diagram showing how the atomic orbitals (A.O.) of two atoms of elemental oxygen interact to form the molecular orbitals (M.O.) of molecular oxygen. The electron distribution is, according to Hund's rule, yielding ground-state molecular oxygen ($^3\Sigma_g^-$)

the highest-energy electrons occupy the same π^*_{2p} orbital. In the second, a $^1\Sigma_g^+$ state lying 15 kcal mol^{-1} higher, each of the π^*_{2p} orbitals is half full (Table 1).

In the gas phase the lifetimes of $^1\Delta$ and $^1\Sigma$ oxygen are 45 min and 7 s, respectively[6]. However, in solution these lifetimes are dramatically reduced through collisional deactivation to approximately 10^{-3} and 10^{-9} s, respectively[6,7]. Because the reactions that concern us are generally carried out in solution, it is the longer-lived $^1\Delta O_2$ that is involved

TABLE 1. The three lowest electronic states of molecular oxygen and selected properties

Electronic state	Configuration of π^*_{2p}	Relative energy (kcal mol^{-1})	Lifetime (s)[6,7]		Valence bond representative
			Gas phase	Liquid phase	
$^1\Sigma_g^+$		37.5	7–12	10^{-7}	
$^1\Delta_g$		22.5	2700	10^{-3}	
$^3\Sigma_g^-$		0	∞	∞	

as the active species. We shall henceforth refer to this longer-lived species as singlet oxygen, $^1O_2$.

A simplified picture of the three lowest electronic states of molecular oxygen and a comparison of some of their properties is presented in Table 1.

The one-electron reduction product of molecular oxygen is the superoxide anion radical. $O_2^{-\cdot}$ differs from $^3O_2$ and $^1O_2$ in that the former has three—not two—electrons in its π^*_{2p} orbitals. This leads to a situation in which one of the two degenerate π^*_{2p} orbitals is totally occupied while the second is only half full, as outlined in equation 1. It should be noted that no Jahn–Teller splitting can occur with diatomic molecules; hence, all three of the π^*_{2p} electrons in $O_2^{-\cdot}$ are of equal energy.

$$^3O_2 \uparrow\uparrow \xrightarrow{+e^-} \uparrow\downarrow \uparrow O_2^{-\cdot} \tag{1}$$

III. TRIPLET MOLECULAR OXYGEN

A. Radical Initiated Autoxidation[8–15]

Autoxidation is a general term used to describe the reaction of a substance with molecular oxygen at a temperature generally below 150–200 °C and in the absence of a flame. We will limit our discussion to the oxidation of labile C—H bonds of hydrocarbons, in which case the primary product is the corresponding hydroperoxide. A wide variety of organic compounds will undergo autoxidative hydroperoxidation with the rate being highly dependent on steric and electronic factors.

Autoxidation has been shown to be a free-radical process consisting of the traditional chain-mechanism elements: initiation, propagation and termination, as outlined in equation 2–7.

Initiation

$$RH \xrightarrow[\text{or enzymatically}]{h\nu,\Delta,R^{\cdot},Mn^{+}} R^{\cdot} \tag{2}$$

Propagation

$$R^{\cdot} + O_2 \longrightarrow ROO^{\cdot} \tag{3}$$

$$ROO^{\cdot} + RH \longrightarrow ROOH + R^{\cdot} \tag{4}$$

Termination

$$R^{\cdot} + R^{\cdot} \longrightarrow R{-}R \tag{5}$$

$$ROO^{\cdot} + R^{\cdot} \longrightarrow ROOR \tag{6}$$

$$ROO^{\cdot} + {}^{\cdot}OOR \longrightarrow ROOOOR \tag{7}$$

$$\longrightarrow \text{Nonradical products}$$

As summarized in equation 2, initiation requires the generation of free radicals via the homolytic cleavage of bonds. This can be accomplished either thermally (hot point), photochemically (in the absence or presence of photosensitizers), chemically (by reacting with another radical generated from peroxides, azo compounds, etc.) enzymatically or via metal ion catalysis. Although the name '*auto*xidation' suggests that this process can occur without the addition of any outside initiators, truly spontaneous processes are extremely rare[16].

Since ground-state molecular oxygen can be considered a triplet biradical, it is not surprising that its coupling with most carbon centered radicals is essentially a diffusion-controlled process. This coupling is in fact the essence of the first step in the propagation (equation 3) which is 10^6 to 10^8 times faster than the rate-determining hydrogen-abstraction step (equation 4). It follows that those steric and electronic factors which weaken the R—H bond will accelerate the rate of autoxidation. Furthermore, the point of autoxidative attack in a molecule, RH, is generally that which leads to the most stable radical, R$^\bullet$, upon cleavage of the C—H bond.

There is, however, one further factor which will be relevant to our discussion of enones, namely, polar effects[17,18]. Electron-donating substituents α to the C—H bond to be broken accelerate autoxidation, while electron-withdrawing groups decrease the rate of this process. Polar effects of this kind are well known in free radical processes and in the case of autoxidation result from the electrophilicity of the hydrogen-abstracting peroxy radical[13,17,18]. It is believed that a dipolar structure plays an important role in the transition state for this reaction (equation 8).

$$R'OO^\bullet + H{:}\overset{\diagup}{\underset{\diagdown}{C}}{-}X \longrightarrow [R'OO{:}^{\overset{\delta}{}} \cdots H{\cdot}\overset{\delta+\diagup}{\underset{\diagdown}{C}}{-}X] \longrightarrow R'OOH + {\cdot}\overset{\diagup}{\underset{\diagdown}{C}}{-}X \qquad (8)$$

B. Base-catalyzed Autoxidation (BCA)[19]

Organic compounds with acidic hydrogens attached to carbon undergo facile reactions with oxygen in basic media. For example, the *t*-butoxide mediated oxygenation of di- and triphenylmethane generates benzophenone and triphenylmethanol respectively, rapidly and in high yield. Russell and coworkers[19] have proposed that these autoxidations are chain reactions (equations 9–11), generally involving a rate-determining deprotonation of the substrate RH which produces a carbanion R:$^-$ (equation 9). The latter is then oxygenated to the corresponding peroxy anion ROO:$^-$ (equation 10) which deprotonates another molecule of starting material (equation 11), thereby initiating another cycle.

Initiation $$RH + B{:} \longrightarrow R{:}^- + BH^+ \qquad (9)$$

Propagation $$R{:}^- + O_2 \longrightarrow ROO{:}^- \qquad (10)$$

$$ROO{:}^- + RH \longrightarrow ROOH + R{:}^- \qquad (11)$$

While the mechanism as written is consistent with the experimental data, the direct combination of a carbanion with triplet dioxygen to yield a peroxy anion violates the Wigner spin-conservation principle (see equation 12)[19a-c,20-26].

$$R\uparrow\downarrow + \overset{\diagup}{\underset{\diagdown}{O}}\!\!\uparrow\!\!\uparrow\overset{\diagup}{\underset{\diagdown}{O}} \not\longrightarrow R\uparrow\downarrow\bar{O}{-}\bar{O}\uparrow\downarrow \qquad (12)$$

$$(R^-) \qquad (^3O_2) \qquad\qquad (R{-}O{-}O^-)$$

Russell and coworkers[19a-c,24] suggest that the carbanion R$^-$ may be converted to a free radical by donating an electron to an acceptor before combining with triplet biradical dioxygen. The acceptor is most commonly dioxygen itself, though peroxy radicals or trace metals may be involved as well. A plausible mechanism could then be the sequence

outlined below:

$$RH + B^- \longrightarrow R^- + BH \tag{9}$$

$$R^- + O_2 \rightleftharpoons R^\cdot + O_2^{-\cdot} \tag{13}$$

$$R^\cdot + O_2 \longrightarrow ROO^\cdot \tag{14}$$

$$ROO^\cdot + O_2^{-\cdot} \longrightarrow ROO^- + O_2 \tag{15}$$

$$ROO^\cdot + R^- \longrightarrow ROO^- + R^\cdot \tag{16}$$

$$ROO^- + RH \longrightarrow ROOH + R^- \tag{11}$$

We have not included in this sequence a radical coupling between $R^\cdot$ and superoxide anion radical, $O_2^{-\cdot}$ (equation 17a), a process with the same outcome as equations 14 and 15 combined. This is simply because electron transfer (see equations 13 and 15) rather than radical coupling is generally observed with superoxide[27] (equation 17b).

$$R^\cdot + O_2^{-\cdot} \longrightarrow RO_2^- \tag{17a}$$

$$\longrightarrow R^- + O_2 \tag{17b}$$

An alternate proposal[21,23,25,26] to that of Russell's is that a change of multiplicity occurs via a carbanion–oxygen complex (equation 18).

$$\underset{\uparrow\downarrow}{R^-} + \underset{\uparrow\uparrow}{O_2} \longrightarrow [\underset{\uparrow}{R^\cdot} \cdots \underset{\uparrow\downarrow}{O_2^{-\cdot}}] \longrightarrow [\underset{\downarrow}{R^\cdot} \cdots \underset{\uparrow\uparrow\downarrow}{O_2^{-\cdot}}] \rightarrow \underset{\uparrow\downarrow}{R{-}O_2^-} \tag{18}$$

Finally, we should note that although the primary products of BCA processes are generally hydroperoxides, these are rarely isolated under the basic reaction conditions. Instead, the corresponding ketones, alcohols, carboxylic acids or related oxidative cleavage products are obtained. The mechanism for some of these transformations are described in the next section.

C. Reactions of Hydroperoxides[28]

We have noted above that hydroperoxides are the major primary autoxidation products. They are, however, generally quite labile and the reaction product(s) actually isolated depends greatly on the reaction and/or workup conditions (solvent, temperature, pH, etc.). To aid in their handling, hydroperoxides are often reduced to the corresponding alcohols by a variety of reagents including Ph_3P, $(PhO)_3P$, $LiAlH_4$, $NaBH_4$, Na_2SO_3 and Me_2S. In many instances, however, the hydroperoxide product rearranges before it can be treated. It will be of value, therefore, to acquaint ourselves with some of these transformations before we delve into a discussion of enone oxygenations.

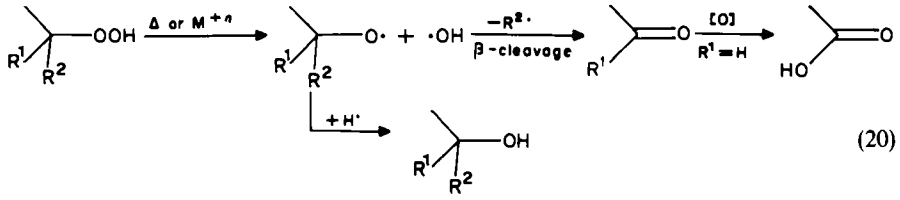
1. Homolysis of the peroxy linkage

Owing to the relative weakness of the peroxide bond, its homolysis to alkoxy radicals at room temperature or above (e.g. GLC injector port) is a prevalent phenomenon. In many cases this reaction is to be considered a metal-catalyzed process, particularly since precautions are rarely taken to eliminate the trace amount (10^{-8} mol) of metal ions which suffice to catalyze the homolytic decomposition of hydroperoxides[29] (equation 19).

$$ROOH + M^{+n} \longrightarrow RO^\cdot + HO^- + M^{+(n+1)} \tag{19}$$

Several reaction pathways are available to the alkoxy radical thus generated (equation 20)[30–33]. First, an alcohol can be formed via hydrogen abstraction. Alterna-

tively, β cleavage of a neighboring β hydrogen, alkyl or alkoxy group would lead to a carbonyl compound. In the case of primary and secondary hydroperoxides, loss of a hydrogen atom is quite prevalent. In sum total, this corresponds to the elimination of the elements of water from the hydroperoxide, a process commonly called 'Hock dehydration' (not to be confused with Hock cleavage; Section III.C.3). For tertiary hydroperoxides, carbonyl formation requires carbon–carbon bond scission, while for α-hydroperoxy ethers or esters carbon–oxygen cleavage often results.

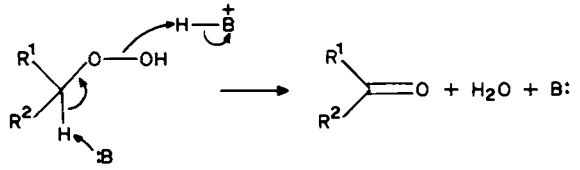


(20)

Whenever the expected product is an aldehyde, it may undergo rapid oxidation to the corresponding acid (via the labile peracid).

2. *Kornblum–DeLaMare reaction*

In the presence of bases (even as weak as dilute aqueous hydroxide, pyridine or basic alumina), peroxides (including hydroperoxides) possessing α-hydrogens can undergo the Kornblum–DeLaMare reaction[34–36]. In this process, which can be viewed as an oxygen analog of an E2 elimination, primary and secondary hydroperoxides are dehydrated to aldehydes or ketones, respectively (equation 21). As might be expected, the reaction is particularly preferred when the resulting ketone is conjugated.



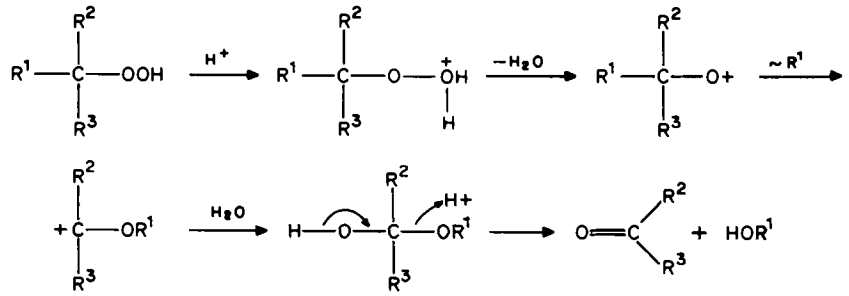
(21)

It should be noted, however, that most alkali bases contain substantial amounts of metal ions which may catalyze competing homolytic decomposition. Hence, Kornblum–DeLaMare dehydrations may well be accompanied by alcohol formation. In some cases, the metal-catalyzed homolysis can be inhibited by the addition of EDTA.

3. *Hock cleavage*[28]

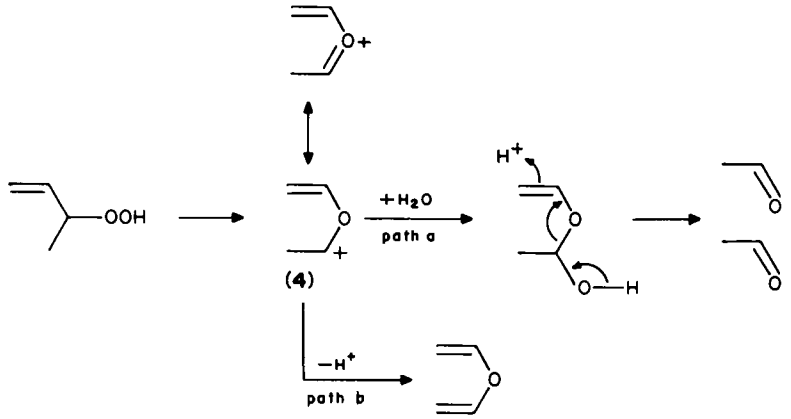
In principle, the heterolysis of the peroxide bond should generate both a negative and a positive oxygen fragment. The instability of the latter with respect to a carbocation would then initiate skeletal changes in the carbon framework resulting from migration of groups to the electron-deficient oxygen. Such heterolysis and ensuing rearrangements have indeed been observed with hydroperoxides and are generally acid-catalyzed. One classic example is the acid-catalyzed cleavage of a hydroperoxide to an alcoholic and a ketonic fragment, for which the accepted mechanism, first suggested by Criegée[37–40], is outlined in Scheme 1. Relative migratory aptitudes have been determined for this reaction and their qualitative order is as follows[28c].

cyclobutyl > aryl > vinyl > hydrogen > cyclopentyl ≈ cyclohexyl ≫ alkyl



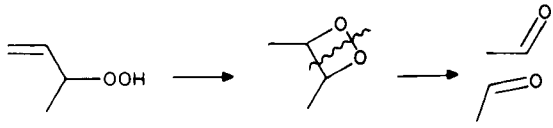
SCHEME 1. Criegée mechanism for the acid-catalyzed cleavage of hydroperoxides

In the particular case of allylic hydroperoxides the migrating group is generally vinylic. In such cases the resulting fragments will both be ketonic (Scheme 2, path a). Because of this fundamental difference in the make-up of the products, this transformation of allylic hydroperoxides to *two* carbonyl fragments, called Hock cleavage[41-45], has for a long time been classified separately. While such cleavages are generally acid-catalyzed[28a,46], several have been reported to occur in the absence of any added acid[28a] and even under basic conditions[47].



SCHEME 2. Acid-catalyzed cleavage of allylic hydroperoxides: path a: Hock cleavage; path b: divinyl ether formation

Recently, there has been growing experimental evidence[28a,46,48,49] that in some substrates, Hock cleavage can proceed not only via a Criegée mechanism but also through a cyclic dioxetane mechanism, first proposed by Farmer and Sundralingam[28b,50] (equation 22). For example, hydroperoxide **1** has been shown to rearrange to dioxetane **2**, which cleaves slowly in turn to acetoxy keto ester **3** (equation 23)[48,49].



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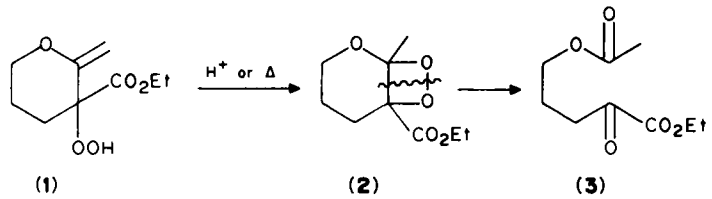
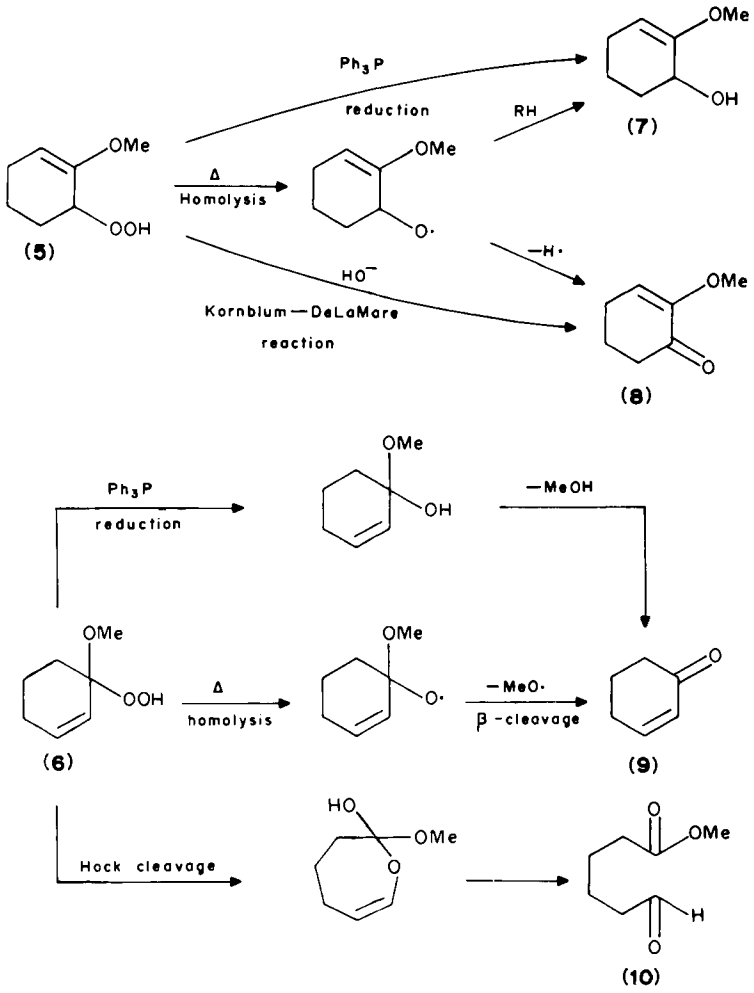


(23)

A variation on the Hock cleavage theme is shown in Scheme 2 (path b). In this variant a proton is eliminated α to the oxycarbonium ion **4** yielding a divinyl ether. Several examples are known, but it is generally uncommon[28a,b,d].

An interesting example[51,52] of some of the transformations discussed above is the decomposition of isomeric hydroperoxides **5** and **6** (Scheme 3). The former yields 2-

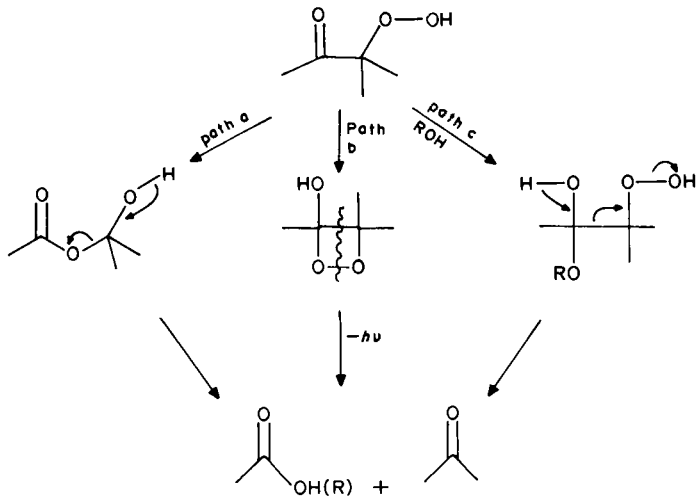


SCHEME 3. Decomposition of hydroperoxides **5** and **6**.

methoxy-2-cyclohexen-1-ol (**7**) and 1-one (**8**). Peracetal **6** loses the elements of methyl hydroperoxide yielding **9**, while Hock cleavage generates aldehydo ester **10**. Compounds **7** and **9** can be formed directly upon reduction of **5** and **6** respectively with triphenylphosphine. Finally, the Kornblum–DeLaMare dehydration of **5** yields cyclohexenone 8.

4. Transformations of hydroperoxy carbonyl compounds

α-Hydroperoxy carbonyl compounds undergo oxidative cleavage catalyzed either thermally, photochemically, by acids or by bases, yielding the corresponding carbonyl fragments. Three mechanisms have been considered (Scheme 4). The first involves acyl group migration (path a) which corresponds to the Criegée hydroperoxide cleavage mechanism (Scheme 1) where the migrating group R′ is RCO. The second mechanism (path b) involves a cyclic α-hydroxy dioxetane intermediate. The third mechanism (path c) involves nucleophilic solvent attack on the carbonyl, with the resulting tetrahedral intermediate cleaving to products.

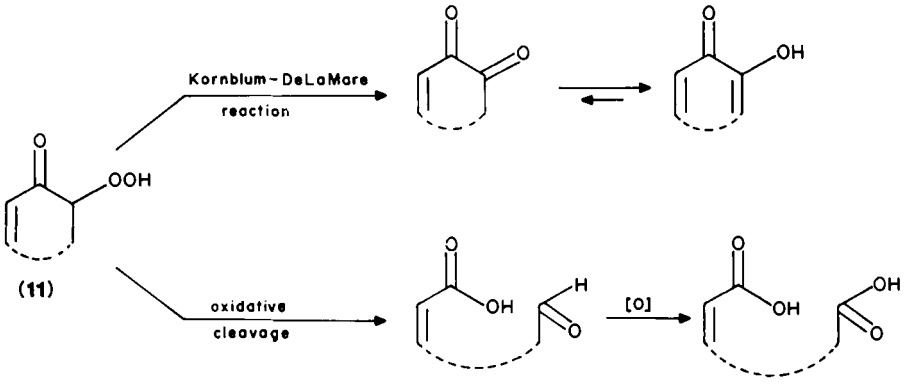


SCHEME 4. Possible mechanistic routes for the oxidative cleavage of α-hydroperoxy carbonyl compounds

Work by Sawaki and Ogata[53–55] has revealed that under acid conditions acyl migration (Scheme 4, path a) is preferred. Nucleophilic base (e.g. hydroxide and methoxide) catalyzed decomposition involves primarily an intermolecular carbonyl addition mechanism (path c) with concomitant direct formation of esters, though a small amount of product is formed via a competing chemiluminescent dioxetane route (path b). Jefford's group[56] has also shown that bulky bases, such as *t*-butoxide, which cannot approach and bond to the carbonyl group, promote base-catalyzed cyclization to a dioxetane (path b) which spontaneously cleaves with chemiluminescence. Photochemical decomposition also seems to proceed via a dioxetane[57,58].

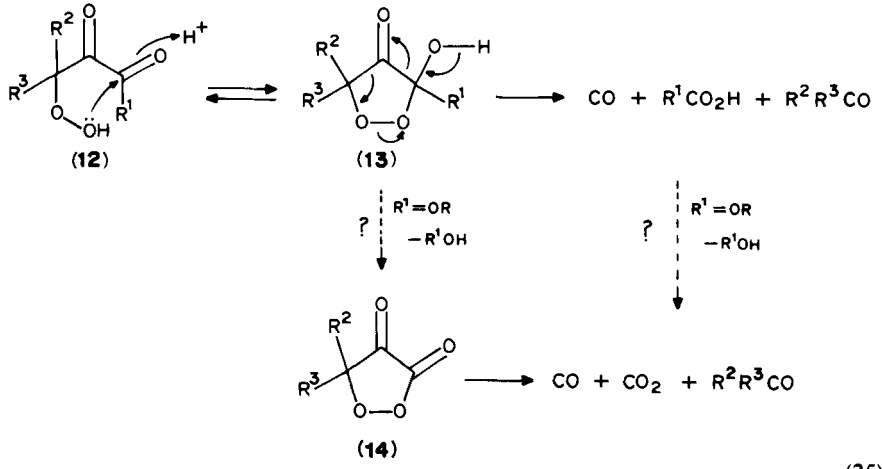
The reader is reminded that under basic conditions aldehydes are often autoxidized to acids. Furthermore, 1° and 2° hydroperoxides can undergo Kornblum–DeLaMare

dehydration to the corresponding ketone (Section III.C.2 above), and this is true for α-hydroperoxy carbonyl compounds as well. The exact mode of decomposition of the latter under basic conditions is quite sensitive to the structure of the substrate. The predominant reaction in the case of unsaturated α-hydroperoxy ketones such as **11** (equation 24) and steroidal α-keto hydroperoxides is dehydration to diketones, while simple saturated α-hydroperoxy ketones generally cleave to diacids[59,60].



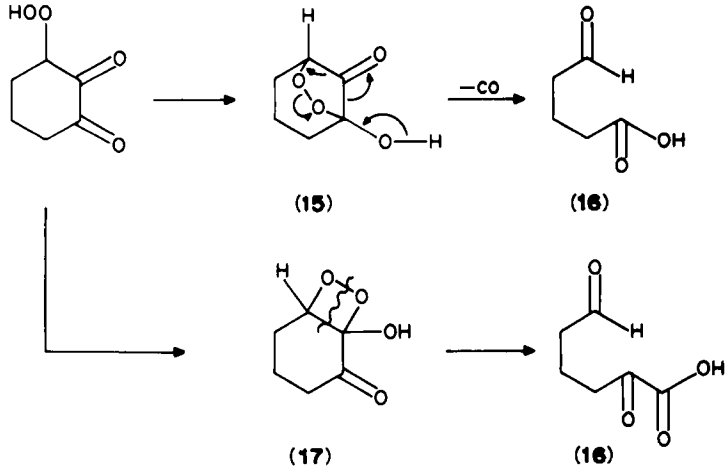
(24)

3-Hydroperoxy-1,2-dicarbonyl compounds (**12**, equation 25) are generally quite labile and decompose to carbon monoxide, a carbonyl compound, and a carboxylic acid[61–76]. A likely intermediate is the perlactol **13**, though Mayers and Kagan[77] have suggested a role for perlactone **14** when the distant carbonyl moiety is an ester ($R^1 = OR$).



(25)

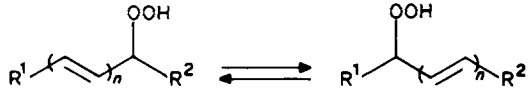
A simple example of these transformations is the decomposition of 3-hydroperoxycyclohexane-1,2-dione which cleaves primarily to aldehydo acid **16** via peroxy lactol **15**. A small amount of aldehydo keto acid **18** is also produced, presumably through dioxetane **17** (equation 26).



(26)

5. 1,3-Allylic hydroperoxide rearrangement

Before closing this section, we should mention the 1,3-allylic hydroperoxide rearrangement (equation 27, $n = 1$), for which an analogous 1,5-pentadienyl hydroperoxide shift (equation 27, $n = 2$) is also known[28b,d]. The driving force for this transformation seems to be the greater stability of the olefinic linkage in the final product. Thus, allylic hydroperoxide **19**, in which the double bond is trisubstituted, rearranges to isomer **20** in which the olefinic linkage is now tetrasubstituted (equation 28)[48,49].



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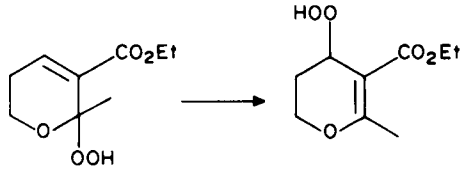


(19) (20)

(28)

Three mechanisms have been suggested for these[28b,28d,78–82] processes, and they are outlined in Figure 2. The first is a stepwise mechanism involving the intermediacy of a cyclic five-membered ring peroxide (**21**) possessing a free radical at the position 4. The second is a concerted mechanism with the formation of a cyclic five-membered ring transition state (**22**) linking the two allylic hydroperoxy radicals. The final possibility is a β-scission of an allylic peroxy radical to form molecular oxygen and an allyl carbon radical **23**.

The intermediacy of **21** in this transformation can be ruled out because no oxygen entrapment of this radical was observed[80], although authentic **21** does undergo facile oxygenation[81]. Oxygen-18 labeled hydroperoxides rearrange without loss of the label, suggesting the involvement of the concerted mechanism via transition state **22**[82].

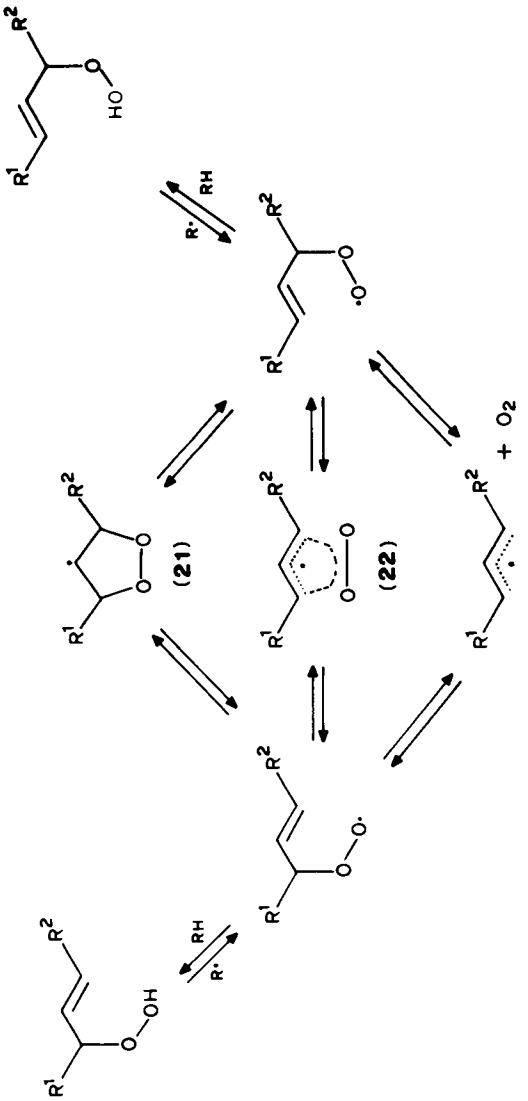


FIGURE 2. Possible mechanisms for the 1,3-allylic hydroperoxide rearrangement

It should be noted that in the corresponding pentadienyl case, the label is lost[78], indicating that in this case the rearrangement proceeds via β-scission yielding a pentadienyl radical, the vinylog of **23**.

D. Autoxidation of Enones

1. General considerations

α,β-Unsaturated carbonyl compounds (**24**, equation 29) are generally quite stable towards autoxidation, despite the fact that the resulting radical **25** is stabilized by the extended conjugation. The inhibition of the rate-determining hydrogen-abstraction step of the propagation (equation 4) can be attributed to the aforementioned 'polar effect' (Section III.A) resulting from the electron-withdrawing carbonyl group. By contrast, β,γ-unsaturated systems (**26**) autoxidize substantially more rapidly—even though the resulting radical (**25**) is the same and the polar effect is also at play (equation 29). The explanation here is that the lower stability of the β,γ system presumably results in a lower activation energy for hydrogen abstraction leading to the conjugated radical **25** (Figure 3).

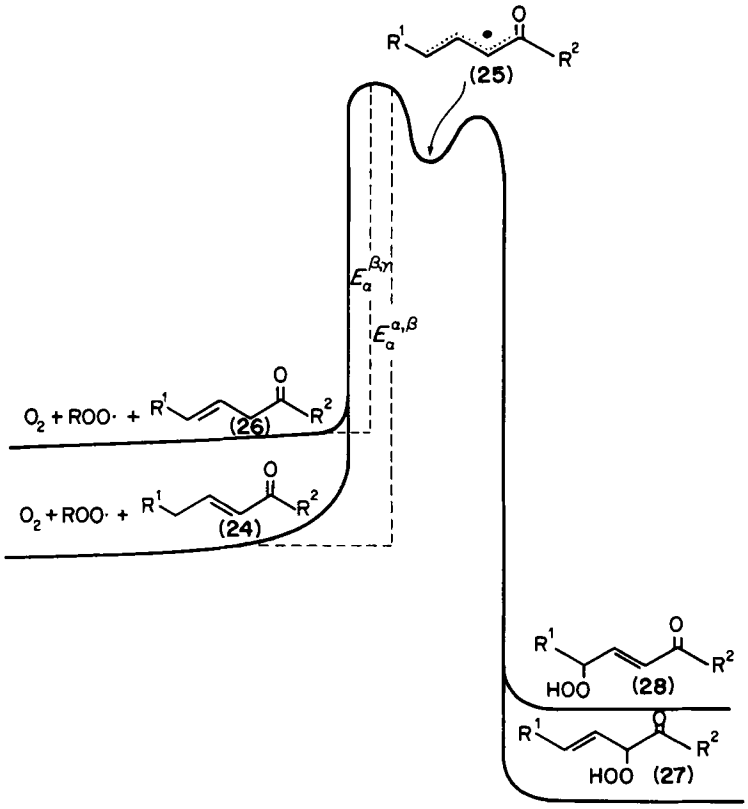
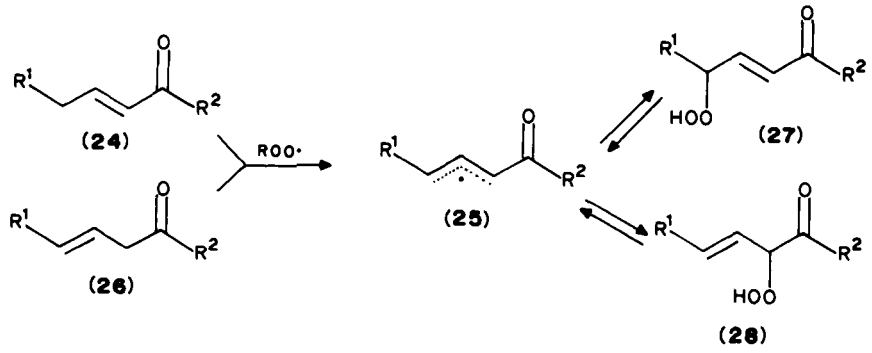


FIGURE 3. Energy profiles for the free radical autoxidation of α,β-enones **24** versus the β,γ-enones **26**

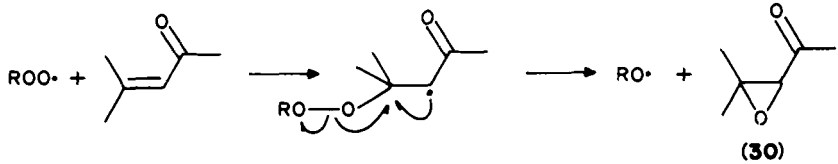
Of the two possible isomeric hydroperoxides **27** and **28**, the conjugated **27** is generally preferred for thermodynamic reasons.



(29)

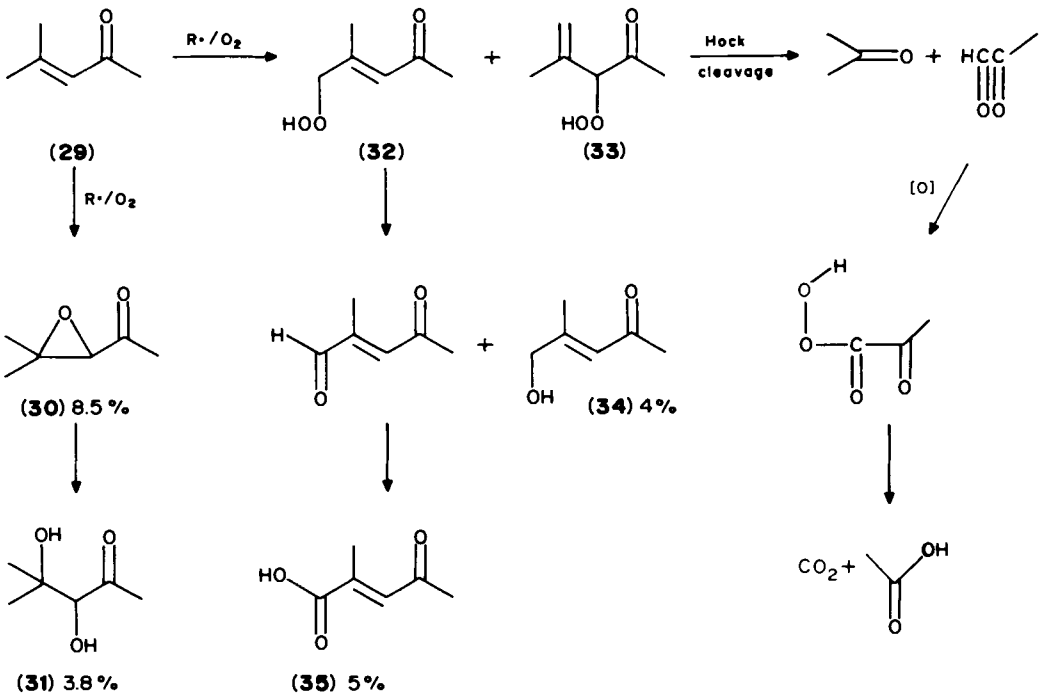
2. α,β-Unsaturated carbonyl compounds

a. Simple enones. Early work in this field was seriously hampered by the complexity of the products and the relatively low yields. By the early fifties scientists had succeeded in unravelling the mysteries of the autoxidation of simple olefins and had learned how to initiate and control these processes. Progress in the related enone systems followed soon after. Hawkins, with one of the first research groups to carry out careful studies on the autoxidation of α,β-unsaturated ketones,[83] explored the cobalt naphthenate catalyzed autoxidation of mesityl oxide (**29**, 10 h, 75% conversion, 25% yield) and isophorone (**36**, 24 h, 35% conversion, 25% yield) at 100 °C. In the absence of the catalyst, the reaction proceeded substantially more sluggishly and in poorer yields. The major products in the autoxidation of mesityl oxide (Scheme 5) were epoxide **30** and its hydrolysis product glycol **31**, alcohol **34** and acid **35** as well as several low-molecular-weight oxidative cleavage products. In Scheme 5 we have proposed what we believe to be a plausible, though purely speculative, mechanism to explain the formation of these products. There are essentially three fundamental modes of reaction: (a) hydroperoxidation, (b) epoxidation and (c) oxidative cleavage. The first of these modes yields **32** and **33** with the former undergoing homolytic cleavage (see equation 20) ultimately generating the derived alcohol **34** and acid **35**. Hydroperoxide **33** may undergo Hock cleavage to acetone and pyruvaldehyde which, under the reaction conditions, is oxidatively cleaved to acetic acid and carbon dioxide. Epoxide **30** is most likely formed via the addition of a peroxy radical (possibly the precursor to **32** or **33**) to the enone system (equation 30).



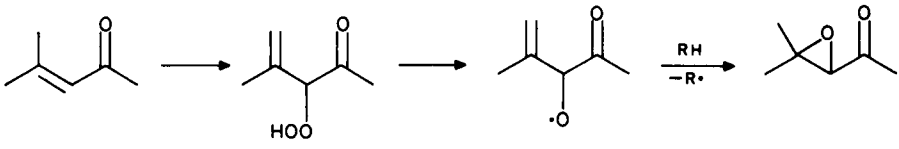
(30)

It should be noted at this juncture that there are authors[84] who have suggested that the epoxy ketones result from the rearrangement of the α-oxygenation product (e.g. **33**), as



SCHEME 5. Mechanism proposed for the autoxidation of mesityl oxide

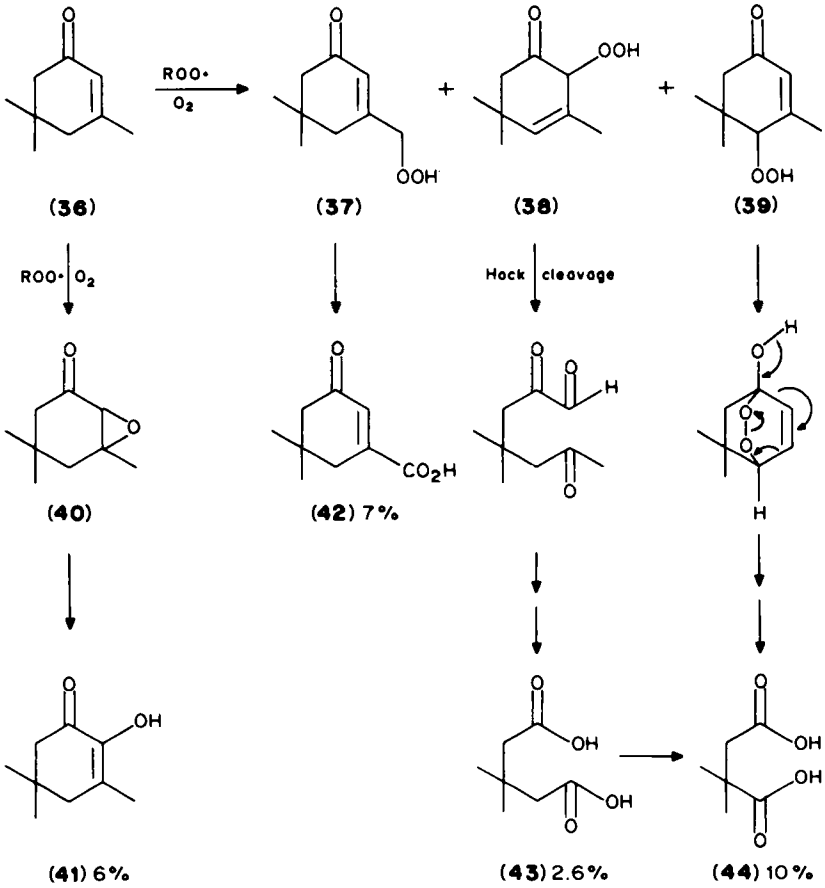
outlined in equation 31.



(29) (33) (30)

(31)

Indeed, one documented example of such a conversion exists in the instance of allylic hydroperoxides[85]. Nevertheless, we prefer the mechanism of equation 30 which is a well-precedented process[14] in the case of simple olefin oxidation. The mechanism of equation 30 has also been invoked by Moslov and Blyumberg[86] to explain the formation of α-epoxypropionaldehydes in the autoxidation of α-alkylacrylaldehydes (see Section III.D.2.c).



(36) (37) (38) (39)

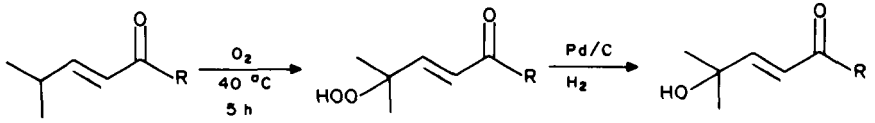
(40) (42) 7%

(41) 6% (43) 2.6% (44) 10%

SCHEME 6. Proposed mechanism for the autoxidation of isophorone 36

In the case of isophorone **36**, enol **41** and acids **42–44** are the major products. The enol is ostensibly formed via expoxide **40**, while the acids presumably result from the oxidative cleavage of the corresponding hydroperoxides **37**, **38** and **39**, respectively. The various plausible pathways are outlined in Scheme 6, but again the mechanisms are purely speculative.

While the oxidative cleavage products reported in the work of Hawkins[83] seem to require α-oxygenation and the formation of the unconjugated hydroperoxy enones **33** and **38**, most subsequent reports involve the γ-hydroperoxide exclusively. Thus Tischenko and Stanishevskii[87,88] have reported that a series of homologous β-isopropyl enones **45** were converted to the corresponding alcohols **47** in relatively high yields by oxygenation and subsequent catalytic reduction (equation 32).



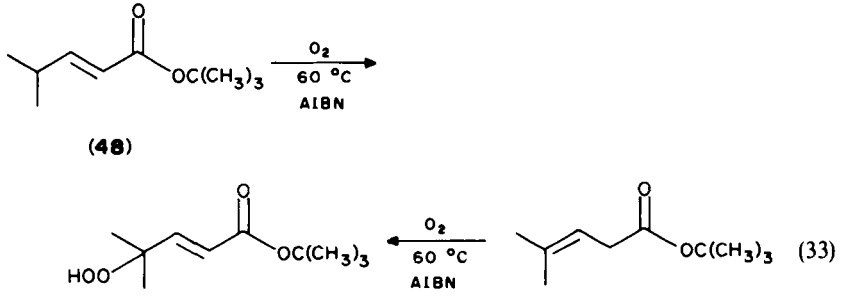
(45) (a) R = Me
(b) R = Et
(c) R = Bu

(46)

(47) 85–95%

(32)

The groups of Volger[89] and Watt[90a] have found that such reactions can be initiated by AIBN (2,2-azoisobutyronitrile) and/or *t*-butyl hydroperoxide at 60 °C. Similarly, Gersman's group[90b] has reported that ester **48** (as well as its β,γ-unsaturated analog, **50**) gave only γ-oxidation product **49** upon AIBN initiation (equation 33).



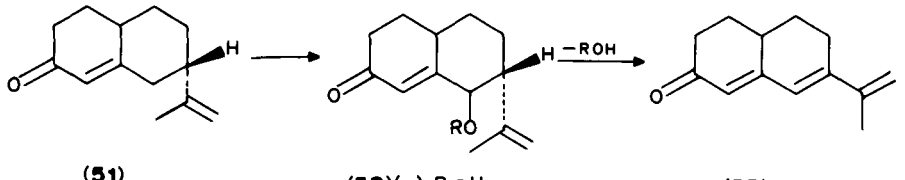
(48)

(49)

(50)

(33)

Epi-α-cyperone (**51**), after standing at room temperature in air for 15 months, gave a 50% yield of triene **53** which is presumably the dehydration product of the γ-alcohol **52a** or the corresponding hydroperoxide **52b** (equation 34)[91].



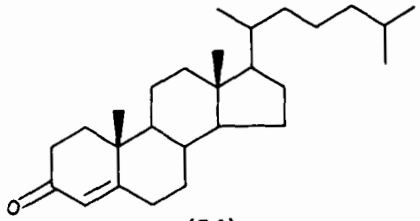
(51)

(52) (a) R = H
(b) R = OH

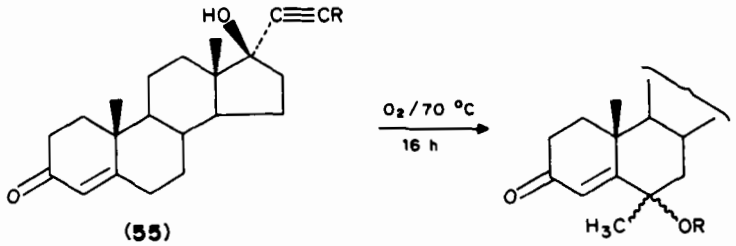
(53)

(34)

Most conjugated steroids, such as cholest-4-en-3-one (**54**), are not particularly sensitive to autoxidation[15,92,93] (equation 35). Dimethisterone (**55**), too, is stable when exposed to air at 55 °C for as long as 16 h[94]. However, when it is subjected to higher temperatures (65–70 °C) for similar periods, TLC reveals the formation of trace amounts of the corresponding epimeric 6α- and 6β-hydroperoxides **56a**, as well as the derived epimeric alcohols **56b** (equation 36).

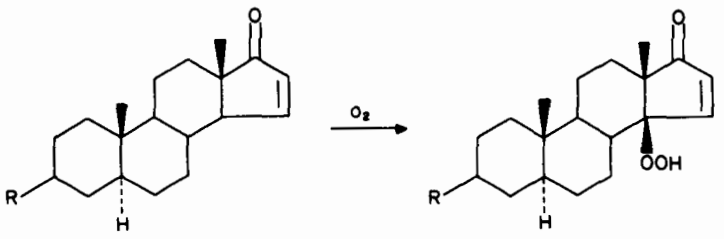


(54) (35)

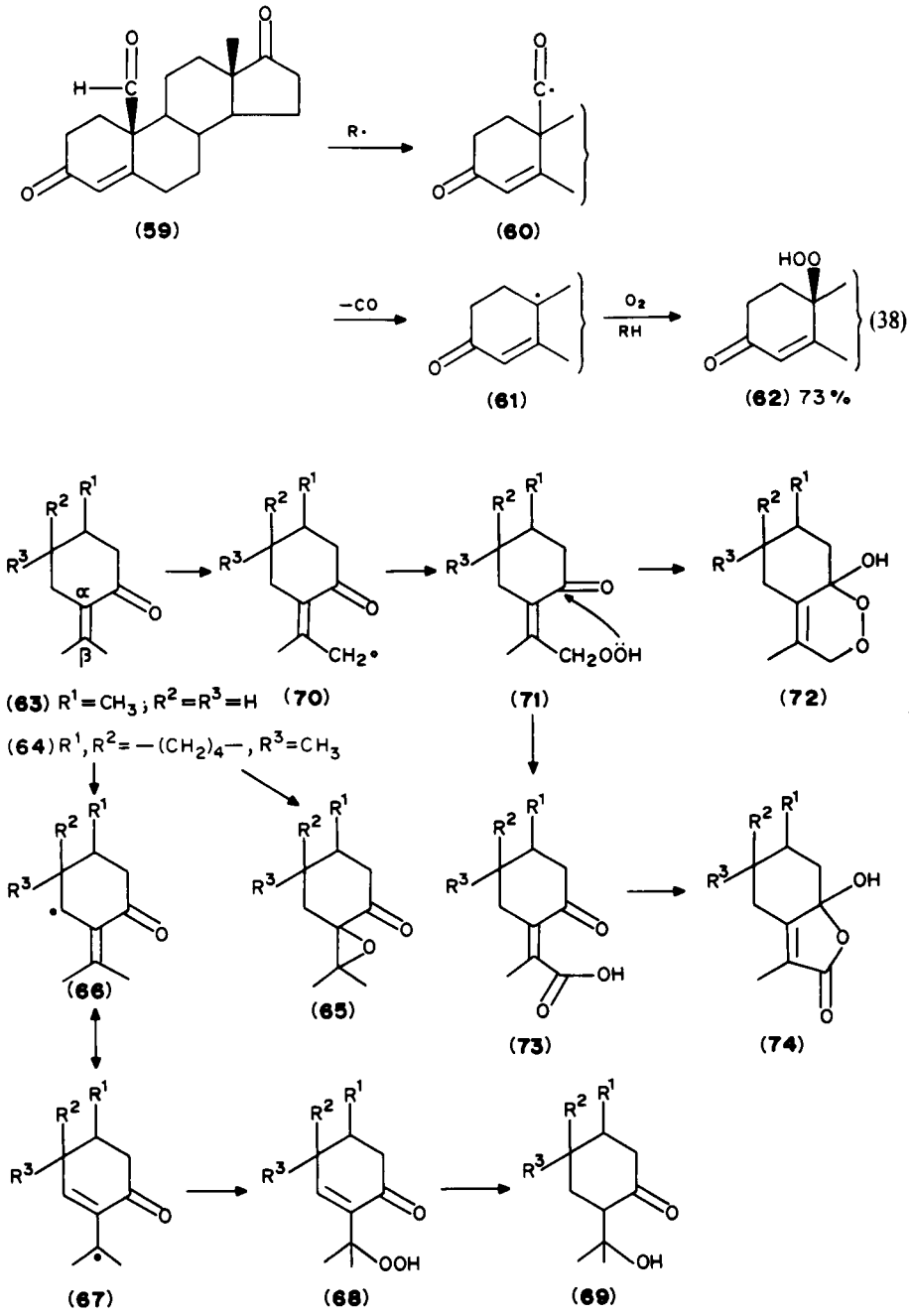


(55) (56) (a) R = OH (b) R = H (36)

In light of this insensitivity to autoxidation, it is a bit surprising that the air oxidation of the α,β-enone 5α,14α-androst-15-en-17-one **57** gives the related 14-hydroperoxide **58** in high yield (equation 37)[95,96]. Similarly, a variety of 19-oxosteroids, including 10β-aldehydes and 10β-carboxylic acids, are readily oxidized by air in free radical type reactions to the corresponding 19-nor-10β-hydroperoxides and/or 10β-alcohols[15,97]. Thus androstenal **59** is converted to hydroperoxide **62** with the evolution of carbon monoxide after 3 days of aeration at 50° in the presence of the radical initiator AIBN[97]. A possible mechanism is outlined below (equation 38).

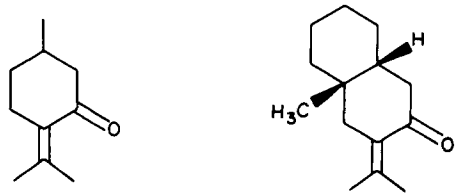


(57) (58) (37)



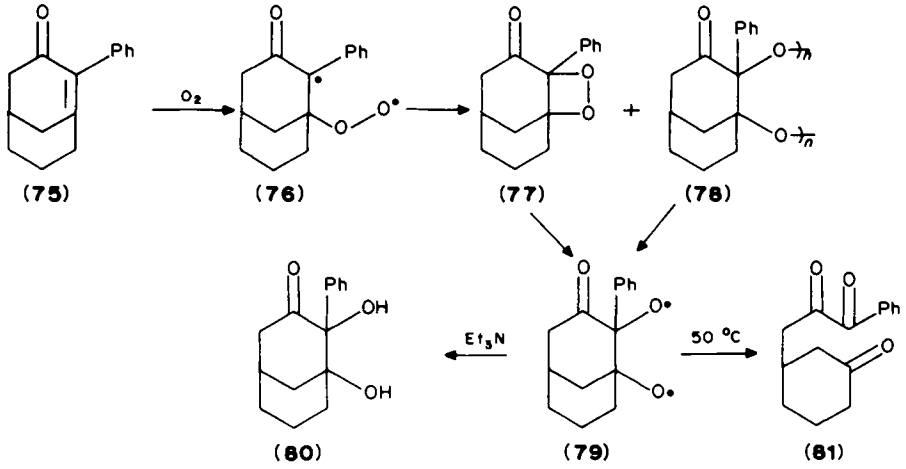
SCHEME 7. The proposed mechanism for the autoxidation of pulegone (63) and fukinone (64)

The exocyclic enones pulegone (**63**) and fukinone (**64**) are autoxidized to the corresponding epoxides **65**, hydroxy enones **69**, lactols **74** and cyclic peroxide **72**[84,98]. The likely mechanism is shown in Scheme 7.



(**63**) (**64**)

There is an interesting report in the literature of a spontaneous oxidation of an enone whose double bond is distorted[99,100]. Phenyl-substituted bicyclo[3.3.1]nonenone **75** reacts with oxygen (possibly via diradical **76**) to yield a solid mixture of peroxides, presumably dioxetane **77** and polyperoxide **78**. The peroxides reacted with Et_3N to form the corresponding diol **80** and rearranged thermally (53 °C) to triketone **81** (Scheme 8).



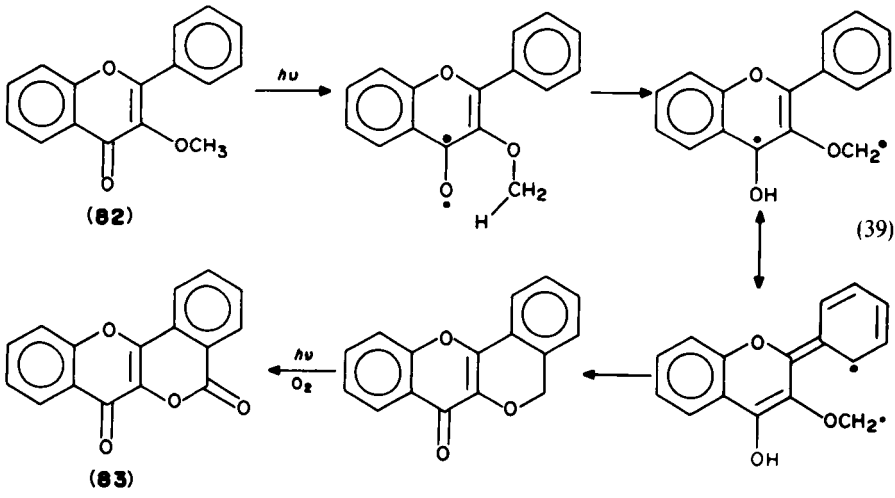
(**75**) (**76**) (**77**) (**78**) (**80**) (**79**) (**81**)

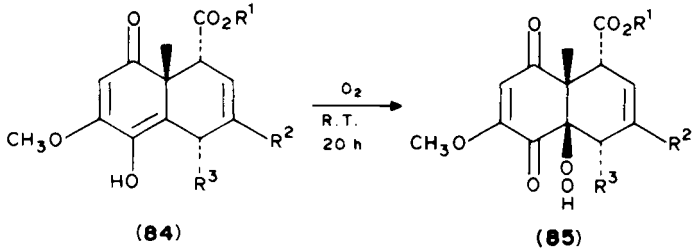
SCHEME 8. Mechanism for the oxygenation of 2-phenylbicyclo[3.3.1]non-1-en-3-one **75**

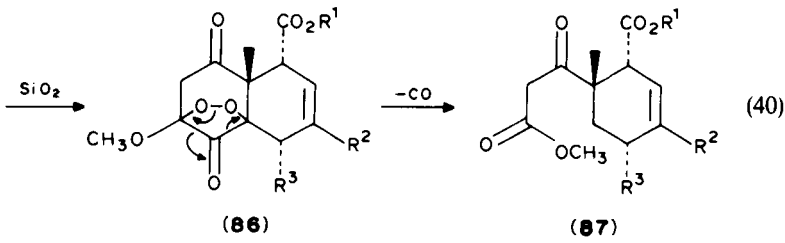
Finally, the unsensitized photooxidation of simple 3-methoxyflavones (**82**) yields lactone **83**, possibly via the mechanism outlined in equation 39[101–104].

b. Hydroxy enones and aci-reductones. Little has been reported regarding the autoxidation of stable keto enols. Recently, however, Hayakawa and coworkers[105] have investigated 4-hydroxy-2,4-dien-1-one **84**, which is stable in the solid state but undergoes facile aerial oxidation in solution. Thus on standing at room temperature (20 h), it is converted to the corresponding hydroperoxide **85**. Percolation of the latter through a silica-gel column resulted in a spontaneous evolution of CO to give ester **87**. The likely intermediate is endoperoxide **86** (equation 40).

Other examples in this category are β-diketones, which exist essentially in their 3-hydroxy-2-en-1-one (keto enol) form[106]. Interestingly, Bredereck and Bauer[107] report that

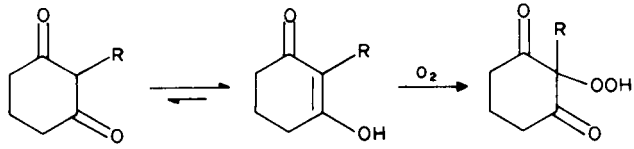






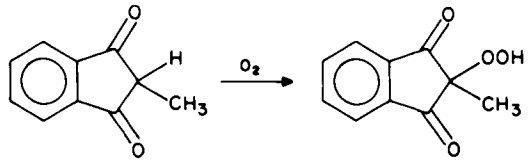
(40)

autoxidation of cyclic 1, 3-diketones with a tertiary C_2 carbon yields the corresponding 2-hydroperoxy-1, 3-diones (equations 41 and 42).



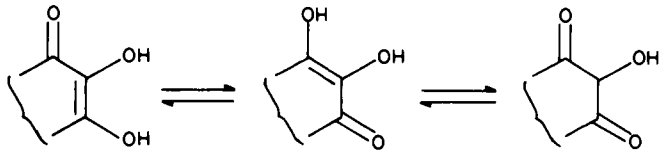
(41)

R = Me, Et, *i*-Pr, *t*-Bu, CH_2Ph_2, Ph

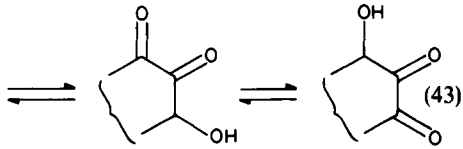


(42)

An interesting group of keto enols are the aci-reductones (α-oxo enediols). These are 2, 3-dihydroxy-2-en-1-ones (**88**), which are in equilibrium with various tautomeric forms[108,109] (equation 43).

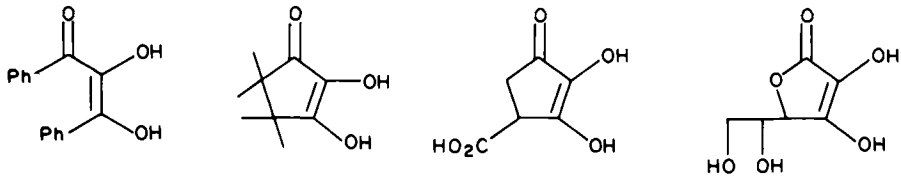


(**88**)

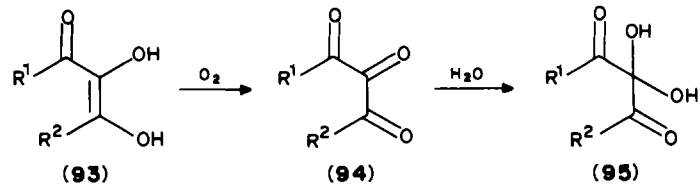


(43)

Several reductones, including **89**[110], **90**[111] and **91**[112], have been reported to undergo facile autoxidation to the corresponding triketones **94**, which are hydrated in turn in aqueous solvents yielding **95** (equation 44).



(**89**) (**90**) (**91**) (**92**)



(**93**) (**94**) (**95**)

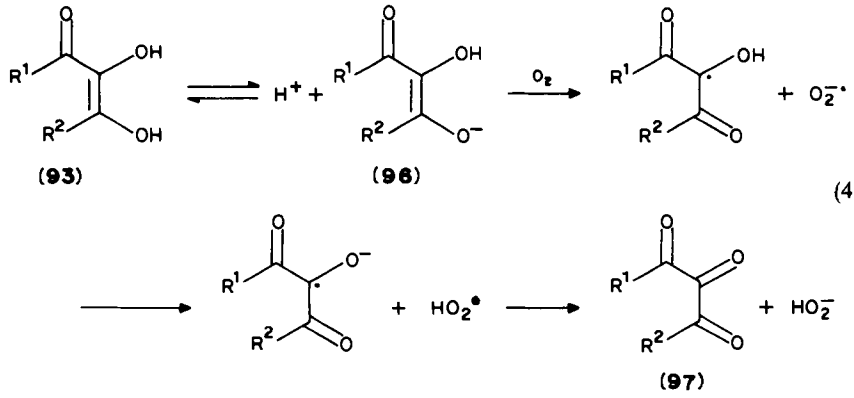
(44)

Perhaps the most famous and extensively studied[113–115] reductone is the biologically important antioxidant ascorbic acid (vitamin C, **92**). Ascorbic acid is a reactive reductant, but its free radical analog is relatively non-reactive. As a result, ascorbic acid does not undergo rapid autoxidation[116,117] and is quite stable in the solid state. There are,

however, several reports of successful oxygenations of this reductone to the triketone (dehydroascorbic acid) carried out in protic media in the presence of either charcoal[118,119] or palladium carbon catalyst[120].

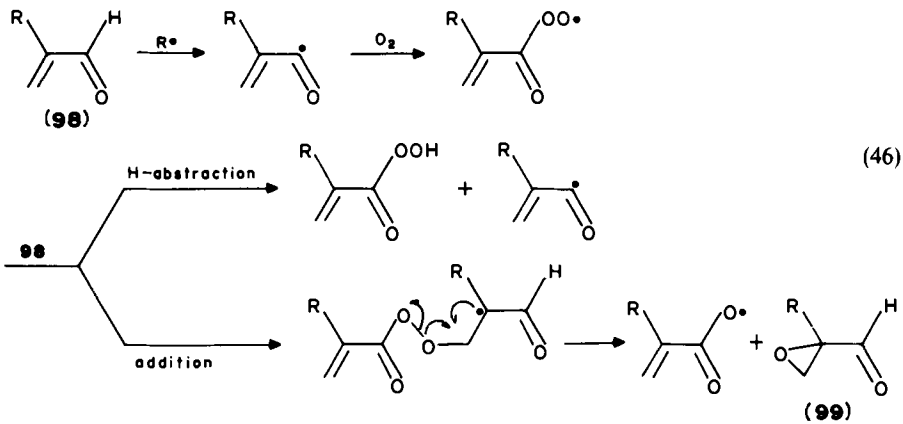
The mechanistic details for the autoxidative conversion of reductones to triketones has only been explored in the case of Vitamin C. It has been shown that $O_2^{-\cdot}$ is formed in this process[121,122] and, furthermore, that the oxidation rate for the neutral non-dissociated form of ascorbic acid is close to zero[123]. All this suggests that oxidation occurs from the ionized form and that the role of oxygen is not to oxygenate the radical intermediates but to function as an electron acceptor.

A plausible mechanism for the formation of the triketone dehydroascorbic acid is shown in equation 45[124].



(45)

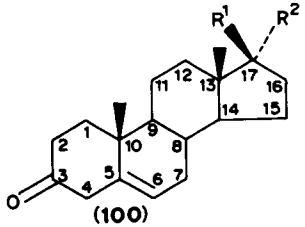
c. α,β-Unsaturated aldehydes. These compounds are oxidized to the related carboxylic acids several orders of magnitude more slowly than the corresponding saturated analogs[19e,86,125]. In addition, Moslov and Blyumberg[86] report the formation of α-epoxypropionaldehyde **99** as a side-product in the autoxidation of α-alkylacrylaldehydes. The mechanism for this process is outlined in equation 46.



(46)

3. β,γ-Unsaturated carbonyl compounds

It has long been known that β,γ-enones are labile compounds which rearrange readily to their α,β-conjugated analogs and also undergo facile air oxidation at room temperature. The exact nature of these oxidation products was studied by Fieser and colleagues[126-129] who reported that Δ^5-cholesten-3-one (**100a**) combines with molecular oxygen in hexane at 25 °C to yield a 1:1 mixture of 6α- and 6β-hydroperoxy-Δ^4-cholesten-3-one (**101a** and **102a**). Best results (82% yield) are obtained by overnight aeration in the dark of a cyclohexane solution (at 40–50 °C) of the Δ^5-steroid containing a little benzoyl peroxide. The two hydroperoxides are quite stable and are separable by crystallization. Upon reduction with sodium iodide in acetic acid, each of these hydroperoxides is converted to their respective 6-hydroxy compounds **103a** and **104a** (equation 47). Similar results have been observed for Δ^5-androstenone (**100b**)[130,131], Δ^5-androstene-3,17-dione (**100c**)[132] and Δ^5-pregnene-3, 20-dione (**100d**)[132].



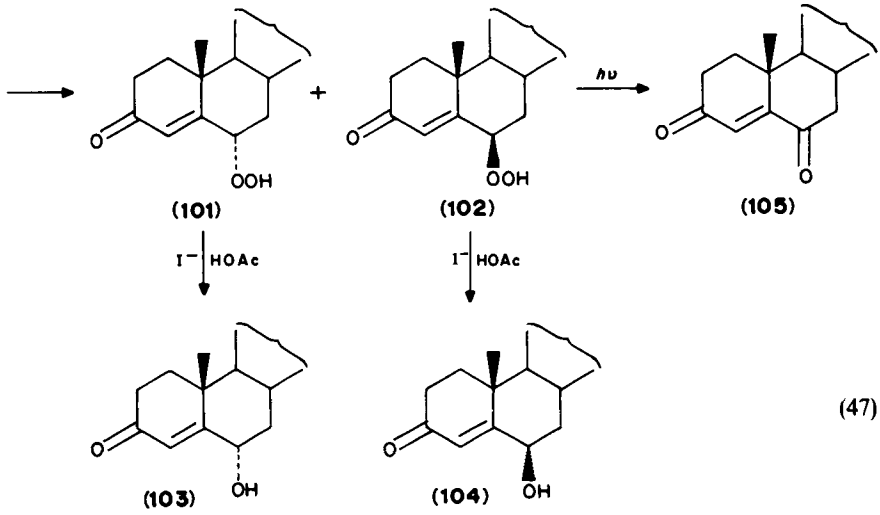
(100)

(a) R^1=CH(CH$_3$)(CH$_2$)$_3$C(CH$_3$)$_2$; R^2=H

(b) R^1=OH; R^2=CH$_3$

(c) R^1, R^2 = =O

(d) R^1=COCH$_3$; R^2=H



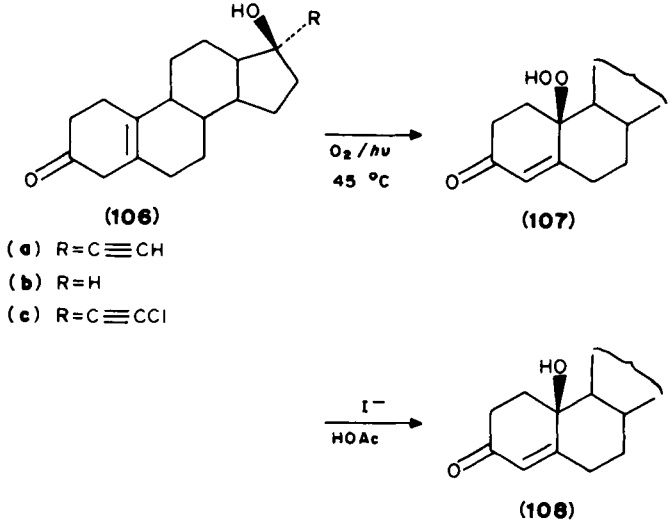
(47)

Nickon and Mendelson[133] report that when the autoxidation of Δ^5-cholestenone **100a** is initiated photochemically (in the absence of sensitizers), after 42 hours of irradiation and

subsequent reduction, a 50% yield of a mixture of **103a** and **104a** as well as a 3% yield of diketone **105a** are isolated (equation 47).

de la Mare and Wilson[134] have carried out kinetic studies on these reactions and found that the oxidation of cholest-5-en-3-one (**100a**) with air in CCl_4 at 20 °C is slow, autocatalytic, catalyzed by dibenzoyl peroxide and inhibited by 3, 5-di-*t*-butylanisole. The products are **101a** and **102a** as in the corresponding reaction in cyclohexane reported by Cox[128]. The same reaction in ethanol was seven times faster. The products were entirely those of oxidation, namely **101a–105a**, and no rearrangement to the Δ^4 analog **54** was observed.

Shapiro and colleagues[130,131] studied the related oxidation of the 19-nor systems **106a–c** and again obtained the corresponding γ-oxidation products, 10β-hydroperoxy compounds **107** (40% yield). The latter are reduced to alcohols **108** with iodide (equation 48). These oxidations occur under a variety of conditions, i.e. with or without fluorescent light irradiation, with or without radical initiators (benzoyl peroxide or AIBN), or it may occur on a suitable substrate such as silica gel. Kirdani and Layne[135] found that, as compared to organic media, the oxidation of norethynodrel **106a** occurs quite slowly in aqueous solution with the initial products being **107a** and **108a**. The oxidation is rapidly catalyzed by horseradish peroxidase in the presence of hydrogen peroxide and manganese ion or by hemoglobin.



(**106**)

(**a**) R=C≡CH

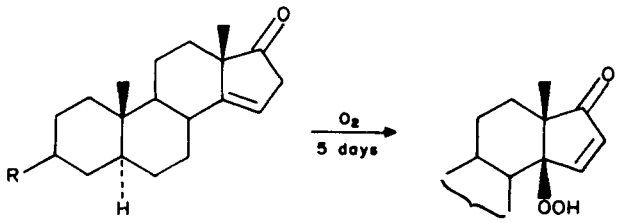
(**b**) R=H

(**c**) R=C≡CCl

(**107**)

(**108**) (48)

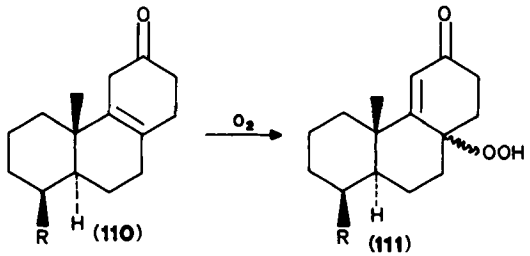
β,γ-Unsaturated 17-ketones are also sensitive to air oxidation. Thus, androstenone **109** gives the related 14-hydroperoxide **58** in high yield (equation 49; cf. equation 37)[95,96,136].



(**109**) (49)

(**58**) 82 % yields

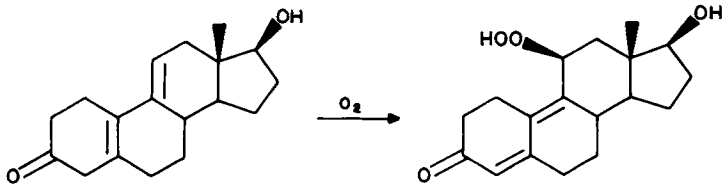
In a related study[137], γ-hydroperoxides **111** can be produced in fair yields by merely allowing the corresponding β,γ-unsaturated podocarpenones **110** to stand under oxygen in ether solution for several days (equation 50). Oxygen bubbling as well as fluorescent lamp irradiation hastens the process.



(50)

R=CO_2H, CO_2CH_3 or CH_2OH

In the case of β,γ,δ,ε-dienones, oxygenation occurs at the ε position with the double bond shifting, in tandem, into conjugation[138-141]. Thus, solid $\Delta^{5(10),9(11)}$-3-ketone **112** is reported to undergo autoxidation to the corresponding $\Delta^{4,9(10)}$-10β-hydroperoxide **113** on standing overnight at room temperature (equation 51).



(51)

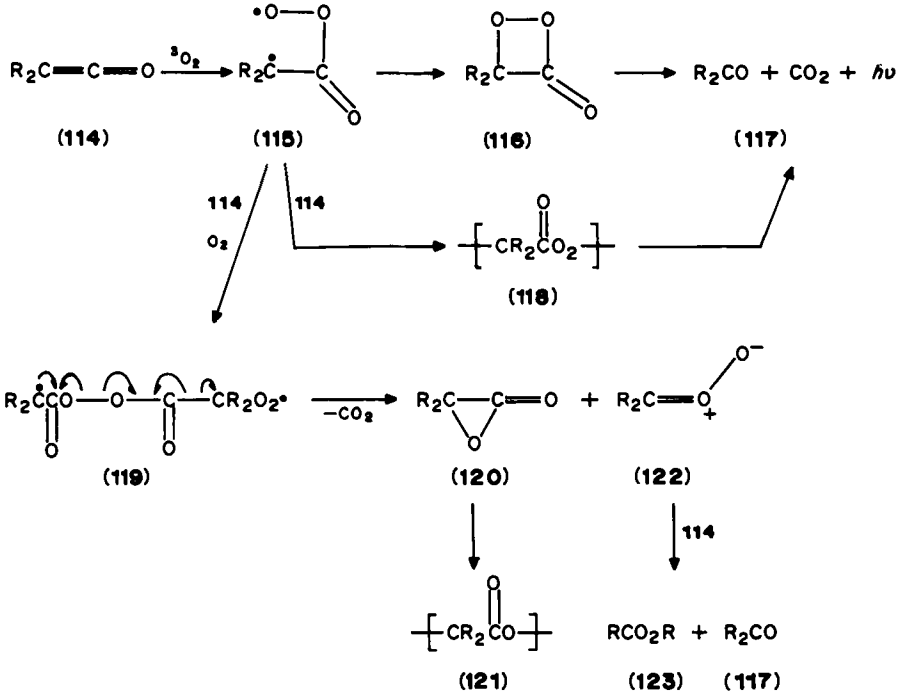
(112) (113)

We have already noted above (equation 33)[90b] that β,γ-unsaturated ester **50** yields the same γ-hydroperoxide as its α,β-unsaturated analog **48**. The same is true for 5-methyl-4-hexen-2-one and its α,β-analog **45a**[89]. In both these cases the β,γ-enone reacted much faster than its conjugated isomer.

4. *Ketenes*[142,143]

Ketenes are a very unique group of enones which exemplify the high reactivity of cumulenes as well as substituent-dependent behaviour. Unsubstituted ketenes (**114**,R = H, Scheme 9) do not autoxidized readily. On the other hand, dialkylketenes react to completion even at −20 °C after several hours, producing polyperester **118** in a 96% yield along with <4% polyester **121**. Alkylarylketenes are oxygenated at room temperature generating polyester **121** in about 50% yield. The remaining products, ketone **117** and CO_2, presumably result from the thermal cleavage of the corresponding polyperester **118**. At low temperatures (−78 °C), peroxy lactone **116** can be isolated in low yields.

Diphenylketene autoxidizes sluggishly at room temperature reaching completion only after 3 days. In this case polybenzilic acid (**121**, R = C_6H_5) is formed in a 65% yield along with 20% benzophenone (**117**, R = C_6H_5), CO_2 and 15% phenyl benzoate (**123**, R = C_6H_5). The proposed mechanism is shown is Scheme 9 and involves the intermediacy of an α-lactone **120**, and α-peroxy lactone **116** and carbonyl oxide **122**. One interesting facet of this reaction is that it appears to be initiated completely spontaneously[16].



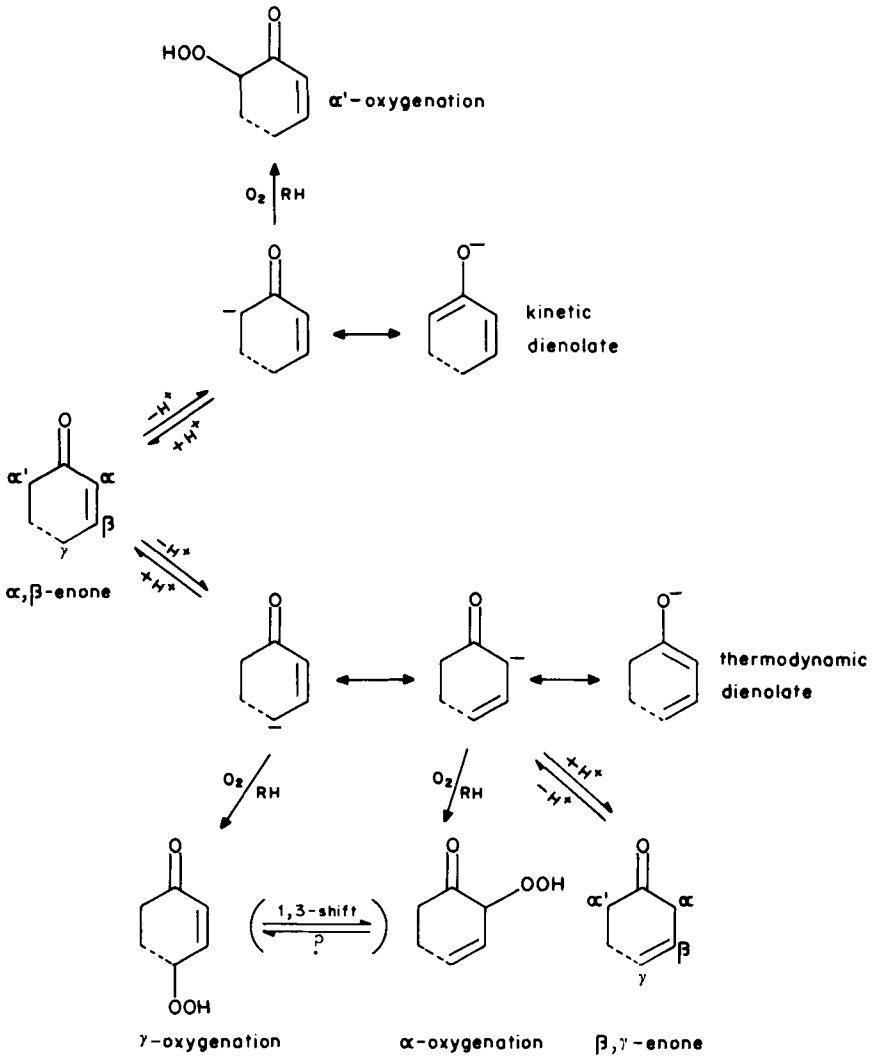
SCHEME 9. Autoxidation of ketenes

E. Base-catalyzed Autoxidation of Enones

1. General mechanism

In α,β-unsaturated carbonyl systems, two different acidic protons are often present, positioned at the α' and γ carbons. Of the two, the α'-hydrogen is the more acidic, presumably for inductive reasons. Nevertheless, abstraction of the γ-hydrogen is thermodynamically preferred since the completely conjugated dienolate anion formed is more stable than its cross-conjugated isomer[144] (Scheme 10).

As a result, enones can give dienolate anion mixtures of various composition, depending on whether the enolates are formed under circumstances in which the composition was determined by the relative rates of proton abstraction (kinetic control) or via equilibration of the various enolate anions (equilibrium or thermodynamic control). A rapid equilibrium between the enolates is achieved only when some proton donor, such as a protic solvent (e.g. *t*-butoxide in *t*-butanol) or excess unionized ketone, is present in the reaction mixture. Consequently, a kinetically controlled mixture of enolates is obtained by slowly adding a ketone to excess of strong base in an aprotic solvent at low temperature. On the other hand, protic solvents and elevated temperatures, the slow addition of a strong base to a ketone, or the presence of excess ketone in a solution of enolate anions, all favor the formation of the thermodynamic dienolate[144-148]. Recent research has further shown that high selectivity in the formation of either the linear-conjugated or the cross-conjugated dienolates can be obtained by choosing the correct base–solvent combination[149].

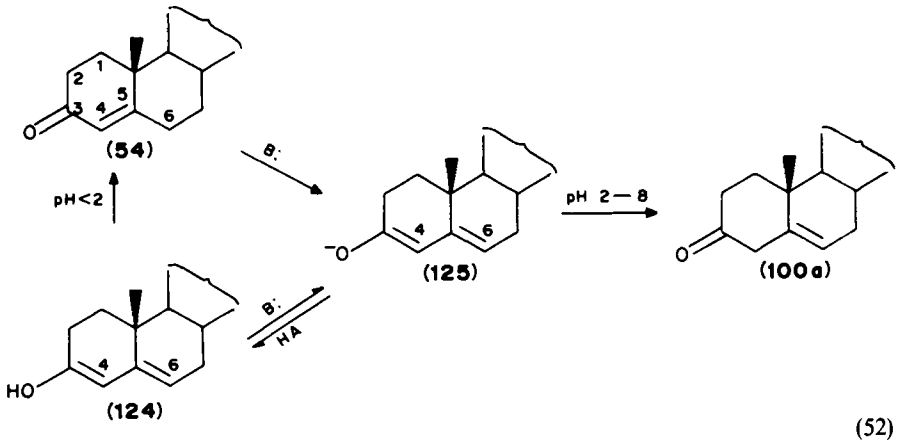


SCHEME 10. Scheme for the deprotonation and oxygenation of enones

The kinetic dienolate reacts with electrophiles (alkyl halide, protons, molecular dioxygen, etc.) at the α' position, while the thermodynamic dienolate theoretically provides opportunities for electrophilic attack at either the α or γ positions. In fact, however, the thermodynamic dienolates invariably undergo intermolecular alkylation and protonation at the α position, even when that site is sterically quite congested[148,150-152].

We have spoken thus far only about enolate formation and have essentially neglected the intermediacy of the corresponding enol. This is because at basic pH, it is the enolate alone which is the predominant reactive species. In studies[152] on the tautomerization of the conjugated enol **124** of cholest-4-en-3-one (**54**), it has been shown that over a broad pH

range (2–8) it is the enolate anion **125** which is protonated during ketonization (equation 52). Only at very low pH is the enol itself protonated. Furthermore, while the enolate is protonated kinetically at the center of the conjugated system (i.e. at C_α or C_4 in **125**), the enol is protonated at the end (i.e. at C_γ or C_6 in **124**). For our purposes, however, it should be noted that the enolate is so much more reactive than the enol that enol–enolate equilibration provides sufficient enolate to favor C_α protonation under most conditions[152].



(52)

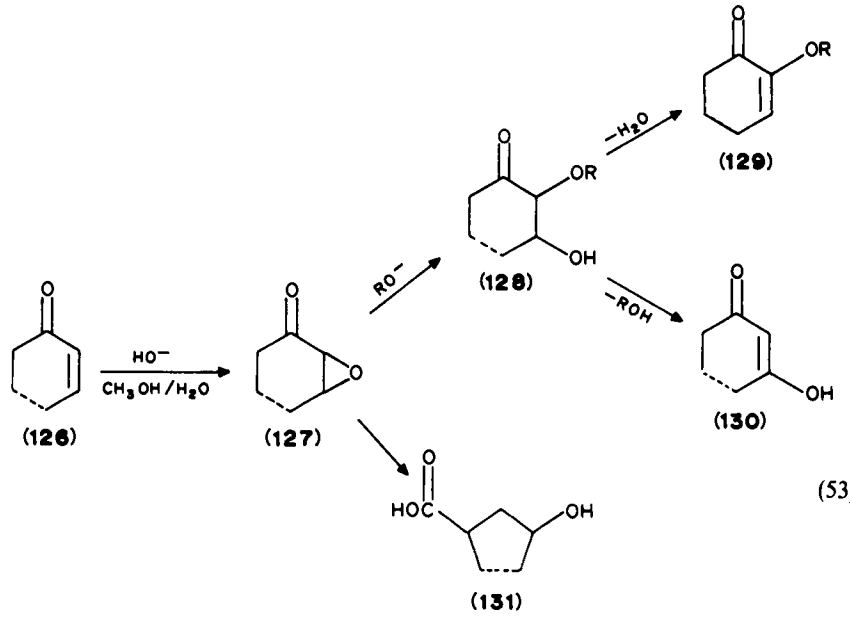
As we shall see shortly, in the case of the *oxygenation* of enolates, while α oxygenation is preferred, both α and γ products are known. Nevertheless, in light of the aforementioned 1,3-allylic hydroperoxide shift (Section III.C.5), it is quite possible that γ-oxygenation products result from the rearrangement of the initially formed α products (see bottom of Scheme 10). This question deserves further investigation.

In the case of β,γ-enones, abstraction of the α-hydrogen is preferred both kinetically and thermodynamically. Thus, deprotonation of β,γ-unsaturated carbonyl compounds permits easy access to the 'thermodynamic dienolate' of the α,β-enone system (see Scheme 10) even when the reaction is carried out at low temperatures and aprotic media. We will return to this point a bit later (Section III.E.4).

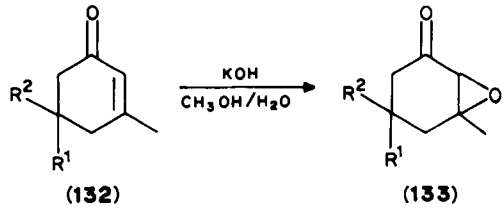
2. *Epoxidation of α,β-enones*

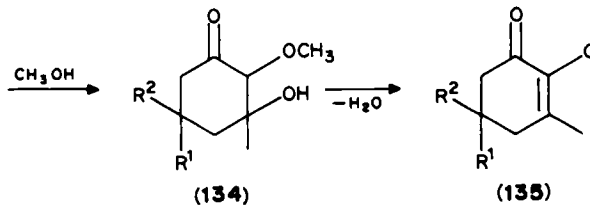
The first studies on the base-catalyzed autoxidation (BCA) of enones were carried out at the turn of the century by Harries[153] and Stahler[154], but it was not until three decades later that systematic research was begun by Treibs[155–161]. The early reactions were carried out in aqueous methanol, above room temperature, and for lengthy reaction times. The yields isolated were generally quite low (<15%). Hydroperoxides formed via α'- or γ-proton abstraction were undoubtedly the primary products, but neither these nor the corresponding ketones or alcohols were isolated. Undoubtedly, these underwent further oxidation and cleavage and unidentified acidic compounds represented the bulk of the products. The major isolated product was the corresponding epoxide **127** or its derivatives formed in a variety of subsequent hydrolytic and/or oxidative rearrangement steps (equation 53).

For example[161], 3-methylcyclohex-2-en-1-one (**132a**), as well as its 5-methyl and 5,5-dimethyl analogs (**132b** and **132c**), yield the corresponding diosphenol methyl ethers **135a–c** (equation 54). Similarly, diosphenol **137** was the main product in the autoxidation of verbenone (**136**, equation 55).



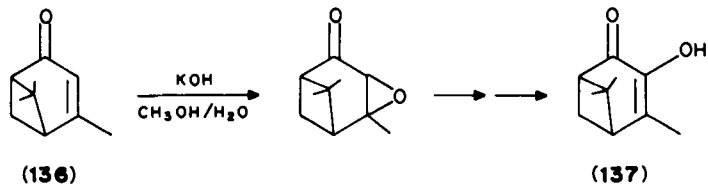
(53)





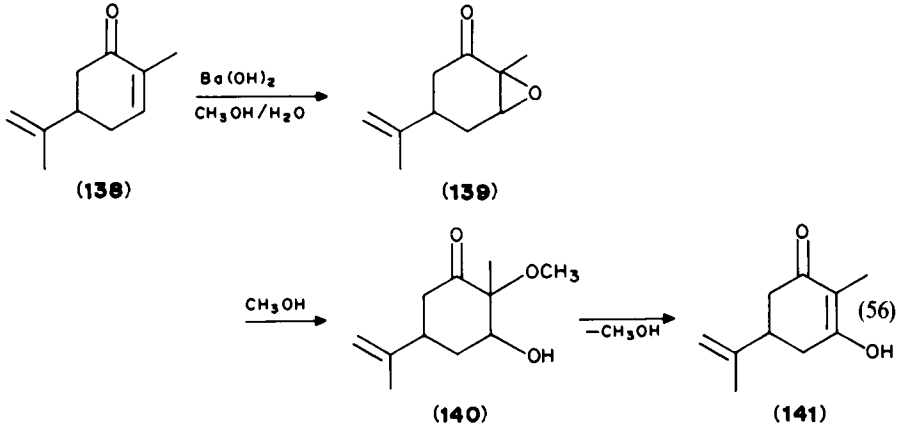
(54)

(a) $R^1, R^2 = H$; (b) $R^1 = H, R^2 = CH_3$; (c) $R^1 = R^2 = CH_3$

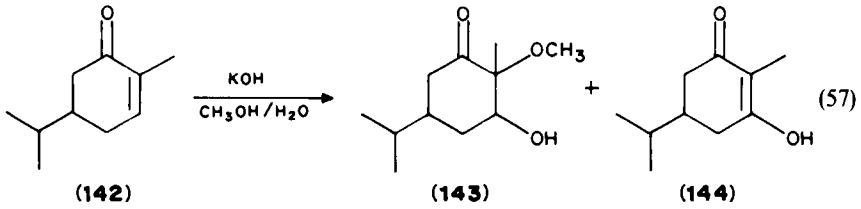


(55)

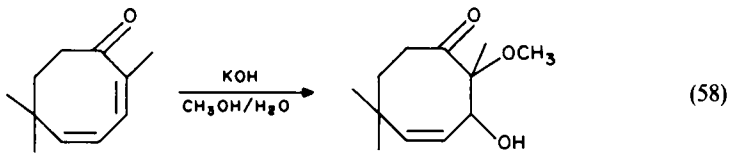
On the other hand, carvone[153-156,159,161] (**138**) and carvotanacetone[161] (**142**), which lack a hydrogen α to the carbonyl, form 3-hydroxy enones **141** and **144** (equations 56 and 57). In the case of enone **142**, addition product **143** was also isolated (equation 57), while the analogous addition product **146** was the sole compound isolated from the autoxidation of eucarvone (**145**, equation 58).



(138) (139) (140) (141)



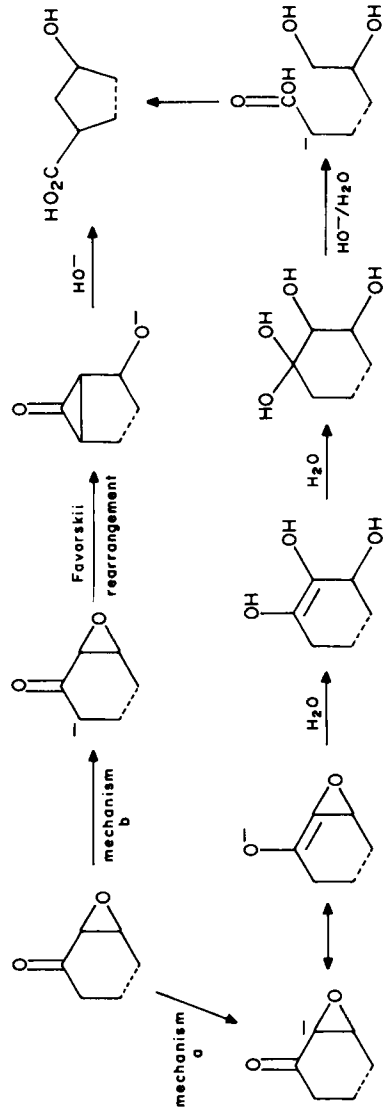
(142) (143) (144)



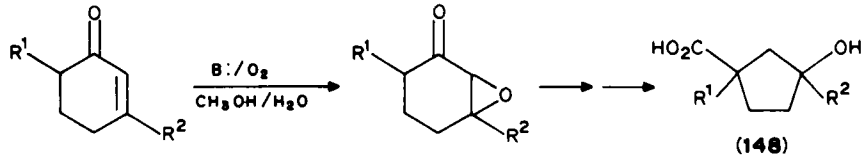
(145) (146)

Finally, α-hydroxy acids **148** are the primary products from the autoxidation of piperitone (**147a**)[155,157,158,160,161] and carvenone (**147b**)[155,158] as outlined in equation 59.

The mechanism suggested by Treibs[157] (Scheme 11, path a) and quoted by Sosnovsky and Zaret[19d] for the formation of β-hydroxy acids **148** is unnecessarily complicated and in many aspects unprecedented. We prefer the intermediacy of a Favorskii rearrangement (Scheme 11, path b) which is well precedented for α,β-epoxy ketones[162,163].



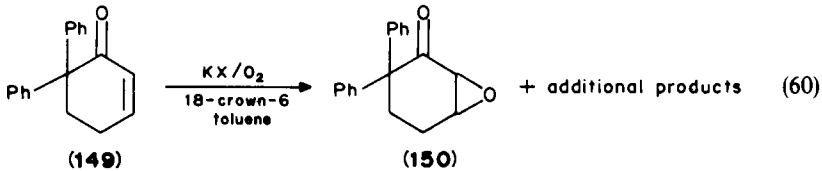
SCHEME 11. Possible mechanisms for the formation of β-hydroxyacids from enones



(147)(a) $R^1 = i\text{-Pr}$; $R^2 = Me$
(b) $R^1 = Me$; $R^2 = i\text{-Pr}$ (59)

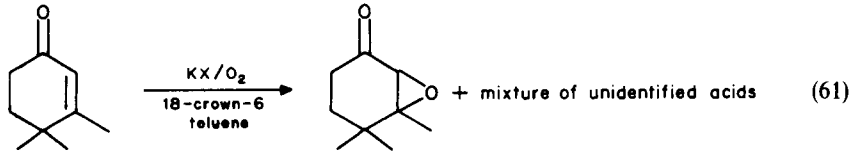
The intermediacy of epoxides in all the above cases was verified by demonstrating that pure epoxides generate the same products under the same reaction conditions. Various condensation products were also formed in some instances; however, the vast majority of the product components were unidentified as noted in the beginning of this section.

Related systems have been explored by Frimer and his students[164,165] in aprotic media using potassium hydroxide, superoxide and *t*-butoxide solubilized in toluene or benzene with 18-crown-6-polyether. These researchers obtained low to moderate yields of epoxides in the BCA of cyclohex-2-en-1-ones **149** and **151** (equations 60 and 61). (For further discussion of this reaction see Section III.E.3.b.)



(60)

KOH/25 °C	36% yield
KO_2/25 °C	50%
$t\text{-}C_4H_9OK$/−40 °C	40%

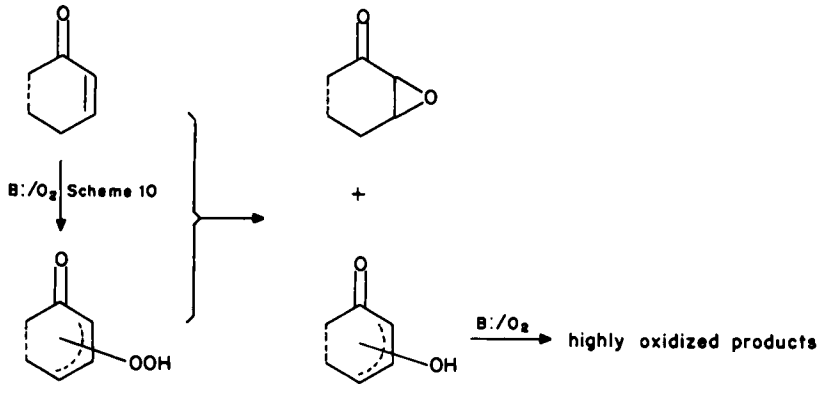


(61)

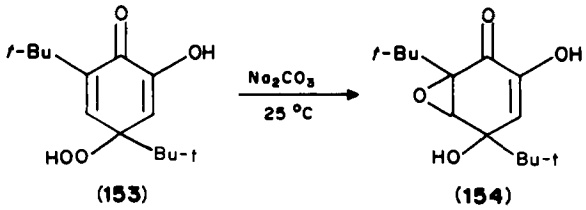
KOH/25 °C	33% yield
$t\text{-}C_4H_9OK$/−40 °C	50%

The issue that remains to be resolved is the mechanism of epoxidation in all these cases. Karnojitzky[19e] suggests that 'hydrogen peroxide, formed by the hydrolysis of the allylic hydroperoxide produced initially, can serve as the epoxidizing agent'. Since epoxides are obtained in aprotic media as well, we believe it much more likely that these allylic hydroperoxides themselves are the active agents (equation 62)[164], a suggestion that has been confirmed by recent work of Sugawara and Baizer[166].

In the same vein, Jensen and Foote[167] recently reported that hydroperoxide **153** is converted to epoxide **154** upon treatment with Na_2CO_3 (equation 63).



(62)



(153) (154)

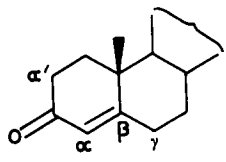
(63)

3. *Hydroperoxidation of α,β-enones*

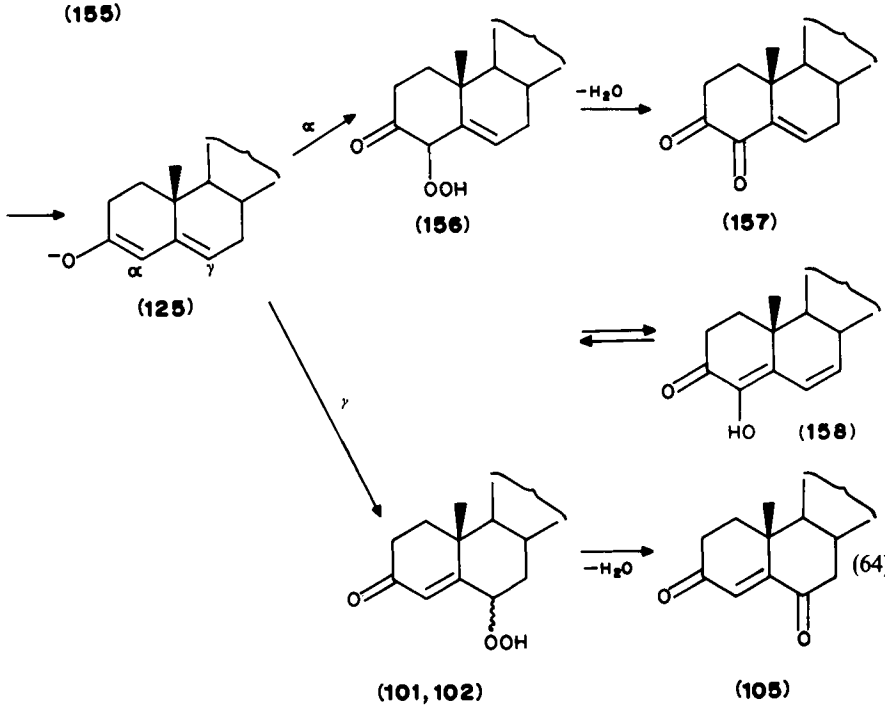
a. Protic media. For nearly three decades following the work of Treibs[155–161], further work on the BCA of enones was essentially abandoned. The obvious reasons were the low yields and the complicated reaction mixtures. In the mid 1950s and early 1960s, the research groups of Doering and Barton[168–171] reported on the utility of the non-nucleophilic strong base *t*-butoxide (commonly dissolved in *t*-butanol) for carrying out BCA reactions. When applied to enone systems, the reaction yields improved somewhat and the products (ketones, aldehydes, alcohols or acids) obtained could be readily rationalized in terms of the expected hydroperoxides. Nevertheless, the yields were generally below 50% and it was therefore difficult to be sure as to the true course of the overall reaction.

Camerino, Patelli and Sciaky[172,173] using *t*-butoxide in *t*-butanol carried out extensive studies on the base-catalyzed oxygenation of various steroids including the 3-oxo-Δ^4 system (**155**, equation 64). They reported low yields of 4-hydroxy dienone **158** and enedione **105** (see Table 2) which clearly result from the oxygenations of the α(C-4) and γ(C-6) carbons of the thermodynamic enolate **125**, followed by Kornblum–DeLaMare dehydration of the resulting hydroperoxides **156** and **101**, **102** (equation 64). Other groups have found similar results under slightly different BCA conditions[174,175] (see Table 2).

Camerino and coworkers[172,173] also found that $\Delta^{1,4}$-3-oxosteroids react in a similar fashion. $\Delta^{1,4}$-Pregnadien-11β-ol-3-one-BMD yielded the corresponding 4-hydroxy-1,4,6-triene-3-one in a 35% yield. Holland's group[176,177], on the other hand, found that $\Delta^{1,4}$- and $\Delta^{4,6}$-dien-3-ones were unreactive towards oxygen when the BCA is mediated by Na_2O_2 in aqueous ethanol. Various 4-chloro-3-oxo-Δ^4 steroids (**159**) also undergo BCA oxidation with *t*-butoxide in *t*-butanol yielding **158**. A probable mechanism is shown in equation 65.

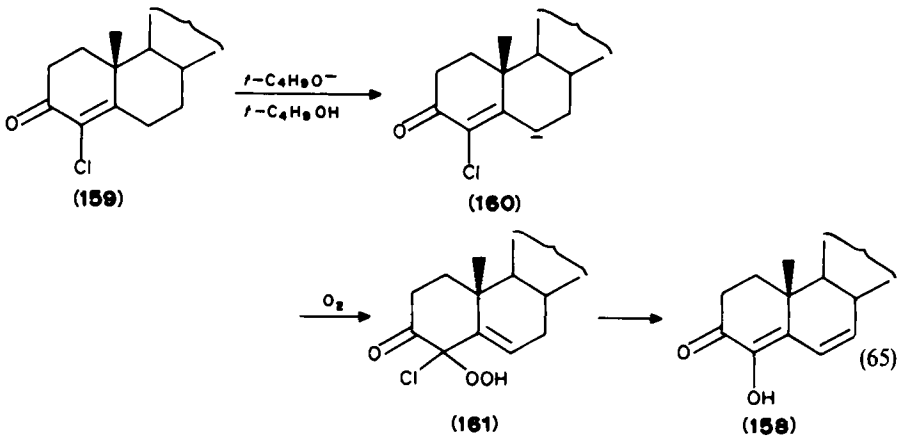


(155)



(125) (156) (157) (158) (101, 102) (105)

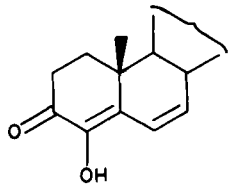
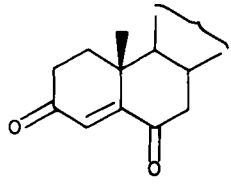
(64)



(159) (160) (161) (158)

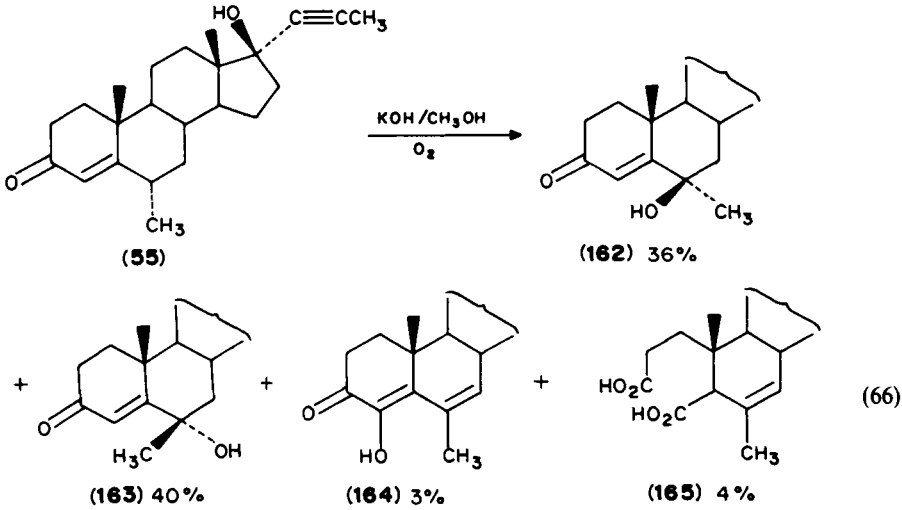
(65)

TABLE 2. Product distribution in the base-catalyzed autoxidation of selected[a] Δ^4-3-oxosteroids in protic media

Substrate **155**	Conditions[b]	**158** 	**105** 	Reference
Δ^4-Cholesten-3-one	1	14%	4%	172, 173
	2	—	56%	176, 177
Cortisone–BMD	1	25%	70%	172, 173
Hydrocortisone–BMD	1	30%	33%	172, 173
17α-Methyltestosterone	1	15%	*c*	172, 173
Testosterone	2	—	43%	176, 177
Progesterone	1	20%	*c*	172, 173
	2	—	63%	176, 177
	3	—	11%	175
20-Methylpregn-4-en-3-one	1	30%	—	174
Androst-4-en-3, 17-dione	2	—	55%	176, 177

[a]Many of the steroid systems studied by Camerino's group[172,173] are not included in this table because no product yields were reported.
[b]Conditions: 1—*t*-butoxide in *t*-butanol for > 24 h at 25 °C. 2—Na_2O_2 in aqueous ethanol for 2 h at 25 °C. 3—KOH in methanol at 50 °C for ½ h.
[c]An absorption at ~250 mμ was observed but no product could be isolated.

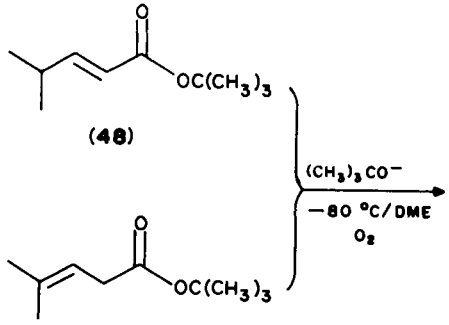
Majewski and colleagues[94] have explored the BCA of the 6-methyl-3-oxo Δ^4-steroid dimethisterone (**55**). The reaction was run in 2 M methanolic KOH for five days at room temperature, using a stream of air as the oxygen source. The major product (76% yield) was a 1:1 mixture of the epimeric 6-hydroxy analogs **162** and **163**. The 4-hydroxy dienone **164** and diacid **165** were also isolated in low yields (equation 66).

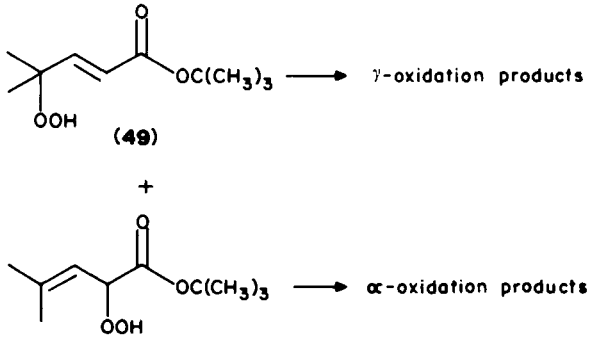


(66)

As in the case of the unsubstituted 3-oxo-Δ^4 steroids (equation 64), the primary products under protic conditions are the 4- and 6-hydroperoxides. In the present case, however, Kornblum–DeLaMare dehydration of the latter is precluded; hence homolytic cleavage (Section III.C.1) leading to alcohols **162** and **163** is observed. The 4-hydroperoxide yields **164** (via Kornblum–DeLaMare dehydration and enolization) and diacid **165**, via an oxidative cleavage typical of α-hydroperoxy ketones (Section III.C.4).

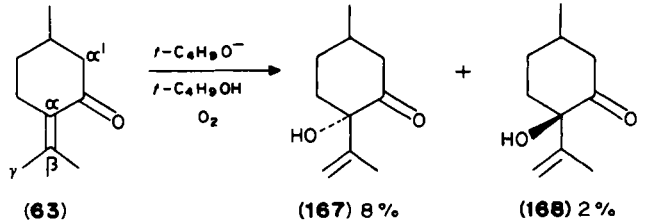
In a non-steroidal system, Gersman and colleagues[90b] found that BCA of α,β-unsaturated ester **48** (as well as its β,γ-unsaturated analog **50**) results in a 25% yield of the α-product (**166**, equation 67). This is in contradistinction to free radical autoxidation where only γ-oxidation product **49** is isolated (equation 33).



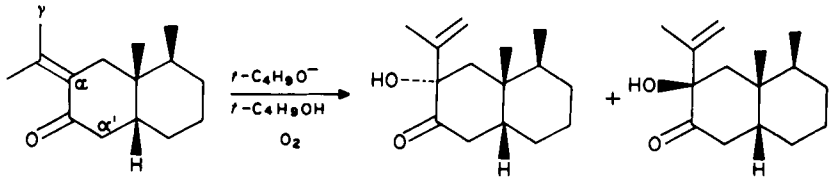


(67)

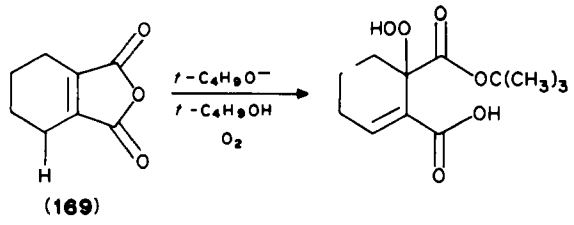
α-Oxidation is strongly preferred in many, if not most, cases over γ-oxidation products. This is true, for example, for pulegone (**63**)[178], fukinone (**64**)[178] and dialkylmaleic anhydrides (**169**)[179] (equations 68–70).



(68)

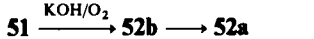


(69)

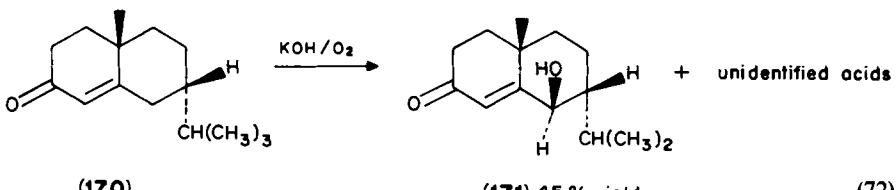


(70)

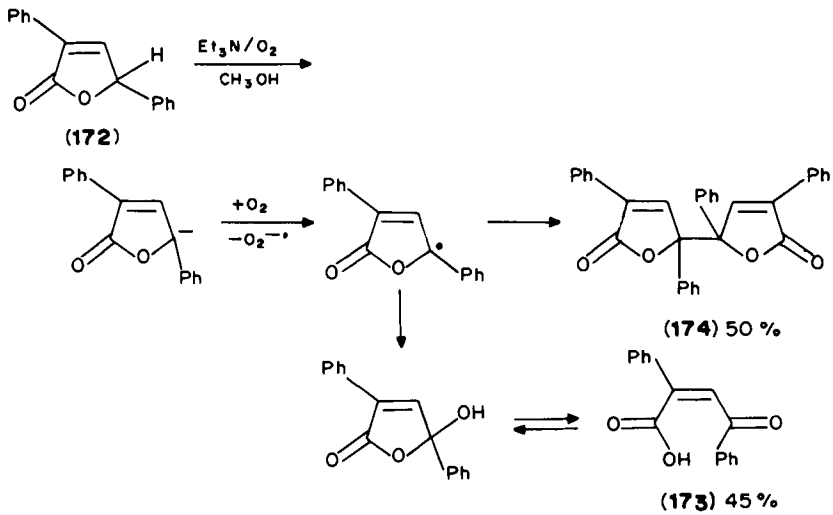
γ-Oxidation products, on the other hand, are preferred for epi-α-cyperone (**51**), its dihydro analog **170** (equations 71 and 72)[91], and for butenolide **172** (equation 73)[89]. In the latter case even the weak base triethylamine works efficiently.



(71)

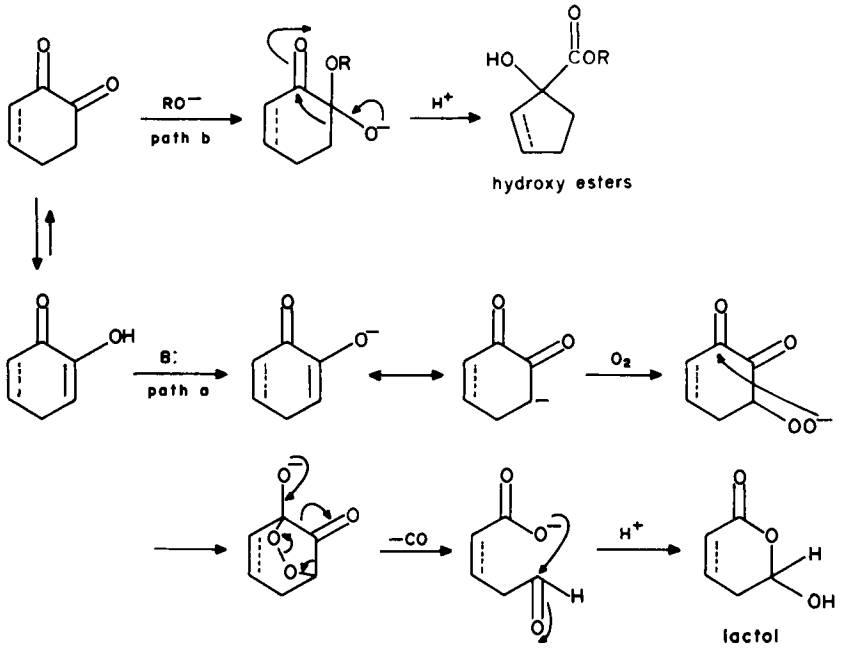


(72)



(73)

β-Oxidation products are also observed in the case of diosphenols, i.e. 2-hydroxy-2-en-1-ones[31,61–66,180–185]. Deprotonation of the acidic enol followed by oxygenation at the enolate carbanion results in the formation of a 3-hydroperoxy-1, 2-diketone system (Scheme 12, path a). The latter decomposes as discussed previously (Section III C.4) to CO, a carboxylic acid and a carbonyl group. In the case of cyclic systems, the acid and carbonyl moieties often cyclize to a lactol[31,61–66,180–185]. In addition, since 2-hydroxy-2-en-1-ones are merely the enolic form of α- diketones, it should not be surprising that a benzil–benzilic acid rearrangement (yielding an α-hydroxy acid) often competes in these base-catalyzed processes (Scheme 12, path b)[170,186–191]. As a general rule, nucleophilic bases (HO^-, CH_3O^-, $C_2H_5O^-$) favor hydroxy acid or ester formation, while the stronger base *t*-butoxide favors lactol formation.

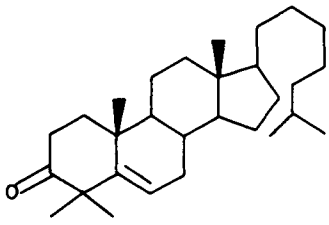


SCHEME 12. *β*-Oxidation and benzilic acid rearrangement of 2-hydroxy-2-en-1-ones

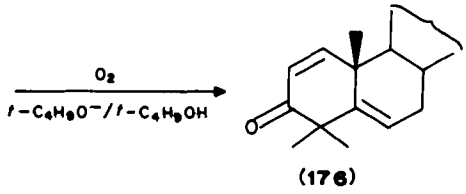
An example of these transformations was reported by Hanna and Ourisson[61a,181], who studied the *t*-butoxide mediated autoxidation of 4,4-dimethyl-Δ^5-cholestenone (**175**) which yields lactol **177** via the corresponding enol **176** (equation 74). The latter can be isolated and, when treated with ethoxide in ethanol, yields α-hydroxy acid **178** rather than lactol **177**.

A more recent example[64] is the BCA of 2-hydroxypiperitone (**179**) which, under micellar catalysis, yields an acyclic keto acid as the major product (equation 75, path a). In the absence of micellar material, several acidic by-products are formed, some of which presumably involve benzil–benzilic acid rearrangements (equation 75, path b). We will see several more examples in Section III.E.3.b.

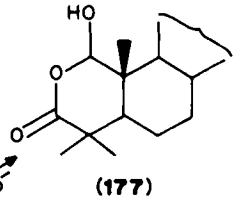
At this juncture, we should discuss briefly the BCA of ascorbic acid (**92**, AH_2). We have already noted (Section II.D.2.b) that the autoxidation of **92** at neutral pH proceeds via the



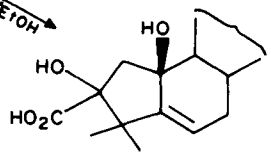
(175)



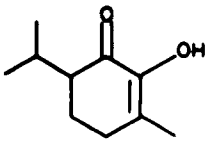
(176)



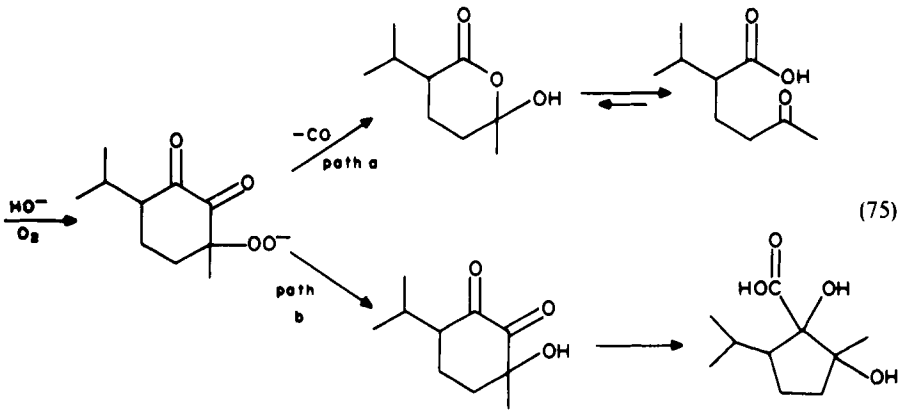
(177)



(178) (74)



(179)



(75)

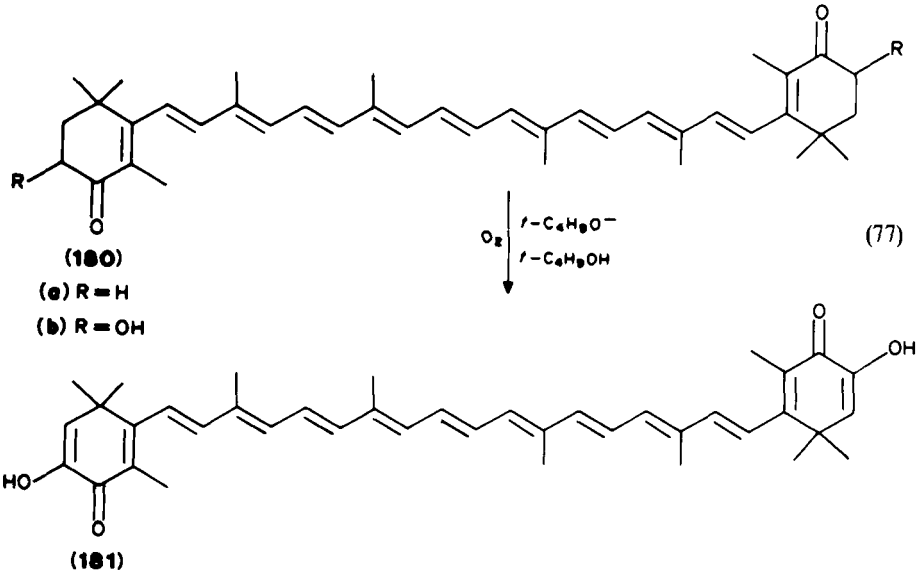
ascorbate ion (AH^-, equation 45) and that the primary role of O_2 is that of an electron acceptor. In general, there is a more rapid uptake of oxygen at basic pH values than at neutral or acidic value with the oxidation product being the triketone dehydroascorbic acid (A). Recently, Afanas'ev and his colleagues[124] reported that the rate of ascorbate anion oxidation in aqueous solution is independent of pH (at pH 6–10) and is completely inhibited by EDTA. This suggests, then, that metal (Fe^{+3}) catalyzed oxidation is the primary mode of reaction in aqueous solution (equation 76).

$$AH^- + Fe^{3+} \longrightarrow AH^{\cdot} + Fe^{2+} \xrightarrow{O_2} A + HO_2^- + Fe^{3+} \qquad (76)$$

Presumably the highly hydrated ascorbate is not able to transfer an electron directly to molecular oxygen. In acetonitrile, on the other hand, the solvent apparently forms an unreactive complex with Fe^{+3} ion and inhibits the catalytic process. As a result, only an uncatalyzed direct electron transfer to dioxygen occurs (equation 45).

α′-Oxidation of an α,β-unsaturated enone occurs when one of the following conditions is fulfilled: (1) when there are no abstractable γ-hydrogens; (2) when the α′ carbon is already partially oxidized; (3) when the reaction is under kinetic control.

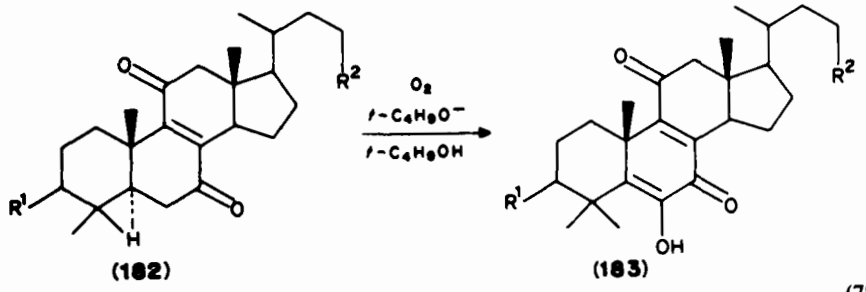
An example of the first category is the oxidation of the carotenoids canthaxanthin (**180a**)[192] and astaxanthin (**180b**)[193] which proceeds under base catalysis to yield astacene (**181**, equation 77).



(77)

Similarly, Kreiser and Ulrich[194] report that lanosterols **182a–c**, which lack γ hydrogens, are readily converted in 80–100% yields to the corresponding diosphenol **183** (equation 78).

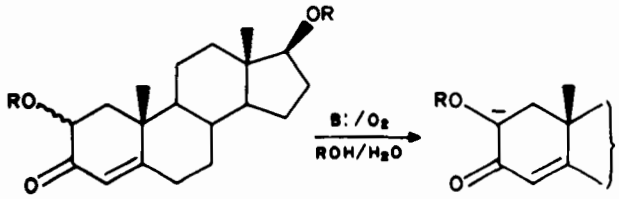
In the second category, we can include the oxidation of a series of α- and β-2-hydroxy and 2-acetoxytestosterones (**184**, equation 79) to the corresponding enols **185**[195,196]. Aqueous alcohol media and various bases (KOH, NaOH, $KHCO_3$, K_2CO_3) have been used to effect this transformation which proceeds in high yield at the α′-carbon, despite an abstractable γ-hydrogen. This is undoubtedly due to the fact that the electron-withdrawing hydroxy group stabilizes the adjacent carbanion[197].



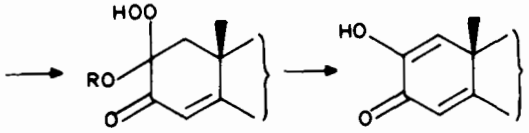
(182) (183)

(78)

(a) R^1=OH, R^2=$CH_2CH(CH_3)_2$
(b) R^1=O, R^2=$CH_2CH(CH_3)_2$
(c) R^1=OH, R^2=CO_2H



(184) R=H or $COCH_3$

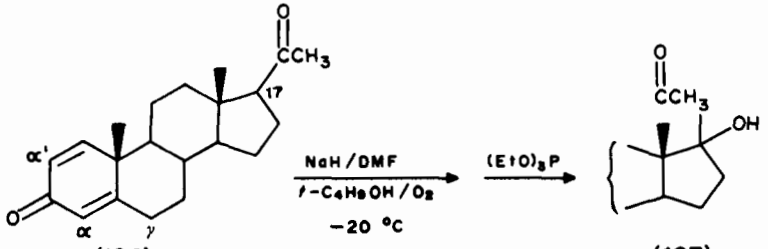


(79)

(185) 70—85%

Kinetic control as a factor in directing oxidation towards the α′ carbon will be discussed in Section III.E.3.b.

We have thus far reviewed α, β, γ and α′ oxidation in the enone system. Gardner and coworkers[198] report that in the case of progesterone, oxidation of these positions competes with oxidation at C-17 resulting in a 'gummy product'. However, in the $\Delta^{1,4}$-analog **186**, neither α nor γ oxidation is observed; the major product results from C-17 hydroperoxidation, yielding sterol **187** upon triethylphosphite reduction (equation 80).



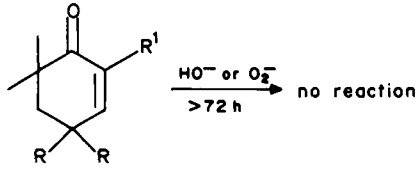
(186) (187)

(80)

The oxygenation of 3-hydroxyflavones in protic media will be discussed at the end of Section III.E.3.b.

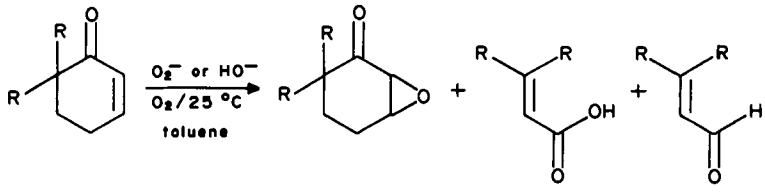
b. Aprotic media. By the 1970s, chemists had discovered that crown ethers and phase transfer agents would enable them to solubilize a whole variety of inorganic bases even in non-polar aprotic media such as benzene. The BCA reactions of enones carried out in aprotic media proved to give cleaner reaction mixtures in higher yields; what is more, they were easier to control. One of the new bases explored was superoxide anion radical [$O_2^{-\cdot}$], commonly generated from potassium superoxide [KO_2] and 18-crown-6 polyethers. We will discuss this and some of superoxide's other properties in Section V; meanwhile, let us simply note that the base strength of $O_2^{-\cdot}$ in aprotic media is qualitatively less than *t*-butoxide but greater than hydroxide[27b,d].

Frimer and coworkers[27b,68,164,165] studied the superoxide, *t*-butoxide and hydroxide mediated oxidation of variously substituted cyclohex-2-en-1-ones. 4,4,6,6-Tetrasubstituted cyclohexenones **188** are totally inert to hydroxide and superoxide even after prolonged reaction times (equation 81). This is not surprising, of course, since **188** lacks abstractable acidic hydrogens.



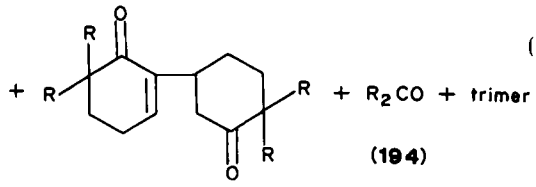
(188) (81)

In the case of 6,6-disubstituted cyclohexenones **189**, epoxides **190**, acids **191**, aldehydes **192**, dimers **193** and ketones **194** are the isolated products, with the product distribution depending on the nature of the substituents (equation 82). When the BCA of **189a** is mediated by *t*-butoxide in toluene at $-40\,^{\circ}C$, the two major products are epoxide **190a** and hydroxyacid **195** (equation 83).

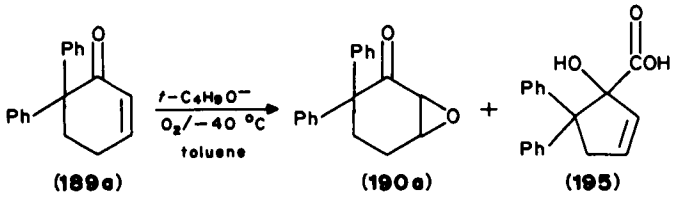


(189) (190) (191) (192)

(a) R=Ph
(b) R=CH_3
(c) R=H



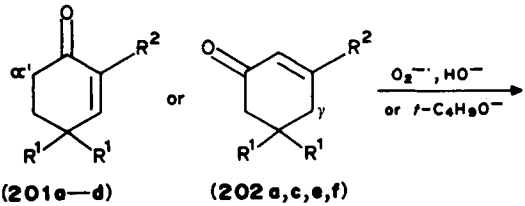
(193) (194) (82)



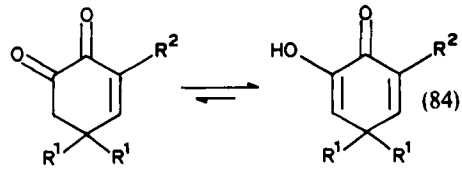
(83)

The mechanism proposed for both these transformations is outlined in Scheme 13. Following initial γ-proton removal, condensation of the resulting anion with starting material ultimately produces dimer **193**, while oxygenation generates hydroperoxide, **196**. The latter can epoxidize the substrate, yielding **190**, or decompose to enol **198**. As noted previously, α-ketoenol **198** can undergo either benzil–benzilic acid rearrangement to α-hydroxyacid **195** or oxidation to the lactol **199**. We speculate that this lactol loses CO_2 generating α-hydroperoxy ketone **200** which cleaves to aldehyde **192**. Oxidation of the latter to the corresponding acid **191** is a facile process.

Both 4,4- and 5,5-disubstituted cyclohexenones (**201** and **202** respectively) yield the corresponding enols **204** in generally high yields (equation 84). In the case of **201** it is the α' hydrogen that is removed, since the γ position is blocked. Oxygenation ultimately yields the diketone **203**, which in turn enolizes to **204**. In the case of **202**, the γ hydrogen is preferentially removed generating the thermodynamic enolate (see Scheme 10). The latter is oxygenated α to the carbonyl, leading again to diketone **203** and enol **204**. It should be noted that these enols can be further oxidized under the reaction conditions to the corresponding lactols **205** which, upon $NaBH_4$ reduction, yield lactones **206** (equation 85). Indeed, Frimer and Gilinsky[68] have been able to convert enones to lactols in a one-pot reaction followed by reduction of the lactols to the corresponding δ-valerolactones (**206**) in overall yields approaching 85%.



(201a—d) (202a,c,e,f)

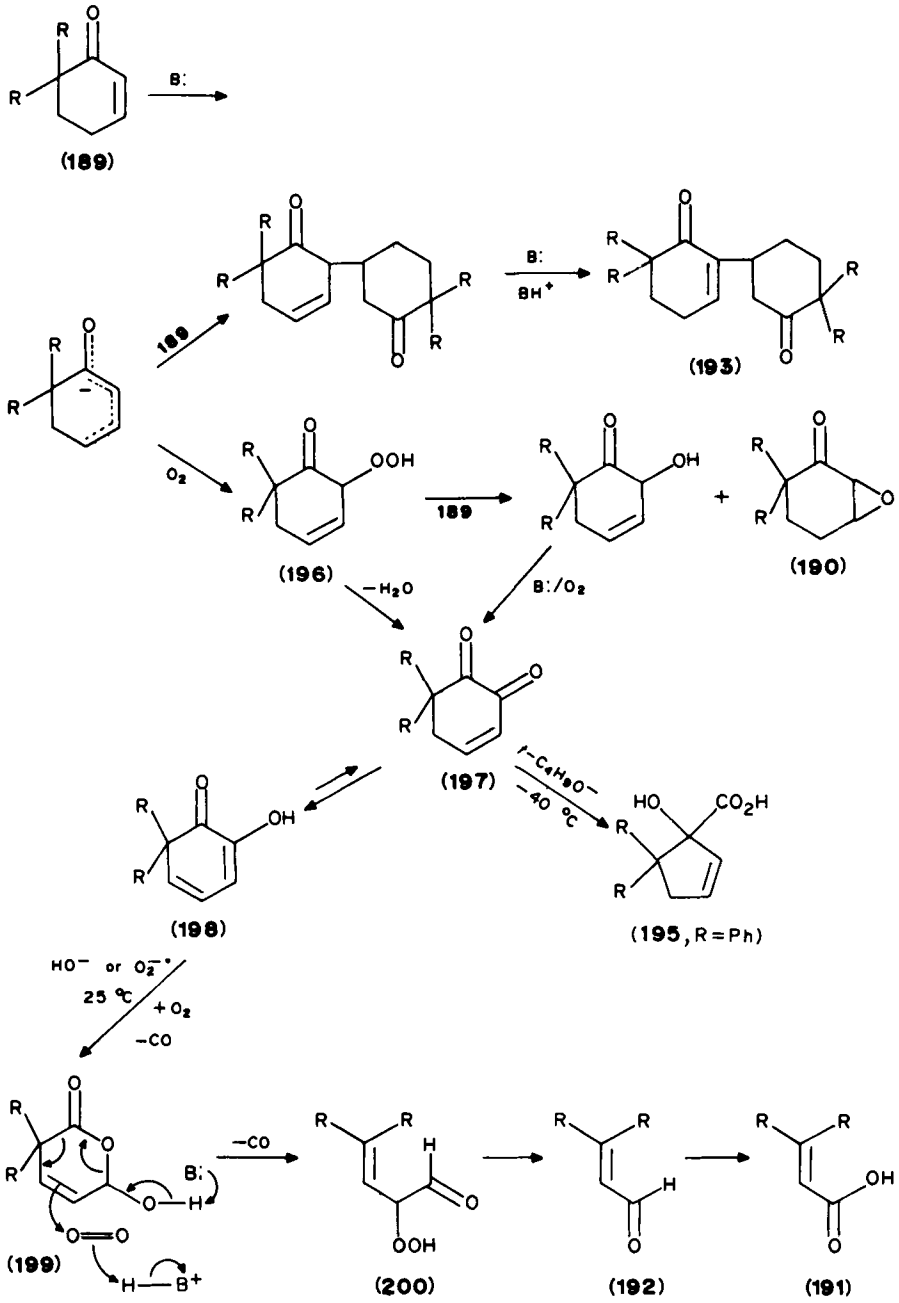


(84)

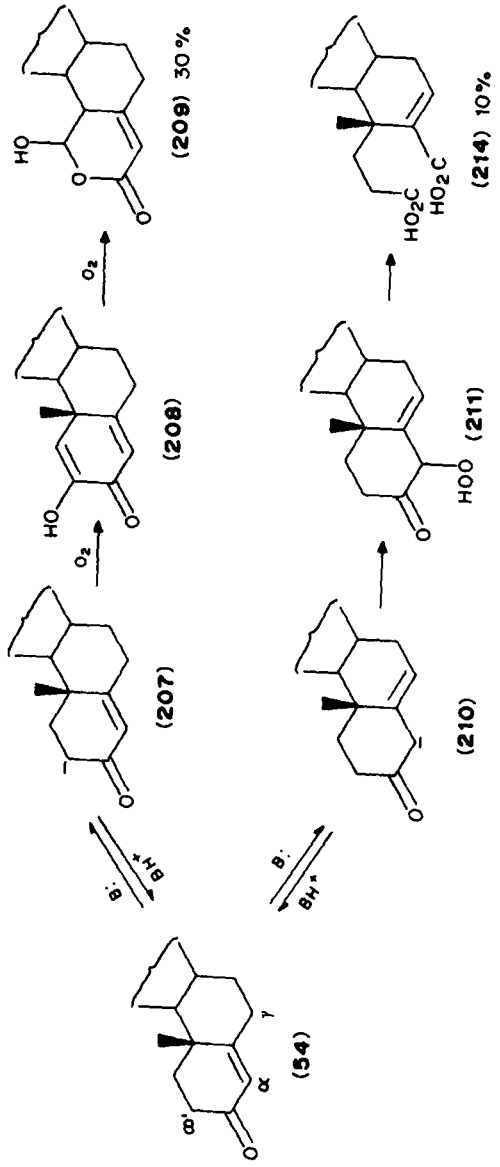
(203a—f) (204a—f)

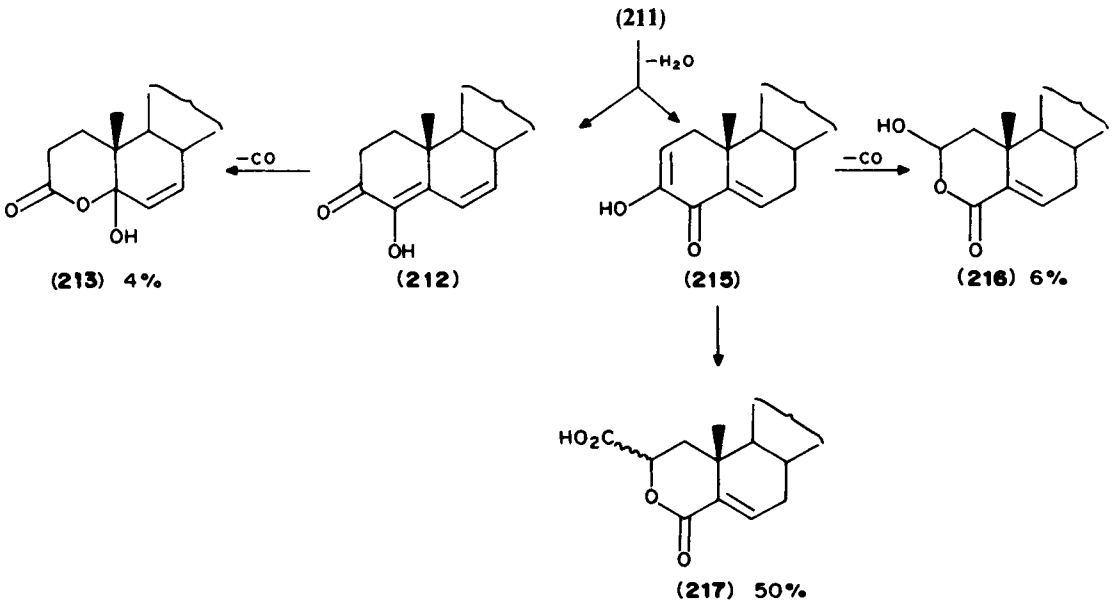
75—95%

(a) $R^1 = Me$, $R^2 = H$
(b) $R^1 = Ph$, $R^2 = H$
(c) $R^1 = Me$, $R^2 = OEt$
(d) $R^1 = Me$, $R^2 = OMe$
(e) $R^1 = R^2 = Me$
(f) $R^1, R^1 = -(CH_2)_5-$, $R^2 = OMe$

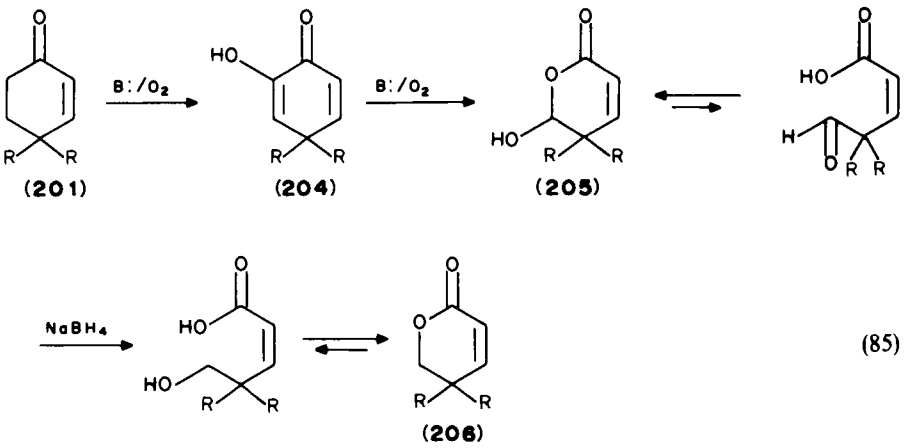


SCHEME 13. Base-catalyzed autoxidation of cyclohexenones with t-$C_4H_4O^-$ (at $-40\,°C$) and $O_2^{-\cdot}$ or HO^- (at $25\,°C$)


(209) 30 %
(208)
(207)
(214) 10%
(211)
(210)
(54)
HO
HOO
HO_2C
HO_2C
O_2
O_2
$:B$
BH^+
$B\cdot$
BH^+
α
γ
ω'

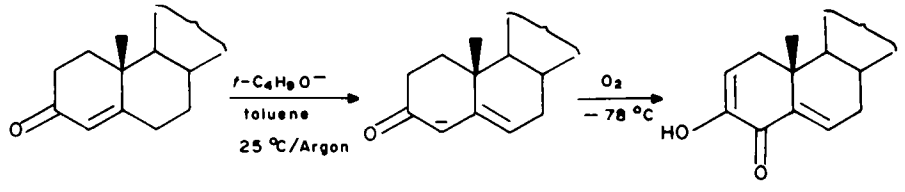


SCHEME 14. Superoxide-, hydroxide- and *t*-butoxide-catalyzed autoxidation of Δ^4-cholestenone[54] in benzene



(85)

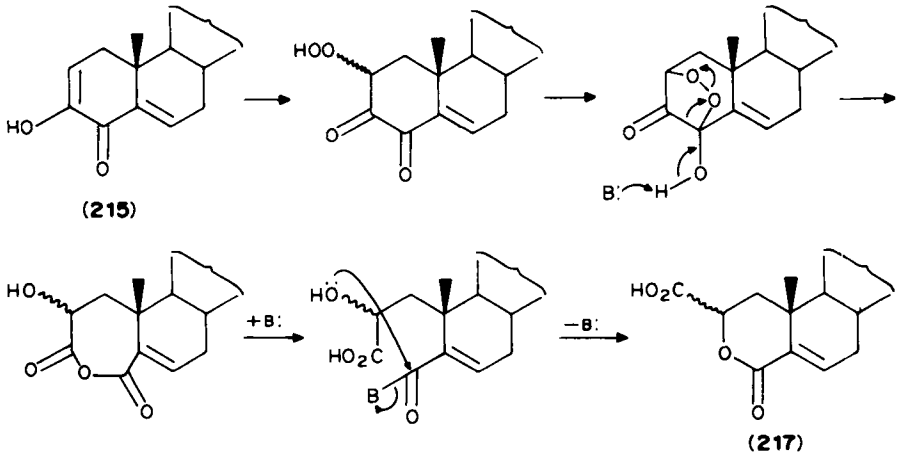
Frimer and coworkers[199–202] next explored the superoxide, *t*-butoxide and hydroxide mediated BCA of 3-oxo-Δ^4 steroids in benzene. A plethora of products were obtained (Scheme 14) which differed substantially from those obtained by Camerino and collaborators[172,173] using *t*-butoxide in *t*-butanol (Section III.E.3.a). In addition, the overall product yield so obtained was nearly quantitative. Lactol **209** stems from oxygenation of the kinetic enolate **207**, and enol **208** can be isolated after short reaction times. On the other hand, lactols **213** and **216** and acids **214** and **217** are generated from the thermodynamic enolate **210** via mechanisms discussed above (Sections III.C.4 and III.E.3.a) though the corresponding enols **212** and **215** could not be isolated under the reaction conditions. Hameiri[202] found, however, that if the thermodynamic enolate **210** is generated at room temperature under argon and if the oxygenation is carried out at $-78\,^{\circ}C$, then a 15% yield of enol **215** can be isolated (equation 86).



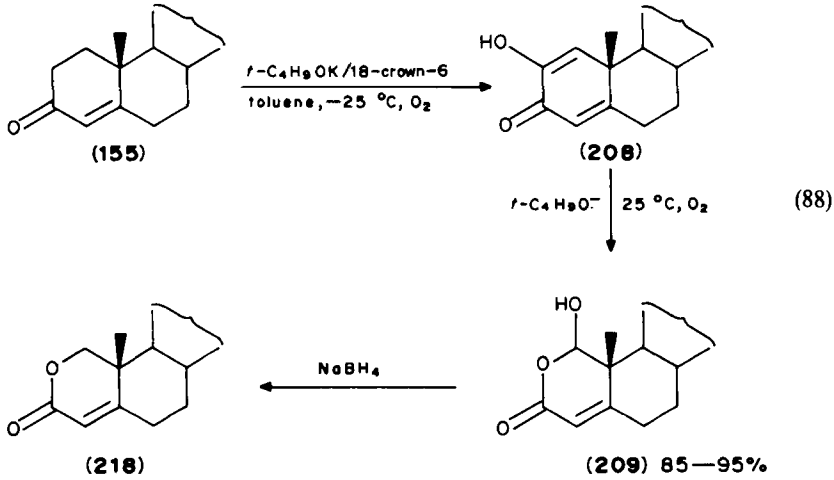
(86)

Regarding the formation of acids **217**, Frimer and coworkers speculate that they are generated from the endoperoxide precursor of **216**, which decomposes without loss of carbon monoxide (equation 87).

These researchers found that by lowering the reaction temperature to $-20\,^{\circ}C$, they could essentially inhibit the isomerization of **207** to **210**, such that the former could be oxygenated quantitatively. Thus when the 3-oxo-Δ^4 steroids (**155**) cholestenone, testosterone, 17α-methyltestosterone, 17α-hydroxyprogesterone, progesterone, cortisone–BMD and cortisolone–BMD are autoxidized with *t*-butoxide in toluene at $-25\,^{\circ}C$ for 1.5–4 h, enol **208** can be isolated in yields of 85–95%. If instead of quenching the reaction to isolate the enol, the reaction is allowed to continue at room temperature for 1–3 days, lactol **209** can be obtained in similar yields. $NaBH_4$ reduction of lactols **209** yields the corresponding therapeutically active 2-oxa-3-oxo-Δ^4 steroid lactones **218** (equation 88)[201].



(87)

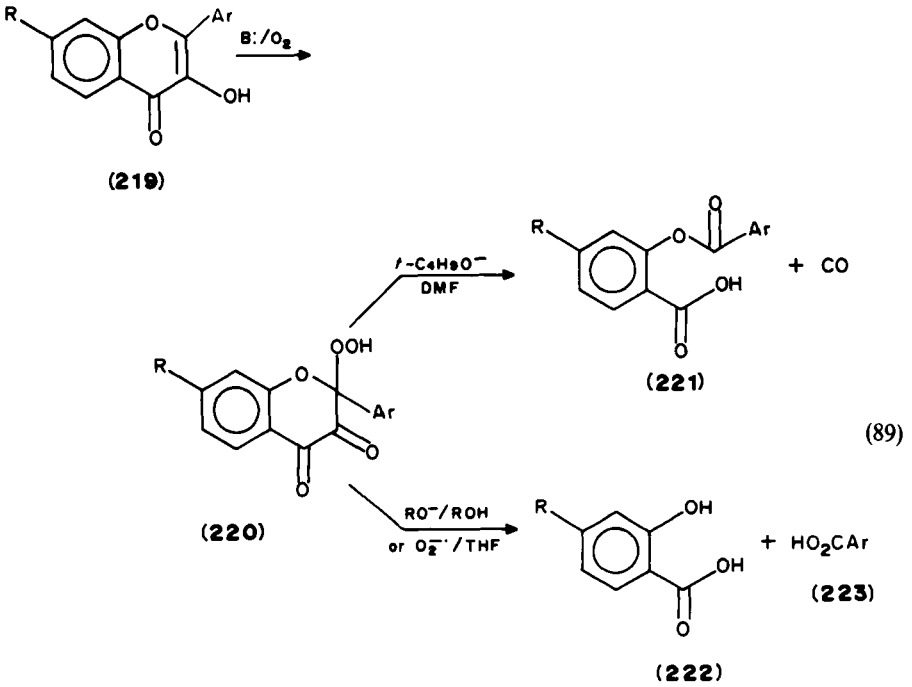


(88)

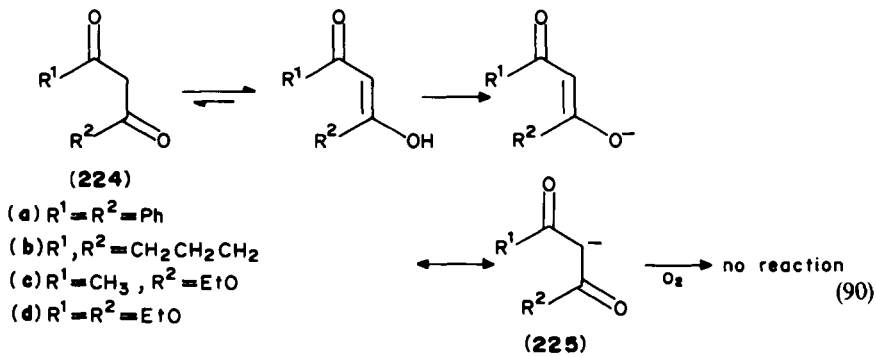
Related to the steroidal diosphenols are the 3-hydroxyflavones **219** whose biological role and reactions will be discussed in Section III.F.2. This class of compounds undergoes rapid *t*-butoxide mediated BCA in DMF or DMSO yielding depside **221** and carbon monoxide[62,63,65]. In protic media (H_2O–NaOH or MeOH–MeONa) or in the case of superoxide mediated BCA[180,184,185] the oxidation proceeds slowly to give a mixture of the depside **221** and its solvolysis products **222** and **223** (equation 89).

c. Miscellaneous. We have cited above (Section III.D.2.b) that the radical autoxidation of acyclic 1,3-diketones with a tertiary C_2-carbon yields the corresponding 2-hydroxyperoxy-1,3-diones[107]. Interestingly, although dibenzoylmethane (**224a**), 1,3-cyclohexadione (**224b**), ethyl acetoacetate (**224c**) and diethyl malonate (**224d**) are all easily deprotonated by a variety of bases (including superoxide anion), the resulting diketo carbanions **225** are stable to oxygenation[171,203–207] (equation 90). A similar resistance to

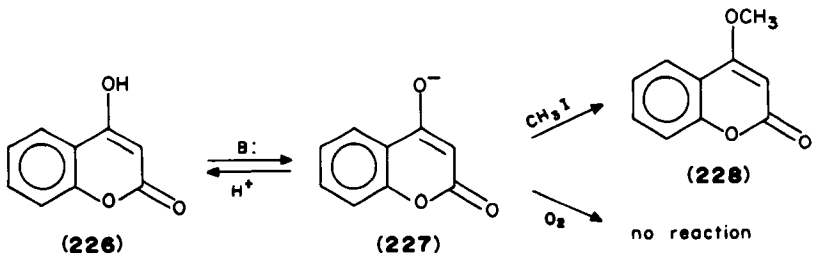
BCA ($O_2^{-\cdot}$ and t-$C_4H_7O^-$ mediated) has been recently reported by Frimer's groups[68,208] for 4-hydroxycoumarin **226**. Deprotonation was verified by methylating the oxyanions **227** with CH_3I (equation 91).



(89)

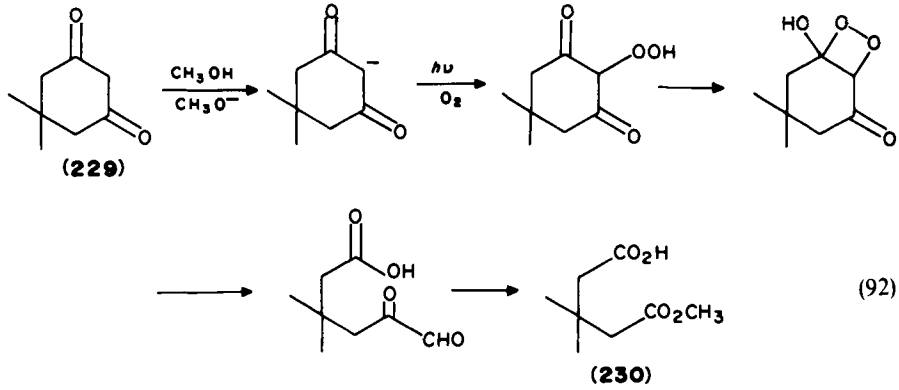


(90)



(91)

Nevertheless, as in the radical autoxidation case, once the C_2-atom is alkylated or arylated it is susceptible to oxygenation[103,206,207]. Thus, diethyl 2-methyl-, 2-ethyl- and 2-phenylmalonate all yield products resulting from initial hydroperoxidation at C_2. Furthermore, Young reports[209] that the unsensitized photooxidation of dimedone **229** in basic solution leads to a mixture of products from which one can isolate the monomethyl ester of glutamic acid **230**. A likely mechanism is outlined in equation 92.

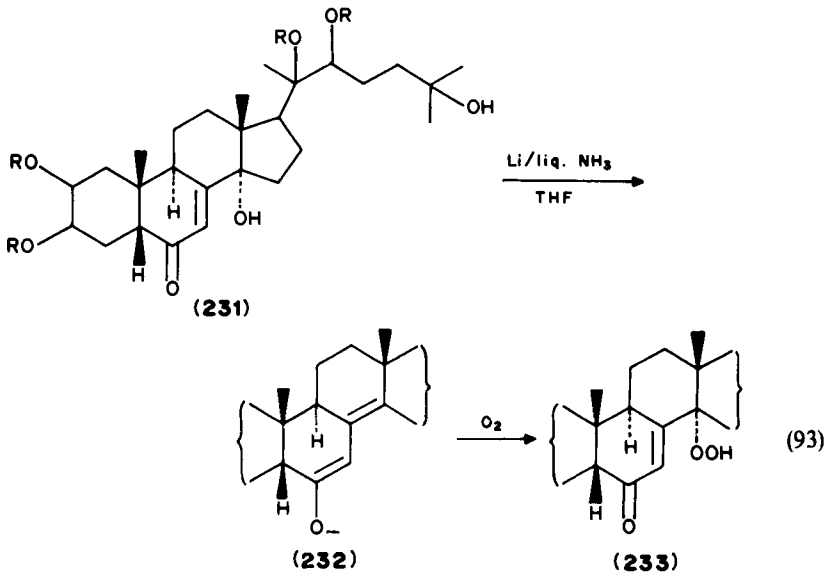


(92)

Canonica and colleagues[210] find that 14-hydroxy-7-en-6-keto steroid **231** is converted to the corresponding 14α-hydroperoxide **233** under reductive elimination conditions (lithium metal in liquid ammonia–THF) without the rigorous exclusion of O_2 during workup. These authors suggest that oxygenation proceeds via the BCA of a dienolate anion **232** resulting from the elimination of the C-4 alkoxide group, as outlined in equation 93.

4. *Hydroperoxidation of β,γ-enones*

In contradistinction to the sluggish reaction of α,β-enones, the BCA of β,γ-enones is a very facile process. Of the latter group, the Δ^5-3-ketosteroidal system has been the most actively investigated (Table 3 and Scheme 15). In aqueous ethanol, Na_2O_2-mediated BCA of Δ^5-cholestenone (**100a**)[211] yields Δ^4-3,6-dione **105**. In *t*-butanol[174], on the other hand, the *t*-butoxide mediated oxidation of Δ^5-cholesten-3-one yields dienol **212** in a 10% yield. Stern[212,213] studied this same BCA in toluene using *t*-butoxide at −78 °C and superoxide at 0 °C. At the lower temperature, α-oxygenation product **215** is formed exclusively, while γ-products **103** and **104** predominate for the latter conditions. [We have already had the opportunity to speculate whether γ-oxidation products result directly from γ-oxygenation



(93)

of enolate **210**γ or perhaps indirectly from α-oxygenation via a 1,3-hydroperoxide shift (Section III.C.5).]

$\Delta^{5(10)}$- and $\Delta^{5(10),9(11)}$-19-nor-steroids are oxidized in high yield at C-10 and C-11 respectively[214–216]. Interestingly, bases as weak as pyridine or Et_3N suffice to effect BCA. Two examples are shown below.

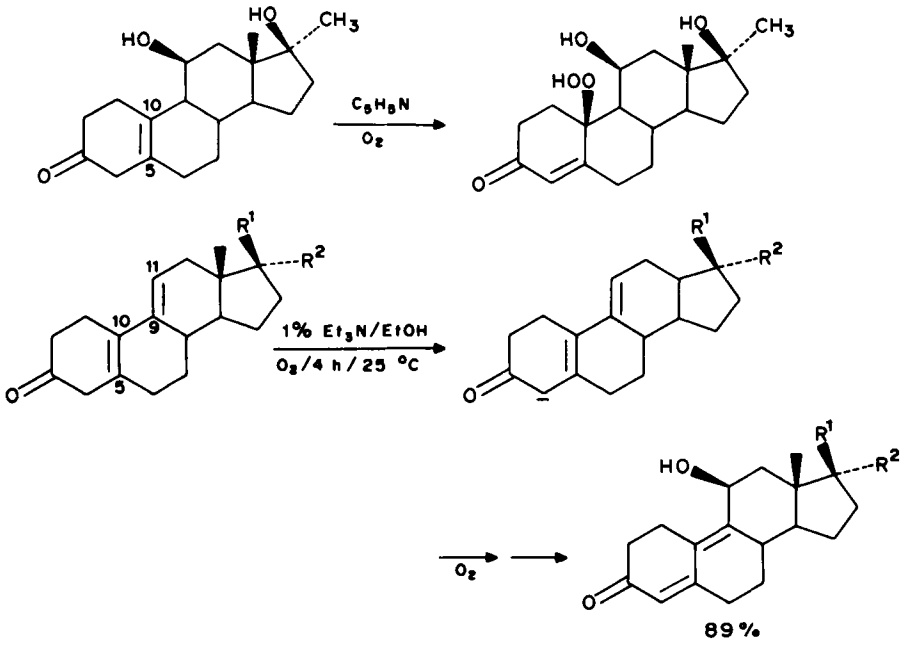
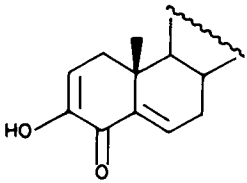
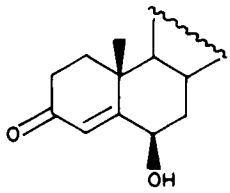
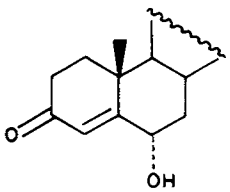
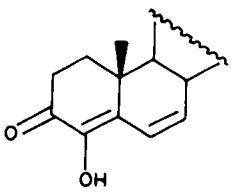
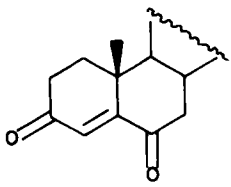
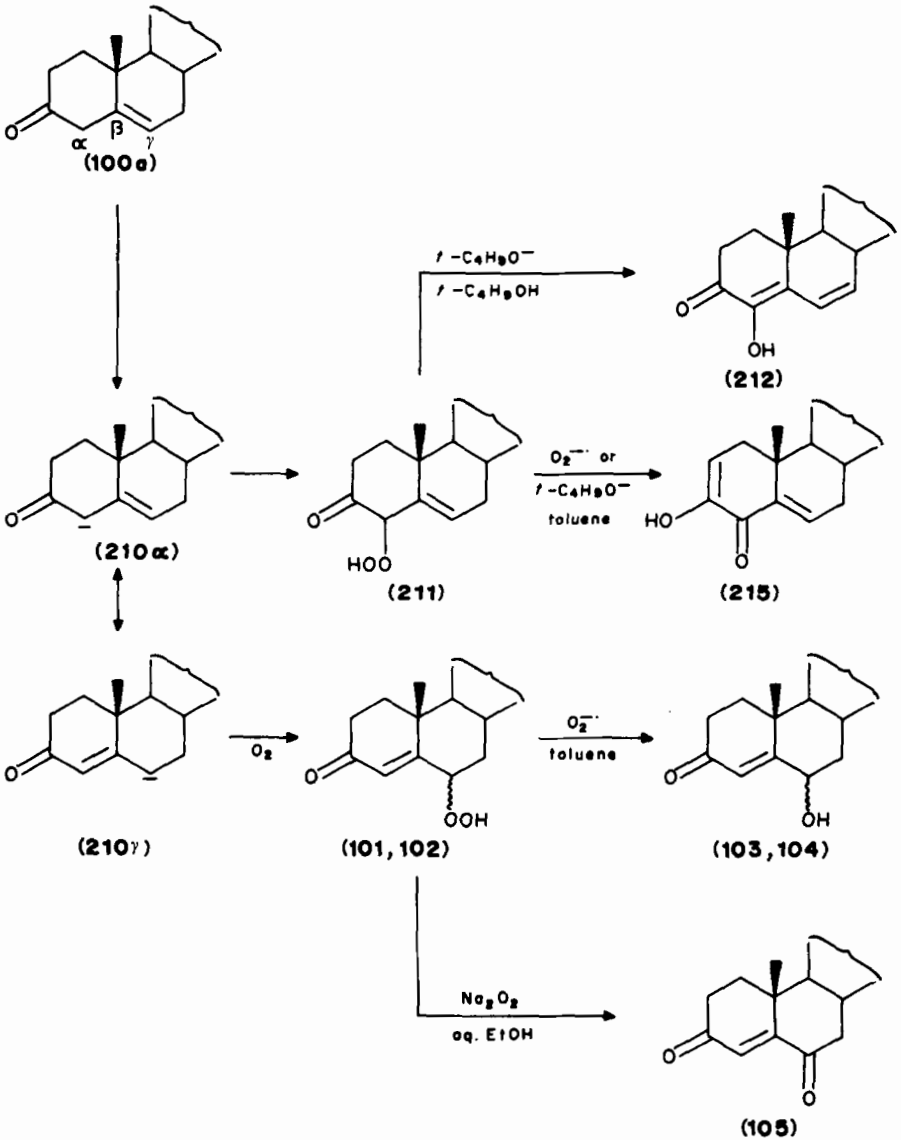


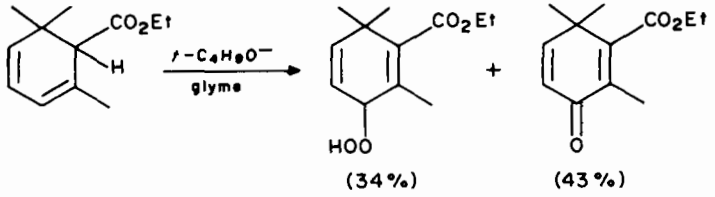
TABLE 3. Product yields in the base-catalyzed autoxidation of Δ^5-cholestenone

Base: *Solvent*: *Temperature* (°C): *Time* (h):		Na_2O_2 aq. ethanol 25 2	*t*-butoxide *t*-butanol 25 1.5	*t*-butoxide toluene −78 1	superoxide toluene 0 0.75
	**215**	—	—	100%	31%
	**104**	—	—	—	36%
	**103**	—	—	—	25%
	**212**	—	10%	—	—
	**105**	20%	—	—	—
Reference:		211	174	212	212



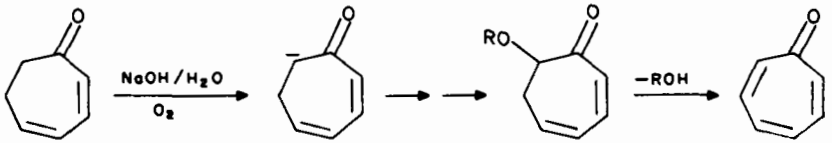
SCHEME 15. Mechanism for product formation in the BCA of Δ^5-cholesten-3-one (**100a**)

We have already noted above that β,γ-unsaturated ester **50** yields the corresponding γ-oxidation product (equation 67). Similarly, α-safranate undergoes facile *t*-butoxide mediated BCA in glyme to yield a divinyl methylhydroperoxide and its corresponding dehydration product[217].



5. Double-bond formation and aromatization

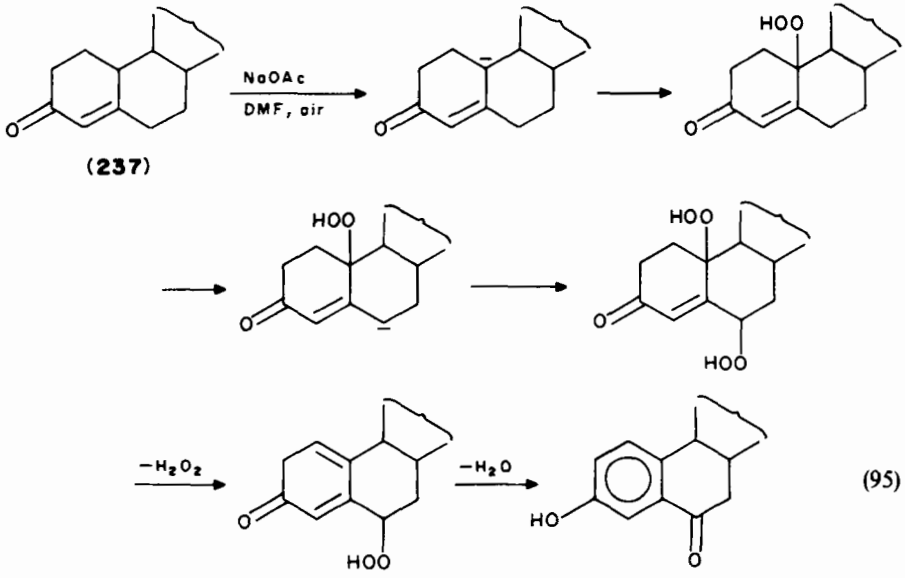
An interesting variation on the theme of hydroperoxidation is the subsequent elimination of H_2O_2 (or H_2O) from the oxidized product. We have already seen this process previously, in the case of the free radical autoxidation of epi-α-cyperone **51** (equation 34). The driving force for the elimination is the formation of a conjugated trienone system. Similarly, 2,4-cycloheptadienone (**234**) upon BCA yields tropone (**236**), presumably via hydroperoxide **235a** or alcohol **235b** (equation 94)[218].



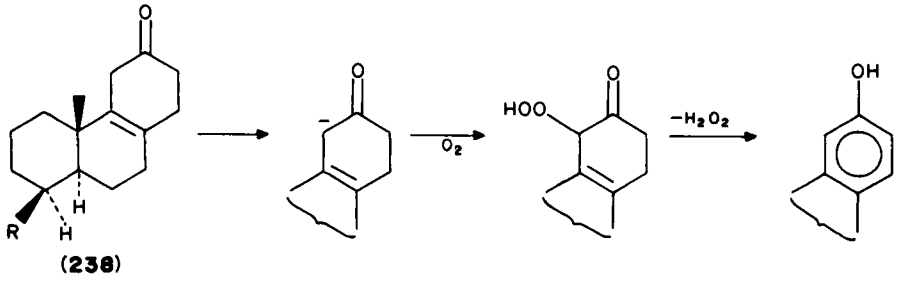
(94)

(234) (235) (235)(a) R=OH (236)
(b) R=H

In the case of enones **237** and **238** the final products are the corresponding phenols[219]. Plausible mechanisms (not necessarily those suggested by the authors) are outlined in equations 95 and 96.



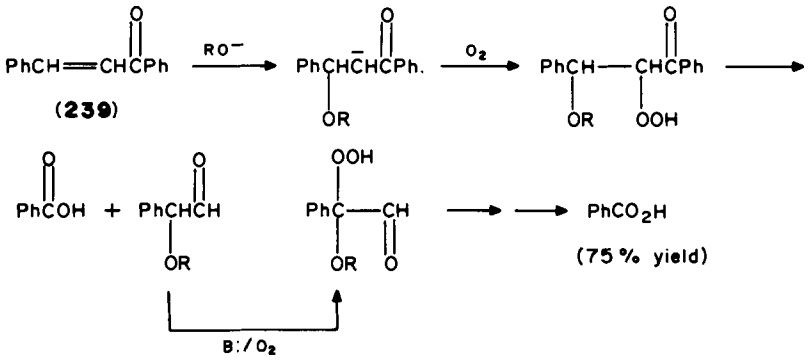
(95)



(96)

6. Addition-initiated oxidation

There are several examples in the literature where a BCA process is initiated by Michael addition of the base to an enone system. The resulting enolates are then oxidized α to the carbonyl generating α-hydroperoxy carbonyl compounds which, as we have seen (Section III.C.4), are quite labile and often undergo oxidative cleavage. In one of the earliest investigations of addition-initiated autoxidations, Doering and Haines[171] oxidized dypnone, benzalacetophenone and benzpinacolone in *t*-butanol containing *t*-butoxide by shaking with oxygen at a pressure of two atmospheres. Oxidative cleavage was observed in each case yielding respectively benzoic acid (38%), benzoic acid (75%) and pivalic acid (55%). However, dypnone which bears an acidic γ hydrogen was oxidized very much faster than the other two, suggesting that it undergoes a normal BCA process, while the others follow a different autoxidative pathway. The addition-initiated process suggested in the case of benzalacetophenone (**239**) is outlined in equation 97.

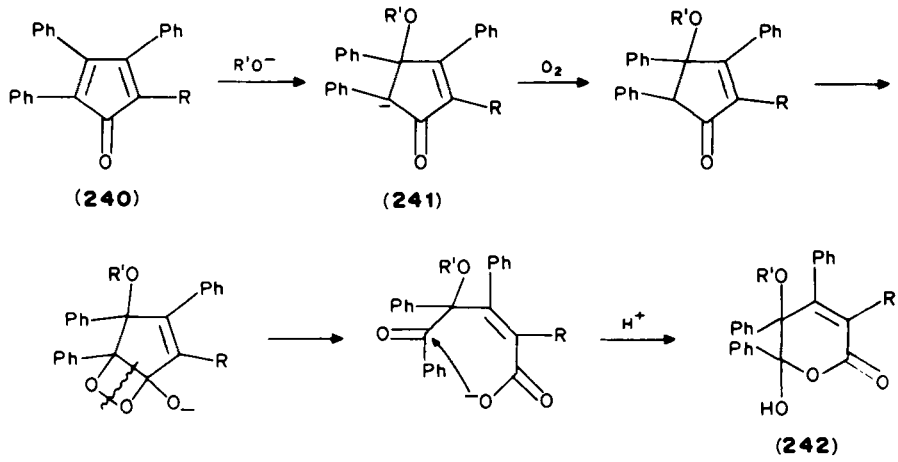


(97)

Muckensturm[220] also found that even though they lack acidic hydrogens, cyclopentadienones (cyclones, **240**) can be autoxidized under basic conditions. The mechanism of this process (equation 98) involves initial Michael addition of base, giving a carbanion **241** which is oxygenated ultimately yielding lactol **242** (equation 98).

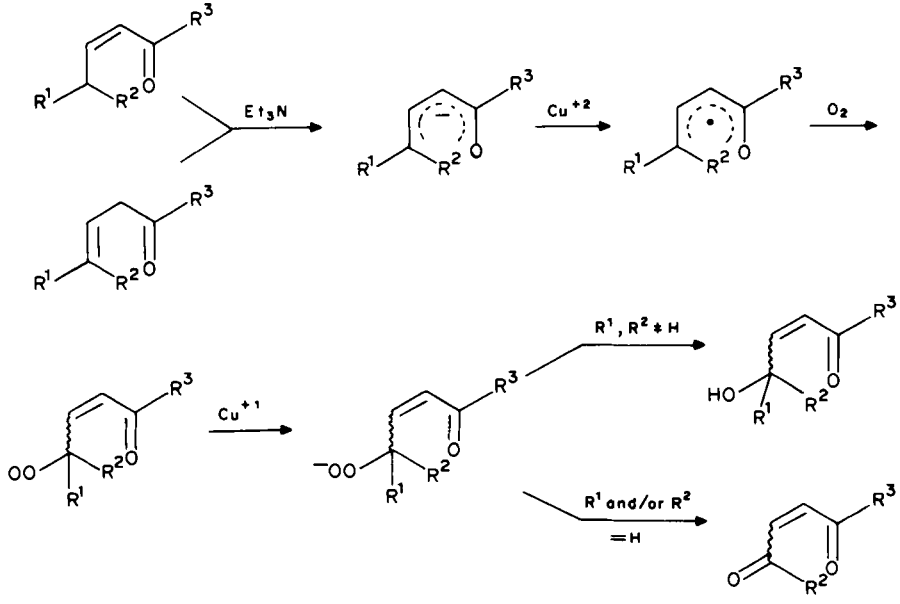
7. Copper(II)-base catalyzed autoxidations

One major drawback of base-catalyzed autoxidations is that they generally require quite vigorous conditions to effect deprotonation and oxidation. Mild bases such as triethylamine can effect equilibration between β,γ- and α,β-unsaturated carbonyl



(98)

compounds[221], but little if any oxidation is observed. Volger and coworkers[222–224] have found, however, that the oxidation of α,β- and β,γ-unsaturated aldehydes and ketones, capable of forming a conjugated dienol, can be effected in mildly alkaline methanolic solutions containing triethylamine and catalytic amounts of cupric-pyridine complexes. A



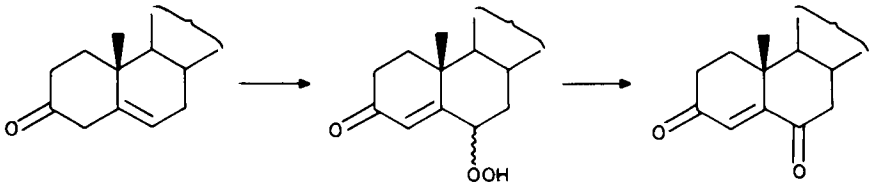
SCHEME 16. General mechanism for autoxidation in the cupric–pyridine–triethylamine–methanol system

variety of enones were investigated and the order of decreasing reactivity is:

Δ^5-cholestenone (**100a**) > 5-methyl-4-hexen-2-one (**252**) > isomesityl oxide (**247**) > crotonaldehyde (**243**) > tiglaldehyde > dypnone (**246**) > mesityl oxide $\approx \Delta^4$-cholestenone (**54**) $\approx$ 5-methyl-3-hexen-2-one (**45a**, inert).

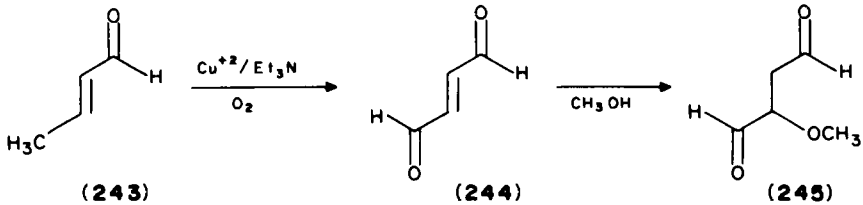
Saturated aldehydes and ketones, as well as acrolein, methacrolein, benzaldehyde, cinnamaldehyde, sorbic aldehyde and methyl vinyl ketone are essentially unreactive. The above order demonstrates that the rate of oxygenation corresponds to the ease of deprotonation generating the extended dienolate. As noted above, this is more facile with β,γ-enones than with their α,β-conjugated analogs. The role of the cupric ion then, is to oxidize the resulting dienolate anion to the corresponding radical, thereby catalyzing oxygenation, as outlined in Scheme 16.

The products obtained in each case indicate specific oxidation of the γ-carbon and can be rationalized in terms of an almost exclusive formation of a γ-hydroperoxy-α,β-unsaturated carbonyl compound. Thus Δ^5-cholestenone gave a 75% yield of the corresponding Δ^4-3,6-dione within ten minutes (equation 99). Similarly, crotonaldehyde **243** was oxidized to the corresponding dialdehyde **244**, which was solvolyzed in turn to methoxysuccinaldehyde **245** (62% yield) (equation 100).



(100a) (101,102) (105)

(99)



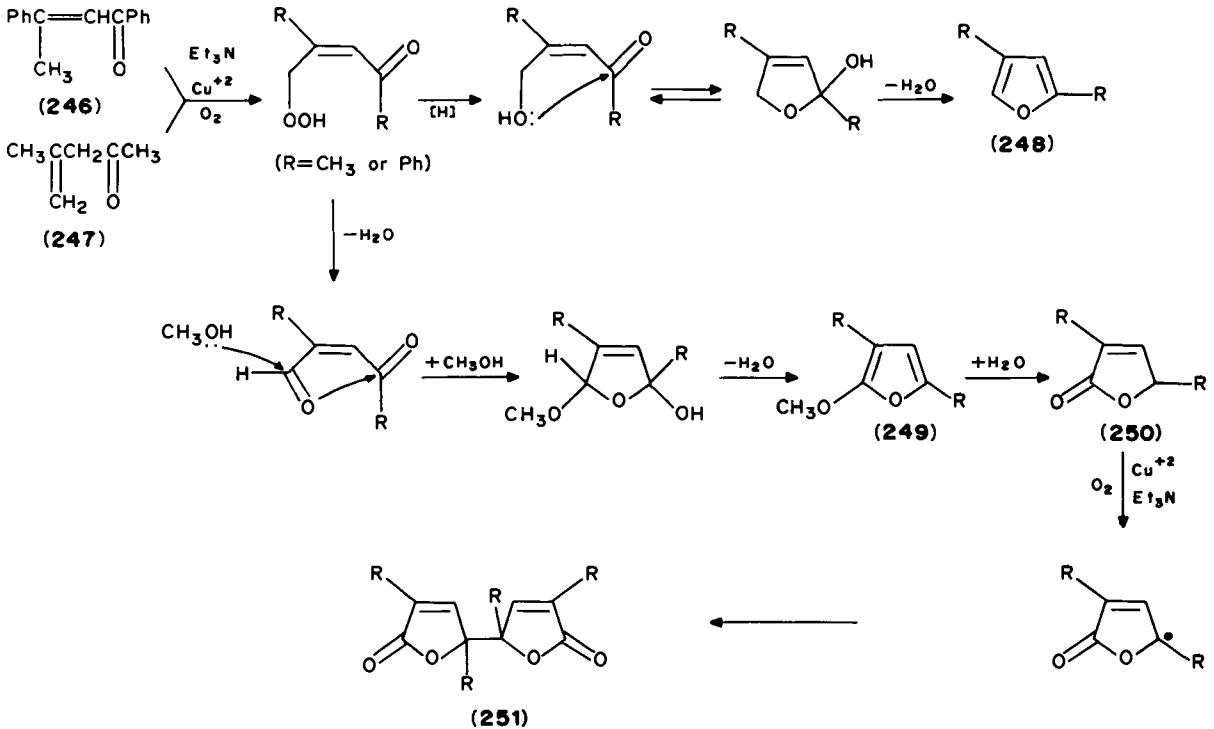
(243) (244) (245)

(100)

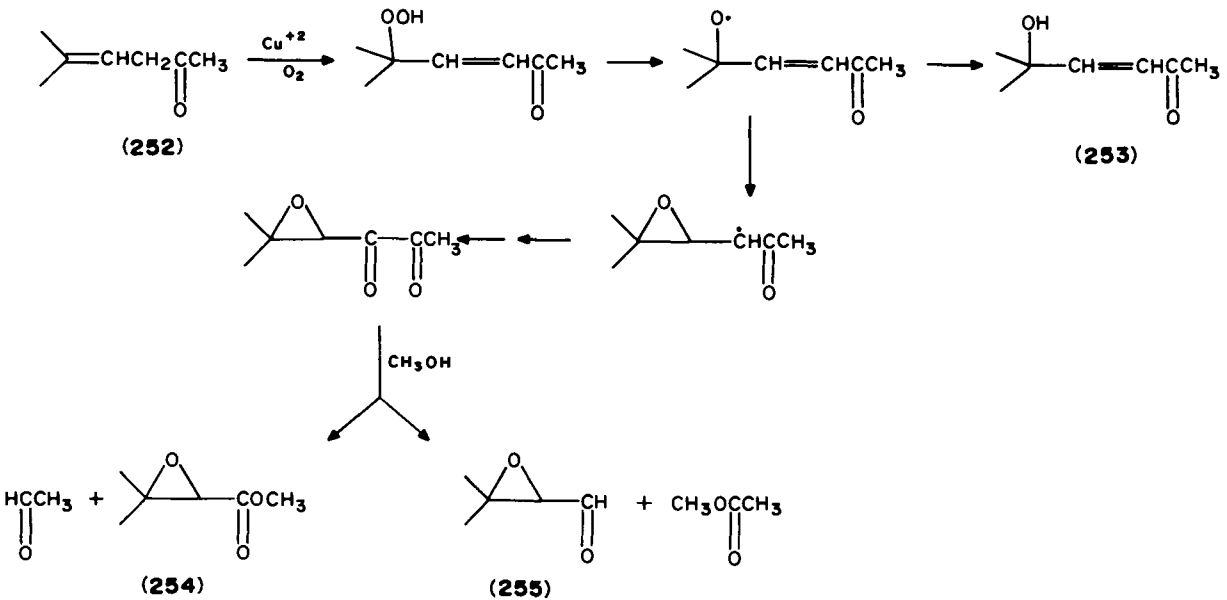
The oxidation sequence in the case of dypnone **246** and isomesityl oxide **247** involves not only alkaline oxidative cleavage but solvolysis, cyclization and dimerization as outlined in Scheme 17. Finally, 5-methyl-4-hexen-2-one **252** yields not only the expected γ-alcohol **253** but also epoxyester **254** and epoxyaldehyde **255**. The proposed mechanism for this reaction is outlined in Scheme 18. This scheme invokes a methanolysis of a diketone to an ester and an aldehyde, a precedented process[225].

F. Biological Oxidations

The field of biological oxidations has been encyclopedically reviewed recently[226–230] with the major emphasis on steroids and polyunsaturated fatty acids. A survey of the



SCHEME 17. Proposed mechanism for the formation of products **248–251** in the Cu^{+2}-catalyzed BCA of dypnone **246** and of isomesityl oxide **247**



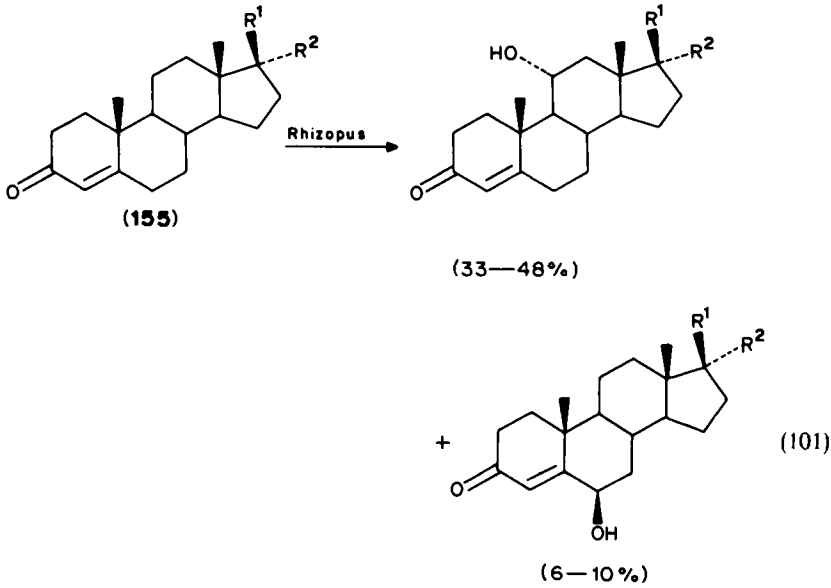
SCHEME 18. Mechanism for product formation in the cupric-cation-base catalyzed autoxidation of 5-methyl-4-hexen-2-one **252**

plethora of enone systems investigated is beyond the scope of this review. For the purpose of comparison we will highlight several of the systems discussed elsewhere in this review, namely steroids, cyclohexenones, flavones and chalcones.

1. 3-Oxosteroids and cyclohexenones

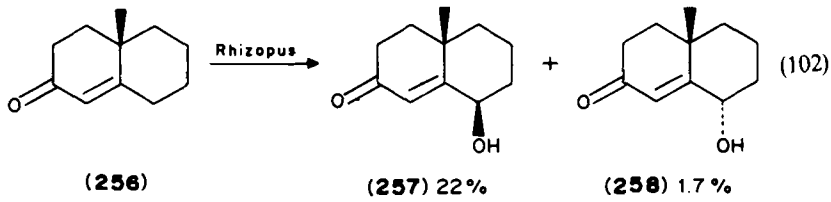
a. Microbial hydroxylation. The microbial oxygenation of Δ^4-3-oxosteroids[226-236] results in hydroxylation at C-2β, C-6β, C-11α, C-16α (carbonyl at C-17), C-17α (carbonyl at C-20) and C-21 (carbonyl at C-20). It has been clearly established that these are reactions which involve the direct incorporation of molecular oxygen, but are generally not simple free radical autoxidations. On the contrary, they seem to involve the electrophilic attack of a positively charged hydroxylating species (perhaps HO^+) upon an enol or enolate species. Several representative examples follow.

Aspergillus niger effects the C-21 hydroxylation of progesterone[234], while the oxidation of 17-methyltestosterone, testosterone and 4-androstene-3, 17-dione by various species of the fungi *Rhizopus* yields the 11α- and the 6β-hydroxy analogs in a ratio of approximately 4:1 (equation 101).



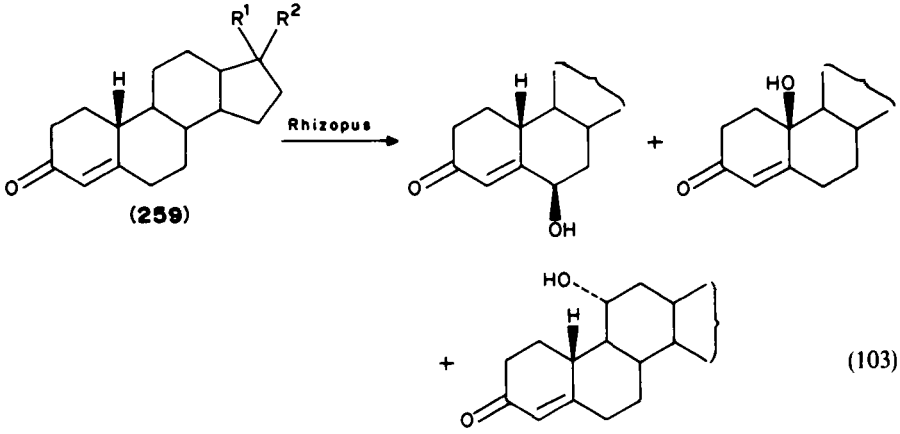
(101)

By comparison, the related hexahydronaphthalenone **256** undergoes oxygenation[235] solely at the C-6 carbon (using the steroidal numering system) with the β-epimer **257** predominating over the α (**258**) by a ratio of 13:1 (equation 102).



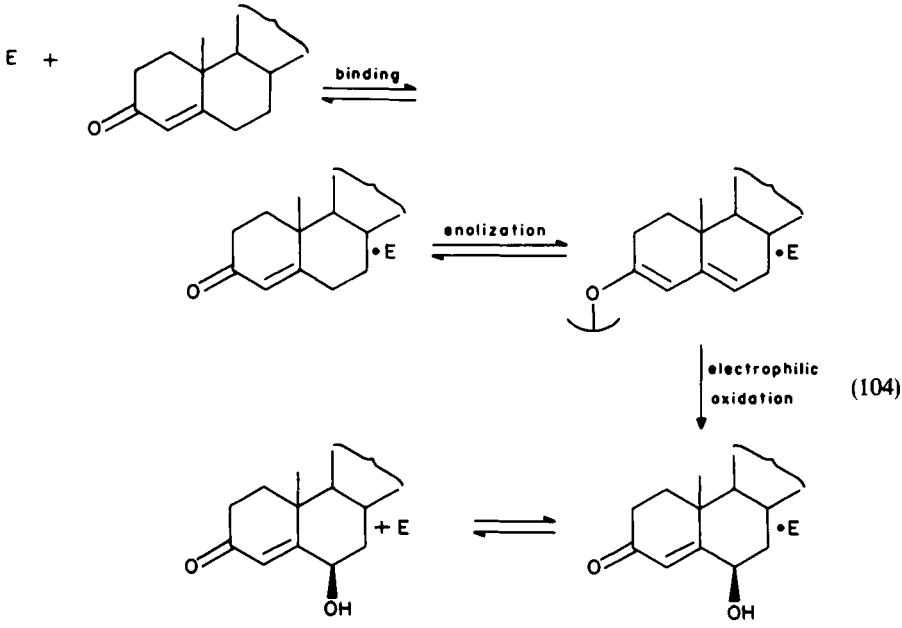
(102)

In the case of 19-nor-Δ^4-3-ketosteroids (**259**) microbial hydroxylation generally occurs at C-6β, C-10β and C-11α (equation 103)[235].



(103)

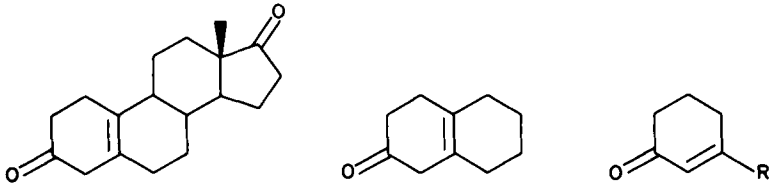
The C-21 hydroxylation of progesterone by *A. niger* has been shown to involve a direct insertion of an oxygen atom into the C—H bond[234]. This is also the mechanism observed for hydroxylations at saturated carbon (e.g. C-11) not adjacent or vinylogous to carbonyl moieties. The available data[226–236] confirm the suggestion that the hydroxylations at C-2, C-6 and C-17 of progesterone proceed via the aforementioned electrophilic attack of a positively charged hydroxylating species (perhaps HO^+) which is activated by enolization at these positions. A proposed mechanism for C_6-hydroxylation of Δ^4-3-ketosteroids is outlined in equation 104.



(104)

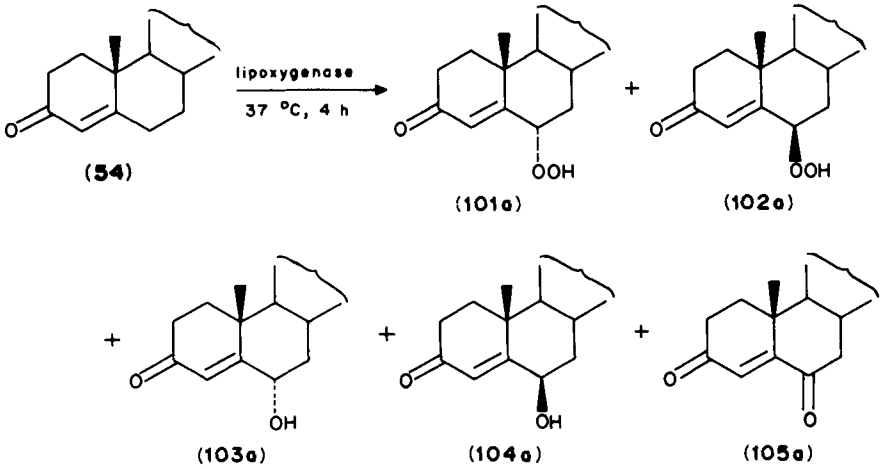
$\Delta^{5(6)}$-3-ketosteroids have also been reacted with *Rhizopus* species to yield the rearranged Δ^4-analog; hydroxylation at C-6β, C-6α and C-11α, as well as ketone formation at C-6[236]. The formation of the C-6α hydroxylated and ketonic products, unknown in other microbial oxidations but observed in the absence of fungus, as well as other evidence, suggests[236] that in this instance enzymic and non-enzymic processes are competing. Furthermore, the first step in the enzymic process involves isomerization of the Δ^5- to the isomeric Δ^4-steroid.

Interestingly, 19-nor-$\Delta^{5(10)}$-3-ketosteroid **260** as well as enones **261** and **262** are unreactive when incubated with *Rhizopus* species[235].



(260) (261) (262)

b. Lipoxygenase oxidation. Teng and Smith[237] report that soybean lipoxygenase oxidation of Δ^4-cholesten-3-one (**54**) yields a mixture of the corresponding 6α- and 6β-hydroperoxides **101** and **102**, 6α- and 6β-alcohols **103** and **104** and the 3,6-dione **105** (equation 105). The ratio of **101**:**102**:(**103** + **104**):**105** at pH 9.0 is 10:20:3:1.



(105)

The evidence indicates that hydroperoxides **101** and **102** are the primary products, which are then thermally decomposed to alcohol and ketone derivatives **103**–**105**.

Interestingly, these authors further report that the interconversion of **101** and **102** occurred on storage of the solid sample and in organic solvent solutions. Epimerization of the quasiaxial **102** to the quasiequatorial **101** was favored over the reverse epimerization, which also occurred but to a lesser extent. This epimerization undoubtedly proceeds via the aforementioned β-cleavage process described above (Section III.C.5). For **101** the prominent mode of transformation is dehydration to **105**.

c. Horseradish peroxidase. 6β-Hydroperoxyprogesterone (**102d**) and 6β-hydroperoxyandrostenedione (**102c**) were biochemically synthesized from the corresponding Δ^5-3-ketosteroids (**100**) by using horseradish peroxidase or bovine adrenal mitochondria as the enzyme source[132] (see equation 47). Hydroperoxide **102d** is further metabolized in the adrenals to 6-keto (**105d**) and 6β-hydroxyprogesterone (**103d**).

2. 3-Hydroxyflavones

The flavonol quercetin (5,7,3',4'-tetrahydroxyflavone, **263** R = H) is present in the leaves and flowers of higher plants as the 3-*O*-glycoside rutin which contributes a cream pigmentation. Rutin is aerobically degraded to carbon monoxide and water-soluble products by extracellular enzymes from *Aspergillus* and *Pullularia* species[65,238,239]. Rutin is first hydrolyzed to rutinose and quercetin and the latter is then oxidatively decarbonylated by the action of the dioxygenase quercetinase to give carbon monoxide and depside **266**. In the last step, the depside is hydrolyzed to 2,4,6-trihydroxybenzoic acid **267** and protocatechuic acid **268**. The likely mechanism is outlined in Scheme 19, path a (cf. end of Section III.E.3.b and Section IV.C.2). This mechanism involves endoperoxides **265** and is supported by tracer experiments which reveal that the carbon monoxide expelled stems from C-3, and that an oxygen molecule is incorporated into depside **266** and its hydrolyzed products but not into carbon monoxide. These data rule out the intermediacy of dioxetane **269** (Scheme 19, path b)[65,238,239].

3. Chalcones

The peroxidase-catalyzed oxidation of 4,2',4'-trihydroxychalcone **271** has also been explored extensively[240–245]. The major primary product is the corresponding dioxetane **272** which is transformed under the reaction conditions to flavonol **273** and benzoxepinone-spiro-cyclohexadienone **274** or reduced, depending on the contaminants present, to hydrated aurone **275** and dihydroflavonol **276**. The mechanism suggested for these processes is outlined in Scheme 20. Wilson and Wong[243] have demonstrated that the peroxidase-catalyzed oxidation of chalcone **271** to dioxetane **272** utilizes molecular oxygen in equimolar amounts. Although the reaction requires the presence of H_2O_2, only a catalytic net consumption occurs. Thus, the role of the peroxidase is simply to initiate the radical autoxidation of the chalcone.

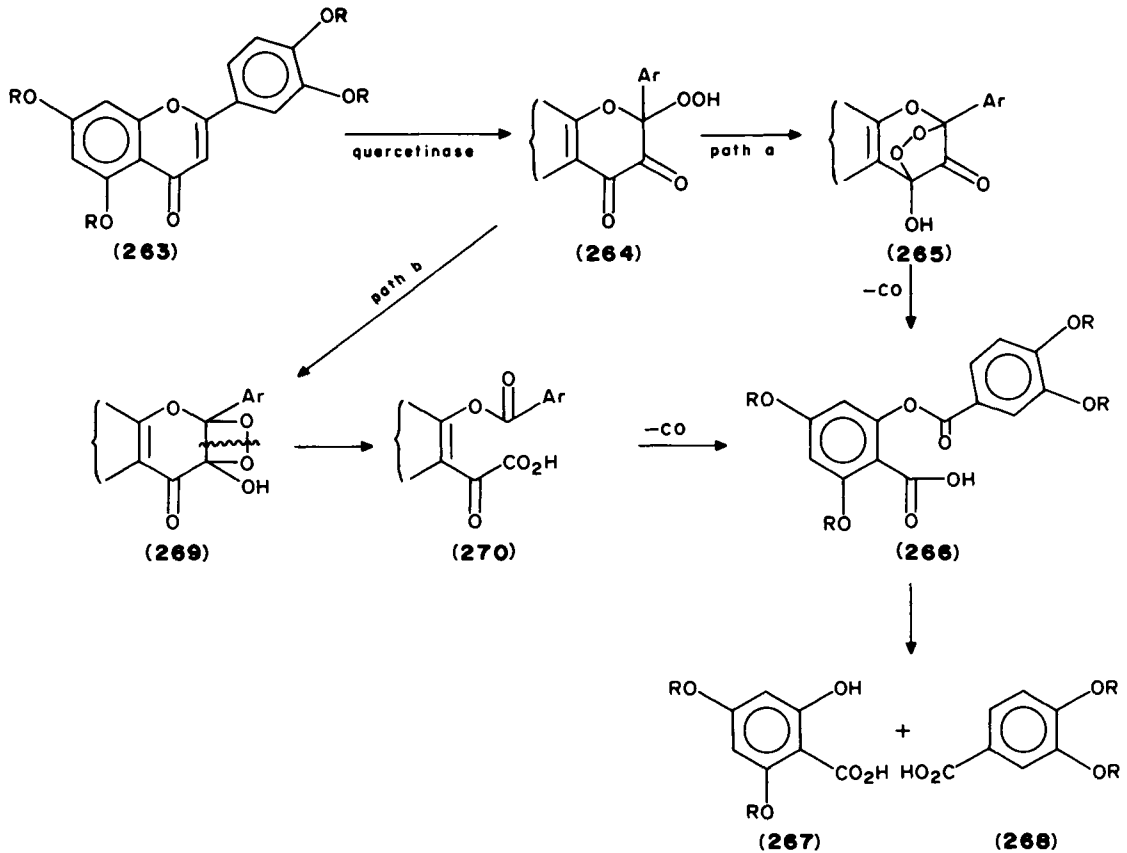
4. Tetracyclone

The soybean lipoxidase-mediated oxygenation of tetraphenylcyclopentadienone (tetracyclone) yields a benzoylfuranone[246], presumably via the oxidative cleavage outlined in equation 106, path a, and not *cis*-dibenzoylstilbene as earlier suggested (equation 106, path b)[247].

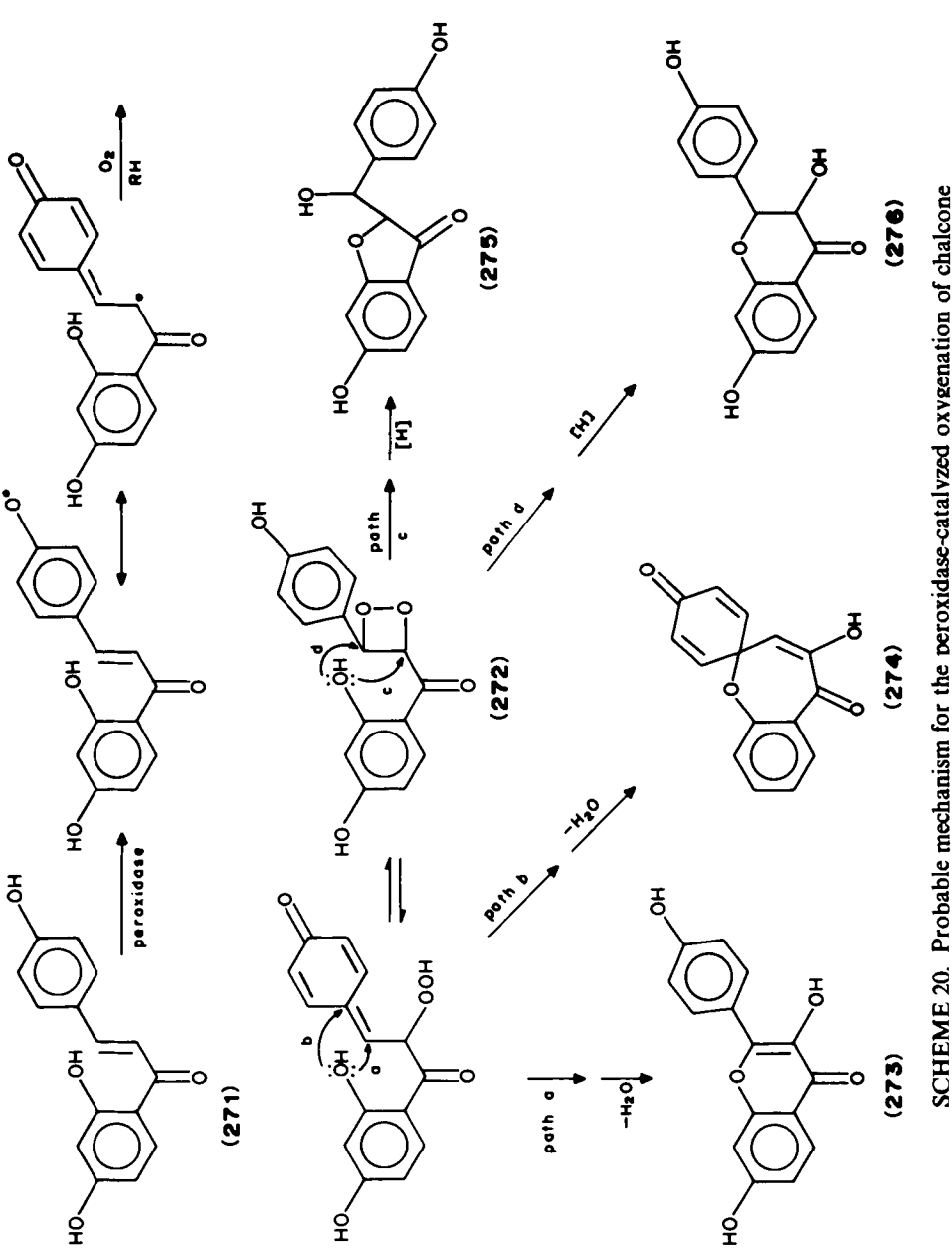
G. Miscellaneous Oxygenations

1. ^{60}Co initiated

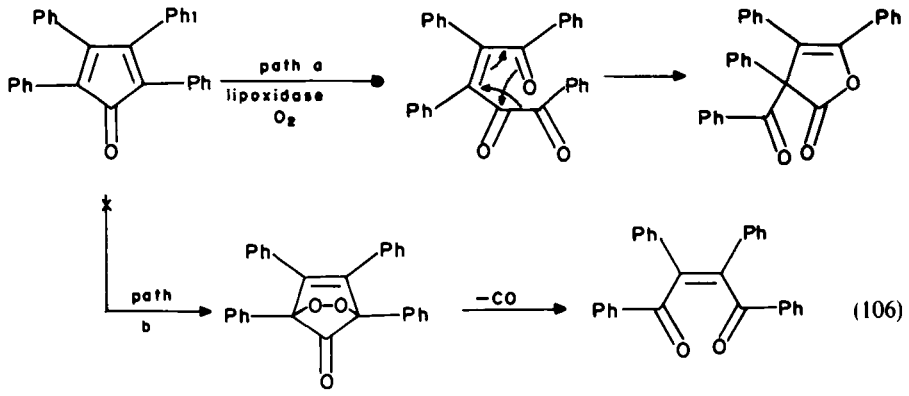
Δ^4-cholesten-3-one **54** remains unaffected by ^{60}Co gamma irradiation[92]. We have, however, seen that this steroid is susceptible to lipoxygenase-mediated oxidation (Section III.F.1.b)[237]. The differential behaviour of the ketone in the two systems may be understood if we assume that the enolization of **54** to 3,5-cholestadien-3-ol (**124**; see



SCHEME 19. Proposed mechanism for the biological oxygenation of 3-hydroxyflavones



SCHEME 20. Probable mechanism for the peroxidase-catalyzed oxygenation of chalcone



(106)

equation 52), the likely active steroid intermediate, is more facile in aqueous-buffered enzyme systems than in the solid state[237].

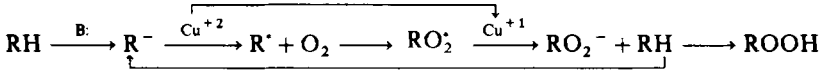
The autoxidation of Δ^5 cholesten-3-one **100a** is initiated by ^{60}Co gamma irradiation. Δ^4-3,6-Dione **105** is the only product formed, presumably as a dehydration product of isomeric hydroperoxides **101** and **102**[92] (see equation 47).

2. *Pt catalyzed*

While Δ^4-cholestenone **54** resists platinum-catalyzed oxidation, Δ^5-analog **100a** is converted to **54** (2%), alcohols **103** (18%) and **104** (20%) as well as dione **105** (29%)[248]. As in other oxidations of **100**, **103–105** are presumed to result from hydroperoxides **101** and **102**. This process is assumed to be a free radical type autoxidation initiated by the platinum catalyst[248].

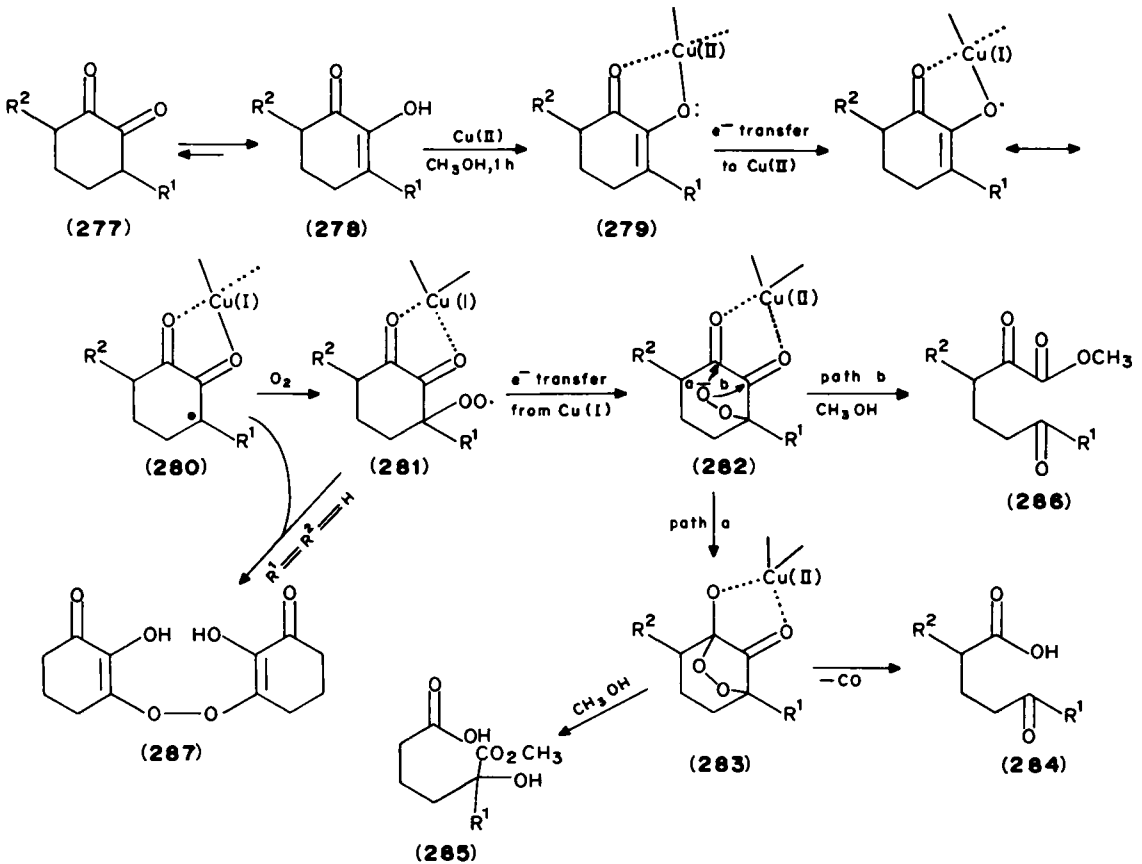
3. *Cu catalyzed*

We have already mentioned above the catalytic role copper(II) ions play in the base-catalyzed autoxidation of various enones (Section III.E.7). In such cases the metal ion serves both as an electron acceptor, facilitating the oxygenation of the carbanion, and later as an electron donor to convert the peroxy radical to a peroxyanion (equation 107).



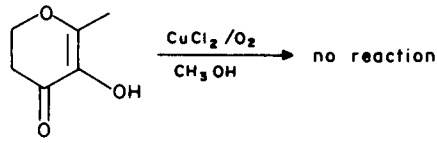
(107)

a. 2-Hydroxy-2-en-1-ones. Cu(II) salts are also effective in mediating the oxidation of 2-hydroxy-2-en-1-ones under neutral conditions[71,249]. Thus 1,2-cyclohexanediones **277**, which exist primarily in the keto enol form **278**, were rapidly (~ 1 h) oxygenated with the aid of $CuCl_2 \cdot H_2O$ in methanol affording (Scheme 21) the corresponding 1,5- keto acid **284** as the major product along with carbon monoxide, as well as smaller amounts of methyl α-hydroxyadipate (**285**), oxidative cleavage product **286** and coupling product **287** ($R = R^1 = H$). The mechanism outlined in Scheme 21 invokes the initial formation of a Cu(II) complex **279**. The latter is in fact a copper enolate. However, as noted above (Section III.E.3.b), were this a simple BCA, the oxygenation in methanol would have taken 24 h not 1 h[180,185]. Thus, as in the case of the copper-catalyzed BCA, an electron transfer to the copper ion initiates a radical process. Oxygenation at the β-carbon, reduction of the



SCHEME 21. Copper(II)-catalyzed oxidation of 2-hydroxy-2-en-1-ones (for R^1=CH_3, R^2 = *i*-C_3H_7 the yields are **284**; 73%; **285**; 80%; **286**; 9%; and **287**; 5%)

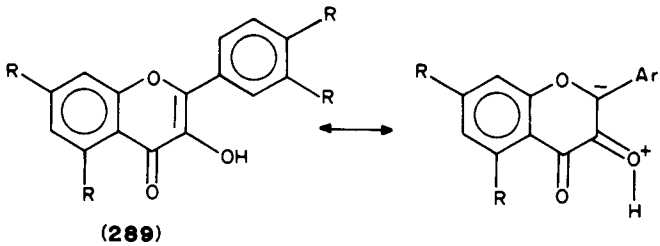
peroxy radical by Cu(I) and cyclization of **282** (Scheme 21, path a) yields endo-peroxide **283**. Loss of CO generates keto acid **284**, while methanolysis yields ester **285**. The α-keto peroxy anion **282** can also undergo oxidative cleavage (Section III.C.4) yielding **286** (Scheme 21, path b). Peroxide **287** results from the radical coupling of carbon radical **280** and peroxy radical **281**. These authors[71,249] further report that 1,2-cyclopentanediones (2-hydroxy-2-cyclopenten-1-ones) undergo copper ion catalyzed oxygenation in a similar way. 2-Hydroxy-2-methyl-4-pyrone (maltol, **288**, equation 108) is unreactive. This inertness appears strange since, as we shall see below, 3-hydroxyflavones which share the pyrone structure are reactive, though via a mechanism different from that of the aforementioned diones.



(108)

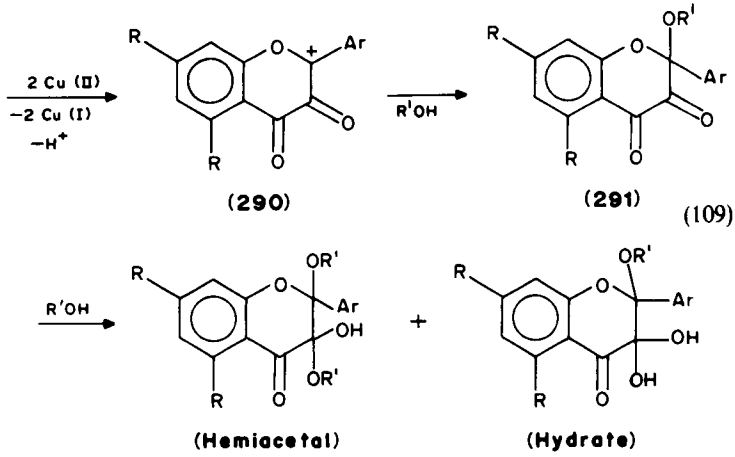
(288)

b. 3-Hydroxyflavones. In the case of 3-hydroxyflavones **289**, oxygenation occurs quite slowly to yield the corresponding 2-alkoxyflavan-3, 4-diones **291** which are isolated in methanol as hemiacetals or hydrates (equation 109)[250]. One mole equivalent of oxygen is



(289)

(a) R=OH, (b) R=H



(290) **(291)** (109)

(Hemiacetal) **(Hydrate)**

absorbed but no carbon monoxide is expelled. The rate of reaction is extremely sensitive to the electron density of C-2; thus, for **289a** the reaction reaches completion after 10 h at 20 °C, while for **289b** 26 h at 50 °C is required. The authors invoke the intermediacy of cation **290** generated by the abstraction of two electrons from enol **289** by copper(II). The oxygen does not oxygenate the substrate directly, but rather serves to drive the reaction by reoxidizing Cu^{I} back to Cu^{II}, as outlined in equation 110.

$$2Cu^{I} + \frac{1}{2}O_2 + 2H^{+} \rightarrow 2Cu^{II} + H_2O \qquad (110)$$

Interestingly, Matsuura and colleagues[239,251] report that in aprotic media, the situation is substantially different. When a copper(II) or cobalt(II) chelate of 3-hydroxyflavone **289b** is treated with oxygen in various aprotic organic solvents (DMF, DMSO, pyridine or CH_2Cl_2), no reaction takes place. However, in the presence of excess flavone oxygenation does occur, yielding the corresponding depside **221** accompanied by carbon monoxide evolution (equation 111).

The depside **221** is also obtained in a 37% yield when the flavone is oxidized using catalytic amounts of Cu(II) acetate. Utaka and Takeda[250] report that the remaining 60% in this latter case is a lactol, formed without carbon monoxide generation. The corresponding lactol is the sole product when **289a** is the substrate (equation 111).

c. Ascorbic acid. The copper-catalyzed oxidation of vitamin C to dehydroascorbic acid has been extensively explored and does not involve a direct oxygenation of the substrate[109,252–254]. As in the case of 3-hydroxyflavone in protic media, it is Cu^{II} that oxidizes the substrate while O_2 merely cycles Cu^{I} back to Cu^{II}.

4. *Acid catalyzed*

de la Mare and Wilson[134] have carried out a thorough study of the autoxidation of Δ^5-cholesten-3-one **100a** in acetic acid. In addition to isomerization to the Δ^4-analog **54**, the oxygenation results in the formation of **103–105** in an overall product yield of 72% (equation 112).

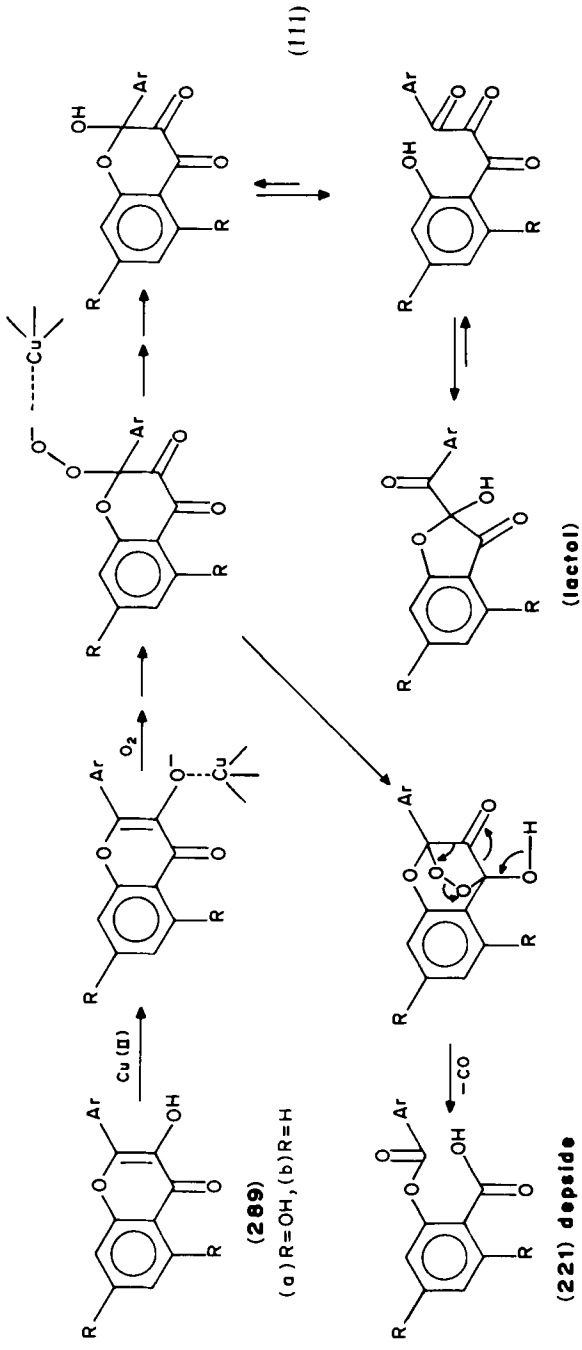
The rate of autoxidation in HOAc is fourfold faster than the accompanying isomerization and 500 times faster than the rate of radical autoxidation in CCl_4. These authors also find that this oxidation requires the presence of trace amounts of metals, is arrested by EDTA and is attenuated by radical inhibitors. Based on a variety of kinetic considerations, they conclude that the reaction proceeds via a close ion pair **292** (equation 112).

5. *Photooxidative rearrangement*

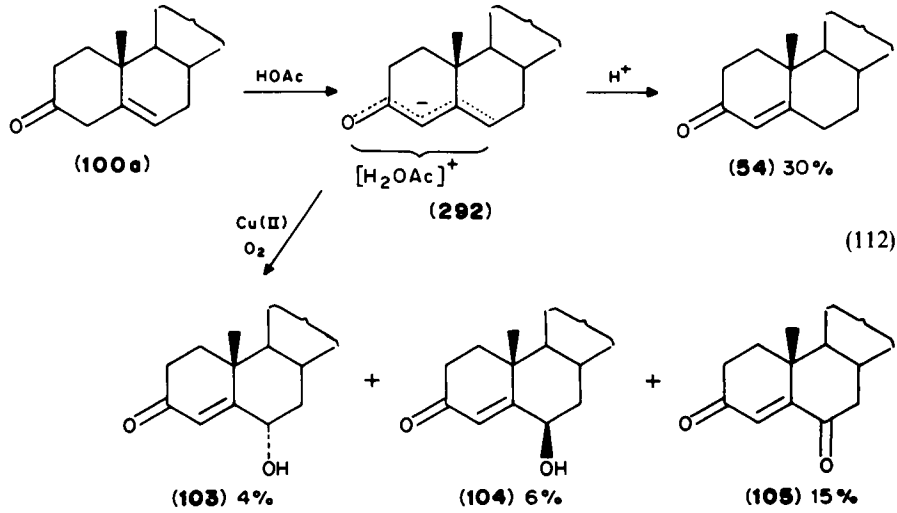
A variety of enones undergo photoinitiated oxidation, which involves photorearrangement accompanied by free radical autoxidation[60,255,256]. (Singlet oxygen is not involved in these processes.) For example, the solar irradiation of carvone (**138**) proceeds with the uptake of oxygen and produces acids **294** and **295** as the oxidative rearrangement products. These are probably formed via the intermediacy of carvonecamphor **293** (equation 113).

The direct photooxidation of menaquinones **296** produces hydroperoxide **297**. At − 30 °C under high pressure of oxygen, trioxanes **298** are isolated. The mechanism of these transformations is outlined in equation 114[257].

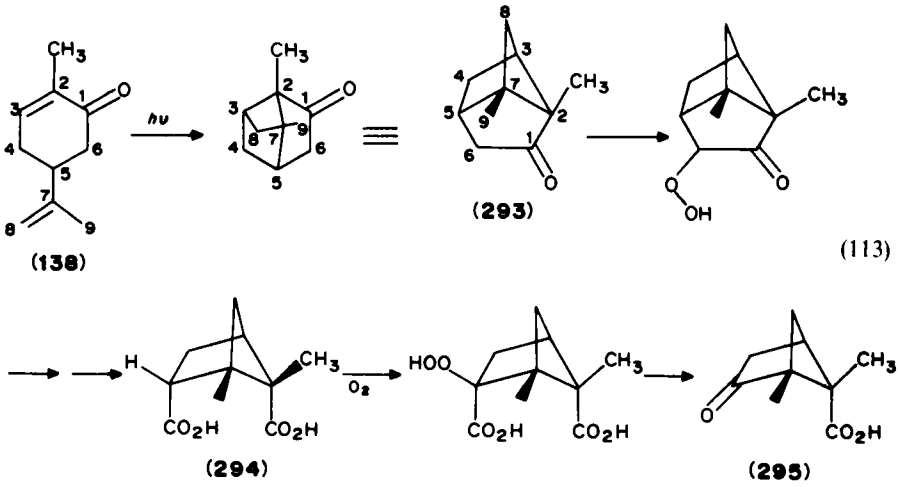
The photooxidative cyclization of 3-methoxyflavones **82** has been discussed above (Section III.D.2.a).



(111)



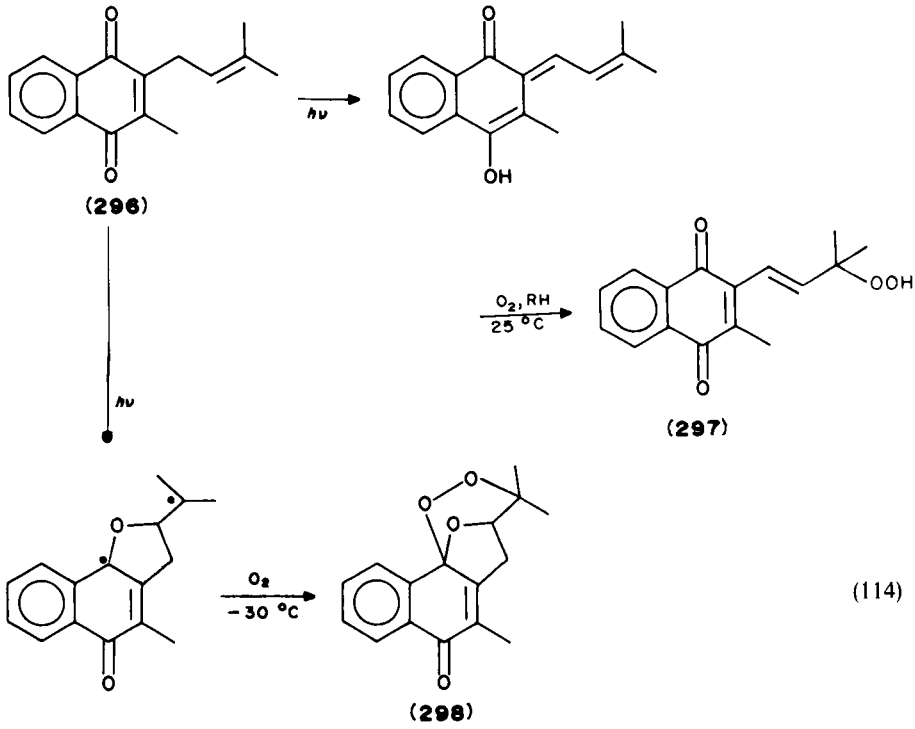
(112)



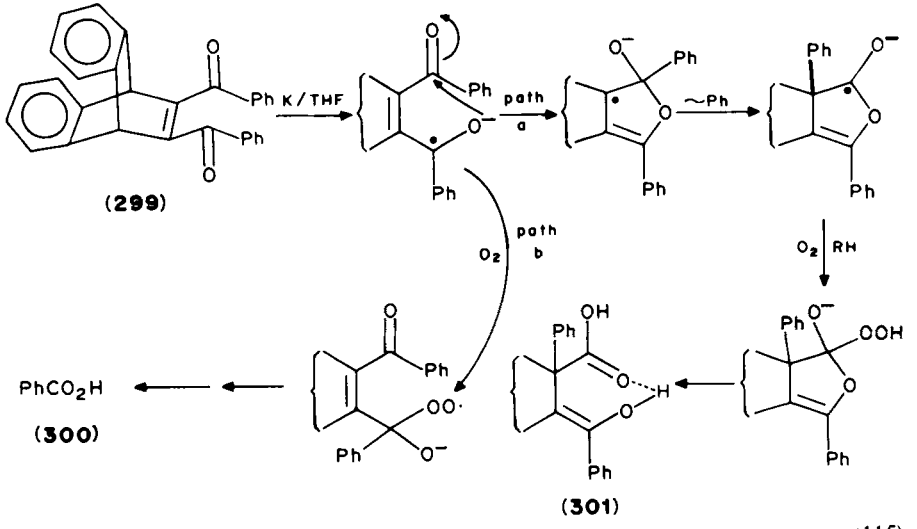
(113)

6. Reductive oxygenation

Alkali metals add to 1,2-dibenzoylalkenes to give radical anion intermediates, which subsequently undergo a variety of transformations depending on the nature of the substrate and the reaction conditions. If, for example, the reaction mixture is exposed to air, oxygenation of these radical anions can occur. Thus, when enedione **299** is reduced with potassium and then exposed to air, acids **300** and **301** are formed[258]. A plausible mechanism is outlined in equation 115.


hν
OH
(296)
O2, RH
25 °C
OOH
(297)
hν
O2
−30 °C
(298)

(114)


Ph
K / THF
path
a
~Ph
(299)
O2
path
b
O2, RH
PhCO2H
(300)
(301)

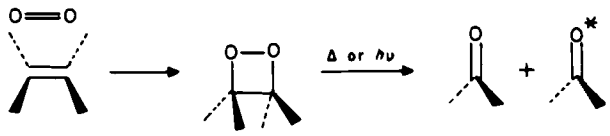
(115)

IV. SINGLET MOLECULAR OXYGEN

A. Modes of Reaction[259-262]

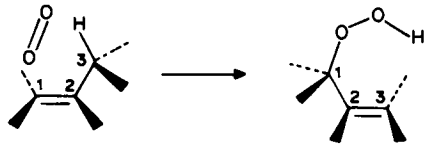
Unlike $^3O_2$, which displays a biradical character, all the electrons in $^1O_2$ are paired. Hence, the type of reaction it undergoes is expected to involves electron pairs. What's more, it is convenient to think of $^1O_2$ as the oxygen analogues of ethylene. Indeed, each of the three modes in which $^1O_2$ reacts with unsaturated compounds finds a precedent in one of the reaction pathways of ethylene.

The first of these modes is a [2 + 2] cycloaddition to a double bond to form a 1,2-dioxacyclobutane or dioxetane (equation 116). These cyclic peroxides are sometimes of moderate stability but readily cleave thermally or photochemically into two carbonyl-containing fragments. The cleavage is quite often accompanied by chemiluminescence.



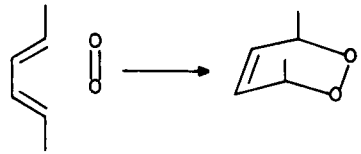
(116)

The second mode bears a striking resemblence to the Alder 'ene' reaction[263,264]. In the $^1O_2$ ene reaction, olefins containing an allylic hydrogen are oxidized to the corresponding allylic hydroperoxides in which the double bond has shifted to a position adjacent to the original double bond (equation 117).



(117)

The third and final mode involves a [4 + 2] Diels–Alder-type addition of singlet oxygen to a diene producing endoperoxides (equation 118).



(118)

The question of the mechanism in these three reaction types has been the subject of much heated debate over the past decade. The highlights of this long-standing controversy have been reviewed by this author[28b,28d] and a detailed discussion is beyond the scope of this review.

A variety of factors has been shown to control all singlet oxygen reactions[262]. The rate of reaction within a homologous series of compounds is generally inversely proportional to their ionization potential. This suggests that singlet oxygen is mildly electrophilic and sensitive to the nucleophilicity of the olefinic bond[265]. Thus as a rule, alkyl substitution increases the reactivity of olefins 10–100-fold per group. Solvent has only a minimal effect on the rate of reaction; changes in rate are commonly due to solvent effects on the lifetime of singlet oxygen. Because of the low activation energy for singlet oxygen processes (1–5 kcal)[266,267] little if any temperature effect on the rate of reaction is observed. Regarding

the mode of reaction, electron-rich olefins (such as vinyl sulfides, enol ethers and enamines) as well as sterically hindered alkenes (such as 2,2-biadamantylidene[268] and 7,7-binorbornylidene[269]) tend to prefer dioxetane formation, though two modes often compete. Finally, the direction of singlet oxygen attack is predominantly, if not exclusively, from the less hindered side of the molecule.

B. Singlet Oxygen Sources

1. General

An impressive variety of physical and chemical sources of $^1O_2$ is now available for laboratory-scale purposes. These include photosensitization, oxidation of H_2O_2, decomposition of phosphite ozonides and endoperoxides, and microwave discharge. These various sources have been extensively reviewed[28a,270,271]. Of all the techniques available for generating $^1O_2$, photosensitization is clearly the most convenient and, by far, the most commonly used, since it is applicable to a large spectrum of reaction temperatures, solvents and sensitizers. Most importantly for unreactive substrates, this physical method, unlike the chemical methods mentioned above, requires no additional reagents, merely longer photolysis times. It is for this reason that we focus briefly on this method in particular.

2. Photosensitization

By the beginning of the twentieth century there were several reports describing the oxidation of organic and biological substrates in the presence of oxygen, light and a photosensitizer. It has become apparent during the last two decades that there are in fact two general classes of photooxidations. In the first, called Type I, the sensitizer serves as a photochemically activated free-radical initiator. In its excited state, the sensitizer reacts with a molecule of a substrate, resulting in either hydrogen atom abstraction or electron transfer. The radicals thus formed react further with $^3O_2$ or other molecules. In the second class of reactions, dubbed Type II, the sensitizer triplet (sens^3), formed via intersystem crossing (ISC) of the excited singlet state sensitizer (sens^{1*}), interacts with oxygen, most commonly by transferring excitation, to produce $^1O_2$ (equations 119 and 120). The direct absorption of light by $^3O_2$ to produce $^1O_2$ is a spin-forbidden process. Type II generally predominates with colored sensitizers (dyes), such as methylene blue (MB), tetraphenylporphyrin (TPP) and rose Bengal (RB), which absorb visible light and have triplet energies (E_T) ranging from 30 to 46 kcal mol^{-1}. Type I processes are favored by high-energy, UV-absorbing sensitizers.

$$\text{sens}^1 \xrightarrow{h\nu} \text{sens}^{1*} \xrightarrow{\text{ISC}} \text{sens}^3 \tag{119}$$

$$\text{sens}^3 + {}^3O_2 \rightarrow \text{sens}^1 + {}^1O_2 \tag{120}$$

A variety of photochemical apparatus and procedures has been described[272,273]. In a typical reaction, the substrate and the sensitizer (10^{-3}–10^{-5} M) are dissolved in an appropriate solvent and photolyzed (250–1000 W) while oxygen is bubbled through the reaction mixture. Alternatively, the solution is rapidly stirred under an oxygen atmosphere with the uptake of oxygen followed by means of a gas buret. A UV cutoff filter is often placed between the light source and the reaction vessel to prevent the initiation of free-radical reactions.

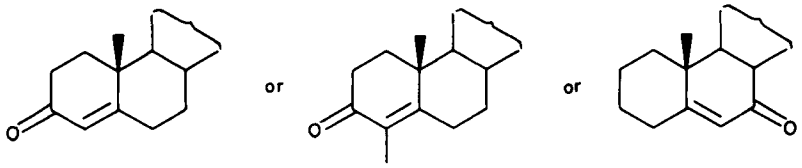
Recently, the use of polymer-based or adsorbant-bound sensitizers[274–279] has become quite popular and several products are commmercially available. Problems such as solubility, removal, recovery and bleaching, often confronted with unbound sensitizers,

are eliminated by using this heterogeneous photooxygenation method. The polymer-based sensitizer need simply be suspended in any (mostly organic) solvent which will 'wet' the polymer. Upon conclusion of the photolysis, the sensitizer may be filtered off, washed and reused if so desired.

C. Reaction of Singlet Oxygen with α,β-Unsaturated Carbonyl Compounds

1. Simple systems

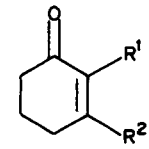
a. s-trans *conformation.* Despite the intense investigation of $^1O_2$ reaction over the past two decades, there were, until recently, only relatively few examples of the successful oxidation of alkenes that are substituted with electron-withdrawing groups[262]. This is consistent with the observation that singlet oxygen is weakly electrophilic[265]. Numerous examples of the attempted photosensitized oxidation of 3-keto-Δ^4-steroids (**155**), their 4-methyl analogs (**302**) and their 7-keto-Δ^5 analog (**303**) have shown that these enone systems are unreactive towards singlet oxygen[262,280] (equation 121).



(155) (302) (303)

$\xrightarrow{^1O_2}$ no reaction (121)

Further research by Ensley's group[280,281] has revealed that the reactivity of α,β-unsaturated carbonyls towards $^1O_2$ is strongly dependent on the conformation of the saturated system. Thus, those enones which prefer or are constrained to an *s-trans* conformation react slowly, if at all. For example, in addition to steroids **155**, **302** and **303**, cyclohexenones **304a–c**[280,281], 3-methoxyflavones **82**[104], cyclopentenones **305a, b**[280,281], cyclopropenone **306**[282] and cyclobutenones[283] are unreactive.

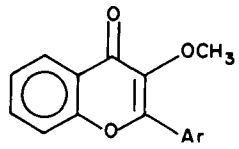


(304)

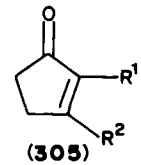
(a) $R^1 = Et$, $R^2 = CH_3$

(b) $R^1 = H$, $R^2 = OCH_3$

(c) $R^1 = CH_3$, $R^2 = OCH_3$



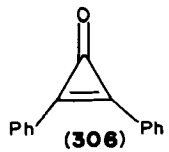
(82)



(305)

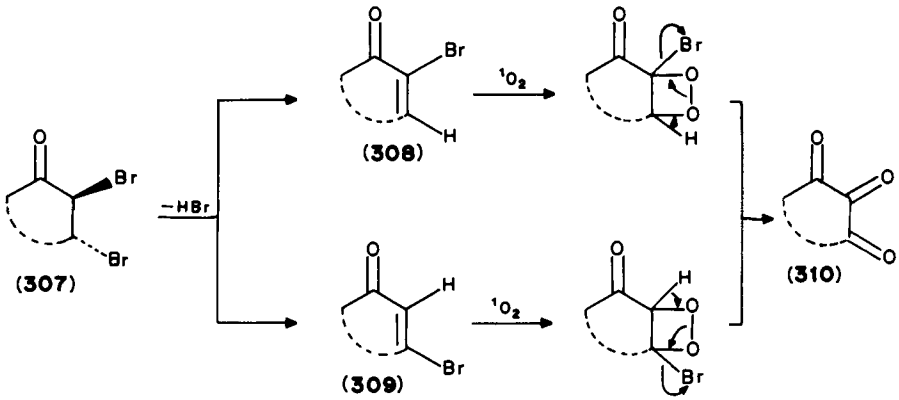
(a) $R^1 = n\text{-}C_5H_{11}$, $R^2 = CH_3$

(b) $R^1 = CH_3$, $R^2 = OCH_3$



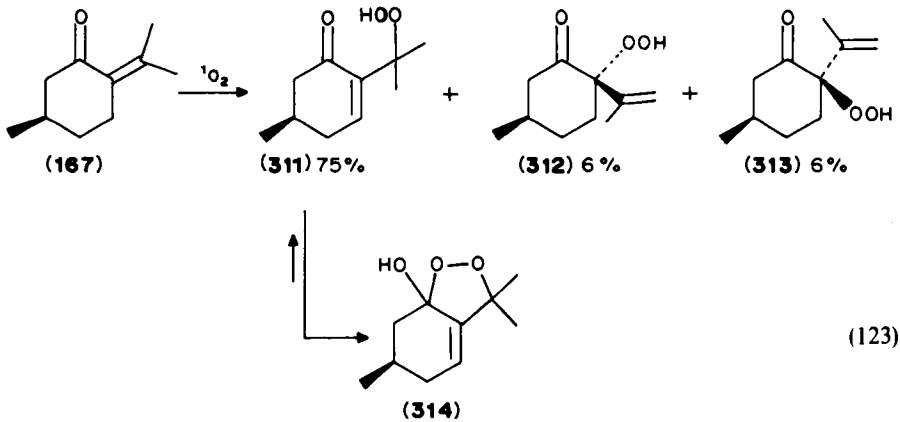
(306)

The only known class of exceptions are α- and β-hydroxyenones whose base-catalyzed singlet oxygenation will be discussed in Section IV.C.2. It should be noted, however, that Wamhoff and coworkers[284] find that the singlet oxygenation of dihaloketones **307** to vicinal triketones **310** proceeds via the corresponding α- and/or β-haloenones **308** and **309**. A dioxetane mechanism is invoked (equation 122).



(122)

b. s-cis *conformation.* Ensley's group[280,281,285–287] has further demonstrated that those α,β-unsaturated carbonyl systems which prefer or are constrained to the *s-cis* conformation are rapidly oxidized by singlet oxygen to yield ene reaction products. Thus pulegone[281,285–287] **167** yields allylic hydroperoxides **311**, **312** and **313** (equation 123). β-Hydroperoxy ketone **311** cyclizes spontaneously to peroxide **314**.

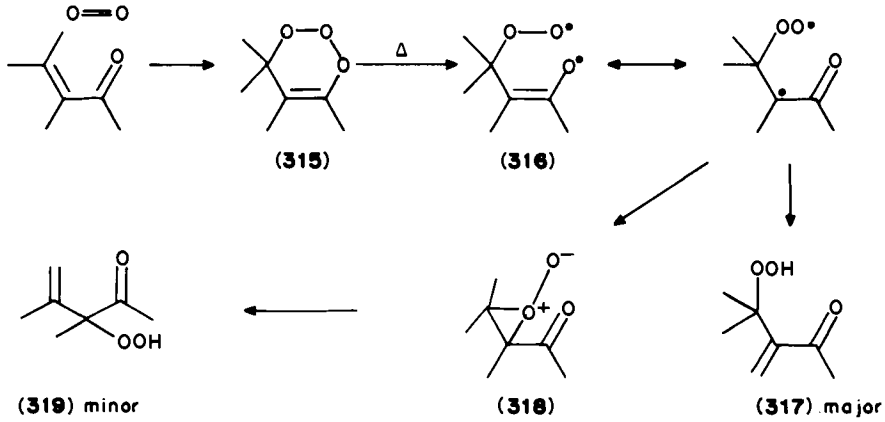


(123)

What is interesting is that in this and the related cases[281,288–293] of α,β-unsaturated ketones, aldehydes, acids, esters and lactones, as well as β-alkoxy enones, the reaction product formed preferentially, if not exclusively, is always the *conjugated* carbonyl. Put somewhat differently, allylic hydrogen abstraction in the ene reaction is preferred from the group geminal to the carbonyl. This 'geminal effect' is surprising since singlet oxygen reactions do not normally show a strong Markownikoff directing effect[259]. Nor can the

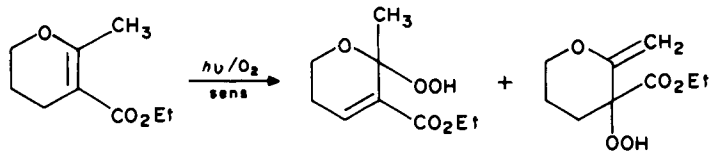
reactivity of the *s-cis* conformations be explained on the basis of ionization potential[280]. Finally, although singlet oxygen normally abstracts allylic hydrogens from the most crowded side of the olefin ('*cis* effect'), in enone systems the geminal effect takes precedence[291].

Ensley[280,281] has proposed (equation 124) that the initial step involves a [4 + 2] cycloaddition of $^1O_2$ to the enone system generating a 1,2,3-trioxine **315**. (A related intermediate has been invoked in the singlet oxygenation of pyrazolium-4-olate and dithiolium-4-olate[294].) Thermolysis of **315** yields diradical **316** which rearranges directly to the major product, conjugated carbonyl **317**, or via perepoxide **318** to the minor product, unconjugated isomer **319** (equation 124).



(124)

Chan and colleagues[292,293] have presented evidence for an alternative mechanism for the singlet oxygen reaction of dihydropyrancarboxylic acid **320**. In benzene, hydroperoxides **321** and **322** are formed in a 9:1 ratio as expected by the 'geminal effect' (equation 125). However, there is a profound solvent effects. In proceeding from benzene ($\varepsilon = 2.3$) to CH_2Cl_2 ($\varepsilon = 9.1$) to CH_3CN ($\varepsilon = 37.5$), product ratio flips from 90:10 to 35:65.

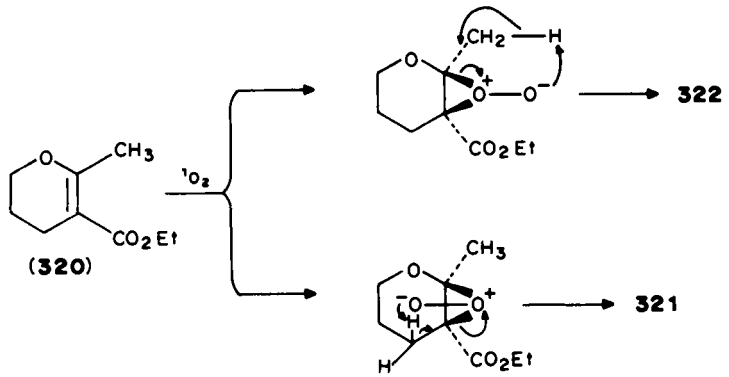


(125)

(320) (321) (322)

Benzene/TPP	90%	10%
CH_2Cl_2/TPP	50%	50%
CH_3CN/MB	35%	65%

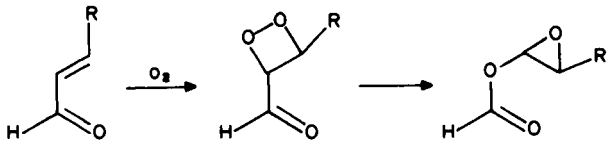
This role of solvent is not explained by the trioxine mechanism of Ensley. Chan's group suggests, along the lines of Frimer and Bartlett and coworkers[295], that singlet oxygen adds to the double bond to form either an extended or collapsed perepoxide. It is the former which is preferentially stabilized by the polar solvent, and leads to conjugated enones **322** (equation 126).



(126)

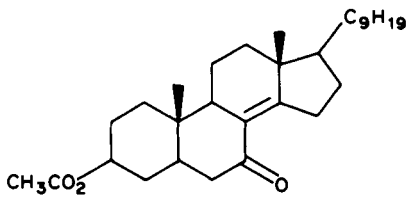
It should be noted, however, that this profound solvent effect, so typical of enol ethers[295–298], is not observed in the case of pulegone[296] and, hence, **320** may prove to be the exception rather than the rule.

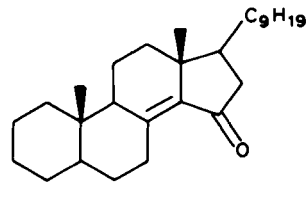
In a gas-phase low-temperature (– 190 °C to – 150 °C) study of the singlet oxygenation of acrolein and crotonaldehyde (**323**), Carmier and Deglise[299] present IR spectral evidence suggesting that the reaction proceeds via a dioxetane (**324**), which rearranges to an epoxy enol formate (**325**) (equation 127). Such a transformation is completely unprecedented and this reaction deserves further investigation.

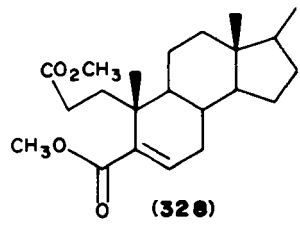


R=H or CH_3

(127)







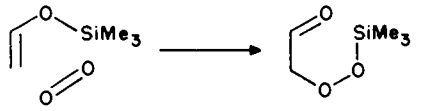
We close this section by pointing out a few anomalies in steroidal systems that have yet to be explained. For example, although **326** takes up one equivalent of oxygen under photooxidative conditions, **327** is not reactive—though it too is locked into a *cis* configuration[262]. Similarly, **328** is inert to $^1O_2$ although an s-*cis* conformation should be readily attainable[262]. Perhaps subtle steric or conformational effects are at play.

2. Keto enols

We have described above the $^1O_2$ ene reaction of olefins containing at least one allylic hydrogen. In this process, allylic hydroperoxides are generated in which the double bond has shifted to a position adjacent to the original double bond. In its most general form, the normal $^1O_2$ ene reaction (equation 129) can be written as shown in equation 128, where 'A' is CH_2 and 'B' is H. Silyloxyolefins (in equation 128, A = O, B = $SiMe_3$) also undergo an ene reaction with $^1O_2$ producing silylperoxy ketones (equation 130)[300–305]. In this transformation, the trimethylsilyl group takes the place of an allylic hydrogen while oxygen replaces the allylic carbon.

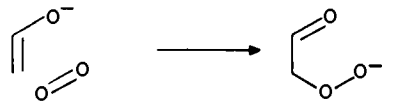
(128)

(129)



(130)

(131)

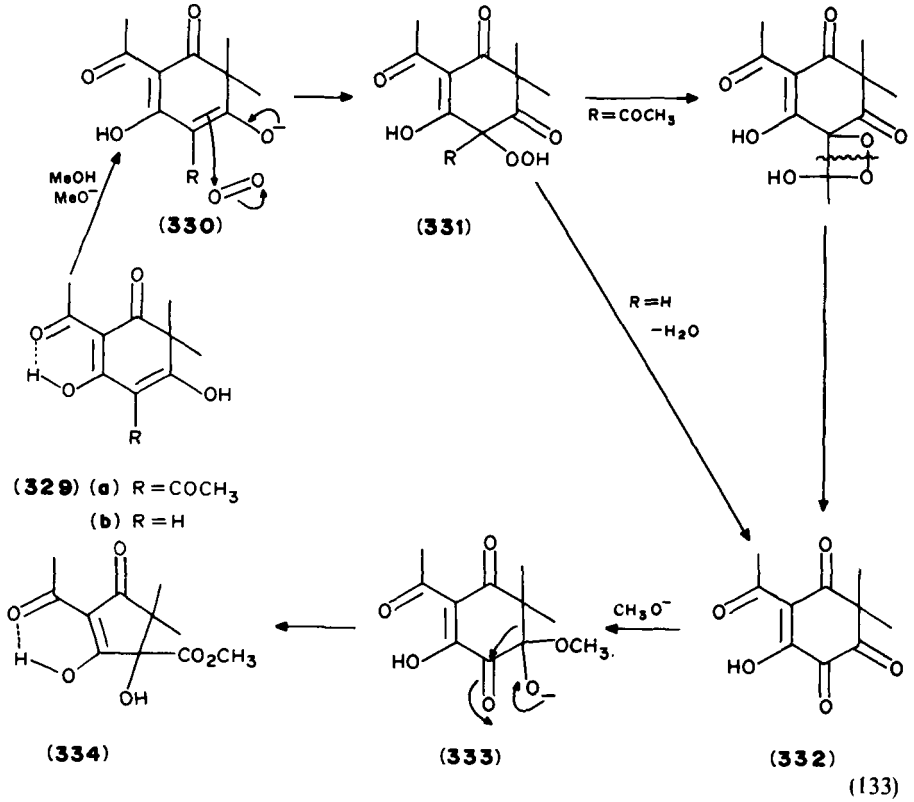


(132)

In the same fashion, enols (A = O, B = H) and enolates (A = O, B = $^-$) have been shown to undergo ene-type reactions (equations 131 and 132 respectively)[306]. For example, Matsuura reported that the photosensitized oxygenation of the stable keto enols, 3-hydroxyflavones **263**, like the enzymatic oxidation (Section III.F.2; see Scheme 19) and the corresponding BCA (Section III.E.3.b), yielded depsides **266**. However, in this case both carbon monoxide and carbon dioxide were formed[61b,104,307]. From the fact that CO is stable under the reaction conditions and that the photosensitized oxygenation of *p*-methoxyphenylglyoxylic acid gives anisic acid and carbon dioxide in good yield, it was

concluded that two mechanistic pathways are operative (path a and path b in Scheme 19). The initially formed 3-hydroperoxy-1, 2-diketone **264** can decompose (see Section III.C.4) to depside **266** via either cyclic peroxide **265** (path a) or dioxetane **269** (path b). It should be noted that the corresponding 3-methoxyflavones (**82**, Section III.D.2.a) are inert to singlet oxygen[61b,104,307].

Simultaneously with Matsuura's study of the enol of α-diketones, Young and Hart[308,309] observed that β-hydroxy enones (enols of β-diketones) and δ-hydroxydienones (enols of α,β-unsaturated-δ-diketones) can be oxygenated in basic methanol. Thus, the enolate of diacetylfilicinic acid **329a** reacts with $^1O_2$ giving hydroxy ester **334**. The latter is presumably formed via α-hydroperoxy ketone **331**, which undergoes oxidative cleavage (see Section III.C.4) to α-diketone **332**. Benzilic acid rearrangement of the latter generates **334** (equation 133). A similar reaction is observed with monoacetylfilicinic acid **329b** with a Kornblum–DeLaMare reaction (Section III.C.2) converting **331** to **332**.

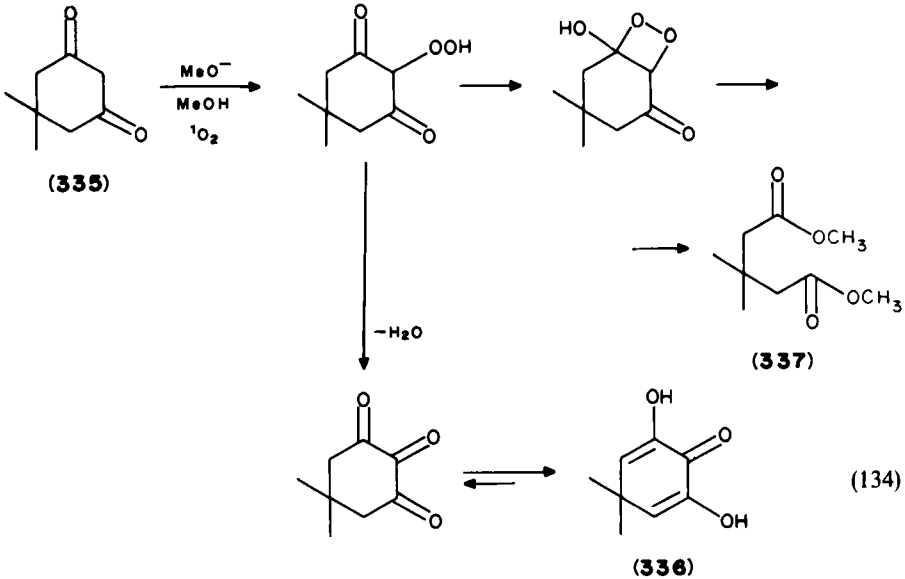


(133)

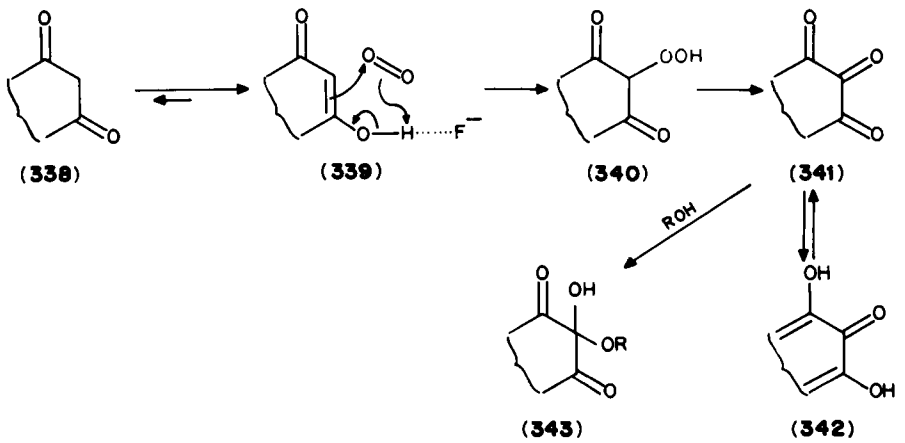
Similarly, dimedone **335** is oxidized[72,310] under these conditions to a mixture of products containing enol **336** and esters of 3, 3-dimethylglutaric acid **337** (equation 134).

Wasserman and Pickett[69,72] have recently reinvestigated the photooxidation of enols and have discovered that fluoride ion catalyzes this process giving higher yields of the oxidations products and cleaner reaction mixtures. Enols stemming from β-diketones, β-keto esters and α-diketones have been photooxidized under these conditions and the yields of the resulting hydroperoxy diketones are generally around 70% after only 2 h of reaction

when carried out in aprotic media (e.g. $CHCl_3$). The uptake of oxygen is sluggish at most in the absence of fluoride. The latter presumably hydrogen bonds with the enol hydrogen, thereby increasing the electron density on the oxygen and the nucleophilicity of the double bond. In the case of β-diketones **338**, the resulting hydroperoxide **340** dehydrates to the corresponding vicinal triketone **341**. The latter undergoes enolization to **342** or solvent addition to **343** (equation 135).



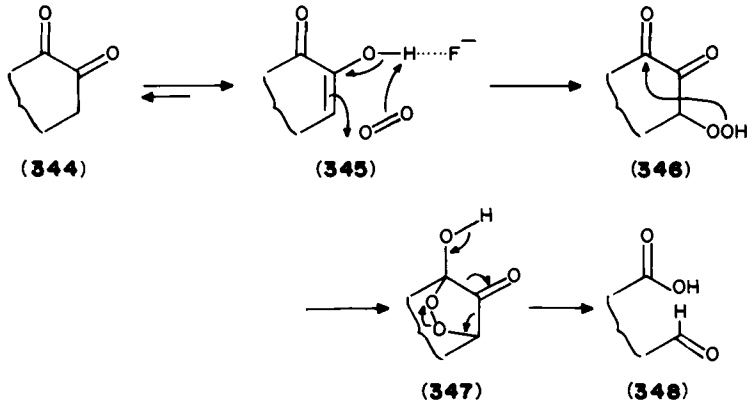
(134)



(135)

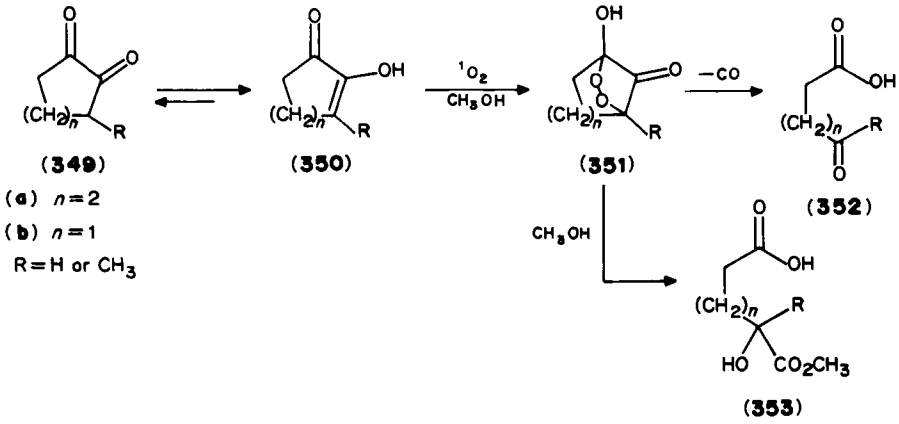
α-Diketones **344** generate the corresponding 3-hydroperoxy-1,2-diketones **346** which (as discussed in Section III.C.4) cyclize to endoperoxide **347**. The latter collapses with loss of carbon monoxide to the corresponding aldehydo carboxylic acid **348** (equation 136).

In contradistinction to the 3-hydroxyflavone oxygenation, no CO_2 was detected, which rules out the intermediacy of a dioxetane (see Scheme 19, path b).



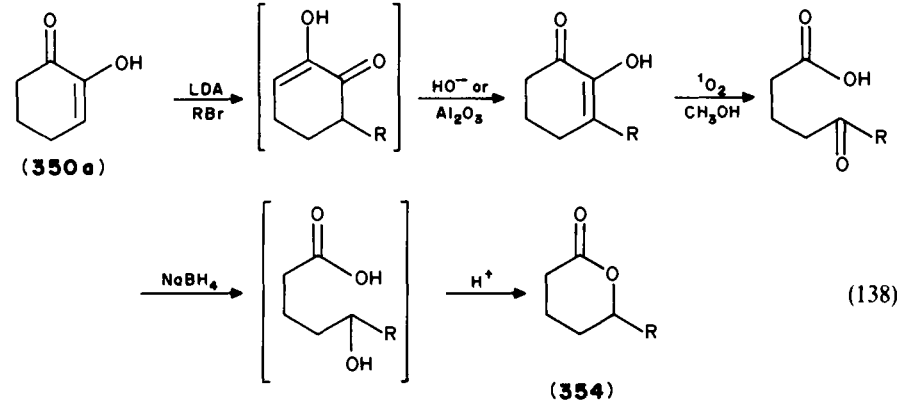
(136)

Takeda and coworkers have found that 1,2-cyclohexanediones **349a**[70,73,75,311] and 1,2-cyclopentanediones **349b**[76] undergo this singlet oxygenation in methanol in the absence of fluoride to yield oxoalkanoic acids **352** and hydroxy acids **353**. Interestingly, though the exact product distribution is highly dependent upon the reaction temperature, **352** is the major product in the case of the cyclohexanediones **349a**, while **353** predominates in the case of the cyclopentanediones **349b**. The latter product results from the solvent trapping of cyclic peroxide **351** (equation 137). It has yet to be explained why the five-membered ring diones several times slower than their higher homologs.



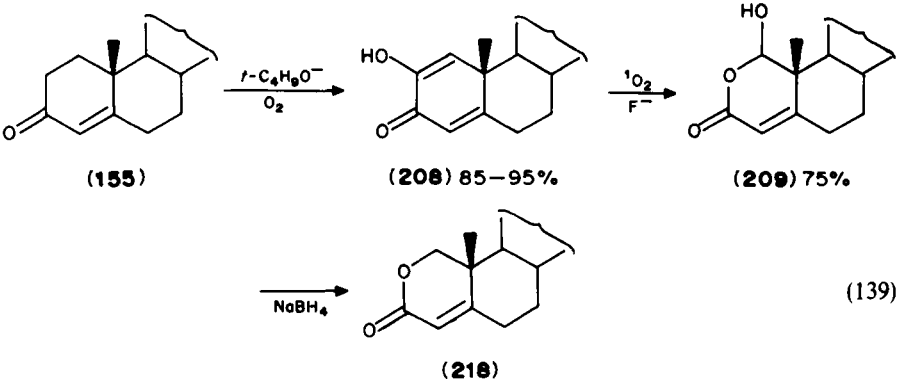
(137)

The rate of oxygenation of 3-alkyl-1,2-cyclohexanediones is approximately equal to that of the tetrasubstituted olefin tetramethylethylene (TME)[73]. As a result, the enol can be oxidized in preference to disubstituted olefinic linkages present in the molecule. This observation has enabled Takeda's group[73,75,311] to carry out a new synthetic approach to jasmine lactone and related δ-lactones (**354**) from 1,2-cyclohexanedione, as outlined in equation 138.



(350a) (354) (138)

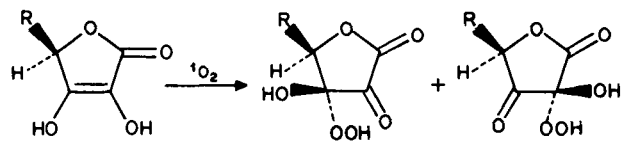
We mentioned above (Section III.E.3.b) the base-catalyzed autoxidative (BCA) approach Frimer and coworkers[201] have used to convert 3-oxo-Δ^4 steroids **155** to the pharmacologically important 2-oxa analogs **218** (equation 88). At the center of this reaction sequence is the BCA conversion of enol **208** to lactol **209**. This step requires strongly basic conditions and several days of reaction. Using the much milder Wasserman and Pickett procedure[72], this conversion has been carried out on the enols of cholestenone, testosterone, 17α-methyltestosterone, 17α-hydroxyprogesterone, progesterone cortisolone–BMD and cortisone–BMD. Yields are generally 75% and the oxygenation requires only a few hours (equation 139)[312a]. Photooxidation as suggested by Takeda's group proved ineffective.



(155) (208) 85–95% (209) 75%

(218) (139)

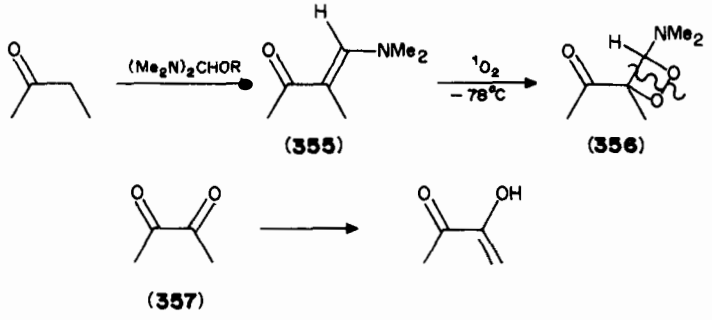
A preliminary report on the low-temperature photooxidation of ascorbic acid and its derivatives has appeared recently[312b,c]. The major products are the isomeric hydroperoxyketones and, as expected, oxygenation occurs on the less hindered face of the ring, i.e. opposite to the 'R' group.



The photooxidation of tropolones is discussed in Section IV.C.5.c.

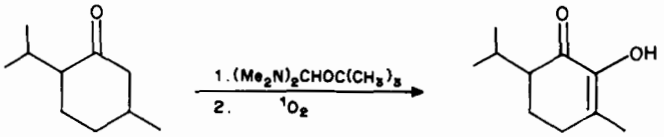
3. Enamino carbonyl systems

Unlike carbonyl systems which react through an ene mechanism, simple enamino carbonyl compounds **355** with an electron-rich double bond react via dioxetanes **356**, which then cleave to the corresponding α-dicarbonyl compounds **357** (equation 140).

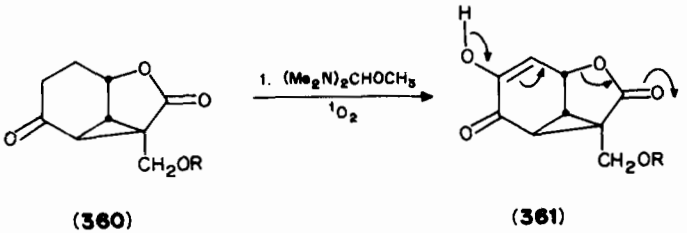


(355) (356) (357) (140)

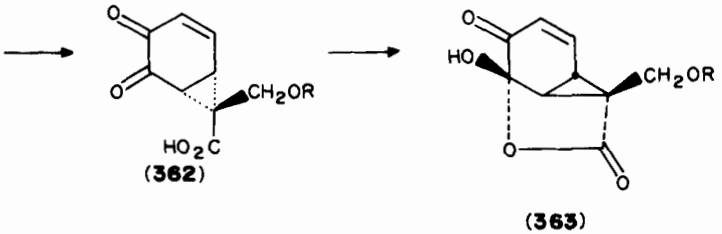
Wasserman and Ives[313–317] have used this technique to prepare various α-keto derivatives of lactones, esters, amides, lactams and ketones. The sequence is particularly simple since the enamine **355** need not be isolated, and can be converted to the corresponding diketone **357** using polymer-bound rose bengal which facilitates its isolation. The utility of this method is illustrated by the conversion of methone **358** to the corresponding enol **359** in 81% yield (equation 141). Ziegler and coworkers[318] utilized this procedure in the synthesis of a transient α-diketone **361**, which subsequently rearranged to **363** (equation 142).



(358) (359) (141)

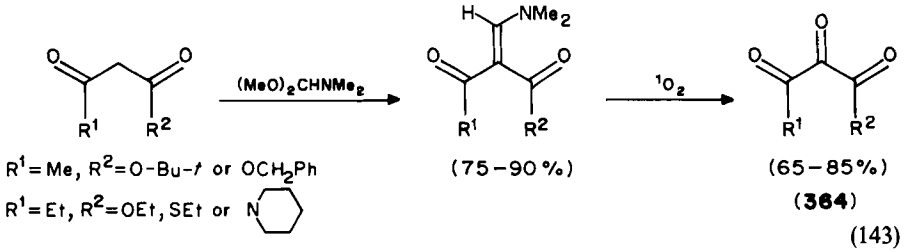


(360) (361)

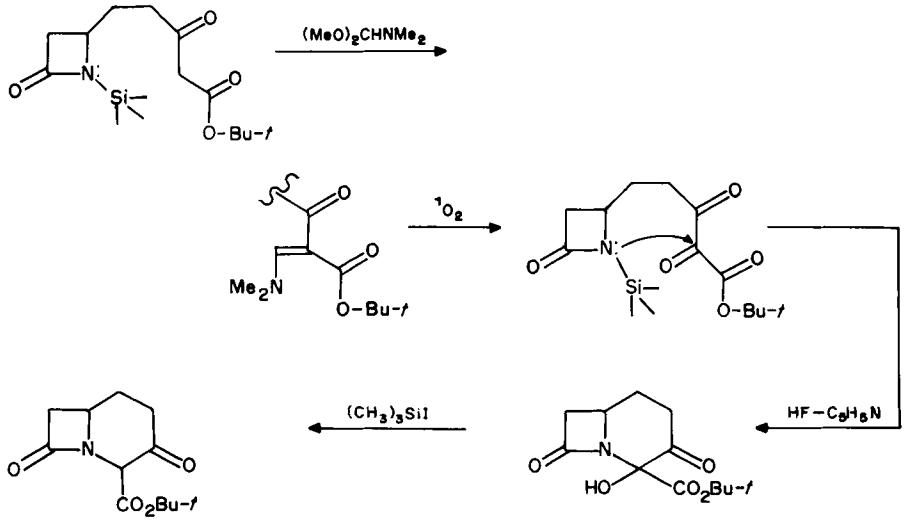


(362) (363) (142)

Wasserman and Han[317] have further extended this technique to the preparation of vicinal tricarbonyl systems (**364**). The β-dicarbonyl precursors are reacted with DMF acetal to form enamines, which are cleaved by photooxidation (equation 143). This method has been successfully applied to the formation of carbacepham **365** (equation 144)[317].



(143)



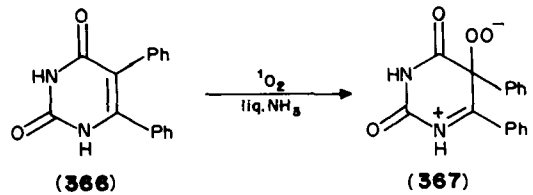
(144)

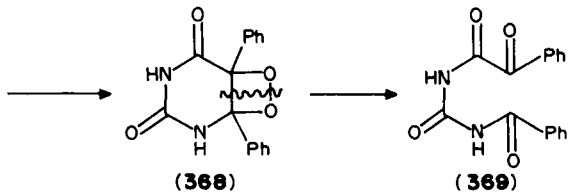
More complicated or conjugated enamino systems tend to react by an ene mode generating zwitterionic intermediates, which may cyclize in turn to the related dioxetanes. For example, the pyrimidine, 5,6-diphenyluracil **366**, on sensitized photooxidation in liquid ammonia at $-70\,^{\circ}C$, gives an unstable peroxide **367** which, on warming, breaks down to the cleavage product **369**, presumably via dioxetane **368** (equation 145)[319].

The pyrimidinium-4-olates of type **370** or **374** react with $^1O_2$ generated chemically or photochemically to yield a 1,4-dipolar cycloaddition product, namely stable endoperoxides **373** and **375** in high yields[320] (equations 146 and 147). Although the authors hesitate to suggest a mechanism, we believe that the intermediate here as well is the zwitterion **371**, which cyclizes in this case to endoperoxide **373**.

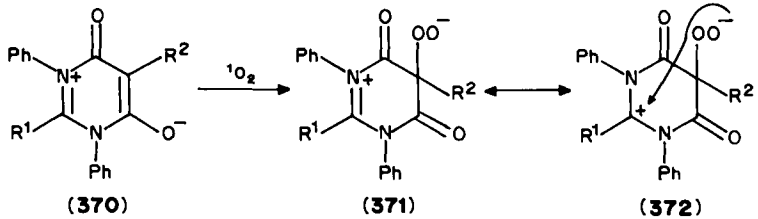
Orito and colleagues[321] report that enamino ketone **376** is oxidatively rearranged to ketolactone **379**. The mechanism of this process has been the subject of some disagreement

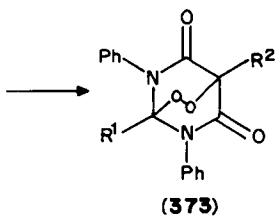
and speculation[38b,316,321,322]. Presumably the initially formed hydroperoxide or peroxyanion **377** rearranges to hydroxydioxetane **378**, which collapses to ketolactone **379** (equation 148).



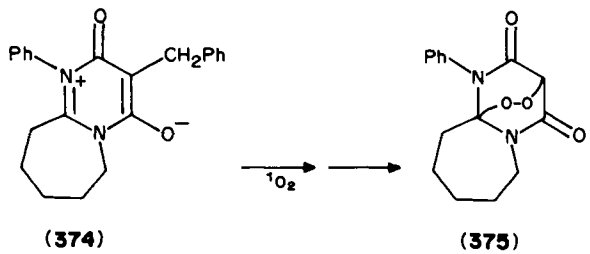


(145)

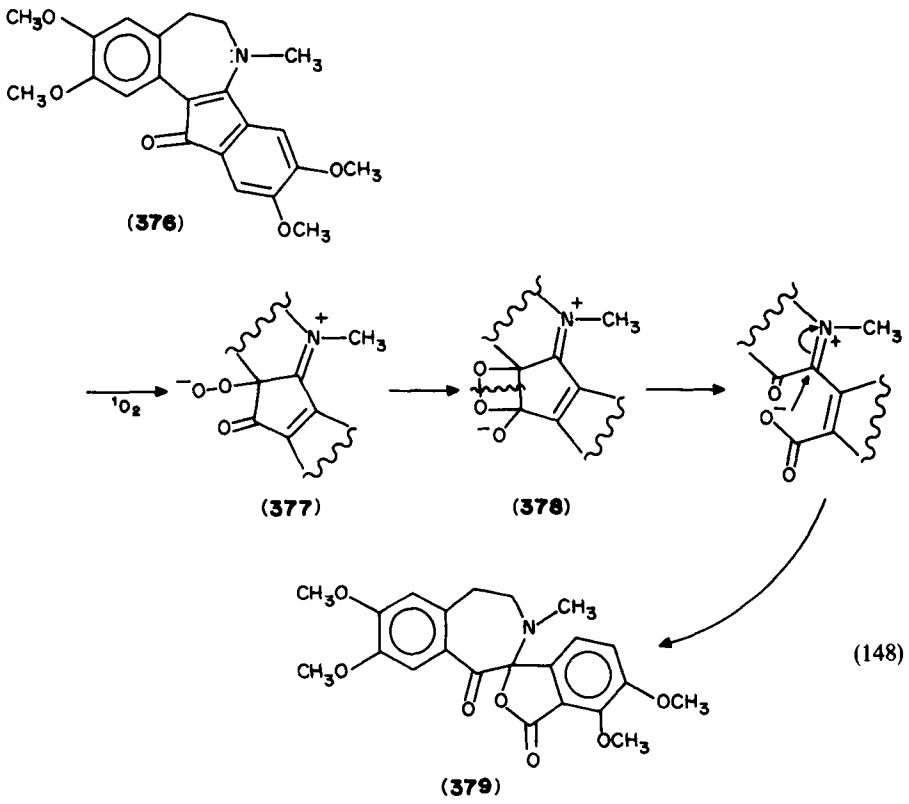




(146)

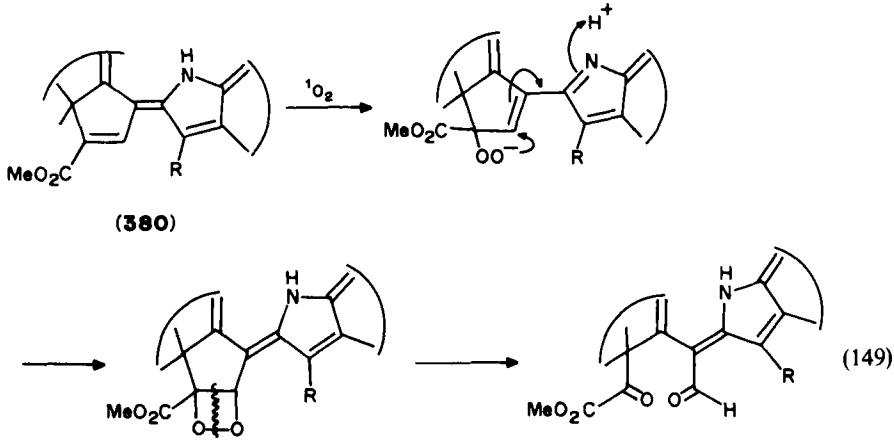


(147)



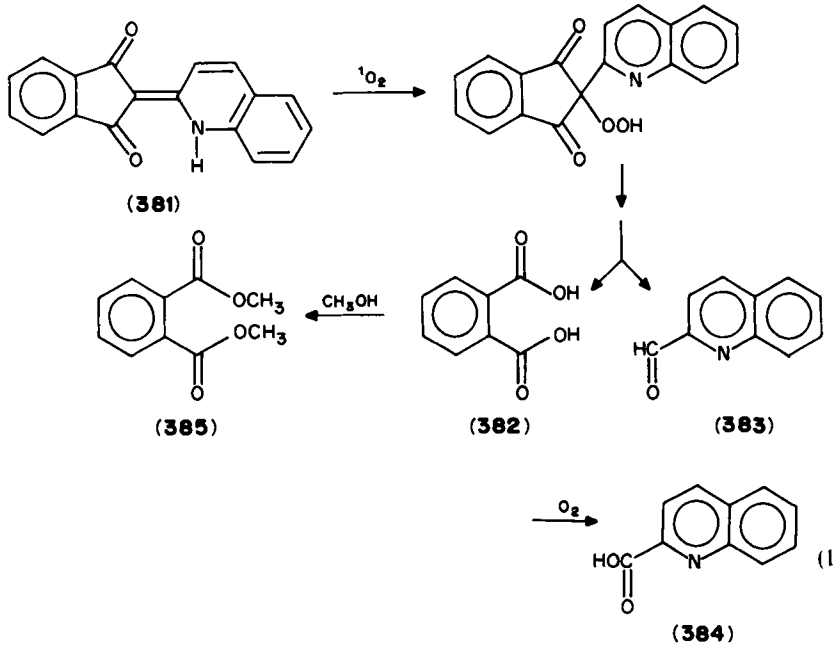
(148)

As shown in equation 149[316], a similar process may be involved in the photooxidation of chlorin **380**, in which the cyclopentene ring is cleaved[323,324].



(149)

Related to the photooxidation of enamino β-diketones[317] is the singlet oxygenation of 2-(2-quinolyl)indan-1,3-dione **381**, which yields phthalic acid **382**, quinoline-2-carbaldehyde **383** and quinoline-2-carboxylic acid **384**. Again, in this conjugated enamino system, an initial ene mode is observed (equation 128, A = N, B = H), not dioxetane formation (equation 150)[324,325].



(381) (385) (382) (383) (384) (150)

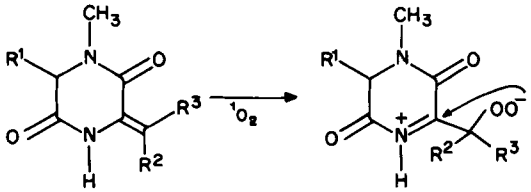
All the enamino ketones described above had the amine group at the β olefinic carbon with respect to the carbonyl. Machin and Sammes[326] have reported on the photosensitized oxidations of 3-benzylidenepiperazine-2,5-diones **386a–c** to the corresponding piperazinetriones **389** (equation 151).

NMR evidence was presented for the intermediacy of dioxetane **388**. Interestingly, however, both the *E* and *Z* isomers (**386a** and **386b** respectively) yield the *same* dioxetane. This suggests that oxidation of at least one of the arylmethylene isomers proceeds with inversion of configuration, and hence that non-concerted dioxetane formation via zwitterion **387** is involved. To further verify the involvement of acyliminium derivative **387**, nitrogen participation was inhibited by preparing imidate ether **390**. The latter indeed proved inert to $^1O_2$ (equation 152).

The photooxidation of purines and other nitrogen heterocycles has been extensively reviewed[327,328].

4. Chalcones

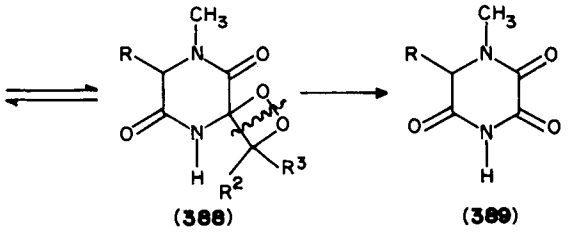
Chalcones (1,3-diarylpropenones, **391**) which lack alkyl groups on the double bond are precluded from undergoing a $^1O_2$ ene reaction. Nevertheless Chawla and coworkers[329,330] report that prolonged photosensitized irradiation (70–115 h) of these compounds under air lead to oxidative cleavage products, such as **394–397**, which these



(386)(a) $R^1 = R^3 = H$; $R^2 = Ph$ (387)

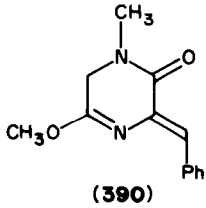
(b) $R^1 = R^2 = H$; $R^3 = Ph$

(c) $R^1 = CH_3$; $R^2 = H$; $R^3 = Ph$



(388) (389)

(151)

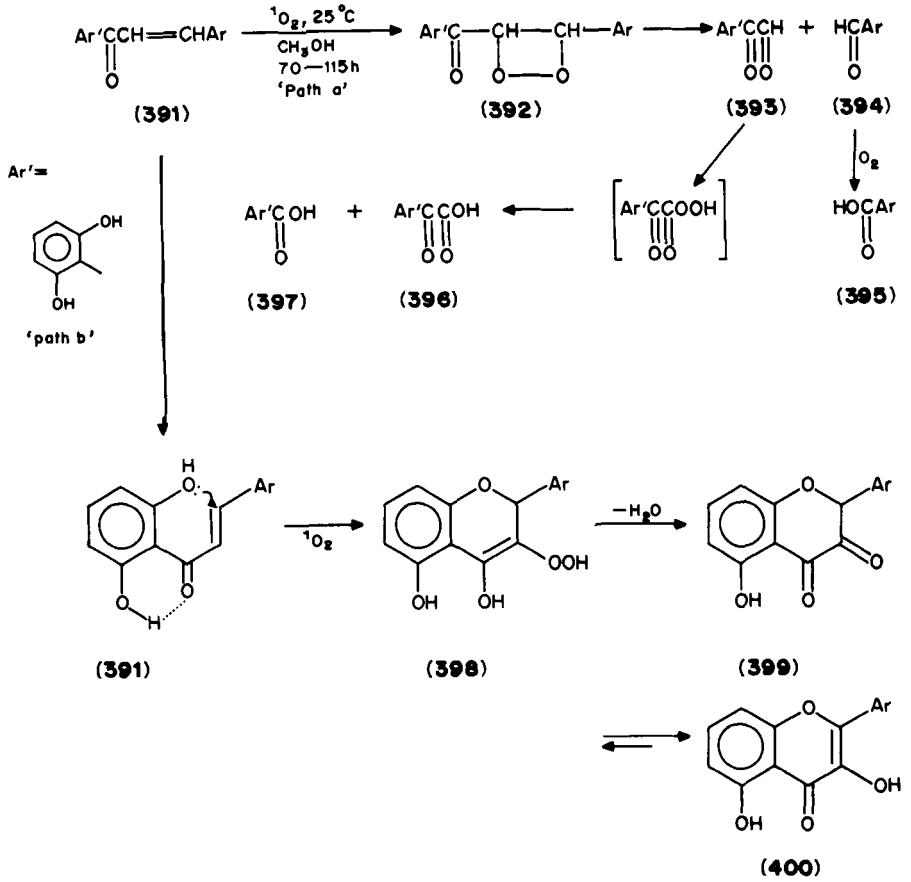


(390)

no reaction (152)

authors presume result from dioxetane **392** formation (see Scheme 22). The involvement of $^1O_2$ in this reaction was verified by the anticipated quenching of the reaction with DABCO. When, however, *both* the 2′ and 6′ positions bear hydroxyl groups, 5-hydroxyflavonols **400** (in a 25–50% yield) are formed as well. The mechanism proposed by Chawla and colleagues[329,330] (Scheme 22, path b) invokes a nucleophilic attack of the 2′-hydroxy group on the enone system. Nucleophilic attack is facilitated by the hydrogen bonding of the carbonyl with the 6′-hydroxy group, which on the one hand increases the electrophilicity of the enone moiety and secondly 'locks' the attacking 2′-hydroxy group in close proximity to the enone system.

Wong[331] has recently reexamined the photosensitized oxidation of 2′,4′,4-trihydroxychalcones and finds not only the 5-hydroxyflavonol **400** but also products **403** and **404** (Scheme 23). Interestingly, these same products are observed in the enzymatic[240–245] oxidation of chalcones (see Section III.F.3) which is a free radical process. These authors conclude that although singlet oxygen is formed in this reaction, the oxygenation of the enones is initiated by the formation of a phenoxy radical which results[327] in turn from the phenol–singlet oxygen interaction (Scheme 23; cf. Scheme 20). Nucleophilic attack by the phenol group on the dioxetane at either the α or β carbons leads to product **403** and **404** (Scheme 23, path c) or **400** (path b).

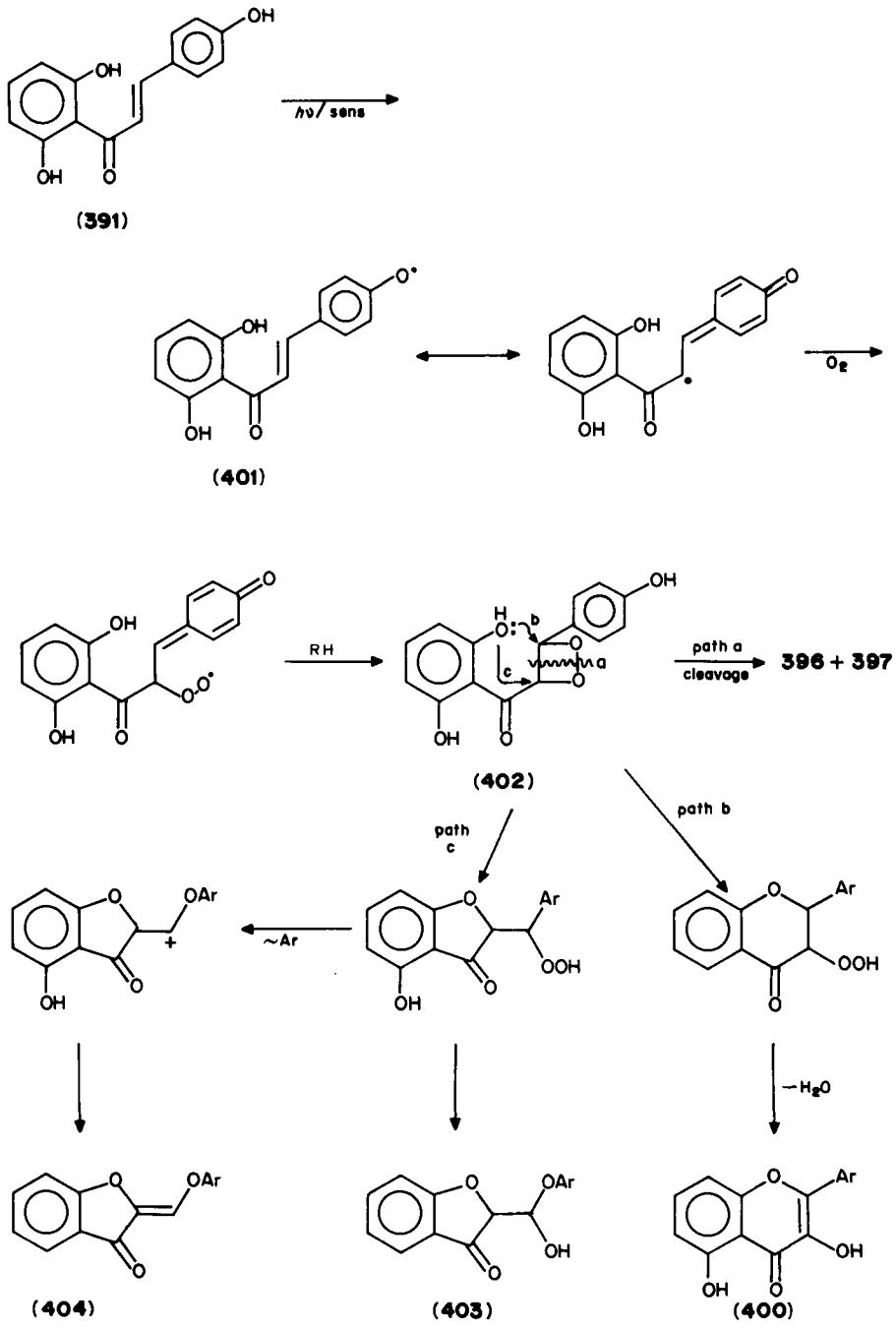


SCHEME 22. Chawla[329,330] mechanism for the singlet oxygenation of chalcones

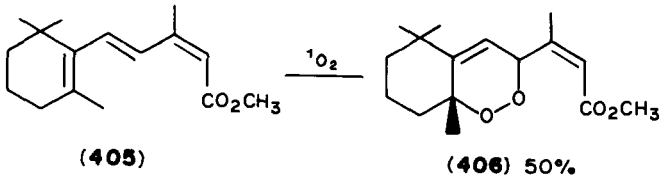
5. *Retinoids and acyclic polyenoates*

Polyene carbonyls related to the retinoid family were extensively studied by Mousseron-Canet[332–341] and others[262,342–346] in the late 1960s. Because allylic hydrogens and diene moieties are present, both ene and Diels–Alder modes are observed. For example, ester **405** yields endoperoxide **406** and two ene products, diallylic hydroperoxide **407** and allene **408**[338] (equation 153). The formation of allene **408** is quite surprising, since it requires the abstraction of a vinyl hydrogen.

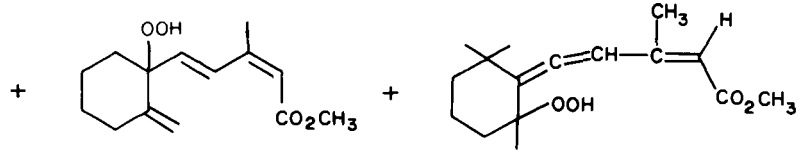
More recently, acyclic conjugated polyenoates have been investigated by Matsumoto and Kuroda[347]. These researchers find that monoolefinic esters such as ethyl crotonate **409** and even dienoates such as ethyl sorbate **410** are essentially inert to $^1O_2$ (equation 154). However, the introduction of an additional methyl group to **410** yields **411** which reacts to generate an endoperoxide product **412** (equation 155). The next-higher vinylog of **411**, trienoate **413** is reactive to $^1O_2$ as well, yielding endoperoxide **414** (equation 156). The introduction of a methyl group to **413** yields trienoate **415**, which reacts by all three singlet oxygen modes (equation 157).



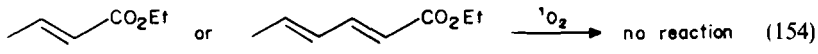
SCHEME 23. The Wong[331] mechanism for the singlet oxygenation of chalcones



(405) (406) 50%

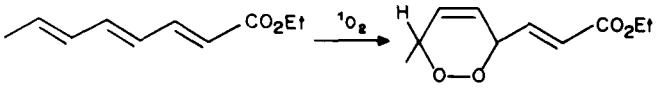


(407) 38% (408) 12% (153)



(409) (410) (154)

(411) (412) (155)



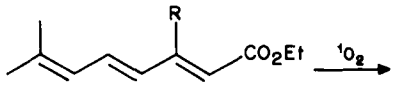
(413) (414) (156)

Interestingly, singlet-oxygen attacks occur in all the above cases at the double bond furthest from the carbonyl. This may be a result of the increased nucleophilicity of the double bond as we get further from the carbonyl. These authors also note that the distribution of the products in the photooxidation of **415a** and **415b** among the three singlet-oxygen reaction modes (i.e. ene, dioxetane and Diels–Alder) is remarkably affected by the solvent used and the reaction temperature. In particular, polar solvents favor ene-product formation while low temperatures favor dioxetane product.

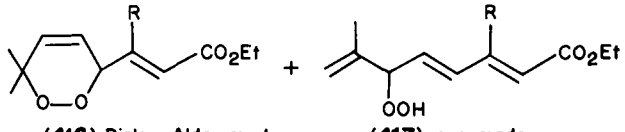
6. *Polyenic steroids*

We have noted above (Section IV.C.1.a) that the enone moiety in Δ^4- and $\Delta^{1,4}$-2-oxosteroids is inert and other olefinic linkages present in the molecule are oxidized in preference to them[262]. Thus, the α,β-double bond in the enone moiety of steroid **420** (and in the corresponding $\Delta^{1,4}$-analog) remains unaffected by photooxidation[262] (equation 158).

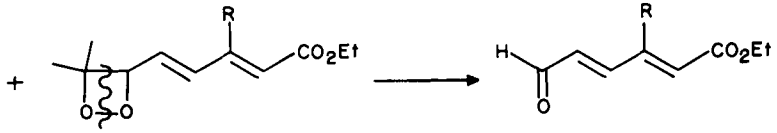
Interestingly 19-nor-$\Delta^{4,9(10)}$-3-oxo steroids do react via a $^1O_2$-ene mode at the terminal double bond. Thus, steroid **422** is oxidized to phenol **424**[348] (equation 159).



(415)
(a) R=H
(b) R=CH_3

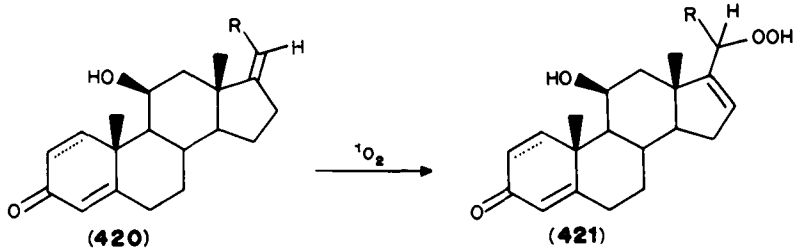


(416) Diels—Alder mode (417) ene mode



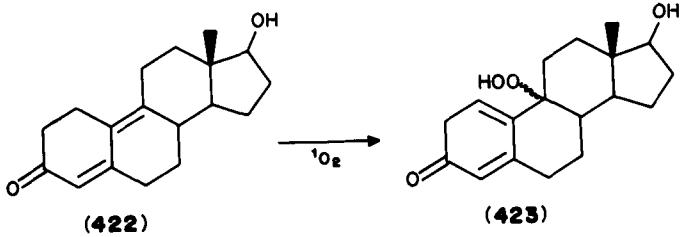
(418) dioxetone mode (419)

(157)

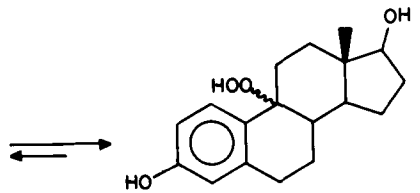


(420) (421)

(158)



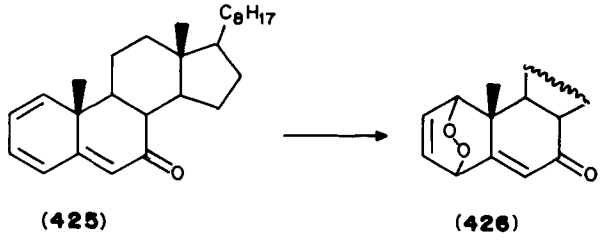
(422) (423)



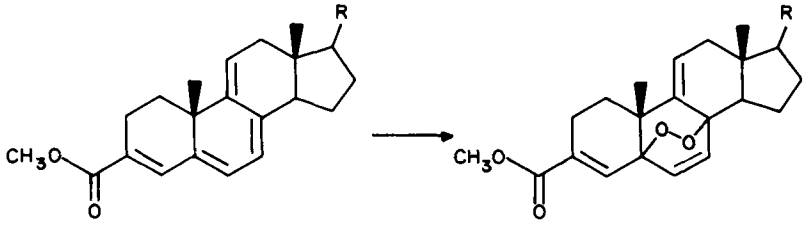
(424)

(159)

Conjugated steroidal polyenones undergo a 2 + 4 cycloaddition with $^1O_2$ at the homoannalar diene. Thus 7-oxo-$\Delta^{1,3,5}$ steroid **425** yields endoperoxide **426** (equation 160)[349] while tetraenone **427** yields **428** (equation 161)[350,351].



(425) (426) (160)



(427) (428) (161)

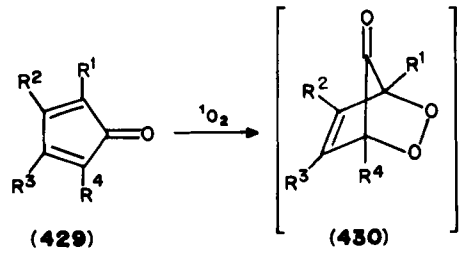
Clearly, a Diels–Alder-type addition at the homoannular diene moiety is preferred over other modes possible, particularly ene reaction.

7. *Homoannular polyenones*

a. Cyclones. Homoannular dienones as a class are extremely susceptible to Diels–Alder $^1O_2$ reactions. The smallest ring in this class is cyclopentadienone and, indeed, the photooxidation of arylated cyclopentadienones (cyclones, **429**) has been known for nearly half a century[352–359]. These compounds are generally colored and hence their photochemical singlet oxygenation is often a self-sensitized process. Singlet oxygen for these reactions has also been generated by chemical means including triphenylphosphite ozonide and H_2O_2/NaOCl. As shown in equation 162, the primary product is the corresponding endoperoxide **430** which is generally unstable and loses carbon monoxide yielding the *cis*-ene dione **431**. If structurally feasible, the latter will be converted photochemically (UV) or chemically (traces of acid or base) to the more stable *trans* isomer (**432**)[357,359–362].

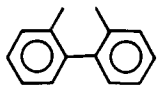
To verify the intermediacy of the endoperoxide **430**, Chaney and Brown[359] carried out the photooxidation using a molecular oxygen mixture containing $^{16}O_2$ and $^{18}O_2$. The results indicated that indeed the photooxidation of tetracyclone proceeded by a one-molecule mechanism, whereby both oxygen atoms in the resulting dibenzoylstilbene are derived from the same molecule of molecular oxygen.

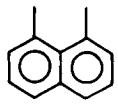
Bikales and Becker[356] have studied the photooxidation of tetracyclone **429a** and report that, in addition to dibenzoylstilbenes **431** and **432**, they succeeded in isolating pyrone **434**. (A similar product was obtained by Dilthey and coworkers[352] in their study of **429b**.) Bikales and Becker suggest that these pyrones result from a side-reaction with ozone

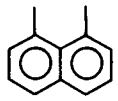


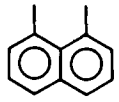
(429) (430)

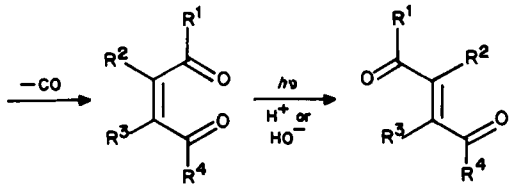
(a) $R^1=R^2=R^3=R^4=Ph$

(b) $R^1=R^4=Ph$; $R^2+R^3=$ 

(c) $R^1=R^4=Ph$; $R^2+R^3=$ 

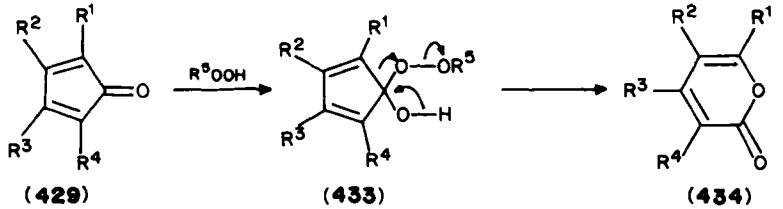
(d) $R^1=R^4=i\text{-}C_3H_7$; $R^2+R^3=$ 

(e) $R^1=R^4=-(CH_2)_{12}-$; $R^2+R^3=$ 



(431) (432) (162)

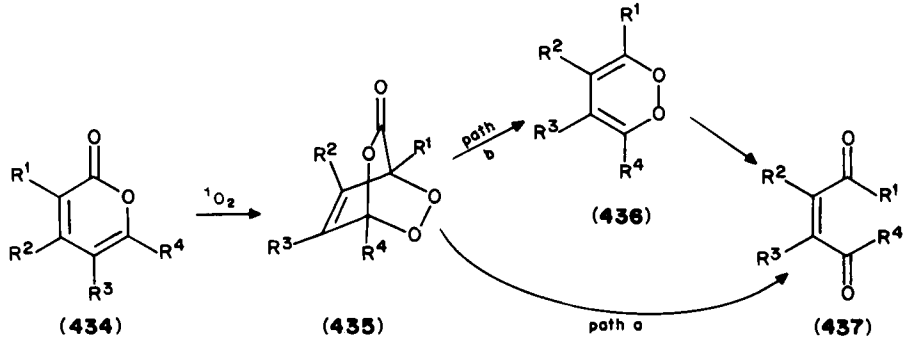
formed during the prolonged UV irradiation. We suggest, however, that it results from a Baeyer–Villiger reaction with peroxides formed during the 7–14 days of irradiation required for the completion of this reaction (equation 163). The conversion of cyclones to pyrones with peracids is known[352,358].



(429) (433) (434) (163)

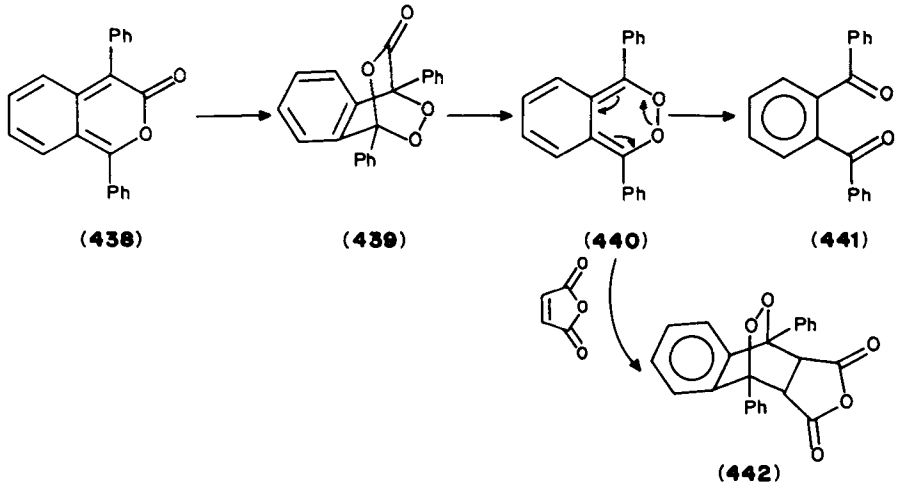
b. Cyclohexadienones. Simple cyclohexadienones exist as the corresponding phenols. The singlet-oxygen chemistry of the latter has been discussed recently[306] and is beyond the scope of this review. Surprisingly, however, the photosensitized oxygenation of 6,6-disubstituted cyclohexa-2,4-dien-1-ones does not seem to have been explored extensively. Koch[363], who investigated the thermodynamics of singlet-oxygen reactions, reports that the energy of activation of the reaction of 6,6-dimethylcyclohexa-2,4-dien-1-one is 3.6 kcal mol^{-1}, assuming that endoperoxide product is formed in both cases. Nevertheless, no product study seems to have been carried out.

The research groups of Adam[364,365] and Schuster[366] have shown that α-pyrone endoperoxides **435** are conveniently accessible through singlet oxygenation of α-pyrones **434**. These endoperoxides are hyperenergetic and chemiluminescence accompanies their thermal decomposition (equation 164).



(164)

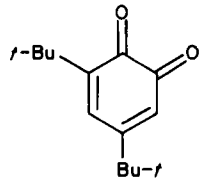
Work by Schuster and Smith[366] on the benzopyrone system **438** suggests that the decomposition of endoperoxide **439** proceeds via the interesting *o*-oxylylene peroxide **440**, which can be trapped by maleic anhydride (equation 165).



(165)

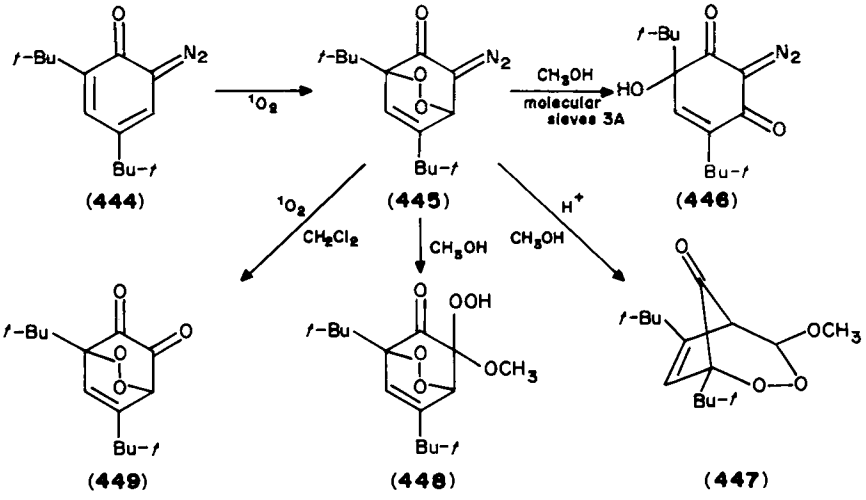
In the non-benzo analogs, however, Adam and Erden[364] were unsuccessful in trapping the corresponding dioxin **436** even with such reactive dienophiles as 4-phenyl-1,2,4-triazoline-3,5-dione. This suggests that either **436** is not formed (equation 164, path a) or that it suffers valence isomerization to diacylethylene **437** (equation 164, path b) before bimolecular trapping can occur.

3,5-di-*t*-Butyl-*o*-benzoquinone, **443**, is unreactive to $^1O_2$ (equation 166)[367]. However, the corresponding diazo compound **444** yielded endoperoxide **445** as the primary product (equation 167)[367–369]. Peroxide **445** is quite labile and can be transformed to various products **446–449**.



(443)

$^1O_2$ → no reaction (166)

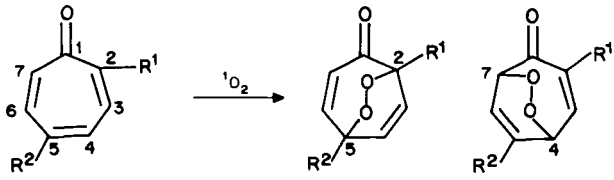


(167)

c. Tropones. The dye-sensitized photooxidation of tropones **450** can lead to two endoperoxides **451** or **452**, corresponding to addition across either the 2, 5 or 4, 7 positions (see Table 4). With the exception of **450e** and **f**, oxygenation takes place predominantly at the electron-rich 2, 5 positions rather than at the less-hindered 4, 7 positions. In the case of **450e** and **f**, the preference for the 4, 7 additions is attributed to the quenching effect exerted by the hydroxyl groups[374] on the C-2 substituents on the approaching singlet oxygen. In the case of **450g**, the electron-withdrawing nitrobenzoyl group lowers the nucleophilicity of the diene system sufficiently to render it inert to the electrophilic singlet dioxygen.

With the exception of **451b**, all the other endoperoxides are stable at room temperature. *In situ* reduction of the labile peroxy linkage in **451b** yields 5-hydroxytropolone **453**. Peroxide **451b** rearranges in CS_2 to lactone **454** which, upon workup, isomerizes to **455**. If

TABLE 4. Product distribution in the photooxidation of tropones **450**



	(450)	(451)	(452)	Total yield	Reference
(a)	$R^1 = R^2 = H$	100%	—	90%	370
(b)	$R^1 = OCH_3$; $R^2 = H$	100%[a]	—	88%	371, 372
(c)	R^1=Ar(Ph, *p*-Tol, *p*-An or *p*-ClC_6H_4); R^2=H	70%	30%	100%	373
(d)	R^1=CH_2Ph; $R^2 = H$	50%	50%	63%	374
(e)	R^1=$CH_2C_6H_4NO_2$-*p*; R^2=H	40%	60%	80%	374
(f)	R^1=$CH_2COC_6H_4NO_2$-*p*; R^2=H	36%	64%	84%	374
(g)	R^1=$COC_6H_4NO_2$-*p*; R^2=H	—	—	no reaction	374
(h)	R^1=Cl; R^2=OEt	100%	—	95%	375
(i)	R^1=R^2=OCH_3	100%	—	85%	375
(j)	R^1=R^2=Ph	*b*	*b*	*c*	376

[a]Ustable at room temperature. Similar results are observed with 4- and 6-isopropyl-2-methoxy tropone[371].
[b]Mixture of positional isomers.
[c]No yield reported.

5% methanol is added to the CS_2, **451b** is converted to diester **456**. The simplest mechanism for these transformations is outlined in equation 168 (though Forbes and Griffiths have presented data suggesting the presence and perhaps intermediacy of a ketene[372]).

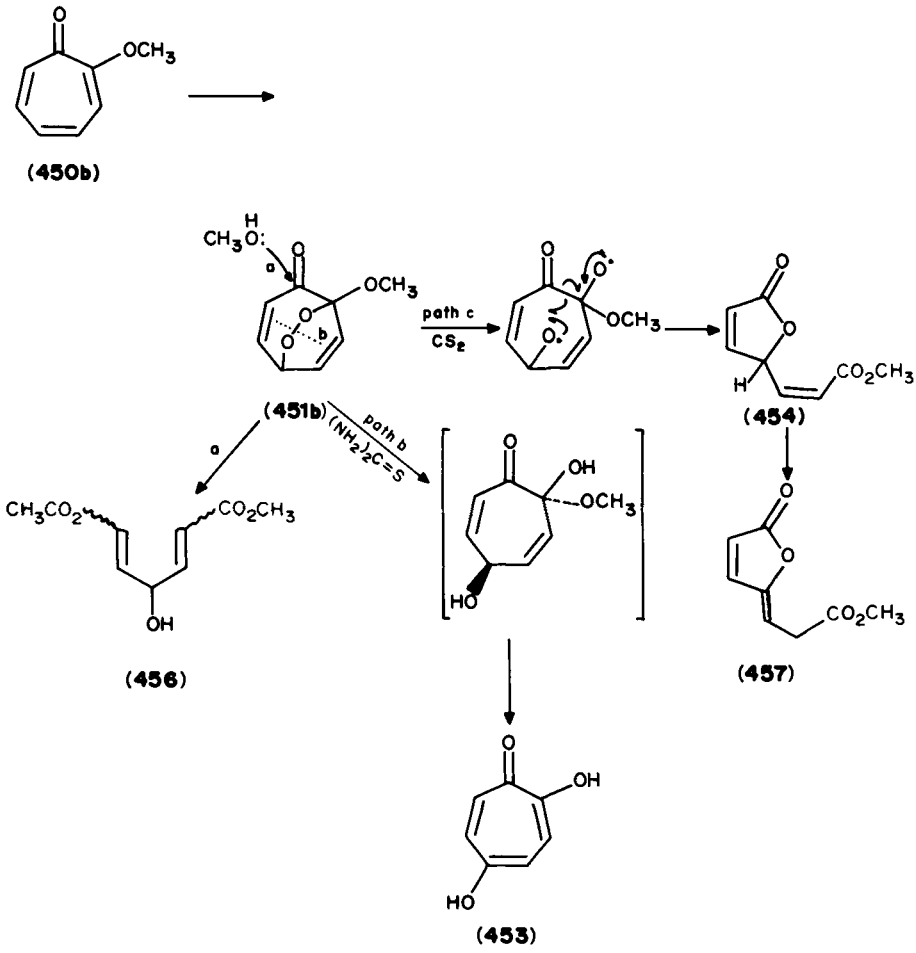
Benztropones **457** undergo photosensitized oxidation to give high yields of lactones **458** (equation 169)[372] via a process analogous to path b of equation 168.

Finally, 2,3-homotropone **459** yields the corresponding endoperoxide **460**. As with other endoperoxides, thiourea reduction yields diol **461** (equation 170)[377].

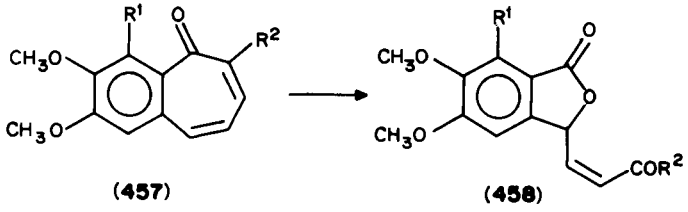
d. Tropolones. Tropolones are 2-hydroxytropones, and as with other tropones endoperoxides are expected to be the primary products of singlet oxygenation. Although a variety of tropolones have been reacted, no stable endoperoxides have been isolated. For example, 5-hydroxytropolone **462** yields not endoperoxide **463**, but the tautomeric hydroperoxide **464** (equation 171)[375].

Tropolone (**465**) itself yielded cyclohepta-3,6-diene-1,2,5-trione (**467**, equation 172)[373]. In this case, a Kornblum–DeLaMare reaction (see Section III.C.2) of hydroperoxide **466** may be involved, though other mechanisms have been suggested[375].

Takeshita and coworkers[371] have obtained utakin **472** in 21% yield from the photooxygenation of 4-*i*-propyltropolone **463**. The proposed mechanism is outlined in equation 173.

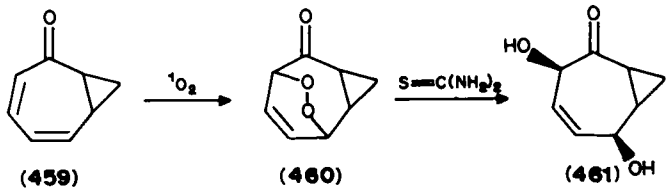


(168)

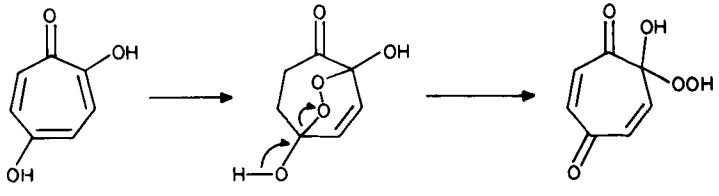


(169)

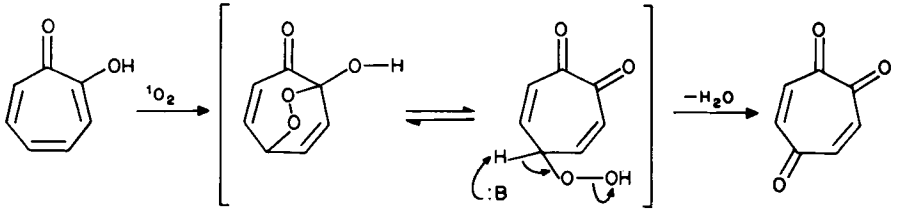
(a) R^1=H, R^2=OMe
(b) R^1=OH, R^2=OMe
(c) R^1=OH, R^2=H



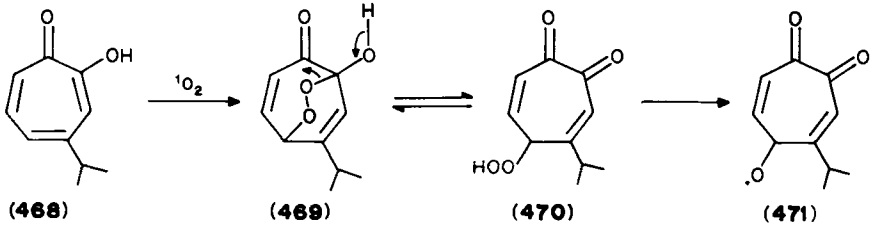
(459) (460) (461) (170)



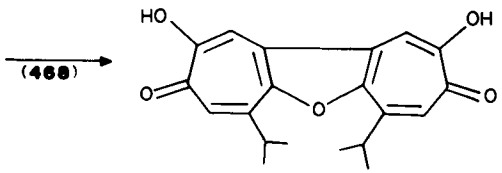
(462) (463) (464) (171)



(465) (466) (467) (172)



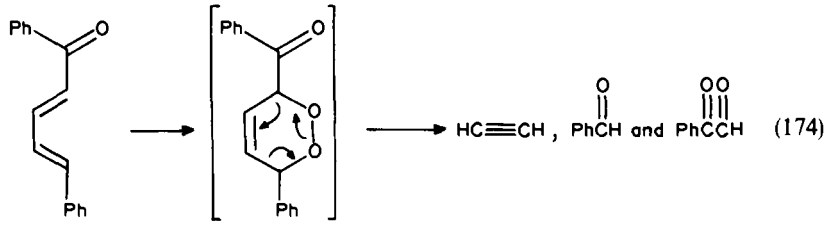
(468) (469) (470) (471)



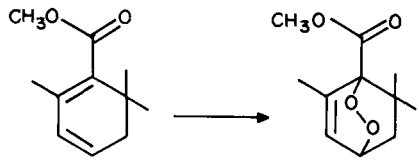
(472) (173)

8. Miscellaneous

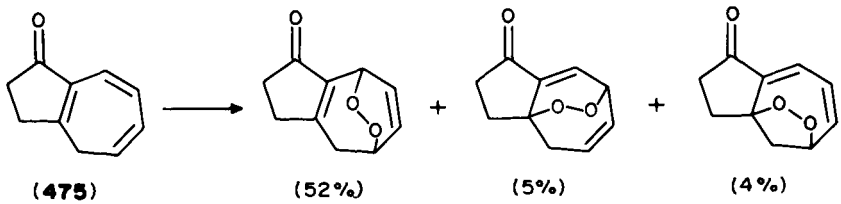
A variety of other dienones react with $^1O_2$ to yield the corresponding endoperoxides, including **473**[378], **474**[379,380] and **475**[381,382] (equations 174–176).

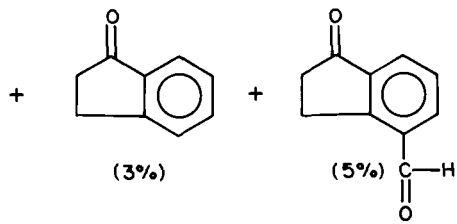


(174)



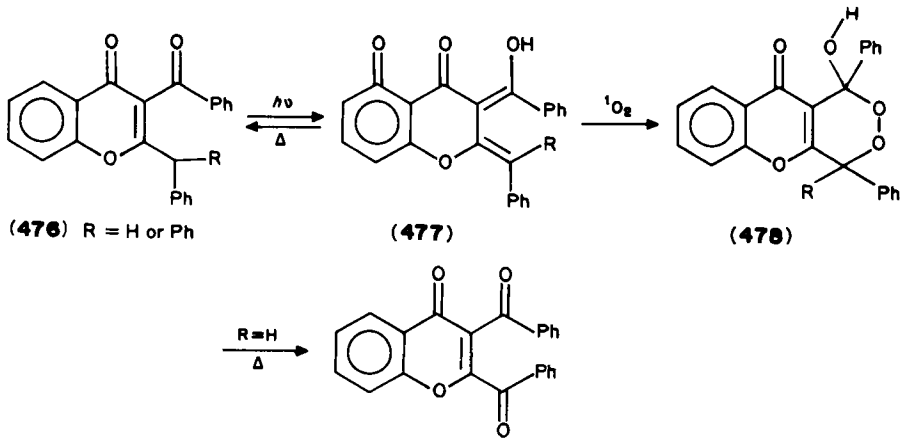
(175)





(176)

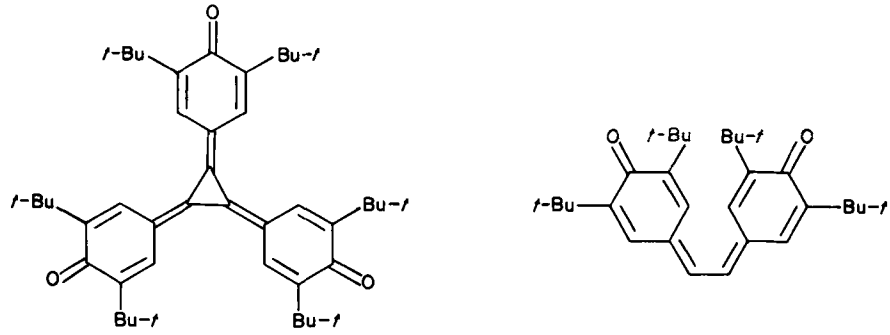
Unsensitized photooxygenation[383] of the photochromic compound **476**, which produces photoenol **477** on normal photolysis, is reported to give peroxide **478** and ultimately dione **479**. The mechanism suggested[306] is outlined below and involves attack of $^1O_2$ on the photoenol **477**.



(476) R = H or Ph (477) (478)

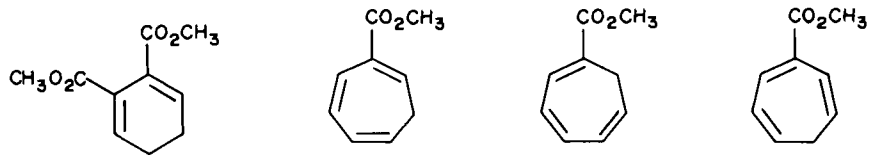
(479)

Ketones **480**[384] and **481**[385] are reported to have low-lying triplets, are efficient physical quenchers of $^1O_2$ and are presumably unreactive.



(480) (481)

Finally, polyene carboxylate diester **482**[386] as well as esters **483**–**485**[387] are all reportedly inert to $^1O_2$.



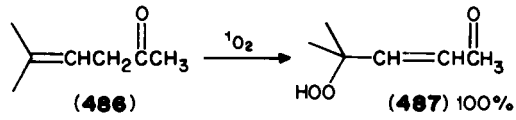
(482) (483) (484) (485)

D. Reaction of $^1O_2$ with β,γ-Unsaturated Carbonyl Compounds

1. Simple systems

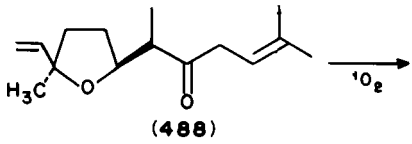
We have noted above the general sluggishness or inertness of simple α,β-unsaturated enones towards singlet oxygen, with the notable exception of those in an *s-cisoid*

conformation. This is consistent with the weak electrophilicity of singlet oxygen. Not surprisingly, therefore, the related β,γ-unsaturated enones serve as good substrates for $^1O_2$, generally generating the corresponding γ-hydroperoxy-α,β-unsaturated enone as the primary, if not sole product. This is true for enones **486**[388,389], **488**[390], **491**[389,391,392], **493**[393] and **495**[394] (equations 177–181).

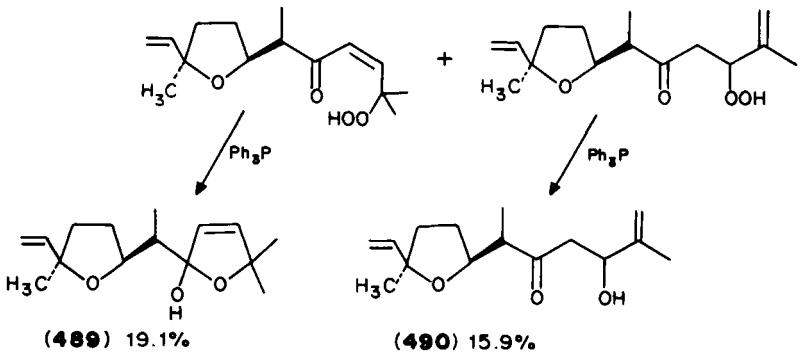


(486) (487) 100%

(177)

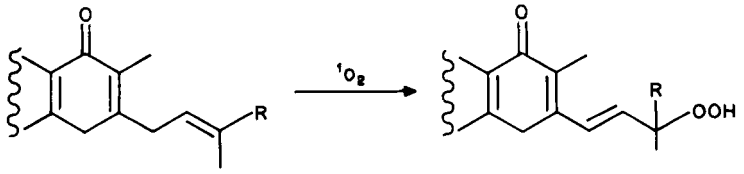


(488)



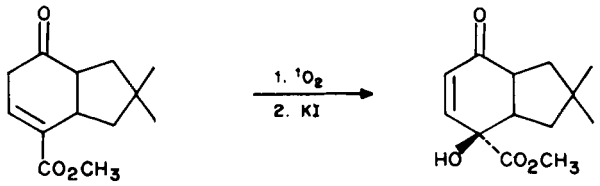
(489) 19.1% (490) 15.9%

(178)



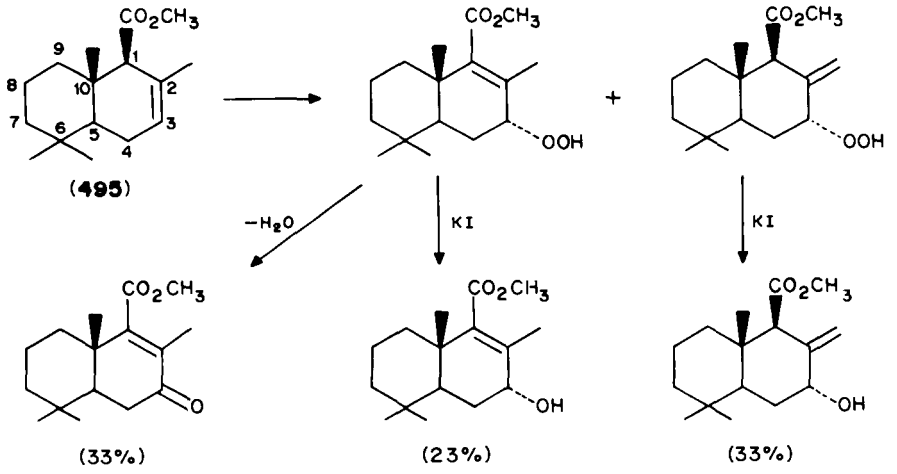
(491) (492)

(179)



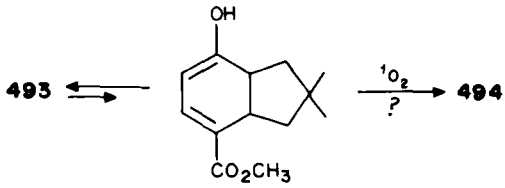
(493) (494)

(180)



(181)

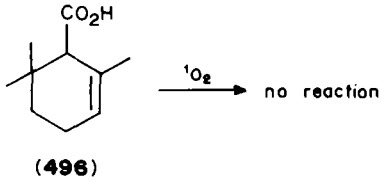
In the case of **493**, the authors[392] suggest that the species undergoing oxidation is actually a dienol (equation 182). The resulting endoperoxide presumably opens to the hydroperoxy precursor of **494**, as observed with tropolones (cf. equations 171–173).



(182)

From compounds **488** and **495** both conjugated and non-conjugated products are formed, though the former predominate. In the case of **495**, the oxygen approaches the ring exclusively *trans* to the C-10 angular methyl group. As noted above, singlet oxygen is quite sensitive to steric considerations and the methyl and carboxylate groups inhibit approach of $^1O_2$ to the top side of the compound.

In the light of the facile oxygenation of esters **493** and **495**, it is surprising that cyclohexenecarboxylic acid **496** is unreactive to $^1O_2$[262] (equation 183).

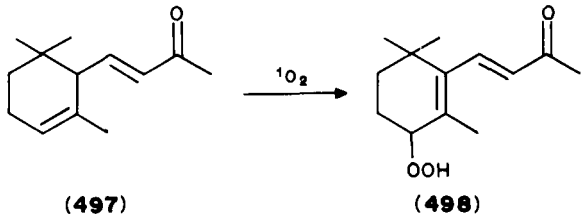


(183)

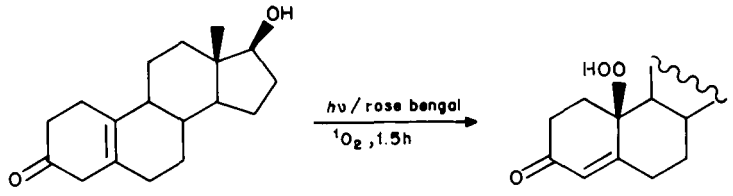
Vinylogous reactions are also known. Thus α, β, δ, ε-dienone **497** yields the conjugated **498**[336] (equation 184).

A series of steroidal compounds have also been explored and again the conjugated product predominates. 17β-Hydroxyester-5(10)-en-3-one **499** reacts rapidly with singlet oxygen to give a high yield of 10β- and 10α-hydroperoxides **500** and **501** (equation 185)[395].

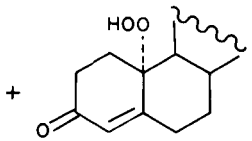
This is to be compared with the slow, low-yield autoxidation of **499** which yields **500** exclusively[130,131] (equation 186; cf. equation 48).



(497) (498) (184)



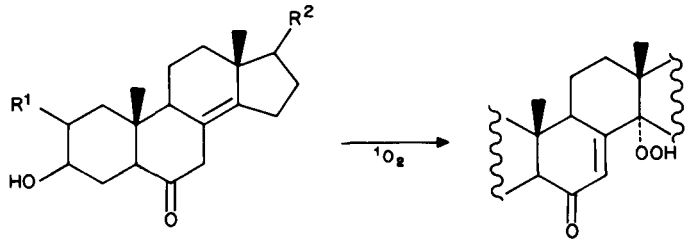
(499) (500) 70%



(501) 20% (185)

$$\mathbf{499} \xrightarrow[^3O_2,\,90\,h]{h\upsilon} \mathbf{500}\ (31\%) \qquad (186)$$

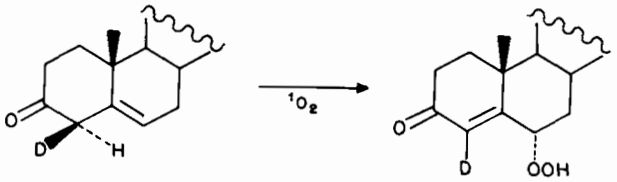
Similarly 6-oxo-$\Delta^{8(14)}$ steroids **502** yield the 14α-hydroxy-7-en-6-ones (**503**) (equation 187)[388,396].



(502) (503) (187)

Finally, Furutachi and colleagues[388] report that while the autoxidation of Δ^5-cholesten-3-one **100a** produces a mixture of the conjugated 6α- and 6β-hydroperoxides **101** and **102**, singlet oxygenation generates **101** exclusively[388]. The stereoselectivity of this

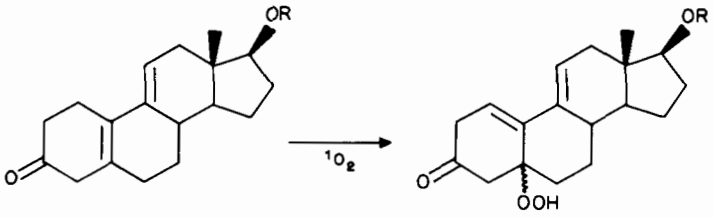
reaction was confirmed by deuterium labelling (equation 188). It should be noted that there are earlier reports[397] suggesting that both **101** and **102** are obtained in hematoporphyrin-sensitized reactions. These, however, probably involve free-radical processes.



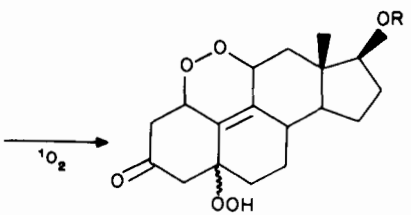
(100d) 90%D (101d) 85%D (188)

2. Non-conjugated polyene carbonyls

We have already mentioned above the oxygenation of dienone retinoid **497** in which one of the double bonds is conjugated with the carbonyl group, while the remote double bond is not. In this case, reaction occurs so as to bring the second double bond into conjugation as well (equation 184)[336]. In steroid **112**, on the other hand, both double bonds are out of conjugation with the carbonyl but are conjugated to one another. Because of the *s-trans* conformation, Diels–Alder reaction is precluded. Singlet oxygen reacts with this system via an ene mode to give as the initial product diene **504**, in which the olefinic linkages remain conjugated. Since they are now cisoid, a rapid $^1O_2$ Diels–Alder addition ensues producing a mixture of α- and β-endoperoxides **505** (equation 189)[398].

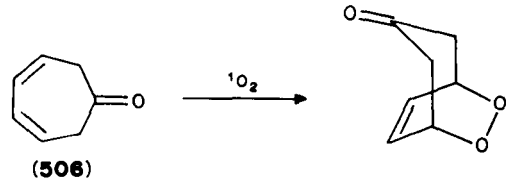


(112) (504)

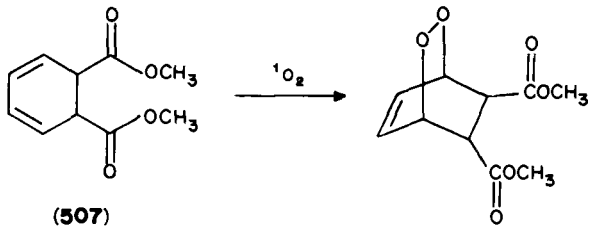


(505) (189)

As expected, where an *s-cis* conformation is feasible 2 + 4 cycloaddition is observed. Thus 3,5-cycloheptadienone **506**[399a] and cyclohexadiene **507**[399b] yield the related endoperoxides (equations 190 and 191).

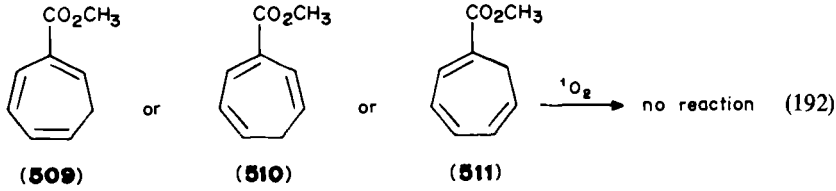


(506) (190)

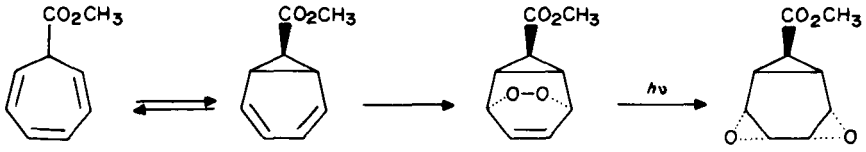


(507) (191)

Of the four isomeric cycloheptatrienecarboxylic acid esters (**508**–**511**), only the 2,4,6-isomer **508** proved reactive to singlet oxygen generated via photosensitization or microwave discharge (equation 192 and 193)[387,400]. In both cases, the norcaradiene endoperoxide **513** was the major product; however, under photosensitization the corresponding diepoxide **514** is formed.



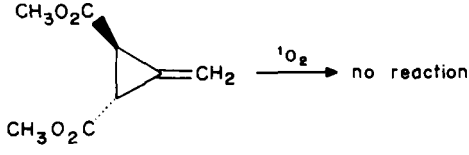
(509) (510) (511) (192)



(508) (512) (513) (514)

(193)

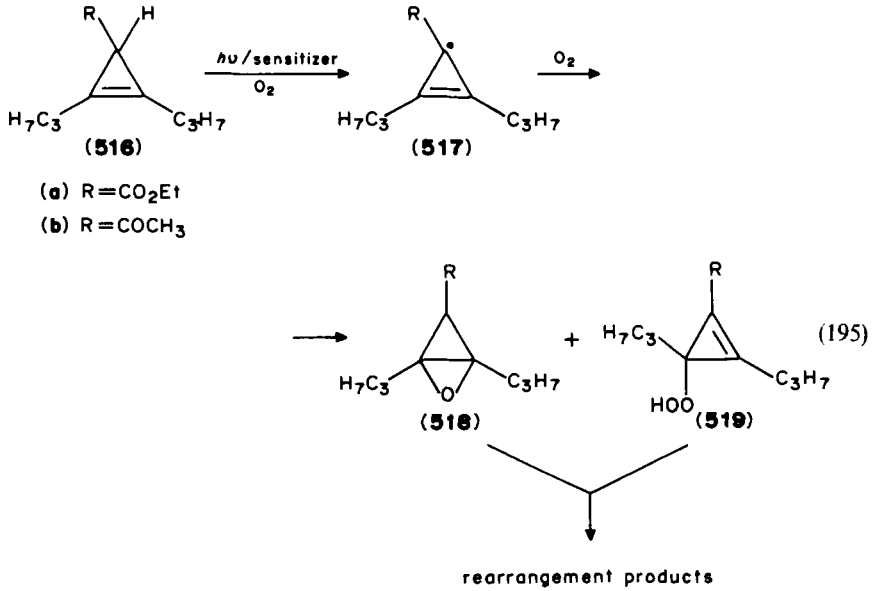
Frimer and coworkers have studied the effect of strain on singlet-oxygen reactions[401–405]. Presumably, because of the early transition state of such processes, $^1O_2$ is essentially insensitive to the increase of strain in the ultimate products. It is surprising, therefore, that ester **515** as well as other methylenecyclopropanes are inert to singlet oxygen (equation 194).



(515) (194)

Frimer[401,404] has attributed this inactivity to an excessively large interatomic distance between the α-olefinic carbon and the γ-allylic hydrogen, a distance which must be spanned by the molecular oxygen irrespective of mechanism. For methylencyclopropane, the C_α-$H_{allylic}$ distance is 3.27 Å compared to only 3.02 Å in isobutylene. Frimer suggests that as a result of this increment of 0.25 Å, the ring allylic hydrogens are essentially 'out of reach' for the abstracting oxygen atom.

Frimer and Antebi[401,405] also studied the photosensitized oxidation of two other ring-strained β,γ-unsaturated carbonyl compounds, ester **516a** and ketone **516b**. Although the uptake of oxygen proved quite rapid, the reaction was slowed by radical inhibitors but not by $^1O_2$ quenchers. This and other evidence clearly indicates that the primary products, epoxide **518** and allylic hydroperoxide **519**, result not from a singlet-oxygen (Type II) reaction but from free-radical (Type I) processes (equation 195).



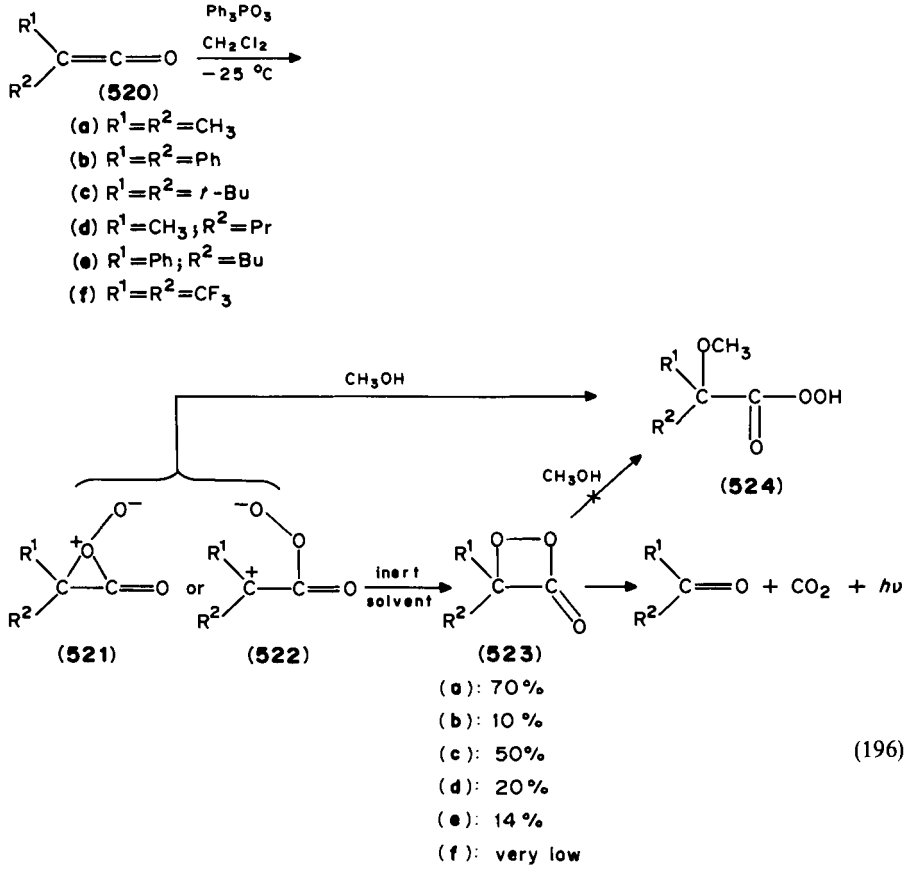
(195)

The question remains, however, as to why no $^1O_2$ reaction is observed. The answer would seem to be related to the relatively high ionization potential of cyclopropene[406,407] (see Section IV.A). With the rate of $^1O_2$ reaction slowed substantially, the competing photochemically initiated free-radical autoxidation predominates.

E. Ketenes

The low-temperature (−25 °C) reaction of a variety of ketenes **520** with singlet oxygen (chemically generated from triphenylphosphite ozonide) yields the corresponding dioxetanes, α-peroxy lactones **523** (equation 196)[408,409]. The latter cleaves to ketone and CO_2 with fluorescence. The formation of these α-peroxy lactones by photooxygenation at −78 °C could be established by spectroscopy (characteristic IR absorption ~1880 cm^{-1}). However, the yields were generally much lower than those listed in equation 196, presumably because of competing autoxidation yielding peresters (see Section III.D.4) and possibly because of the instability of α-peroxy lactones to these photooxidative reaction

conditions. In methanol, α-peroxy lactone formation is completely suppressed and α-methoxyperacetic acids **524** are produced instead. Since the peroxy lactones are stable to methanol, peracids **524** could well result from an intercepted perepoxide **521** or zwitterion **522** intermediate.



(196)

V. SUPEROXIDE ANION RADICAL

A. Generation

Despite the omnipresence of one-electron processes in nature, free-radical damage presents a serious and constant threat to living organisms[410–412]. One available source of radicals in the body is the surperoxide radical $O_2^{-\bullet}$, which is formed in a large number of reactions of biological importance in both enzymic and non-enzymic processes[2,3]. It follows then that it is of great value to understand the organic chemistry of $O_2^{-\bullet}$ for, as Fridovich[413] has poignantly noted: 'If we are going to know how it does its dirty work, we have to know what it is capable of doing'. Nevertheless, had convenient methods not been found for generating $O_2^{-\bullet}$ in aprotic organic solvents, progress in this direction would have undoubtedly been slow and tedious.

Two basic approaches have been developed and are presently in use. The first involves *in situ* generation of $O_2^{-\cdot}$ by the electrolytic reduction of molecular oxygen[414-416]. This method permits the controlled generation of low concentrations ($< 10^{-2}$ M) of pure $O_2^{-\cdot}$ and is well suited for mechanistic studies. This is particularly true for cyclic voltammetry, which allows the researcher to follow the course of the reaction and detect unstable intermediates. Efficient product studies, however, require greater $O_2^{-\cdot}$ levels.

An alternate approach utilizes superoxide salts which are well-defined sources of $O_2^{-\cdot}$. The inorganic salts, such as the commercially available potassium superoxide (KO_2), are generally insoluble in aprotic organic solvents, though they are slightly soluble in those of high polarity like DMSO. Nevertheless, solutions of KO_2 have been conveniently prepared in benzene, toluene, acetonitrile, DMSO, pyridine, triethylamine, THF, etc. through the agency of phase-transfer catalysts such as crown ethers[417]. Tetramethylammonium superoxide has also been synthesized and, in contrast to its alkali-metal analogues, is quite soluble in a number of aprotic solvents[418,419].

It should be noted that the halogenated solvents (Freons, CCl_4, $HCCl_3$, CH_2Cl_2) are unsuitable since they react with superoxide[420-424]. Protic media induce the acid-catalyzed disproportionation of superoxide to triplet molecular oxygen ($^3O_2$) and hydroperoxy anion (equation 197)[27]. This process involves primarily two steps (equations 198 and 199) for which kinetic and thermodynamic data have been evaluated by pulse radiolysis[425]. In aprotic media, on the other hand, this solvent-induced disproportionation is absent, while highly unfavorable energetics (equation 200)[426] rule out a spontaneous disproportionation.

$$H^+ + 2O_2^{-\cdot} \rightleftharpoons HO_2^- + O_2 \tag{197}$$

$$H^+ + O_2^{-\cdot} \rightleftharpoons HO_2^{\cdot} \qquad pK_a(HO_2^{\cdot}) = 4.69 \tag{198}$$

$$HO_2^{\cdot} + O_2^{-\cdot} \rightarrow HO_2^- + O_2 \qquad k = 1 \times 10^8\ M^{-1}\,s^{-1} \tag{199}$$

$$2O_2^{-\cdot} \rightarrow HO_2^- + O_2^{-2} \qquad \Delta G > 28\ \text{kcal mol}^{-1} \tag{200}$$

B. Modes of Reaction

The data obtained over the past decade have led scientists to suggest four basic modes of action for $O_2^{-\cdot}$ in aprotic media, namely electron transfer (equation 201), nucleophilic substitution (equation 202), deprotonation (equation 203) and perhaps hydrogen atom abstraction (equation 204)[27]. It is important to remember, however, that subsequent to each of these primary modes, secondary oxidative processes can and generally do take over. Hence, one must proceed with due caution in any attempt to determine the mechanism of reaction simply based on product analysis. Let us now examine each of these modes in a bit more detail.

$$R + O_2^{-\cdot} \rightarrow R^{-\cdot} + O_2 \tag{201}$$

$$RX + O_2^{-\cdot} \rightarrow RO_2^{\cdot} + X^- \tag{202}$$

$$RH + O_2^{-\cdot} \rightarrow R^- + HOO^{\cdot} \tag{203}$$

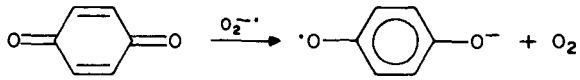
$$RH + O_2^{-\cdot} \rightarrow R^{\cdot} + HOO^- \tag{204}$$

1. Electron transfer

Electron transfer is one of the most common modes of $O_2^{-\cdot}$ action in biological systems and is the essence of the disproportionation process (equation 199). This is of course not

surprising, considering that the redox potential of the $O_2/O_2^{-\cdot}$ couple (vs. NHE) is -0.33 V in water and -0.6 V in organic solvents[427,428]. This quarter of a volt gap between aqueous and aprotic media cannot be attributed to differences in the dielectric constants of the media, since the electrochemical potential of oxygen is relatively insensitive to the differing dielectric constants of a variety of aprotic solvents[427-430]. To understand this and many other phenomena related to $O_2^{-\cdot}$ activity (e.g. nucleophilicity and basicity; *vide infra*), we must recall that $O_2^{-\cdot}$ is a small, hard, non-polarizable anion. In aqueous/protic media it will be highly and tightly solvated and, hence, *thermodynamically* more stable than in aprotic media in which such solvation mechanisms are generally absent.

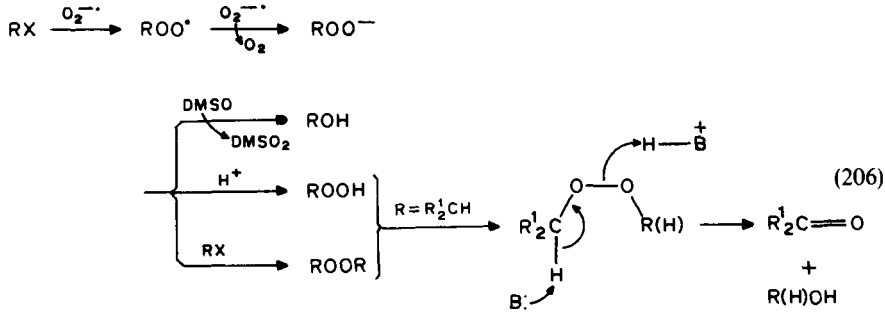
Superoxide does not interact with simple olefins or aromatic compounds. It will, however, transfer electrons to good electron acceptors such as quinones, which are converted to the corresponding semiquinones (equation 205)[431-435].



(205)

2. Nucleophilic attack

In aprotic media, $O_2^{-\cdot}$ is an extremely vigorous nucleophile[27]. This 'supernucleophilicity' has been rationalized in terms of the α-effect and is related to the destabilizing effect of the vicinal pairs of non-bonding electrons[27]. Superoxide reacts with halides and sulfonates by an S_N2 process to produce hydroperoxides, peroxides, alcohols or carbonyl compounds depending on the substrate, reaction conditions and work-up procedures, as outlined in equation 206.



(206)

Similarly esters, including linoleates and acyl halides, undergo nucleophilic attack yielding the corresponding diacyl peroxides or carboxylic acids ('saponification'). Evidence has recently been presented, however, which suggests that, in some systems at least, 'saponification' proceeds via an electron transfer process[436,437].

In protic media by comparison, $O_2^{-\cdot}$ reacts by this mode sluggishly, if at all, as a result of the inhibitory effect of the tight hydration sphere surrounding this small, charged anion.

3. Deprotonation

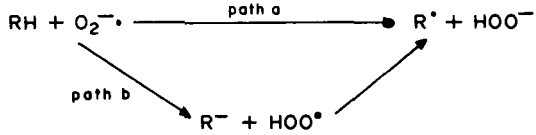
The pK_a of HOO·, determined by aqueous radiolytic studies, is 4.69 (equation 198)[425]. Its conjugate base $O_2^{-\cdot}$ should therefore be as weakly basic as acetate. Nevertheless, in

aprotic media superoxide has proven to be a powerful mediator of base-catalyzed process. This greater basicity has been rationalized from three perspectives. Firstly, $O_2^{-\cdot}$ in aprotic media lacks the 'stifling' solvation sphere commonplace for small hard anions in aqueous and protic media. Furthermore, in the poorly solvating aprotic media the equilibrium described by equation 198 should be shifted away from the charged species $O_2^{-\cdot}$ towards its electroneutral counterpart HOO·. Indeed Sawyer[438] has reported a higher pK_a value (~ 12) for HOO· in DMF, and this value should be even higher in non-polar solvents. More importantly, however, unlike the low fluxes of superoxide obtained when it is generated enzymatically or radiolytically, $O_2^{-\cdot}$ is longer lived and generally present in much higher concentration in aprotic media. In the presence of excess $O_2^{-\cdot}$, the facile disproportionation reaction (equation 199) between $O_2^{-\cdot}$ and its conjugate acid (HOO·) drives the unfavorable deprotonation (equation 198) to the right. This in turn raises the effective basicity of $O_2^{-\cdot}$, i.e. the efficiency with which $O_2^{-\cdot}$ can effect proton transfer. Indeed, calculations[27] show that $O_2^{-\cdot}$ can promote proton transfer from substrates to an extent equivalent to that of a conjugate base of an acid with a pK_a of ~ 25.

In light of superoxide's apparent basicity, it is not surprising that it induces elimination reactions as well as base-catalyzed autoxidation (BCA). Qualitatively, Frimer and coworkers[27] have consistently found that the rate of a BCA process depends on the exact nature of the base utilized and decreases in the order: *t*-butoxide > superoxide > hydroxide.

4. Hydrogen abstraction

Radical reactions are the final modes of action anticipated for superoxide anion radical. Surprisingly, $O_2^{-\cdot}$ *in aprotic media* turns out to be a rather unreactive radical. Regarding superoxide's ability to abstract hydrogen atoms, thermodynamic calculations[439] suggest that $O_2^{-\cdot}$ is only likely to do so from those very rare substrates bearing R—H bonds with bond energies as low as 66 kcal. Indeed, the reinvestigation of systems originally assumed to be initiated by hydrogen-atom abstraction mediated by $O_2^{-\cdot}$ (equation 207, path a) have nearly all turned out to be proton abstraction, followed by oxidation of the resulting anion either by the concomitantly formed hydroperoxy radical or molecular oxygen (equation 207, path b)[27].



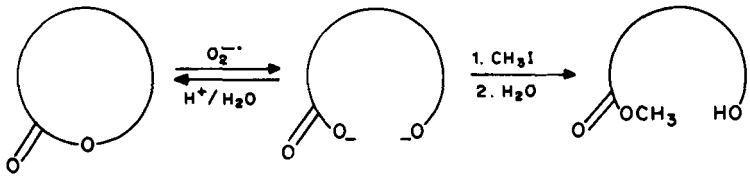
(207)

We have noted above that superoxide is generally unreactive with olefins, and here again thermodynamic calculations confirm that the radical addition of superoxide to the olefinic double bonds is more than 18 kcal endothermic[27d]. $O_2^{-\cdot}$ does not initiate free-radical chain polymerization and actually inhibits styrene polymerization[440,441]. Finally, radical–radical coupling, so common and rapid with normal radicals, is quite rare for $O_2^{-\cdot}$, with the noted exception of superoxide anion-radical cation couplings[27]. By contrast, *in aqueous media* superoxide can serve as an oxidant and thereby initiate radical processes[442,443].

5. Work-up conditions

Frimer and coworkers have described[444] two methods for working-up superoxide reactions. In the first, the reaction is quenched with aqueous acid (e.g. 10% HCl) and the

acidic products are extracted by saturated sodium bicarbonate washings. In the second, a tenfold excess of methyl iodide is added to the reaction mixture prior to aqueous work-up. This has the effect of converting the excess superoxide to methoxide or dimethyl ether, in addition to methylating the oxyanions present. As we shall see shortly, this latter method has been found to be particularly useful for detecting and trapping 'saponification' products which, under aqueous workup, simply recyclize back to starting material (equation 208).

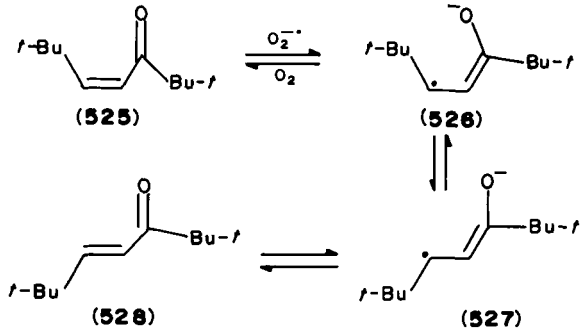


(208)

C. Reaction of Superoxide with Enones Lacking Labile Hydrogens

1. Simple enones

The simple enone moiety *per se* is generally unreactive to $O_2^{-\cdot}$. Thus, 4,4,6,6-tetrasubstituted cyclohex-2-en-1-ones **188** have proved totally inert to superoxide, even after being in contact for several days[27b,68,164,165] (see equation 81). Some reversible electron transfer does seem to occur, however. Gibian and Russo[445,446] have demonstrated that $O_2^{-\cdot}$ induces the extremely rapid *cis* to *trans* isomerization of *cis*-2,2,6,6-tetramethylhept-4-en-3-one **525** (equation 209). The isomerization to the *trans* isomer **528** presumably proceeds via ketyls **526** and **527**, although radical species could not be observed by CIDNP. It should be noted that *trans* **528** is slowly converted to unidentified products. Neither pivalic acid nor 3,3-dimethylpyruvic acid were observed, products analogous to those ultimately obtained from chalcones (see next section).

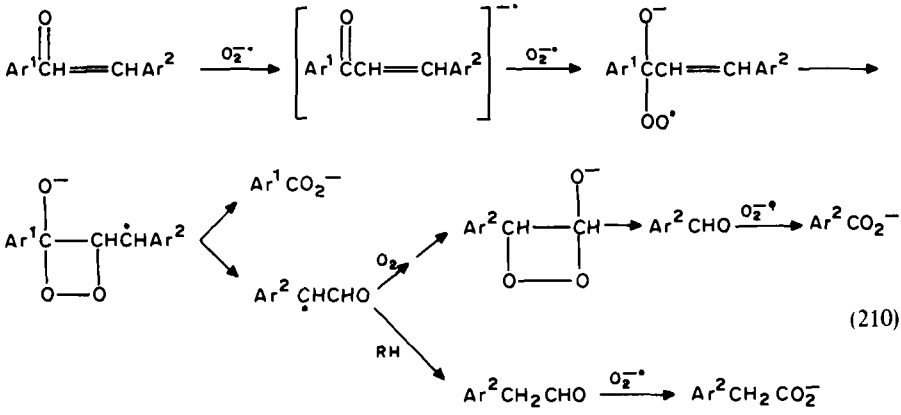


(209)

2. Aryl enones

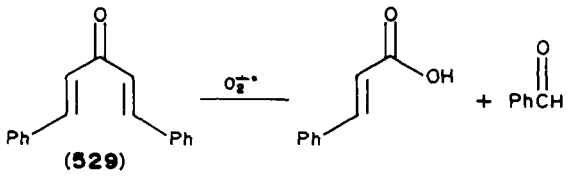
When the π system is extended, the electron transfer from $O_2^{-\cdot}$ to substrate becomes a much more facile process. Frimer and Rosenthal[447,448] have studied the oxidative cleavage of chalcones mediated by $O_2^{-\cdot}$. Carboxylic acids were obtained as the final products and no intermediate epoxide formation could be detected. A Michael-type addition to the enone system was further excluded on the basis of $K^{18}O_2$ experiments

which showed very little label incorporation. The mechanism suggested involves electron transfer (equation 210).



(210)

In a related study, dibenzylideneacetone **529** reacted with $O_2^{-\cdot}$ to yield cinnamic acid and benzaldehyde (equation 211)[449].



(211)

(529)

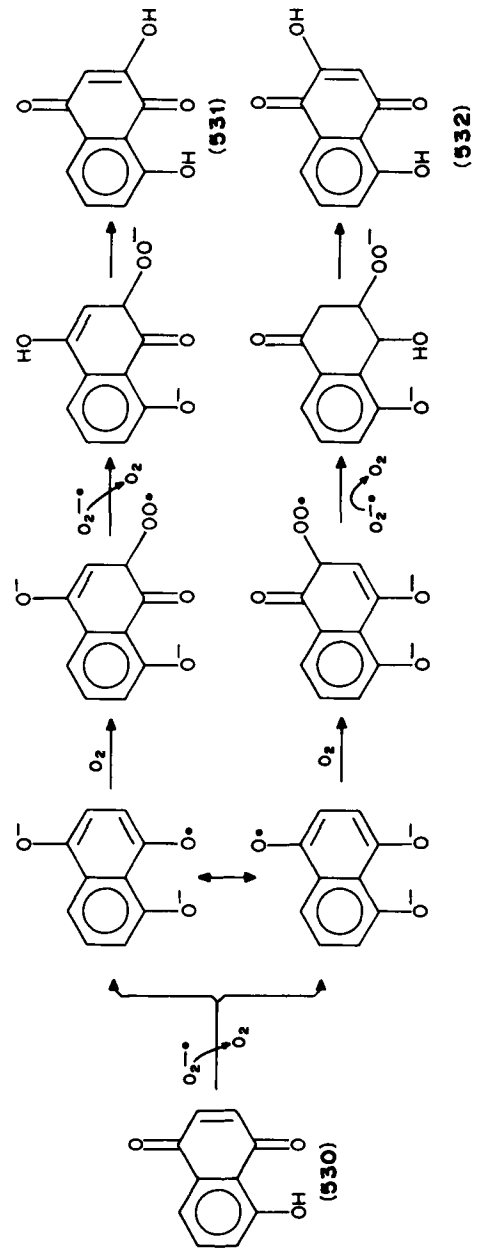
3. Quinones

Several research groups report that anion radicals can be detected by ESR in the reaction of $O_2^{-\cdot}$ with various benzoquinones[431-435]. However, other than the reversible formation of radical anions, no oxidation products have been isolated in these cases.

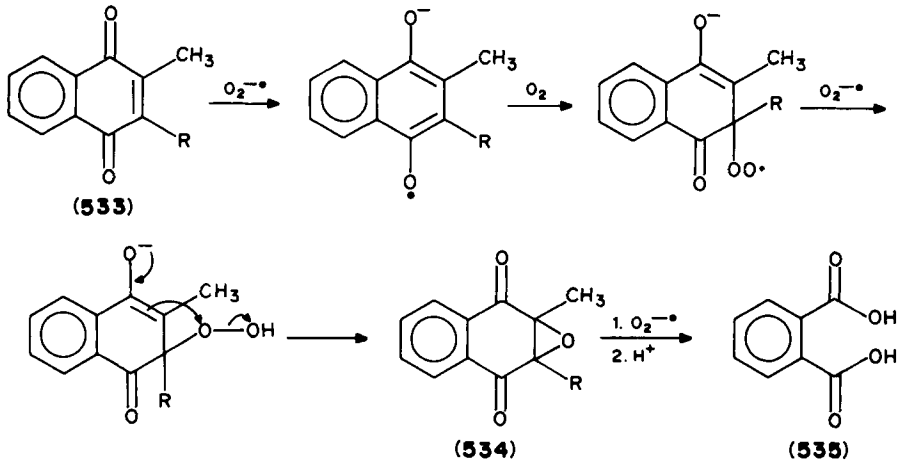
De Min and coworkers[435] have recently studied the reaction of superoxide (generated from KO_2 in toluene in the *absence* of 18-crown-6) with juglone (5-hydroxy-1, 4-naphthaquinone; **530**). They report that isomeric enols **531** and **532** are the ultimate oxidation products formed following initial electron transfer of $O_2^{-\cdot}$ to the quinone substrate. The suggested mechanism is outlined in Scheme 24.

Saito and colleagues[450] report that 2,3-dimethyl-1,4-napthaquinone **533** and other vitamin-K-related compounds react with KO_2/18-crown-6 to give the corresponding oxirane **534** and its secondary oxidation product phthalic acid in a 25–35% yield. The remaining products are unidentified and the mechanistic details are unclear. Based on the reactions of other benzoquinones[431-435] initial electron transfer is likely here as well (equation 212), although other mechanisms involving deprotonation have been suggested[27d].

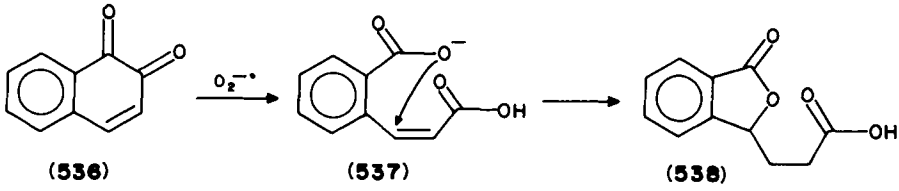
1,2-Naphthaquinone (**536**) is oxidatively cleaved[451], like other α-diketones[27], to the corresponding diacid **537**. Under the basic reaction conditions, the latter undergoes intramolecular Michael addition to furanone **538** (equation 213).



SCHEME 24. Superoxide mediated oxidation of Juglone (530)



(212)

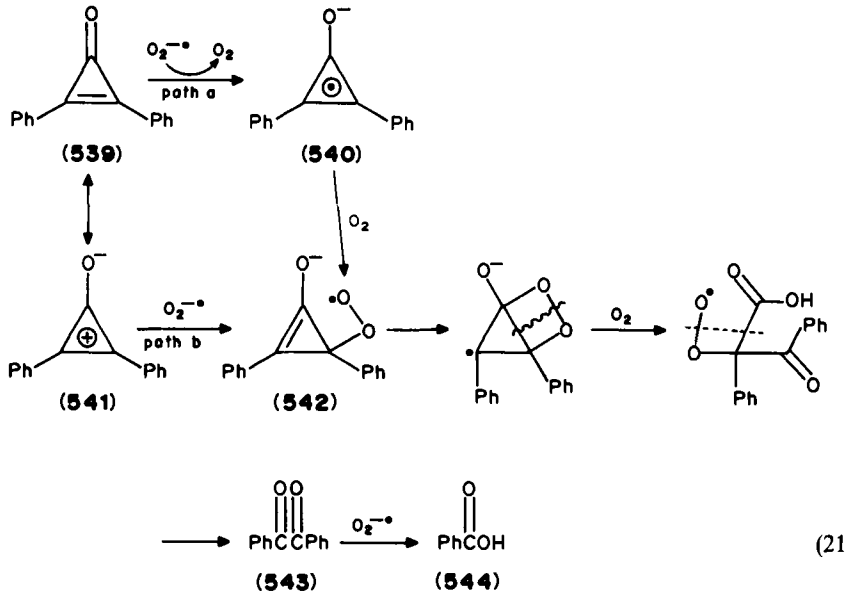


(213)

4. Annelones

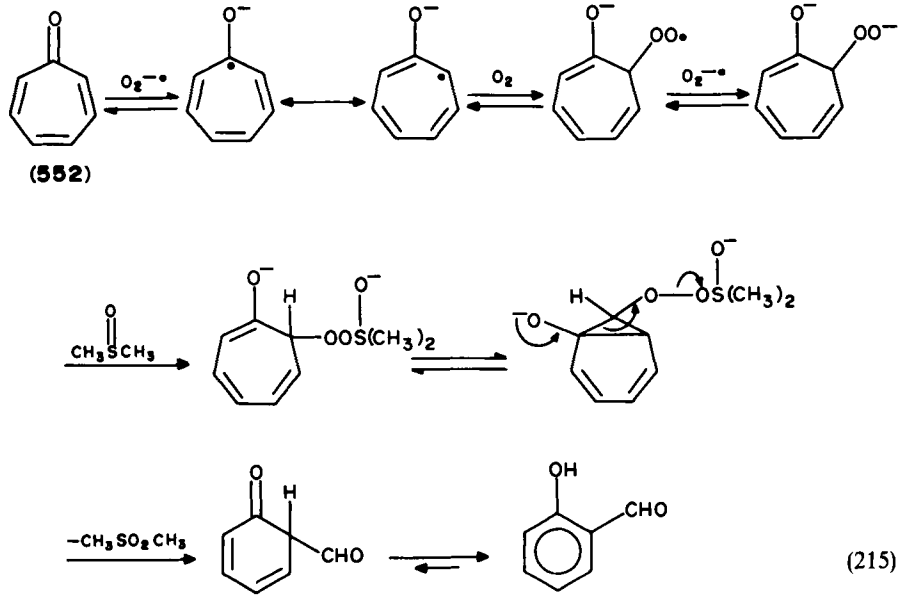
a. Cyclopropenones. Diphenylcyclopropenone **539** reacts slowly with superoxide (85% conversion after 7 days)[452] to give benzil **543** (18%) and its oxidative cleavage product[27], benzoic acid **544** (27%). Neckers and Hauck[452] presume that an electron transfer reaction is involved, since the aromatic radical anion **540** is reported to form benzil in the presence of oxygen[453] (equation 214, path a). Nevertheless, diphenylcyclopropenone **539** is also known to react with nucleophiles, as a consequence of the large contribution of aromatic mesomeric structure **541**. Nucleophilic attack of $O_2^{-\bullet}$ on **541** (equation 214, path b) is expected to give the same initial oxygen adduct **542**.

b. Cyclopentadienones. The reaction of tetracyclones **545** with $O_2^{-\bullet}$ leads to 2-pyrone **548**, 2-hydroxyfuranones **549** and benzoic acids **550** and **551**[447,448,452,454] (see Scheme 25). Although the pyrones can be formed via the corresponding epoxides, these were not observed as intermediates in this reaction. As before, electron transfer is presumed to be the first step generating radical anion **546**. Highest unpaired electron density is expected α to the carbonyl (as in **547**) which allows for extended conjugation as well as double allylic and benzylic stabilization of the radical. Oxygenation, followed by cyclization, along path a or path b ultimately leads to pyranone **548** or furanone **549** respectively. The benzoic acids presumably result from oxidative cleavage of various intermediates along the reaction route (see Scheme 25).

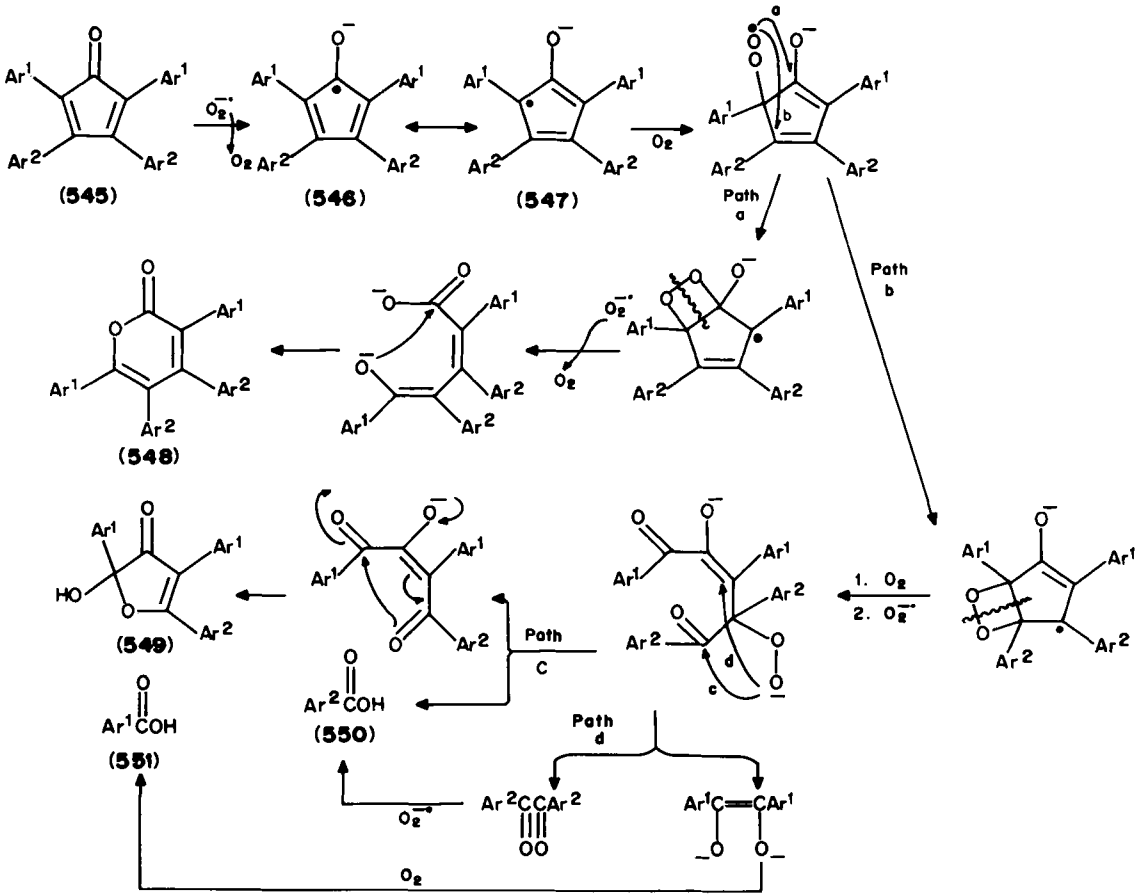


(214)

c. Cycloheptatrienones. Kobayashi and coworkers[455] report that tropone **552** reacts with $O_2^{-\bullet}$ in DMSO, generating salicylaldehyde. Here, too, electron transfer is proposed as the initial step. Surprisingly, however, no reaction occurs in either DMF, benzene or acetonitrile. This anomaly leads the authors to conclude that the oxidation of DMSO by a reversibly formed intermediate is a crucial step in this reaction (equation 215).



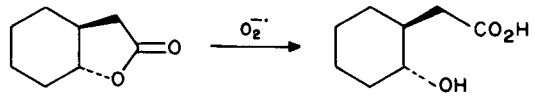
(215)



SCHEME 25. Mechanism for the $O_2^{-\cdot}$ mediated oxidation of tetracyclones

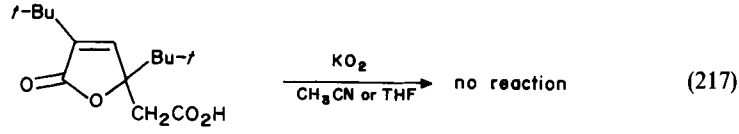
5. *Lactones*

a. 2-Furanones. Lactones, like esters, are expected to undergo $O_2^{-\cdot}$ mediated saponification[27]. Indeed, dihydrofuranone **553** reacts with KO_2/crown ether to generate, upon aqueous work-up, the corresponding hydroxy acid **554** (equation 216)[456].

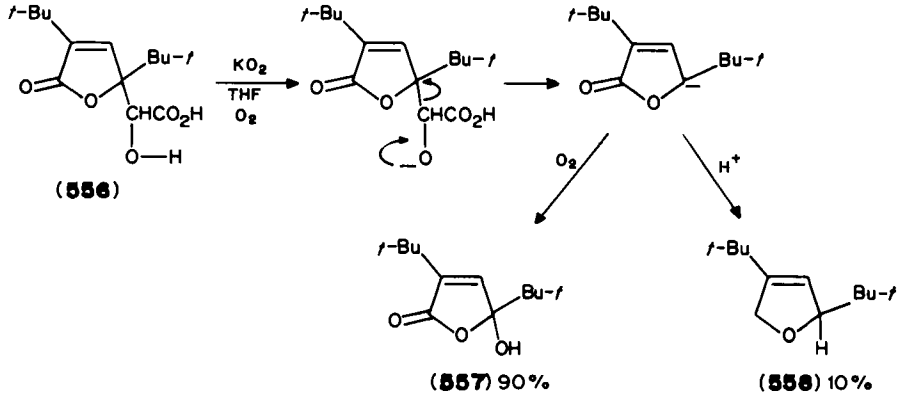


(553) (554) (216)

Interestingly, however, reaction is not always observed with the corresponding unsaturated analogs. Thus Moro-oka and Foote[457] report that 2-furanone **555** was unreactive to KO_2 introduced to the reaction mixture as a powder dispersion in CH_3CN or THF (equation 217). Related furanone **556** was converted to **557** and **558** but again no saponification products were observed (equation 218).



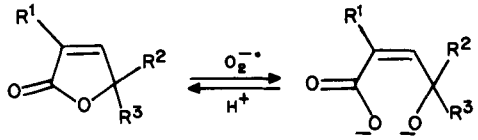
(555) (217)



(556)

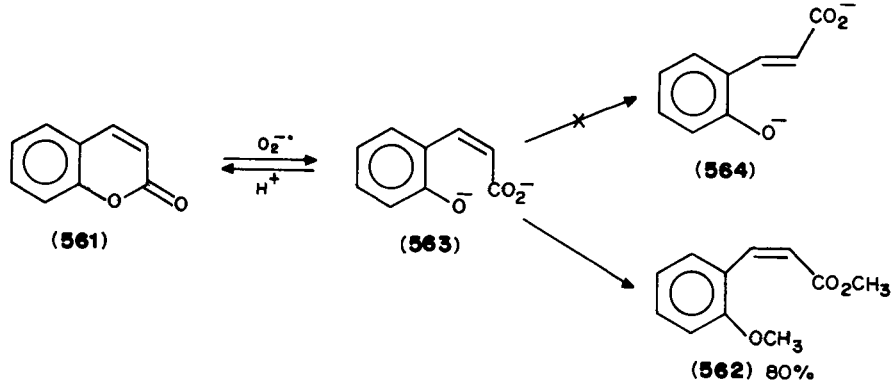
(557) 90% (558) 10% (218)

It is likely that the absence of saponification products results from the facile recyclization of these hydroxy acids back to lactones under the aqueous work-up conditions (equation 219). In contradistinction to the saturated analogs, free rotation is not allowed and the alcohol and acid fragments are held in proximity to one another. This in turn facilitates lactonization, even under mild conditions. The validity of this hypothesis has been demonstrated in the coumarin system described in the next section.



(559) (560) (219)

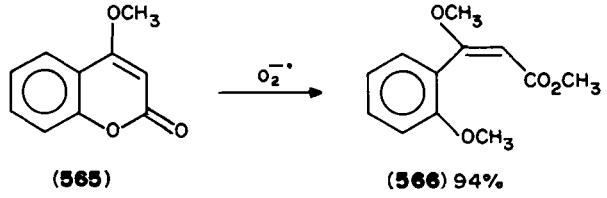
b. Coumarins. When the α,β-unsaturated lactone coumarin **561** was reacted with $O_2^{-\cdot}$ in aprotic media followed by aqueous acid work-up, only starting material was isolated. When, however, methyl iodide was used to quench the reaction and convert oxy-anions to methoxy species, an 80% yield of the methyl esters of *o*-methoxy-*cis*-cinnamic acid **562** was obtained (equation 220)[443]. This clearly indicates that the primary process is nucleophilic attack by $O_2^{-\cdot}$ at the lactone carbonyl carbon yielding saponification product **563**.



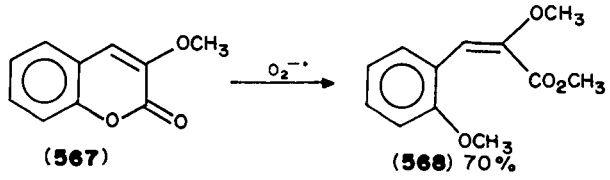
(561) (563) (564) (562) 80% (220)

It is worth noting that no Michael addition of $O_2^{-\cdot}$ has been observed. Furthermore, despite the long reaction time (16 h), there was no evidence for the isomerization of *cis*-**563** (the dianion of *o*-coumarinic acid) to *trans*-**564** (the dianion of *o*-coumaric acid).

By similar processes, methoxycoumarins **565** and **567** are saponified by $O_2^{-\cdot}$, generating esters **566** and **568** (equations 221 and 222)[443].



(565) (566) 94% (221)



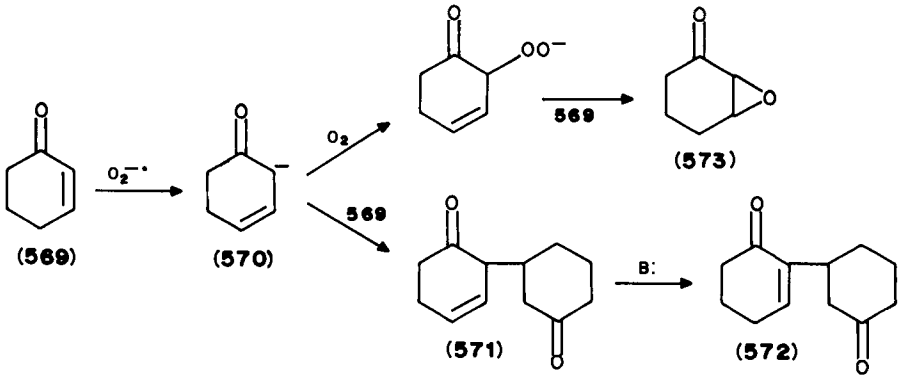
(567) (568) 70% (222)

D. Reaction with Enones Bearing Labile Hydrogens

1. C—H bonds

In discussing the properties of superoxide (Section V.B.3), we noted that its experimental effective basicity is somewhere in between hydroxide and *t*-butoxide. It is not surprising, therefore, that the deprotonation of labile hydrogens is probably the most prevalent mode of action for $O_2^{-\cdot}$ in aprotic media. The results obtained in base-catalyzed autoxidation processes mediated by superoxide are generally the same as those obtained with other bases of comparable base strength.

We have already described above the superoxide-mediated oxidation of cyclohexenones[27b,68,164,165] and steroids[199,200,212] (see Sections III.E.3.b and III.E.4). One interesting discrepancy observed in this regard relates to the superoxide-mediated oxidation of the unsubstituted cyclohex-2-en-1-one, **569** (equation 223). Frimer's group[27b,68,164,165], using KO_2/18-crown-6, observed only dimer **572** and trimer formation but no oxidation products. On the other hand, Dietz and coworkers[458], using electrogenerated $O_2^{-\cdot}$, reported a 30% yield of epoxide **573**. *Both* these results have been reconfirmed by Sugawara and Baizer[207] who suggest that, in the case of the electrochemical generation of $O_2^{-\cdot}$, the solvent is saturated with oxygen. In the absence of excess oxygen, the anion of cyclohexenone **570** has too little opportunity to form the hydroperoxide essential for the epoxidation reaction, and reacts by the available alternative pathway, Michael addition.

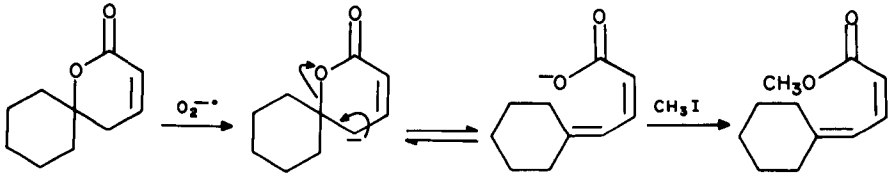


(223)

To test this hypothesis, the reaction of cyclohexenone with KO_2/18-crown-6 was repeated, but this time the reaction mixture was bubbled vigorously with oxygen[165]. An NMR analysis of the product mixture indicated the presence of a 10% yield of epoxide. A small amount of dimer (~ 3%) was formed, but no trimer could be detected. The remaining products seem to be the result of multiple oxidation and could not be characterized.

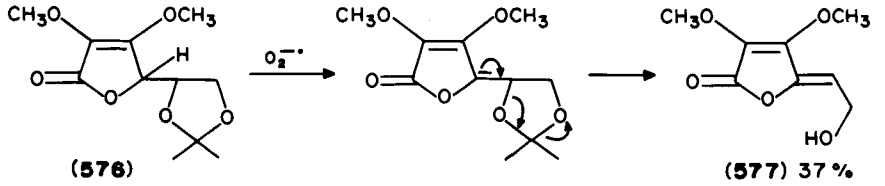
This simple example indicates that oxygenation is not always the preferred reaction course for a carbanion. Gilinsky-Sharon and Frimer[459] report that 5,6-dihydropyrone **574** reacts with superoxide to give dienone **575** in 90% yield, upon methyl iodide work-up of the reaction mixture (equation 224). Such base-induced elimination processes are precedented in the dihydropyrone[460] family.

A similar elimination reaction is observed[459] for ascorbic acid derivative **576**, which is converted by superoxide to alkylidene furanone **577**. This reaction, too, is precedented with other bases[461] (equation 225).



(574) (575) 90%

(224)



(576) (577) 37%

(225)

We note in passing that in both these cases saponification of the lactone linkage is not observed (cf. Section V.C.5).

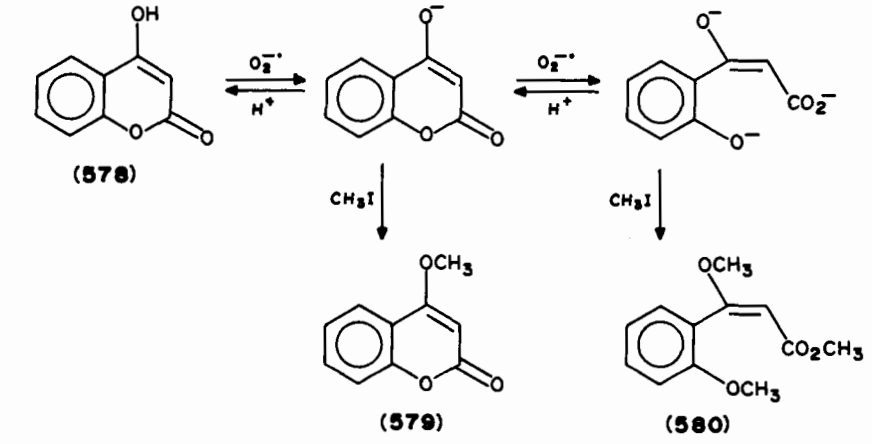
2. O—H bonds

a. Enols. In our discussion of base-catalyzed autoxidation we have already described superoxides' ability to deprotonate cyclohexenone and steroidal enols and induce their transformation to the corresponding lactols and/or other oxygenation products (see Section III.E.3.b)[27b,68,164,199,200]. The enols of 1,3-diones are also rapidly deprotonated by superoxide[205,207], but resist further oxygenation (see equation 72)[171,203–207].

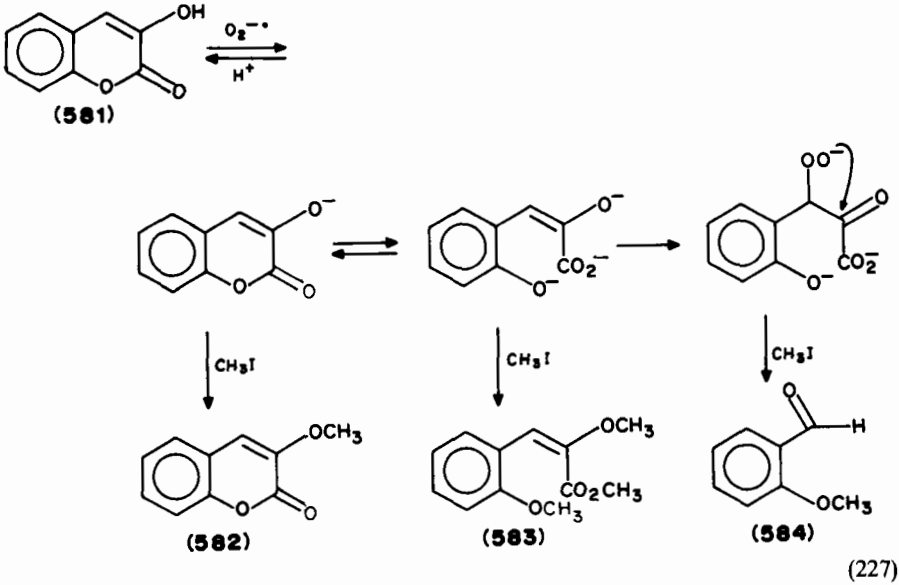
3-Hydroxyflavones **219** undergo $O_2^{-\cdot}$ mediated autoxidation[180,184,185] to a mixture of depsides **221** and its 'saponification' products **222** and **223** (equation 89). Takahama[180] carried out this reaction in aqueous media using the photooxidation of riboflavin as his $O_2^{-\cdot}$ source. El-Sukkary and Speier[194] observe the same reaction using KO_2/18-crown-6 in THF. Surprisingly, however, this reaction does not occur when benzene or toluene are the solvents[462]. This raises some serious doubts as to the inertness of THF. The problematic nature of THF was in fact noted two decades ago by two pioneers in the superoxide field, Le Berre and Berguer[463], who discussed the instability of THF superoxide solutions.

In Section V.C.5 we noted that coumarins undergo 'saponification' of the lactone linkage with superoxide. However, in the case of the enols, 4- and 3-hydroxycoumarins, **578** and **581** (equations 226 and 227), deprotonation precedes saponification[68,443]. When **578** is reacted with $O_2^{-\cdot}$ for one hour, a 30% yield of simple deprotonation product **579** can be isolated subsequent to CH_3I work-up. At longer reaction times (16 h), deprotonation plus saponification affords **580** in 83% yield (equation 226).

Similarly, when **581** is reacted with $O_2^{-\cdot}$ for one hour, simple deprotonation product **582** and deprotonation plus saponification product **583** are isolated in 20% and 40% yields respectively. The remaining 40% is the oxidative cleavage product *o*-methoxybenzaldehyde **584**, which becomes the major product (93% yield) after 16 h of reaction. The probable mechanism is outlined in equation 227.



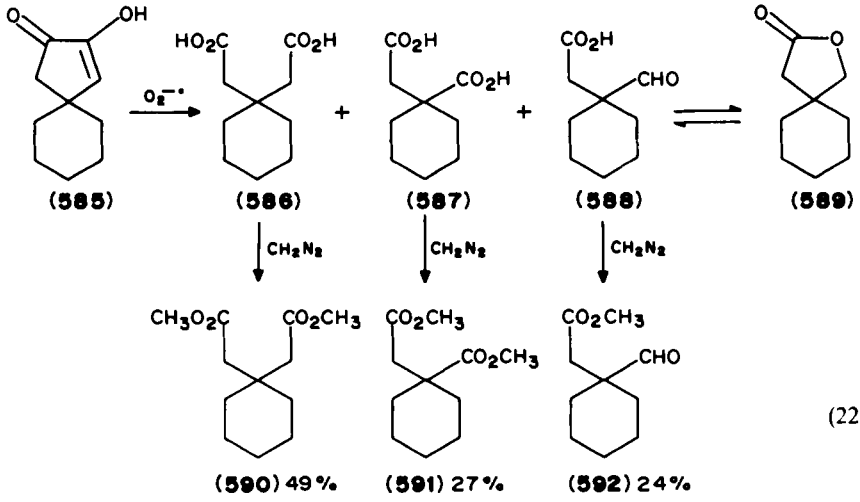
(226)



(227)

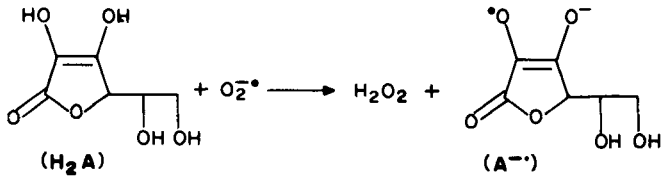
Gilinsky-Sharon[459] reports that enol **585** reacts with superoxide to give a quantitative yield of acidic products. When the product mixture was diazotized and separated by GLC, three products in a ratio of 2:1:1 were isolated and identified as diesters **590** and **591** and aldehydoester **592**, respectively. These three are presumably formed from the corresponding acids **586** and **587**, and lactone **589** (equation 228).

The formation of lactols from enols is a well-precedented base-catalyzed autoxidation process and hence the formation of lactol **589** is expected. Superoxide is also known to oxidize aldehydes to acids and to effect the oxidative cleavage of diketones to diacids[27]; hence, the oxidation of **588** to **587** and generation of **586** from **585** is not surprising.

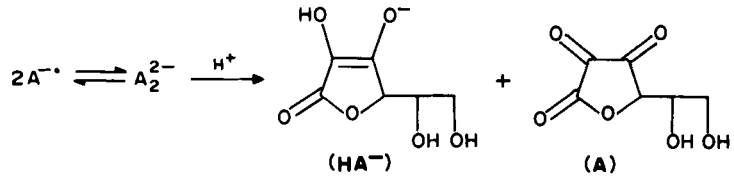


(228)

b. Reductones and ascorbic acid derivatives. The aqueous solution oxidation of ascorbic acid (H_2A) and its anion (HA^-) to dehydroascorbic acid (A) by superoxide ion ($O_2^{-\cdot}$) and its conjugate acid, perhydroxyl radical ($HO_2^{\cdot}$), has been demonstrated to be a direct one-electron transfer process ($k \approx 10^5\ M^{-1}\,s^{-1}$). The anion radical of ascorbic acid ($A^{-\cdot}$) is generally assumed to be the initial product[464-466] (equation 229). A subsequent study[467] has suggested that $A^{-\cdot}$ disproportionates to HA^- and dehydroascorbic acid (A) via an initial dimerization (equation 230). These results are consistent with the biochemical study of Nishikimi[468] on ascorbate oxidation at pH 7.4 by $O_2^{-\cdot}$ ($k \sim 10^5\ M^{-1}\,s^{-1}$) that was generated enzymatically (xanthine–xanthine oxidase).



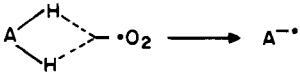
(229)



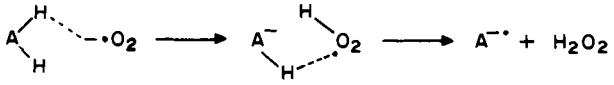
(230)

Comparable studies have been carried out in aprotic media using electrogenerated superoxide to mediate the oxidation of H_2A to A. Sawyer and coworkers[469-472] find that the stoichiometry for this reaction requires three molecules of ascorbic acid and two molecules of superoxide. In addition, superoxide mediates this process without the formation of molecular oxygen. As a result of these observations, Sawyer suggests that the

initial rate-determining step is a concerted (equation 231) or rapid sequential (equation 232) transfer of a proton and a hydrogen atom to superoxide generating $A^{-\cdot}$ and H_2O_2 ($k = 2.8 \times 10^4\ M^{-1}s^{-1}$). Subsequent reactions involve the proton-induced disproportionation of $A^{-\cdot}$ (equation 233) and oxidation of the resulting HA^- by H_2O_2 to yield A (equation 234). The sum total of these processes (equation 235) has the proper stoichiometry.



(231)



(232)

$$2A^{-\cdot} + H_2A \rightarrow A + 2HA^- \quad (233)$$

$$HA^- + H_2O_2 \rightarrow A + H_2O + HO^- \quad (234)$$

$$3H_2A + 2O_2^{-\cdot} \rightarrow 3A + 3H_2O + 2HO^- \quad (235)$$

Very recently, Afanas'ev and colleagues[473] have taken issue with Sawyer's mechanism for the superoxide–ascorbic acid system. The Russian group reports that a 50–70% yield of ascorbate anion is formed when electrogenerated superoxide reacts with H_2A in acetonitrile. They posit that this high yield of ascorbate can only be explained by a deprotonation of AH_2 effected by superoxide. They believe, therefore, that deprotonation (equation 236) is the main if not sole pathway of interaction of superoxide with ascorbic acid. Any oxygen generated from the disproportionation of superoxide (equation 237) is presumably converted back to superoxide upon interaction with ascorbate (equation 238). However, the disproportionation is prevented by a series of competing processes (equations 239–242) which eventually convert ascorbate to dehydroascorbic acid.

$$O_2^{-\cdot} + AH_2 \rightarrow HO_2^{\cdot} + AH^- \quad (236)$$

$$HO_2^{\cdot} + O_2^{-\cdot} \rightarrow HO_2^- + O_2 \quad (237)$$

$$AH^- + O_2 \rightarrow AH^{\cdot} + O_2^{-\cdot} \quad (238)$$

$$HO_2^{\cdot} + AH_2 \rightarrow H_2O_2 + AH^{\cdot} \quad (239)$$

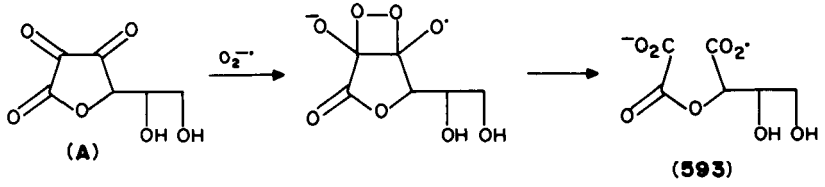
$$HO_2^{\cdot} + AH^- \rightarrow H_2O_2 + A^{-\cdot} \quad (240)$$

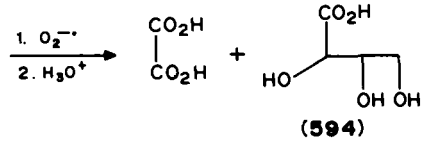
$$HO_2^{\cdot} + AH^{\cdot} \rightarrow H_2O_2 + A \quad (241)$$

$$HO_2^{\cdot} + A^{-\cdot} \rightarrow HO_2^- + A \quad (242)$$

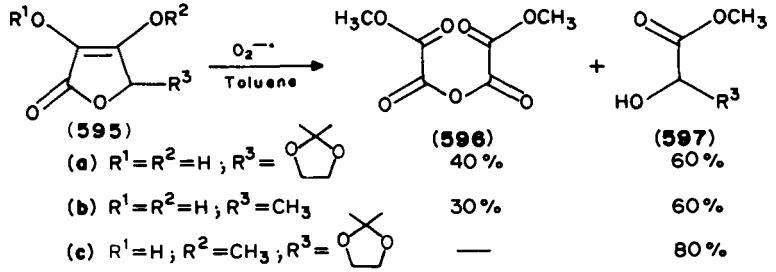
Sawyer and coworkers[469–472] also report that superoxide reacts further with the dehydroascorbic acid producing oxalate and (by inference) the anion of threonic acid **594**. They suggest that this proceeds via nucleophilic attack of $O_2^{-\cdot}$ at the C_3-carbonyl followed by dioxetane formation and cleavage generating ketoester **593**. Saponification of the latter would yield the observed products (equation 243). It should be noted that products were not isolated in the above studies, and the evidence is based on a combination of spectral and electrochemical data of the reaction mixtures.

Frimer and coworkers[459,474,475] have reacted a variety of reductones with KO_2/crown ether in toluene in the hope that the products isolated would shed some light on the question of mechanism. Gilinsky-Sharon[459,474] reacted ascorbic acid derivatives **595a** and **b** with $O_2^{-\cdot}$ and isolated ketoesters **596** as well as the corresponding threonic acid derivatives **597** (equation 244).



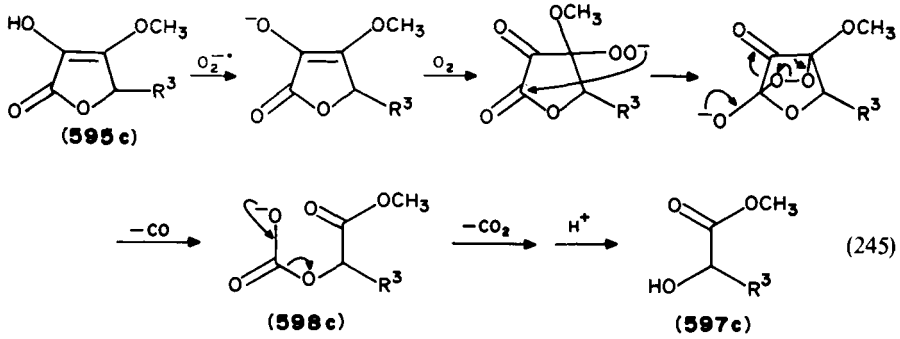


(243)



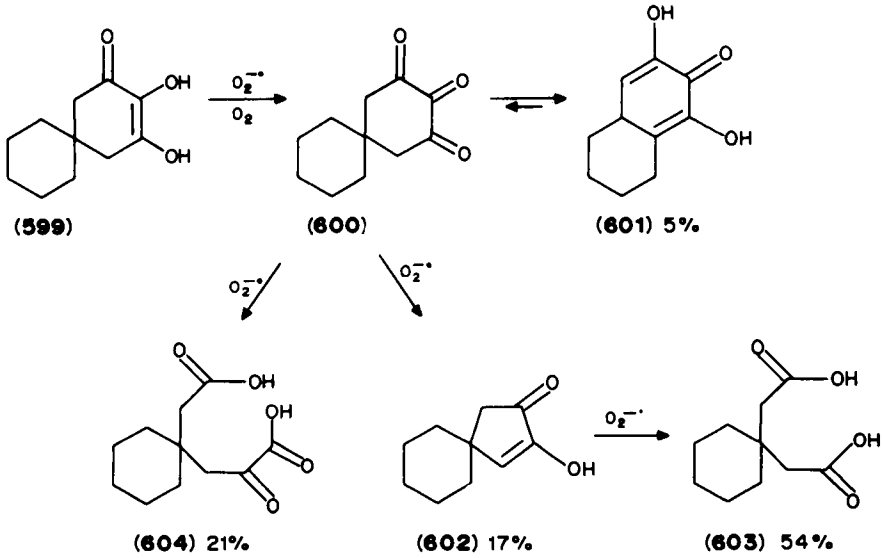
(244)

Assuming that reductones **595a** and **595b** are initially oxidized to the corresponding triketones (analogous to dehydroascorbic acid, **A**) and then on to the observed products these results confirm the mechanism for the oxidation of dehydroascorbic acid as outlined in equation 243. Interestingly, however, enol ether **595c** also yields **597c**, though no **596c** was observed. This is somewhat surprising since the 3-methoxy group is expected to prevent the oxidation of **595c** to the corresponding triketone, the precursor required by the mechanism of equation 243. In this case, the course of the reaction can be readily rationalized in terms of an initial deprotonation of the α-hydroxy group (equation 245). Oxygenation then proceeds as described for the base-catalyzed autoxidation of enols to lactols (Section III.E.3.a). In this case, however, loss of carbon monoxide generates carbonate **598**, which further loses CO_2 generating **597c** in high yield and as the sole product.



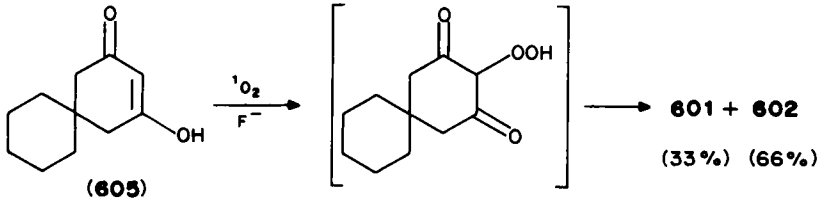
(245)

Spiroreductone **599** was reacted[459] with an equivalent of $O_2^{-\cdot}$ under an oxygen atmosphere generating enols **601** and **602** as well as diacids **603** and **604** (equation 246). When oxygen is scrupulously removed from this system prior to reaction (by six freeze–thaw cycles) then only **601** and **602** are formed in a 90% yield and in a 1:2 ratio. The mechanism suggested is outlined in equation 246.



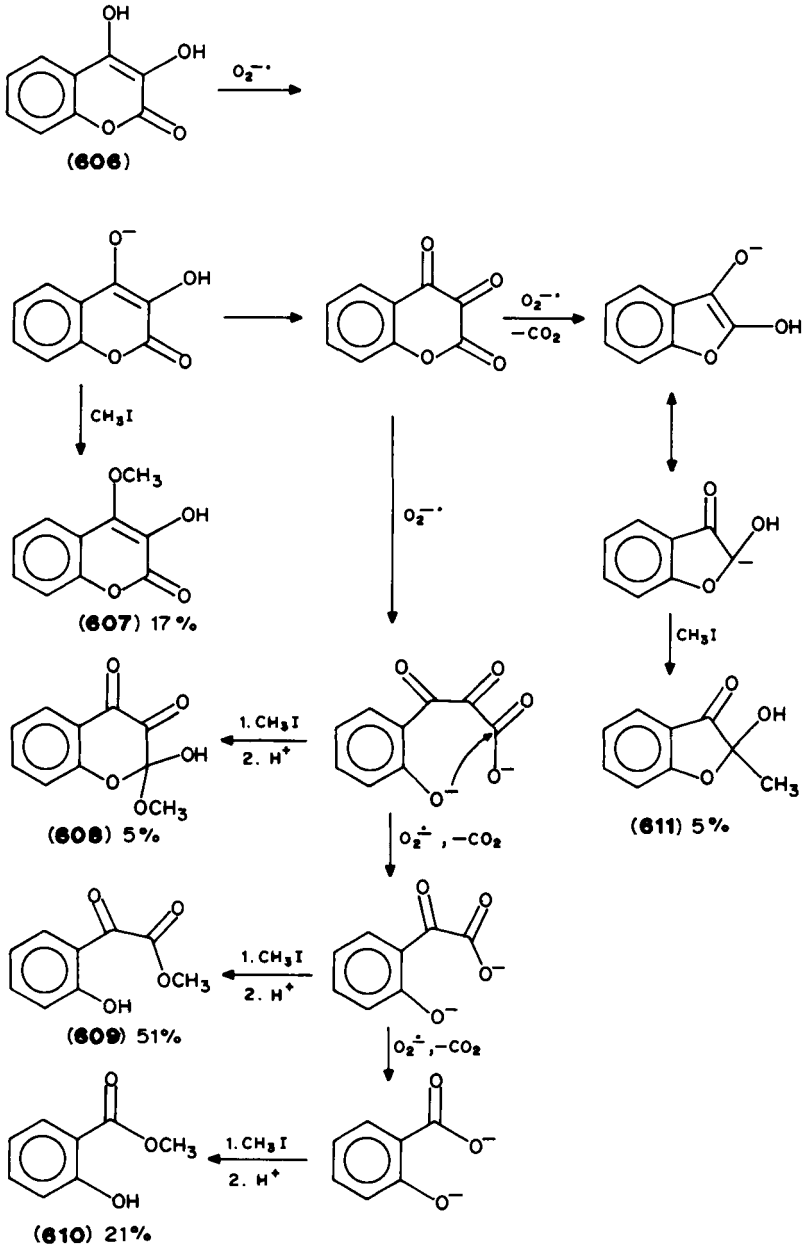
(246)

The initial step involves formation of triketone **600** which tautomerizes to **601**, undergoes benzylic acid rearrangement and decarboxylation to **602**, or cleaves oxidatively (in the fashion of diketones) to **604**. Oxidative cleavage of **602** yields diacid **603**. Gilinsky-Sharon[459] succeeded in synthesizing **601** independently via the fluoride-catalyzed singlet oxygenation[69,72] of enol **605** (equation 247; see Section IV.C.2).



(247)

Finally, coumarin reductone **606** reacts[475] with KO_2/crown ether in THF yielding, upon methyl iodide work-up, products **607–611**. The proposed reaction mechanism is outlined in Scheme 26. The isolation of substantial amounts of **607** tends to confirm Afanas'ev's suggestion[473] that superoxide reacts with reductones via initial deprotonation.



SCHEME 26. Product formation in the $O_2^{-\cdot}$ mediated oxidation of coumarin reductone **606**

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CHAPTER **18**

Reduction of α,β-unsaturated carbonyl compounds

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I. INTRODUCTION

The two main reduction modes of α,β-unsaturated aldehydes and ketones involve formal hydride attack at either the C-1 or C-3 of the enone system, leading to allylic alcohol

or saturated carbonyl compound, respectively. It has been suggested that the relative importance of these paths depends on the relative 'hardness' or 'softness' of the substrate, defined in terms of coefficients of the lowest unoccupied molecular orbital (LUMO) (*vide infra*). While the 1,2 addition is considered to be a more charge-controlled process, 1,4 addition is a frontier-orbital controlled process.

In addition to these two reduction modes, which involve formal addition of a single hydrogen molecule to the substrate, it is also possible to add two hydrogen molecules, yielding the corresponding saturated alcohol. Alternatively, formal addition of two molecules of hydrogen may completely deoxygenate the substrate, giving the unsaturated hydrocarbon. Finally, total reduction with three hydrogen molecules would provide the saturated hydrocarbon.

The synthetic application of a given reduction method should be considered primarily in terms of its regioselectivity, stereochemical control and chemoselectivity. Regioselectivity refers mainly to selection between the 1,4- and 1,2-reduction modes. Stereochemical control refers to the relative and absolute configuration of the newly formed sp^3 centers at positions 1, 2 or 3 of the enone system. Chemoselectivity refers to the opportunity of selectively reducing the desired functionality in a complex molecule containing other easily reducible functional groups. Other important factors, particularly for reactions to be carried out in large scale, are the availability and cost of the given reducing system as well as convenience and simplicity of the procedures.

Available methods for reduction of carbonyl functionalities and, in particular, α,β-unsaturated ones may be divided conveniently into four classes, based on historic considerations. The earliest procedures, extensively used prior to the discovery of catalytic hydrogenation and metal hydride reductions, employed dissolving metals. In the broader sense, more recent developments, such as reduction with low-valent transition-metal compounds and electrochemical processes, may also be included in this category as they all proceed, in the mechanistic sense, via sequential addition of electrons and protons to the substrate molecule.

Catalytic hydrogenation may be regarded as the second generation of reducing systems. Indeed, both heterogeneous and homogeneous catalytic hydrogenation replaced many of the earlier dissolving metal techniques, although the latter are still used due to selectivity characteristics or convenience.

The discovery of metal hydrides and complex metal hydrides, particularly those of boron and aluminum in the early 1940s, have revolutionized the reduction of organic functional groups. These reagents may be regarded as the third generation of reducing systems. Extensive studies over the past fifty years have led to a broad variety of hydridic reagents whose reducing power and selectivity are controlled by appropriate modification of the ligands in the metal coordination sphere[1]. Hydridic reagents today include other main-group metal hydrides, such as silicon and tin derivatives, as well as a variety of transition-metal hydrides that are employed in stoichiometric quantities, such as the iron, copper, chromium and cobalt compounds.

The advent of organo-transition-metal chemistry within the past thirty years has generated a plethora of novel synthetic methods that provide new opportunities for selective reduction. Composite reducing systems comprised of a transition-metal catalyst and a relatively nonreactive hydride donor represent the fourth generation of reductants. The generally high selectivities provided by such systems arise from two main facts: (a) specific interaction between the transition-metal catalyst and the substrate functionality, and (b) selective, facile hydride transfer from the hydride-donor to the transition metal, and hence to the substrate. Many of the transfer-hydrogenation methods may be included within this fourth category as well. Therefore, although in many respects several transfer-hydrogenation techniques resemble regular catalytic hydrogenations, they are discussed in Section VI that deals with composite reducing systems.

II. ELECTRON-TRANSFER REDUCTIONS

A. Dissolving-metal Reductions

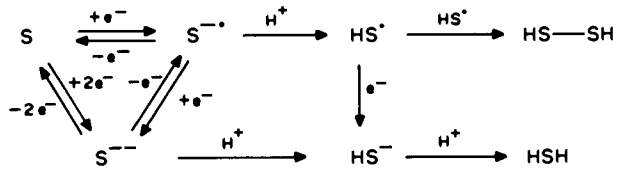
A variety of organic functional groups are reduced by active metal either in the presence of a proton donor,or followed by treatment with a proton donor. This approach is one of the earliest reduction procedures in organic chemistry. Although its importance has decreased with the development of catalytic hydrogenation and metal hydride reduction, there remain a substantial number of dissolving metal reductions still in use due to their advantageous selectivity of reduction. Dissolving metal reductions of α,β-unsaturated carbonyl compounds have been discussed in several review articles[2-10].

Metals commonly utilized include the alkali metals, mainly lithium, sodium and potassium, and also calcium, zinc, magnesium, tin and iron. Alkali metals and calcium have been used in liquid ammonia[10], in low-molecular-weight aliphatic amines[11], in hexamethylphosphoramide[12], in ether or in THF containing crown ethers[13c], or in very dilute solutions in polyethers such as 1,2-dimethoxyethane (DME)[11a,13a,b]. Reactions with metal solutions in liquid ammonia often use a cosolvent, such as ether, THF or DME, to increase solubility of the organic substrate in the reaction mixture. These same metals as well as zinc and magnesium have also been used as suspensions in various solvents including ether, toluene, xylene, etc. In all procedures a proton source (frequently ethanol, isopropanol, *t*-butanol or even water) is provided in the reaction medium, or together with the substrate, or during the workup procedure.

Sodium amalgam, aluminum amalgam, zinc, zinc amalgam, tin and iron have been added directly to solutions of the substrate in hydroxylic solvents such as ethanol, isopropanol, butanol, isoamyl alcohol, acetic acid, water or aqueous mineral acid. With hydroxylic solvents, and especially with relatively acidic ones, metal amalgams are often used rather than free metals to minimize the release of hydrogen gas side-product.

The dissolving-metal reductions are better classified as 'internal' electrolytic reductions in which an electron is transferred from the metal surface (or from the metal in solution) to the substrate. Reduction with low-valent metal ions may also be included in this general class (*vide infra*).

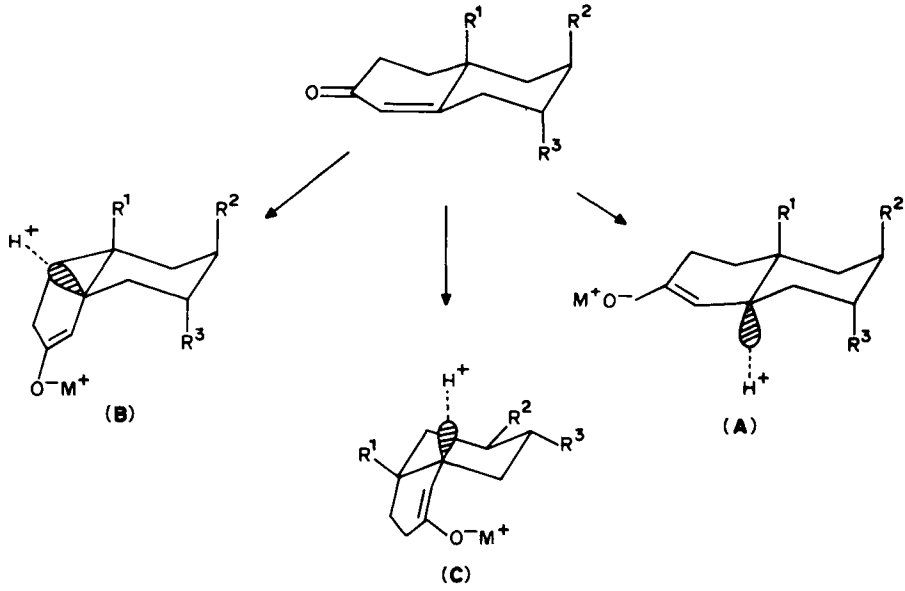
The generally accepted mechanism for dissolving-metal reduction of enones (Scheme 1)[10] involves reversible addition of an electron to a vacant orbital of the substrate (S), yielding a radical anion ($S^{-\cdot}$). The latter can be protonated to give a neutral radical, which may either dimerize or accept another electron and a proton. Alternatively, stepwise or simultaneous reversible addition of two electrons to S can give a dianion capable of accepting two protons. The sequence and timing of these steps should depend upon the substrate, the homogeneity and reduction potential of the medium, and the presence and nature of proton donors in the medium, among other factors.



SCHEME 1

The stereochemistry of reduction has been extensively studied. Metal-ammonia reduction of steroid and terpenoid enones with a β carbon at the fusion of two six-membered rings leads, in general, to the thermodynamically more stable isomer at

that position[14]. Stork has formulated a more general rule, namely that the product will be the more stable of the two isomers having the newly introduced β-hydrogen axial to the ketone ring[15]. This rule has correctly predicted the stereochemical outcome of many metal-ammonia reductions, with very few exceptions. The rule is rationalized in terms of stereoelectronic effects in the transition state (either the radical anion or the dianion stage). For example, in reduction of octalones of the type shown in Scheme 2, only two (**A** and **B**) of three possible anionic transition states involving a half-chair conformation of the enone-containing ring would be allowed stereochemically[15].

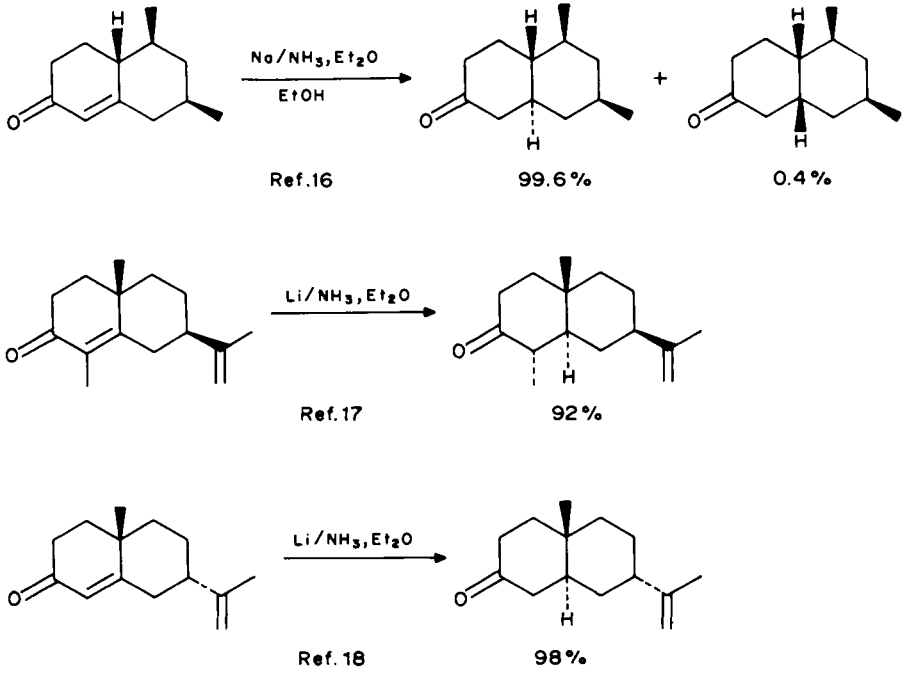


SCHEME 2

In these two conformers the orbital of the developing C—H bond overlaps with the remainder of the π-system of the enolate. The alternative conformer **C** is not allowed because it does not fulfill the overlap requirement. The *trans* transition-state **A** is generally more stable than the *cis* **B**, and the *trans*-2-decalone reduction product would be obtained, despite the fact that the *cis* isomer having a conformation related to **C** should be more stable when R^2 and/or R^3 are larger than a hydrogen atom. This rule of 'axial protonation' has been found to be widely applicable to metal-ammonia reductions of octalones, steroids and other fused-ring systems. Representative examples are given in Scheme 3[15–18].

Generally, the conditions employed in the workup of metal-ammonia reductions lead to products having the more stable configuration at the α-carbon atom, but products having the less stable configuration at this center have been obtained by kinetic protonation of enolate intermediates[19,20]. A more detailed discussion of stereochemistry in metal-ammonia reduction of α,β-unsaturated carbonyl compounds is given in Reference 10.

Scope and limitations. Before the introduction of metal-ammonia solutions for the reduction of α,β-unsaturated carbonyl compounds[10], sodium, sodium amalgam or zinc in protic media were most commonly employed for this purpose. Some early examples of

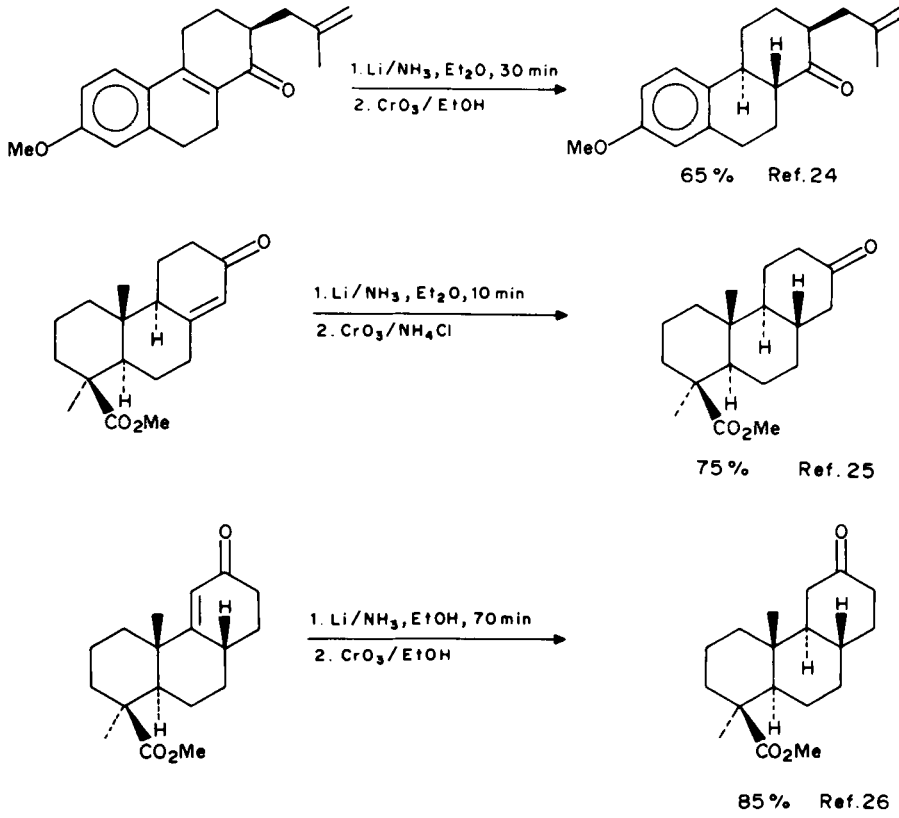


SCHEME 3

their use include the conversion of carvone to dihydrocarvone with zinc in acid or alkaline medium[21], and of cholest-4-en-3-one to cholestanone with sodium in alcohol[22,23]. Reductions using these earlier methods may be complicated by a variety of side-reactions, such as over-reduction, dimerization, skeletal rearrangements, acid- or base-catalyzed isomerizations and aldol condensations, most of which can be significantly minimized by metal-ammonia reduction.

Ketones ranging from simple acyclic varieties to complex polycyclic ones such as steroids, terpenoids and alkaloids have been reduced to saturated ketones, usually in good yield, by metal solutions, mainly in liquid ammonia. A few examples are given in Scheme 4[10,24–26]. The reduction is applicable to compounds with any degree of substitution on the double bond. Although only two equivalents of these metals are required for the conversion of an enone to a saturated ketone, it is often convenient to employ the metal in excess. Proton donors are often employed to prevent competing side-reactions, such as dimerization. The presence of proton donors in the medium may lead to the conversion of an α,β-unsaturated ketone to the saturated alcohol. Obviously, at least four equivalents of metal must be present for that type of reduction to take place.

Alcohols, such as methanol and ethanol, lead to the sole formation of saturated alcohols from unsaturated ketones when the former are present in excess during the reduction. Mixtures of ketone and alcohol are generally formed when one equivalent of these proton donors is employed[27]. These alcohols have acidity comparable to that of saturated ketones, and when they are present, equilibrium can be established between the initially formed metal enolate and the saturated ketone. The latter is then reduced to the saturated alcohol. Such reductions generally do not occur to a very significant extent when one equivalent of *t*-butanol[28] or some less acidic proton donor, such as triphenylcarbinol[27], is



SCHEME 4

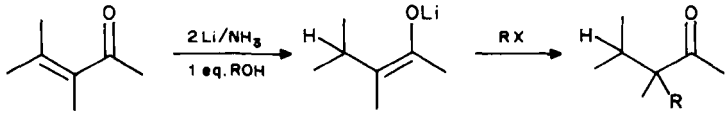
employed. The acidity of the ketone involved as well as the solubility of the metal enolate in the reaction medium are of importance in determining whether alcohols are formed.

Even though the reaction conditions may lead to formation of the metal enolate in high yield, further reduction may occur during the quenching step of the reaction. Alcohols such as methanol and ethanol convert metal enolates to saturated ketones much faster than they react with metals in ammonia[29,30], and quenching of reduction mixtures with these alcohols will usually lead to partial or complete conversion to alcoholic product rather than the saturated ketone. Rapid addition of excess solid ammonium chloride is the commonly employed quench procedure if ketonic products are desired[31].

To prevent alcohol formation, other reagents that destroy solvated electrons before reaction mixture neutralization may be employed. These include sodium benzoate[32], ferric nitrate[33,34], sodium nitrite[35], bromobenzene[36], sodium bromate[37], 1,2-dibromoethane[4], and acetone[14].

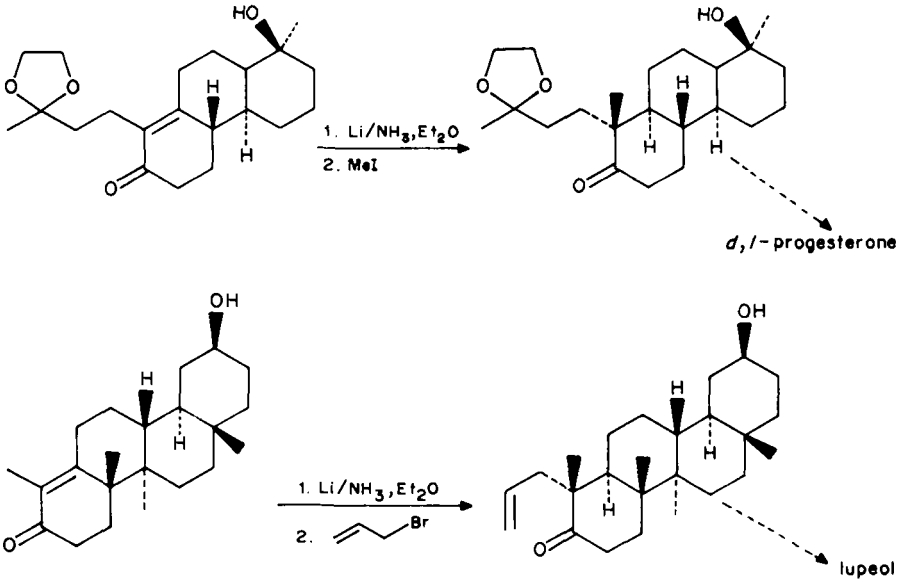
Reduction-alkylation. The versatility of metal-ammonia reduction was considerably advanced by the discovery that the lithium enolates of unsymmetrical ketones generated during reduction can undergo C-alkylation with alkyl halides and carbonation with carbon dioxide[38,39]. These enolate trapping reactions allow regiospecific introduction of

groups at the carbon atoms of unsymmetrical ketones via the appropriate enone precursors. This procedure has been widely employed for ketones of a variety of structural types[28,38–44]. The procedure usually involves generation of a specific lithium enolate of an unsymmetrical ketone by reduction of the corresponding α,β-unsaturated ketone with two equivalents of lithium in liquid ammonia that contains no proton donor or just a single equivalent of alcohol. This enolate is then reacted with excess alkylating agent (Scheme 5).



SCHEME 5

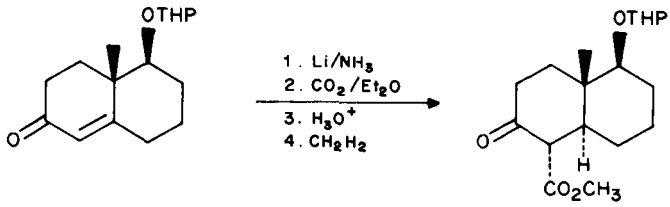
This reduction-alkylation sequence has been extensively used in the total synthesis of natural products. The two transformations shown in Scheme 6 represent key steps in the synthesis of *d,l*-progesterone[45] and lupeol[46].



SCHEME 6

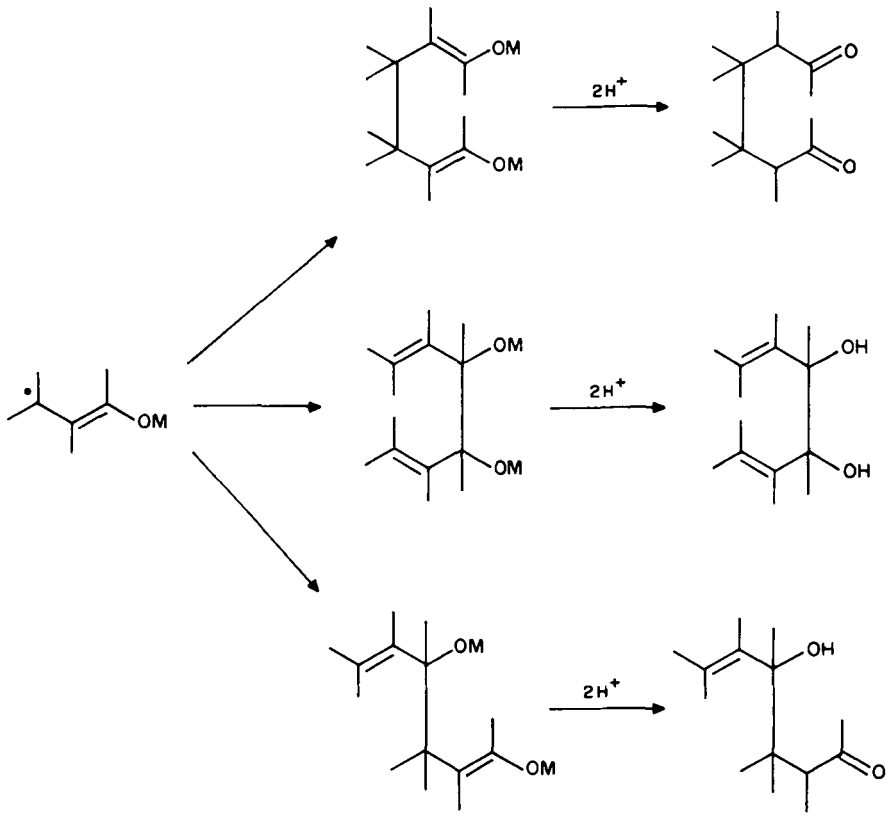
If the ammonia is removed and replaced by anhydrous ether, the intermediate lithium enolate can be converted to β-keto ester by carbonation, followed by acidification and treatment with diazomethane, as illustrated in Scheme 7[47].

Dimerization processes. Because of the intermediacy of radical anions and/or hydroxyallyl free radicals in dissolving-metal reductions of enones, dimerization processes involving these species may compete with simple reduction. Scheme 8 shows the three



SCHEME 7

types of dimers that may be produced. 1,6-Diketones may be formed from coupling of the two radical anions at their β-positions; unsaturated pinacols are produced if coupling occurs at the carbonyl carbon atoms; and unsaturated γ-hydroxy ketones are produced by nonsymmetrical coupling of the β-carbon of one radical anion and the carbonyl carbon of a second such intermediate.

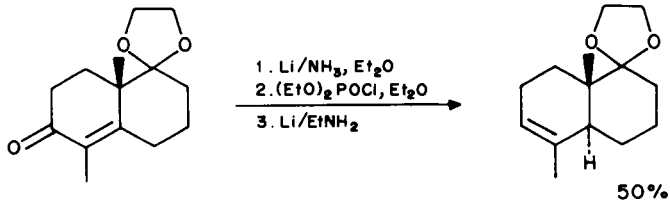


SCHEME 8

The dimerization products shown in Scheme 8 are generally the major ones obtained in electrochemical reductions[48-51] (*vide infra*) or reductions at metal surfaces[48,52], in which

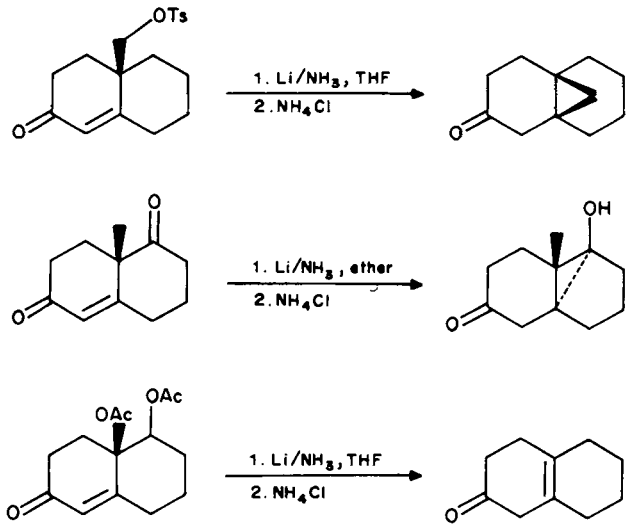
radical anion intermediates must diffuse to a surface before further electron transfer can occur. In metal-ammonia solutions, however, simple reduction is generally favored over dimerization. These solutions provide high concentrations of available electrons, favoring the probability of the radical ion or hydroxyallyl radical to accept a second electron.

Olefin synthesis. Appropriate quenching of a reductively formed lithium enolate with a carboxylic acid anhydride[53,54], chloride[55], methyl chloroformate[56] or diethyl phosphorochloridate yields the corresponding enol esters, enol carbonates or enol phosphates. These derivatives may be transformed into specific olefins via reductive cleavage of the vinyl oxygen function[57], as illustrated by the example in Scheme 9.



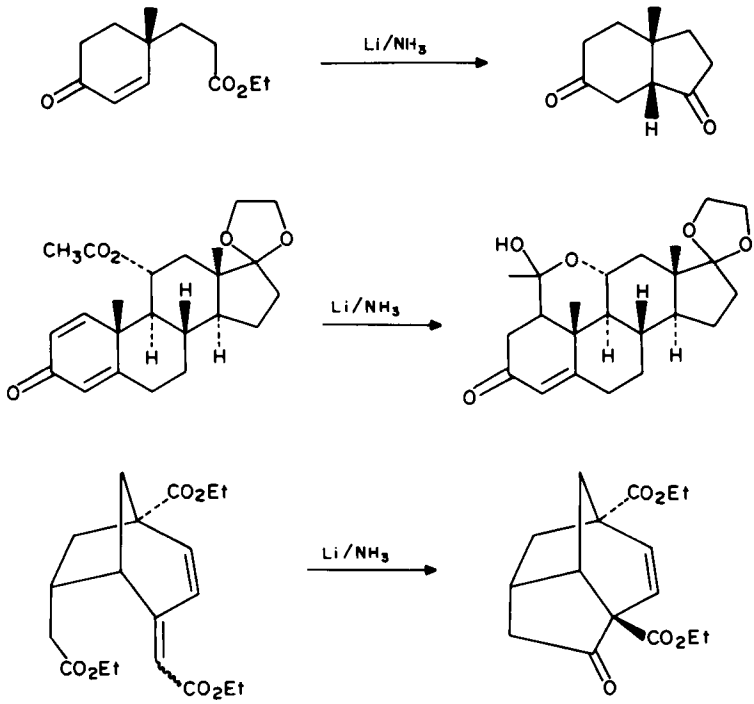
SCHEME 9

Intramolecular reactions. Dissolving-metal reduction of unsaturated ketones involve intermediates with carbanionic character at the β-position. Therefore, intramolecular displacements, additions and eliminations may occur during the reduction of polyfunctional enones. Many α,β-unsaturated carbonyl compounds have structural features which allow such intramolecular reactions. The examples given in Scheme 10 include intramolecular substitution of a tosylate leaving group[58], addition to ketone to form cyclopropanol[59], and elimination of an acetate group to give the unconjugated enone[60].



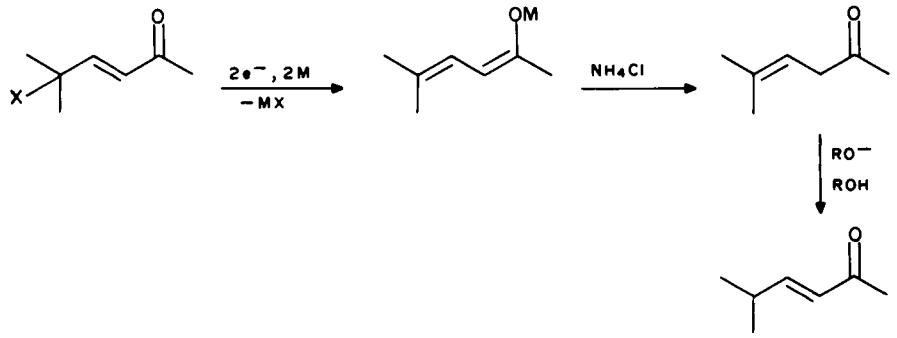
SCHEME 10

The examples given in Scheme 11 include synthesis of a perhydroindanedione skeleton via intramolecular addition to an ester group[61], a related formation of a stable steroidal hemiacetal[62], and lithium-ammonia conversion of a bicyclic unsaturated triester into a tricyclic keto diester[63].



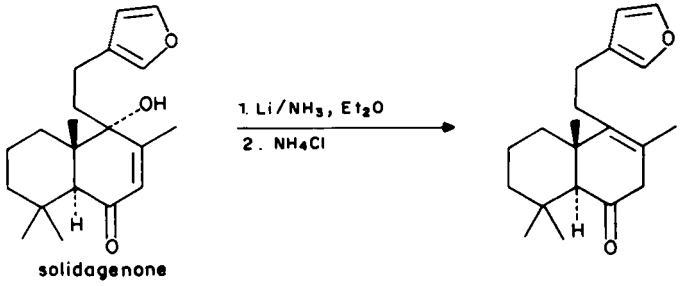
SCHEME 11

α,β-Unsaturated ketones with leaving groups at the γ-position normally undergo reductive elimination with metals in ammonia to give metal dienolates as an initial product (Scheme 12).



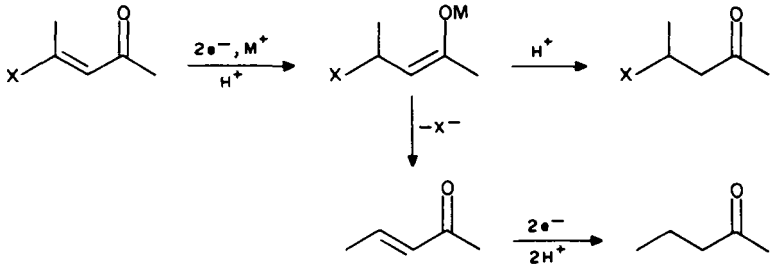
SCHEME 12

Quenching these enolates with ammonium chloride allows the isolation of the β,γ-unsaturated ketone. The latter can isomerize under basic conditions to the conjugated enone. Such processes have been reported with a broad variety of leaving groups, such as hydroxide anion[64,65], alkoxide[66], and acetate[60], as well as during fission of a lactone[67–69] or an epoxide ring[70]. An example involving elimination of hydroxide ion from solidagenone[65] is shown in Scheme 13.



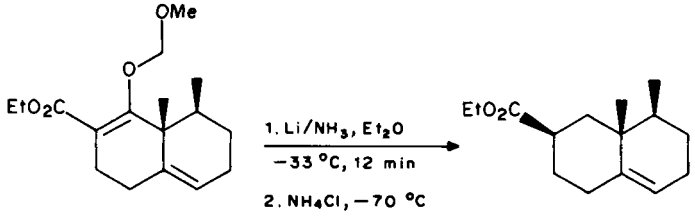
SCHEME 13

α,β-Unsaturated carbonyl compounds having a leaving group at the β position react with dissolving metals to give metal enolates, which may undergo elimination to yield new α,β-unsaturated carbonyl compounds that are susceptible to further reduction (Scheme 14)[43,71–77].



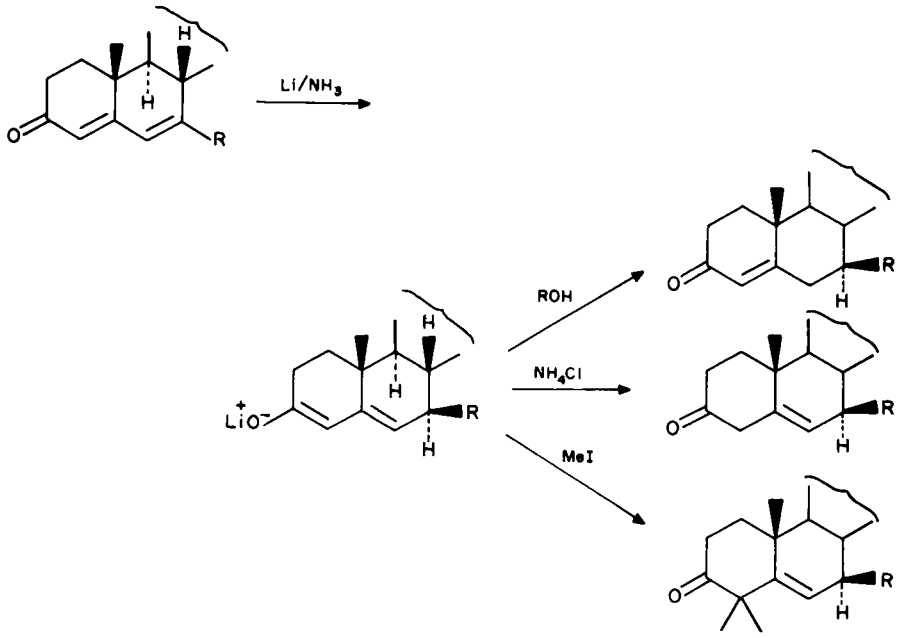
SCHEME 14

For example, β-alkoxy-α,β-unsaturated esters[72,73] and acids[78] have been found to undergo double reduction. This procedure was used as a key step in the total synthesis of eremophilane sesquiterpenes (Scheme 15)[72].



SCHEME 15

Both linear and cross-conjugated dienones are reduced by solutions of metals in liquid ammonia. For example, steroidal 4, 6-dien-3-ones (Scheme 16) and related compounds are reduced initially to 3, 5-dienolates[44,79–86]. While addition of ammonium chloride to the latter leads to formation of the nonconjugated 5-en-3-one system[83], addition of proton donors such as ethanol or water initiates isomerization leading to the more stable, conjugated 4-en-3-one skeleton[80,81]. Treatment of the dienolate with excess methyl iodide rather than a proton donor gives the 4, 4-dimethyl-5-en-3-one[44,87].

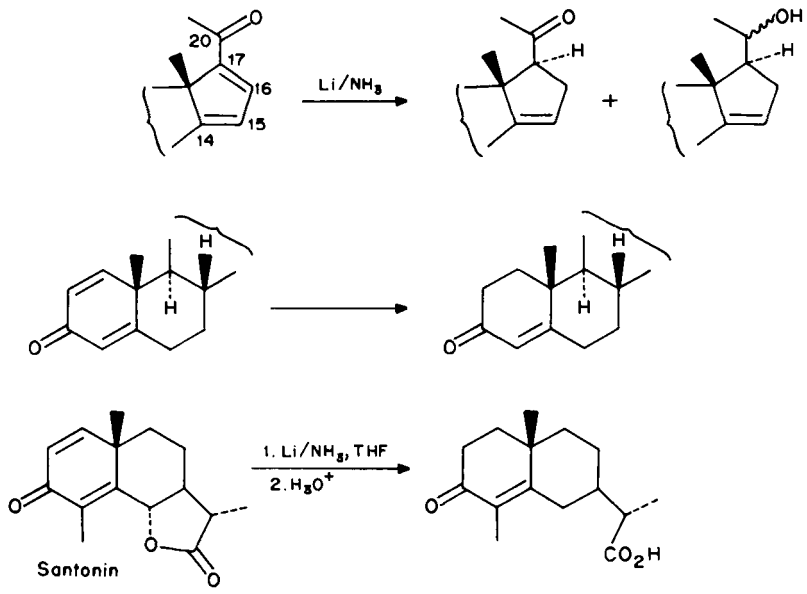


SCHEME 16

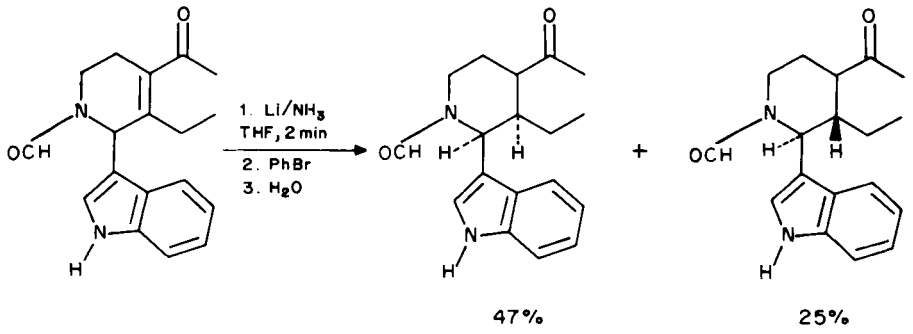
Linearly conjugated dienones may be completely reduced to saturated alcohols using excess lithium in liquid ammonia[88]. In variously substituted dienones, the less substituted double bond is often selectively reduced under these conditions. For example, treatment of steroidal 14, 16-dien-20-one with lithium in liquid ammonia (with or without propanol) leads mainly to reduction of the 16, 17 double bond (Scheme 17)[89,90]. Accordingly, the less substituted double bond of cross-conjugated steroidal dienones[4,44,91,92], santonin or related substrates is selectively reduced under these conditions (Scheme 17)[67–69,93].

Chemoselectivity. Although a host of organic functionalities are reduced by dissolving metals[2,3,5–7,9] it is often possible to reduce double bonds of α,β-unsaturated carbonyl systems without affecting other reducible groups. Internal, isolated olefins are normally stable to metal-ammonia solutions unless they have very low-lying antibonding orbitals[94] or special structural features that stabilize radical anion intermediates[95]. However, terminal olefins may be reduced by dissolving metals[96]. Mono- and polycyclic aromatic compounds undergo reduction with dissolving metals in liquid ammonia (Birch reduction)[2,3,5,8,97,98], but these reactions are generally slow unless proton donors are added. It is therefore possible to reduce α,β-unsaturated ketones selectively in the presence of

aromatic rings[99–102]. Selective reduction preserving a reducible indole ring is illustrated in Scheme 18[103].



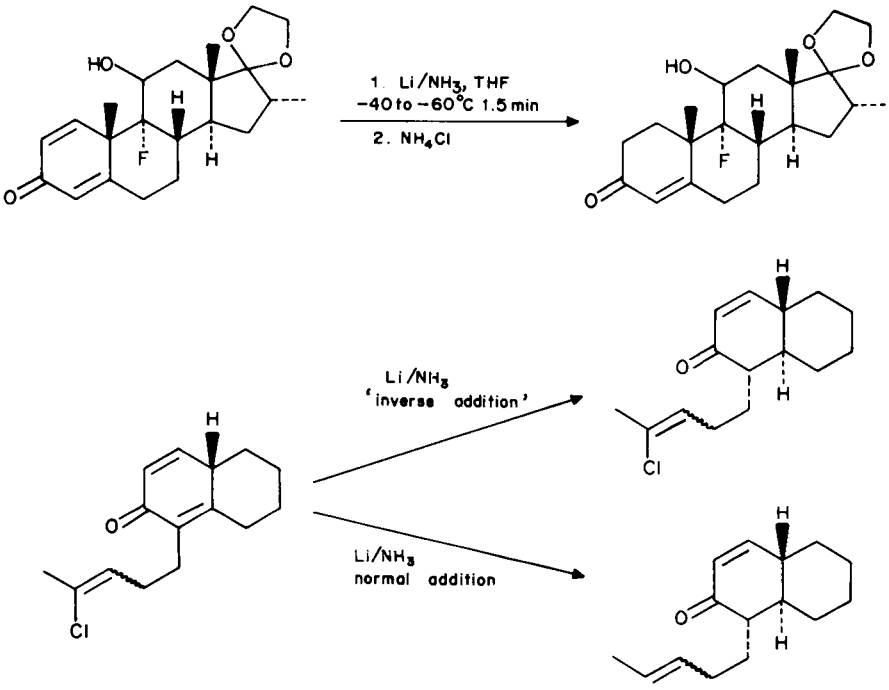
SCHEME 17



SCHEME 18

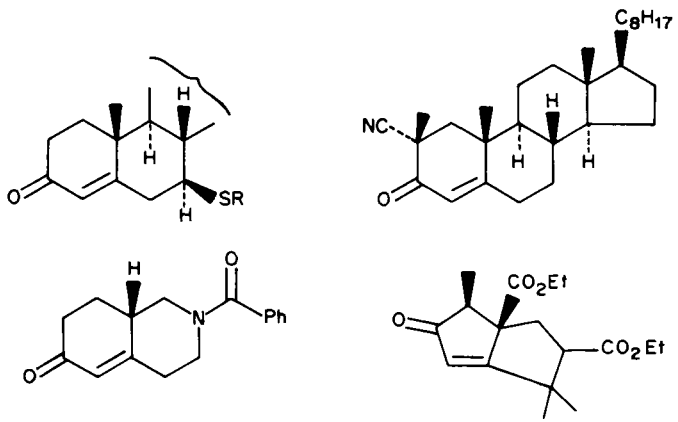
Ethynyl carbinols are reduced to allyl alcohols and eventually to olefins with metal-ammonia solutions containing proton donors[104]. However, by excluding proton donors, selective reduction of conjugated enones has been carried out despite the presence of ethynyl carbinol groups[34,105–107]. Similarly, selective reduction of conjugated enones containing allylic alcohols has also been achieved[34,105,107]. Carbon–halogen bonds of alkyl and vinyl halides are readily cleaved by metals in ammonia[5,8,9]. Yet, as shown in Scheme 19, fluoride substituent may be retained by limiting reaction times[92] and a rather

sensitive vinyl chloride functionality is preserved by using an inverse addition technique[108].



SCHEME 19

Scheme 20 presents a number of enone-containing compounds that bear additional reducible functionalities, all of which were chemoselectively reduced at the enone site. For



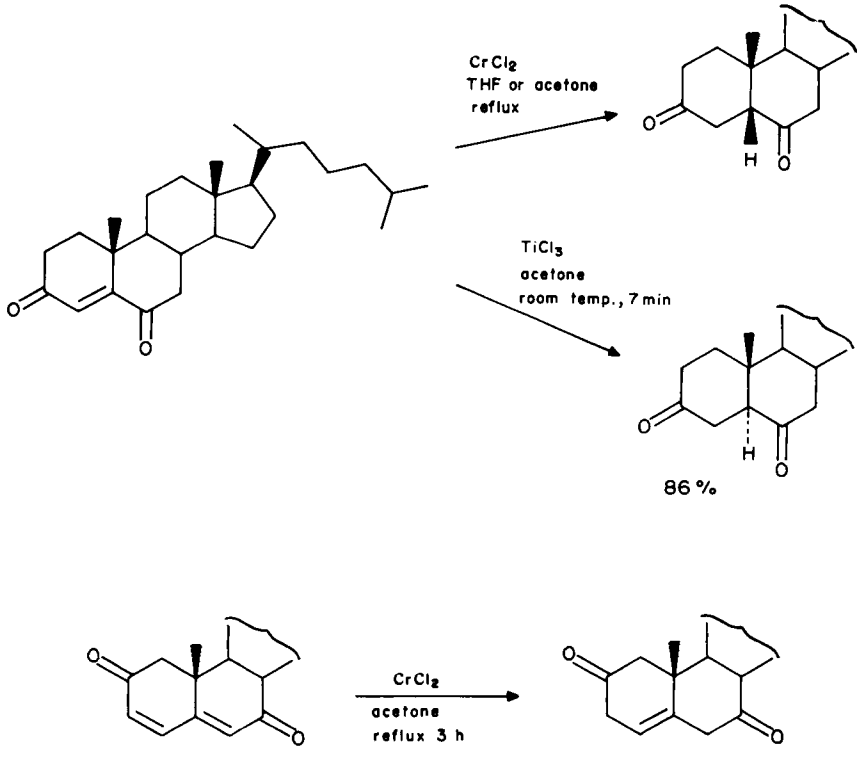
SCHEME 20

example, the C—S bond of many thioethers and thioketals are readily cleaved by dissolving metals[5,8,9,109]. Yet, there are examples of conjugate reduction of enones in the presence of a thioalkyl ether group[109,110]. Selective enone reduction in the presence of a reducible nitrile group was illustrated with another steroidal enone[111]. While carboxylic acids, because of salt formation, are not reduced by dissolving metals, esters[112] and amides[2,8] are easily reduced to saturated alcohols and aldehydes or alcohols, respectively. However, metal-ammonia reduction of enones is faster than that of either esters or amides. This allows selective enone reduction in the presence of esters[113] and amides[36,114,115] using short reaction times and limited amounts of lithium in ammonia.

B. Reduction with Low-valent Transition Metals

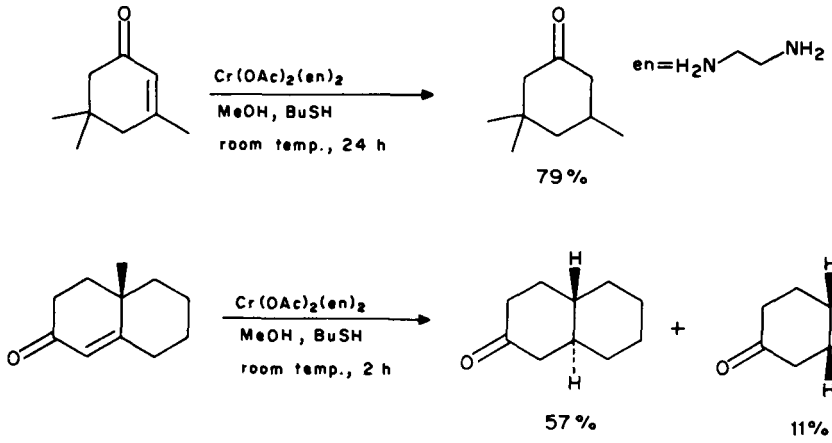
Low-valent species of early transition metals, such as chromium(II)[116], titanium(II), titanium(III)[117], vanadium, molybdenum and tungsten, are useful reducing agents[118]. Electron-deficient olefins and acetylenes are easily reduced by chromium(II) sulfate, *Z*-alkenes being more rapidly reduced than the corresponding *E*-isomers[119]. Titanium(III) species are weaker reducing agents, exhibiting higher chemoselectivity[120].

Several steroid enediones have been reduced by chromium(II) chloride[121]. Interestingly, reduction of cholest-4-ene-3,6-dione yields a different product than that obtained by titanium(III) reduction of the identical substrate (Scheme 21)[120c].



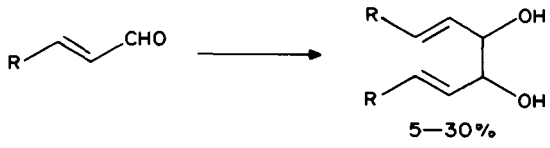
SCHEME 21

Solutions of chromium-bis(ethylenediamine)diacetate complex in methanol are capable of reducing simple α,β-unsaturated ketones to the corresponding saturated ketones. Useful yields are obtained, provided a proton donor (AcOH) and a good hydrogen donor (BuSH) are present in the reaction mixture (Scheme 22)[122].



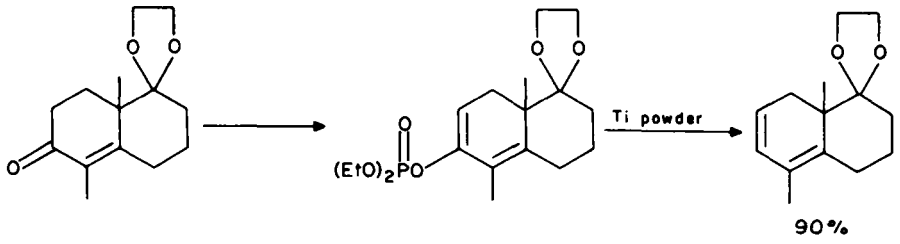
SCHEME 22

Reductive dimerization of α,β-unsaturated ketones is effected by either Cr(II) or V(II) chloride to give 1,4-diketones, and aliphatic α,β-unsaturated aldehydes are dimerized to the allylic glycals (Scheme 23)[123]. Interestingly, nonconjugated aldehydes are stable towards these reagents. Similar pinacolic couplings of aldehydes and ketones with Ti(II) reagents were developed by Corey[124].



SCHEME 23

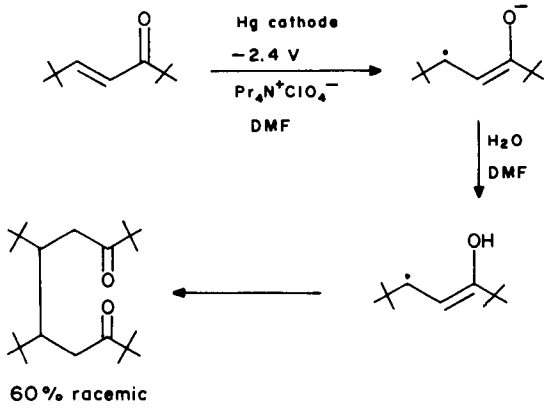
Highly reactive metallic titanium, prepared from $TiCl_3$ and potassium, was found useful for reduction of enol phosphate to alkenes, permitting regioselective synthesis of dienes from α,β-unsaturated ketones (Scheme 24)[125].



SCHEME 24

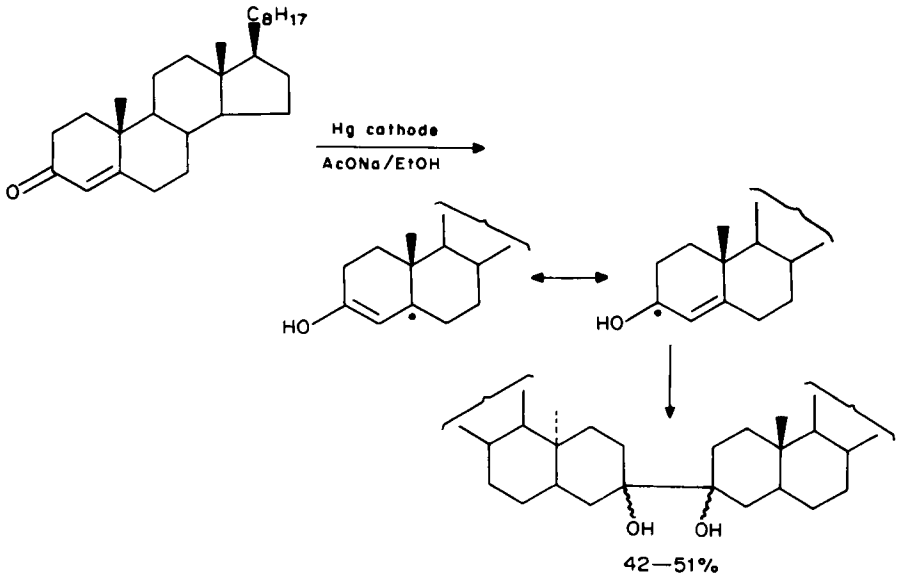
C. Electrochemical Reductions

The electrochemical reduction of α,β-unsaturated ketones and related compounds[5] in aprotic media in the absence of metal cations can, in some cases, lead to relatively stable anion radicals[12c,126]. However, in the presence of proton donors the latter are protonated to form hydroxyallyl radicals, which tend to dimerize more rapidly than they diffuse back to the electrode to undergo further reduction (Scheme 25)[12c].



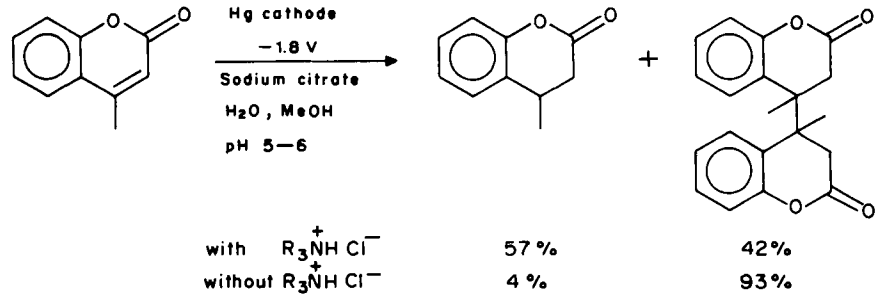
SCHEME 25

Although these allyl radicals prefer to dimerize by coupling at the β-position, if this position is sterically hindered, as in the case of cholest-4-en-3-one, coupling at the carbonyl carbon may be observed yielding a pinacol (Scheme 26)[127].



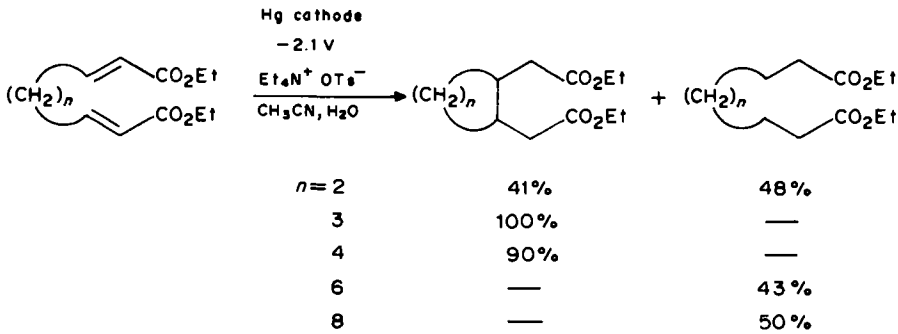
SCHEME 26

As noted above, such reductive dimerizations have been recorded when unsaturated carbonyl compounds are reacted with various metals, such as lithium, sodium, sodium amalgam, potassium, aluminum amalgam, zinc or magnesium[128,129]. Formation of monomeric reduction products is impeded in these reactions because the intermediate allylic radical must diffuse back to the electrode surface or metal particle for further reduction. A possible solution to this problem might be concurrent electrochemical generation of a soluble reducing agent that can intercept radical intermediates before their dimerization. For example, solutions of magnesium in liquid ammonia can be generated electrochemically[130c]. Similarly, tertiary amine salts, such as yohimbine hydrochloride, can participate in the electrochemical reduction of enones (Scheme 27)[130a,b], via concurrent reduction of the amine to a radical which transfers a hydrogen atom to the intermediate allyl radical.



SCHEME 27

Reductive dimerization of enones to form a new carbon–carbon bond at the β-position, known as hydrodimerization or electrohydrodimerization, has considerable synthetic utility[131]. For example, high yields of cyclic products are achieved when cyclization is kinetically favorable, leading to three- to six-membered rings from the corresponding unsaturated diesters (Scheme 28)[131d].



SCHEME 28

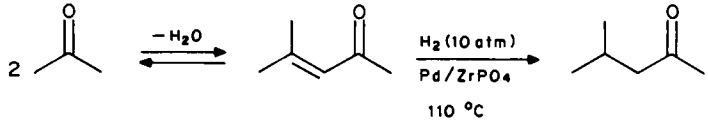
The product ratio in electrochemical reduction of benzalacetone is significantly altered by surfactants and various cations, which cause micellar and/or ion-pairing effects. Using these additives, it is possible to control the partitioning of the initially formed radical anion

between the two main reaction pathways: either dimerization or further reduction to the saturated ketone[132]. Additionally, micellar surfactants allow the use of aqueous media without cosolvents.

III. CATALYTIC HYDROGENATION

Addition of molecular hydrogen to α,β-unsaturated carbonyl compounds has been extensively reviewed[5,133–135]. Enones can be converted to saturated ketones or to unsaturated or saturated alcohols. Usually, double bonds conjugated to the carbonyl moiety are reduced prior to nonconjugated ones. 1,2-Reduction to allylic alcohols via catalytic hydrogenation is quite rare, and this transformation is more conveniently performed with hydridic reducing agents, such as boron- and aluminum-hydrides (*vide infra*). Nevertheless, there are a number of reported cases where 1,2-reduction is preferred over 1,4-selectivity. Citronellal, for example, is reduced preferentially at the carbonyl function using nickel on silica-gel as a catalyst, while hydrogenation catalyzed by $Pd/BaSO_4$ yields the corresponding saturated aldehyde[136]. Reduction to the saturated alcohol is achieved by catalytic hydrogenation over nickel[137], copper chromite[138], or nickel–aluminum alloy in NaOH[139].

Enones are reduced to saturated ketones by catalytic hydrogenation, provided the reaction is stopped following the absorption of 1 mole of hydrogen[140]. A number of catalysts were found useful for this, including platinum[141], platinum oxide[142,143], Pt/C[140], Pd/C[140,144], Rh/C[140], tris(triphenylphosphine)rhodium chloride[145,146], nickel–aluminum alloy in 10% aqueous NaOH[147], and zinc-reduced nickel in an aqueous medium[148]. Mesityl oxide is formed from acetone and reduced in a single pot to methyl isobutyl ketone using a bifunctional catalyst comprised of palladium and zirconium phosphate (Scheme 29)[149].

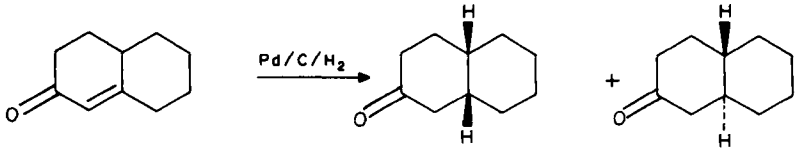


SCHEME 29

Both the ease and the stereochemical course of hydrogenation of α,β-unsaturated ketones are strongly influenced by various factors, particularly the nature of the solvent and the acidity or basicity of the reaction mixture. It is usually difficult to predict the product distribution in a particular reaction under a given set of conditions. Some efforts have been made to rationalize the effect of the various parameters on the relative proportions of 1,2- to 1,4-addition, as well as on the stereochemistry of reduction[150].

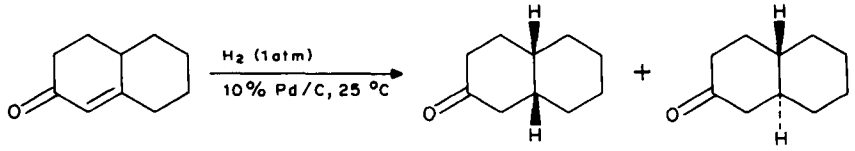
For example, the product distribution in β-octalone hydrogenation in neutral media is related to the polarity of the solvent if the solvents are divided into aprotic and protic groups. The relative amount of *cis*-β-decalone decreases steadily with decreasing dielectric constant in aprotic solvents, and increases with dielectric constant in protic solvents, as exemplified in Scheme 30 (dielectric constants of the solvents are indicated in parentheses)[151]. Similar results were observed in the hydrogenation of cholestenone and on testosterone[152]. In polar aprotic solvents 1,4-addition predominates, whereas in a nonpolar aprotic solvent hydrogenation occurs mainly in the 1,2-addition mode.

Acids and bases have a crucial effect on product stereochemistry in hydrogenation of ring-fused enone systems, as illustrated in Scheme 31[153].



DMF (38)	79 : 21
AcOEt (6)	57 : 43
diethyl ether (4.34)	58 : 42
hexane (1.89)	48 : 52
methanol (33.6)	41 : 59
proponol (21.8)	68 : 32
t-butanol (10.9)	91 : 9

SCHEME 30

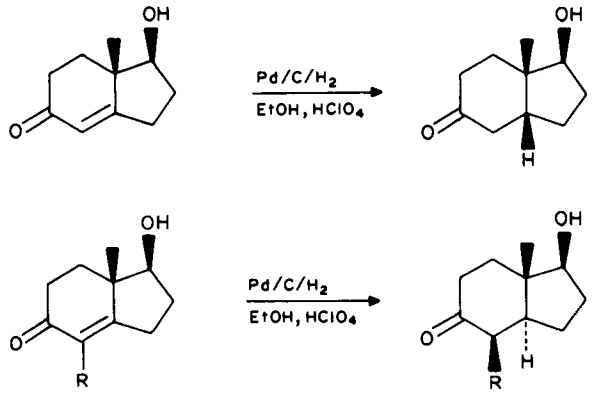


EtOH	53 : 47
EtOH, H_2O, HCl	93 : 7
EtOH, KOH	35—50 : 65—50

SCHEME 31

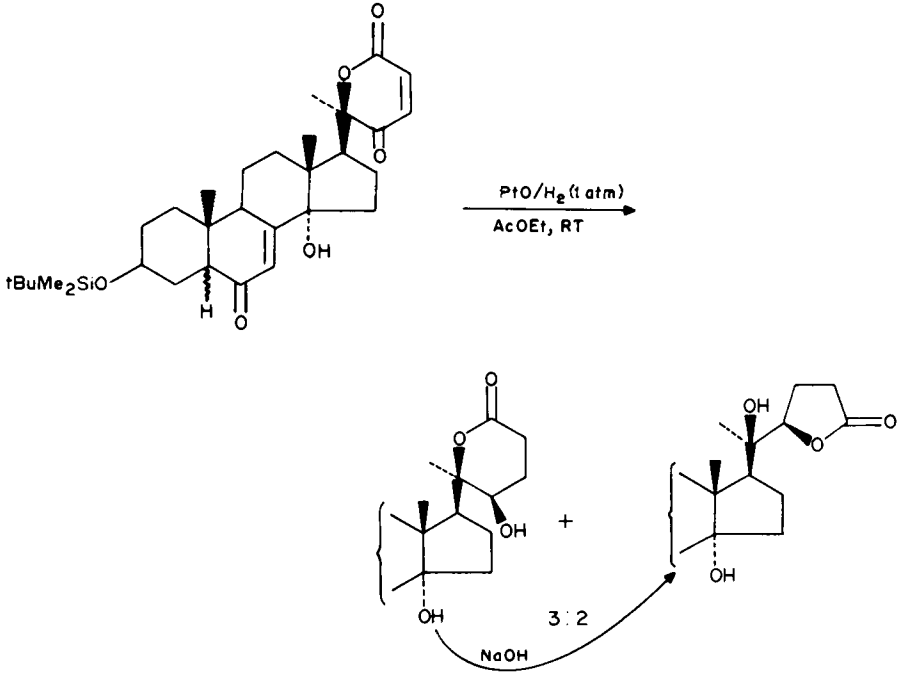
The increased amounts of *trans*-fused product obtained in basic solutions was suggested to arise from hydrogenation of the relatively flat enolate ion which adsorbs irreversibly onto the catalyst surface. Hydrogenation proceeds by hydride ion-transfer from the metal catalyst, followed by protonation. Conversely, in acidic medium, protonation occurs initially, followed by irreversible adsorption on the catalyst, and then transfer of a hydride ion[150]. Stereochemistry of reduction is also related to catalyst activity, catalyst concentration, pressure and stirring rate, as they all affect hydrogen availability at the catalyst surface. Under conditions of low hydrogen availability a reversible adsorption is favorable, and therefore the product stereochemistry is determined by the relative stability of the *cis*- and *trans*-adsorbed species. However, under conditions of high hydrogen availability, product stereochemistry is determined mainly by the nature of the initial adsorption[150,151]. Platinum catalysts, more than palladium varieties, give products determined by the initial adsorption.

Substrate structure has an important influence on stereoselectivity of hydrogenation. For example, hydrogenation of hydrindanone having a trisubstituted double bond gives mainly the *cis* product (Scheme 32)[154], whereas similar compounds with a tetrasubstituted olefin tend to give the *trans* isomer. This phenomenon has been rationalized in terms of preferred conformation of the adsorbed enone, which minimizes steric interactions[154,155].



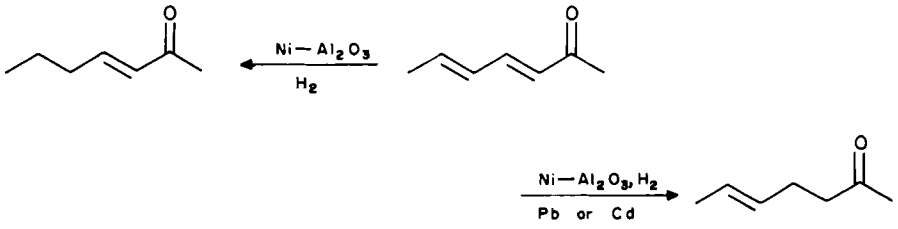
SCHEME 32

The key step in the synthesis of 2-deoxycrustecdysone from the corresponding 20-oxo steroid is the stereoselective catalytic hydrogenation of the α,β-unsaturated lactone shown in Scheme 33 to afford a 2:3 mixture of δ- and γ-lactones, respectively[156]. This crude product was converted into the thermodynamically more stable γ-lactone by treatment with aqueous NaOH.



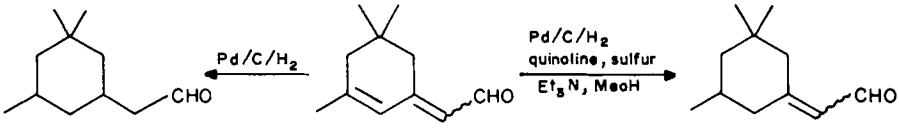
SCHEME 33

In the case of multiply unsaturated carbonyl compounds, regioselectivity is also sensitive to the nature of the catalyst, to reaction conditions and to the structure and degree of substitution of the hydrogenated double bonds. For example, hydrogenation of 3, 5-heptadien-2-one over nickel-on-alumina or nickel-on-zinc oxide occurs mainly at the γ,δ-double bond. But if the catalyst is modified by the addition of lead or cadmium, reduction occurs mainly at the α,β-double bond (Scheme 34)[157].



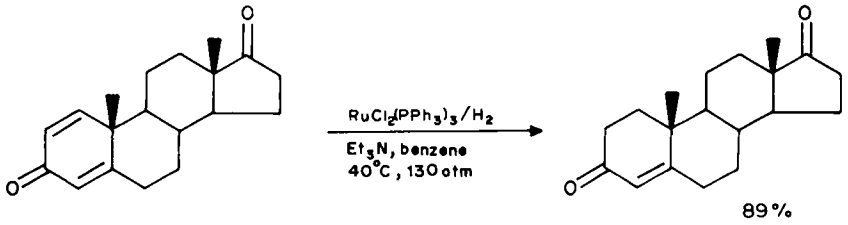
SCHEME 34

Selective reduction the γ,δ-double bond of the dienal shown in Scheme 35 was achieved by hydrogenation over palladium-on-carbon inhibited by quinoline and sulfur. Without inhibition, hydrogenation to the saturated aldehyde was observed[158].



SCHEME 35

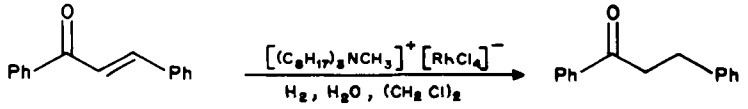
Homogeneous catalysts, such as $RhCl(PPh_3)_3$[146] and $RuCl_2(PPh_3)_3$[159], have proved efficient in the selective hydrogenation of enones and dienones. For example, the hydrogenation selectivity of 1, 4-androstadiene-3, 17-dione to 4-androstene-3, 17-dione is increased by elevated pressures, low temperatures and the presence of optimal amount of amines (Scheme 36)[159].



SCHEME 36

The solvated ion-pair $[(C_8H_{17})_3NCH_3]^+[RhCl_4]^-$, formed from aqueous rhodium trichloride and Aliquat-336 in a two-phase liquid system, hydrogenates α,β-unsaturated ketones and esters selectively at the C=C double bond (Scheme 37)[160]. The reduction of benzylideneacetone follows first-order kinetics in substrate below 0.2 M, and approaches

second-order in hydrogen at partial pressures below 0.12 atm. The catalysis is also depends on the nature of the solvent, the phase-transfer catalyst and stirring rates.



SCHEME 37

The homogeneous water-soluble hydrogenation catalyst $K_3(Co(CN)_5H)$ is very active for hydrogenating conjugated dienes and α,β-unsaturated ketones under phase-transfer reaction conditions[161]. Thus, conjugated dienes are converted into monoenes, generally with overall 1,4-addition to yield *E*-olefins, and α,β-unsaturated ketones are reduced to saturated ketones in high yields. These conditions are not useful with α,β-unsaturated aldehydes, as they lead to polymerization of the starting material.

IV. REDUCTIONS WITH MAIN-GROUP METAL HYDRIDES

A. Boron Hydrides

Although $NaBH_4$ does not attack isolated olefins, C=C double bonds conjugated to strong anion-stabilizing groups may be reduced by this reagent[162–164].

Rationalization of the regioselectivity of borohydride reduction of α,β-unsaturated aldehydes and ketones has been attempted using the 'hard' and 'soft' acid-base concept[165] (*vide infra*, discussion of aluminum hydrides). It is assumed that the relatively 'soft' hydrides add preferentially to the enone system via a 1,4-mode while 'hard' reagents attack the carbonyl carbon. Borohydrides are considered softer than the corresponding aluminum hydrides. Replacement of a hydride group on boron by alkoxide makes it a harder reagent. Lithium salts are harder than sodium species. Thus, $LiAlH_4$ gives more 1,2-attack than $LiBH_4$, which, in turn, gives more than $NaBH_4$. $NaBH(OMe)_3$ yields more 1,2-reduction product than $NaBH_4$, and when production of alkoxyborates is prevented, 1,4-reduction predominates. This implies that slow addition of borohydride to a substrate solution should help to build up alkoxyborate species and increase the relative amount of 1,2-reduction. Generally, aldehydes undergo more 1,2-reduction than the corresponding ketones.

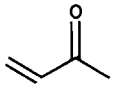
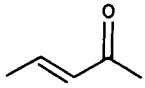
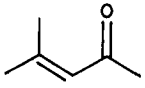
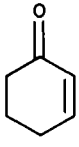
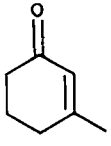
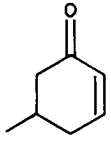
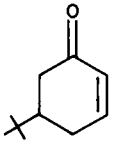
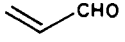
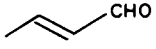
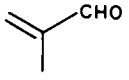
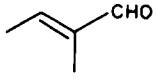
The reduction of α,β-unsaturated aldehydes and ketones by sodium borohydride leads, in general, to substantial amounts of fully saturated alcohols. In alcoholic solvents, saturated β-alkoxy alcohols are formed via conjugate addition of the solvent[166]. This latter process becomes the main reaction path when reduction is performed in isopropanol in the presence of sodium isopropoxide. In a base, a homoallylic alcohol can become the major product of borohydride reduction of an enone[166].

Analysis of the influence of substrate structure on $NaBH_4$ reduction has shown that increasing steric hindrance on the enone increases 1,2-attack (Table 1)[166].

$NaBH_4$ reduction of 3-substituted 5,5-dimethylcyclohex-2-enones in alkaline solution of water–dioxane occurs exclusively at the 1,2-positions. The rate of reduction is strongly dependent on the 3-substituent. A Hammett-type correlation revealed similar reaction characteristics to those of borohydride reduction of substituted acetophenones[167].

In order to study the factors determining the regioselectivity of sodium borohydride reduction of α,β-unsaturated ketones, reactions with 3-methylcyclohexenone, carvone and cholestenone were carried out in 2-propanol, diglyme, triglyme or pyridine[168]. Mixtures of 1,2- and 1,4-reduction products were obtained in the alcoholic and etheric

TABLE 1. The effect of the structure of α,β-unsaturated ketones and aldehydes on their reduction with $NaBH_4$ and $LiAlH_4$[a]

Substrate	$NaBH_4$ in 1:1 H_2O/EtOH	$LiAlH_4$ in ether
	86(57:43)	79(92:8)
	90(65:35)	85(99:1)
	89(92:8)	82(100:0)
	90(59:41)	97(98:2)
	90(70:30)	88(100:0)
	100(49:51)	99(91:9)
	100(42:58)	99(93:7)
	70(85:15)	70(98:2)
	91(92:8)	94(100:0)
	100(> 99: < 1)	98(100:0)
	95(> 99: < 1)	82(100:0)

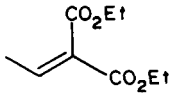
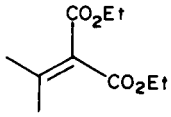
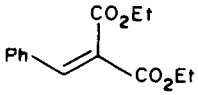
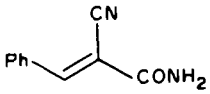
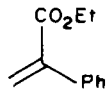
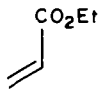
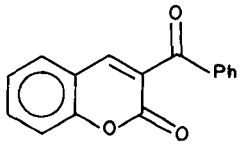
[a]The numbers represent the overall reduction yield (%), the numbers in parentheses represent the ratio of 1,2- to 1,4-attack.

solvents, whereas pure 1,4-reduction was observed in pyridine. Addition of triethyl amine to $NaBH_4$ in diglyme led to formation of triethylamine borine, Et_3NBH_3. Similarly, with pyridine, pyridine-borine could be isolated, leading to exclusive 1,4-reductions.

The results were interpreted in terms of steric requirements of the actual reducing species. It was suggested that attack of BH_4^- proceeds exclusively along the 1,4-reduction mode, whereas alkoxyborohydrides (formed as reaction products) prefer the 1,2-reduction mode. The pyridine-borine itself does not reduce enones under the reaction conditions, but it inhibits formation of alkoxyborohydrides[168]. The same trend was observed with aluminum hydride reductions. When $LiAlH_4$ was first reacted with pyridine to form lithium tetrakis(dihydro-*N*-pyridyl) aluminate, 1,4-reduction predominated[168].

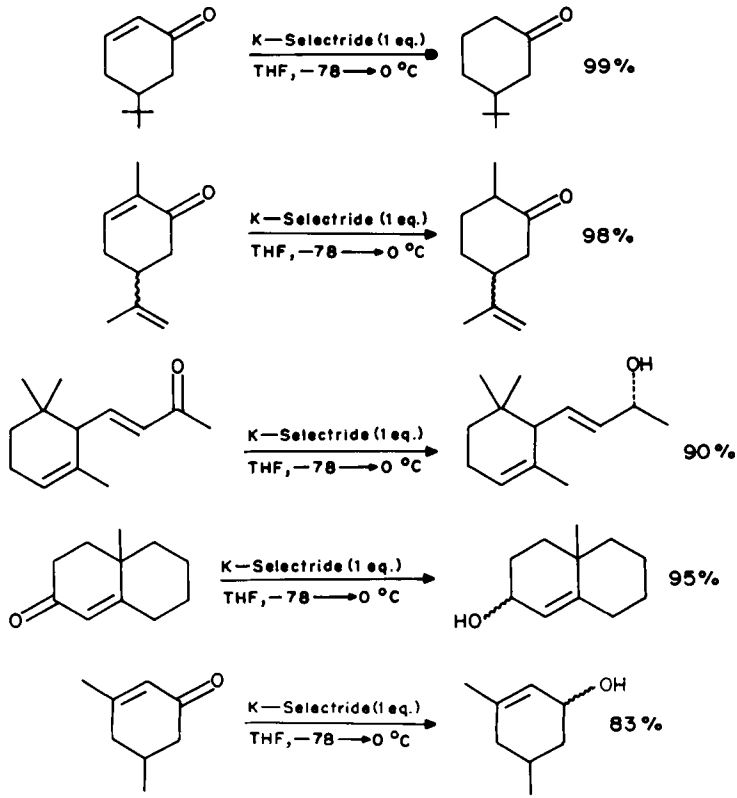
Low regioselectivity is observed in reduction of enones with a 2:1 mixture of sodium cyanoborohydride and zinc chloride in ether at room temperature[169]. A mixture containing 1,2- and 1,4-reduction products is obtained in a ratio that is greatly dependent upon substrate.

TABLE 2. Reduction of α,β-unsaturated carboxylic acid derivatives with $NaBH_4$

Substrate	Yield (%)
	59
	74
	69
	81
	80
	25
	79

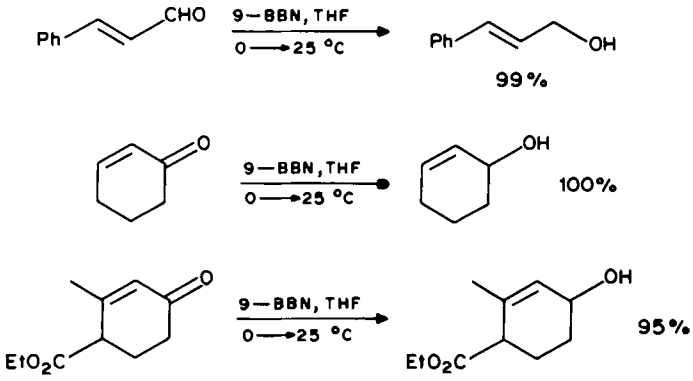
From the reduction in methanol of a series of substituted 2-aryl-(*Z*)- and (*E*)-cinnamates by $NaBH_4$ at room temperature, it was concluded that the facile reduction to give dihydrocinnamates proceeds through an early transition state of considerable polarity[162]. A few more examples are given in a related study (Table 2)[170].

Several organoborohydrides were found to effect the selective 1,4-reduction of enones. For example, lithium and potassium tri-*sec*-butylborohydrides (L- and K-Selectride) and lithium triethylborohydride were found useful for conjugate reduction of α,β-unsaturated ketones and esters. In general, β-unsubstituted cyclohexenones undergo exclusive 1,4-reduction to the corresponding ketone enolate, which can be protonated or alkylated in high yields. Ketones such as 5-*t*-butylcyclohex-2-en-1-one are cleanly reduced to the saturated ketone using K-Selectride at − 78 °C in THF (Scheme 38)[171]. This regioselectivity, however, is not general, but is a result of steric hindrance of the olefin, as well as the size of the ring. Thus alkyl substitution at the β-position completely suppresses the 1,4-reduction mode. While enones in 5- and 7-membered rings are reduced preferably in a 1,2-manner, 6-membered ring enones are reduced in a 1,4-mode. Trapping the intermediate enolate by an alkylating agent (e.g. MeI, allyl bromide) results in an efficient reductive alkylation. Accordingly, when the reduction of α,β-unsaturated esters is performed in dry ether solvents, the major reaction product arises from carbonyl condensation. However, addition of a proton source such as *t*-butanol results in 1,4-reduction.



SCHEME 38

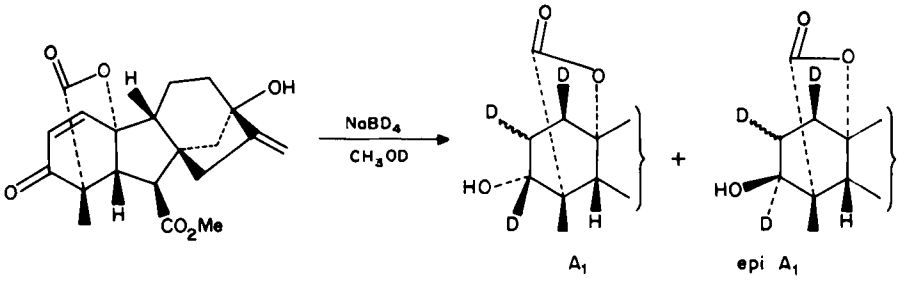
Reduction of α,β-unsaturated aldehydes and ketones with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeds selectively and cleanly to form the corresponding allylic alcohols (Scheme 39)[172]. The reaction tolerates a large variety of functionalities, such as nitro, carboxylic acid, amide, nitrile, sulfide, disulfide, epoxide, etc. Hydroboration of the double bond is a much slower reaction, which does not interfere with carbonyl reduction. For example, 1,2-reduction of cyclohexenone at room temperature with excess of 9-BBN in THF is completed within 10 minutes, while hydroboration of the double bond requires 3 days.



SCHEME 39

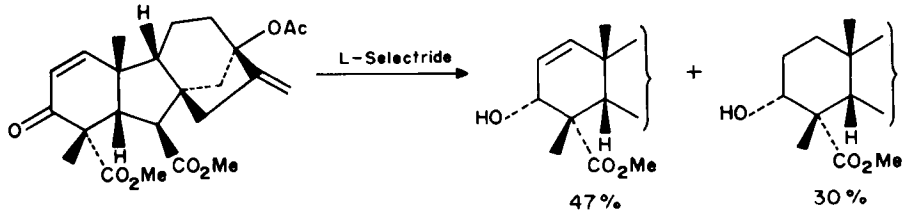
Borohydride reduction of α,β-unsaturated carbonyl compounds has been widely applied in natural product chemistry. A number of α,β-unsaturated ketone derivatives of gibberellins are reduced to the corresponding saturated alcohols by $NaBH_4$[173-176].

Sodium borodeuteride reduction of gibberellin A_3 3-ketone affords gibberellin A_1 and its 3-epimer (Scheme 40)[173,174]. Attack of hydride proceeds stereospecifically from the β-face at C-1. Protonation at C-2 proceeds with limited selectivity. Thus, reduction of the above-mentioned gibberellin with either $NaBH_4$–CuCl in deuterated methanol or $NaBH_4$–LiBr followed by treatment with D_2O gave 2-deuteriogibberellin A_1 methyl ester together with some 3-epi-GA_4 with approximately 2:1 ratio of the 2β:2α deuterides.



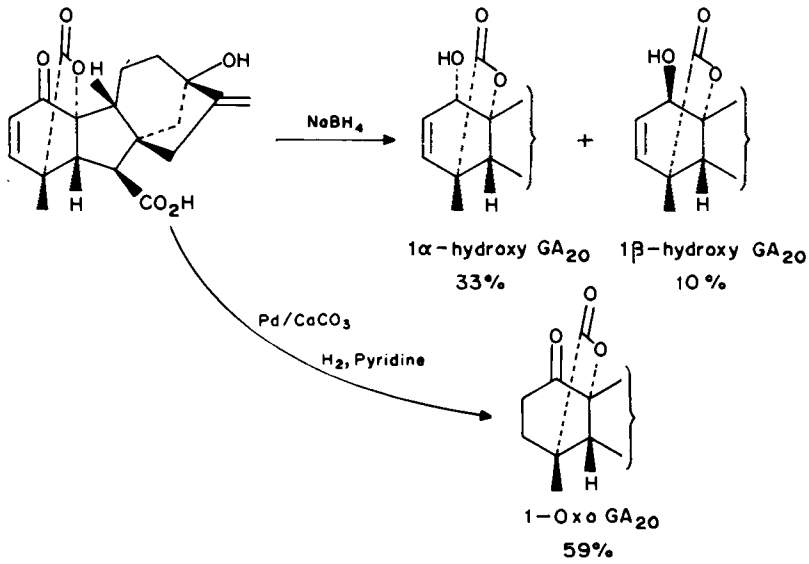
SCHEME 40

Using L-Selectride for the reduction of a similar gibberellin enone derivative resulted mainly in the 1,2-reduction product, affording the 3α-allylic and saturated alcohols in 47% and 30% yields, respectively (Scheme 41)[175].



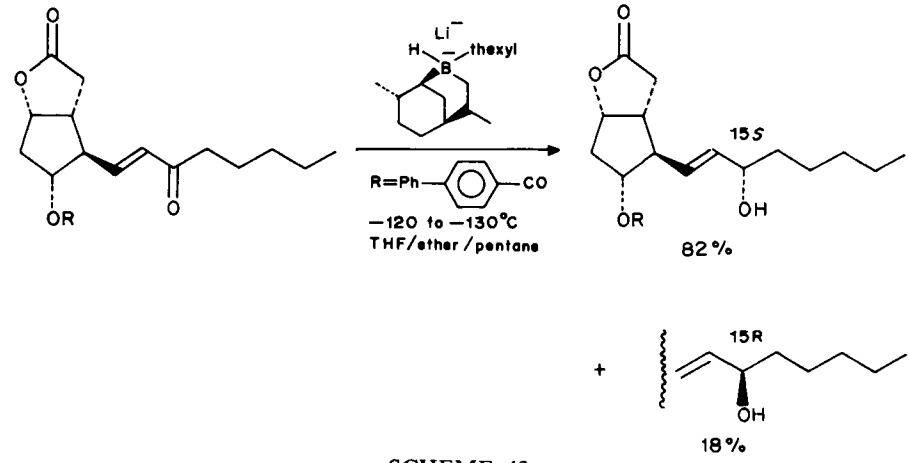
SCHEME 41

Substituted gibberellins, such as 1α- and 1β-hydroxy GA_5 and GA_{20}, were prepared from a single enone precursor by 1,2-reduction with $NaBH_4$ (Scheme 42). The reaction yielded 33% of 1α-hydroxy- and 10% of 1β-hydroxy-GA_5. Conversely, catalytic hydrogenation of the same enone with 10% $Pd/CaCO_3$ in pyridine afforded the 1,4-reduction product, 1-oxo-GA_{20}, in 59% yield[176].



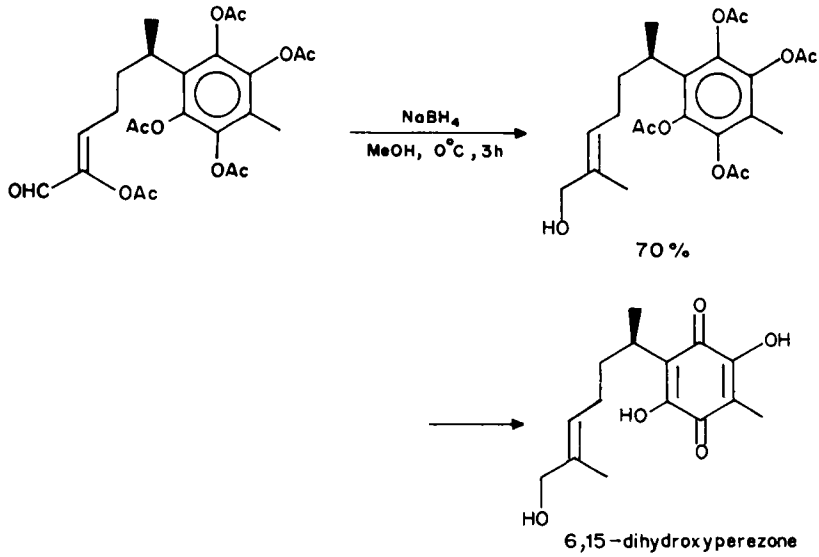
SCHEME 42

The stereoselective 1,2-reduction of the α,β-unsaturated ketone shown in Scheme 43 represents one of the key steps in Corey's approach to prostaglandin synthesis (Scheme 43)[177]. By using various boron and aluminum hydride reagents, mixtures of the corresponding 15*S* and 15*R* allylic alcohols were obtained in various ratios. Purest yields were obtained with highly hindered lithium trialkylborohydrides, such as diisobutyl-*t*-butylborohydride (74:26), tri-*sec*-butylborohydride (78:22), di-*sec*-butylthexylborohydride (80:20), the reagent indicated in Scheme 43 (82:18), etc. Even better stereoselectivity was achieved with *p*-phenylphenylurethane (R = *p*-PhC_6H_4NHCO) as a directing group. This derivative was reduced with thexyl-di-*sec*-butylborohydride and tri-*sec*-butylborohydride with 15*S*:15*R* ratios of 88:12 and 89:11, respectively[177].



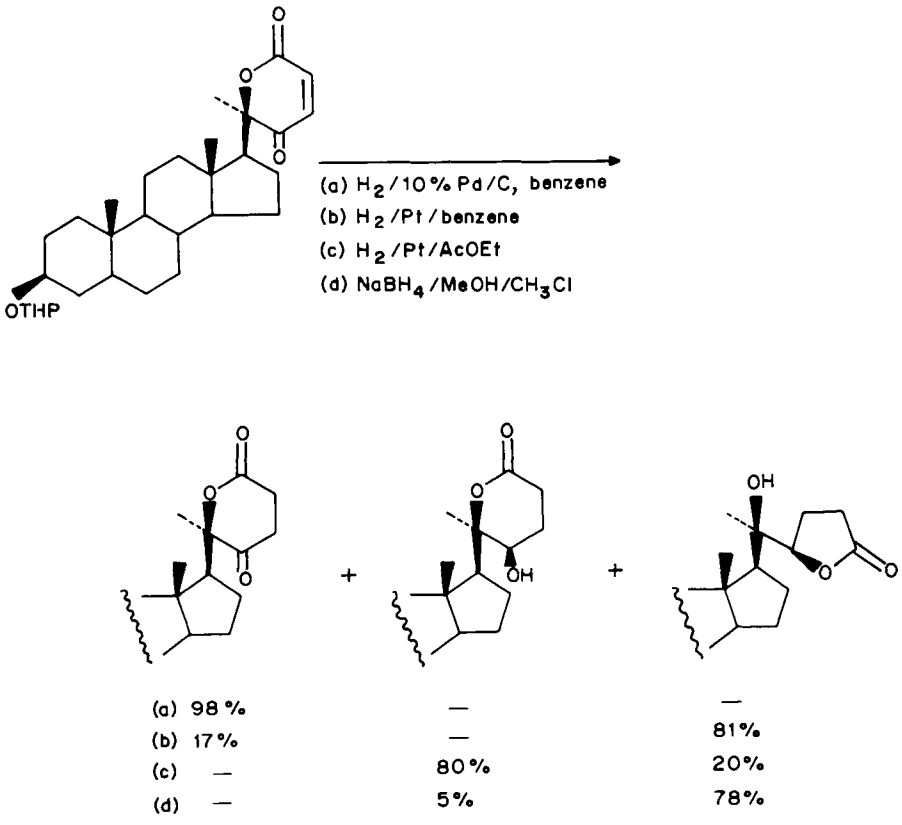
SCHEME 43

1,2-Reduction of an α,β-unsaturated aldehyde with $NaBH_4$ represents one of the steps in the total synthesis of 6,15-dihydroxyperezone (Scheme 44)[178].



SCHEME 44

Stereoselective reduction of an enono-lactone was a key step in the construction of the 20-hydroxyecdysone side-chain. Totally different mixtures of products were obtained when the reduction was carried out with sodium borohydride or by catalytic hydrogenation (Scheme 45)[156]. In all cases, the 1,4-reduction mode is preferred. With borohydride, however, this process is followed by a subsequent reduction of the saturated ketone and base-catalyzed rearrangement of the δ-lactone into a γ-lactone.



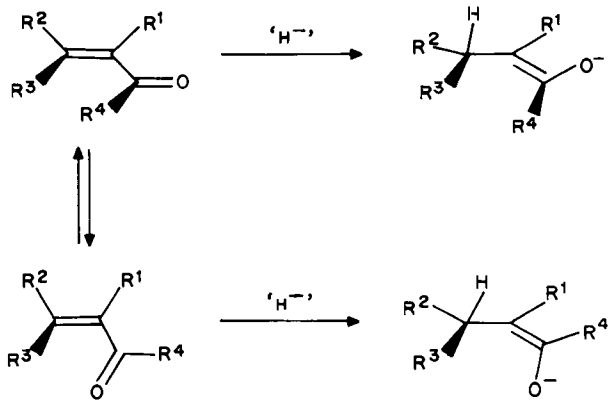
SCHEME 45

The conjugate reduction of acyclic α,β-unsaturated ketones can provide selectively regio- and stereochemically defined enolates that are unattainable by other methods. A knowledge of enone ground-state conformational preferences allows one to predict which enolate geometrical isomer will predominate in these reactions (Scheme 46)[179].

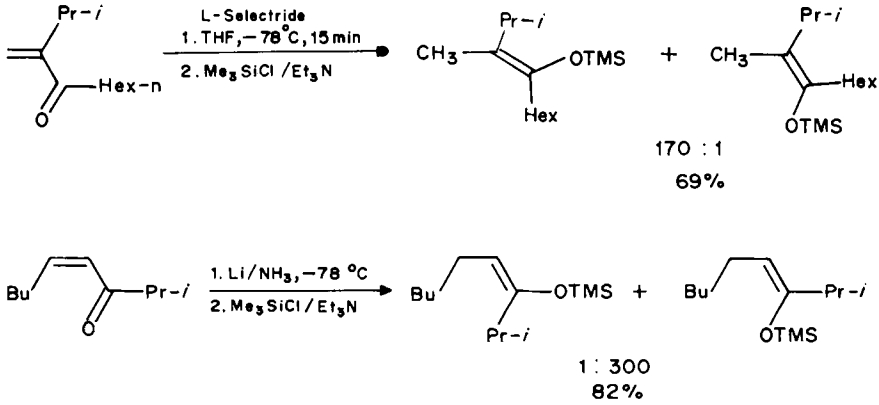
Thus, enones that exist preferentially as *s-trans* conformers will give rise to *E*-enolates whereas conjugate addition by hydride to *s-cis* enone will lead to *Z*-enolates. These can be trapped by trimethylsilyl chloride (TMSCl) to give the corresponding silyl enol ethers (Scheme 47)[179].

Sodium cyanoborohydride ($NaBH_3CN$) or tetrabutylammonium cyanoborohydride in acidic methanol or acidic HMPT reduces α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohol (Scheme 48)[180]. This system is limited to enones in which the double bond is not further conjugated, in which case the allylic hydrocarbon is formed in substantial amounts. Thus, reduction of chalcone gives mainly 1, 3-diphenylpropene (48%) as well as 26% of the allylic ether. Cyclic enones are also not good substrates, as competing 1, 4-addition gives large fractions of saturated alcohols[180].

Lithium butylborohydride is prepared by reacting equimolar amounts of butyl lithium and borane-dimethylsulfide complex[181]. This reagent effectively reduces enones in



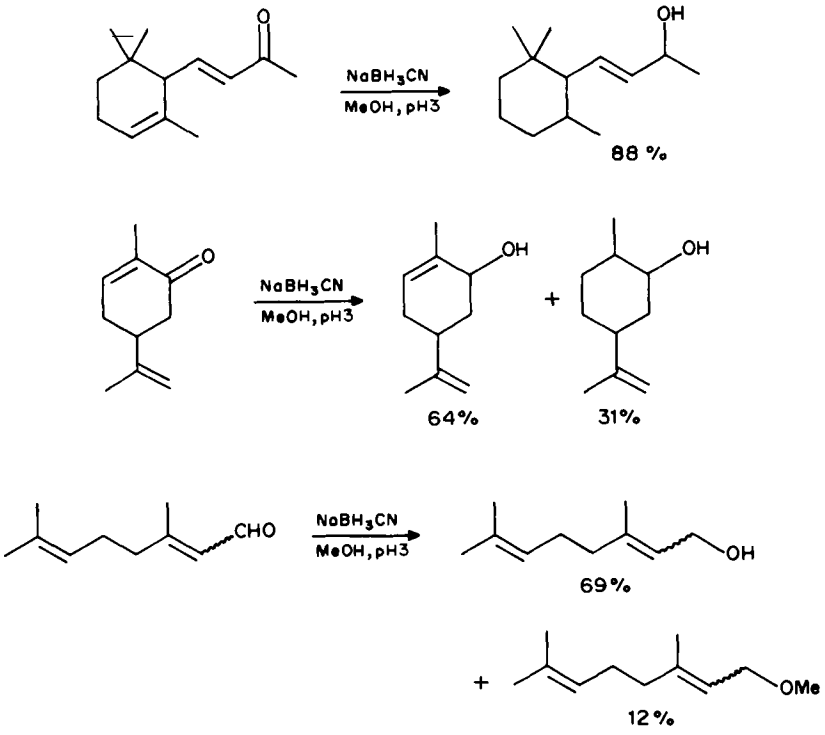
SCHEME 46



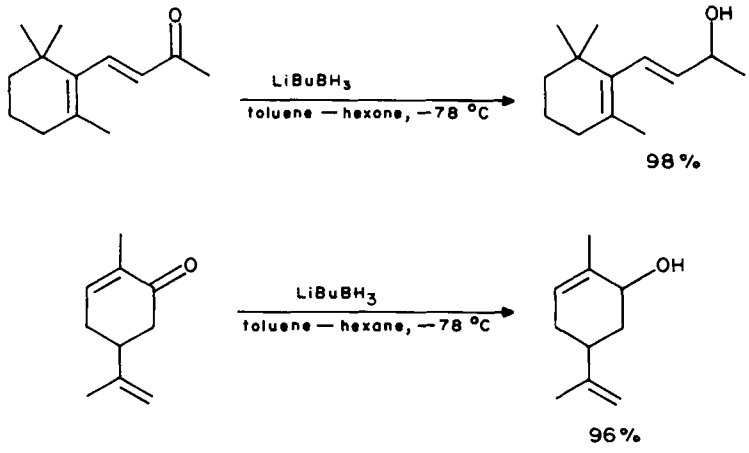
SCHEME 47

toluene–hexane mixtures at − 78 °C to give, in most cases, high yields of the corresponding allylic alcohols (Scheme 49)[181]. Conjugated cyclopentenones, however, give mixtures of 1,2- and 1,4-reduction products. Under identical reaction conditions, saturated ketones are reduced to alcohols. The latter process can take place in the presence of simple esters.

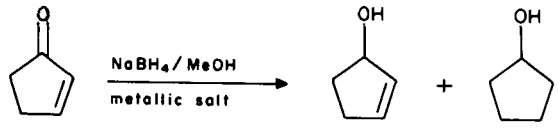
Regioselective 1,2-reduction of enones to the corresponding allylic alcohols is achieved with $NaBH_4$ in the presence of lanthanide ions, such as La^{3+}, Ce^{3+}, Sm^{3+}, Eu^{3+}, Yb^{3+} and Y^{3+}[182]. This procedure is complementary to those giving predominantly 1,4-selectivity, such as $NaBH_4$ in pyridine[168]. The general utility of $NaBH_4$–$CeCl_3$ selective reduction is illustrated by the conversion of cyclopentenone to cyclopentenol in 97% yield and only 3% of cyclopentanol, although conjugate reduction of cyclopentenone systems by most hydride reagents is usually highly favored (Scheme 50).



SCHEME 48



SCHEME 49

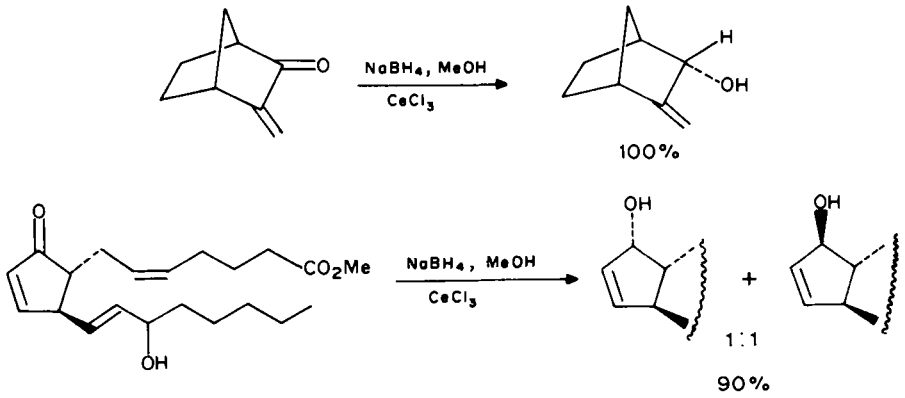


La^{3+}	90	:	10
Ce^{3+}	97	:	3
Sm^{3+}	94	:	6
Eu^{3+}	93	:	7
Yb^{3+}	89	:	11
Y^{3+}	86	:	14
Li^{+}	1	:	99

SCHEME 50

Thus, reaction of equimolar amounts of α,β-unsaturated ketones and either samarium or cerium chloride hexahydrate in methanol with sodium borohydride produced high yields of the corresponding allylic alcohols (Scheme 51)[182]. This approach was applied in the synthesis of 7, 7-dimethylnorbornadiene, whereas reduction of 4, 4-dimethylcyclopent-2-enone with sodium borohydride and cerium chloride in methanol afforded dimethylcyclopentenol in 93% yield[183].

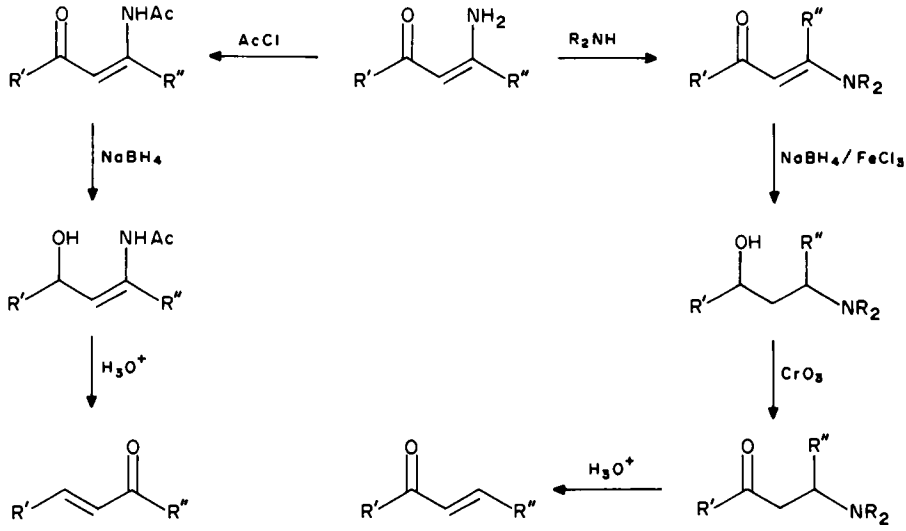
A mechanistic study of the role of the lanthanide cations suggests that they catalyze decomposition of borohydride by the hydroxylic solvent to afford alkoxyborohydrides, which may be responsible for the observed regioselectivity. The stereoselectivity of the process is also modified by the presence of Ln^{3+} ions, in that axial attack of cyclohexenone systems is enhanced[182].



SCHEME 51

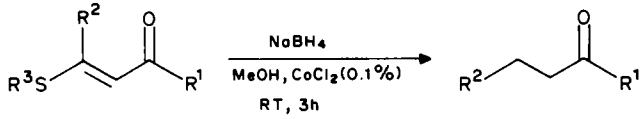
β-Dialkylamino conjugated enones are reduced to the corresponding γ-amino alcohols with $NaBH_4$ in the presence of $FeCl_3$. These aminoalcohols could be converted into conjugated enones by chromic acid oxidation and deamination (Scheme 52)[184]. On the other hand, β-acylamino conjugated enones are reduced by $NaBH_4$ to afford β,γ-

unsaturated γ-acylamino alcohols, which are regioselectively hydrolyzed to conjugated enones.



SCHEME 52

Reduction of β-sulfenylated α,β-unsaturated ketones with $NaBH_4$ in the presence of catalytic amounts of $CoCl_2$ or $NiCl_2$ in methanol produces the corresponding desulfenylated, saturated ketones (Scheme 53)[185]. These substrates, however, were not affected by combinations of $NaBH_4$ and other metal salts, including $FeCl_2$, $FeCl_3$, CuI and $CuCl_2$.



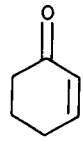
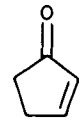
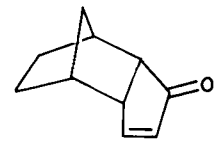
SCHEME 53

B. Aluminum Hydrides

The properties of complex metal hydrides, particularly those of aluminum, and their use in organic synthesis have been compared in a number of papers, review articles and monographs[186–190]. Useful tables, listing the most appropriate hydride reagents for selective reduction of various polyfunctional compounds, have been published[1,189–192]. Use of chiral metal alkoxyaluminum hydride complexes in asymmetric synthesis has also been reviewed[193].

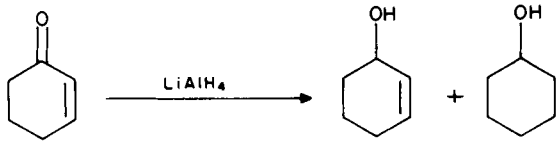
The two modes of reduction of α,β-unsaturated aldehydes and ketones, 1,2- and 1,4-addition of metal hydride to the enone system, lead respectively to either an allylic alcohol or a saturated ketone. It has been suggested that the relative importance of these paths depends upon substrate 'hardness' or 'softness', as defined in terms of the coefficients of the lowest unoccupied molecular orbital (LUMO) (*vide supra*, the discussion of borohydrides).

TABLE 3. Ratio of 1,4- to 1,2-reduction products

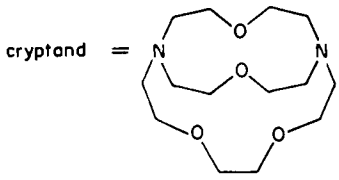
			
$LiAlH(OMe)_3$	5:95	10:90	24:76
$LiAlH_4$	22:78	86:14	100:0
$LiAlH(SMe)_3$	56:44	95:5	
$LiAlH(OBu\text{-}t)_3$	78:22	100:0	100:0
$LiAlH(SBu\text{-}t)_3$	95:5	100:0	

While 1,2-addition is considered to be a mainly charge-controlled process, 1,4-addition is a frontier orbital-controlled process[194]. These considerations predict, for example, that the 1,4-addition of a given metal hydride to cyclopentenone should always be faster than a similar addition to cyclohexenone[195]. Moreover, in cases where the enone system is further conjugated to a phenyl ring, as in cinnamaldehyde, increased frontier-orbital control should render the enone more prone to 1,4-addition[196]. Obviously, the course of reduction of conjugated carbonyl compounds is also highly influenced by the nature of the metal hydride. According to Pearson's concept of 'soft' and 'hard' acids and bases[197,198], hard metal hydrides add preferentially to the 2-position and soft metal hydrides to the 4-position of the conjugated enone system[194–196]. As shown in Table 3, these predictions agree well with representative experimental results[195,199].

Because of their electrophilic nature, Li^+ cations accelerate the reduction of carbonyl compounds by $LiAlH_4$ or $NaBH_4$, an effect that is significantly inhibited by Li^+-complexing agents, such as cryptands, crown ethers or polyamines, which decrease the rate of reduction[200]. In the case of α,β-unsaturated ketones, this slowdown is associated with altered regioselectivity. For example, $LiAlH_4$ reduction of cyclohexenones in the absence



THF	86 : 14	98%
ether	98 : 2	98%
THF, cryptand(1.2 eq)	14 : 86	85%
ether, cryptand (1.2 eq)	23 : 77	80%

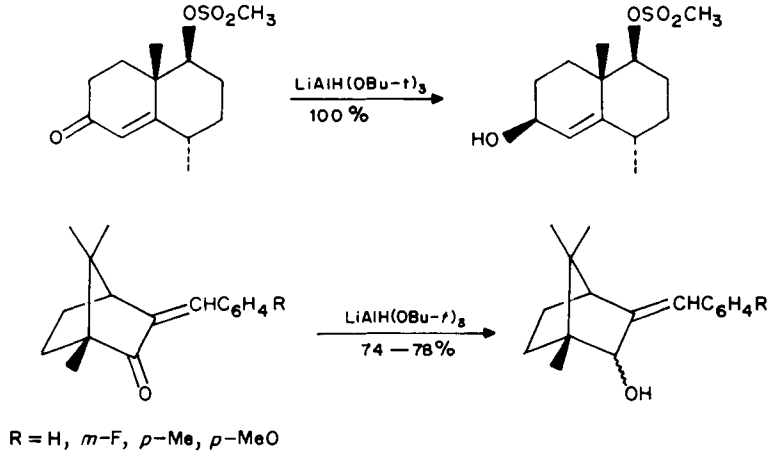


SCHEME 54

of the cryptand proceeds predominantly with 1,2-reduction. In the presence of the cryptand, 1,4-attack is favored. This selectivity is more pronounced with $LiAlH_4$ than with $NaBH_4$ (Scheme 54)[200] and is also highly dependent on solvent. In diethyl ether, 1,2-attack is essentially exclusive. However, when the cation is complexed, 1,4-addition again predominates.

This effect is explained in terms of Frontier Molecular Orbitals treatment[200]. The regioselectivity of reduction depends upon the relative values of the C_1 and C_3 atomic coefficients in the LUMO. The atom with the larger coefficient corresponds to the predominant site of attack. When Li^+ is complexed by the α-enone, the C_1 coefficient is larger than that of C_3, and C_1 attack is favored. In the absence of such complexation, the C_3 coefficient is larger, leading to 1,4-attack. The strength of carbonyl–Li^+ interaction is strongly dependent upon the solvent, the nature of the complexing agent and the interaction between the Li^+ ion and the reducing agent. Thus, in strongly coordinated solvents such as pyridine[168], 1,4-reduction predominates.

Steric and electronic factors in the enone substrate may also alter selectivity. For example, the high tendency of $LiAlH(OBu\text{-}t)_3$ to undergo 1,4-addition with simple enones is modified in the two examples given in Scheme 55[201].

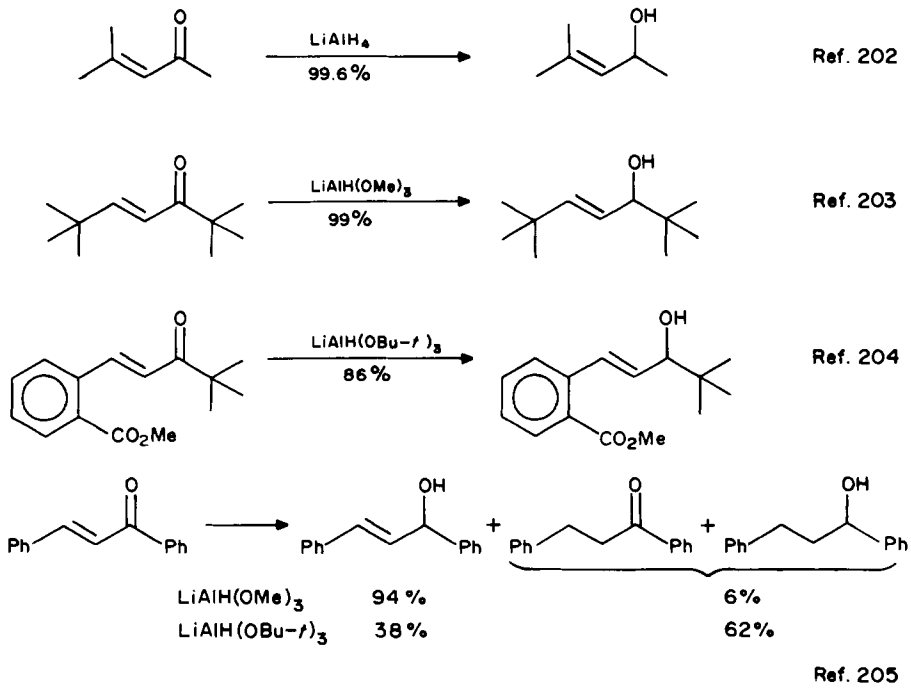


SCHEME 55

The ratio of 1,2- to 1,4-addition of aluminum hydride to an α,β-unsaturated ketone is highly dependent on the enone structure, solvent, relative initial concentrations of reactants, temperature, and softness or hardness of the hydride reagent. These reductions can be controlled to proceed with either 1,2- or 1,4-addition, with high selectivity[186]. The examples presented in Scheme 56[202–205] illustrate the prominent tendency of $LiAlH_4$ and $LiAlH(OMe)_3$ to yield 1,2- rather than 1,4-adducts, as compared to $LiAlH(OBu\text{-}t)_3$.

The reagent $NaAlH_2(OCH_2CH_2OCH_3)_2$ favors 1,2-addition to cyclic enones with greater selectivity than with either $LiAlH(OMe)_3$[195] or AlH_3[199]. Several examples are presented in Scheme 57[203,206–210].

In most of these examples, reductions are nonstereoselective. In some cases, however, such as in the reduction of 9-oxoisolongifolene to the allylic 9α- or 9β-alcohols (Scheme 58), reversal of stereochemistry occurs when $NaAlH_2(OCH_2CH_2OCH_3)_2$ is used instead of $LiAlH_4$ or $NaBH_4$[211]. While the latter two reagents lead to formation of the thermody-



SCHEME 56

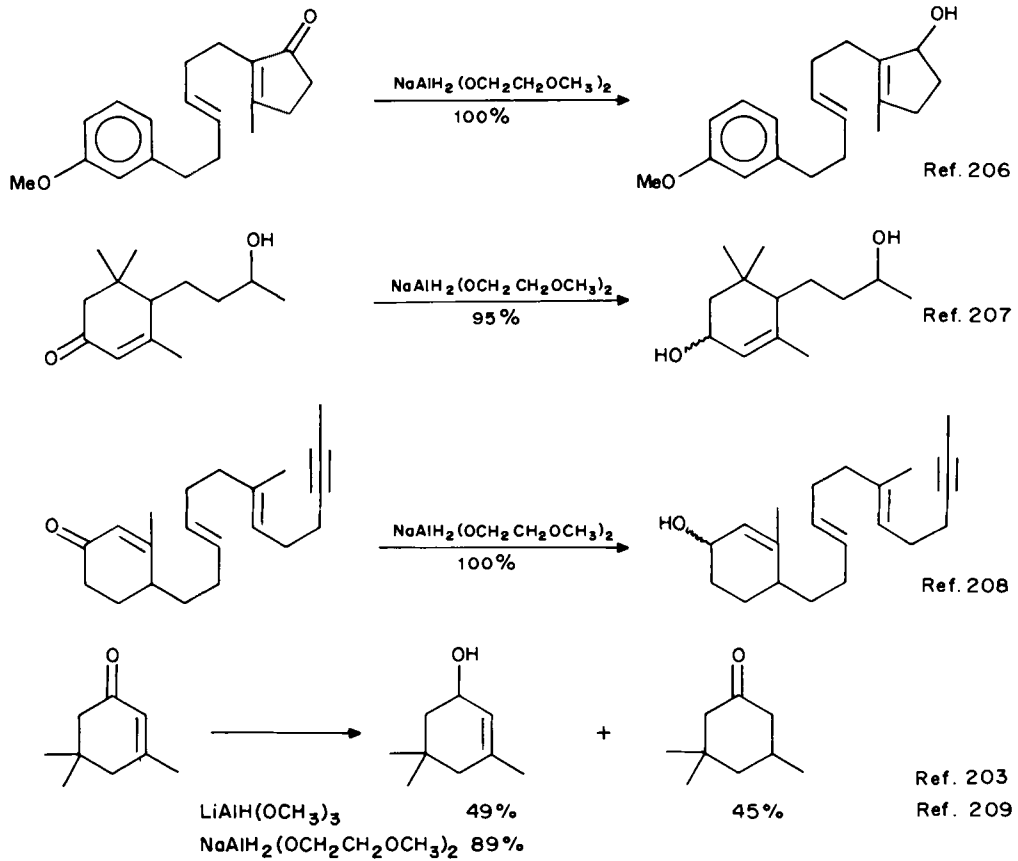
namically more stable α-alcohol as the major product, increased steric bulk of the former seems to favor the less stable β-isomer.

Sterically unhindered enones, such as cyclohexenone, are reduced by $LiAlH(OBu\text{-}t)_3$ to give predominantly the corresponding saturated ketone[195]. More sterically congested systems are cleanly reduced via the 1, 2-mode to give the allylic alcohol, usually with high stereoselectivity (Scheme 59)[212–215].

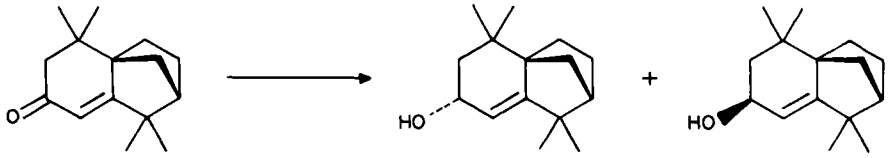
1, 2-Reduction has been reported for other hydride reagents, such as diisobutylaluminum hydride[194,216,217], aluminum hydride[199] and 9-borabicyclononane (9-BBN)[218], as illustrated by the example in Scheme 60.

1, 4-Reduction of enones can be effected with high selectivity with $AlH(OBu\text{-}t)_2$, $AlH(OPr\text{-}i)_2$, $AlH(NPr^i_2)_2$ or HBI_2, forming saturated ketones in 90–100% yield. $AlH(NPr^i_2)_2$ exhibited the lowest selectivity, as no 1, 4-reduction of mesityl oxide or isophorone is observed with this reagent. The same reagent with methyl vinyl ketone or cyclohexenone led to mixture of products. *Trans*-chalcone also undergoes quantitative 1, 4-reduction with the above-mentioned hydrides[217]. Similarly, reduction of 9-anthryl styryl ketone or anthracene-9, 10-diyl-bis(styryl ketone) with $LiAlH(OBu\text{-}t)_3$ affords the saturated ketone as the sole product[219]. Hydrides such as $LiAlH(OBu\text{-}t)_3$ and $LiAlH(SBu\text{-}t)_3$ favor 1, 4-reduction in cyclopentenones[195,196,199,220–223]. An example is given in Scheme 61, where steric factors allow only *exo* approach of the bulky hydride[224,225].

Scheme 62 illustrates an interesting two-step selective reduction of an enone system, first with sodium hydride and $NaAlH_2(OCH_2CH_2OCH_3)_2$ and then with the same reagent in the presence of 1, 4-diazabicyclo[2.2.2]octane. Specific reduction, however, is not achieved with $NaBH_4$, $LiBH_4$, $LiBH(s\text{-}Bu)_3$ or 9-BBN[226].

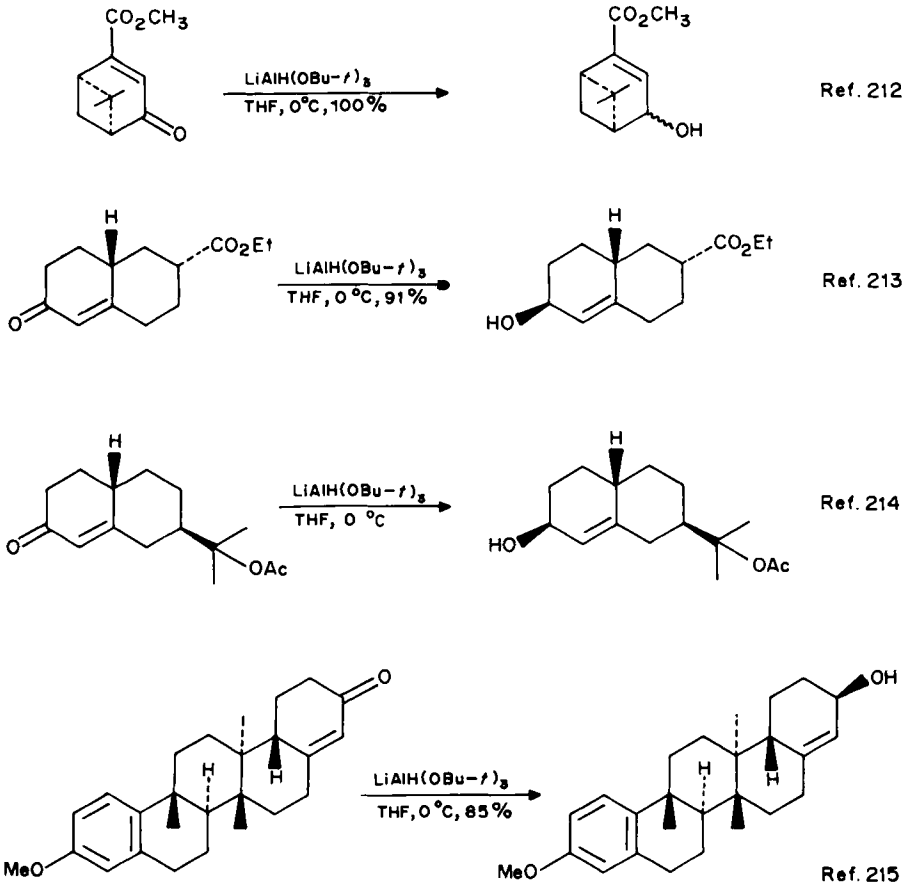

NaAlH2(OCH2CH2OCH3)2
100%
MeO
OH
Ref. 206
NaAlH2(OCH2CH2OCH3)2
95%
HO
Ref. 207
NaAlH2(OCH2CH2OCH3)2
100%
Ref. 208
LiAlH(OCH3)3
49%
NaAlH2(OCH2CH2OCH3)2 89%
45%
Ref. 203
Ref. 209

SCHEME 57

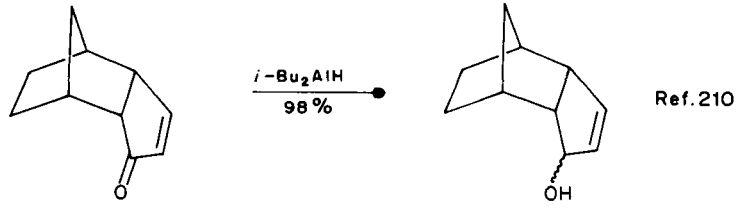


$LiAlH_4$	76 : 24
$NaBH_4$	76 : 24
$NaAlH_2(OCH_2CH_2OCH_3)_2$	18 : 82

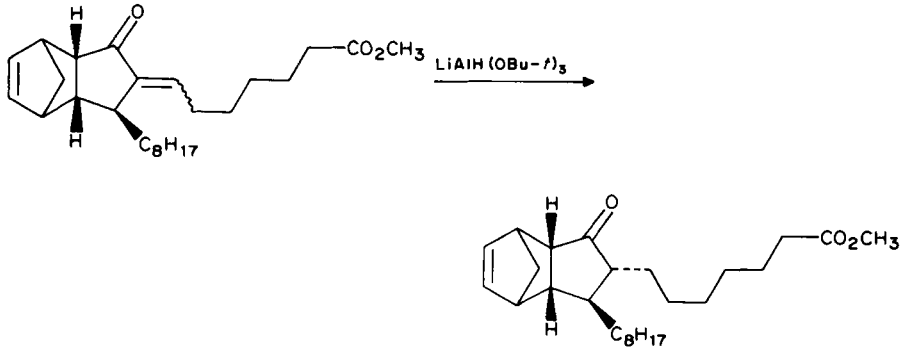
SCHEME 58



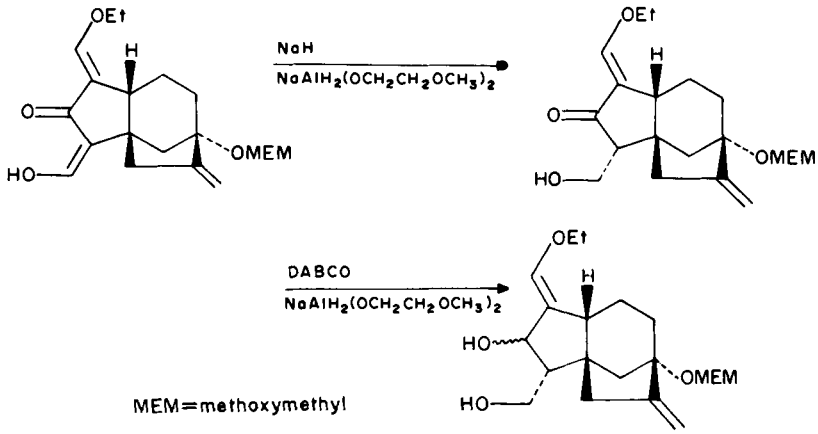
SCHEME 59



SCHEME 60

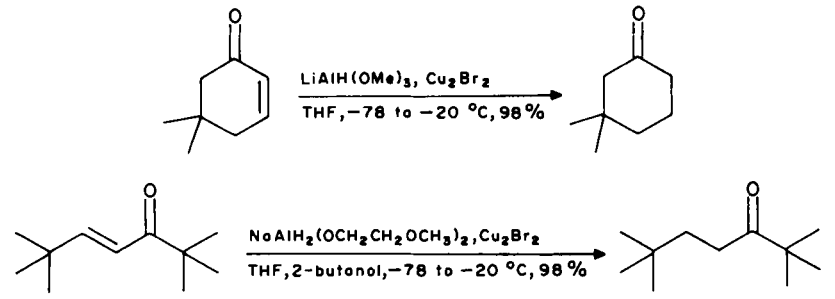


SCHEME 61



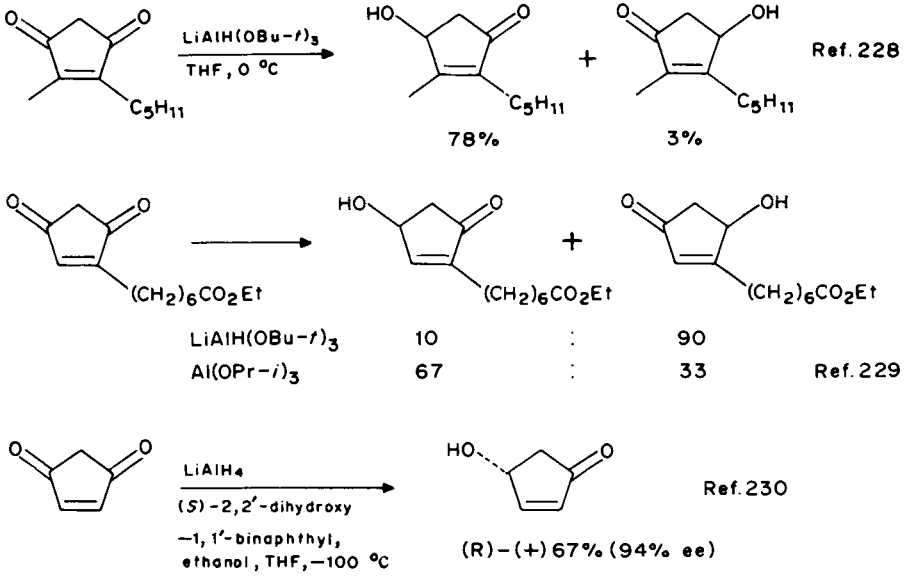
SCHEME 62

Both $LiAlH(OMe)_3$ and $NaAlH_2(OCH_2CH_2OCH_3)_2$ are convenient reducing agents for low-temperature, copper-mediated 1,4-reduction, as shown by the examples in Scheme 63[203,227].



SCHEME 63

Aside from the nature of the hydride reagent, steric effects and lower reactivity of the enone substrate affect the course of reduction in polyfunctional molecules. Several examples of partial reduction of cyclopentenedione systems are given in Scheme 64[228-230].

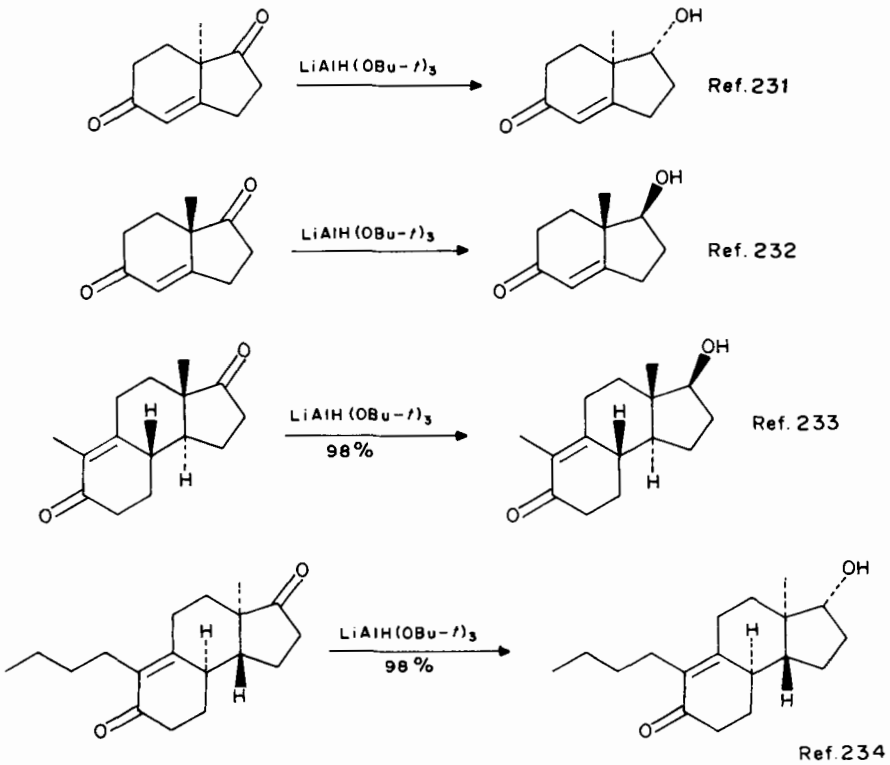


SCHEME 64

There are a number of cases where a less reactive enone group remains intact while a more reactive saturated ketone present in the same substrate is selectively reduced, as shown in Scheme 65[231-234].

Alternatively, there are a number of examples of simultaneous reduction of both saturated and unsaturated ketones or of preferential reduction of the unsaturated one (Scheme 66)[235-237].

Reduction of enol ethers or enol esters of 1,3-diketones followed by acid-catalyzed allylic rearrangement of the reduction product (see p. 85 in Reference 5) is a useful route to

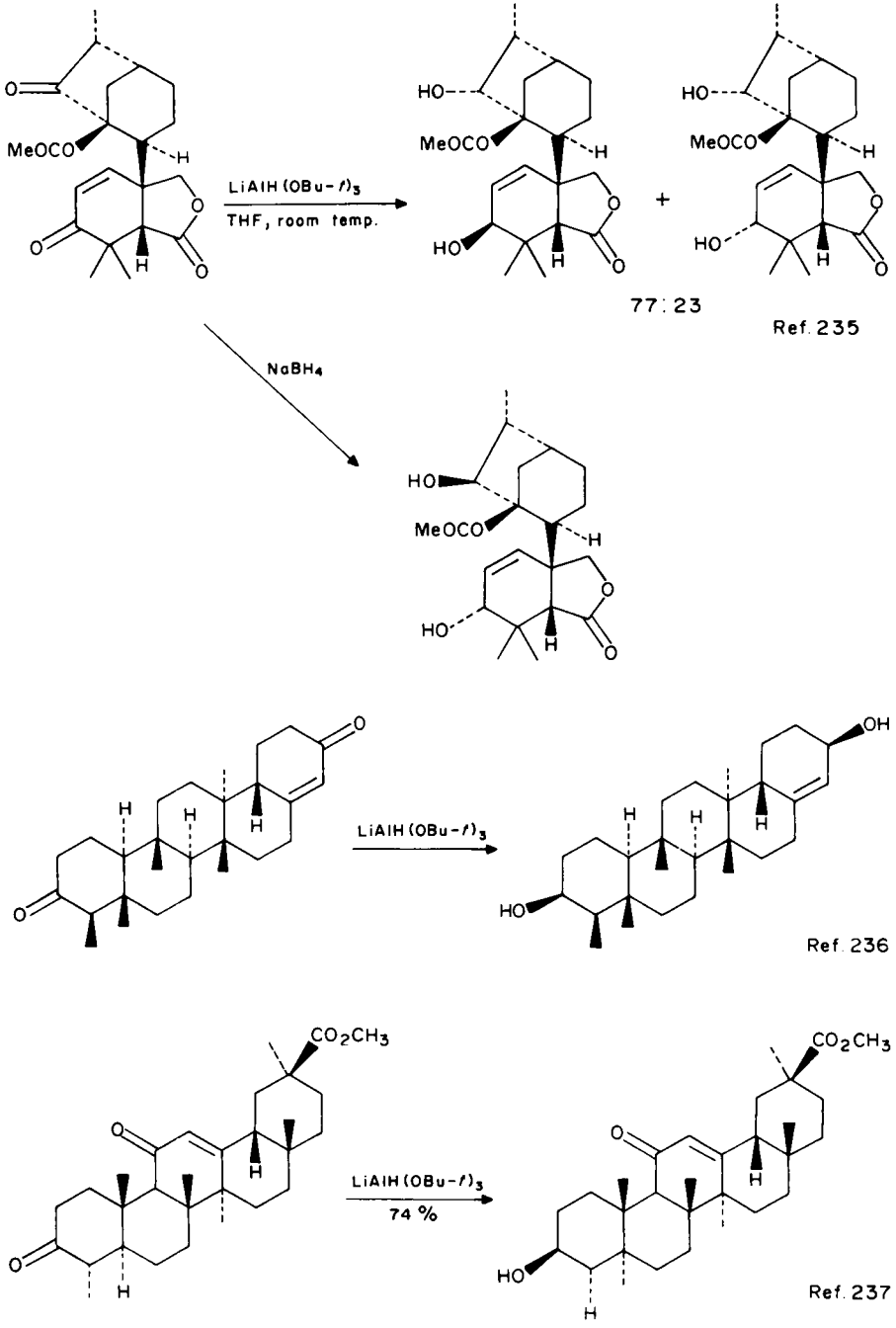


SCHEME 65

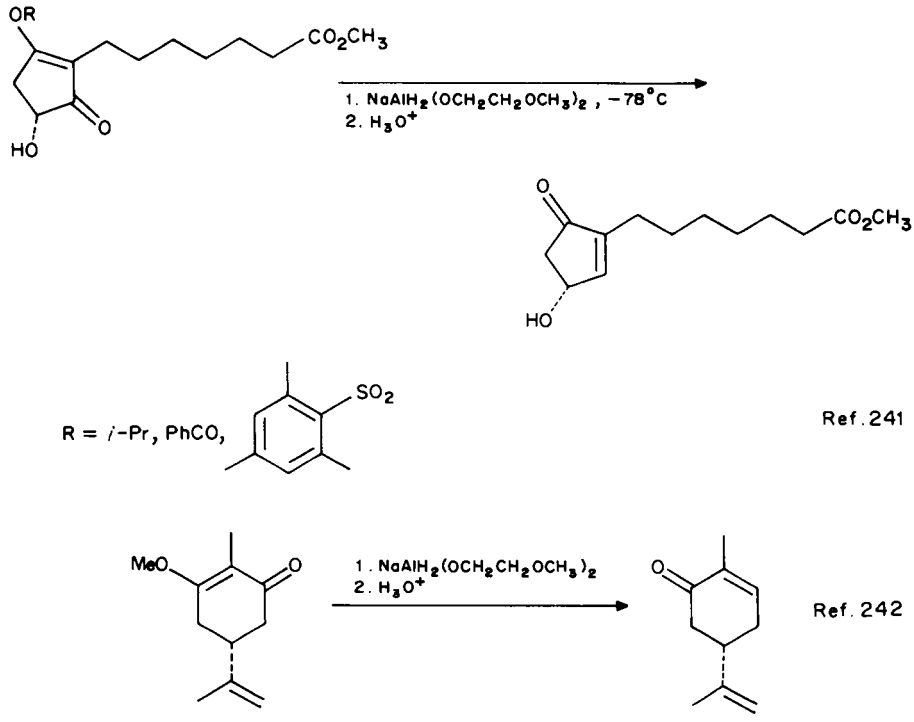
α,β-unsaturated ketones. Aliphatic[238,239] and alicyclic[240] enones have thus been prepared in good yields at low temperatures with $NaAlH_2(OCH_2CH_2OCH_3)_2$ (Scheme 67)[241,242].

Reduction of α,β-unsaturated aldehydes can afford either an unsaturated or saturated primary alcohol, or a mixture of both, depending on reaction conditions. For example, while addition of cinnamaldehyde to $NaAlH_2(OCH_2CH_2OCH_3)_2$ in benzene gives 97% 3-phenylpropanol, inverse addition (of the reducing agent to solution of the substrate) yields 94% cinnamyl alcohol[243,244]. Reduction with $LiAlH_4$ is similarly dependent on the addition sequence. The more sterically hindered hydride $LiAlH(OBu\text{-}t)_3$ is highly selective for 1,2-reduction of aldehydes, even under conditions of normal addition. For example, it reduces cinnamaldehyde cleanly to cinnamyl alcohol, without affecting the olefinic bond[245–247]. Similar behavior is exhibited by $NaAlH_2(OCH_2CH_2OCH_3)_2$, which reduces 2-butenal to 2-butenol in 97% yield[244]. On the other hand, hydrides such as $LiAlH(OMe)_3$[187,245,246] and $NaAl_2H_4(OCH_2CH_2NMe_2)_3$[248] usually yield the saturated primary alcohol. Other examples of 1,2-reduction of α,β-unsaturated aldehydes with these reagents are given in Scheme 68[249–251].

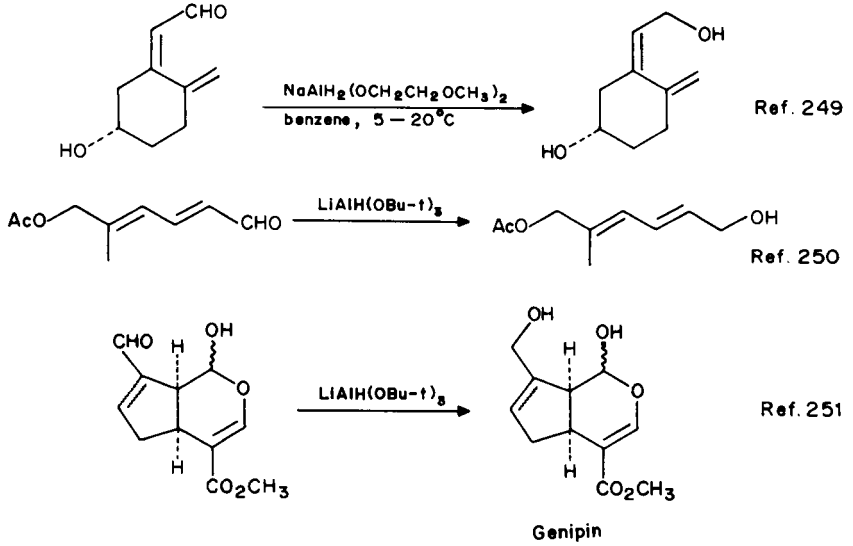
Regioselectivity of enone reduction with diisobutylaluminum hydride (DIBAH) is very susceptible to minor structural changes in the substrate. While five-membered exocyclic enones provide the allylic alcohols which are the normal products for this reagent, reduction of chromones possessing exocyclic six-membered enones yield saturated


MeOCO
LiAlH(OBu-t)3
THF, room temp.
HO
77:23
Ref. 235
NaBH4
LiAlH(OBu-t)3
Ref. 236
CO2CH3
LiAlH(OBu-t)3
74 %
Ref. 237

SCHEME 66

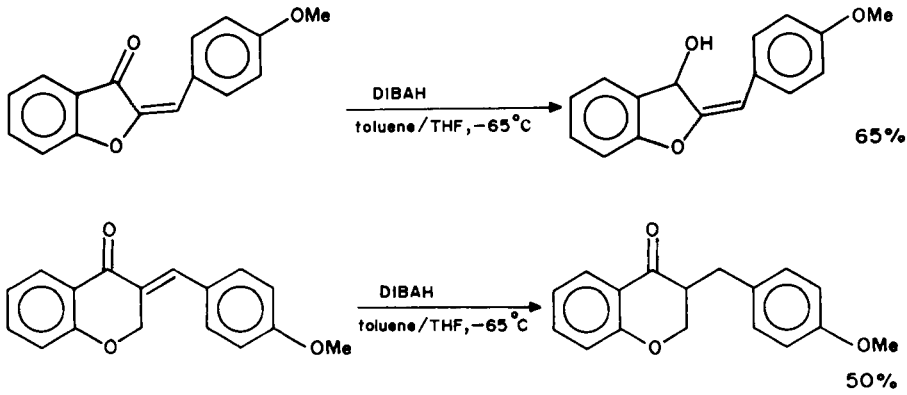


SCHEME 67



SCHEME 68

ketones (Scheme 69)[252]. This was explained by the strict coplanarity of the enone function in the five-membered structure, whereas the enones giving rise to saturated ketones are slightly twisted. Reduction of isoflavones with DIBAH under these conditions provides the corresponding isoflavan-4-ones in very high selectivity[252].



SCHEME 69

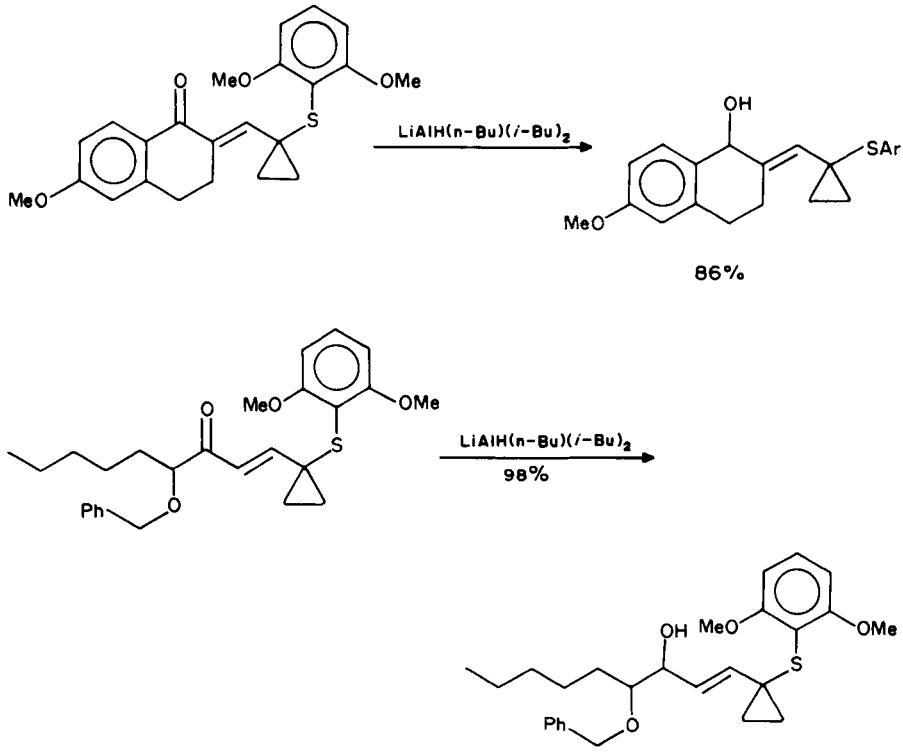
The 'ate' complex $LiAlH(n\text{-}Bu)(i\text{-}Bu)_2$ is prepared from DIBAH and butyllithium in either THF or toluene–hexane. This reagent is more effective for selective 1,2-reduction of enones to the corresponding allylic alcohol than is DIBAH alone[253]. The reagent also reduces esters, lactones and acid chlorides to the corresponding alcohols, and epoxides to the respective alcohols. α,β-Unsaturated ketones derived from dehydration of aldol products from 1-(arylthio)cyclopropanecarboxaldehydes and ketones were selectively reduced by this 'ate' complex or by DIBAH itself, yielding the allylic alcohols with minor amounts of the 1,4-reduction product (Scheme 70)[254]. Yields were typically higher with this reagent than with DIBAH.

Enones may be deoxygenated with $LiAlH_4/AlCl_3$ to give the corresponding olefinic hydrocarbons. The reactive species seem to be $AlHCl_2$ or AlH_2Cl, which act as both Lewis acids and hydride donors. The reaction involves initial 1,2-reduction to form the allylic alcohol, followed by substitution of the allylic hydroxyl group by hydride (mainly via an S_N2' mechanism) to form the corresponding mixture of alkenes (Scheme 71)[255].

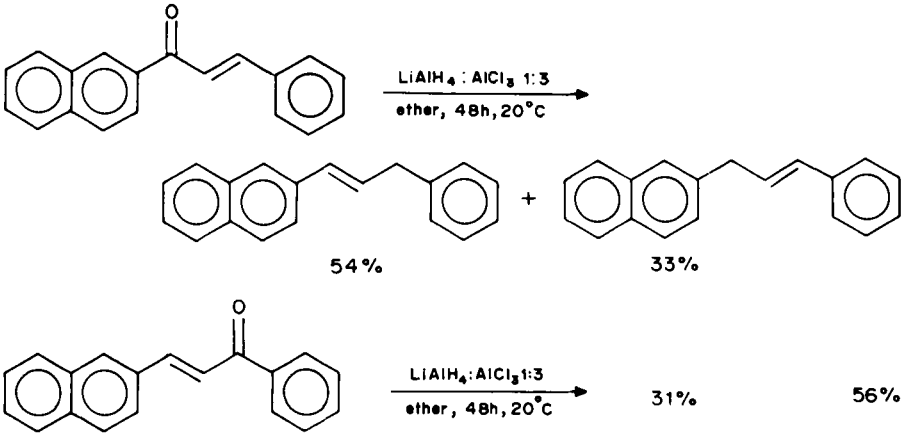
This technique has been applied to the deoxygenation of natural products. By using mixtures of $LiAlH_4$ and $AlCl_3$, flavanone and chalcones were transformed into flavan and diarylpropenes, respectively (Scheme 72)[256].

Conjugate reduction is the major pathway of enone reduction with a mixture of $LiAlH_4$ and excess CuI in THF[257]. It has been shown that the active reducing agent in this mixture is an H_2AlI species and not the copper hydride. Enones of *cis* geometry are reduced much more slowly than the corresponding *trans* compounds, and no reduction was observed with cyclohexenone and 3,3,5-trimethylcyclohexenone. These results suggest that the mechanism involves coordination of the metal to the carbonyl, forming a six-center transition state (Scheme 73)[257].

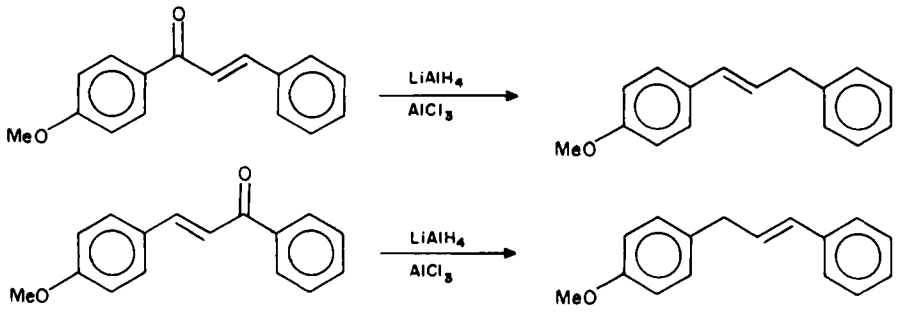
Enones with two alkyl groups at the β-position are reduced very sluggishly under these conditions. Other metal salts, such as HgI_2, $TiCl_3$ and $HgCl_2$, premixed with $LiAlH_4$ in THF, similarly give rise to 1,4-reduction. Yields and selectivities were found to be much lower than with CuI. H_2AlI was found to react in the exact same manner as $LiAlH_4$–CuI, and the series H_2AlI, $HAlI_2$, H_2AlBr, $HAlBr_2$, H_2AlCl and $HAlCl_2$ was therefore



SCHEME 70

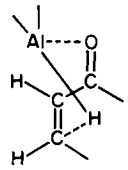


SCHEME 71



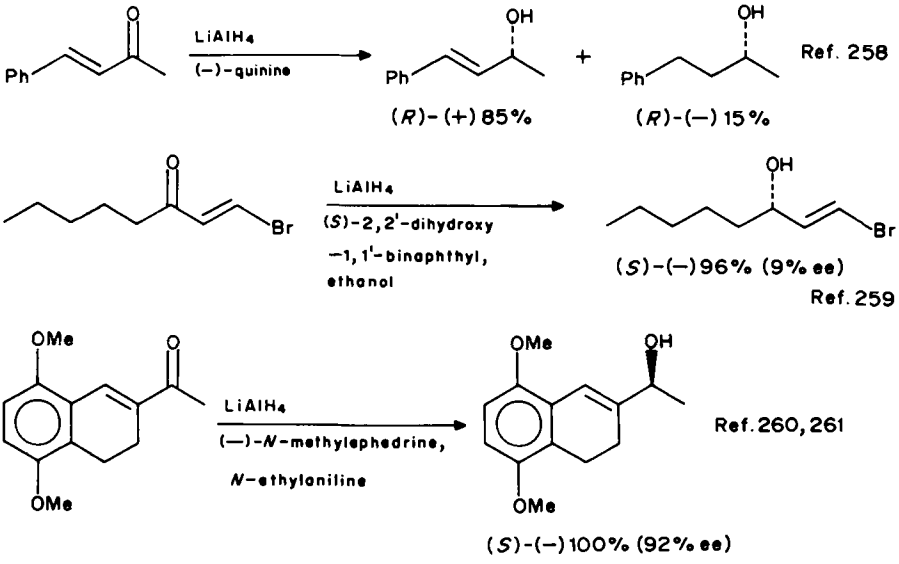
SCHEME 72

prepared. Of these, the iodo compounds exhibited the highest reactivity. $HAlI_2$ reduces enones at a slower rate than H_2AlI, probably due to steric factors.



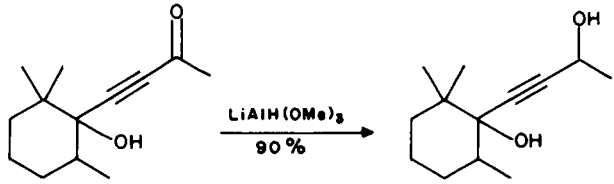
SCHEME 73

Chiral lithium alkoxyaluminumhydride complexes can be used to obtain optically active allylic alcohols (Scheme 74)[258–261]. These reagents are more selective than the polymer-supported $LiAlH_4$ and $LiAlH_4$–monosaccharide complexes[262].



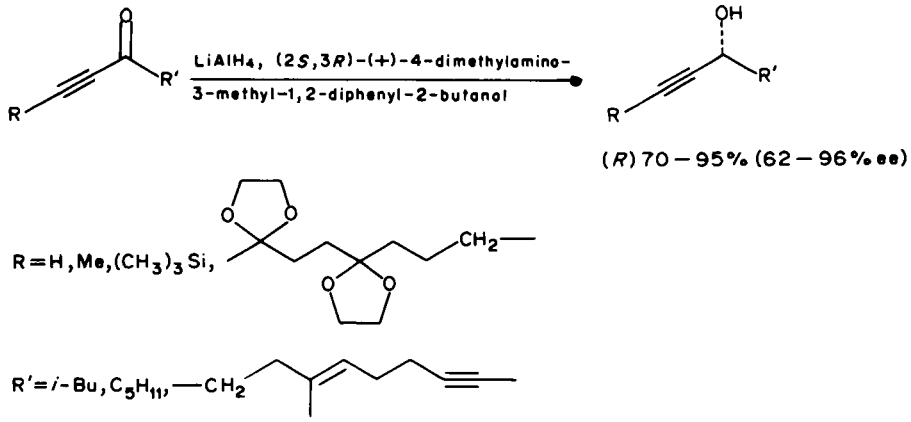
SCHEME 74

α,β-Acetylenic ketones are selectively reduced to the corresponding propargylic alcohols with $LiAlH(OMe)_3$ (Scheme 75).



SCHEME 75

Asymmetric 1,2-reduction of acetylenic ketones is an effective method for preparing optically active propargylic alcohols in high yield and high enantioselectivity. Common chiral reductants for this purpose include the Mosher–Yamaguchi reagent[263–265], the Vigneron–Jacquet complex[266–268] and $LiAlH_4$/2,2′-dihydroxy-1,1′-binaphthyl/methanol (*R* and *S*) complexes[269], as well as the $LiAlH_4$-*N*-methylephedrine/*N*-ethylaniline complex[260]. For example, reduction of simple acetylenic ketones (Scheme 76) with $LiAlH_4$/(2*S*,3*R*)-(+)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol results in propargylic (*R*)-alcohols in 62–95% enantiomeric excess. These chiral building blocks were used in the synthesis of tocopherol, prostaglandins and 11α-hydroxyprogesterone[264,265].

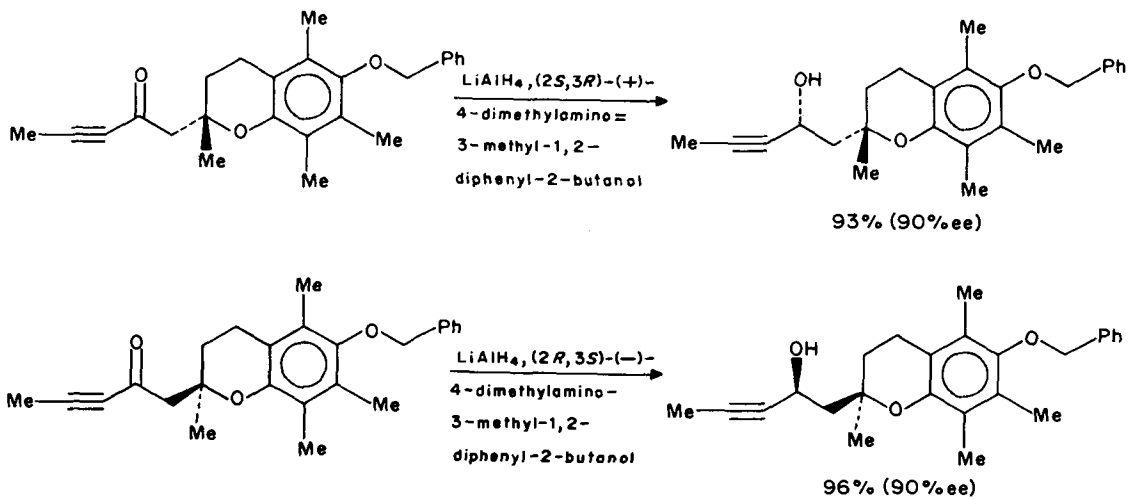


SCHEME 76

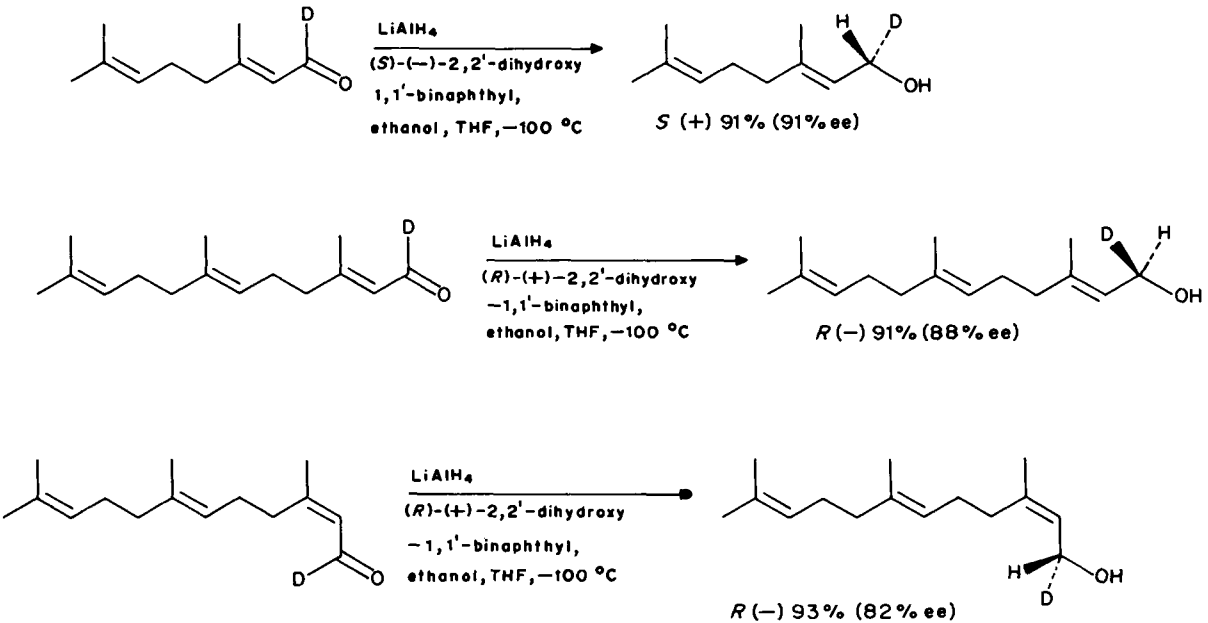
This method can also be used for diastereoselective reduction of optically active acetylenic ketones, as shown in Scheme 77[263].

Enantioselective formation of propargylic alcohols is carried out via reductions with the Vigneron–Jacquet complex[266–268]. However, Landor's chiral $LiAlH_4$–monosaccharide complexes are less selective for this purpose[270–272].

Asymmetric reduction of geranial-d1, neral-d1 and related linear terpenic aldehydes can be achieved with $LiAlH_4$–dihydroxybinaphthyl complex with 72–91% enantiomeric excess (Scheme 78)[273].

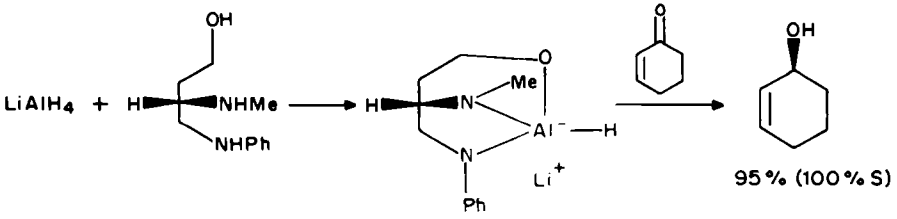

Me
Ph
O
Me
Me
Me
Me
O
LiAlH4, (2S,3R)-(+)-
4-dimethylamino-
3-methyl-1,2-
diphenyl-2-butanol
OH
93% (90% ee)
LiAlH4, (2R,3S)-(−)-
4-dimethylamino-
3-methyl-1,2-
diphenyl-2-butanol
96% (90% ee)

SCHEME 77


D
O
LiAlH4
(S)-(−)-2,2'-dihydroxy
1,1'-binaphthyl,
ethanol, THF, −100 °C
H
D
OH
S (+) 91% (91% ee)
D
O
LiAlH4
(R)-(+)-2,2'-dihydroxy
−1,1'-binaphthyl,
ethanol, THF, −100 °C
D
H
OH
R (−) 91% (88% ee)
D
O
LiAlH4
(R)-(+)-2,2'-dihydroxy
−1,1'-binaphthyl,
ethanol, THF, −100 °C
H
OH
D
R (−) 93% (82% ee)

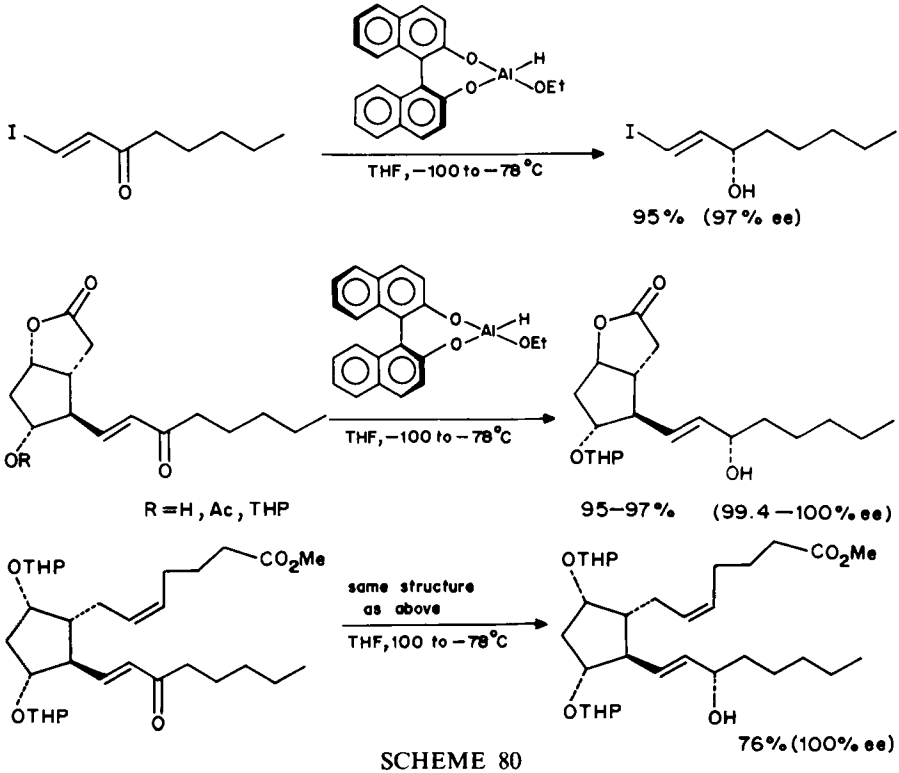
SCHEME 78

Asymmetric reduction of prochiral α,β-unsaturated ketones with chiral hydride reagents derived from $LiAlH_4$ and (*S*)-4-anilino- and (*S*)-4-(2,6-xylidino)-3-methylamino-1-butanol gives (*S*)- and (*R*)- allylic alcohols, respectively, in high chemical and optical yields (Scheme 79)[274].



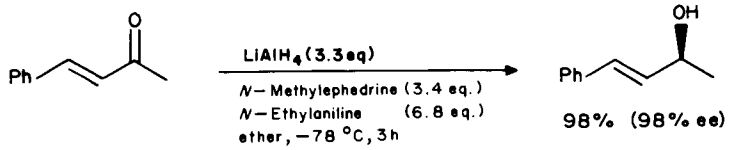
SCHEME 79

A modified aluminum hydride is prepared by treating $LiAlH_4$ in THF with equimolar amounts of ethanol and optically pure *S*-(−)-2,2′-dihydroxy-1,1′-binaphthyl. Allylic alcohols of very high optical purity are obtained in high yield by reduction of α,β-unsaturated ketones with this reagent[275]. Of particular interest are the attractive opportunities provided by this reagent in prostaglandin synthesis. For example, some of the chemical transformation shown in Scheme 80[275] are more effective in both terms of chemical and optical yields than standard microbiological reduction[276].



SCHEME 80

Asymmetric reduction of α,β-unsaturated ketones is achieved with $LiAlH_4$, partially decomposed by (−)-*N*-methylephedrine and ethylaniline (Scheme 81)[260]. This reagent converts open chain enones into the corresponding optically active allylic alcohols in high chemical (92–100%) and optical yields (78–98% ee).



SCHEME 81

C. Silicon Hydrides

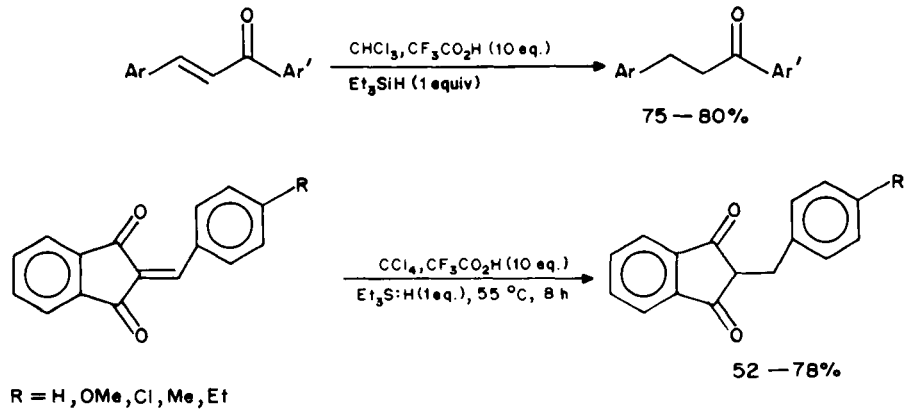
The hydrogen in the Si—H bond is slightly hydridic in nature, as would be expected from the relative electronegativities of silicon (1.7) and hydrogen (2.1). Therefore, silanes may function as hydride transfer agents toward highly electrophilic species such as carbonium ions. The hydridic nature of the Si—H bond may be significantly increased upon interaction with strong anionic ligands, such as fluoride and alkoxides (*vide infra*). In addition, the average bond energy of the Si—H and C—H bonds (70 and 99 kcal mol^{-1}, respectively) suggests that Si—H bonds should be susceptible to hydrogen atom abstraction by carbon radicals. Thus, the dehalogenation of alkyl halides with hydridosilane under homolytic conditions is explained in terms of a radical-chain mechanism[277]. Alternatively, silanes readily transfer a hydride ligand to a variety of transition-metal complexes via oxidative addition, allowing for highly selective transition metal-catalyzed reduction processes (*vide infra*, Section IV, B).

A useful reduction method involving hydridosilane in strongly acidic media, 'ionic hydrogenation', is useful for reduction of a number of organic functional groups[278]. The ionic hydrogenation reaction is based on the principle that the carbonium ion formed by protonation of the double bond reacts with a hydride donor to form the hydrogenated product. Reduction conditions generally involve reflux in strongly acidic media in the presence of the silane. Obviously, reduction is possible only when the substrate can produce carbonium ions under the given conditions. A hydrogenation pair most useful for many reduction processes is comprised of trifluoroacetic acid and a hydridosilane, which exhibits the following order of reactivity[278]:

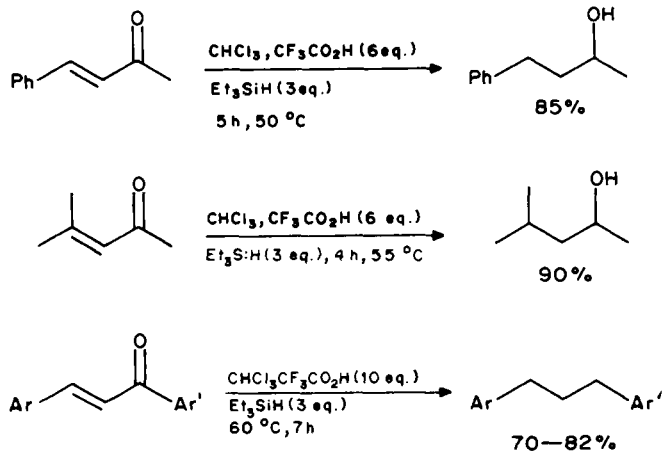
$$Et_3SiH > Octyl_3SiH > Et_2SiH_2 > Ph_2SiH_2 > Ph_3SiH > PhSiH_3$$

These reducing systems tolerate carboxylic acid derivatives, nitriles, nitro groups, sulfonic esters, aromatic rings and, occasionally, olefins, alkyl halides, ethers and alcohols as well. Reduction may be chemoselective in compounds containing many functionalities, with the functional groups most easily capable of stabilizing a carbonium ion being reduced most readily. Thus, for example, aliphatic alkenes are reduced only when they are branched at the alkene carbon atom. With α,β-unsaturated ketones, the reduction can be directed almost exclusively to the C—C double bond. Thus, using only one equivalent of silane, enones are reduced to saturated ketones (Scheme 82)[279].

With excess silane, further reduction of the saturated ketone to the corresponding saturated alcohol occurs in high yields. In case of chalcones, excess silane may affect complete reduction and deoxygenation to yield the corresponding alkane (Scheme 83)[279,280].



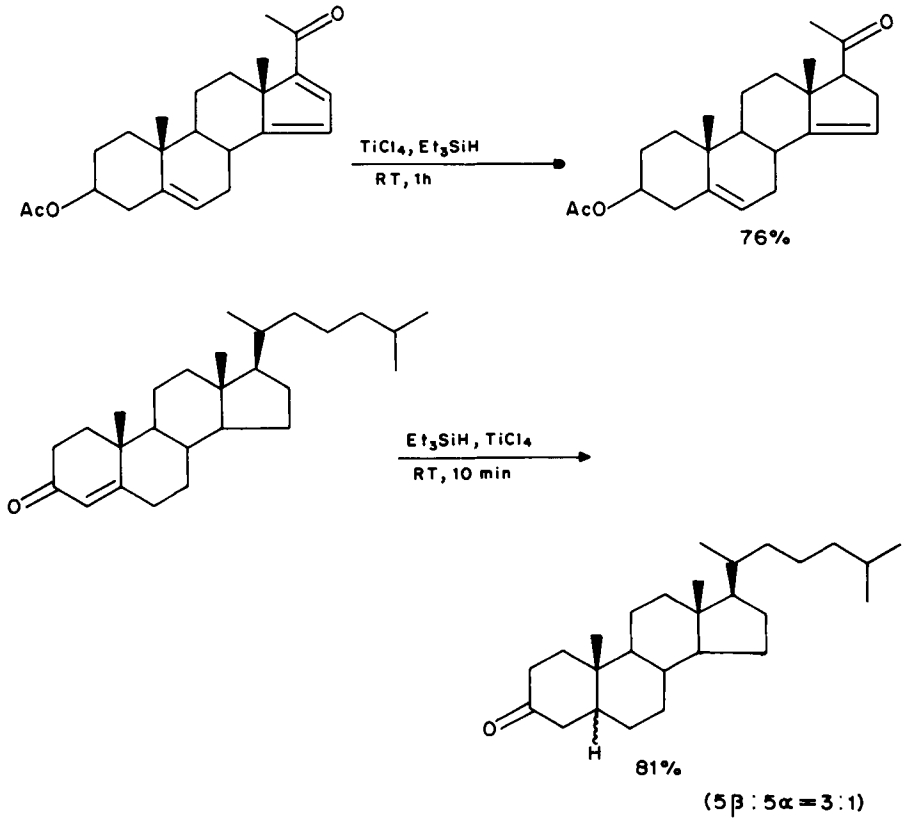
SCHEME 82



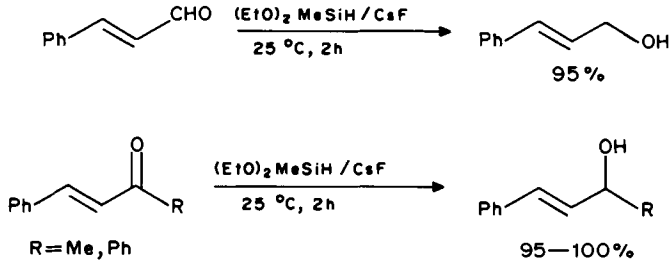
SCHEME 83

The reaction of conjugated enones and dienones with trimethyl- and triethylsilane in the presence of $TiCl_4$ followed by aqueous workup produces the corresponding saturated ketones. This Lewis acid catalysis is particularly useful for conjugated reduction of sterically hindered systems (Scheme 84)[281]. α,β-Unsaturated esters are not reduced under these conditions.

Anionic activation of Si—H bonds[282] by fluorides, such as KF or CsF, or by potassium phthalate, $KHCO_3$, KSCN, etc., yields powerful hydridic reagents that reduce the carbonyl group of aldehydes, ketones and esters[283]. It was postulated that the active species in these reactions is a pentacoordinated or even hexacoordinated hydridosilane. 1,2-Reductions of α,β-unsaturated aldehydes and ketones occur with very high selectivity to give allylic alcohols (Scheme 85)[283]. The analogous activation of hydridosilanes by fluoride ions is also achieved under acidic conditions with boron trifluoride etherate, in which the latter compound is consumed and fluorosilanes are formed[284].



SCHEME 84



SCHEME 85

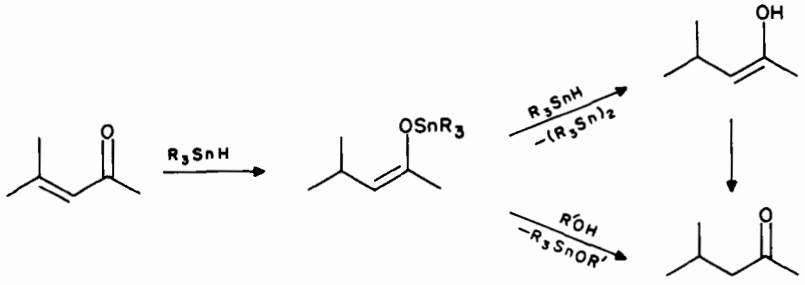
Effective anionic activation of trichlorosilane can be carried out with either catechol or 2, 2′-dihydroxybiphenyl in THF yielding bis(diolato)hydridosilicates (Scheme 86)[285]. Such reagents exhibit reducing power that is reminiscent of the complex aluminum hydrides. Even tertiary amines are useful activators of trichlorosilane, enhancing its hydridic character[286].

SCHEME 86

D. Tin Hydrides

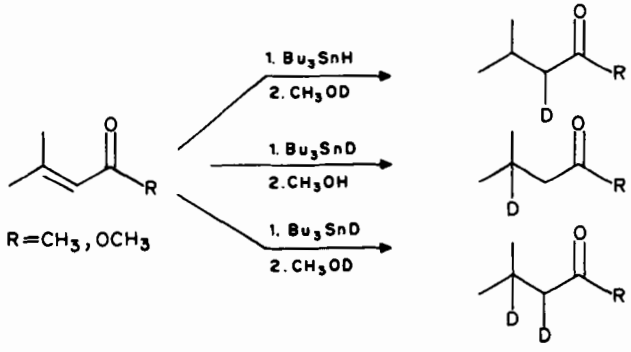
The special characteristics of organotin hydrides as reducing agents are rationalized by the fact that the tin–hydrogen bond is both weaker and less polar than the B—H or Al—H bonds[287]. These characteristics are manifested in reactions that proceed by either a free radical chain or polar mechanism, depending on the substrate, catalyst and reaction conditions.

α,β-Unsaturated aldehydes and ketones are readily reduced by organotin hydrides under rather mild conditions, but the reaction is often obscured by subsequent transformation of the adducts[288]. On heating or under UV irradiation, the organotin monohydrides add mainly at the 1,4-positions of the enone system to form the enol stannane. The latter may be hydrolyzed or cleaved by a second equivalent of tin hydride, resulting in overall reduction of the double bond (Scheme 87)[287,288].



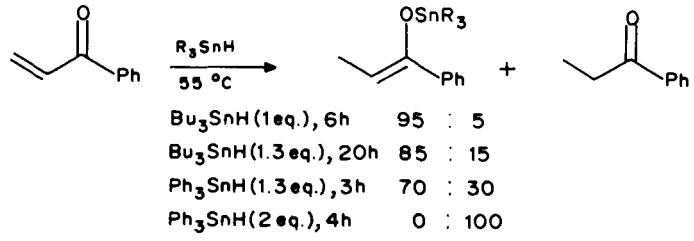
SCHEME 87

The protonolysis pathway was demonstrated in reactions carried out in deuteriated methanol (Scheme 88)[289].



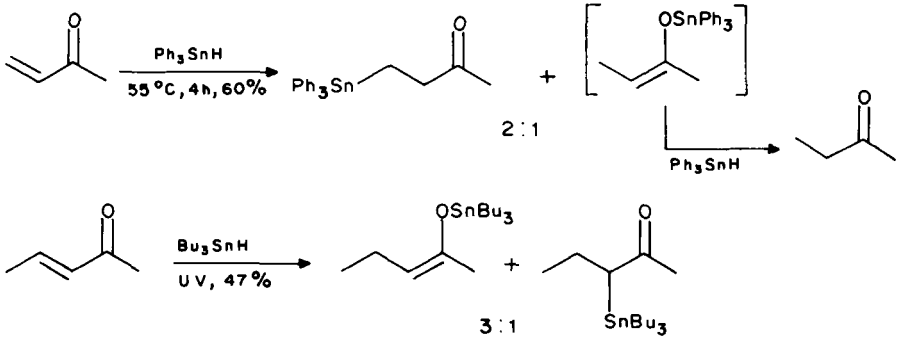
SCHEME 88

Enolate cleavage by a second equivalent of tin hydride is illustrated in Scheme 89[288l]. With Bu_3SnH the reaction proceeds no further, whereas the more electrophilic Ph_3SnH leads to hydrostannolysis of the tin enolate.



SCHEME 89

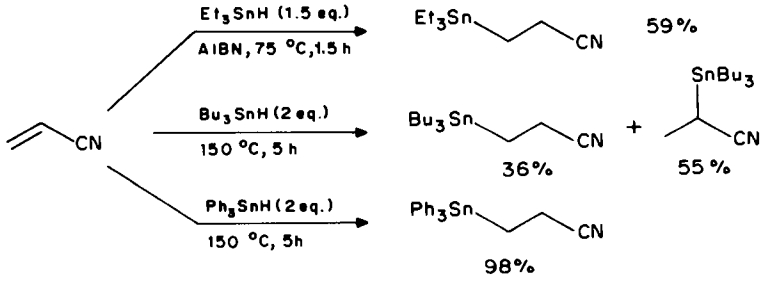
Sterically nonhindered enones may produce mixtures of products, including carbon-stannylated species. For example, methyl vinyl ketone gives rise to significant quantities of the inverted 1,4-adduct, where tin binds at the 4-position, leading to β-stannyl ketone. In the case of methyl propenyl ketone, addition occurs at position 3 and 4, producing α-stannyl ketone (Scheme 90)[288j].



SCHEME 90

In this class of reagents, diphenylstannane exhibited the highest regioselectivity, affording essentially pure 1,4-reduction. Other hydrides, such as Bu_3SnH or Ph_3SnH, give mixtures of 1,2- and 1,4-reduction products and they usually require free radical initiation[290].

In the case of α,β-unsaturated esters and nitriles, hydrostannation may proceed via either a polar or radical mechanism. Compounds containing a terminal multiple bond form the α-stannyl derivative according to a polar mechanism, while β-adducts are formed according to the radical pathway[291]. Other conditions being equal, triarylstannanes are more active than trialkylstannanes in radical processes. In general, α,β-unsaturated nitriles undergo the polar addition more actively than do the corresponding esters. However, with acrylonitrile, the homolytic mechanism is significant as well[292]. With trialkylstannanes under the action of azobis(isobutyronitrile) or UV irradiation or with triphenylstannane on heating, β-adducts are formed exclusively. Mixtures of α- and β-adducts are produced on thermal addition of trialkylstannanes (Scheme 91)[292]. Expectedly, the α/β ratio increases with solvent polarity.



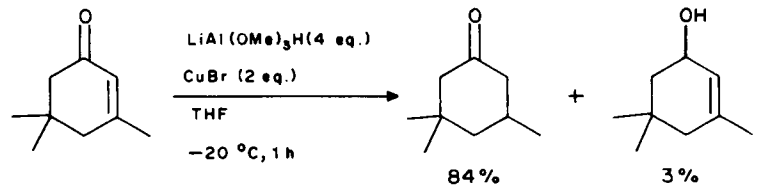
SCHEME 91

Hydrostannation of α-acetylenic esters generally produces a mixture of products. For more details, see Reference 287.

V. REDUCTIONS WITH STOICHIOMETRIC AMOUNTS OF TRANSITION-METAL HYDRIDES

A. Copper Hydrides

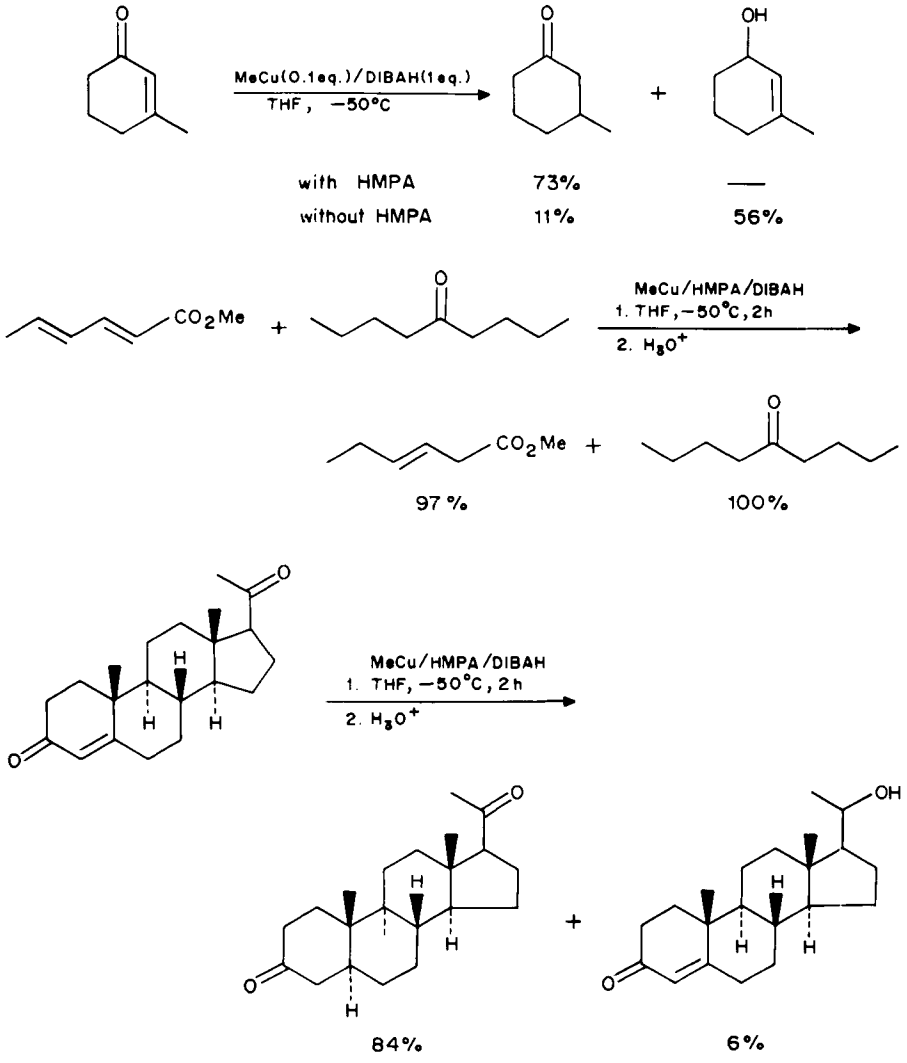
The known preference of organo-copper reagents to engage in 1,4-addition to α,β-unsaturated carbonyl compounds[293] prompted an extensive search for analogous hydrido-copper reagents that would undergo conjugate addition to enones. Indeed, reaction of cuprous bromide with either two equivalents of lithium trimethoxyaluminum hydride or one equivalent of sodium bis(2-methoxyethoxy)aluminum dihydride ('Vitride' by Eastman or 'Red-Al' by Aldrich) in THF produces a heterogeneous mixture capable of 1,4-reduction of α,β-unsaturated ketones and esters[294]. The exact composition of these reagents is not yet known. Reductions usually take place between −20 and −78 °C to give moderate yields of the saturated carbonyl compound along with varying amounts of the 1,2-reduction product (Scheme 92). The use of lithium trimethoxyaluminium deuteride with CuBr produces the saturated ketone deuteriated at the β-position. Addition of D_2O before the aqueous workup leads to deuterium incorporation at the α-position. Because these reagents react with other functional groups (saturated ketones and aldehydes and alkyl bromides being reduced almost as rapidly as enones), their chemoselectivity is limited. The reagent has also been used for the conjugate reduction of α,β-unsaturated nitriles[295].



SCHEME 92

Combination of $LiAlH_4$ and catalytic amounts of CuI in HMPA/THF (1:4) is useful for 1,4-reduction of α,β-unsaturated ketones, aldehydes and esters[296]. Reactions carried out at −78 °C for 1 hour resulted predominantly in the 1,4-reduction product, but traces of the saturated and allylic alcohols were also formed[296]. It was claimed that the ratio

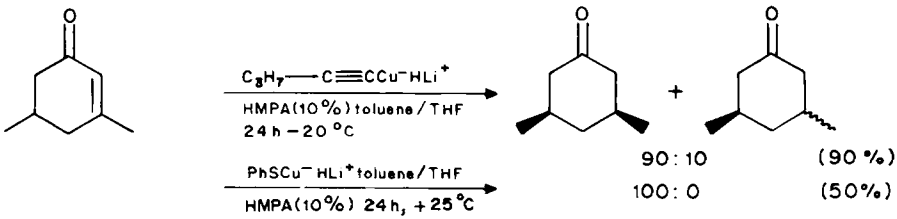
between $LiAlH_4$ and CuI (10:1) as well as the presence of HMPA generates a hydridocuprate species which acts as the actual reducing agent. In contrast, in a previously reported work using either $LiAlH_4$ or AlH_4 and CuI (in a 4:1 ratio) in THF, it was suggested that the active reductant is H_2AlI[257] (*vide supra*). An improved system based on diisobutylaluminum hydride (DIBAH) as the hydride donor and MeCu as the catalyst effects clean conjugate reduction of a variety of α,β-unsaturated carbonyl compounds without 1,2-reduction products. The presence of HMPA, probably acting as a ligand, was found to be of crucial importance for this reducing system, as shown in Scheme 93[297]. Other coordinating solvents including pyridine, DMF and DMSO did not lead to comparable regioselectivity. Chemoselectivity is demonstrated by the selective 1,6-



SCHEME 93

reduction of methyl sorbate in the presence of a saturated ketone, and the conjugate reduction of the enone of progesterone with only minor reduction of the saturated ketone in this molecule.

A series of heterocuprate complexes Li^+HRCu^-, with R representing a nontransferable ligand such as 1-pentynyl, t-BuO^- or PhS^-, was generated in toluene from DIBAH and CuI by addition of RLi. These reagents were used for clean 1,4-reduction of α,β-unsaturated ketones and esters[298]. Yields, however, were quite low in several cases due to the strong basicity of these reagents. Although HMPA was found to facilitate 1,4-reduction in substrates where the β-carbon is highly substituted, enone reduction in multifunctional compounds resulted in low yields (Scheme 94). In a related, independent study, the hydridocuprate complex was prepared by addition of RLi (R = alkyl or alkynyl) to a suspension of CuH in ether or in THF. These reagents were used for clean conjugate reduction of α,β-unsaturated carbonyls[299], however with poor chemoselectivity, as saturated aldehydes and ketones were reduced under these conditions to the corresponding alcohols, and various tosylates and bromides were reductively cleaved.



SCHEME 94

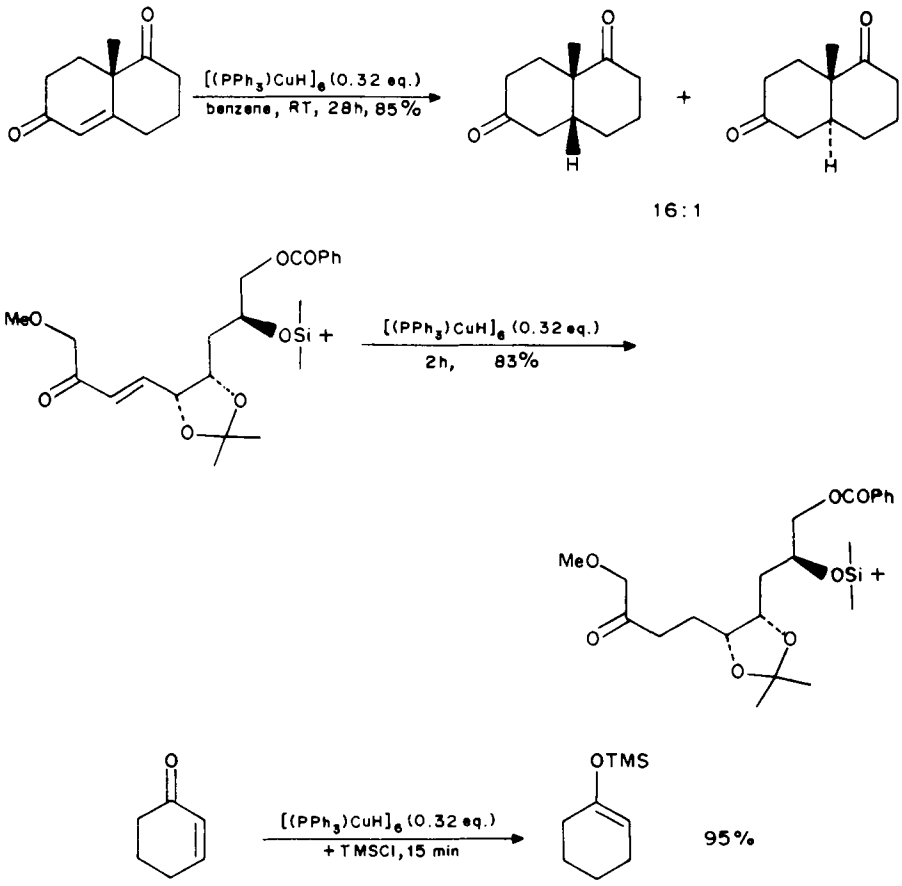
Polyhydrido-copper complexes, such as $LiCuH_2$, Li_2CuH_3, Li_3CuH_4, Li_4CuH_5 and Li_5CuH_6, were prepared[300] by $LiAlH_4$ reduction of $Li_nCu(CH_3)_{n-1}$. Reduction of α,β-unsaturated carbonyl compounds with any of these hydrides in ether or in THF produced mixtures of 1,4- and 1,2-reduction products. These reagents also reduce ketones, alkyl halides, alkyl tosylates and aryl halides.

The stable, well-characterized copper(I) hydride cluster $((PPh_3)CuH)_6$[301] is a useful reagent for conjugate reduction of α,β-unsaturated carbonyl compounds[302]. This hydride donor is chemically compatible with chlorotrimethylsilane, allowing formation of silyl enol ethers via a reductive silation process (Scheme 95).

B. Iron Hydrides

Iron hydrides were also used for selective 1,4-reduction of enones[287b]. For example, tetracarbonylhydridoferrate, $NaHFe(CO)_4$, which is prepared directly by refluxing pentacarbonyl iron with sodium methoxide in methanol, reduces benzalacetone to benzylacetone. Addition of this reagent to an ethanolic sotution containing both an aldehyde and a ketone results in reductive alkylation of the ketone. The reaction probably involves base-catalyzed aldol condensation of the aldehyde and the ketone, followed by elimination of water to give the corresponding α,β-unsaturated ketone. The latter is then reduced by the tetracarbonylhydridoferrate, to afford the saturated ketone[303]. Interestingly, $NaHFe(CO)_4$ in THF reduces α,β-unsaturated carbonyl compounds to the corresponding saturated alcohols with high stereospecificity. For example, (+)- and (−)-carvones are reduced to (−)- and (+)-neodihydrocarveol, respectively[304].

The binuclear hydride $NaHFe_2(CO)_8$[305,306], which is prepared by addition of AcOH to a slurry of $Na_2Fe_2(CO)_8$ in THF, is also useful for clean conjugate reductions. This reagent



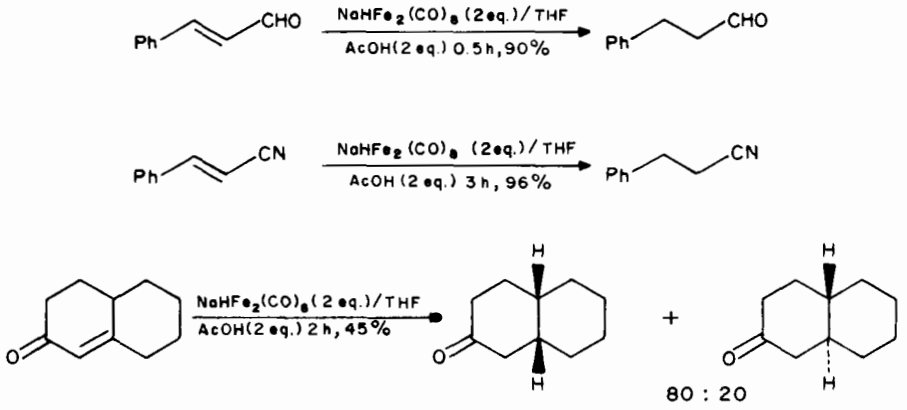
SCHEME 95

is capable of selective 1,4-reduction of α,β-unsaturated ketones, aldehydes, esters, nitriles, amides and lactones in good yields (Scheme 96). Reductions are generally performed at $-50\,^{\circ}C$ in a THF solution of $NaHFe_2(CO)_8$ and HOAc. Usually, two or more equivalents of the reagent are required for the reduction of 1 equivalent of substrate.

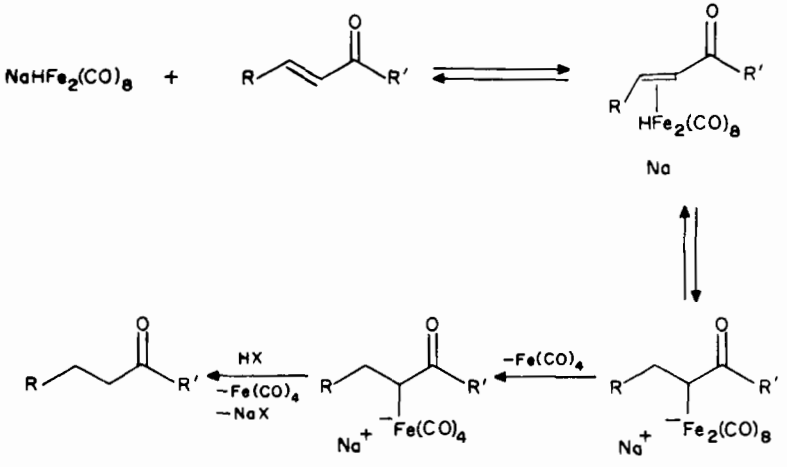
According to a detailed mechanistic study[306], the reaction involves concerted, reversible, regiospecific addition of $NaHFe_2(CO)_8$ to the C=C double bond of the enone, affording the corresponding binuclear iron enolate. Cleavage of the latter to the mononuclear iron enolate represents the rate determining step. Finally, protonolysis of this iron enolate by acetic acid provides the saturated ketone (Scheme 97).

C. Other Transition-metal Hydrides

The intermetallic hydride $LaNi_5H_6$ was found to be an effective reagent for conjugate reduction of enones. Reduction of the resulting saturated carbonyl compound occurs very slowly with this reagent, giving high yields of the 1,4-reduction product[307].



SCHEME 96



SCHEME 97

α,β-Unsaturated carbonyl compounds are reduced selectively and in good yields (55–80%) to the corresponding saturated derivatives by the hydridochromium complex $NaHCr_2(CO)_{10}$ in THF at 66 °C. This latter complex is prepared by stirring chromium-hexacarbonyl with potassium graphite (C_8K) in dry THF with subsequent addition of water[308].

Excess hydridocobaltcarbonyl reduces α,β-unsaturated ketones and aldehydes in moderate yield and good regioselectivity. The reaction involves complexation of the double bond to cobalt, followed by migratory insertion of hydride into the enone, forming an oxa-allyl cobalt complex[309]. Poor chemoselectivity is one of the major drawbacks of this reaction, as simple olefins are rapidly hydroformylated to the corresponding aldehyde under the reaction conditions (25 °C, 1 atm of CO).

α,β-Unsaturated ketones and esters are selectively 1,4-reduced by $Et_4N[\mu\text{-}HMo_2(CO)_{10}]$ and HOAc in refluxing THF[310]. Benzalacetone is quantitatively reduced to benzylacetone under these conditions. However, reduction of cinnamaldehyde gives a mixture of dihydrocinnamaldehyde (3%), cinnamyl alcohol (85%) and phenylpropane (12%).

VI. COMPOSITE REDUCING SYSTEMS

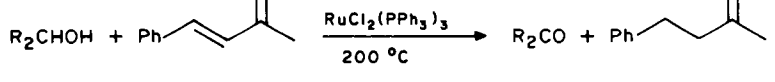
Composite reducing systems are comprised of at least two components, namely a relatively inactive source of hydride ions and a transfer agent to deliver the hydride selectively from that donor to a target functionality. This family of reducing systems will therefore selectively transfer a hydride ion to various electrophilic functional groups, including α,β-unsaturated carbonyl compounds. The acceptor properties of the latter make them excellent ligands for low-valent, electron-rich transition metals and, obviously, good substrates for selective reduction with nonreactive hydride donors.

Such multiple-component reducing systems offer high flexibility because they involve a large number of independent variables that can be tailored to various synthetic tasks, especially in comparison to metal hydride reduction which utilizes a single reagent. Thus, appropriate modification of the hydride donor, judicious selection of a transition metal transfer agent and, in some cases, use of a cocatalyst provide an opportunity for creating a wide variety of reducing systems that exhibit improved chemoselectivity, as well as regio- and stereocontrol.

A. Transfer Hydrogenation Using Alcohols as Hydrogen Donors

Catalytic transfer of hydrogen from an organic donor to a variety of unsaturated organic acceptors is widely documented[311]. This approach has also been applied to the reduction of α,β-unsaturated carbonyl compounds, utilizing a catalyst and an organic compound with a low enough oxidation potential to be oxidized under the reaction conditions by the unsaturated carbonyl substrate[311]. With respect to enone reduction, the most commonly used hydrogen donors are primary or secondary alcohols. Temperatures for catalytic transfer hydrogenation are usually in the range 100–200 °C, depending upon the hydride source.

When α,β-unsaturated ketones are heated with a primary or secondary alcohol in the presence of $RuCl_2(PPh_3)_3$ or $RuHCl(PPh_3)_3$ at 200 °C, hydrogen is transferred selectivity to the olefinic double bond (Scheme 98)[312–314]. The competing equilibrium that reduces the saturated ketone back to the alcohol may be suppressed by use of a primary alcohol such as benzyl alcohol or, more conveniently, by the use of boiling ethylene glycol, since saturated ketones are readily separated from insoluble glyoxal polymers[315]. Polyvinyl alcohol can also be used as convenient hydrogen donor[316]. α,β-Unsaturated ketones give higher yields than the corresponding aldehydes, which undergo self-condensation. α,β-Unsaturated esters undergo transesterification side-reactions with the donor alcohol.



SCHEME 98

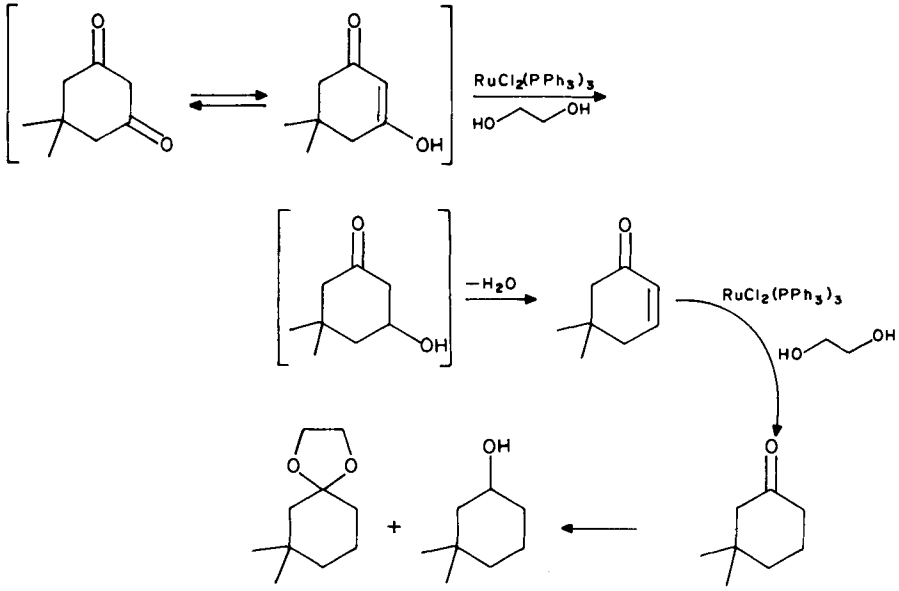
Studies on the role of a Ru(II) catalyst as well as the mechanism of hydrogen transfer in enone reduction with benzyl alcohol at 170–190 °C revealed that $RuCl_2(PPh_3)_3$ is

converted by the primary alcohol into $RuH_2(CO)(PPh_3)_3$, which then hydrogenates benzylideneacetone[317]. The kinetic data are compatible with the expression:

$$\text{reaction rate} = k_{obs}[\text{Ru}][\text{enone}][\text{alcohol}]$$

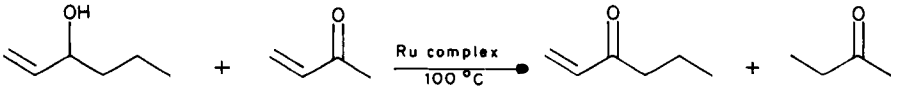
The rate-determining step of this reaction is generally assumed to be hydrogen transfer from the alcohol to a ruthenium species[317].

Transfer hydrogenation catalyzed by $RuCl_2(PPh_3)_3$ has been applied to the synthesis of cyclododecane-1,2-dione in 53% yield from the corresponding 1,2-diol using benzylideneacetone as the hydrogen acceptor[318]. 5,5-Dimethylcyclohexa-1,3-dione reacts via its enol tautomer on heating with ethylene glycol in the presence of $RuCl_2(PPh_3)_3$ to give 3,3-dimethylcyclohexanol, 3,3-dimethylcyclohexanone and its corresponding ketal (Scheme 99)[319].

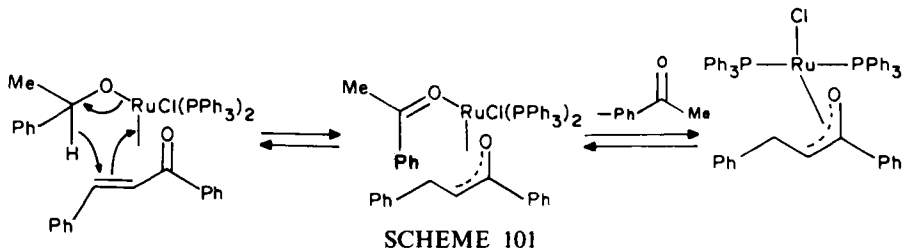


SCHEME 99

Vinyl ketones, such as methylvinyl ketone, are not reduced in the presence of $RuCl_2(PPh_3)_3$ on heating with common primary or secondary alcohols, but they are reduced on heating with allylic alcohols, such as hex-1-en-3-ol, using hydrated $RuCl_3$, $RuCl_2(PPh_3)_3$, $RuHCl(PPh_3)_3$, $RuH(OAc)(PPh_3)_3$ or, most efficiently, $Ru_3O(OAc)_7$ (Scheme 100)[320]. Surprisingly, other ketones, including acetophenone or benzylideneacetone, are not reduced under these conditions.



SCHEME 100



SCHEME 101

As in hydrogen transfer between alcohols and saturated ketones, the rate-determining step in the corresponding reaction with α,β-unsaturated ketones is hydrogen abstraction from the α-carbon atom. It has been suggested that the hydrogen atom is transferred directly to the β-carbon of the enone, yielding an η^3-oxaallyl complex which, following protonation, yields the saturated ketone (Scheme 101)[312].

Unsaturated esters also undergo trasnfer hydrogenation under $RuCl_2(PPh_3)_3$ catalysis to the saturated esters, but significant transesterification reaction with the reacting alcohol also occurs[313]. Simple olefins are reduced, in general, very slowly under the reaction conditions, although $RuCl_2(PPh_3)_3$ is reported to catalyze hydrogen transfer from indoline to cycloheptene in refluxing toluene, to give cycloheptane and indole[321], and other Ru(II) complexes catalyze hydrogen transfer from alcohols to diphenylacetylene to yield *cis*-stilbene[322].

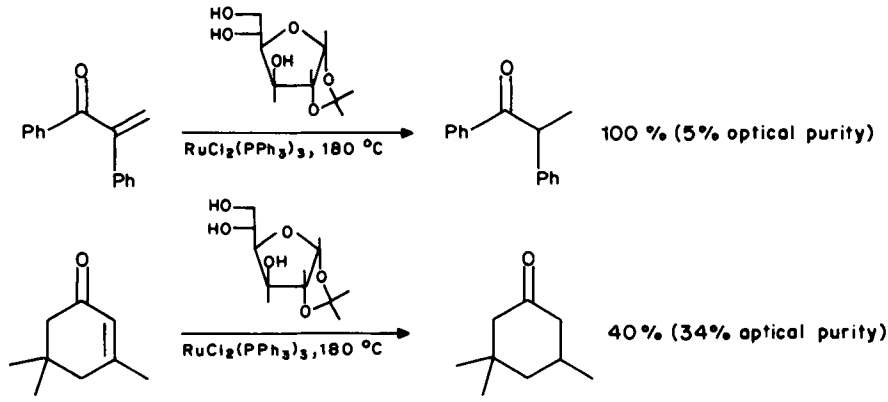
Transfer hydrogenation of a prochiral olefin in the presence of a chiral catalyst may lead to a chiral saturated product. For example, tiglic acid ($MeCH{=}C(Me)CO_2H$) is hydrogenated at 120 °C by either isopropanol in the presence of $Ru_4H_4(CO)_8((-)\text{-diop})_2$[323] (diop = 2, 3-*O*-isopropylidene-2, 3-dihydroxy-1, 4-bis(diphenylphosphino)-butane) or by benzyl alcohol in the presence of $Ru_2Cl_4(diop)_3$ at 190 °C[324]. The optical purities reported for the resulting saturated acids, however, do not exceed 10–15%, a lower figure than that obtained by catalytic hydrogenation with hydrogen gas.

Prochiral α,β-unsaturated esters can also be asymmetrically hydrogenated by benzyl alcohol or 1-phenylethanol and catalytic $Ru_2Cl_4(diop)_3$[324], but the optical purities of the resulting esters are even lower than those obtained from hydrogenating the corresponding acids. Enantioselectivity is also observed in transfer hydrogenation of α,β-unsaturated ketones, such as $PhCH{=}CHCOMe$, by racemic 1-phenylethanol in the presence of Ru(II) chloro complexes containing optically active tertiary phosphines, including diop and neomenthyldiphenylphosphine. Thus the optical purity of 1-phenylpropan-1-ol enriched in the *S*-(−)-isomer is 11% when reacted under these conditions with benzylideneacetone[325].

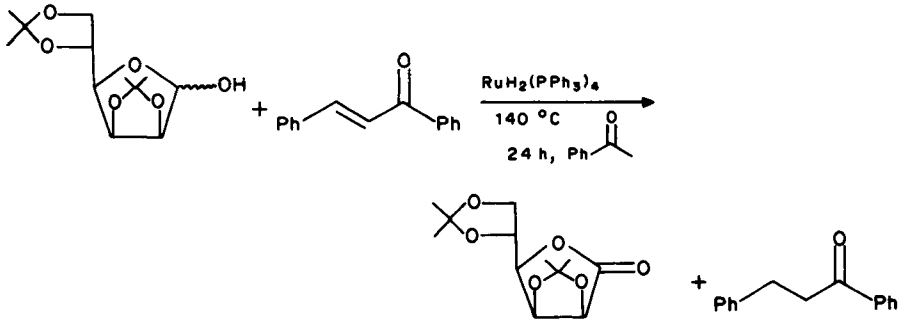
Asymmetric hydrogen transfer from optically active monosaccharides, such as 1, 2-α-D-glucofuranose, to prochiral enones is catalyzed by $RuCl_2(PPh_3)_3$ in diphenyl ether at 180 °C or by $RuH_2(PPh_3)_4$ in toluene at 100 °C (Scheme 102)[326].

Catalytic hydrogen transfer from sugars with free anomeric hydroxyl groups was studied with 2, 3; 5, 6-di-*O*-isopropylidene-D-mannofuranose and $RuH_2(PPh_3)_4$. In an excess of enone acceptor, these sugars were converted in high yields into the corresponding lactones (Scheme 103)[327].

The 1, 4-reduction of styryl ketones by 1-phenylethanol using $RhH(PPh_3)_4$ catalyst can be carried out at 50 °C, a relatively low temperature for transfer hydrogenation. An electron-withdrawing group present in the enone system increases the initial rate of reduction, suggesting a transfer of hydrogen to the enone by an intermediate with hydride-ion character[328]. Isotope labeling of the alcohol donors shows that hydrogen is regioselectively transferred from the carbinol carbon to the β-carbon of the enone, with the

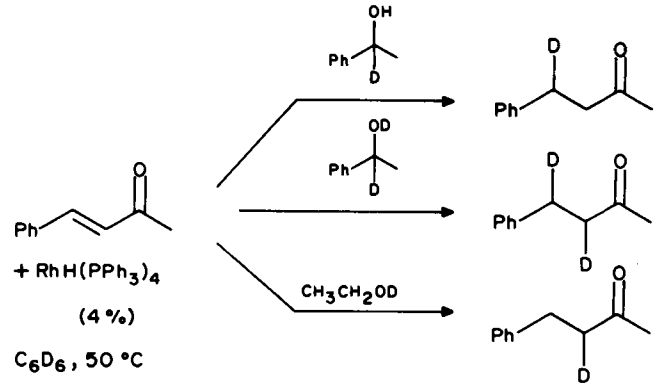


SCHEME 102



SCHEME 103

hydroxylic proton being transferred to the α-position (Scheme 104). Cleavage of an O—H bond is the rate-determining step in this reaction[329].



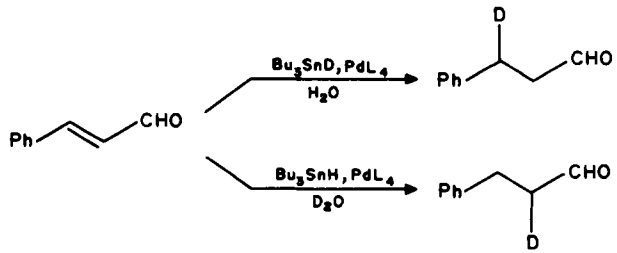
SCHEME 104

High catalytic activities, with turnovers of up to 900 cycles/min, is displayed in the transfer hydrogenation of α,β-unsaturated ketones, such as benzylideneacetone and chalcone, using isopropanol and catalytic amounts of [Ir(3,4,7,8-Me_4-phen)COD]Cl (phen = 1,10-phenanthroline; COD = 1,5-cyclooctadiene) in a weakly alkaline medium[330]. Other Ir-chelated complexes are also active catalysts in this reaction, with over 95% selectivity for the 1,4-reduction mode.

B. Transition Metal-catalyzed Reductions with Group-14 Metal Hydrides

Group-14 metal hydrides, especially those of silicon and tin, are satisfactory nonreactive hydride donors, as in the absence of a catalyst they are, generally, poor reducing agents. Transition-metal complexes are attractive transfer agents because they insert readily into Si—H or Sn—H bonds and they also bind specifically to various functional groups.

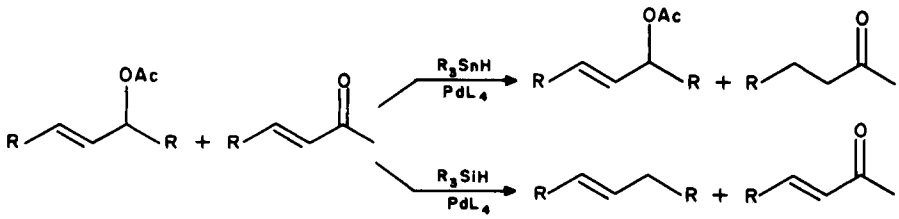
Indeed, a combination of tributyltin hydride, Pd(0) catalyst and a weak acid, such as ammonium chloride, forms an effective, yet mild tool for conjugate reduction of α,β-unsaturated aldehydes and ketones[331]. Similar results are obtained with other acidic cocatalysts, such as zinc chloride, acetic acid and tributyltin triflate[332]. With this system, reductions occur with high regioselectivity, providing a useful approach for deuterium incorporation into either the β- or α-position by using either tributyltin deuteride or D_2O, respectively (Scheme 105)[331].



SCHEME 105

The above-described reducing system comprising tributyltin hydride and a soluble palladium(0) catalyst also allows chemoselective reductive cleavage of allylic heterosubstituents, even in the presence of aldehydes, benzylic acetate and benzylic chloride groups. These latter functions are normally as reactive as the allylic structure when using standard hydride reducing agents[333].

Silicon hydrides offer even greater selectivity in these reductions[334]. Their superiority over tin hydrides is manifested by the greater stability of the palladium catalyst in the reaction solution, and the absence of diene side-products, frequently formed via the competing Pd-catalyzed elimination processes. Moreover, the difference in reactivities between tin and silicon hydrides can be exploited for functional-group differentiation. In the presence of Pd(0), tributyltin hydride, for example, reduces rapidly α,β-unsaturated ketones and aldehydes but silicon hydrides are unable to do so. Thus, the treatment of a mixture of an allylic acetate and an unsaturated ketone with tin hydride and Pd(0) catalyst results in total conjugate reduction of the latter and nonreacted allylic acetate (Scheme 106)[334]. In contrast, employment of silicon hydride provided complementary chemoselectivity: allylic reduction was completed before reduction of the Michael acceptor could be detected.



SCHEME 106

When using either tin or silicon hydrides, allylic substitution occurs with absolute inversion of configuration at the carbon, implying that hydride is initially transferred to palladium and from there to the allylic ligand via migratory insertion[333,334c]. This behavior is reminiscent of the proposed mechanism of the palladium-catalyzed conjugate reduction of enones (*vide infra*).

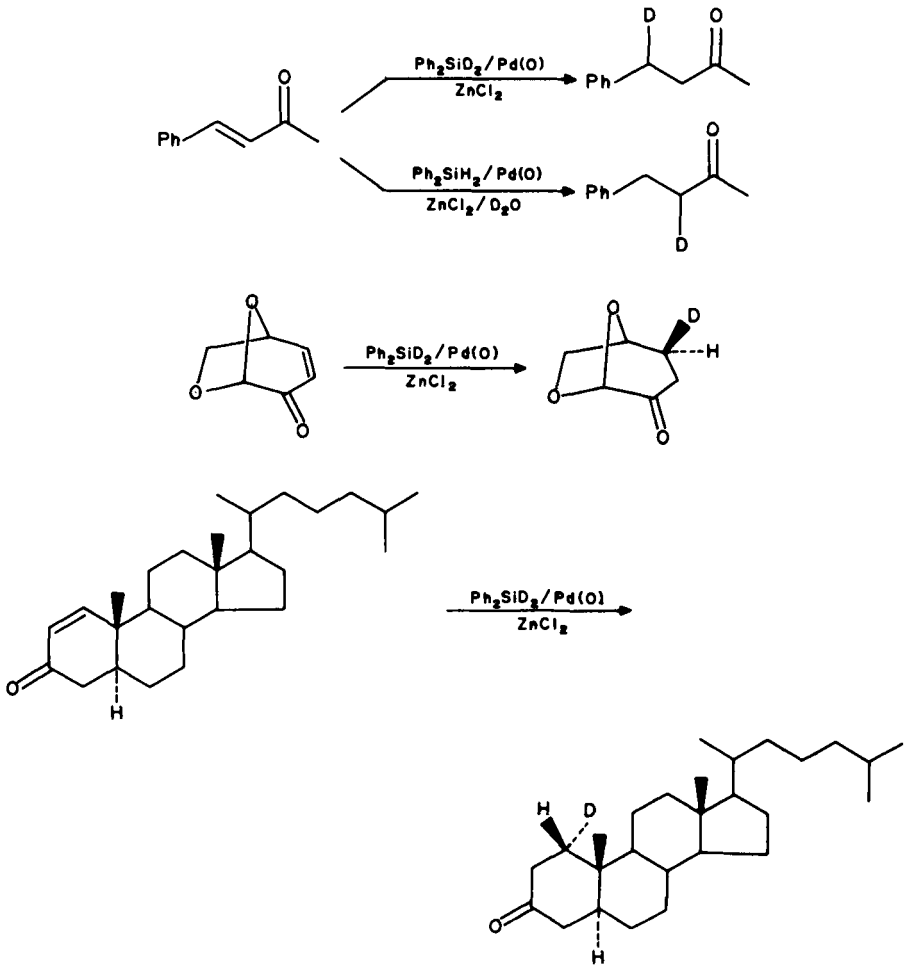
The useful flexibility characteristic of these multicomponent reducing systems is well illustrated by the silicon hydride/Pd(0) mixture. As mentioned above, this combination is essentially useless for reduction of electron-deficient olefins. However, addition of catalytic amounts of zinc chloride fundamentally alters the situation and creates a new three-component mixture that enables rapid conjugate reduction of α,β-unsaturated ketones and aldehydes[335]. In fact, soluble palladium complexes of various oxidation states were equally efficient catalysts, an obvious practical advantage of this approach. The generality of the method with respect to the substrate, its experimental simplicity and its easy applicability to large-scale work make it a method of choice for conjugate reduction of unsaturated ketones and aldehydes.

The reaction was found to be both regio- and stereoselective. In all cases where diphenyldideuteriosilane was used to reduce unsaturated ketones, deuterium was stereoselectively introduced at the less-hindered face of the substrate and regioselectively at the β-position (Scheme 107). Conversely, when reductions were carried out in the presence of traces of D_2O, deuterium incorporation occurred at the α-position[335].

Interestingly, this method is highly selective for unsaturated ketones and aldehydes, as reduction of corresponding α,β-unsaturated carboxylic acid derivatives, such as esters, amides and nitriles, is very sluggish under the conditions used. Thus, benzylideneacetone was selectively and cleanly reduced in the presence of methyl cinnamate, cinnamonitrile or cinnamamide[335].

Based on deuterium-incorporation experiments and ^1H NMR studies, a multistep catalytic cycle was postulated (Scheme 108) in which the first step is rapid, reversible coordination of the Pd(0)-phosphine complex to the electron-deficient olefin, resulting in complex I. Oxidative addition of silicon hydride to palladium in that complex forms hydrido-palladium olefin complex II. Migratory insertion of hydride into the electrophilic β-carbon of the coordinated olefin produces intermediate palladium enolate III which, via reductive elimination of the silicon moiety and enolate ligand, completes the catalytic hydrosilation cycle, resulting in silyl enol ether IV. The latter is prone to acid-catalyzed hydrolysis, yielding the saturated ketone[335].

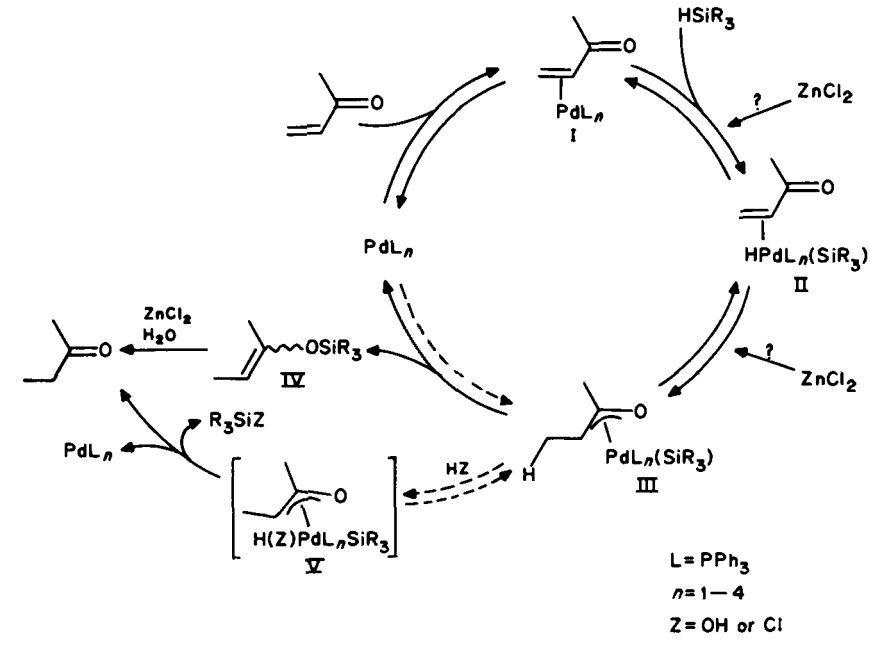
The role of the Lewis acid cocatalyst is not yet fully understood. One may envision a number of points at which intervention of a Lewis acid could promote the reaction. It seems that in addition to its obvious role in catalyzing hydrolysis of the silyl enol ether, $ZnCl_2$ polarizes the substrate, thereby facilitating migratory insertion of hydride into the olefin (II to III in Scheme 108).



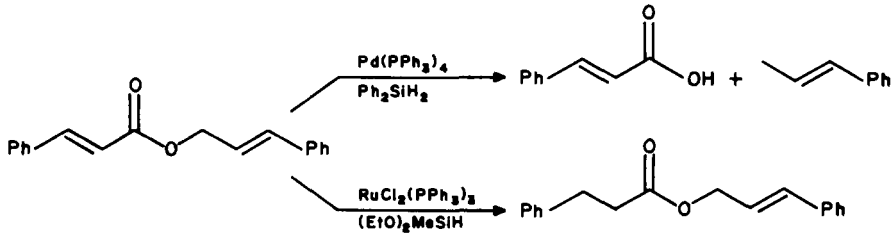
SCHEME 107

Combination of silicon hydrides with catalytic amounts of a ruthenium(II) complex in tetrahydrofuran, chloroform or benzene has afforded a new reducing system capable of efficient reduction of α,β-unsaturated carboxylic acids, esters, amides, etc[336]. Addition of a weak proton source, such as a sterically-hindered phenol, significantly increases reaction rates. The ruthenium mixture was found to exhibit the same regioselectivity observed with the above-described palladium systems.

The order of reactivity of this Ru/silane combination to various functional groups differs greatly from that of its Pd/silane/$ZnCl_2$ analog. While the latter is very useful for allylic reductions and essentially useless for unsaturated esters, the Ru-based system exhibits exactly opposite reactivity. A convincing demonstration of this complementary chemoselectivity is illustrated by the reduction of cinnamyl cinnamate (Scheme 109), a substrate containing both an allylic carboxylic and an α,β-unsaturated ester[336]. Each of



SCHEME 108



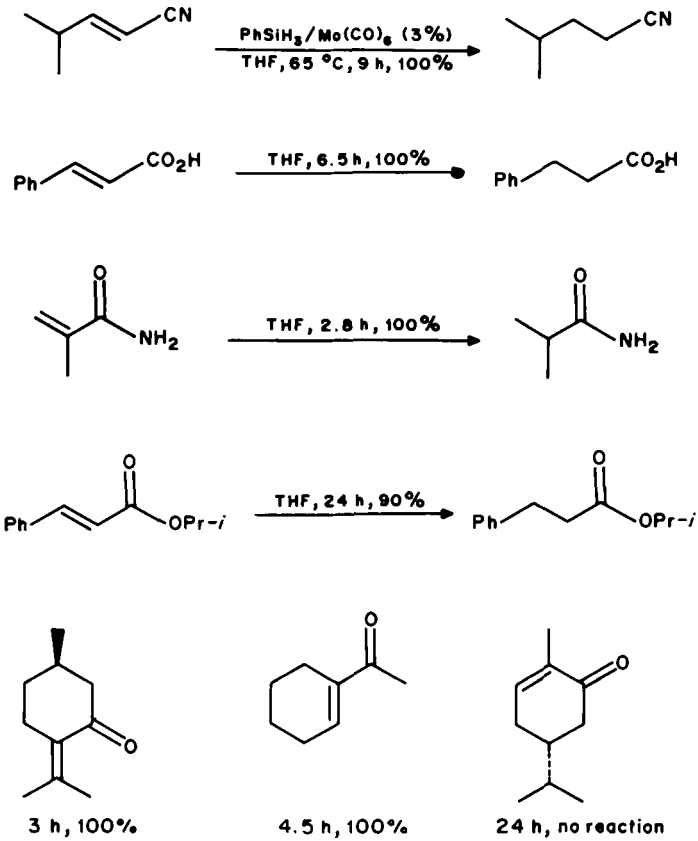
SCHEME 109

these can be reduced separately by silicon hydride and the appropriate transition-metal catalyst.

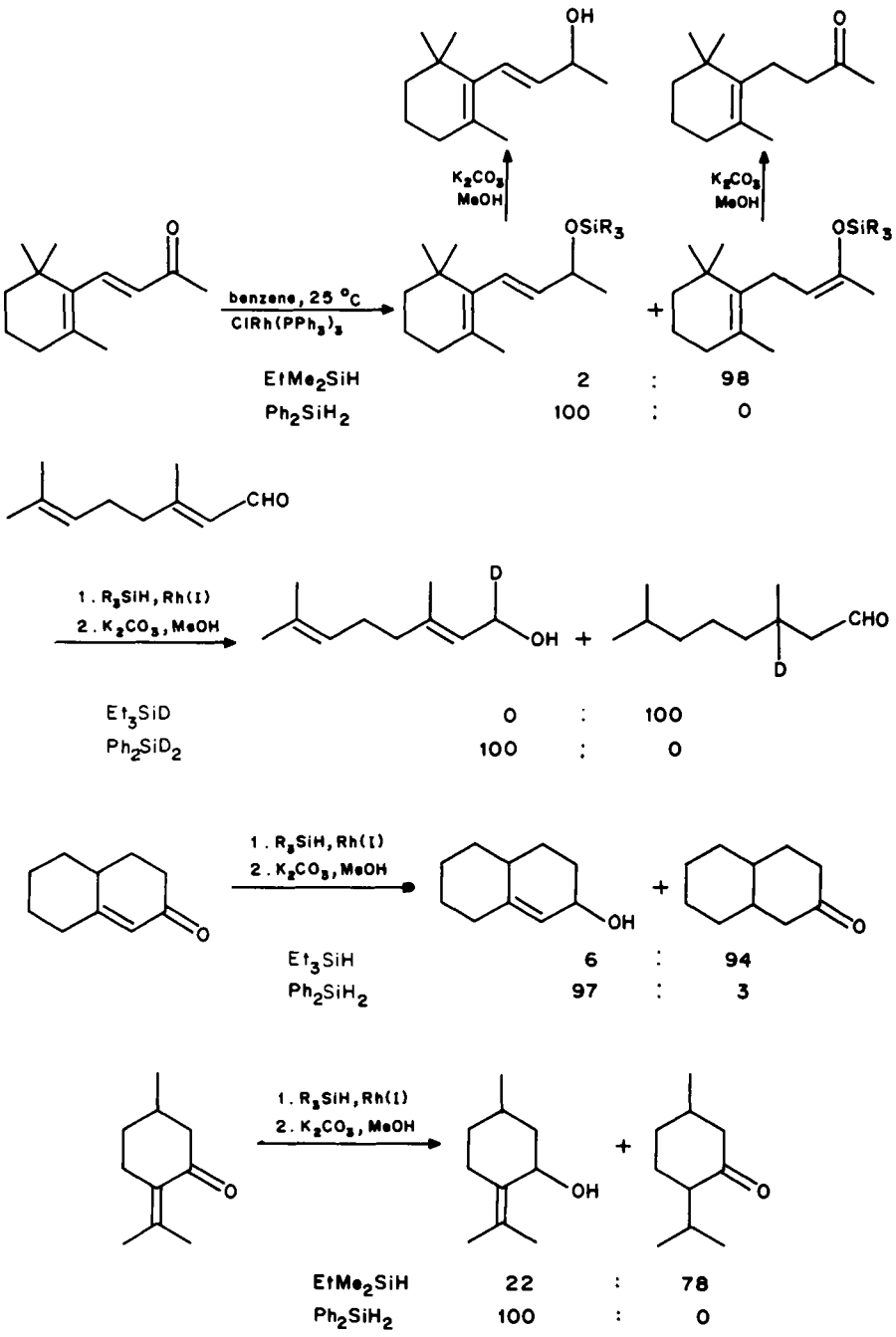
Early transition-metal complexes, including those of group 6, have been rarely used to catalyze transfer hydrogenation[337] and hydrogenation with hydrogen gas[338] and, in particular, little is known about hydrosilation with these catalysts. Under mild thermal conditions, catalytic amounts of $Mo(CO)_6$ and phenylsilane engender a powerful reducing system, suitable for conjugate reduction of α,β-unsaturated ketones, carboxylic acids, esters, amides, etc. The mixture is especially useful for conjugate reduction of unsaturated nitriles, usually difficult to reduce with other media (Scheme 110)[339]. Although the reaction also works with mono- and dihydridosilanes, the general order of silane reactivity

is: $PhSiH_3 > Ph_2SiH_2 > Me(EtO)_2SiH >$ PMHS, $PhMe_2SiH$, Et_3SiH.

Of special interest are the relative rates of reduction of various cyclic enones, such as carvone, acetylcyclohexene and pulegone (Scheme 110). While the enone system in carvone is frozen in its transoid form, in acetylcyclohexenone it is flexible and may adopt either transoid or cisoid conformation. Acetylcyclohexenone is completely reduced while essentially no reaction observed with carvone, demonstrating the clear preference of the cisoid form and indicating that the molybdenum atom interacts simultaneously with both the olefinic bond and the carbonyl of the enone system. Accordingly pulegone, which is frozen in the cisoid form, is reduced much faster than the other two compounds. A similar phenomenon was observed in enone hydrogenation catalyzed by arene-chromium tricarbonyl complex, where the cisoid conformation is also markedly preferred[338c]. With Pd(0) catalyst, however, enones behave as monodentate ligands and reductions of the above-mentioned substrates proceed at comparable rates[335]. These reactivity characteristics may be utilized for chemoselective differentiation between similar enones. For example, benzylideneacetone is quantitatively reduced to benzylacetone in the presence of carvone[339]. Allylic heterosubstituents and α-halo carbonyl compounds are also reduced very efficiently under these conditions[340].



SCHEME 110

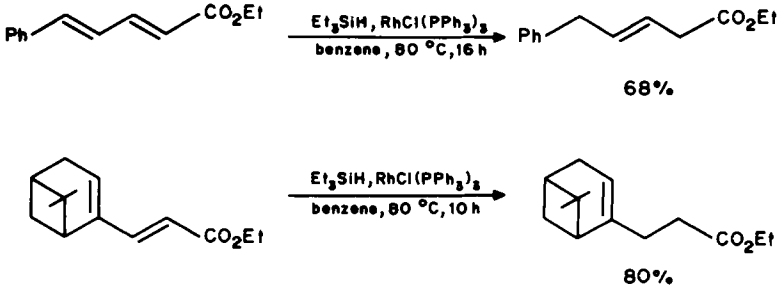

OH
O
K2CO3
MeOH
K2CO3
MeOH
OSiR3
OSiR3
benzene, 25 °C
ClRh(PPh3)3
EtMe2SiH 2 : 98
Ph2SiH2 100 : 0
CHO
1. R3SiH, Rh(I)
2. K2CO3, MeOH
D
OH
CHO
D
Et3SiD 0 : 100
Ph2SiD2 100 : 0
1. R3SiH, Rh(I)
2. K2CO3, MeOH
OH
O
Et3SiH 6 : 94
Ph2SiH2 97 : 3
1. R3SiH, Rh(I)
2. K2CO3, MeOH
OH
O
EtMe2SiH 22 : 78
Ph2SiH2 100 : 0

SCHEME 111

Highly regioselective reduction of α,β-unsaturated ketones and aldehydes to give either the corresponding saturated carbonyls or allylic alcohols as the predominant product is effected by hydrosilation catalyzed by tris(triphenylphosphine)chlororhodium (Wilkinson catalyst), followed by methanolysis of the resulting adducts[341]. Regiospecific deuteriation is also achieved by using deuteriosilanes. Product distribution is mainly dependent upon the structure of the hydrosilane employed. In general, monohydridosilanes afford the 1,4-adduct (silyl enol ether), which may be hydrolyzed to the corresponding saturated carbonyl compound. Diaryl or dialkyl dihydridosilane produce mainly silyl ether (1,2-adduct), which may be hydrolyzed to the corresponding allylic alcohol.

Other factors controlling the regioselectivity of this method include the enone structure, the hydridosilane/substrate ratio, the solvent and temperature. Although regioselectivity here is generally satisfactory (Scheme 111)[341], in some cases mixtures of 1,2- and 1,4-reduction products are obtained, even under maximally optimized conditions. The reaction is usually complete within 30–120 minutes at 0–80 °C in benzene, or in the absence of solvent, using 1.1 equivalents of the hydridosilane and 0.1 mol% of the Rh(I) catalyst.

Treatment of α,β-unsaturated esters with triethylsilane in benzene in the presence of catalytic amounts of $RhCl(PPh_3)_3$ at room temperature yields the corresponding saturated esters. Conjugated diene esters are reduced to the β,γ- or γ,δ-unsaturated esters, depending upon their substitution pattern (Scheme 112)[342].

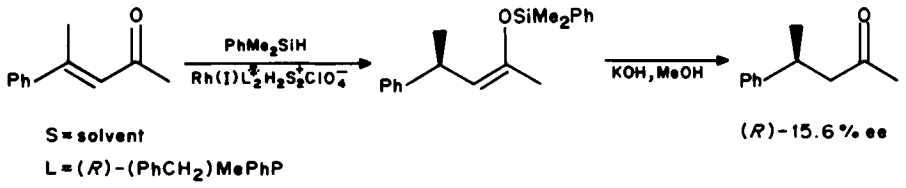


SCHEME 112

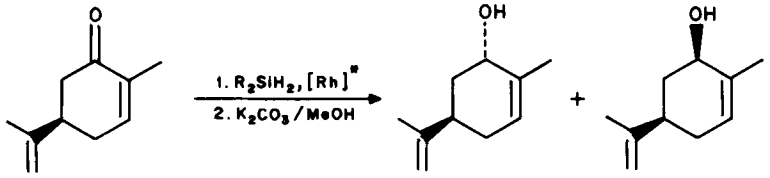
Other Rh catalysts were also employed for hydrosilation of α,β-unsaturated carbonyl compounds and unsaturated nitriles. $Rh(acac)_2$ and a tetrakis(μ-acetato)dirhodium cluster were used as catalysts in the hydrosilation[343] of α,β-unsaturated aldehydes. These reactions, however, are not chemoselective, as acetylenes, conjugated dienes and alkenes are also hydrosilylated, and allylic heterosubstituents are reductively cleaved under reaction conditions.

Optically active, saturated compounds and allylic alcohols were prepared via 1,4- and 1,2-asymmetric hydrosilation of enones using Rh(I) catalysts bearing chiral ligands. For example, 1,4-hydrosilation of α,β-unsaturated ketones afforded the corresponding optically active ketones in 1.4–15.6% enantiomeric excess (Scheme 113)[344]. These reactions were achieved at room temperature with dimethylphenylsilane and either (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane ((−)-diop)[344] or $[Rh\{(R)\text{-}(PhCH_2)MePhP\}_2H_2(solvent)_2]^+ClO_4^-$.

Asymmetric 1,2-hydrosilation in benzene of α,β-unsaturated ketones with dihydridosilanes and a chiral Rh(I) catalyst produced allylic alcohols with up to 69% enantiomeric excess. Thus, varying proportions of carveol isomers were obtained from carvone (Scheme 114)[345].



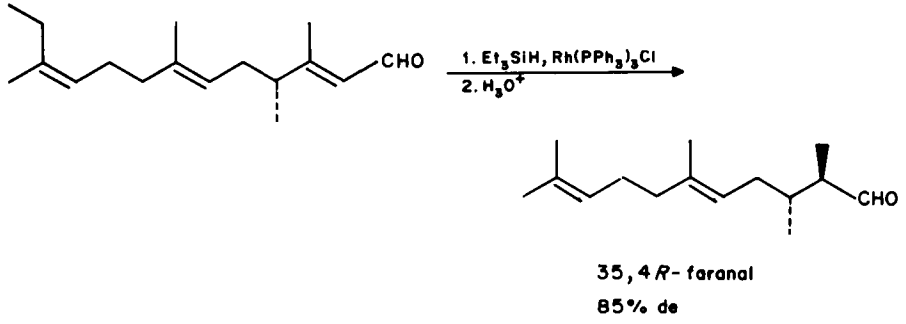
SCHEME 113



Et_2SiH_2/(−)DIOP−Rh(I)	15.5	84.5
α-Naph $PhSiH_2$/(+)DIOP−Rh(I)	78.7	21.3

SCHEME 114

Highly stereoselective 1,2-hydrosilation of an α,β-unsaturated aldehyde was achieved with triethylsilane and nonchiral Wilkinson catalyst[346]. Dehydrofaranal was thus stereoselectivity reduced to the insect pheromone (3*S*,4*R*)-faranal with 85% diastereomeric excess (Scheme 115).

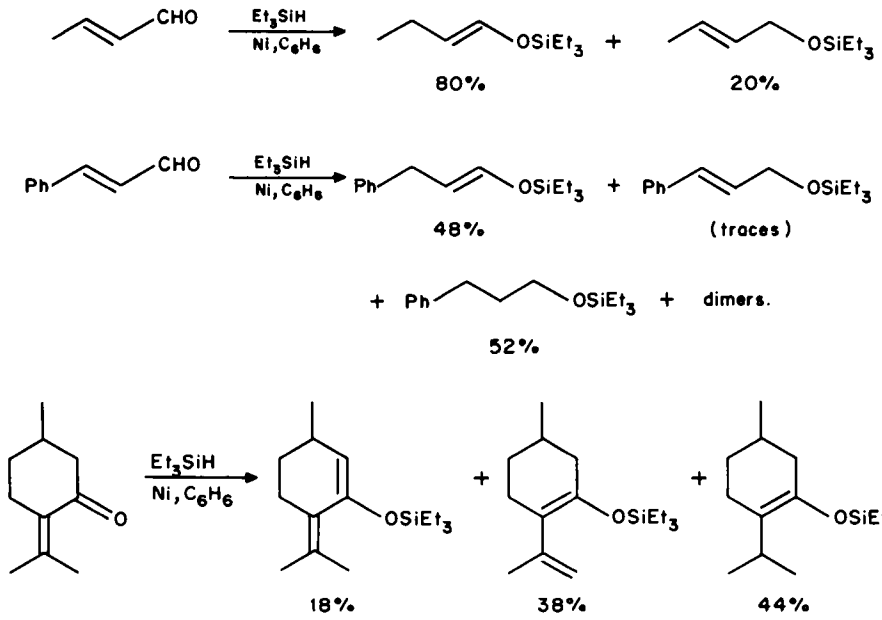


SCHEME 115

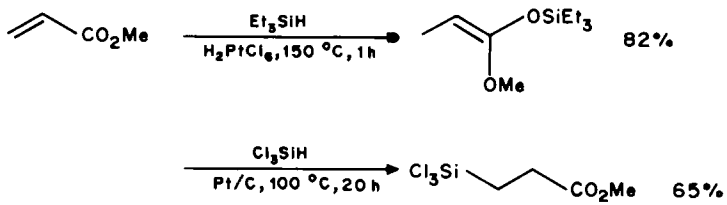
The main product in hydrosilation of α,β-unsaturated ketones and aldehydes catalyzed by chloroplatinic acid, platinum on alumina, or metallic nickel is the corresponding silyl enol ether[347]. With nickel catalyst, product distribution is highly dependent on the enone structure, as exemplified in Scheme 116[348].

Hydridosilanes add to α,β-unsaturated esters, producing the corresponding silyl enolate as well as carbon silylated products. The course of addition depends on substrate

structure and the hydridosilane utilized. Thus, triethylsilane undergoes 1,4-addition to methyl acrylate in the presence of chloroplatinic acid, while trichlorosilane with either chloroplatinic acid or Pt/C gives the β-silyl ester (Scheme 117)[349].



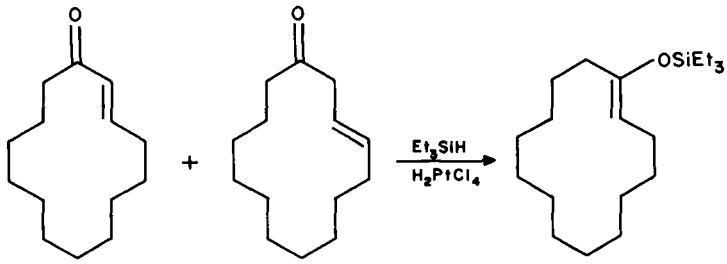
SCHEME 116



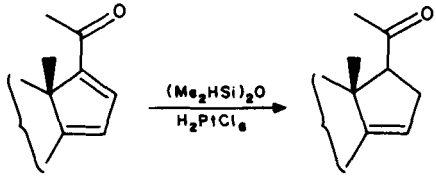
SCHEME 117

This approach was successfully applied to the total synthesis of *d,l*-muscone[350]. Treatment of the α,β- and β,γ-enone mixture (Scheme 118) with triethylsilane in refluxing glyme containing catalytic amounts of chloroplatinic acid afforded 1-triethylsilyloxycyclotetradecene. The two isomeric enones rapidly equilibrate under these conditions.

Selective reduction of pregna-14, 16-dien-20-ones to pregn-14-en-20-ones is achieved via hydrosilation with tetramethyldisiloxane and catalytic amounts of chloroplatinic acid (Scheme 119)[351]. α,β-Unsaturated esters are also reduced to the corresponding saturated esters under these conditions[352].



SCHEME 118



75–80%

SCHEME 119

The platinum dimer $(Pt(\mu\text{-}H)(SiR_3)(PR'_3))_2$ also catalyzes the hydrosilation of α,β-unsaturated aldehydes and ketones. Several aldehydes and ketones were hydrosilated in high yield in the presence of this dimer[353] at 60–100 °C and trialkylsilanes, including $MePh_2SiH$, $EtMe_2SiH$ and Et_3SiH. Triethoxysilane, was inert under these reaction conditions. Excellent regioselectivity was generally observed except in cases of highly sterically hindered enones such as tetraphenylcyclopentadienone, where the 1,2-reduction mode was observed. Saturated aldehydes and ketones were not reduced under these reaction conditions, and unsaturated carboxylic acids and esters were only sluggishly reduced. Unfortunately, terminal olefins and acetylenes were efficiently hydrosilated. A suggested mechanism involves cleavage of the platinum dimer to a platinum hydride species, its coordination to the olefin, and subsequent transfer of the R_3Si group to the carbonyl oxygen, affording a π-allyl platinum complex. Hydride migration from Pt to the allylic ligand produces the corresponding silyl enol ether.

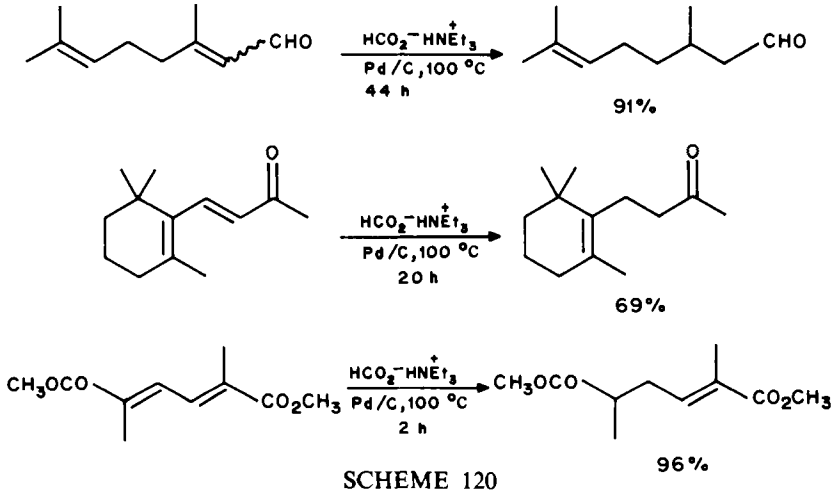
C. Transition Metal-catalyzed Reductions with Other Hydrogen Donors

Aldehydes such as α-naphthaldehyde, *p*-tolualdehyde or *p*-chlorobenzaldehyde and DMF can serve as hydrogen donors and transfer their formyl hydrogen to α,β-unsaturated ketones in the presence of $RuCl_2(PPh_3)_3$. However, in some cases, decarbonylation of the aldehyde is so severe that no transfer hydrogenation is observed[354].

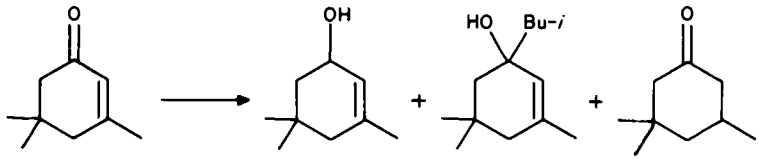
A particularly convenient hydrogen donor is formic acid, which not only hydrogenates α,β-unsaturated ketones[355], but also terminal olefins in the presence of a variety of ruthenium complexes under mild conditions[356].

Trialkylammonium formate and catalytic amounts of palladium on carbon form a convenient reducing system for reduction of a number of organic functional groups, including α,β-unsaturated aldehydes, ketones and esters[357]. Conjugated dienes are

reduced to monoenes with one equivalent of reagent fairly selectively. Typical reductions are carried out at 100 °C with 10% excess formic acid, 30% excess triethyl- or tributylamine, and 1 mol% of palladium in the form of 10% Pd/C. Progress of the reduction is conveniently monitored by measuring the amount of CO_2 evolved. Some examples are given in Scheme 120[357]. The chemoselectivity of this system is somewhat limited, as it affects many other functionalities, such as halo- and nitroaromatic compounds[358], allylic heterosubstituents[359], and terminal acetylenes and olefins[357].



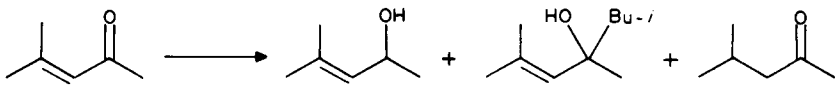
SCHEME 120



i-Bu_3Al (1eq.), 15 h	100%	—	—
1. *i*-Bu_3Al, Ni (mesal)$_2$ 2. NH_4Cl/H_2O	14%	—	85%
1. *i*-Bu_3Al, DMMA, Ni(mesal)$_2$ 2. NH_4Cl/H_2O	3%	—	93%

DMMA = dimethylmenthylamine

mesal = *N*-methylsalicylaldimine

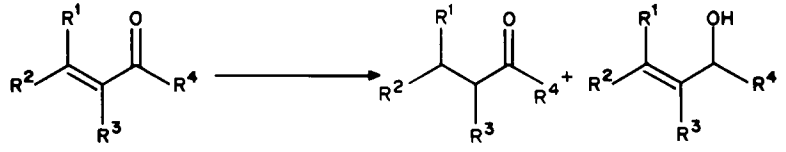


i-Bu_3Al(1eq.), 1h	64%	36%	—
(1) *i*-Bu_3Al, Ni(mesal)$_2$ (2) NH_4Cl, H_2O	20%	4%	73%

SCHEME 121

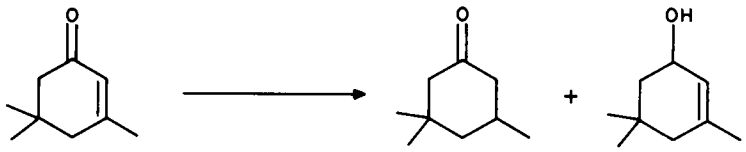
The reaction between triisobutylaluminum and α,β-unsaturated ketones, in pentane at room temperature, leads to products which correspond to a 1,2-addition processes. The extent of such reactions depends both on the structure of the enone and of the concentration ratio between reagent and substrate. Under these experimental conditions, bis(*N*-methylsalicylaldimine)nickel catalyzes conjugate reduction of α,β-unsaturated ketones by triisobutylaluminum[360]. The cyclic and acyclic saturated ketones are obtained in 40–90% yield, the lower figure corresponding to enones substituted at the α-position (Scheme 121). In all cases, 1,2-reduction products were also obtained (probably via noncatalyzed reduction) and, in some cases, side-products containing an isobutyl group were also formed. The reaction is interpreted in terms of a catalytic cycle involving a hydridonickel intermediate formed by reaction of *i*-Bu_3Al with the nickel complex. Addition of the hydridonickel to the olefin affords a nickel enolate that undergoes transmetallation, to aluminum enolate. The latter is finally hydrolyzed to the saturated ketone.

A number of composite reducing systems comprised of heterogeneous mixtures of transition metal salts, sodium alkoxides and sodium hydride were developed, which are



(1) NiCRA–$MgBr_2$ THF, −20 °C 50—99% —

(2) ZnCRA–$MgBr_2$, THF, 20 °C — 45—98%

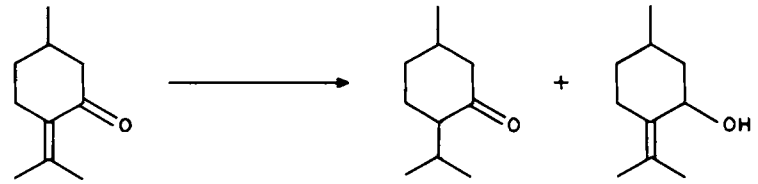


NiCRA, 4.5 h 91% —

NiCRA – $MgBr_2$, 0.5 h 93% —

ZnCRA, 1 h — 68%

ZnCRA – $MgBr_2$, 3.5 h — 90%



(1) NiCRA–$MgBr_2$, THF, 20 °C, 1.5 h 95% —

(2) ZnCRA–$MgBr_2$, THF, 20 °C, 3 h — 93%

SCHEME 122

useful for reduction of various organic functional groups[361]. In organic chemistry, sodium hydride is generally used as a base for proton abstraction. Although some substrates can be reduced by NaH, it is by itself a poor reducing agent.

Typical reducing systems (known as complex reducing agents, CRA)[361] are prepared from a transition-metal chloride or acetate, sodium *tert*-amyloxide and sodium hydride (in 1:1:4 ratio) in either THF or DME. Obviously, neither the exact structure of the actual reducing entity nor their reduction mechanism is fully understood.

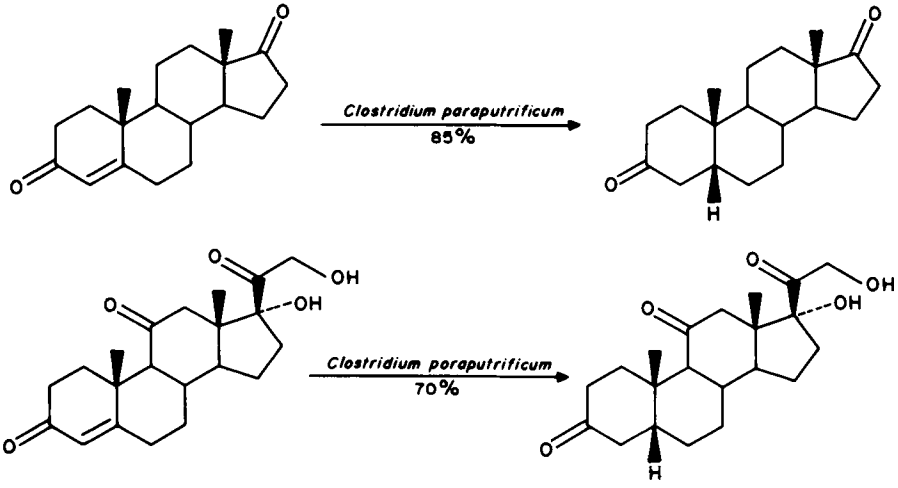
The CRA reagents involving nickel salts exhibit reducing properties that are significantly different from those of the corresponding CRA prepared from zinc or magnesium salts. It was demonstrated that the three-component mixture, $NaH/RONa/Ni(OAc)_2$ (NiCRA), reduces carbon–carbon double bonds[362]. Conversely, the mixture $NaH/RONa/ZnCl_2$ (ZnCRA) reduces olefins poorly but effectively reduces saturated carbonyl functionalities, particularly when mixed with alkaline- or alkaline earth-metal salts[363]. These observations led to the expected complementary regioselectivity when reducing α,β-unsaturated carbonyl compounds with these reagents.

Indeed, NiCRA exhibits very high regioselectivity for 1,4-reduction of a number of α,β-unsaturated ketones, while under the same conditions ZnCRA is an effective reagent mixture for highly regioselective 1,2-reduction of these substrates (Scheme 122)[364]. Addition of magnesium bromide enhances the activity of both reagent mixtures. It is important to remember that the general applicability of CRA reagents is limited, due to their high basicity as well as their tendency to undergo side-reactions via one electron-transfer processes. The heterogeneity of these reagents limits reproducible reduction yields.

VII. BIOCHEMICAL REDUCTIONS

A. Enzymatic Reductions

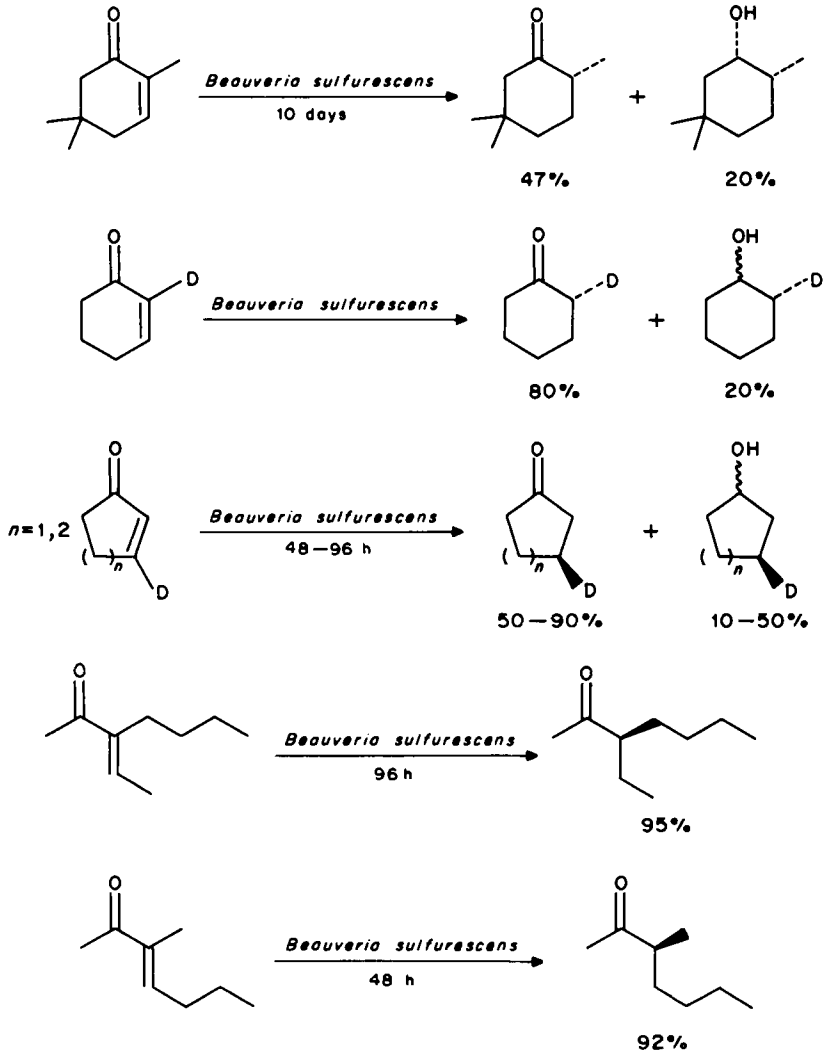
Much work has been published on the microbiological reduction of α,β-unsaturated ketones. Under anaerobic conditions the reduction of Δ^4-3-keto steroids by *Clostridium paraputrificum* led to the 3-keto-5β derivatives[365] (Scheme 123). Similar transformations



SCHEME 123

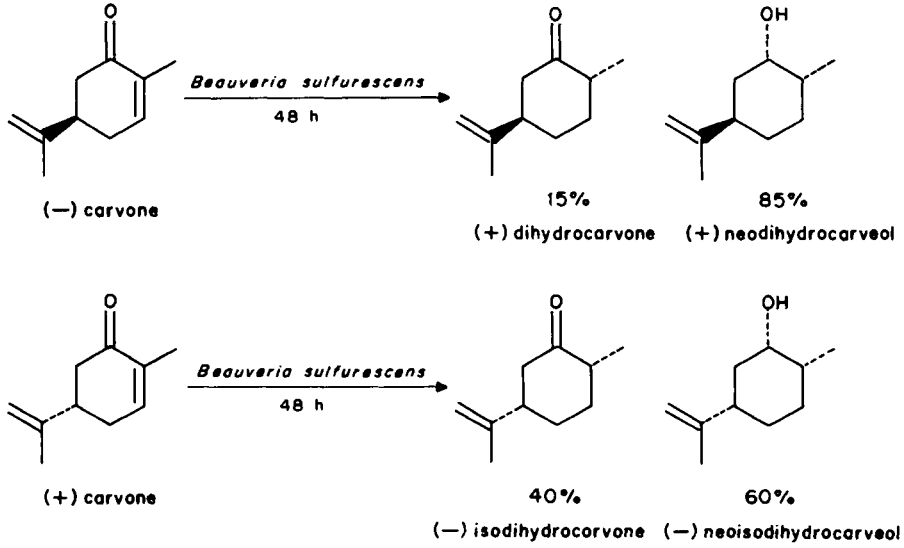
were observed previously with *Bacillus putrificus*[366], *Penicillium decumbens*[367], *Rhizopus nigricans*[368] or *Aspergillus niger*[369]. In most cases further reduction led to the corresponding 3α-hydroxy-5β derivatives.

Highly enantioselective conjugate reductions of substituted cyclopentenones and cyclohexenones were reported by Kergomard using *Beauveria sulfurescens* (ATCC 7159) under anaerobic conditions[370]. The reaction takes place only with substrates containing a small substituent in the α-position and hydrogen in the β-position. The saturated ketones obtained were, in some cases, accompanied by saturated alcohols. A number of useful transformations, including enantioselective reductions of acyclic substrates, are illustrated in Scheme 124.



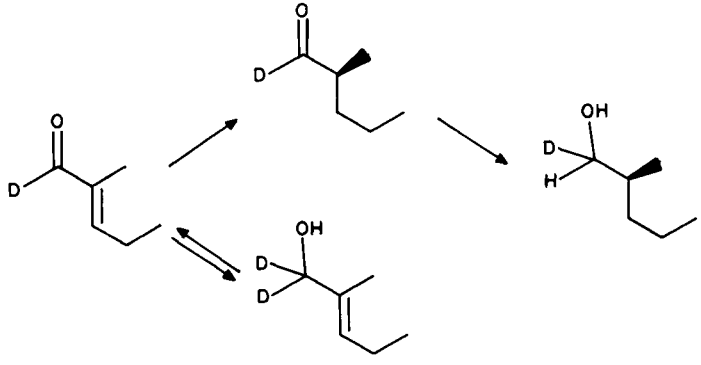
SCHEME 124

Both naturally occurring enantiomers of carvone were selectively reduced by *B. sulfurescens* (Scheme 125). (−)-Carvone was reduced to (+)-dihydrocarvone (*trans*) and further to (−)-neodihydrocarveol, whereas (+)-carvone was reduced to (−)-isodihydrocarvone (*cis*), which was then converted to (−)-neoisodihydrocarveol[371]. Similar reductions with identical stereoselectivities were observed earlier with *Pseudomonas ovalis* (strain 6-1) and with a strain of *Aspergillus niger*[371].



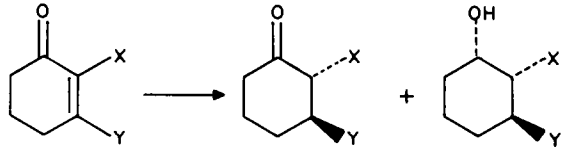
SCHEME 125

The reduction of α,β-unsaturated aldehydes by *Beauveria sulfurescens* proceeds along two mechanistic pathways: (a) reversible formation of the corresponding allylic alcohols and (b) irreversible formation of the saturated alcohol (Scheme 126)[372]. The latter involves initial, slow 1,4-reduction, followed by fast reduction of the resultant saturated aldehyde. A similar sequence was proposed for the reduction of geranial and geraniol to (*R*)-citronellol with *Saccharomyces cerevisiae*.



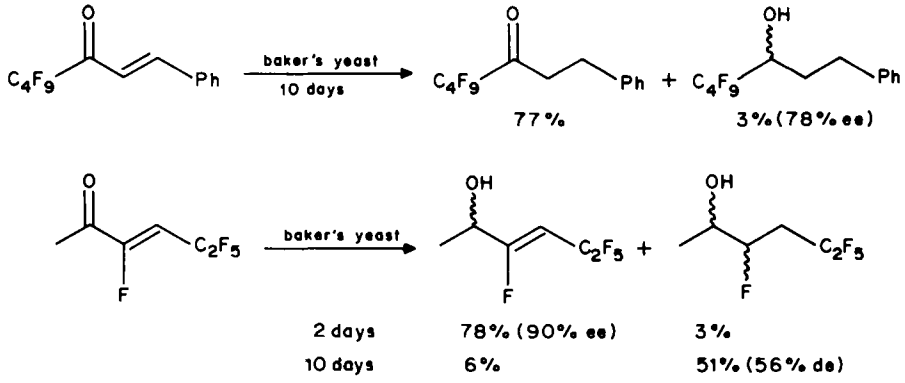
SCHEME 126

The above-described reducing characteristics of *B. sulfurescens* were found to be a general phenomenon exhibited by many types of eukaryotic organisms (six fungi) and prokaryotes (more than 20 Actinomycetes and Clostridium species)[373]. For example, in conjugate reduction of cyclohexenone derivatives the addition of two hydrogen atoms across the olefin occurs with *trans* stereochemistry, as shown in Scheme 127 where X represents a small alkyl group and Y a hydrogen atom. In all cases, the 1,4-reduction mode was completed within 48 hours. As these characteristics are shared by many organisms, it was suggested that they all contain very similar reducing enzymes[373].



SCHEME 127

α,β-Unsaturated ketones bearing perfluoroalkyl groups are reduced by baker's yeast (Scheme 128)[374]. Perfluoroalkyl alkenyl ketones give mainly the saturated ketone, along with a small amount of optically active saturated alcohol. Substrates having a perfluoroalkyl group attached to the alkene moiety give mixtures of optically active allylic as well as saturated alcohols, whose relative concentration is time-dependent.

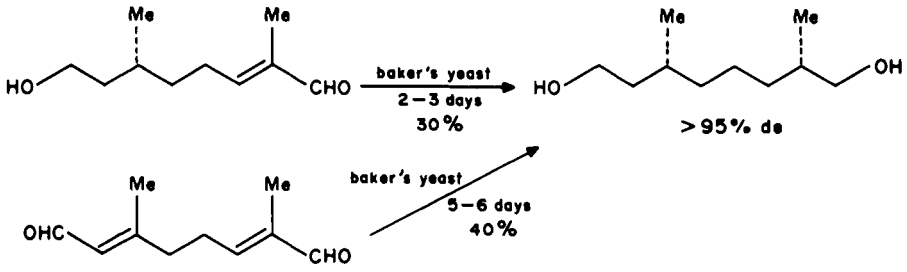


SCHEME 128

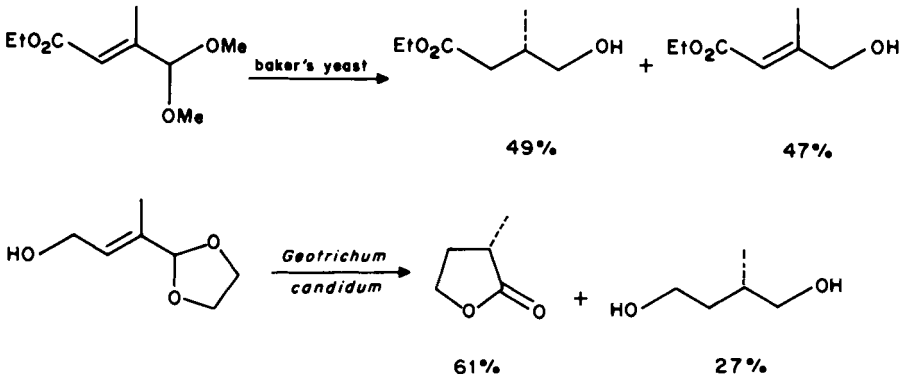
Unsaturated aldehydes derived from citronellol and geraniol are also reduced by baker's yeast to the corresponding saturated primary alcohols with very high enantioselectivity (Scheme 129)[375].

Two key chiral building blocks used in the total synthesis of α-tocopherol were prepared via microbial reduction of unsaturated carbonyl compounds with baker's yeast and with *Geotrichum candidum*, as illustrated in Scheme 130[376].

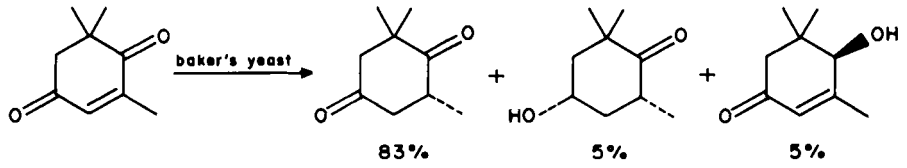
Similarly, a key intermediate in the total synthesis of optically active natural carotenoids was prepared by microbial reduction of oxo-isophorone with baker's yeast (Scheme 131)[377].



SCHEME 129

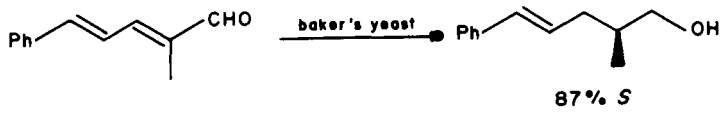


SCHEME 130



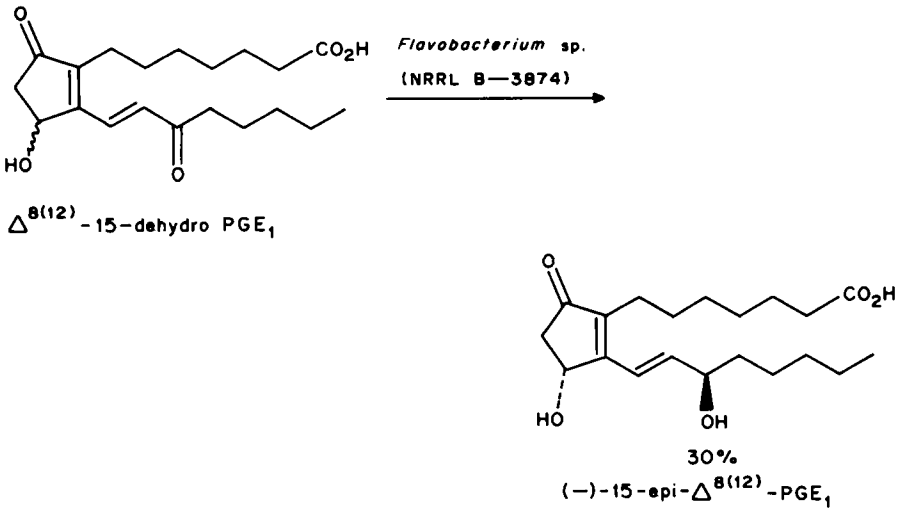
SCHEME 131

An alternative approach to the synthesis of α-tocopherol employs a chiral building block that was obtained by baker's yeast reduction of 2-methyl-5-phenylpentadienal (Scheme 132)[378].



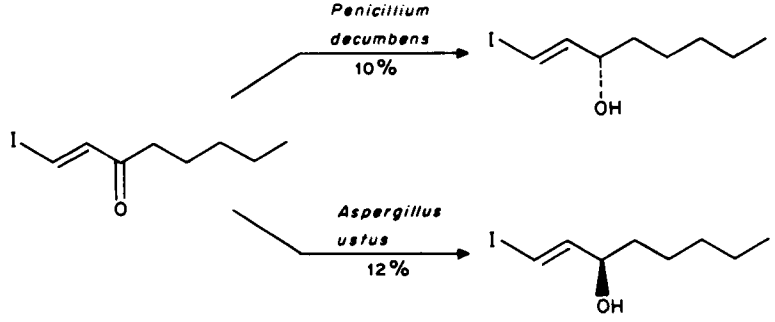
SCHEME 132

Microbial reduction of enones has been applied to prostaglandin synthesis. For example, enantioselective reduction of the enone system in $\Delta^{8(12)}$-15-dehydro-PGE_1 with *Flavobacterium* sp. (NRRL B-3874) provided optically pure (−)-15-*epi*-$\Delta^{8(12)}$-PGE_1 (Scheme 133)[379].



SCHEME 133

As a general rule of enzymatic reductions, the 1,4-reduction of enones is preferred over the 1,2-reduction mode. However, when an electronegative substituent, such as halogen, is introduced that stabilizes the double bond, enzymatic reduction to allylic alcohols may be achieved[276]. A 1,2-reduction of a β-iodo enone is illustrated in Scheme 134.

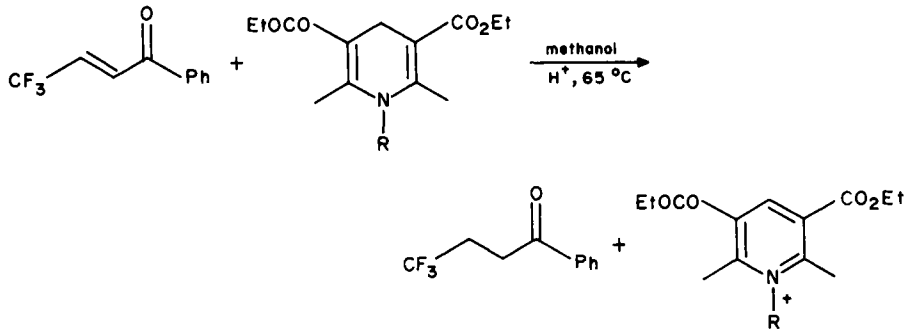


SCHEME 134

B. Biomimetic Reductions with NAD(P)H Models

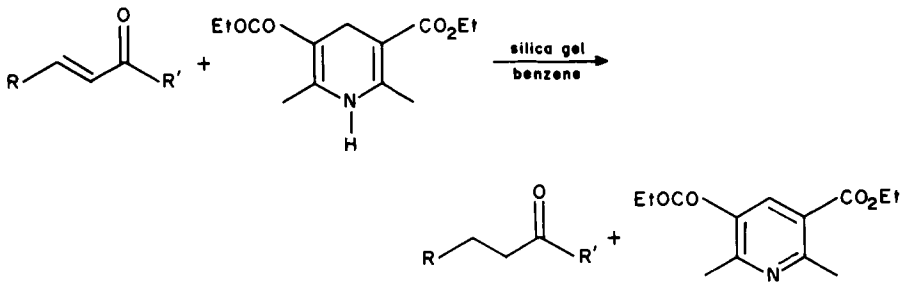
A number of pyridine nucleotide-linked dehydrogenases catalyze the reversible hydrogenation–dehydrogenation of the double bond in α,β-unsaturated ketones[380]. Similar biomimetic conjugate reduction of α,β-unsaturated aldehydes and ketones occurs

with NAD(P)H models, such as 3,5-dicarboethoxy-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester). With highly electron-deficient olefins, such as maleic acid, maleic anhydride, diethyl maleate, diethyl fumarate, etc., reductions proceed well[381]. Similarly, the olefinic bond of 1-phenyl-4,4,4-trifluoro-2-buten-1-one is reduced by dihydropyridines under mild condition (Scheme 135)[382]. Tracer experiments showed that hydrogen is transferred directly from the 4-position of the pyridine ring to the β-position of the enone system. The reaction thus parallels the enzymatic reduction of androstenedione[383].



SCHEME 135

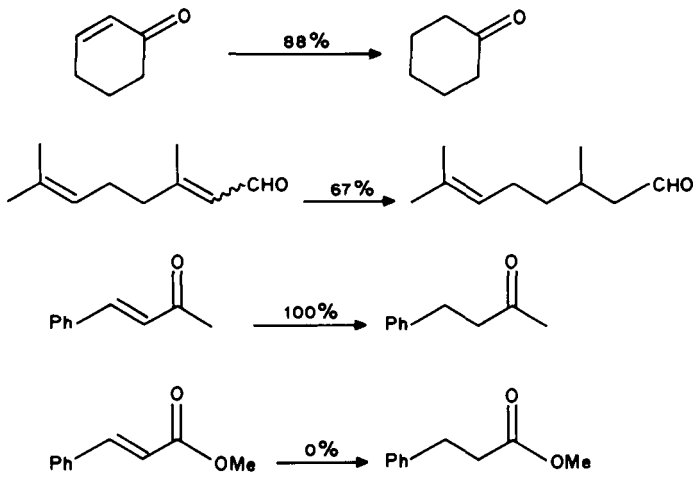
However, these reaction condition (refluxing methanol or photoactivation at room temperature) are useful only for the reduction of highly activated double bonds[384]. Nevertheless, it was found that the reaction is promoted by silica gel[385], broadening the scope of reducible enone substrates (Scheme 136).



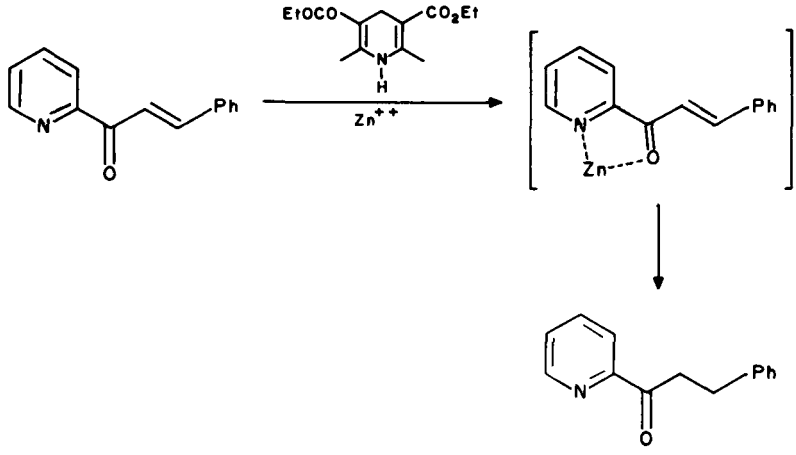
SCHEME 136

The method is highly chemoselective as no alcoholic products are observed, and carbonyl, nitro, cyano, sulfinyl and sulfonyl groups remain intact under the reaction conditions (Scheme 137).

Pandit has provided evidence for the Lewis-acid catalysis postulated to operate in these reductions[386]. The reduction of various cinnamoylpyridines by 1,4-dihydropyridine derivatives to the corresponding saturated ketones is catalyzed by zinc or magnesium cations. The reduction rate was fastest in the case of 2-cinnamoylpyridine, in which the metal ion can complex simultaneously to both the nitrogen and oxygen sites (Scheme 138). This example is regarded as a model of Lewis-acid catalysis of the NADH-dependent enzymatic reduction of δ^4-3-ketosteroids.



SCHEME 137

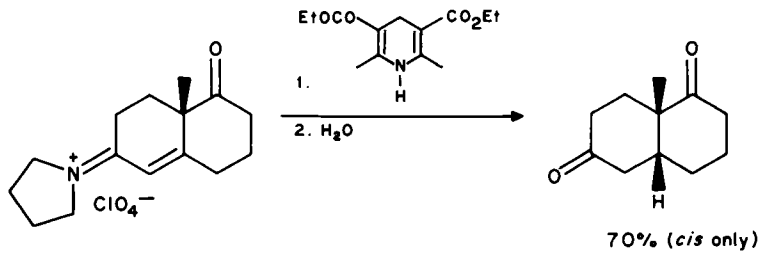


SCHEME 138

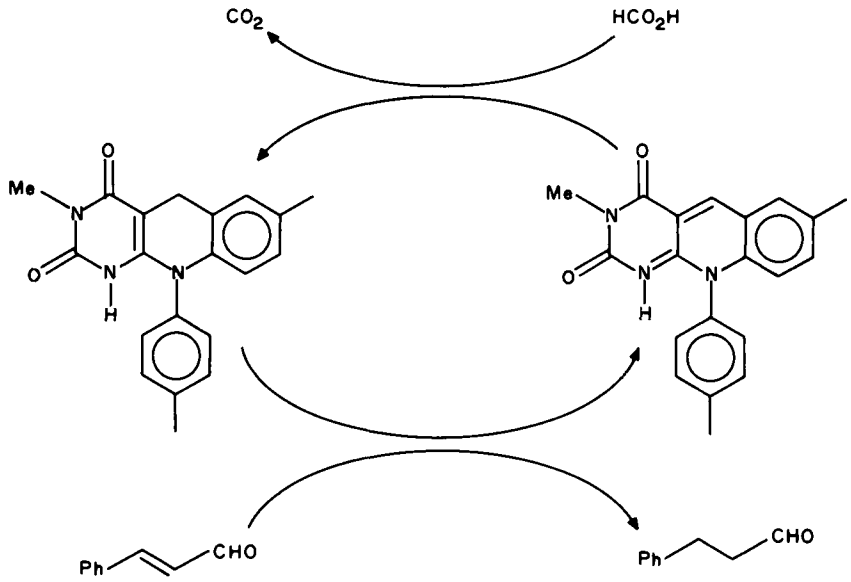
In a similar manner, iminium salts derived from α,β-unsaturated aldehydes and ketones are reduced by Hantzsch ester (Scheme 139)[387]. The ratio between the 1,4- and 1,2-reduction products depends upon the pK_a of the amine component.

An autorecycling system for the specific 1,4-reduction of α,β-unsaturated ketones and aldehydes was based on 1,5-dihydro-5-deazaflavin, which can be regarded as an NADH model[388]. The reaction occurs on heating the substrate with catalytic amounts of 5-deazaflavin in 98% formic acid, typically at 120 °C for 24 h (Scheme 140).

The iminium salts of 3,3,5-trimethylcyclohex-2-en-1-one were reduced with 1,4-dihydronicotinamide sugar pyranosides to give the corresponding optically active



SCHEME 139



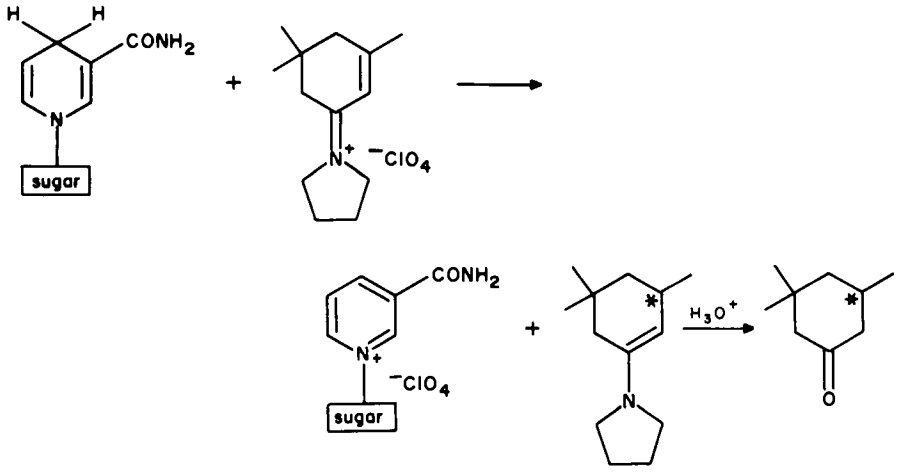
SCHEME 140

saturated ketone in enantiomeric excess ranging over 3–31%. The product stereochemistry changed sensitively with structural variations in the sugar residues (Scheme 141)[389].

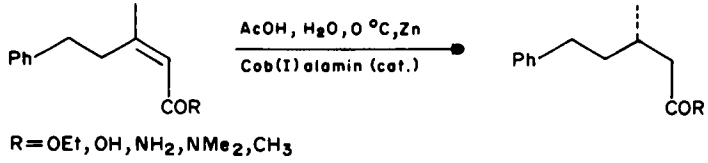
The cob(I)alamin catalyzed reduction of α-methyl-α,β-unsaturated carbonyl compounds produces the corresponding saturated derivatives having an *S* configuration at the α-carbon (Scheme 142)[390]. The highest enantiomeric excess (33%) is exhibited by the *Z*-configurated methyl ketone. The *E*-configurated enone is reduced by this system to the corresponding *R*-product with poor enantiomeric excess.

VIII. MISCELLANEOUS REDUCING AGENTS

Several techniques utilizing miscellaneous reagents, that were not mentioned in the preceding sections, have been reported to effect the 1,4-reduction of α,β-unsaturated aldehydes and ketones.



SCHEME 141



SCHEME 142

Sodium dithionite under nitrogen atmosphere at 80 °C in a water–benzene mixture and in the presence of a phase-transfer catalyst was shown to be a useful reducing agent. Dienoic carboxylic acids and esters were reduced in a 1,6-mode using this approach[391].

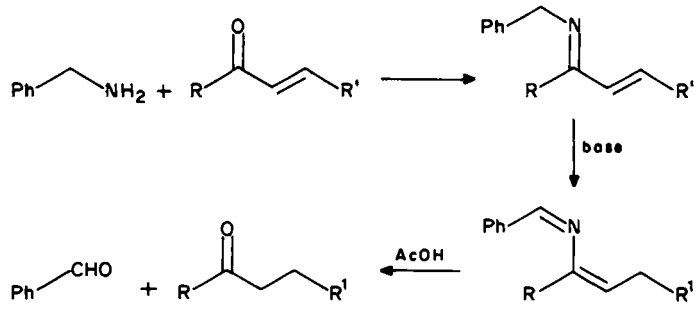
2-Phenylbenzothiazoline reduced α,β-unsaturated carbonyl compounds in a 1,4-fashion in the presence of stoichiometric amounts of aluminum chloride[392]. No 1,2-reduction products or saturated alcohols were detected. The reagent reduces unsaturated esters and aldehydes much less effectively.

Condensation of an α,β-unsaturated ketone with benzylamine gives the corresponding Schiff base. Treatment with a base, such as potassium *t*-butoxide, affects rearrangement to a benzaldehyde derivative, as shown in Scheme 143[393]. Hydrolysis of the latter with dilute acetic acid furnishes the corresponding saturated ketone with concomitant formation of benzaldehyde.

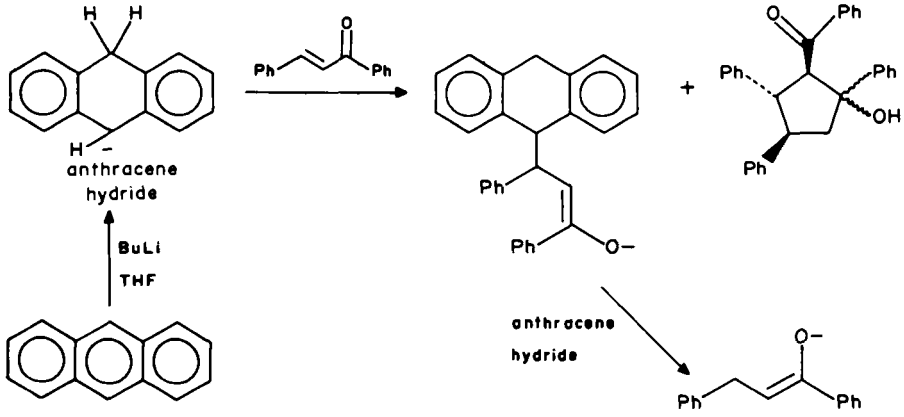
A reagent prepared from tellurium powder and sodium borohydride in ethanol engenders 1,4-reduction of α,β-unsaturated aldehydes, ketones and esters in high yield and with good regio- and chemoselectivity (no 1,2-reduction and no reduction of isolated double bonds)[394].

Anthracene hydride (the anion derived from 9,10-dihydroanthracene) reacts rapidly with chalcone to form an anionic Michael adduct along with a chalcone dimerization product (Scheme 144)[395]. Prolonged reaction in the presence of anthracene hydride cleaves the Michael adduct into anthracene and the enolate of the saturated ketone. The

partial structure RCCCO is essential for this fragmentation, as mesityl oxide, for example, gave only the Michael adduct.



SCHEME 143



SCHEME 144

Photolysis of 4a-methyl-4,4a,9,10-tetrahydro-2-(3*H*)-phenanthrone in isopropanol gave rearranged and 1,4-reduction products, along with traces of 1,2-reduction and small amounts of coupling products[396].

2-Propanol doped on dehydrated alumina reduces at room temperature various aldehydes and ketones to the corresponding alcohols[397]. α,β-Unsaturated aldehydes are selectively reduced under these conditions to the corresponding allylic alcohols. For example, citral is converted to geraniol in 88% yield.

α,β-Unsaturated nitriles are reduced to saturated nitriles with triethylamineformic acid azeotrope in DMF[398].

α,β-Unsaturated ketones are reduced to allylic alcohols with β-branched trialkylaluminum compounds, such as $(i\text{-Bu})_3\text{Al}$ and tris-((*S*)-2-methylbutyl)aluminum. The latter reagent reduces prochiral enones to optically active allylic alcohols with 7–15% enantiomeric excess[399].

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The Chemistry of Enones
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CHAPTER **19**

Organometallic derivatives of α, β-unsaturated enones

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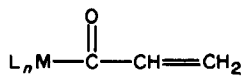
I. INTRODUCTION

The purpose of this chapter is to review the chemistry of α, β-unsaturated enones bound as ligands to low valent mono- and polymetallic transition metal centres. The enone ligand in such complexes may most usefully be classified in terms of the formal number of electrons donated to the metal centre; thus, structures **1** to **7**, for which examples all exist in the literature, represent donation of one, two, three or the maximum of four electrons. For the complexes described here, the set of auxiliary ligands L_n completes the 16- or 18-electron configuration at the metal centre. In general, the normal organic reactivity of the enone is substantially retained in the η^1-structures **2** and **3**, while that of the η^1-acyl structure **1** differs substantially. For low valent metals, η^2-coordination to the C=C bond in **4** is almost invariably preferred relative to coordination to a ketonic lone pair. Three-electron coordination in **5** and **6** is completed by chelation of the C=C bond and a ketonic lone pair respectively, while η^4-complexes contain the enone bound via its 4π-electron system. One may note the potentially facile interconversion of structural types [**1** ⇄ **5**, **3** ⇄ **6**, **4** ⇄ **7**] through loss or gain of a two-electron auxiliary ligand.



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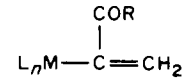

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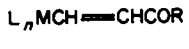

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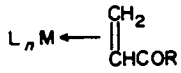

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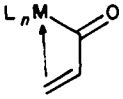

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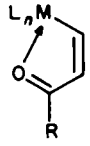

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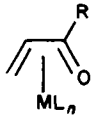
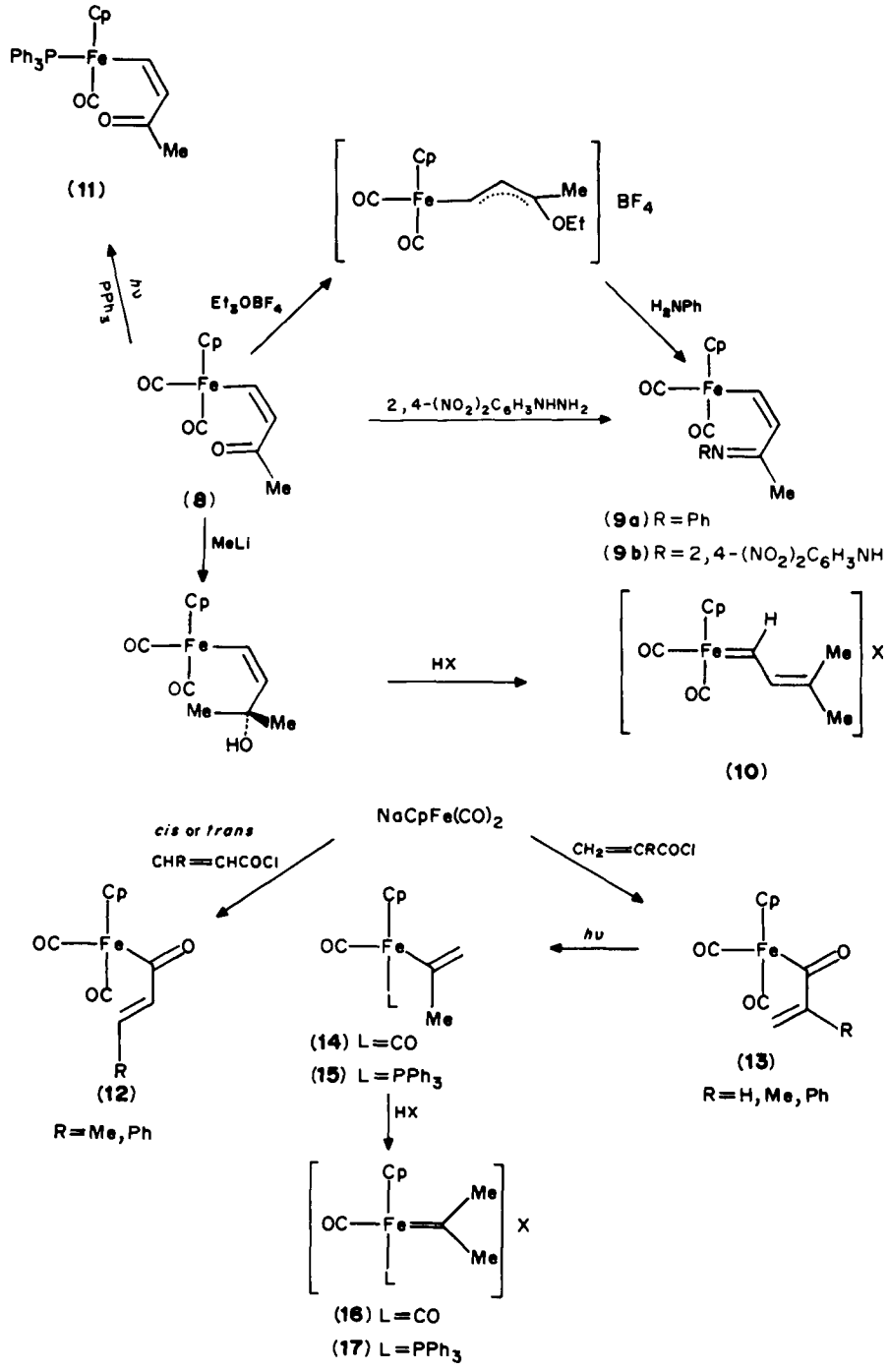


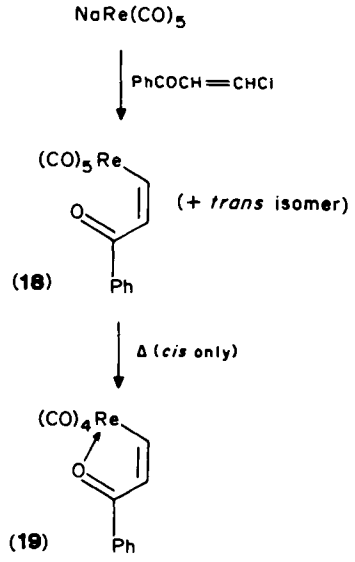
(7)

II. COMPLEXES CONTAINING ONE- AND THREE-ELECTRON DONOR LIGANDS

η^1-complexes may be prepared by reaction of metal anion with β-haloenones. Thus, treatment of $NaCpFe(CO)_2$ with MeCOCH=CHCl yields **8**[1,2]; the normal ketonic reactivity of **8** is demonstrated in formation of the hydrazone **9b**[3] and in reaction with Et_3OBF_4 followed by $PhNH_2$, to give **9a**[4]. Photolysis in the presence of PPh_3 yields **11** rather than the product of insertion or internal chelation[5]. Most interesting is the reaction with MeLi, followed by protonation, to yield the carbene complex **10** which shows potential as a cyclopropanation reagent[1].

The isomeric acyl complexes **12** and **13** may be prepared through a similar reaction of acid chloride with metal anion; only the *trans* isomer of **12** is isolated from either *cis* or *trans* acid chloride[1,6,7]. Complex **13** may be photochemically decarbonylated to the vinyl complex **14** (or **15** in the presence of PPh_3), and protonation yields the carbene derivatives **16** or **17**[1]. Internal chelation under mild conditions has been observed in the transformation of **18** to **19** on heating in hexane[8], and is also observed in complexes amenable to M—H or M—R insertion. Thus, whereas reaction of $Fe(CO)_4^{2-}$ with CH_2=CHCOCl yields the stable acyl anion **20**[9], reaction with *cis*-BrCH=$CHCO_2$Me yields the chelated complex **22a**, presumably via initial formation of the vinyl complex **21** followed by rapid insertion of CO[10]. Complexes of structure **22** are generally more accessible through reaction of alkynes with $HFe(CO)_4^-$, in which the σ-vinyl intermediate is generated by insertion of alkyne into the Fe—H bond[10]. The reactivity of **20** and **22** differs substantially; whereas acidolysis or reaction of **20** with alkyl halide yields aldehyde and ketone respectively[11,12], **22d** is protonated at the carbon β to the metal to give the alkene complex **23**, and is alkylated at oxygen to give the carbene complex **24** which may be oxidized with pyridine-*N*-oxide to **25**[10]. Transient internal chelation may be responsible for the isolation of cyclopentanone and cyclohexanone from the reaction of $Fe(CO)_4^{2-}$ with $Br(CH_2)_nCH$=CH_2 ($n = 2, 3$), followed by acidolysis[13,14]. Thus, the reaction may proceed by insertion of CO into the initial σ complex **26** to give **27**, followed by internal cyclization to give **28** and acidolysis to release the cyclic ketone. The reaction is sensitive to


Cp
Ph3P—Fe
OC
O
Me
(11)
hν
PPh3
Et3OBF4
OC—Fe
OC
Me
OEt
BF4
H2NPh
2,4-(NO2)2C6H3NHNH2
RN
(8)
(9a) R = Ph
(9b) R = 2,4-(NO2)2C6H3NH
MeLi
HO
HX
H
X
(10)
NaCpFe(CO)2
cis or trans
CHR=CHCOCl
CH2=CRCOCl
hν
(12)
R=Me, Ph
(14) L=CO
(15) L=PPh3
(13)
R=H, Me, Ph
(16) L=CO
(17) L=PPh3

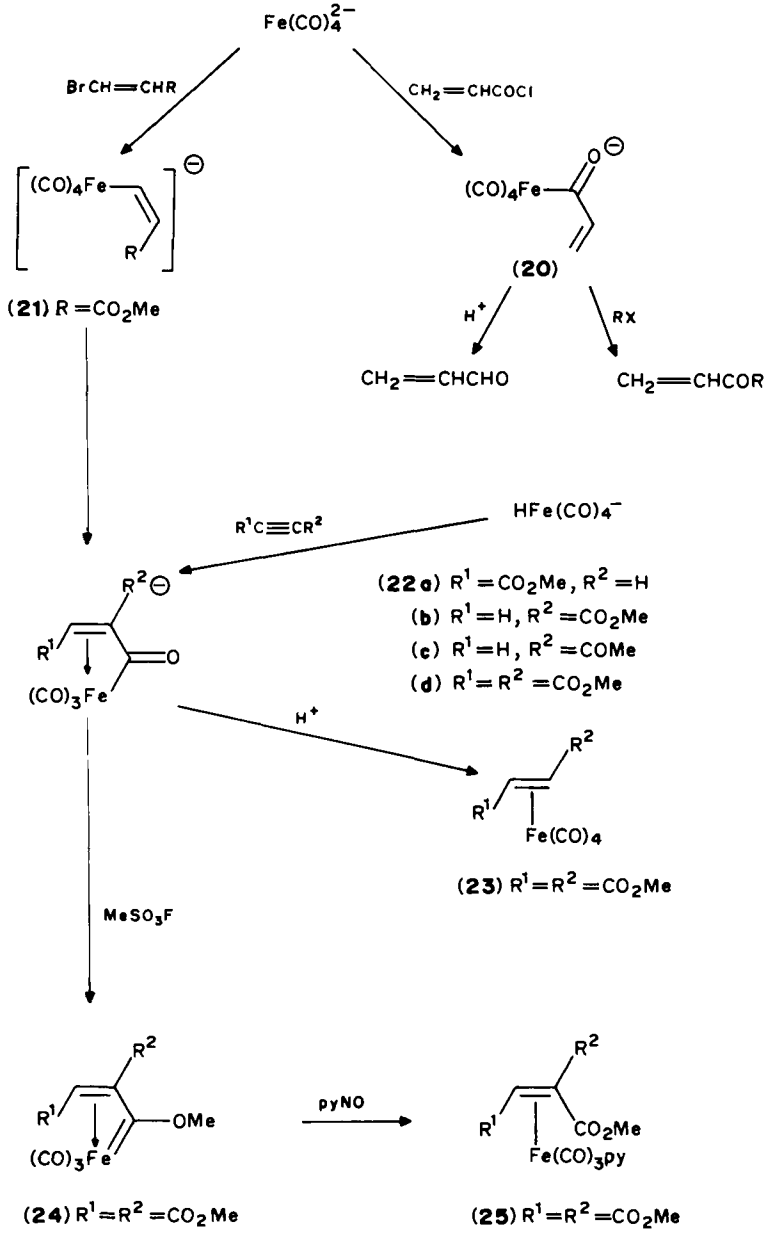


chain length and substituent, and no cyclized product is isolated where $n = 4$, or for halides such as $BrCH(Me)(CH_2)_2CH{=}CH_2$, $Br(CH_2)_3CH{=}CHMe$, or $BrCH_2CH{=}CMe_2$[11,14]. Reaction with the allene $Br(CH_2)_2CH{=}C{=}CH_2$ proceeds in a similar way through intermediate **29** to release **30**[14], though alkylation occurs at oxygen to give the trimethylenemethane complex **31**[15]. Uncyclized intermediates of structure **32** may be obtained from reaction of $[Fe(CO)_4R]^-$ with allene. Alkylation or protonation occurs at oxygen to give **33a, b**; rearrangement of **33b** on mild heating yields the η^4-enone complex **34**[15–19]. Substituted allenes give isomeric mixtures; thus, reaction of $[Fe(CO)_4Et]^-$ with $PhCH{=}C{=}CH_2$ yields an 80:20 mixture of **35** and **36**.

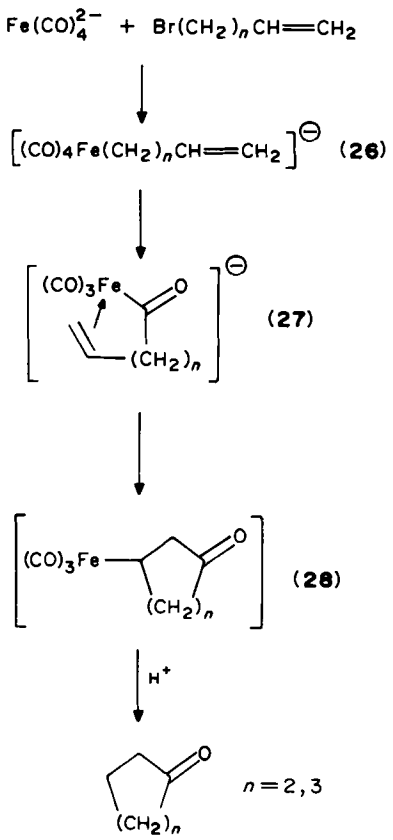
Thermally or photochemically induced insertion of alkynes into metal–acyl bonds, or into metal–alkyl bonds coupled with CO migration, provide general routes to complexes of structure **6**. For metal alkyls, the addition is opposite to that observed for $HFe(CO)_4^-$, implying that CO insertion into the M—R bond, rather than insertion of alkyne, is rate determining. Thermally, forcing conditions are sometimes necessary, and frequently products derived from further reaction of **6** may be isolated. Thus, further insertion of CO generates the η^3-lactone complex **40**, while insertion of a further mole of alkyne generates the η^3- or η^5-pyranyl derivatives **41** or **42**.

The reaction sequence is best illustrated by the transformation of **44**, obtained thermally from **43** and $HC{\equiv}CBu^t$, into the lactone **45** on reaction with CO and into the η^3-pyranyl complex **46** on reaction with further alkyne[20]. Lactone formation may also be promoted by other two-electron ligands, as illustrated by the conversion of complexes of structure **49** into **50** on treatment with PPh_3 or isocyanide[21].

The mechanism of thermal formation of **6** may thus be best represented as a rate-determining, alkyne-assisted insertion of CO to give intermediate **39** followed by fast insertion of alkyne. Kinetic studies of the reaction of $(CO)_5MnMe$ with $MeO_2CC{\equiv}CCO_2Me$[22] and the greater reactivity of the indenyl complex **43** compared to the cyclopentadienyl complex **48** are consistent with this mechanism. The related manganese complexes **53a–c** resist carbonylation to form lactones, but reaction with $PhC{\equiv}CH$ is accompanied by formation of the η^5-pyranyl complex **54**[23]. In contrast to the tail-to-tail linking of alkyne in **46**, the linking in **54** is head-to-tail, implying a reversed insertion of



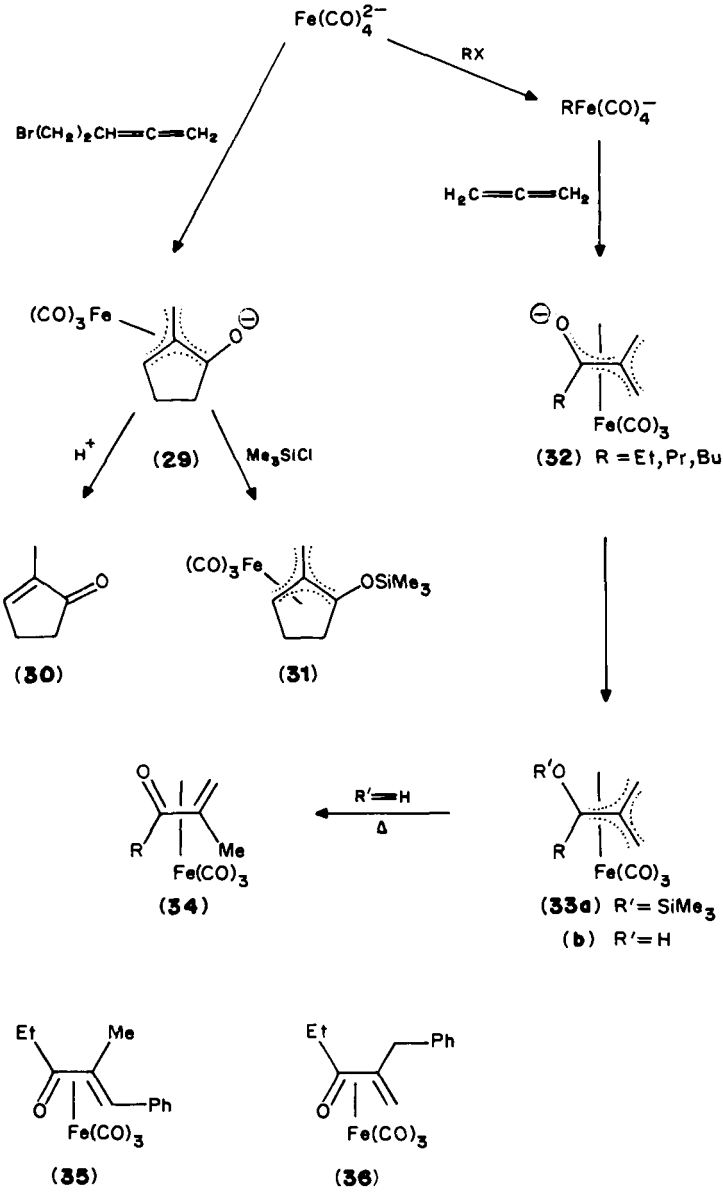
alkyne in the conversion of **39** to **6**. This may be ascribed to the minimized steric hindrance of the Bu^t group in **44**, and to the enhanced electronic stability conferred on the M–C σ bond by the α-phenyl substituent of **53b, c**. Indeed, the indenyl complex **43** reacts photochemically with both MeC≡CH and PhC≡CH to yield the α-substituted complex



55[24–26]. Similarly, $CpFe(CO)_2Me$ reacts photochemically with $CF_3C{\equiv}CH$ to give exclusively the η^5-pyranyl isomer **56**[27]. The direction of initial insertion is sensitive to metal size in sterically crowded complexes. The reaction of the pentamethylcyclopentadienyl complexes **57** with $PhC{\equiv}CH$ yields the sterically preferred isomer **58** in the case of chromium, but the electronically preferred isomer **59** in the case of tungsten[28].

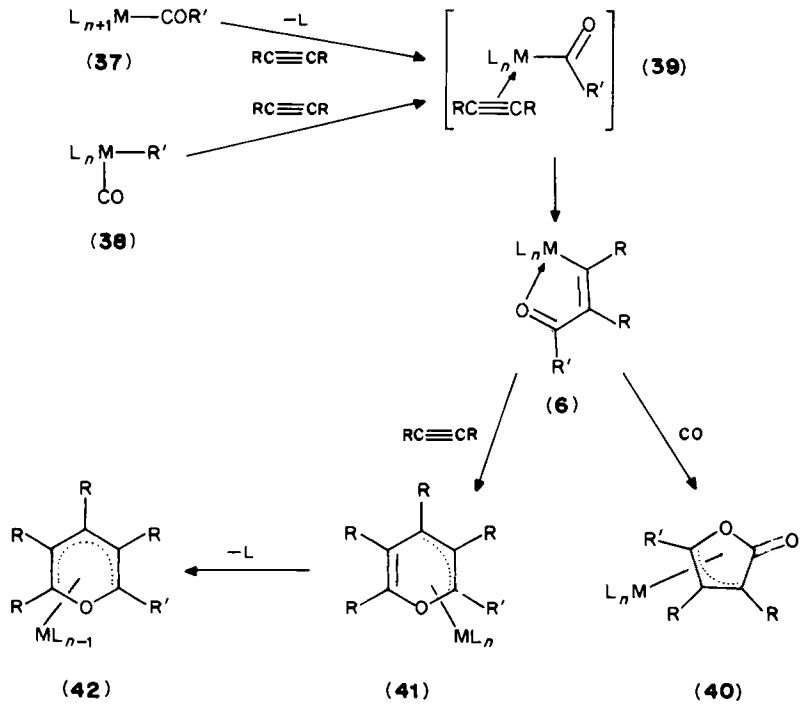
At least in the case of tungsten complexes of structure **48**, the initial stages in the photochemical reaction with alkyne may differ from those postulated for the thermal reaction. The initial product of the photoreaction between $CpW(CO)_3Me$ and $HC{\equiv}CH$ is the *mono*carbonyl complex (**60**) containing a formal four-electron donor alkyne. This undergoes facile reaction with PMe_3 or CO to give the insertion products **61a, b** while more forcing reaction of **61b** with CO, or reaction with $P(OMe)_3$, results in alkyne insertion to give **62a, b**. Use of PMe_3 results in addition of a second mole of PMe_3 at the α-carbon to give **63**[31–33]. Insertion is also promoted by the reaction of **60** with NOCl to give **61c**[34].

Direct conversion of metal acyl **37** to **6** is accompanied by ligand loss (usually carbon monoxide), and therefore becomes increasingly facile towards the right-hand side of the transition metal series. Thus, whereas **47** or **52** requires elevated temperature and/or long reaction times, reaction of cobalt acyls such as **64** with alkynes occurs more easily to yield directly the lactone complex **65**. Hydrogenation yields the free, saturated lactone **66**, but the reaction may be made catalytic in cobalt if the acyl group R^1 contains an activated



hydrogen. Thus, deprotonation of **67** yields the free unsaturated lactone **68** with release of $Co(CO)_4$ which may be recycled to **67** as shown[35].

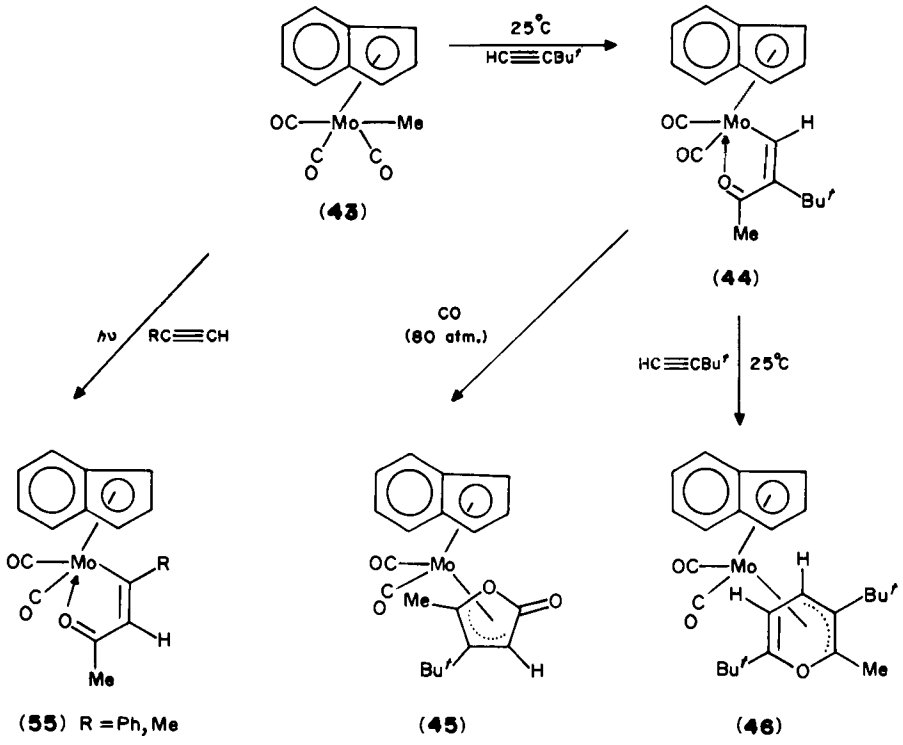
The conversion of acyl chlorides to lactones using $Ni(CO)_4$ may similarly be viewed as proceeding through the intermediates **69** to **71** with final hydrolysis liberating the unsaturated lactone **72**[36]. Part of this reaction has recently been modelled in the



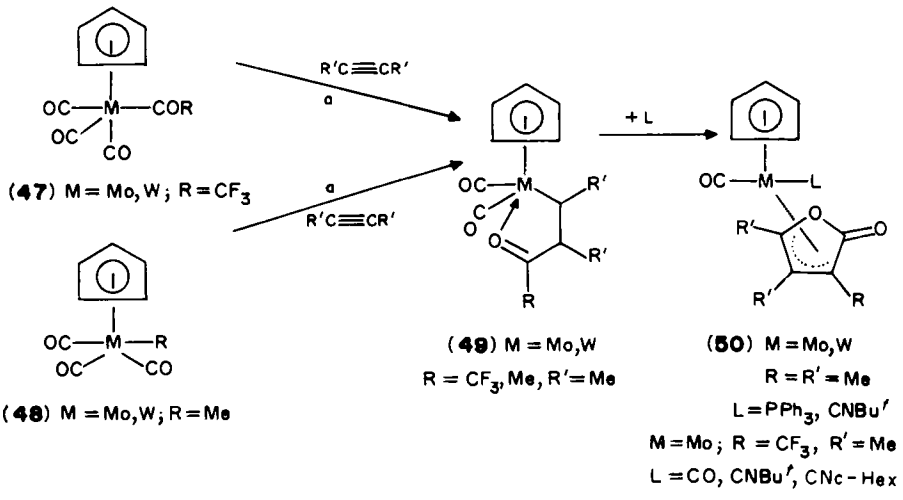
conversion of the acyl complex **73** to **74** on reaction with PhC≡CH; heating results in phosphine migration to the α-carbon to give **75**[37].

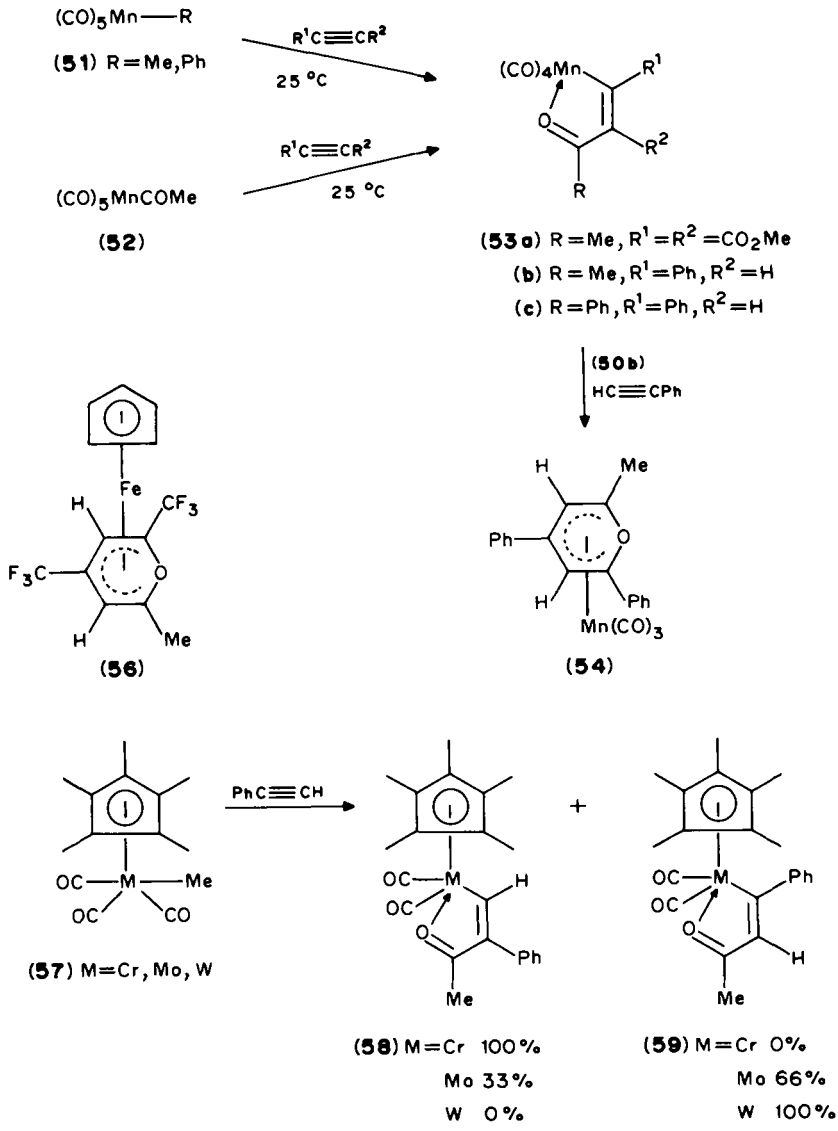
Protonation of **76a** in non-coordinating acid (HBF_4) yields the η^4-enone complex **77**[38], whereas in coordinating acid (CF_3COOH), addition of two moles of acid occurs to **76b, c** to yield either **79** and the liberated ketone or the η^1-complex **78** in which effective hydrogenation of the C=C bond has occurred[39]. Complexes **76c** react with PMe_3 to give both the product of carbonyl substitution **80** and the product of addition at the α-carbon **81**[39]; molybdenum yields only the addition product **81**, whereas further substitution of the tungsten complex occurs to give **82**[40,41]. Protonation of the cyclic derivatives **84** also yields stable η^4-enone complexes **85** and **86** from which the free ketone **87** can be released by treatment of the molybdenum complex with CO[42].

A similar rich chemistry is evident in the reactions of metal thiolates with alkynes; the products isolated depend significantly on the metal, the thiolate and the alkyne. Thus, reaction of tungsten thiolates of structure **88** in which R^1 is electron withdrawing yields stable four-electron donor alkyne complexes **89**[43,44]; where R^1 is alkyl, thermal reaction occurs under mild conditions to yield complexes such as **90a–c**. Isomerisation via a formal 1,3-sulphur shift gives the rearranged products **92a, b** and **94**. The mechanism is strongly dependent on the alkyne substituent; where R = CF_3, the η^2-vinyl complexes **91a, b** may be isolated, whereas where R = CO_2Me, isolable σ-vinyl complexes such as **93** are formed as intermediates. The 1,3-sulphur shift via the η^2-vinyl structure is promoted by electron-donating groups; thus, reaction of $CpW(CO)_3SPr^i$ with $CF_3C{\equiv}CCF_3$ proceeds directly to **91b**. Isomerization of **94** to the more thermodynamically stable isomer **95** occurs on heating, while lactone formation may be induced by reaction of **91b** with two-electron ligands to give **96a**[45–49]. Under more forcing photochemical activation, $CpW(CO)_3SMe$



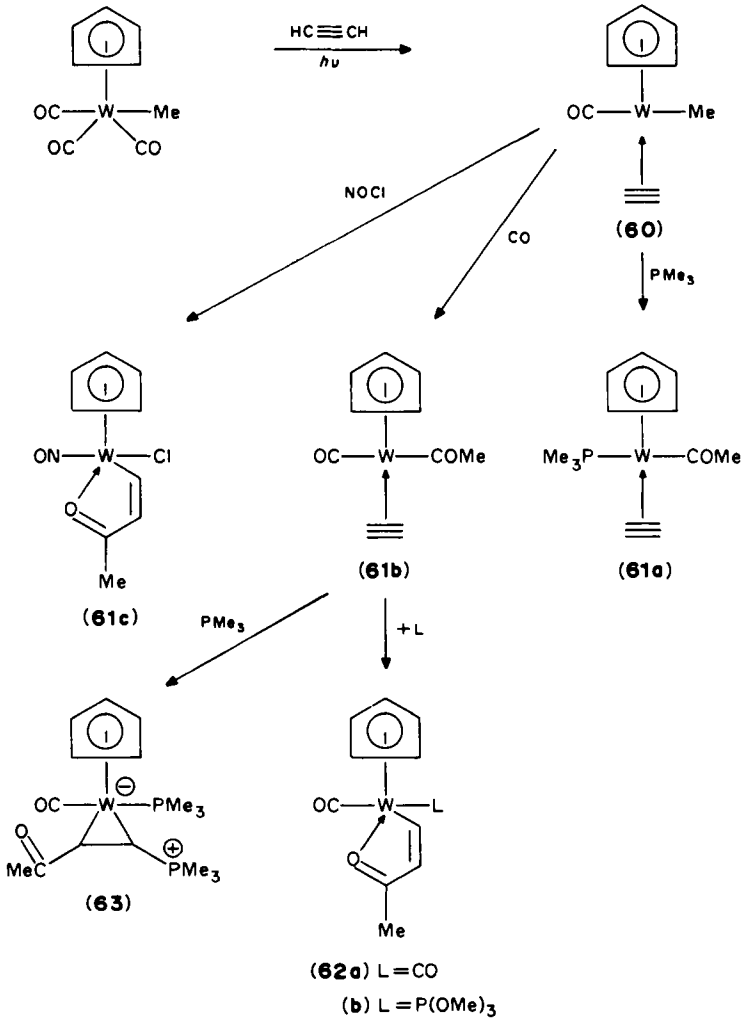
a: M = Mo, 60°C; M = W, hν





yields **92c**, **96b** and complex **97**. Use of $CpMo(CO)_3SMe$ yields the molybdenum analogue of **92c**, together with complex **98** derived from it by CO insertion[50,51].

Similar reactions occur in the analogous iron system. Where R^3 is electron withdrawing, reaction of **99** with alkynes yields only the σ-vinyl complex **100** resulting from insertion[52]; where R^3 is alkyl, complexes of structure **101** are isolated[46,51,53]. These, and the analogous complex **103** derived from reaction of $CpFe(CO)_2AsMe_2$ with $MeO_2CC{\equiv}CCO_2Me$[45], do not undergo sulphur shift, but may be photochemically decarbonylated to **102b, c**. It may be noted that the direction of addition is opposite to that observed for metal–alkyl



bonds; mechanistically, it has been suggested that this is a result of rate-determining attack of sulphur lone pair at an alkyne carbon to give **104** which may collapse to yield either the metal acyl **105** or the σ-vinyl derivative **106**.

III. COMPLEXES CONTAINING TWO- AND FOUR-ELECTRON DONOR LIGANDS

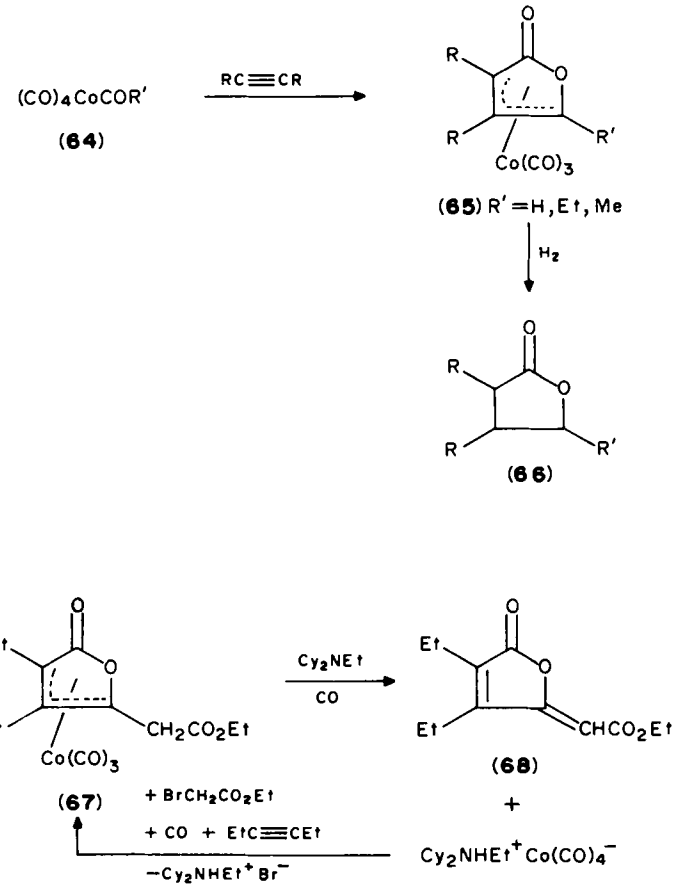
A representative, but not comprehensive, list of monometallic complexes containing two- and four-electron donor enones is given in Table 1, which also shows a list of abbreviations used in this section. With few exceptions, complexes are prepared by interaction of the free enone with an appropriate metal substrate. Exceptions are represented by preparations of complexes **34** and **77** already noted, by the preparation of $CpMn(CO)_2$(mvk) from the

TABLE 1. Monometallic complexes containing two- and four-electron donor enones[a]

η^2-Complex	Reference	η^4-Complex	Reference
$L_2Pt(mvk)$ (L_2 = cod, L = PPh_3)	54		
$Pt(mvk)_3$	54		
$(PPh_3)_2Pt(cinn)$	55		
(chalc)	55		
(bda)	55		
(crot)	56		
$(PPh_3)_2Ni(ac)_2$	57, 61	$Ni(ac)_2$	58, 59
(2, 2′-bipyridyl)$Ni(cinn)_2$	60, 61	(2, 2′-bipyridyl)Ni(bda)	60
$(ac)_2$			
$(crot)_2$			
(2, 2′-bipyridyl)Ni(ac)[b]	62		
(mvk)			
$(Bu^tNC)_2Ni(mvk)$[b]	63		
(ac)			
(cinn)			
(bda)			
(chalc)			
$[P(O\text{-}o\text{-}tolyl)_3]_2Ni(mvk)$[b]	64		
$Ag(mvk)^+$ [b]	65		
$(CO)_4Fe(chalc)$	66–68	$(CO)_3Fe(cinn)$	67–70
(cinn)		(bda)	
(ac)		(chalc)	
$L(CO)_3Fe(cinn)$	72, 73		
(bda)		$(PF_3)_3Fe(mvk)$	71
(chalc)		(crot)	
$L = PMe_2Ph$, $P(OMe)_3$		$L(CO)_2Fe(bda)$	74, 75
		$L = P(OMe)_3$, $P(OPh)_3$	
		PPh_3	
$(CO)_4Ru(mvk)$	76		
$CpMn(CO)_2(mvk)$	77–79		
(bda)			
(cyclohexenone)			
(chalc)			
$[CpFe(CO)_2(mvk)]X$	80–82		
(ac)			
$(CO)_3(PMe_3)_2W(mvk)$	83	$W(mvk)_3$	84
(ac)			
(cinn)		$[(C_5Me_5)W(CO)_2(bda)]BF_4$	38
(crot)			
$(diphos)_2(CO)Mo(mvk)$	85	$(CO)_2Mo(ac)_2$	86
$Cp_2V(mvk)$	87		
(ac)			
(crot)			

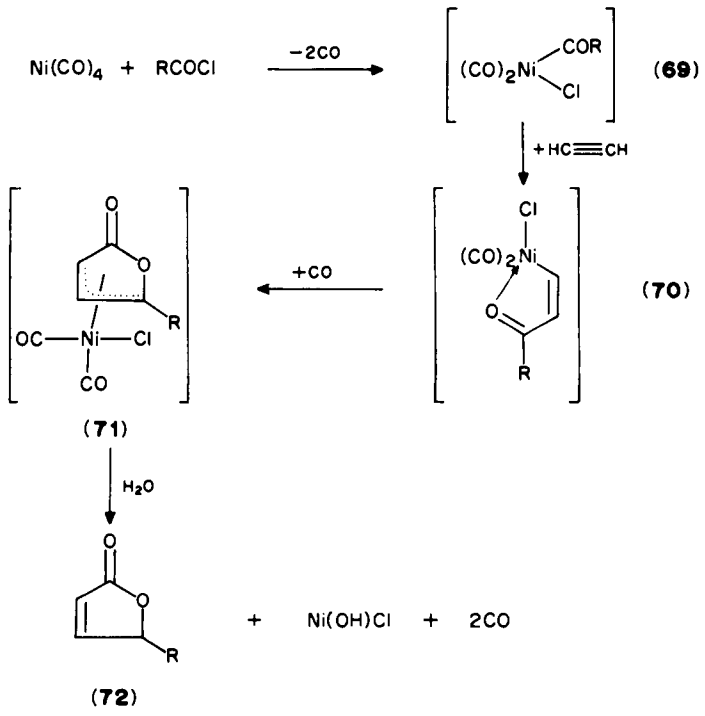
[a] *Abbreviations*: cod = 1, 5-cyclooctadiene; mvk = methyl vinyl ketone (CH_2=CHCOMe); ac = acrolein (CH_2=CHCHO); cinn = cinnamaldehyde (*trans*-PhCH=CHCHO); bda = benzylideneacetone (*trans*-PhCH=CHCOMe); chalc = chalcone (*trans*-PhCH=CHCOPh); crot = crotonaldehyde (*trans*-MeCH=CHCHO); diphosethylenebis(diphenylphosphine) ($Ph_2PCH_2CH_2PPh_2$).

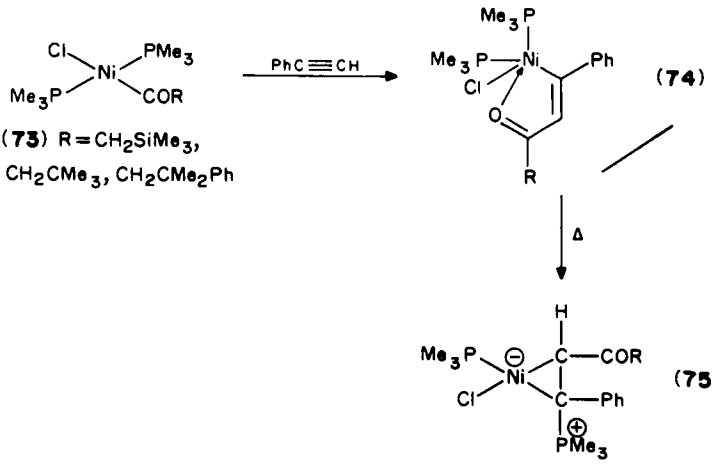
[b] Not isolated.

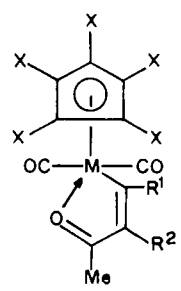


reaction of $CpMn(CO)_2(THF)$ with the diazo compound $N_2C(Me)C(O)Me$[79], and the preparation of $[CpFe(CO)_2(mvk)]BF_4$ from $NaCpFe(CO)_2$ and $H_2C\overset{O}{\diagup\!\diagdown}CHCOMe$[80].

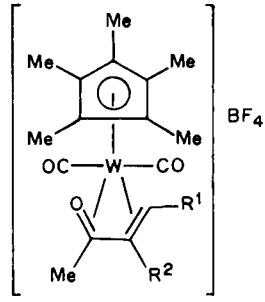
These η^2-complexes range from the strongly bound d^2 vanadium derivatives, which may essentially be regarded as metallacyclopropanes[88,89], to weakly bound d^{10} nickel(0) and silver(I) complexes which are stable only in solution in the presence of excess enone. Within the much broader general class of metal–alkene complexes, the conjugative, electron-withdrawing COR substituent lowers particularly the energy of the π^* orbital, thus increasing the π-acceptor capacity of the alkene. Relative to ethene and its alkyl substituted derivatives, or to electron-rich alkenes such as $CH_2{=}CHOR$, enones form stronger metal–alkene bonds. The difference, however, between the substituents CHO, COR and CO_2R in this respect is sufficiently small that the order of stability can depend on the metal or auxiliary ligands. Thus, whereas stability constants for (2,2'-dipyridyl)Ni(alkene) and $[P(O{-}o\text{-tolyl})_3]_2Ni$(alkene) decrease in the order $CHO \gg COR \approx CO_2R$, infrared data for $(CNBu^t)_2Ni$(alkene) and $(CO)_3(PMe_3)_2W$(alkene) are more consistent with the order $COR > CHO \approx CO_2R$. A much wider variety of metal complexes of mono-ester and di-ester substituted alkenes


Ni(CO)4 + RCOCl
−2CO
(CO)2Ni
COR
Cl
(69)
+HC≡CH
Cl
(CO)2Ni
O
R
(70)
+CO
OC—Ni—Cl
CO
(71)
H2O
+ Ni(OH)Cl + 2CO
(72)

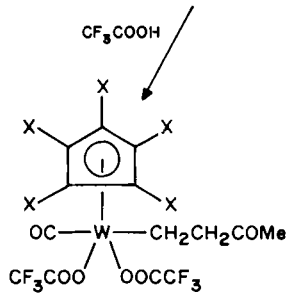

Cl
Ni
PMe3
Me3P
COR
(73) R = CH2SiMe3, CH2CMe3, CH2CMe2Ph
PhC≡CH
Me3P
Me3P
Ni
Ph
Cl
O
R
(74)
Δ
H
Me3P
Ni
C—COR
Cl
C—Ph
PMe3
(75)



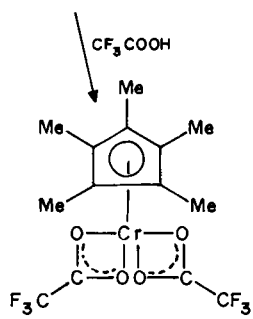
(76a) M = W; X = Me
R^1 = Ph, R^2 = H
R^1 = R^2 = Me
(76b) M = W; X = Me, H
R^1 = R^2 = H
(76c) M = Cr, Mo, W; X = Me
R^1 = R^2 = H



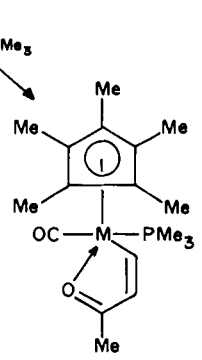
(77)
R^1 = R^2 = Me
R^1 = Ph, R^2 = H



(78) X = H, Me

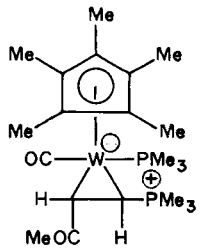


(79)



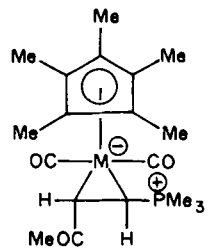
(80) M = Cr

+

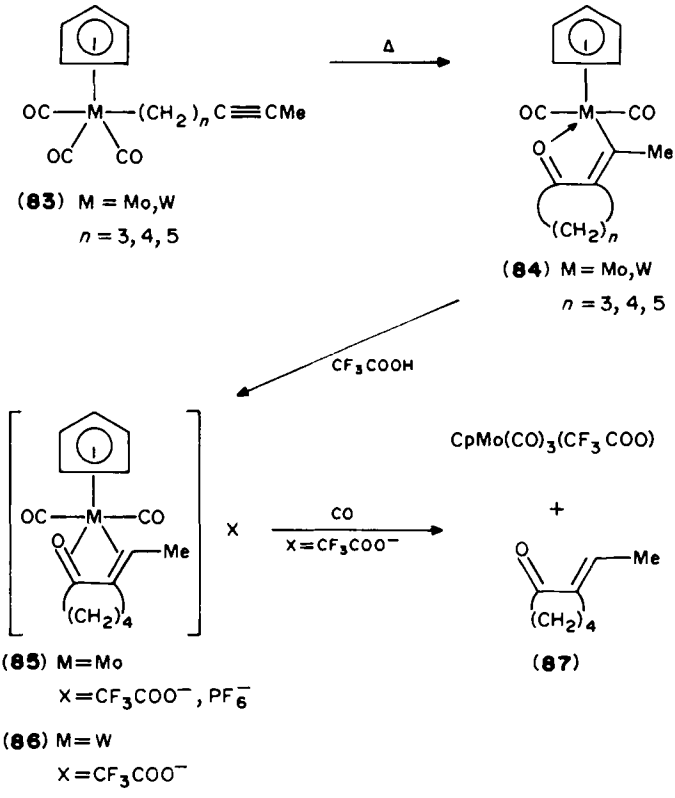


(82)

+



(81) M = Cr, Mo, W



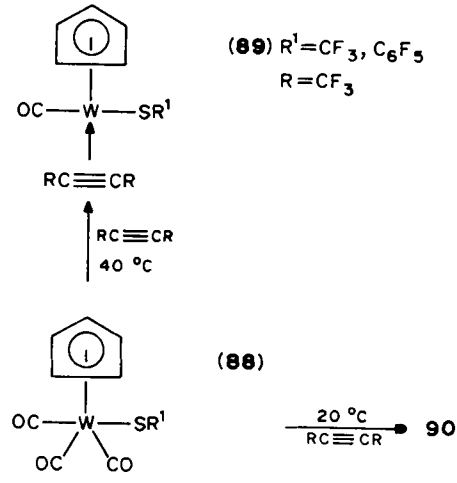
(83) M = Mo,W
$n = 3, 4, 5$

(84) M = Mo,W
$n = 3, 4, 5$

(85) M=Mo
X=CF_3COO^-, PF_6^-

(86) M=W
X=CF_3COO^-

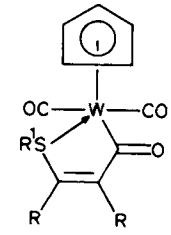
(87)



(89) $R^1=CF_3, C_6F_5$
R=CF_3

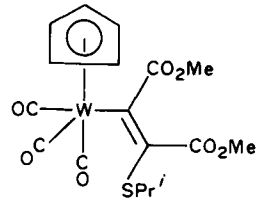
(88)

90



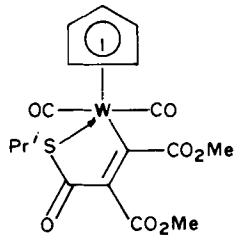
(**90a**) R = CF_3; R^1 = Pr^n
(**b**) R = CF_3; R^1 = Pr^i
(**c**) R = CO_2Me; R^1 = Pr^i
(**d**) R = CF_3; R^1 = Me

60 °C



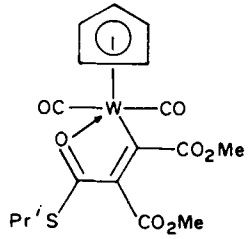
(**93**)

90 °C



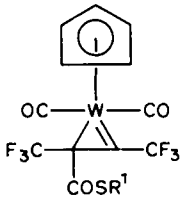
(**94**)

Δ



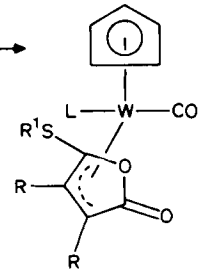
(**95**)

30 °C



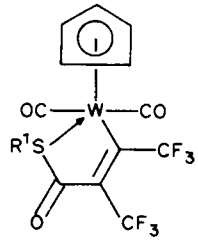
(**91a**) R^1 = Pr^n
(**b**) R^1 = Pr^i

+L
20 °C

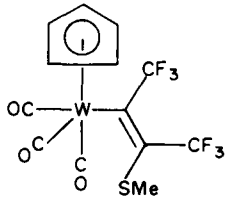


(**96a**) R^1 = Pr^i
L = PMe_2Ph, $P(OMe)_3$, $CNBu^t$, CO
(**b**) R^1 = Me; L = CO

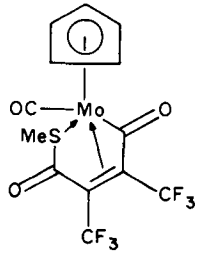
Δ



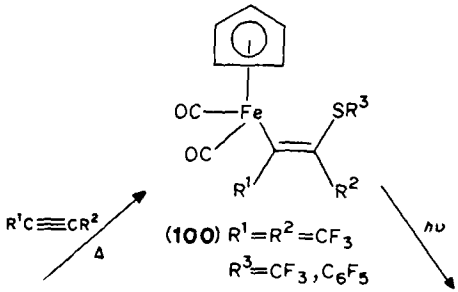
(**92a**) R^1 = Pr^n
(**b**) R^1 = Pr^i
(**c**) R^1 = Me



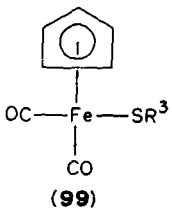
(**97**)



(**98**)

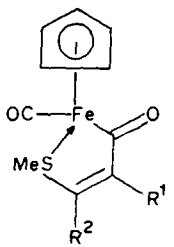


(100) $R^1=R^2=CF_3$
$R^3=CF_3, C_6F_5$



(99)

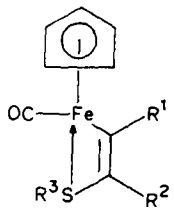
$R^1C\equiv CR^2$, 25 °C



(101a) $R^1=CF_3, R^2=H$

(b) $R^1=R^2=CF_3$

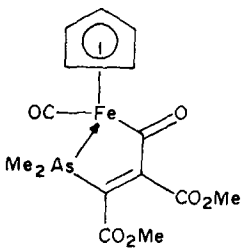
hν



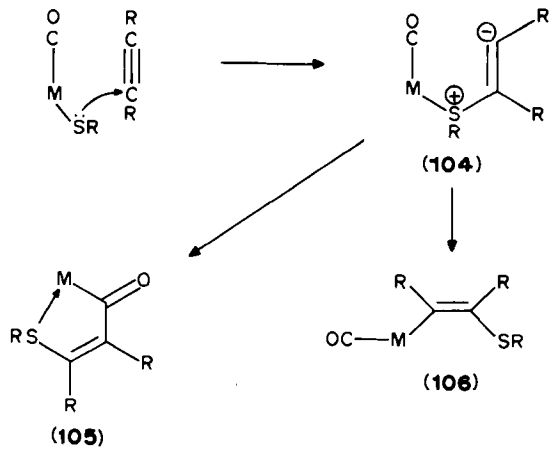
(102a) $R^1=R^2=CF_3$,
$R^3=CF_3, C_6F_5$

(b) $R^1=R^2=CF_3$,
$R^3=Me$

(c) $R^1=CF_3, R^2=H$,
$R^3=Me$

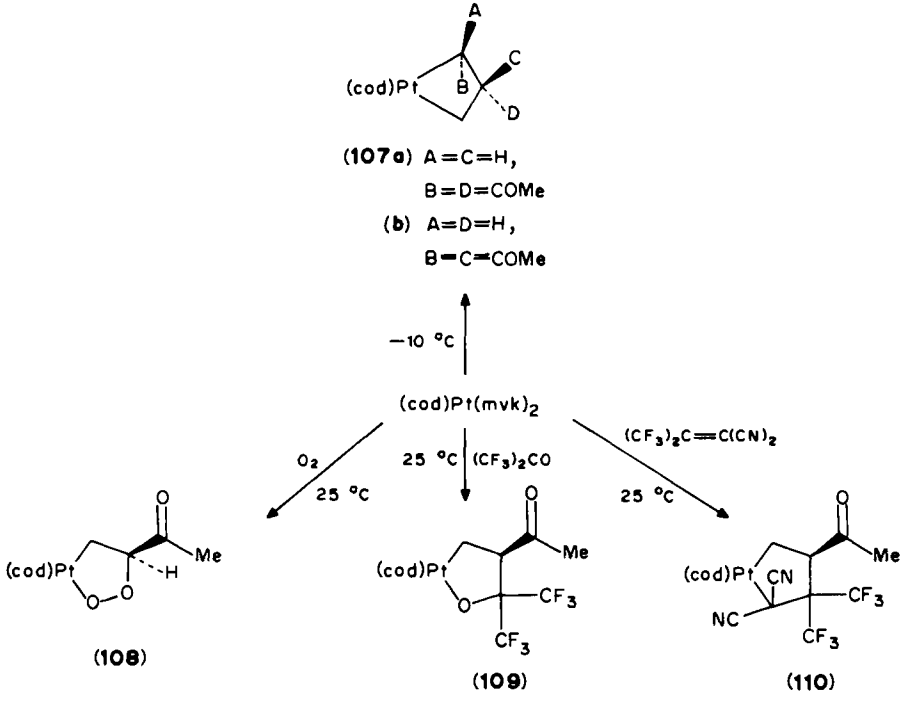


(103)



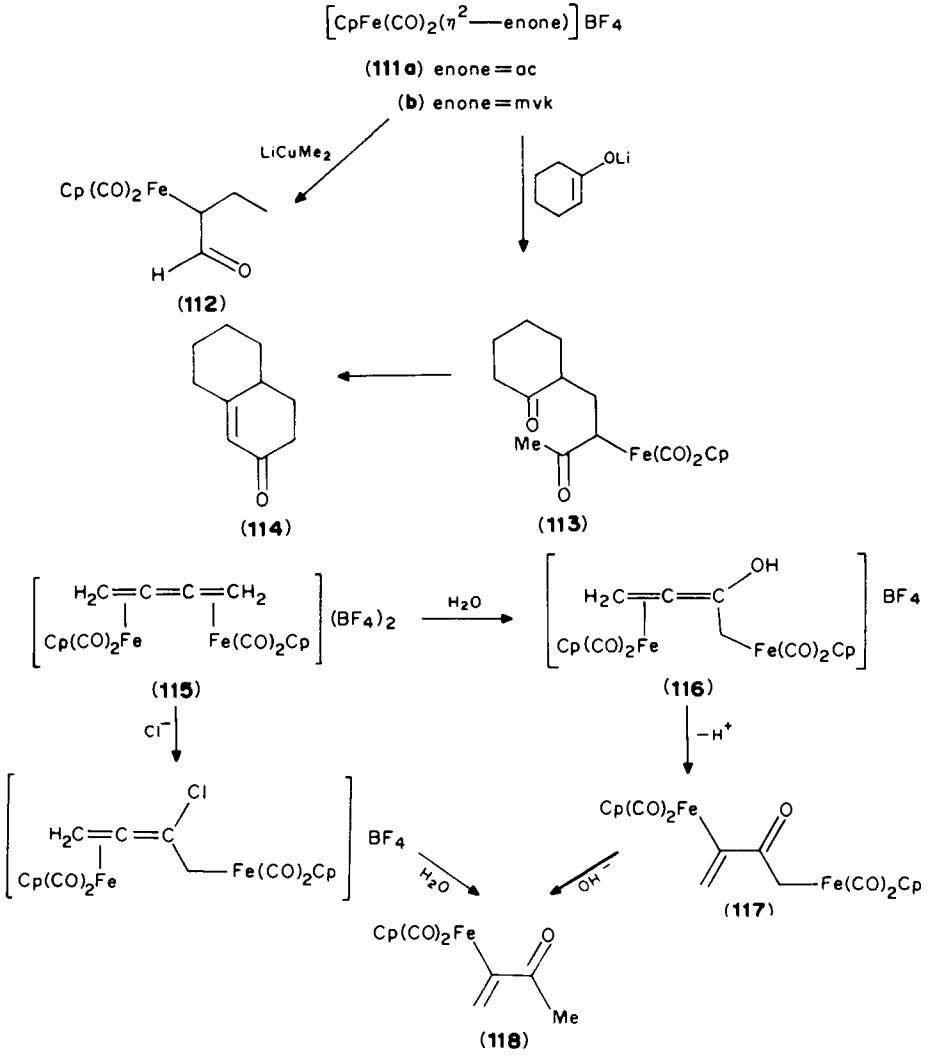
exist; they are not covered here, and are distinguished from enones by their inability to form η^4-complexes.

Structural studies of η^2-complexes indicate a stabilization of the s-*cis* conformation on complexation. Whereas free methyl vinyl ketone and cinnamaldehyde exist predominantly in the s-*trans* conformation[90,91], crystal structures of η^2-mvk complexes reveal only the s-*cis* conformation[92,93], while solution dipole moment studies on (cinn)Fe(CO)$_4$ indicate an s-*cis* ⇄ s-*trans* equilibrium[94].

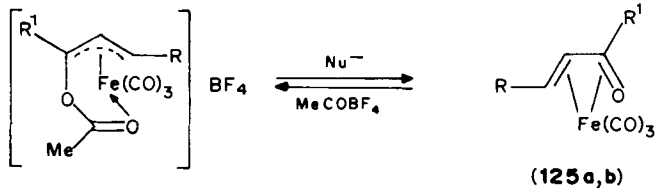


Some aspects of the chemistry of η^2-complexes have been investigated. In the electron-rich (cod)Pt(mvk)$_2$, coupling is induced on mild heating to give the head-to-tail metallocyclopentane as a mixture of isomers (**107a** and **b**), while on treatment with O_2, $(CF_3)_2CO$ or $(CF_3)_2C{=}C(CN)_2$, insertion is accompanied by loss of one mole of mvk to give **108–110**[54].

Like other complexes of its type, [CpFe(CO)$_2$(η^2-enone)]X salts react easily with nucleophiles at the carbon β to the keto group. Treatment of **111a** with $LiCuMe_2$ yields **112**[95], whereas reaction of **111b** with the lithium enolate of cyclohexanone yields **113**, which may be cyclized with loss of metal to the octalone **114**[80]. Such reactions have also been used to generate complexes of structural type **2**. Thus, hydrolysis of the cumulene complex **115** yields sequentially **117** and **118** via initial formation of the unstable enol **116**; complex **118** is also formed by hydrolysis of the related chloride **119**[96,97].

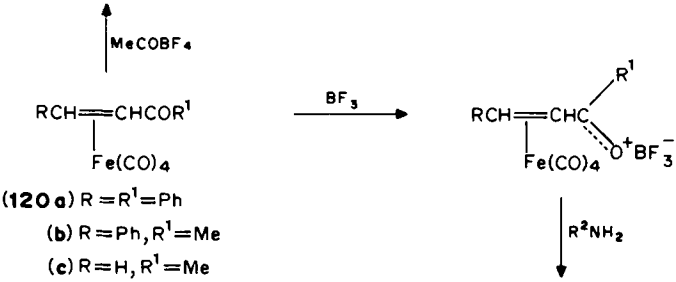


The electrophilic character of the ketonic group is much reduced on complexation of an enone to $Fe(CO)_4$, consistent with the electron-releasing character of this metal fragment; no reaction with amines is observed under conditions where the iron–alkene bond is retained. Adduct formation is, however, observed with BF_3, and further reaction with primary amine generates the carbamoyl chelate complexes **121a, b** which, where R^2 = Me, exist in equilibrium with the η^2-structure **122**; in one case, final conversion to the N-bonded derivative **123** is found[98,99]. Acetylation of **120a, c** proceeds to yield a complex best formulated as **124** which on treatment with nucleophiles generates the η^4-derivative **125**; acetylation of **125** reversibly generates **124**[100].

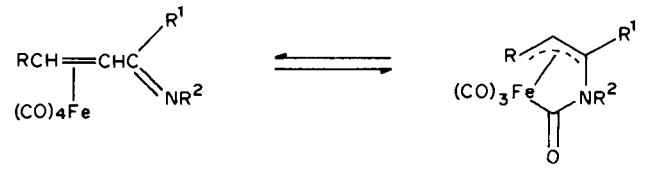


(**124a**) R=H, R^1=Me
(**b**) R=R^1=Ph

(**125a, b**)



(**120a**) R=R^1=Ph
(**b**) R=Ph, R^1=Me
(**c**) R=H, R^1=Me

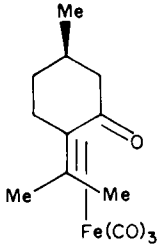


(**122**) R=Ph, R^1=Me
R^2=Pr^i, CH_2Ph, c-Hex

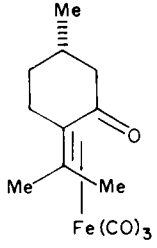
(**121a**) R=R^1=Ph
R^2=Me, c-Hex
(**b**) R=Ph, R^1=Me
R^2=Me, Pr^i, c-Hex, CH_2Ph

(**123**) R=Ph; R^1=R^2=Me

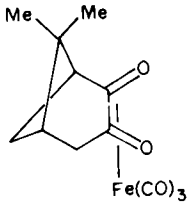
The chemistry of η^4-complexes is primarily concerned with those of tricarbonyliron. Such complexes may be prepared from reaction of the free enone either photochemically with $Fe(CO)_5$[101] or thermally with $Fe_2(CO)_9$[67–70,102,103]. In both cases, (η^2-enone)$Fe(CO)_4$ complexes of varying stability are formed initially; thermally, these undergo transformation on mild heating to the η^4-complex. A kinetic study shows, however, that this proceeds via rate-determining dissociation to enone and $Fe(CO)_4$ followed by rapid CO loss and recoordination of the enone in the η^4-mode[104]. For enones not possessing a symmetry plane, such as pulegone, isomers **126a** and **126b** may be isolated which differ in the orientation of the $Fe(CO)_3$ moiety, though for sterically crowded enones such as pinocarvone, only the single isomer **126c** is isolated[70]. Crystal structures of (pinocarvone)$Fe(CO)_3$[70], (cinn)$Fe(CO)_3$[105] and (bda)$Fe(CO)_3$[106] show these complexes to have the distorted square pyramidal geometry typical of the wider class of (η^4-diene)$Fe(CO)_3$ complexes. In solution, fluxional behaviour involving rotation of the enone relative to the $Fe(CO)_3$ moiety is observed. The barriers to rotation are higher than those for similar (diene)$Fe(CO)_3$ derivatives[107], and together with ^{57}Fe NMR[108] and dipole-moment measurements[109], indicate a greater π-acceptor character for enone relative to diene. Crystal structures of (cinn)$Fe(CO)_2PPh_3$[110], (bda)$Fe(CO)_2L$ ($L = PEt_3$, $PPhMe_2$)[111], and the related (thioacrolein)$Fe(CO)_2PPh_3$[112] show a similar square pyramidal geometry. In the solid state, the phosphine occupies the axial position, though in solution, axial/basal isomeric mixtures are found which interconvert rapidly by enone rotation[113]. The oxidation potentials of (bda)$Fe(CO)_2L$ complexes (L = phosphine) correlate well with the basicity of the phosphine[114].



(126a)

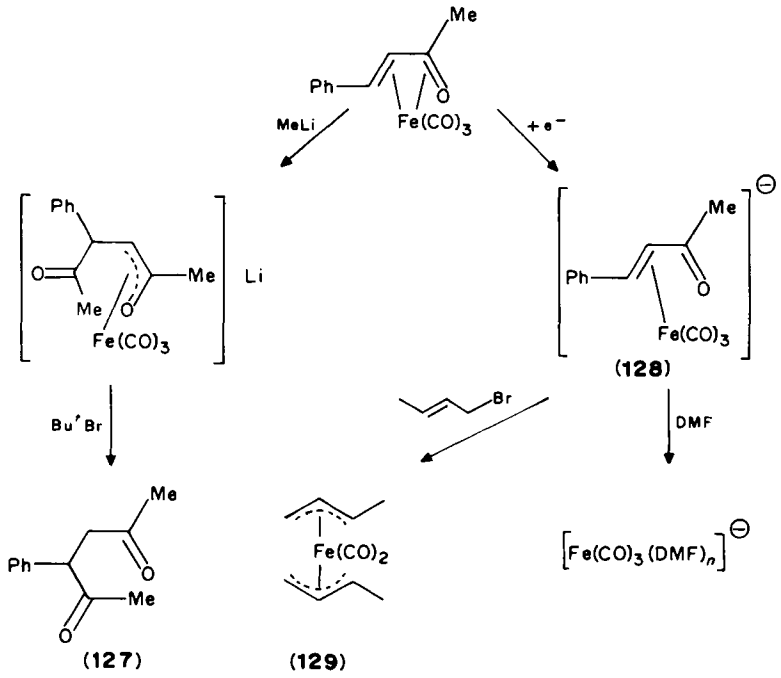


(126b)



(126c)

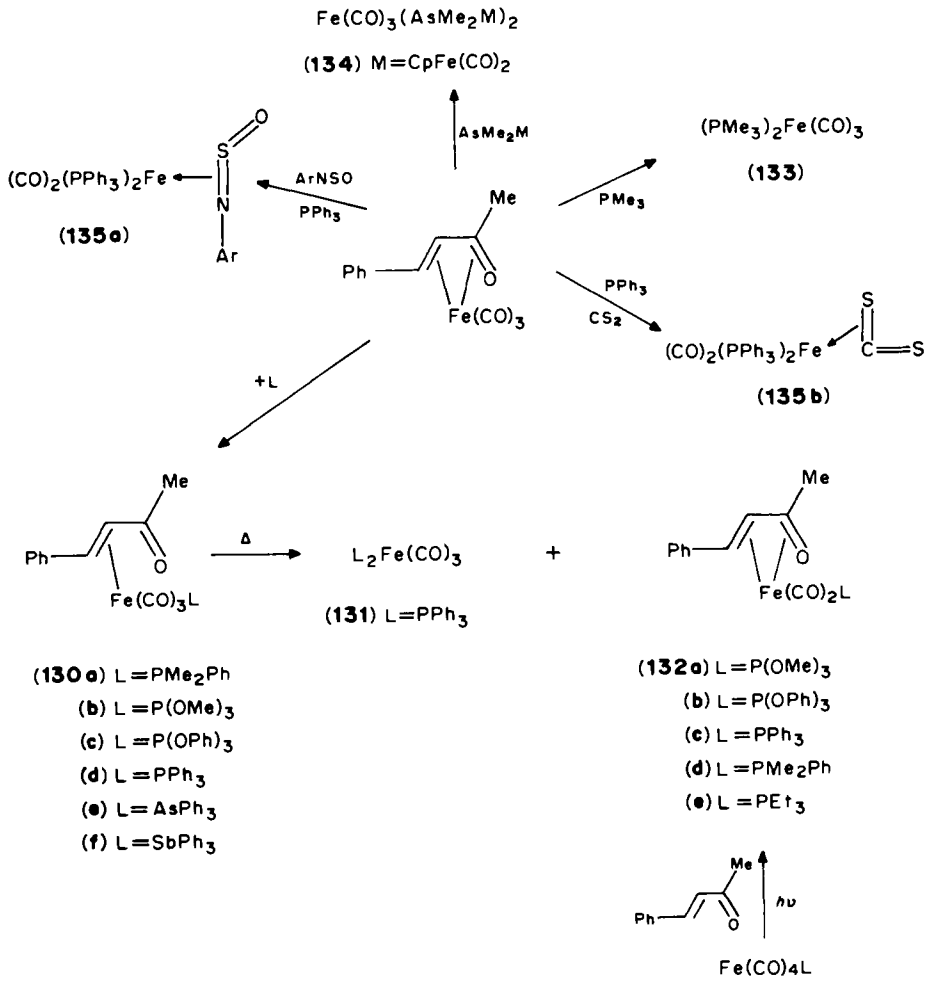
Little has been reported on the reactivity of the bound enone. Electrophilic attack at oxygen has already been noted in the acetylation of **125a, b**, while nucleophilic attack appears to proceed via addition to carbon monoxide to yield, after quenching with the proton source Bu^{t}Br, the diketone **127**[115]. Electrochemical reduction yields a radical anion assigned an η^2-coordination **128**. Treatment with crotyl bromide yields **129**, whereas the enone is liberated in donor solvents such as dimethylformamide to give a reactive solvated $Fe(CO)_3$ radical anion[116].



The great utility of these complexes lies in their substitutional lability towards group V donors (phosphines and phosphites) and conjugated dienes. Reaction of (bda)$Fe(CO)_3$ with ligand(L) proceeds to yield isolable (η^2-bda)$Fe(CO)_3L$ complexes **130a–c**[72,73,117] while **130d–f** may be observed *in situ*; all reactions proceed to completion except that with $SbPh_3$, in which a (bda)$Fe(CO)_3$/(**130f**) equilibrium is established[118]. For the phosphite derivatives, re-chelation of the enone occurs smoothly to yield **132a, b**[74], whereas with PPh_3, the reaction is accompanied by concomitant formation of $(PPh_3)_2Fe(CO)_3$ **131**[118]. Indeed, in the presence of excess ligand, this reaction may be used to advantage to produce $L_2Fe(CO)_3$ complexes such as **133** and **134**[119,120]. Complexes such as **132c–e** are best prepared by photolysis of $Fe(CO)_4L$ in the presence of enone[75,111,121]. Reaction of (bda)$Fe(CO)_3$ with *p*-nitrosulphinylaniline or CS_2 in the presence of PPh_3 yields the novel η^2-complexes **135a, b** respectively[122,123].

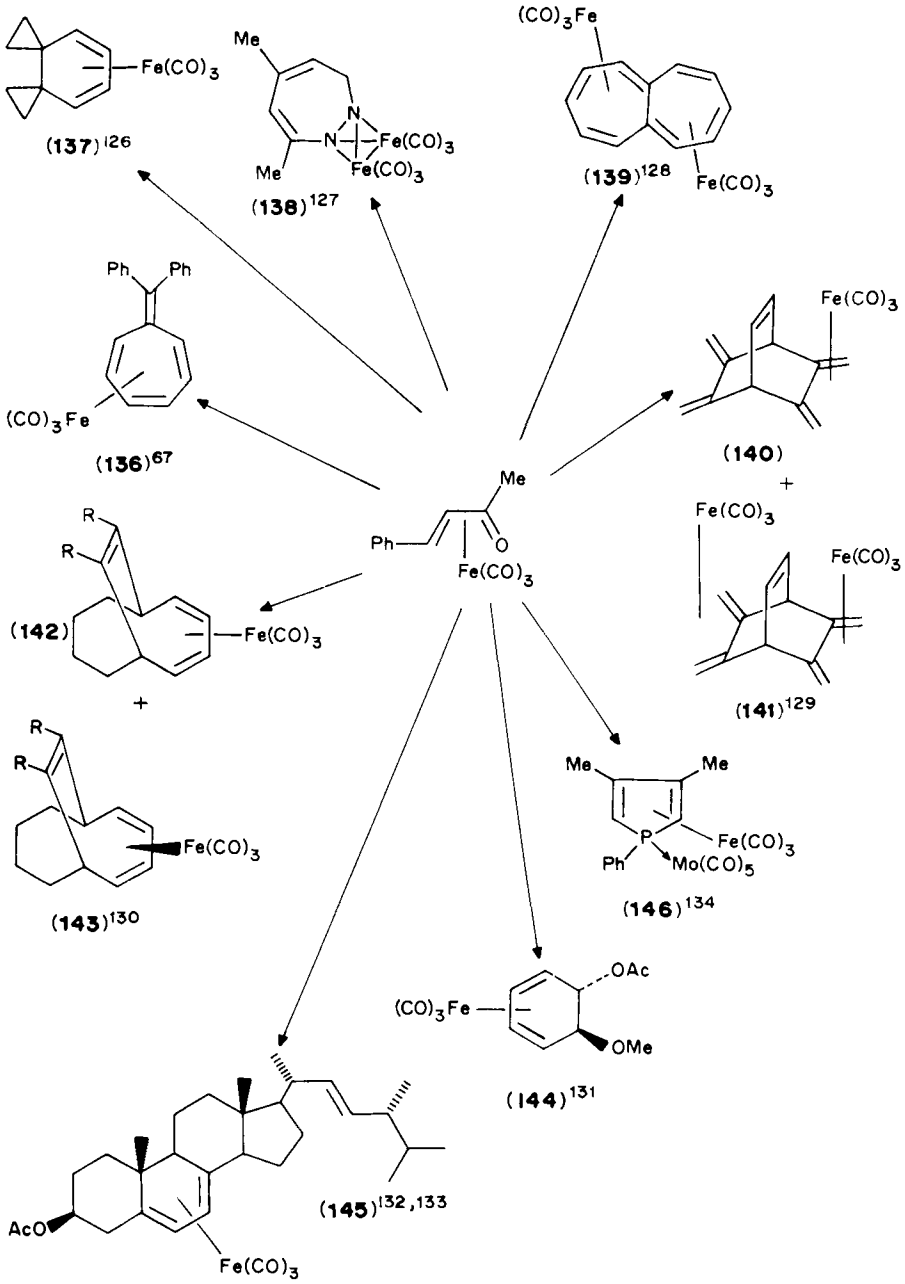
Exchange with cyclic and acyclic conjugated dienes proceeds smoothly to yield the (η^4-diene)$Fe(CO)_3$ complex[124,125]. The mild conditions required (50–80 °C, toluene) make this the reaction of choice for dienes sensitive to heat or light, and several examples are shown below. Dienes not containing a plane of symmetry can give isomeric mixtures; thus, where R = H, both **142** and **143** are isolated, whereas when R = Me, only the less sterically hindered **142** is obtained. The isolation of exclusively **144** may perhaps be ascribed to initial interaction with the ester group, followed by transfer of $Fe(CO)_3$ to the same face. (Bda)$Fe(CO)_3$ also functions as a reactive source of $Fe(CO)_3$ in the ring opening of methylenecyclopropenes, alkyne coupling to give **149**, and CO elimination to give the *o*-xylylene complex **150**.

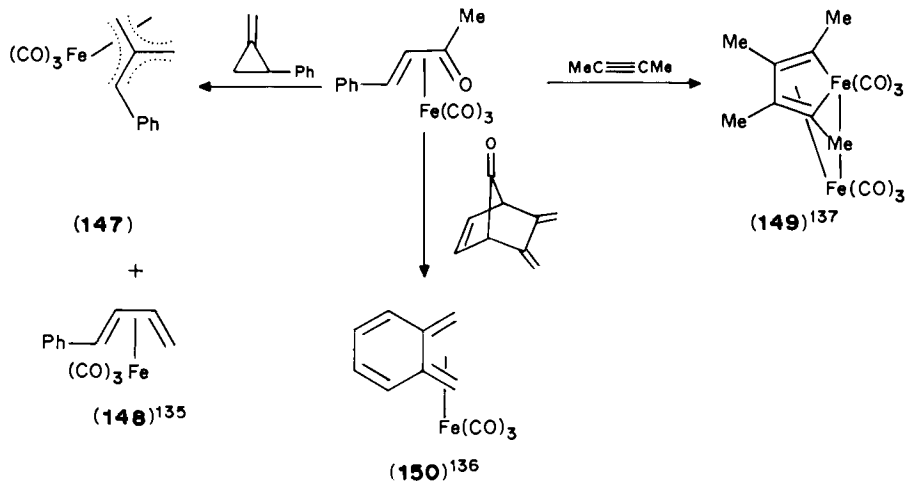
The high selectivity towards cyclic dienes, and cyclohexadiene in particular, may be used in the extraction of unstable tautomers from C_6-diene/C_8-triene equilibria. Thus, although the concentration of diene in the **151** ⇄ **152** and **154** ⇄ **155** equilibria is small, only **153** and **156** are isolated from reaction with (bda)$Fe(CO)_3$[101,138,139]. The unstable



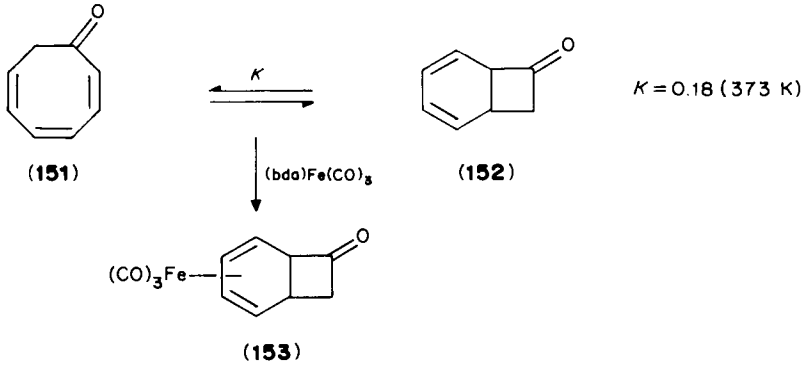
tautomers may be released by low-temperature oxidation. Diene exchange is also observed with (enone)$Fe(CO)_2L$ complexes such as **132c–e**, though at much reduced rates[140]. Lateral coordination of the $Fe(CO)_3$ moiety confers chirality on complexes of unsymmetrically substituted dienes such as **157**, and diene exchange using chiral enones such as (−)-cholest-4-ene-3, 6-dione or (−)-3β-(acetyloxy)pregna-5, 16-dien-20-one proceeds with significant asymmetric induction to give enantiomeric excesses of up to 43%[141].

Structural and chemical data on other η^4-complexes is sparse. $W(mvk)_3$, which has a trigonal prismatic geometry in common with $W(butadiene)_3$[142,143], reacts with Ph_3PCH_2 to yield a complex of formula $W(CH_2PPh_3)_3$ with loss of mvk[144]. $Mo(CO)_2(ac)_2$ is initially isolated as a soluble monomer, but deposits a polymer on standing in which acrolein is thought to act as a bridging ligand between metal atoms. Such a four-electron donation, bridging two metals in the *s-trans* configuration, has been structurally characterized in the two copper complexes $Cu_4Cl_4(mvk)_4$ (**158**)[93] and $[CuCl(ac)]_n$ (**159**)[145]. The enone is weakly bound, and the coordination observed may be relevant to copper-catalysed conjugate addition reactions of enones.

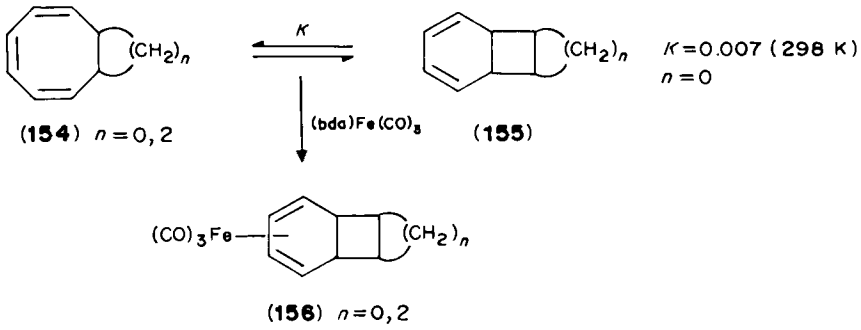

Fe(CO)3
(137)126
Me
N
N
Fe(CO)3
Me
Fe(CO)3
(138)127
(CO)3Fe
(139)128
Fe(CO)3
Ph
Ph
(CO)3Fe
(136)67
Fe(CO)3
(140)
+
Me
Ph
O
Fe(CO)3
R
R
(142)
Fe(CO)3
+
Fe(CO)3
Fe(CO)3
(141)129
R
R
Fe(CO)3
(143)130
Me
Me
P
Fe(CO)3
Ph
Mo(CO)5
(146)134
OAc
(CO)3Fe
OMe
(144)131
AcO
Fe(CO)3
(145)132,133



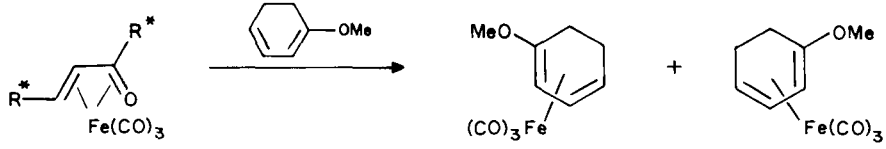
(147) + (148)[135] (149)[137] (150)[136]



(151) (152) (153)



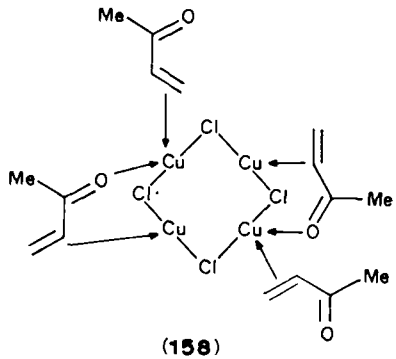
(154) $n = 0, 2$ (155) (156) $n = 0, 2$



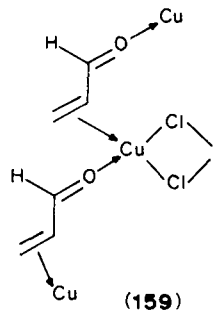
R*= chiral centre(s)

(157a) (1R)-(−)

(157b) (1S)-(+)



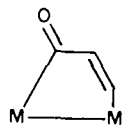
(158)



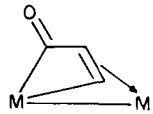
(159)

IV. ENONES IN POLYMETALLIC COMPLEXES

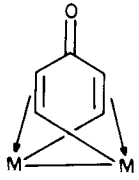
Polymetallic complexes containing bound enones may also be derived from either CO/alkyne coupling or by reaction of an enone with a metal substrate. The former most commonly yields coordination geometries represented in their simplest form by the mono- and dimetallacyclic structures **160** and **161**, though structural types **162** and **163** derived formally from addition of a further mole of alkyne have also been observed.



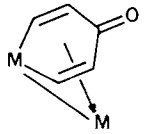
(160)



(161)

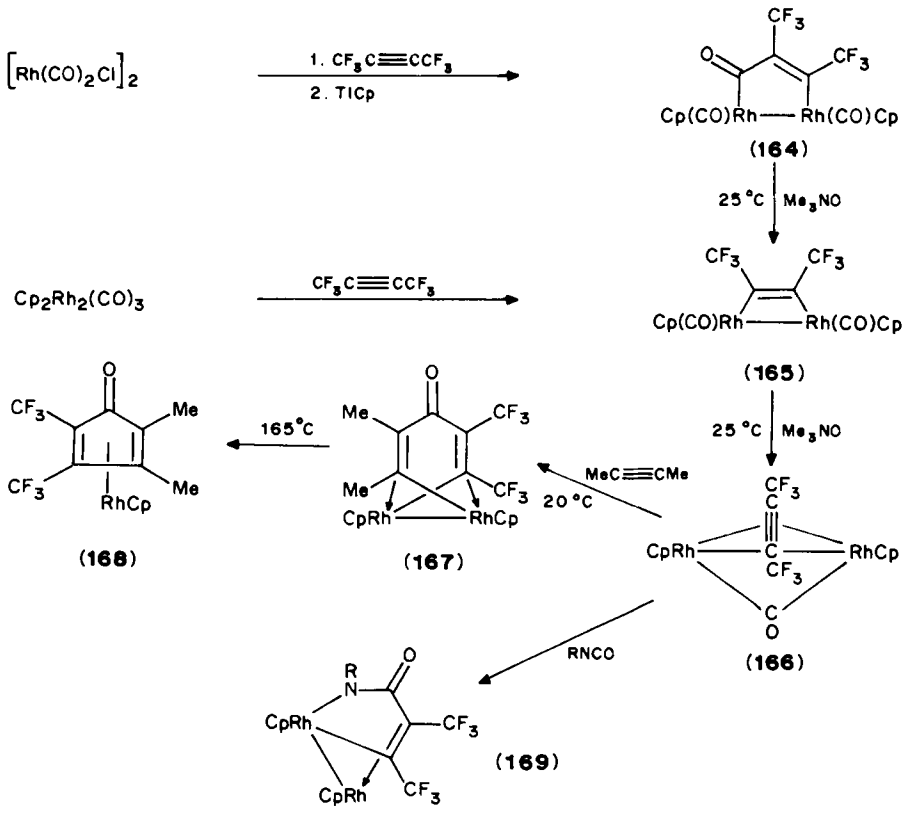


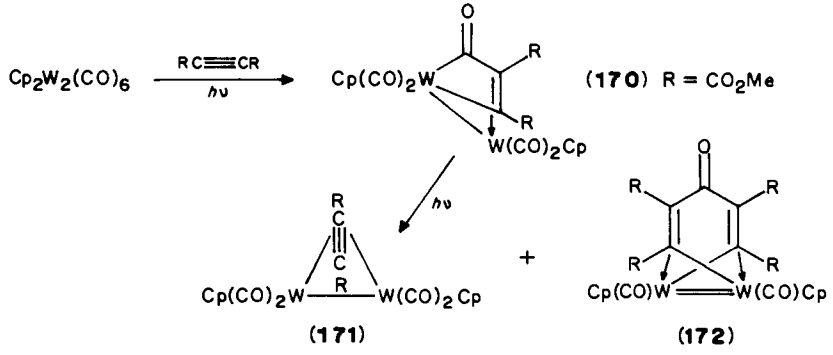
(162)

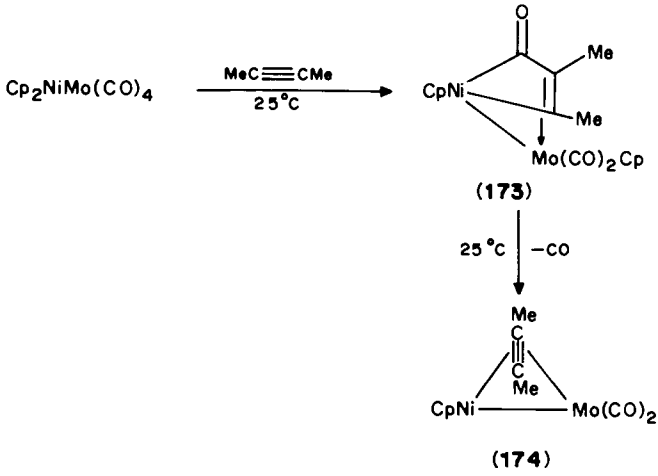


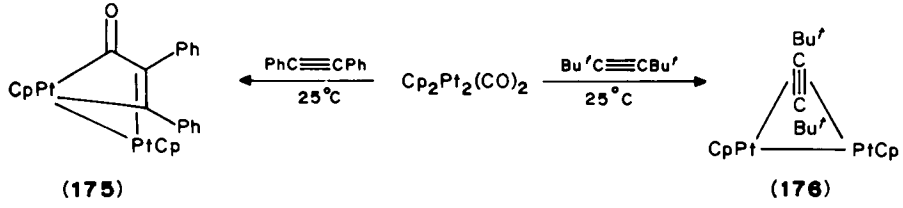
(163)

Reaction sequences which illustrate these structures are shown below. In most cases, the equations greatly underestimate the complexity of the reaction and, in particular, do not show the plethora of products derived from alkyne coupling without CO incorporation. Thus, complex **164** undergoes facile loss of CO to give **165** [also available from direct reaction of $Cp_2Rh_2(CO)_3$ with alkyne] containing a two-electron alkyne bound parallel to the M–M axis. Further loss of CO yields the four-electron transversely bounded complex **166** which, on reaction with 2-butyne, undergoes alkyne/CO coupling to give the 'flyover' complex **167**. Thermolysis results in ring closure to the cyclopentadienone derivative **168**[146,147]. Treatment of **166** with isocyanate also results in coupling to give the amide **169**[148]. Reaction with analogous cobalt systems proceeds directly to the complex of structure **168**[149,150]. $Cp_2W_2(CO)_6$[151], the mixed metal dimer $Cp_2NiMo(CO)_4$[152] and

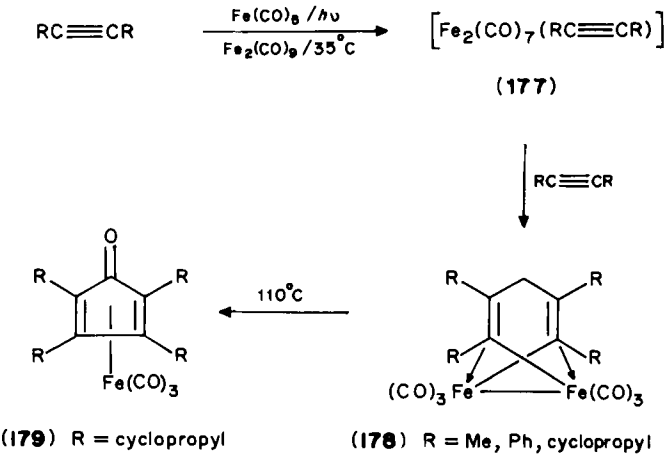








$Cp_2Pt_2(CO)_2$[153] react with alkynes to yield complexes of structural type **162**. Both **170** and **173** undergo CO loss to give transversely bonded alkyne complexes, while small amounts of **172** may also be isolated. Reaction of $Cp_2Pt_2(CO)_2$ with $Bu^tC{\equiv}CBu^t$ proceeds directly to the alkyne complex **176**. Reaction of iron carbonyls with alkynes initially yields unstable complexes of stoichiometry **177**; addition of a further mole of alkyne to give **178** is followed by ring closure to the cyclopentadienone **179** on thermolysis[154–156].

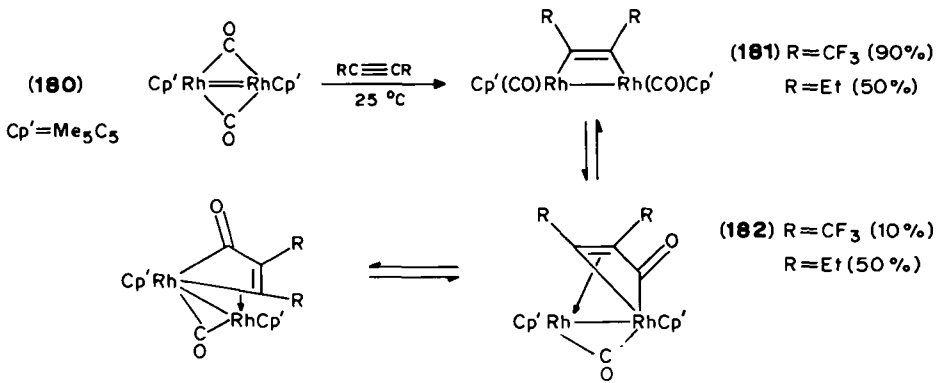


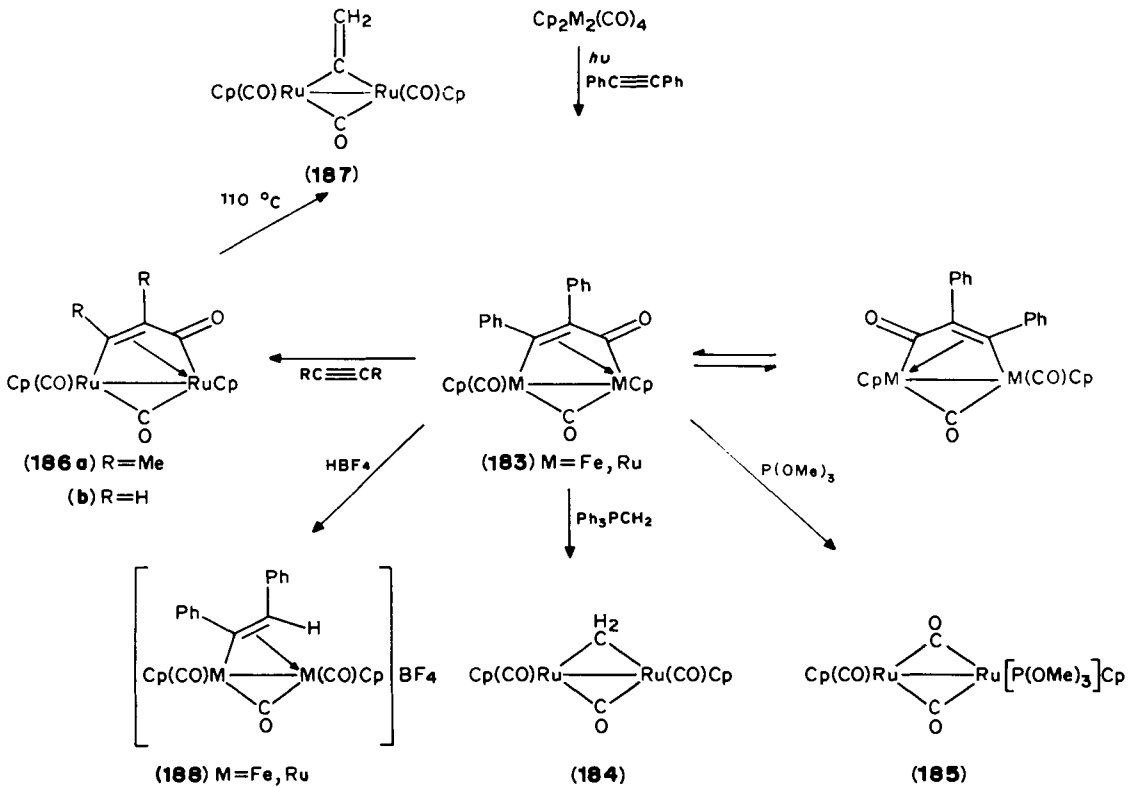
(179) R = cyclopropyl (178) R = Me, Ph, cyclopropyl

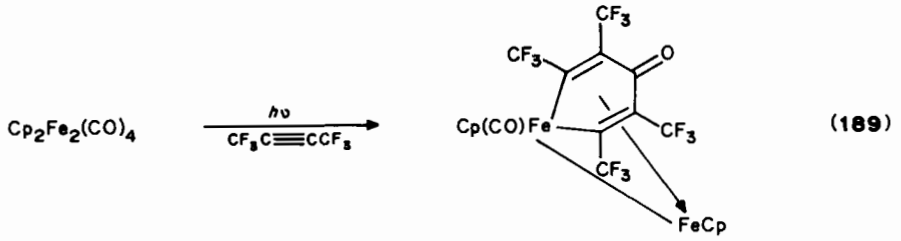
Reactions can be quite sensitive to an auxiliary ligand; thus, treatment of **180** with alkyne yields **181**, the pentamethylcyclopentadienyl analogue of **165**. In contrast, **181** exists in rapid equilibrium with **182** in proportions which depend on the alkyne substituent; the rapid M—CO/acyl interconversion is further demonstrated by the fluxional interconversion of the rhodium atoms in **182**[157,158]. A similar facile acyl flipping is evident in **183**; in the ruthenium complex, this is also manifest by facile loss of PhC≡CPh on reaction with two-electron ligands to give **184** and **185**, and in exchange with other alkynes to give **186a, b** which are not directly accessible from $Cp_2Ru_2(CO)_4$[159–161]. Thermolysis of **186b** results in isomerization to **187**[162], while the protonation of **183**[163] may be compared to that of **22d**. Examples of structural type **164** are provided by complexes **189**[164] and **190**; the latter undergoes CO loss on thermolysis to give the metallacyclopentadiene **191**[165,166].

In contrast, reaction of $Co_2(CO)_8$ with alkynes under CO results in coupling of two moles of CO with one of alkyne to yield the butenolide **193**. The reaction proceeds via the $Co_2(CO)_6$(alkyne) complex **192** and is regiospecific in the case of terminal alkynes, incorporating hydrogen into the position α to the bridging carbon[167,168]. Treatment of **193** with a further mole of propyne releases the "bifurandione" **194**, mainly as the *trans*-dimethyl isomer[169]. Reaction of the alkyne complex **192** with alkenes provides an efficient synthesis of cyclopentenones; with asymmetric alkynes, the substituent is incorporated regiospecifically α to the ketone group (as in **195**)[170], though isomeric mixtures are obtained on reaction with unsymmetrical alkenes (as in **196a, b**)[171].

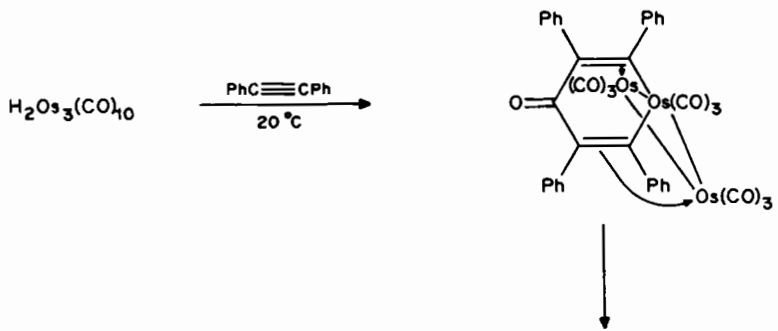
Reactions of clusters or cluster precursors with enones generally proceed by oxidative addition of the β-vinylic hydrogen and, in the case of aldehydes, oxidative addition of the aldehydic C—H. Thus, treatment of α,β-unsaturated ketones with $Os_3(CO)_{10}(NCMe)_2$ yields complexes of structure **197** whereas with aldehydes, complex **198** is also formed. Methyl vinyl ketone is unique, forming initially the linear cluster **199** which thermally isomerizes to **202**, related to **197** by internal chelation of the C=C bond. The higher energy isomeric forms **200** and **201a** may be formed under milder conditions by reaction of HC≡CCOMe with $H_2Os_3(CO)_{10}$, but isomerize thermally to **199**. Complex **201b** is formed in the analogous reaction of $H_2Os_3(CO)_{10}$ with PhC≡CCHO[172,173]. The ruthenium dimer **203** with an enone coordination similar to **202** has been prepared[174], while complexes such as **205**, containing an enone coordination similar to **198**, have been isolated from carbon monoxide insertion into bridging vinyl derivatives such as **204**[175]. The bridged phosphido derivative **206** undergoes CO/alkyne coupling on reaction with PhC≡CPh to give **207**, similar in coordination to **169**[176].


(180)
Cp'=Me5C5
Cp'Rh
RhCp'
RC≡CR
25 °C
Cp'(CO)Rh
Rh(CO)Cp'
(181) R=CF3 (90%)
R=Et (50%)
(182) R=CF3 (10%)
R=Et (50%)


Cp2M2(CO)4
hν
PhC≡CPh
(187)
110 °C
RC≡CR
(186 a) R=Me
(b) R=H
(183) M=Fe, Ru
HBF4
Ph3PCH2
P(OMe)3
(188) M=Fe, Ru
(184)
(185)

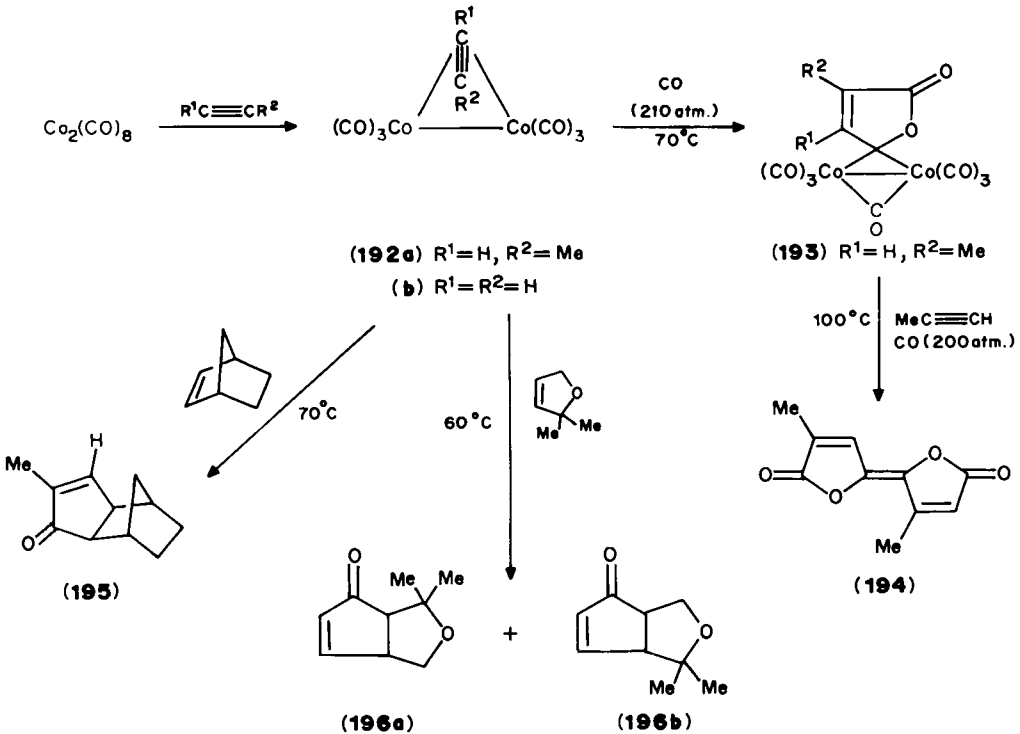

Cp2Fe2(CO)4
hν
CF3C≡CCF3
CF3
CF3
O
Cp(CO)Fe
CF3
CF3
FeCp

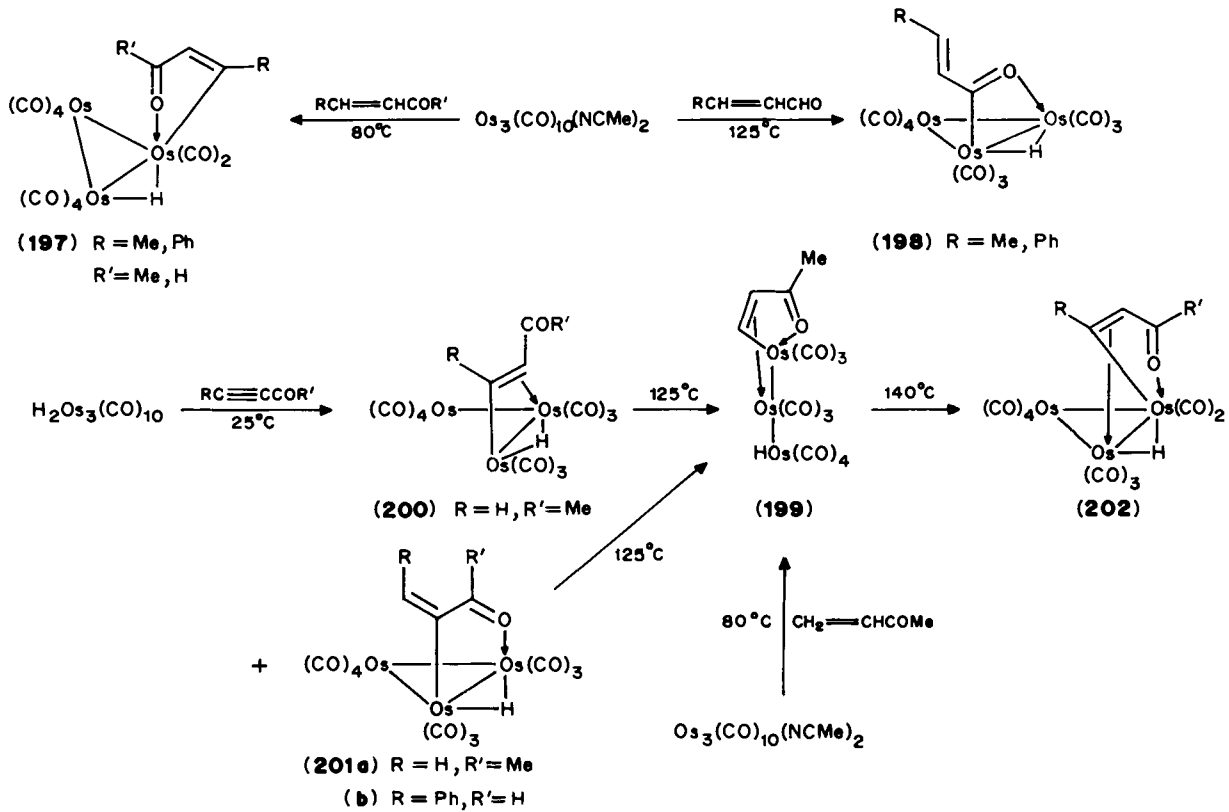
(189)

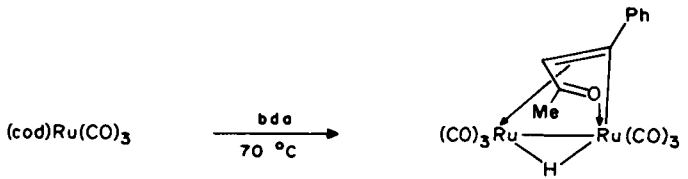

H2Os3(CO)10
PhC≡CPh
20 °C
Ph
Ph
(CO)3Os
O
Os(CO)3
Ph
Ph
Os(CO)3
Ph
Ph
(CO)3
Os
Ph
Os
(CO)3
Os(CO)3

(190)

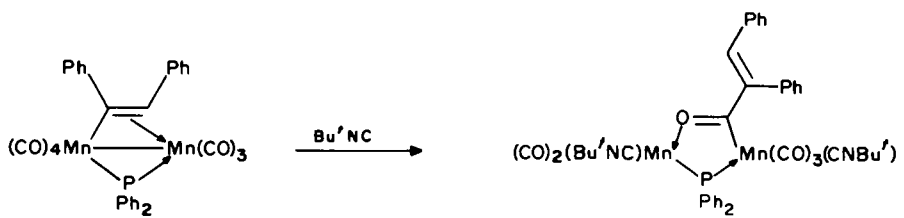
(191)


Co2(CO)8
R1C≡CR2
(CO)3Co
Co(CO)3
CO
(210 atm.)
70°C
(192a) R1=H, R2=Me
(b) R1=R2=H
(193) R1=H, R2=Me
100°C
MeC≡CH
CO(200 atm.)
70°C
60°C
(195)
(196a)
(196b)
(194)

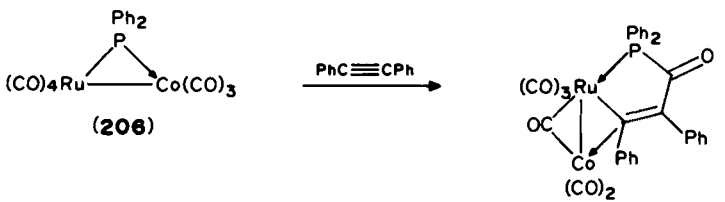

RCH=CHCOR'
80°C
Os3(CO)10(NCMe)2
RCH=CHCHO
125°C
(197) R = Me, Ph
R' = Me, H
(198) R = Me, Ph
H2Os3(CO)10
RC≡CCOR'
25°C
(200) R = H, R' = Me
125°C
(199)
140°C
(202)
125°C
80°C
CH2=CHCOMe
Os3(CO)10(NCMe)2
(201a) R = H, R' = Me
(b) R = Ph, R' = H



(203)



(204) (205)



(206) (207)

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The Chemistry of Enones
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CHAPTER **20**

Dienols (enolization of enones)

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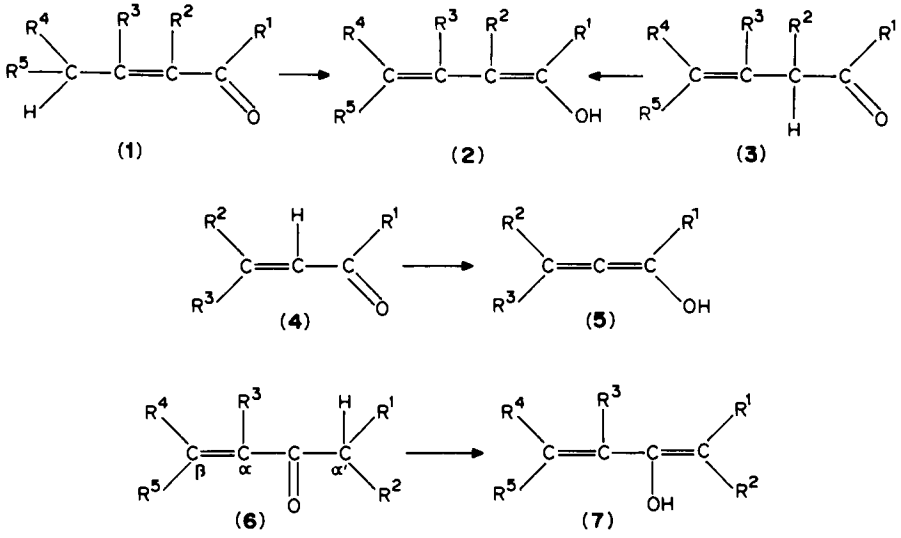
I. INTRODUCTION

This chapter is mainly concerned with the chemistry of 1,3-dien-1-ols (**2**) which may formally be generated by the enolization of α,β- (**1**) or β,γ- (**3**) unsaturated carbonyl compounds. This may be achieved either thermally with the aid of catalysts, or photochemically. As photoenolization was reviewed by Sammes in 1976[1] and by Wagner in 1980[2] only the properties of the dienols obtained by photoenolization will be considered in this chapter, not the details of the photoenolization process.

α,β-Unsaturated carbonyl compounds with a proton attached to the α-carbon (**4**) may formally also undergo enolization to yield 1,2-dienols (**5**), and α,β-unsaturated ketones with a hydrogen at the α'-position (**6**) may formally enolize to 1,3-dien-2-ols (**7**).

For many years dienols and their anions could only be studied indirectly, usually by studying the reactions of enones and inferring the properties of the presumed dienol and dienolate intermediates. Many of the results reported in this chapter will be of this type. However, more recently methods have become available for generating dienols in the gas phase and in solution, so that they can be detected spectroscopically and sometimes isolated; hence direct measurements of their properties are now possible.



II. THE 1,3-BUTADIEN-1-OLS

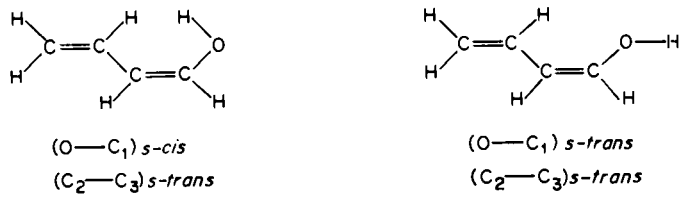
A. Conformations and Relative Stabilities

The simplest 1,3-dienols are (*Z*)- and (*E*)-1,3-butadien-1-ol (**2**, R^1, R^2, R^3, R^4, R^5 = H). Four planar conformations for each of these are possible, depending on the orientation around the O—C_1 and C_2—C_3 bonds (see Scheme 1). In addition there are an infinite number of non-planar *gauche* conformations. As discussed below (Section II.C) the ^{1}H-NMR spectra indicate that, in solution, the stable conformation of the (*E*)-isomer is *s-cis, s-trans* and of the (*Z*)-isomer, *s-trans, s-trans.*

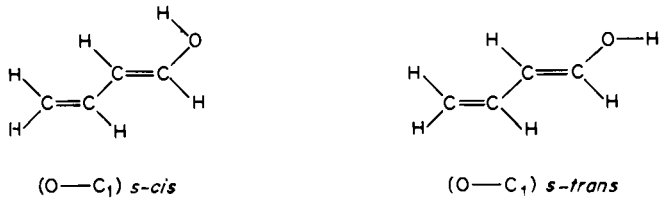
Calculations of the relative energies of (*Z*)- and (*E*)-1,3-butadien-1-ols in their less stable (C_2—C_3)*s-cis* conformations have been reported in two papers whose main purpose was to elucidate the mechanism of photoenolization[3,4]. The *ab initio* methods (STO-3G, 4–31G basis sets)[4] give the *Z*-dienol as more stable by 4–5 kcal mol^{-1}. This is much larger than would be expected on the basis of the experimental heats of formation[5,6], presumably because the enols exist mainly in the (C_2—C_3)*s-trans* conformation. MNDO calculations were reported for these[5,6] and they agree quite well with the experimental heats of formation, but neither these calculations nor the experimental results are sufficiently accurate to determine where (*Z*)- or (*E*)-1,3-butadien-1-ol is more stable. However, if the corresponding ethyl ethers can be taken as a model, the (*E*)-dienol would be expected to be slightly more stable as (*E*)-1,3-butadienyl ethyl ether is more stable than its (*Z*)-isomer with $\Delta H° = 0.92$ kcal mol^{-1} at 25 °C in hexane[7].

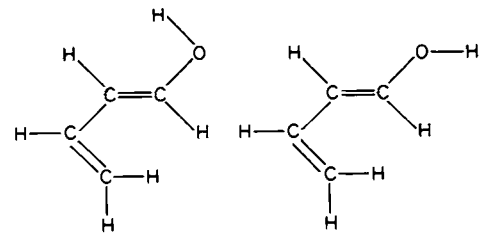
B. Generation in the Gas Phase

A 1,3-butadien-1-ol was postulated as an intermediate in the gas-phase photoisomerization of crotonaldehyde into 3-butenal[8] and tentatively assigned as one of the products of the gas-phase photolysis of crotonaldehyde on the basis of its IR spectrum ($\nu = 3630, 1100\,cm^{-1}$)[9]. Turečck and coworkers[5] generated (*Z*)- and (*E*)-butadien-1-ol by high vacuum flash pyrolysis of the Diels–Alder adducts **8** and **9**. The deuterium-labelled dienols with deuterium on oxygen and on C_1 were also generated from labelled precursors.



(*Z*)-1,3-Butadien-1-ol



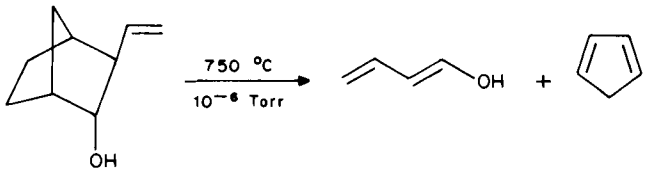


(*E*)-1,3-Butadien-1-ol

SCHEME 1. Planar conformations of (*Z*)- and (*E*)-1,3-butadien-1-ols

The dienols, mixed with a maximum of 10–15% crotonaldehyde, were characterized by their 75 eV electron-impact mass spectra and by the collision-induced decomposition spectra of their molecular ions[10]. The EI mass spectra of the (*Z*)- and (*E*)-isomers showed only small differences and the main basis for the assignment of stereochemistry was the known stereospecificity of the retro-Diels–Alder reaction and the expected high energy of

activation for the E–Z isomerization. The heats of formation of the dienols were estimated from their threshold ionization energies and the heats of formation of the corresponding cation radicals to be $\Delta H^{\circ}_{f,298}(E) = -21 \pm 2$ kcal mol^{-1} and $\Delta H^{\circ}_{f,298}(Z) = -21.5 \pm 2$ kcal mol^{-1}. They are therefore less stable than the conjugated aldehyde, crotonaldehyde, for which $\Delta H^{\circ}_{f,298} = -25.6$ kcal mol^{-1} but more stable than the non-conjugated 3-butenal for which $\Delta H^{\circ}_{f,298}$ was estimated to be -80 kJ mol^{-1} by applying Benson's additivity rules. It was calculated that the barrier of intramolecular ketonization was too high for this to be a viable pathway for formation of crotonaldehyde (or its Z-isomer) under the conditions used and that the 10–15% of crotonaldehyde detected must have been formed by a surface catalysed process.



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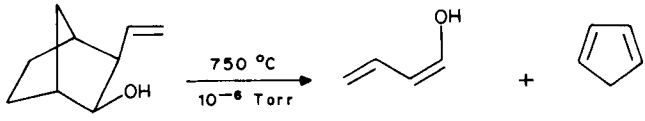


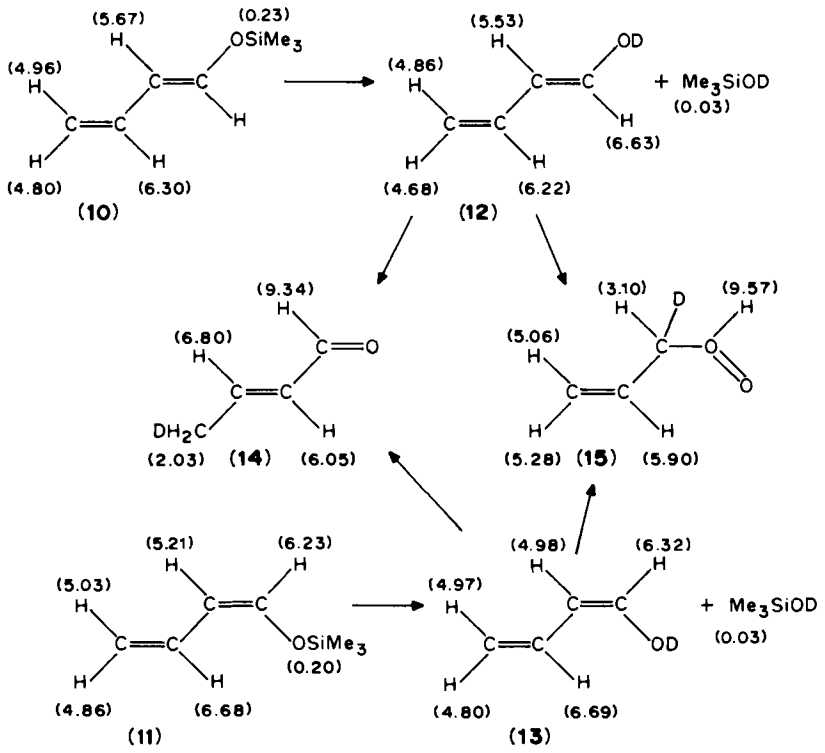
(9)

C. Generation in Solution

(E)- and (Z)-[O-^{2}H]-1,3-butadien-1-ol (**12** and **13**) have been generated in solution by hydrolysis of their trimethylsilyl derivatives (**10** and **11**) in CD_3CN:D_2O (9:1 v/v) which contained DCl (3.16×10^{-3} M) at 32 °C. The ^{1}H NMR spectral changes indicated in Scheme 2 took place. With both isomers, after 1 hour the signals of their trimethylsilyl groups at $\delta = ca\ 0.2$ had disappeared completely and been replaced by a signal at $\delta = 0.03$ ascribed to trimethylsilanol or hexamethyl disiloxane[11]. Only small changes were observed in the rest of the spectra which were ascribed to the (E)- and (Z)-[O-^{2}H]-1,3-butadien-1-ol. These were stable in solution for several hours but were slowly converted, by γ- and δ-deuteriation respectively, into a mixture of the deuteriated (E)-2-butenal and 3-butenal (**14** and **15**).

The coupling constant J_{2-3} in the ^{1}H NMR spectra of both dienols is 10–11 Hz, similar to that reported for alkoxybutadienes and interpreted as indicating that the stable conformation about the C-2—C-3 bond is *s-trans*[12]. The OH enols were also generated in a mixture of DMSO-d_6 and CH_3OH (90:10 v/v) at 32 °C. The signals of the oxygen-bound protons were doublets with $\delta = ca\ 8.91$ and the signals of the protons attached to C-1 were four line signals. The HO—C_1—H coupling constants for the (E)- and (Z)-isomers were respectively 8.8 and 5.8 Hz. This is similar to what is found for (E)- and (Z)-1-propenols[13] and suggested that the (E)-isomer is predominantly in the *s-cis* conformation and the (Z)-isomer is predominantly in the *s-trans* conformation around the C—O bond. It is therefore concluded that the most stable conformations are *s-cis*, *s-trans* (E-isomer) and *s-trans*, *s-trans* (Z-isomer) (see Scheme 1).

The pH–rate profiles for the ketonization of both dienols in water are U-shaped curves, consistent with there being H_3O^+, HO^- and water catalysed processes. The overall rate



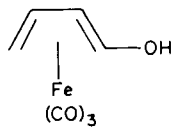
SCHEME 2. The ^{1}H NMR spectral changes that take place on hydrolysis of (*E*)- and (*Z*)-1-trimethylsilyloxy-1, 3-butadiene in CD_3CN: D_2O(9:1 v/v) which contains DCl (3.16×10^{-3} M) at 32 °C. The numbers in brackets are δ values

constants for protonation at both the α- and γ-position at the minima of the pH- rate profile (pH 3–5) are 3×10^{-3} to 4×10^{-3} s^{-1} at 25 °C which correspond to a half life of about 3 to 4 minutes. The (*E*)-isomer is slightly longer lived than the (*Z*)-isomer.

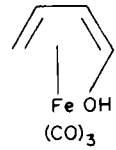
The ketonization of the dienols to yield 3-butenal involves α-protonation and is analogous to the ketonization of vinyl alcohol[14,15] but is much slower. Thus the additional double bond causes a decrease in k_{H^+} by factors of 1544 (*Z*-isomer) and 918 (*E*-isomer). The value of k_{H^+} for ketonization with γ-protonation is 7.3 times faster with the (*E*)-isomer than with the (*Z*)-isomer. This is a little less than can be calculated for the relative rates of protonation of the corresponding (*E*)- and (*Z*)-butadienyl ethers in 80% aqueous dioxan[16]. It seems that the transmission of positive charge to the oxygen in the transition state for protonation at the γ-position is more efficient with the (*E*)- than with the (*Z*)-isomers of both dienols and dienyl ethers, possibly because it is easier for the former to attain a planar conformation. The greater reactivity at the 4-position of the (*E*)-isomer is also shown in the water and hydroxide-ion-catalysed reaction of the dienols. These last reactions presumably involve the dienolate ions and relative rates of protonation of these and of the dienols at the α and γ positions are discussed in Sections V and IV.

Attempts have been made to generate the iron–carbonyl complexes of these dienols **16** and **17** by treatment of the corresponding acetates with methyl lithium in diethyl ether, but not with as much success as in the generation of the complex of 1, 3-butadien-2-ol (see

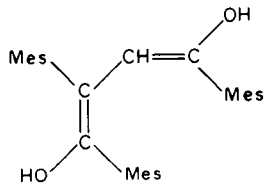
Section VII), probably because they are oxidised more rapidly. It was thought that the complex of the (*E*)-dienol (**16**) was generated as it could be trapped with benzoyl bromide although it was not possible to record its NMR spectrum. Attempts to generate the complex of the (*Z*)-dienol (**17**) seemed to yield the complex of the (*E*)-dienol at room temperature as trapping experiments with benzoyl bromide yield the benzoate of the (*E*)-dienol, but at $-60\,^{\circ}C$ a 30:70 mixture of (*Z*-) and (*E*-) dienyl benzoates was obtained[17].



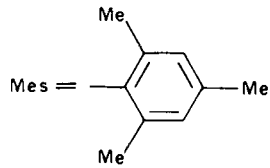
(**16**)



(**17**)



(**18**)



The introduction of mesityl groups has a stabilizing effect on dienols[18] similar to that found with mono enols. Thus the dien-diol **18** has been isolated crystalline[18].

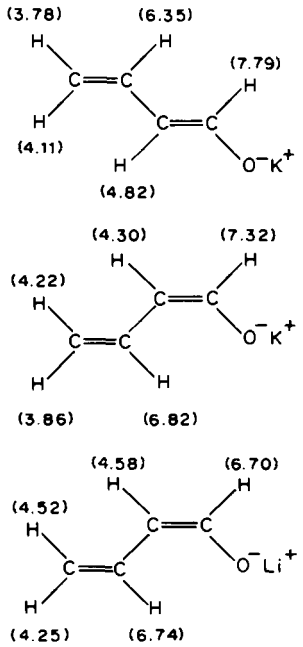
D. Generation of 1,3-Butadien-1-olate Anions

The *trans*-buta-1,3-dien-1-olate ion has been generated as its potassium salt by treatment of crotonaldehyde with potassium amide in liquid ammonia and characterized by its ^1H NMR spectrum (see Scheme 3)[19] and as its lithium salt by cleavage of 2-substituted-4,7-dihydro-1,3-dioxepines with butyl lithium[20]. The corresponding *cis* ion has been obtained by cleavage of 2,5-dihydrofuran either with potassium amide in liquid ammonia to yield the potassium salt[21] or with *n*-butyl lithium in *n*-hexane to yield the lithium salt[22,23]. It should be noted that the ^1H NMR spectra of the potassium and lithium salts show substantial chemical shift differences (see Scheme 3). The ^{13}C NMR spectrum of the lithium salt of the *cis* anion has also been reported and π-electron densities calculated by CNDO/2[23]. It has also been generated and its presence inferred on the basis of trapping experiments[24]. In addition the 1,3,5-hexatrien-1-olate anion has been generated and characterized by ^{13}C NMR spectroscopy[23].

III. PHOTOCHEMICALLY GENERATED 1,3-DIEN-1-OLS

A. From *o*-Substituted Aromatic Carbonyl Compounds

Photoenolization[1] was discovered by Yang and Rivas[25]. In the initial experiments the evidence for a process like that shown in equation 1 was indirect, such as incorporation of deuterium when the solvent was CH_3OD, and trapping with dimethyl acetylene-dicarboxylate. However, later, by the use of flash photolysis, two intermediates were detected on photoenolization of *o*-benzylbenzophenone in cyclohexane, one of which was



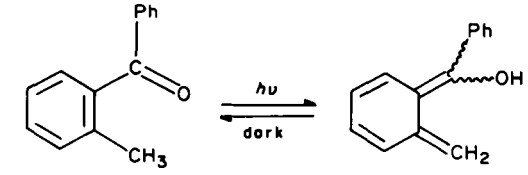
$J_{1,2} = 10.5\,Hz, J_{2,3} = 10.6\,Hz,$
$J_{3,4t} = 16.5\,Hz, J_{3,4c} = 10.7\,Hz,$
$J_{4c,4t} = 3.2\,Hz$ (Ref.19)

$J_{1,2} = 4.5\,Hz, J_{2,3} = 11.0\,Hz,$
$J_{3,4t} = 17.2\,Hz, J_{3,4c} = 10.2\,Hz,$
$J_{4c,4t} = 3.3\,Hz$ (Ref.21)

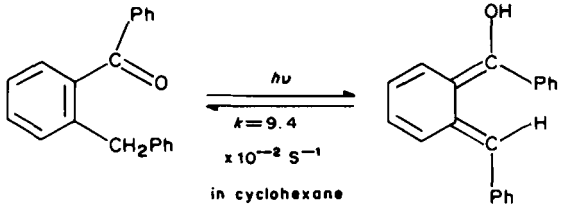
$J_{1,2} = 6\,Hz, J_{2,3} = 10.5\,Hz,$
$J_{3,4t} = 17.0\,Hz, J_{3,4c} = 10.5\,Hz,$
$J_{4c,4t} = 2\,Hz$ (Ref.22)

SCHEME 3. ^1H NMR spectral data of buta-1, 3-dienolate anions. The numbers in brackets are δ values

thought to be an excited state, and the other a dienol.* This latter species reformed the starting material with a rate constant, $9.4 \times 10^{-3}\,s^{-1}$ (temperature *ca* 20 °C) (equation 2)[26].



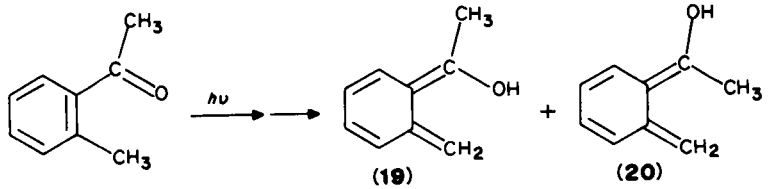
(1)

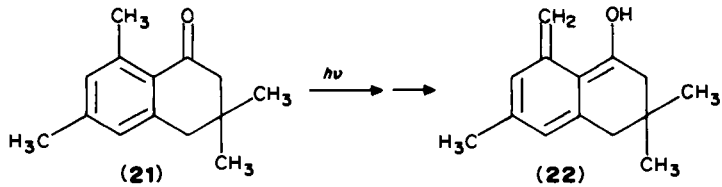


(2)

*These species have four double bonds and thus are really tetraenols, but their formation and ketonization appears to be qualitatively similar to that of analogous species which lack the two endocyclic double bonds (see Section III.B).

Subsequent work using laser flash photolysis lead to detection of both the (*Z*)- and (*E*)-dienols in this type of reaction. Thus, three transients were detected on photolysis of 2-methylacetophenone[26], one of which ($\lambda_{max} = 330$ nm) was quenched by oxygen and was ascribed to an excited triplet state of the dienols[27] (a 1,4-biradical)[28] and the other two ($\lambda_{max} = 390$ nm) were ascribed to the (*Z*)- and (*E*)-dienols, **19** and **20**, themselves. That ascribed to the (*Z*)-isomer (**19**), which can undergo intramolecular ketonization, had a very short lifetime which depended on the solvent. Thus in cyclohexane it was < 20 ns but in HMPA, 160 μs[27]. At low temperature this reaction probably involves tunnelling as the isotope effect, k_H/k_D, for the ketonization of the dienol generated from 2-[$^2H_3$]-methylacetophenone increased from 3 to 180 between 300 and 140 K[29]. The transient ascribed to the (*E*)-isomer **20** decayed much more slowly and had a lifetime of several seconds in cyclohexane[30,31]. Support for this assignment was obtained by an investigation of **21** which only yielded a short-lived dienol, presumably **22**[27].



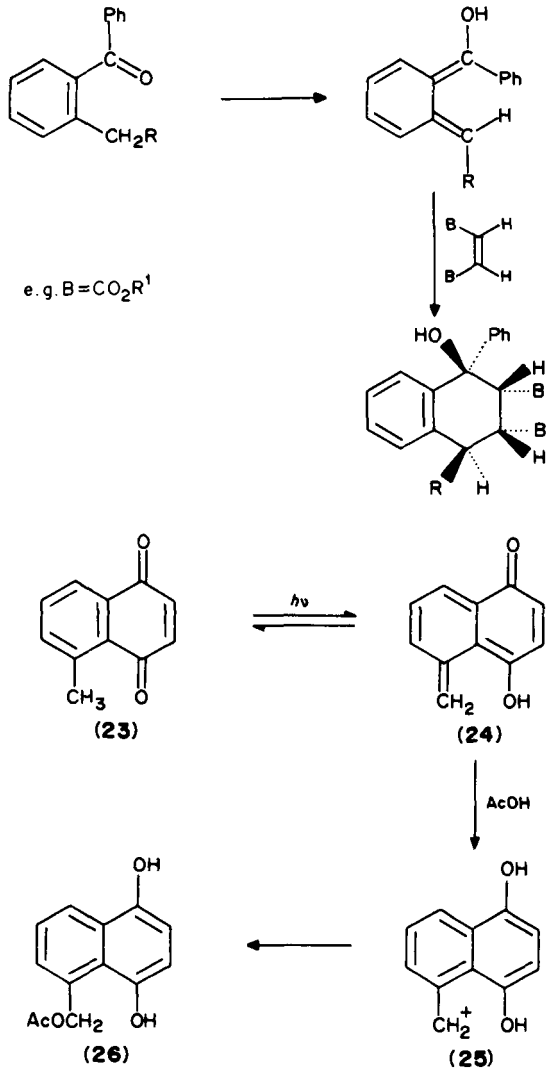


A dienol thought to be the (*Z*)-form, **19**, was also detected (by IR spectroscopy) on irradiation of 2-methylacetophenone in propan-2-ol at 77 K[32]. This reverts to the ketone on warming to 100 K. In contrast, similar treatment of 2-methylbenzaldehyde yielded a dienol which is stable up to the melting point of the propan-2-ol (180 K) and was therefore thought to be the (*E*)-dienol. This dienol could also be generated by irradiation of 2-methylbenzaldehyde in matrices in Ar, N_2, Xe and CO. However, 2-methylacetophenone was apparently unreactive under these conditions, but may form the (*Z*)-dienol **19** which, under these conditions, reverts too rapidly to starting material to be detected, probably via a tunnel process[32,29]. In propan-2-ol the (*Z*)-enol is probably stabilized by hydrogen bonding and so can be detected, but in the other matrices it is not so stabilized.

Frequently, photochemically generated (*E*)-dienols are sufficiently long-lived to be trapped by dienophiles such as maleic anhydride, methyl fumarate and phenyl fumarate (equation 3)[33], but (*Z*)-dienols can only be trapped in special circumstances, such as with **24**. In a mixture of acetonitrile and acetic acid, **24**, generated by flash photolysis of **23**, is trapped by protonation on oxygen to yield the acetate **26**, formed presumably from the carbocation **25**. The lifetime of the dienol **24** is strongly solvent-dependent (see Table 1)[34].

B. From Acyclic and Alicyclic Carbonyl Compounds

Photoenolization has also been postulated to occur on irradiation of aliphatic α,β-unsaturated ketones (e.g. equation 4 and 5)[35,36], α,β-unsaturated esters (e.g. equation 6)[37,38] and of alicyclic α,β-unsaturated ketones (e.g. equation 7)[39]. With all of

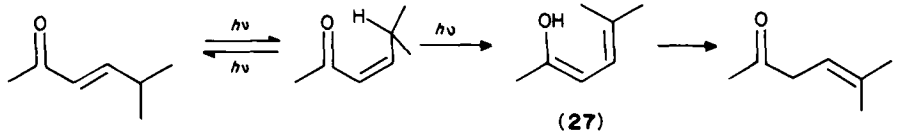


(3)

TABLE 1. Lifetime of **24** in different solvents at room temperature[34]

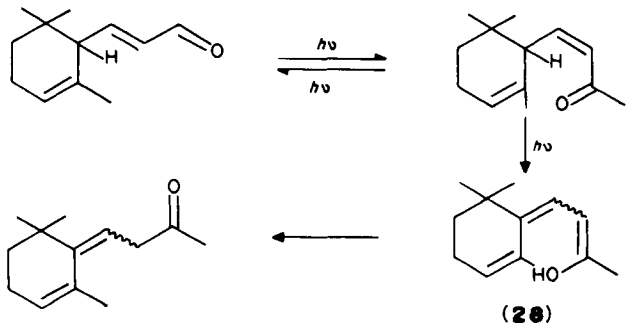
Solvent	Lifetime	Solvent	Lifetime
Cyclohexane	8 μs	Ethanol	0.8 ms
Benzene	40 μs	Acetonitrile + 1% water	0.8 ms
Diethyl ether	2 ms	Acetonitrile + 30% water	1.3 ms
Acetonitrile	3 ms	Acetic acid	26 μs
Tetrahydrofuran	7 ms		
Dimethyl sulphoxide	11 ms		
HMPA	90 ms		

these the first step is the conversion of the (*E*)- to the (*Z*)-form. In further steps the (*Z*)-form is converted into the β,γ-unsaturated isomer through presumed dienol intermediates (**27–30**). None of these were detected, however. The success of these 'deconjugation' reactions depends on the dienols undergoing some ketonization with protonation at the α-position and on the resulting β,γ-unsaturated carbonyl compounds not undergoing photochemical reversion to their α,β-unsaturated isomers. However, the relative amounts of ketonization with protonation at the α- and γ-positions are not known, although it should in principle be possible to determine them by using a medium such as CH_3OD and measuring the amount of deuterium incorporation at the α- and γ-positions of the products.



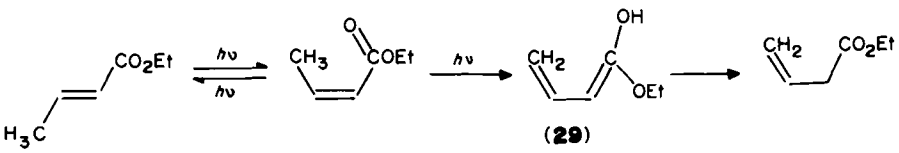
(**27**)

(4)



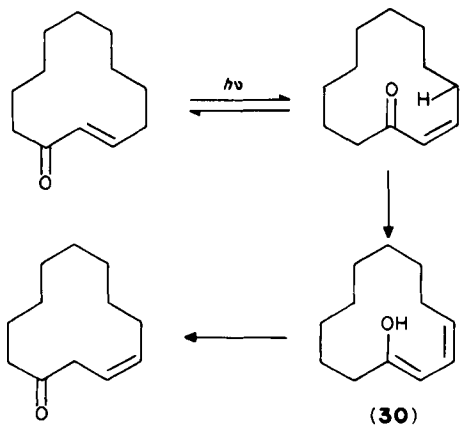
(**28**)

(5)



(**29**)

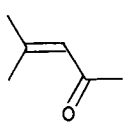
(6)



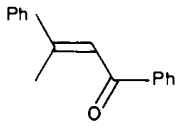
(**30**)

(7)

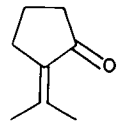
Photoenolization of α, β-unsaturated ketones does not always lead to formation of their β, γ-unsaturated isomers. Thus ketones **31**, **32**, **33** and **34** appear to undergo photoenolization in deuteriomethanol, as deuterium is incorporated into the γ-methyl groups, although there was no isomerization to β, γ-unsaturated ketones[40]. Rapid *cis–trans* isomerization about the C—C double bonds also occurs, as with **31**, **33** and **34** the rates of incorporation of deuterium into the methyl group *cis* and *trans* to the carbonyl group are almost the same, and with **32** the isomerization was demonstrated by the observation of the signal of the methyl group of its (*Z*)-isomer in the ^{1}H NMR spectrum. The formation of the dienols was also demonstrated by IR spectroscopy on irradiation of matrices of **31** and **34** in a mixture of methylcyclohexane and 2-methyltetrahydrofuran (2:1) at liquid nitrogen temperatures. It therefore seems that the dienols generated from these α, β-unsaturated ketones have a strong tendency to ketonize by re-forming the starting materials, possibly by an intramolecular 1, 5-migration. In the presence of hydrochloric acid, however, **32** and **34** isomerize to their β, γ-unsaturated isomers[41]. Intermolecular protonation at the α-position is now competing with intramolecular protonation at the γ-position.



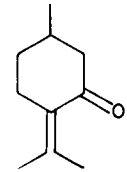
(**31**)



(**32**)

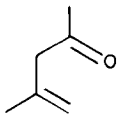


(**33**)

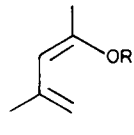


(**34**)

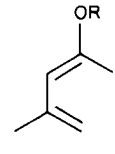
Similar behaviour is found in the presence of a base. Thus in the presence of imidazole[42,43] or pyridine[43,44] in DMF, mesityl oxide (**31**) yields the deconjugated ketone **35** upon irradiation. Now the dienols **36a** and **37a** can be trapped by trimethylsilyl chloride to yield the trimethylsilyl ethers **36b** and **37b**. The major product was the (*Z*)-isomer **36b** which suggests that the reaction proceeds through a singlet excited state which yields the *Z*-dienol **36a** in a concerted process. The (*E*)-isomer **37b** which was only detected after *ca* 60% conversion was thought to be formed from the (*Z*)-isomer **36b** by triplet energy transfer. In the absence of base the dienol **36a** reverts to starting mesityl oxide, possibly by a 1, 5-sigmatropic rearrangement, but in the presence of base ketonization involves the dienolate ion (**38**) which undergoes preferential α-protonation. A similar effect of base is found in the 'deconjugation' of α, β-unsaturated esters[45].



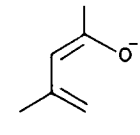
(**35**)



(**36**)
(**a**) R=H
(**b**) R=SiMe$_3$



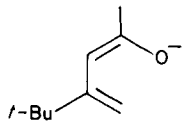
(**37**)
(**a**) R=H
(**b**) R=SiMe$_3$



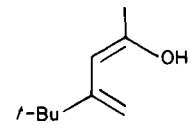
(**38**)

The pH dependence of the photochemical deconjugation of mesityl oxide has been reported. The quantum yield increases from 0.007 to 0.1 when the pH is changed from 2.5 to 13. This presumably reflects the higher proportion of α/γ protonation of the dienolate ion (**38**) compared to the dienol (**36a**)[46]. As can be seen from the discussion in Sections IV and V, dienolate ions normally undergo a higher proportion of protonation at the α-position than the corresponding dienols.

The dienolate ion derived from mesityl oxide, **38**, and the corresponding ion (**39**) with a *t*-butyl substituent have been detected as transients (λ_{max} 290 nm) in flash photolysis experiments[47a]. These transients were only detected at pH > 9.5 and their concentration increase with increasing pH, so they were assigned to the dienolate ions rather than to the dienols themselves. Analysis of the variation of the rate of decay of these transients with pH yields reasonable values for the K_a of the enols, of $3.8 \pm 0.17 \times 10^{-11}$ M (**36a**) and $1.07 \pm 0.5 \times 10^{-11}$ M (**40**), and for the rate constants for the ketonization of the enolate ions at 23 °C: $539 \pm 17\ s^{-1}$ (**38**) and $1184 \pm 21\ s^{-1}$ (**39**). From these results values of k_{HO^-} for the ketonization of the dienols are $2 \times 10^6\ M^{-1}\ s^{-1}$ (**36a**) and $1.2 \times 10^6\ M^{-1}\ s^{-1}$ (**40**) at 23 °C. These should be compared with values for the (*E*)- and (*Z*)-1,3-butadien-1-ol of 1.28×10^5 and $1.14 \times 10^5\ M^{-1}\ s^{-1}$ at 25 °C[11]. It was possible to evaluate the rate constant for the uncatalysed ketonization of dienol (**40**) to be $40 \pm 13\ s^{-1}$ at 23 °C. This is much higher than the rate constant for the uncatalysed ketonization of vinyl alcohol[14] or for the uncatalysed ketonization of cyclohexan-1,3-dienol[48] and suggests that there is a special mechanism for the ketonization of this dienol (**40**) which involves a 1,5-hydrogen shift[47a].



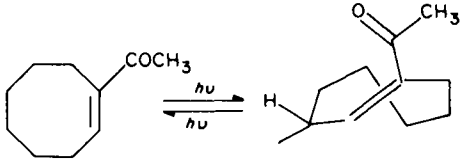
(**39**)



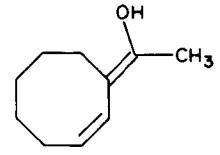
(**40**)

Recently the dienols **36a** and **40** themselves have been detected by ^{1}H NMR spectroscopy on irradiation of their keto forms in methanol solution at − 76 °C. There was about 50% conversion to the dienols and the ketonization of the latter was followed by NMR spectroscopy at temperatures up to − 23 °C[47b].

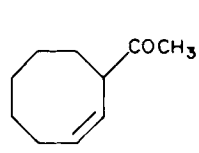
Detection of long-lived dienol intermediates in photoenolization at room temperature by NMR spectroscopy has also proved possible in certain instances. Thus, when 1-acetylcyclooctene (**41**) in acetonitrile solution is irradiated under nitrogen it is converted to a 5:1 mixture of the dienols **42** and **43** which were characterized by their NMR, IR and UV spectra[49]. Again the first step in this reaction was thought to be an (*E*) → (*Z*) isomerization. The dienols **42** and **43** were very sensitive to oxygen, but in the absence of oxygen they were converted slowly (or rapidly in the presence of catalysts) to a mixture of α, β- (**41**) and β, γ- (**44**) unsaturated ketones, the composition of which depended on the conditions. Thus in



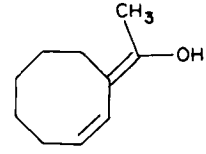
(**41**)



(**42**) +



(**44**)



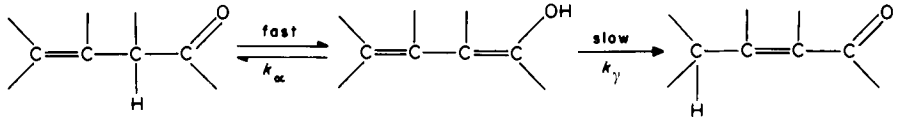
(**43**)

the presence of a trace of sulphuric acid the $\beta,\gamma/\alpha,\beta$ ratio (α to γ protonation) was 75:25, but in the presence of *t*-BuOK/*t*-BuOH it was 100:0. This suggests that protonation of the dienolate anion at the α-position is relatively more favourable than that of the dienol. This is similar to what is found with other dienols and their anions (see Sections IV and V). It is not clear if the stability of these dienols is just kinetic, or whether they are thermodynamically more stable than other dienols which have not been detected, since there are no measurements of the equilibrium constants for enolization.

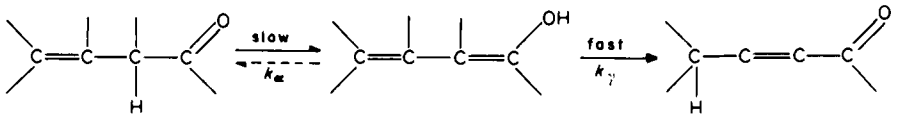
IV. POSITION OF PROTONATION OF 1,3-DIEN-1-OLS

Most of the evidence on the position of protonation of dienols has been obtained indirectly from studies on the isomerization of β,γ-enones into α,β-dienones for which the dienols are the presumed intermediates. However, the recent preparation of solutions of the simplest conjugated dienols, i.e. 1,3-butadien-1-ols, has enabled their protonation to be studied directly.

The conversion of β,γ-dienones into α,β-dienones falls into two extreme types (equations 8 and 9) depending on whether the enolization of the β,γ-dienone is rapid and reversible (equation 8) or the slow rate-determining step (equation 9). These two situations of course correspond to preferential α-protonation of the dienol ($k_\alpha/k_\gamma \gg 1$) and preferential γ-protonation ($k_\gamma/k_\alpha \gg 1$), respectively. There are two ways of distinguishing between these mechanisms: (i) the solvent isotope effect and (ii) deuterium incorporation. For the mechanism of equation 8 ($k_\alpha/k_\gamma \gg 1$) deuterium incorporation into the β,γ-enone should be detected when a deuteriated medium is used and the deuterium isotope effect for isomerization k_{H^+}/k_{D^+} should be greater than 1 (4 to 6 is common). For the mechanism of equation 9, however, there should be no deuterium incorporation when a deuteriated medium is used and k_{H^+}/k_{D^+} should be less than 1 (0.6–0.9 is common). Examination of the results in Table 2 suggests that the following two structural features favour γ-protonation of dienols: (i) planarity of the dienol system and (ii) the presence of a substituent on the β-carbon. On the other hand, non-planarity of the system favours α-protonation.



(8)



(9)

As discussed by Whalen and coworkers[50], the C_γ/C_α protonation ratio must depend on the relative abilities of the two transition states to delocalize the developing positive charge onto the oxygen. This will be a maximum for γ-protonation when the angle ϕ between the double bonds is 0°, which is probably the situation with the acyclic dienols (Table 2, entries 1, 2, 4) and the cyclopentadienol (Table 2, entry 3). In contrast, this angle has been estimated to be respectively 18° and 64° for the cyclohexadienol (Table 2, entry 7) and the cyclooctadienol (Table 2, entry 9), so that protonation at the γ-position is disfavoured and protonation occurs mainly at the α-position.

TABLE 2. Position of protonation of 1,3-dienols to form carbonyl compounds[a]

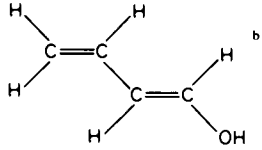
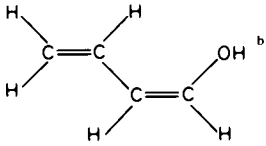
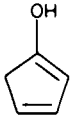
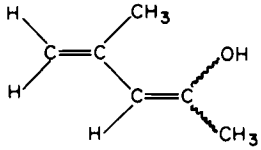
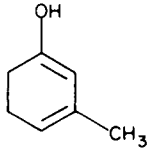
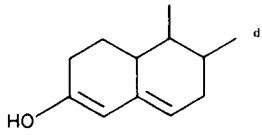
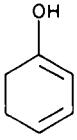
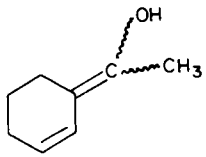
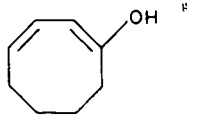
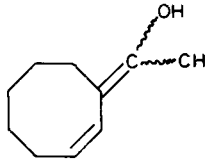
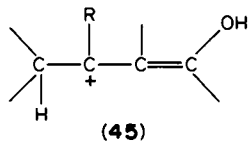
No.	Enol	% α	% γ	k_{H^+}/k_{D^+} for isomerization of β,γ- into α,β-enone	Ref.
		Dienols which are Protonated Mainly at the γ-Position			
1	 [b]	9.9	90.1	—	11
2	 [b]	30.2	69.8	—	11
3		0	100[c]	0.91	50
4		—	—	0.59–0.83	51a
5.		—	—	0.77	51b
6	 [d] Cholesteryl system	< 10	> 90	0.61	52–55
		Dienols which are Protonated Mainly at the α-Position			
7	 [e]	98	2	5	51b

TABLE 2. (*continued*)

No.	Enol	% α	% γ	k_{H^+}/k_{D^+} for isomerization of β,γ- into α,β-enone	Ref.
8		90	10	1.0	51a
9		*ca* 100	*ca* 0	—	56
10		75	25	—	40

[a] Except for the first two and the last entries the positions of protonation were determined by studying deuterium incorporation concurrent with the isomerization of the β,γ-enone into the α,β-enone in a deuteriated medium.
[b] Direct measurement of the products from pregenerated dienol (see Section II.C).
[c] No deuterium incorporation into the α-position of the product.
[d] When cholest-5-en-3-one was allowed to isomerize by treatment with the DCl in diglyme–D_2O, the product cholest-4-en-3-one contained less than 0.1 atom of deuterium at C-4. When the reaction was stopped at 70% reaction no deuterium incorporation into the starting material was detected[52]. Similar treatment of 17β-hydroxyandrost-5-en-3-one showed 0.08 atom of deuterium at C-4 of the starting material when it was recovered after 50% reaction[52]. A kinetic investigation of the isomerization of androst-5-ene-3, 17-dione into androst-4-ene-3, 17-dione and of 17α-ethynyl-17β-hydroxy-5-estren-3-one into 17α-ethynyl-17β-hydroxy-4-estren-3-one in DCl/D_2O showed non-first-order behaviour from which it was concluded that 'partitioning of the dienols' is kinetically significant[54]. It therefore seems that the tendency to α-protonation is greater in the androstenone and estrenone series than in the cholestenone series.
[e] Rate of enolization of β,γ-enone is reported to be about 50 times the rate of isomerization into the α,β-enone.
[f] Rate of enolization of β,γ-enone is reported to be nearly 10 times the rate of isomerization into the α,β-enone. The isotope effect $k_{H^+}/k_{D^+} = 1$ was attributed to it being a complex function of the rate constants for enolization of the β,γ-enone and for ketonization of the dienol to yield β,γ- and α,β-enones; i.e. the mechanism is not the limiting one.
[g] Extensive deuterium incorporation into the β,γ-enone was reported under conditions where no isomerization into the α,β-enone could be detected.
[h] Direct measurement of the products from the photochemically generated dienol (see Section III).

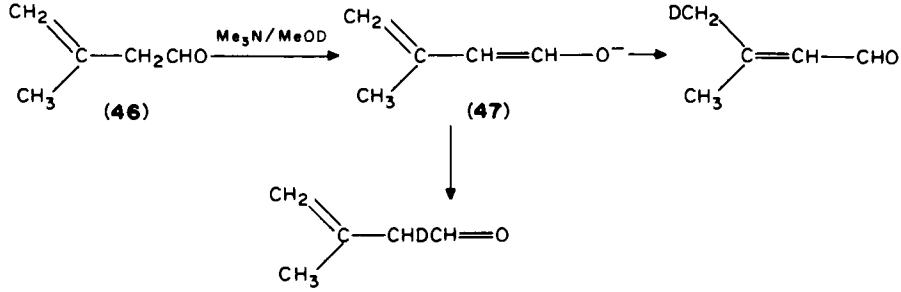
Alkyl substituents at the β-position also favour γ-protonation, as illustrated by entries 5 and 6 in Table 2. This is easily rationalized as resulting from stabilization of one of the canonical structures of the transition state as shown in **45**.



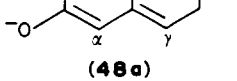
(45)

V. POSITION OF PROTONATION OF 1,3-DIEN-1-OLATE ANIONS

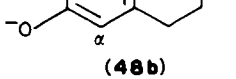
Dienolate ions usually undergo protonation faster at the α-position than at the γ-position ($k_\alpha/k_\gamma > 1$), an observation which can be correlated with the charge densities at these positions[57–59]. The preference for α-protonation is however relatively slight, unless the dienolate system is non-planar. Thus, for deuteriation by $D_2PO_4^-$ of the cyclopentadienolate ion, which is planar, k_α/k_γ is 3.2[50] and $k^\alpha_{HO^-}/k^\gamma_{HO^-}$ for the ketonization of the (*Z*)- and (*E*)-1,3-butadien-1-ols, which presumably pass through the dienolate ions, is 4.1 and 1.2 respectively[11]. It also seems that the value of k_α/k_γ for ion **47** is similar since isomesityl oxide (**46**) on treatment with trimethyl amine in CH_3OD undergoes exchange about four times faster than it is isomerized into mesityl oxide[60].



In contrast, the values of k_α/k_γ for deuteriation of the non-planar cyclooctadienolate[56] and cyclohexadienolate[50] ions are respectively > 1700 and 575. This last observation is similar to many results reported for steroidal dienolate[54,59,61–65] of general structure **48a** or **48b**. As discussed by several workers[57–59,64,66], if it is assumed that the transition state for protonation of the dienolate ion is 'early', then there should be a correlation between k_α/k_γ and the charge densities at these positions. The relative charge densities will however depend on how close the dienolate ion is to planarity and the negative charge ratio q_γ/q_α should be a maximum when the system is planar with the dihedral angle ϕ between the double bonds equal to zero. This is probably the situation with the butadienolate and cyclopentadienolate ions and k_α/k_γ is less than about 4[11,50]. However, in the cyclohexadienolate ion ϕ is 10 to 15° and k_α/k_γ is 575[50], and in the cyclooctadienolate ion ϕ is 64° and k_α/k_γ is greater than 1700[56].



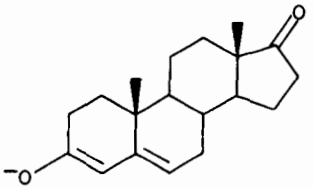
(48a)



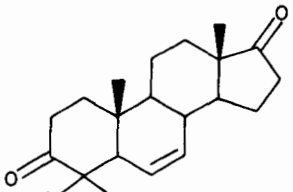
(48b)

This apparently tidy picture is complicated by the report that, in aqueous solution, the dienolate ion derived from androst-5-ene-3,17-dione **49** 'may pick up a proton at C-4 and C-6 with comparable ease'[67]. The experimental basis for this claim, which seems to be sound, was that a deuterium isotope effect of $k_H/k_D = 3.2$ was measured for the isomerization of **50** into **51** by carrying out measurements early in the reaction, and that the first-order plot for the deuteriated substrate **50b** was curved and that the slope eventually became equal to that for the non-deuteriated substrate **50a**, which indicates that complete exchange had taken place. The apparent disagreement between this result and other work on steroidal dienolates of this general structure, which indicates that α-

protonation is much faster than γ-protonation[54,59,61–65], was attributed to a difference in solvent[67]. Clearly this warrants further investigation.



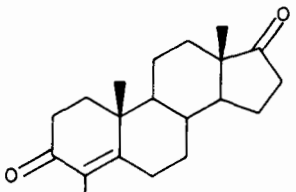
(49)



(50)

(a) L=H

(b) L=D

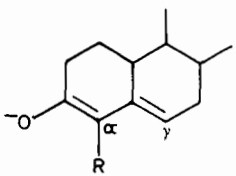


(51)

(a) L=H

(b) L=D

Substituents affect the site of protonation of steroidal dienolate ions. Thus, the percentage of α-protonation of the dienolate ions **52** derived from cholestenone are 95, 60 and < 5% with the substituents R = H, Me and MeO[66].



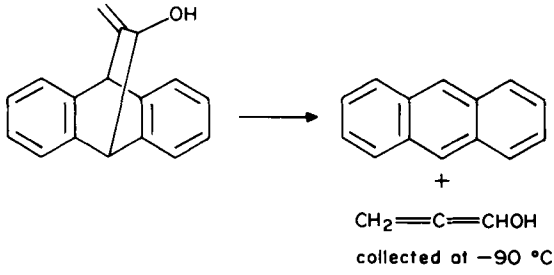
(52)

Dienolate ions derived from α,β-unsaturated esters also undergo predominant protonation at the α-position. These ions are acyclic and, like those derived from acyclic aldehydes and ketones, the preference for α-protonation is not high. Thus k_α/k_γ for protonation of the dienolate ion derived from ethyl crotonate is 6.7 and that derived from ethyl 3-methyl-2-butenoate is 4.3[68].

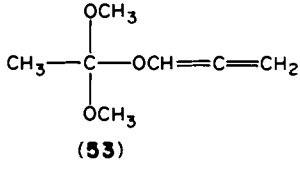
VI. 1,2-DIENOLS

1,2-Dienols (**5**) are formally derived by enolization of α,β-unsaturated carbonyl compounds which have a proton attached to the α-carbon atom. The simplest 1,2-dienol, propa-1,2-dienol, the enol of acraldehyde, has been generated by flash thermolysis of its

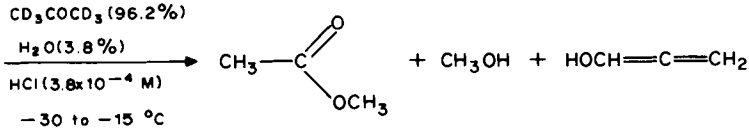
Diels–Alder adduct with anthracene (equation 10)[69] and by hydrolysis of the orthoester precursors **53** and **54**[70].

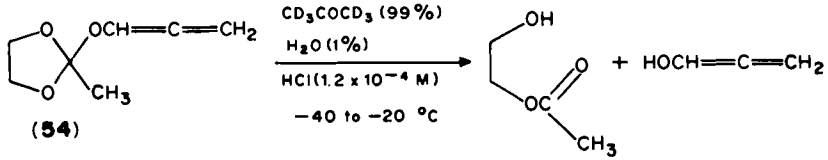


(10)



(53)

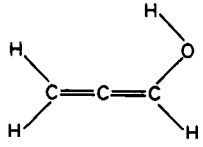




(54)

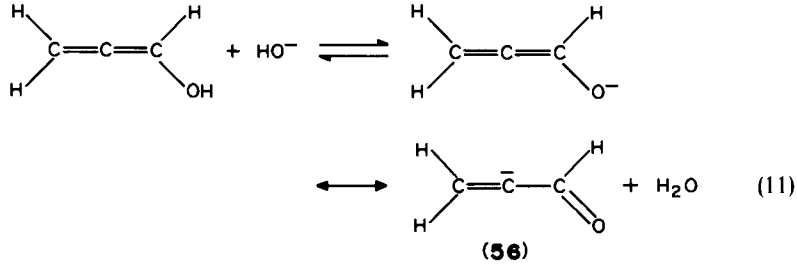
The ^{1}H NMR spectrum of the product obtained by flash thermolysis was measured in $CFCl_3$ solution at $-90\,^\circ C$ and showed signals with $\delta = 5.3$ (d, 6 Hz, 2H), 6.56 (dt, 6 and 10 Hz, 1H) and 7.00 (d, 10 Hz, OH) and the IR spectrum of the solid material at $-196\,^\circ C$ showed a band with $\nu = 1980$–$1960\,cm^{-1}$ ascribed to a vibration of the C=C=C system. When prepared in this way the propadienol tautomerizes quantitatively into acraldehyde at $-50\,^\circ C$.

The same compound was prepared in a mixture of CD_3COCD_3 and H_2O which contained a small amount of HCl at -40 to $-15\,^\circ C$. When prepared from **54** in CD_3COCD_3 (99%)–H_2O (1%) its ^{1}H NMR spectrum showed the following signals at $-40\,^\circ C$: $\delta = 5.23$ (d, $J = 5.8$ Hz, 2H), 6.73 (dt, $J = 5.8$ and 9.5 Hz, 1 H) and 7.05 (d, $J =$ 9.5 Hz, OH), so the spectra of the compound prepared in the two different ways in two different solvents were very similar. In CD_3COCD_3–H_2O mixture the position of the OH peak depended on the temperature, moving downfield on cooling and upfield on warming with $\delta = 7.5$ at $-100\,^\circ C$ and 6.8 at $-20\,^\circ C$[70]. The 9.5 Hz coupling between the OH and α-CH protons is similar to that reported for vinyl alcohol[13] and suggests that the *s-cis* conformation, **55**, is the predominant one. The ^{13}C NMR spectrum was also measured and showed $\delta = 87.4$, 116.8 and 203.4 ascribed, respectively, to C-3, C-1 and C-2.



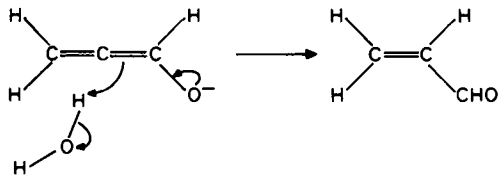
(55)

The kinetics of conversion of propadienol into acraldehyde were measured for an aqueous solution at 15 °C. The pH–rate profile was a bell-shaped curve for which the following rate constants were evaluated: $k_{H^+} = 5.6\ M^{-1}\ s^{-1}$, $k_{HO^-} = 1.11 \times 10^9\ M^{-1}\ s^{-1}$ and $k_{H_2O} = 7.61 \times 10^{-3}\ s^{-1}$. The values of k_{H^+} and k_{H_2O} are slightly smaller than those reported for vinyl alcohol ($k_{H^+} = 20.2\ M^{-1}\ s^{-1}$, $k_{H_2O} = 1.38 \times 10^{-2}\ s^{-1}$) but k_{HO^-} is 74 times greater than that for vinyl alcohol ($k_{HO^-} = 1.5 \times 10^7\ M^{-1}\ s^{-1}$). This was interpreted in terms of a mechanism which involved a rapid and reversible ionization followed by limiting protonation of the dienolate ion (equations 11 and 12). It was thought[70] that the latter and the transition state for its protonation would be more stable than the corresponding structure in the ketonization of vinyl alcohol, since there is a contributing resonance structure **56** which is a vinylic carbanion and these species are normally more stable than alkyl carbanions.



(56)

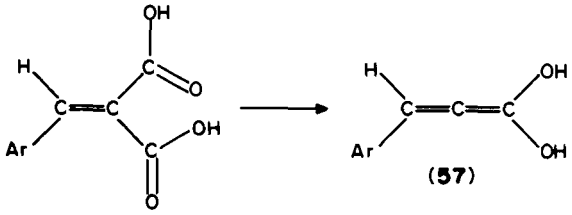
(11)



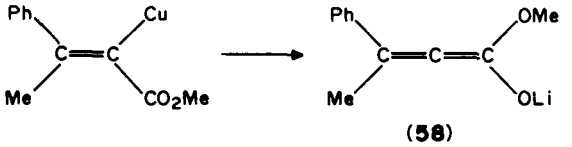
(12)

In addition to the direct spectroscopic detection of propa-1,2-dienol described above, various allenic enols have been suggested as reaction intermediates. Thus gem-allenic dienols **57** have been proposed as intermediates in the decarboxylation of α,β-unsaturated malonic acids and dienolate ions such as **58** were thought to be formed on treatment of the organocopper derivatives with methyl lithium[71,72].

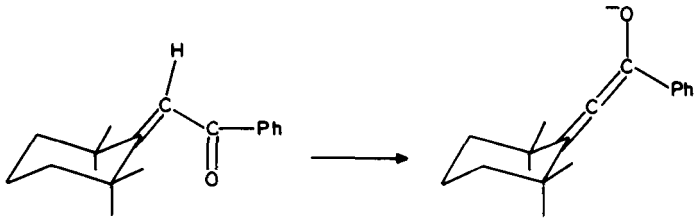
The formation of an allenic enolate ion by the direct removal of the α-proton of an α,β-unsaturated ketone has been proposed to occur in the racemization and deuterium exchange of ketone **59** in methanolic sodium methoxide. The ratio of the rate constants for these processes at 50 °C, $k_e/k_r = 1.43$, indicates about 40% retention of optical activity which was attributed to internal return[73].



(57)

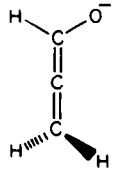


(58)

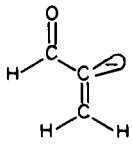


(59)

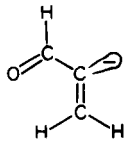
On the basis of MO calculations (4–31G basis set) it was concluded that the allenic enolate ion **60** was 17 and 21 kcal mol^{-1} more stable than the isomeric enone anions **61** and **62**, respectively. However, in cyclization reactions (equation 13) in which the size of the ring being formed precludes formation of the allenic enolates, it was thought that the enone ions were intermediates[74].



(60)



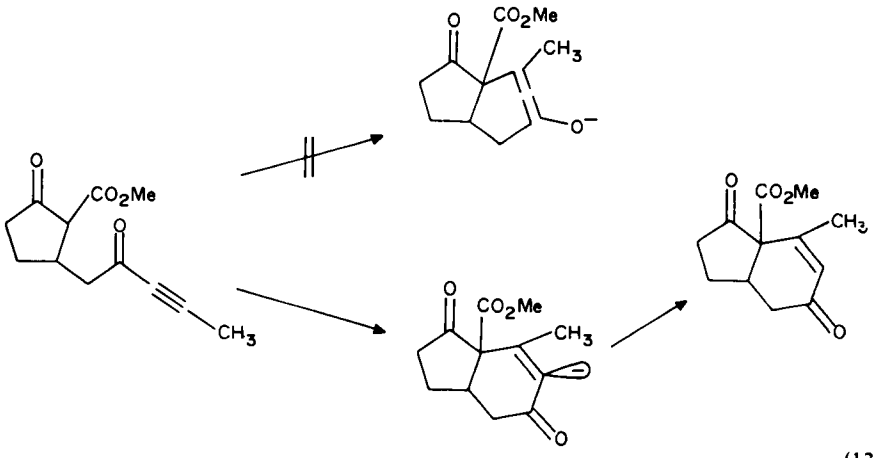
(61)



(62)

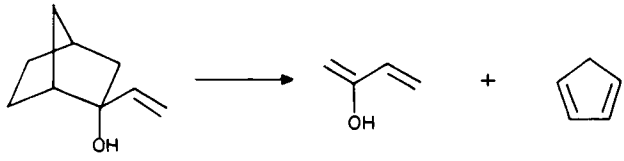
VII. 1,3-DIEN-2-OLS

The simplest 1,3-dien-2-ol, 1,3-butadien-2-ol (**64**), has been generated in the gas phase by flash pyrolysis of 5-*exo*-vinyl-5-norbornenol (**63**) at 800 °C (2×10^{-6} torr). It was reported that the 75 eV mass spectrum of (**64**) 'differs from those of stable C_4H_6O isomers with a C—C—C(O)—C, C—C—C—C—O or cyclic frame'. Methyl vinyl ketone (20–30%, IE = 9.65 eV) was thought to be present as well as **64** (IE = 8.68 eV) on the basis of the deconvoluted ionization efficiency curve. This was thought to be formed by surface-catalysed isomerization. The heat of formation of the dienol was estimated to be − 18.4



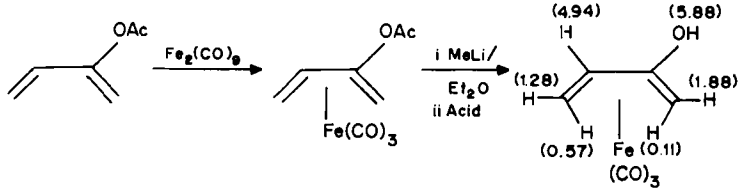
(13)

± 1.2 kcal mol^{-1} compared to that for the keto form, -26.8 kcal mol^{-1}, i.e. *ca* 6.2 kcal mol^{-1} less stable. This compares to a value of 10 kcal mol^{-1} for the 2-propenol acetone pair[75].



(**63**) (**64**)

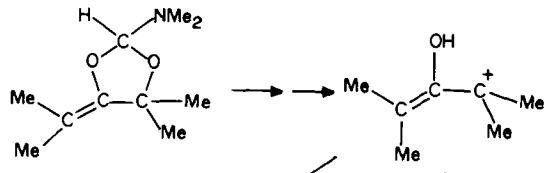
The same dienol has been generated as its tricarbonyl iron complex in solution (equation 14). The ^{1}H NMR spectrum had signals with the chemical shifts (δ values) indicated and the pK_a was determined to be 9.24 in 48% aqueous ethanol (estimated 8.5 in water)[17].



(14)

A more complex 1,3-dien-2-ol, 2,4-dimethyl-1,3-pentadien-3-ol (**67**), was generated in solution from the amide-acetal precursor (**65**). The best reagents for the generation of **67** appear to be a slight excess of *t*-butyl alcohol in CCl_4 or dimethyl sulphoxide which contains traces of moisture or acid. If an excess of methanol or water is present and the solvent is CCl_4 monoenols (**66**) are mainly formed. In dimethyl sulphoxide solution the dienol (**67**) was stable for several days[76,77].

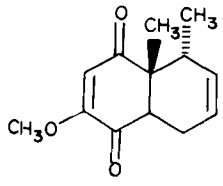
A series of stable bicyclic 1,3-dien-2-ols (referred to by the authors as enols) has been reported by Reusch[78] and Kanematsu[79] and their coworkers. Thus dienol **69** spontaneously crystallized from a mixture of **68** (its keto form) and an isomer and the dienols **70**,



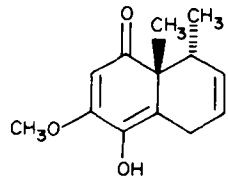
(65)

(66) (67)

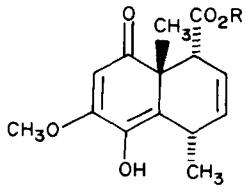
ROH = MeOH, H_2O



(68)

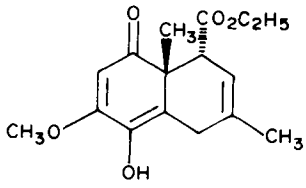


(69)

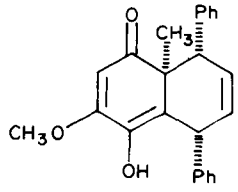


(70)

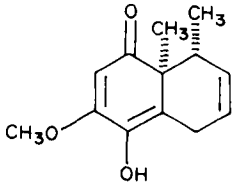
$R = CH_3$ or CH_2CH_3



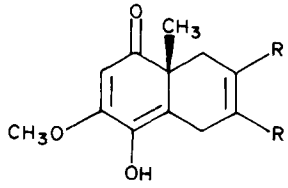
(71)



(72)



(73)



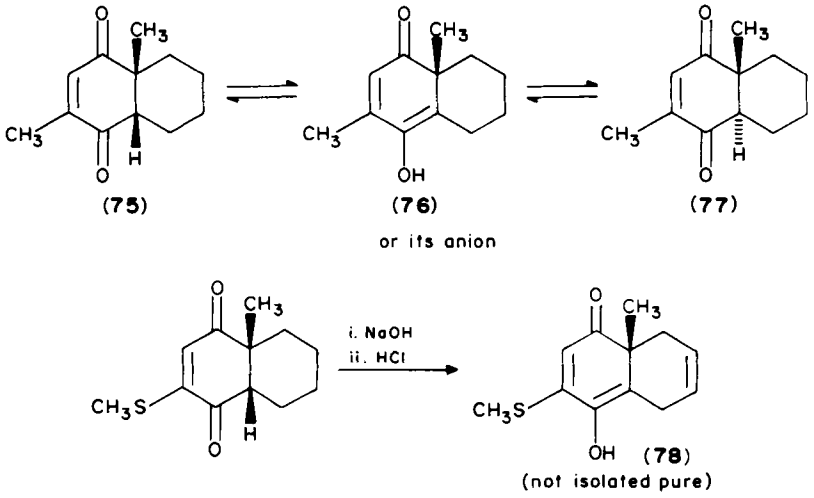
(74)

(a) R = H

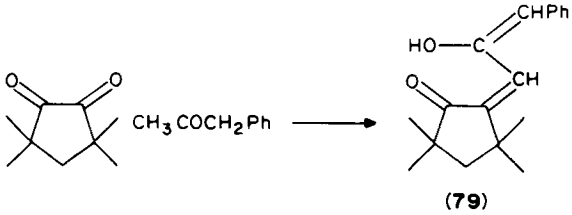
(b) $R = CH_3$

71 and **72** were isolated from the Diels–Alder reaction of 2-methoxy-5-methylbenzoquinone and the corresponding dienes, while dienols **73** and **74** were isolated by treatment of the corresponding *cis*-fused keto forms with base (*t*-BuOK in *t*-BuOH or NaOH in dioxan) followed by rapid acidification. Enols **69**, **71** and **72** were also prepared by this method.

This presence of the angular methyl group is essential for dienol formation since, when this is replaced by a hydrogen, base treatment of the keto form leads to aromatization. The presence of the methoxyl group is also necessary for the dienol to be detected or isolated, since base treatment of the *cis*-fused keto form **75** leads to formation of the *trans*-fused keto form **77**, but dienol **76**, the anion of which is presumably an intermediate, could be neither isolated nor detected. When the methoxyl group of **74b** was replaced by a methylthio group, the enol **78** was detected as an intermediate by NMR spectroscopy, but could not be isolated. It was suggested that the heteroatom stabilizied the enol by intramolecular hydrogen bonding and that a methylthio group[79].



It is possible that the keto group in the γ'-position to the enolic hydroxyl also exerts a stabilizing influence on the enolic form and a simpler 1,3-dien-2-ol with this structural feature has also been isolated. This (**79**) was obtained (along with a ring-closed isomer) from the reaction of 3, 3, 5, 5-tetramethylcyclopentane-1, 2-dione with benzyl methyl ketone (equation 15). However, with **79**, unlike with the bicyclic dienols, there is the possibility of an intramolecular hydrogen bond between the enolic hydroxyl group and the keto group. That there is in fact such a hydrogen bond in the solid state was demonstrated by X-ray crystallography, which indicated a short O–O interatomic distance of 2.55–



(15)

2.58 Å. The dienolic structure also persists in $CDCl_3$ solution. The ^1H NMR spectrum shows the signal of the enolic proton at $\delta = 11.72$ with a long-range allylic coupling of 1.7 Hz. The intramolecular hydrogen bond also causes a shift in the ^{13}C NMR resonance of the carbonyl group to $\delta = 216.7$ compared with $\delta = 204$ to 208 for other cyclopentenones[80].

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The Chemistry of Enones
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CHAPTER **21**

Asymmetric synthesis with chiral enones

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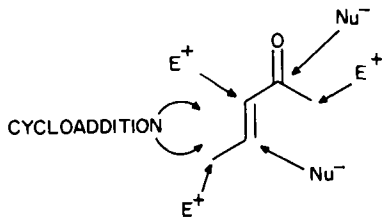
I. INTRODUCTION

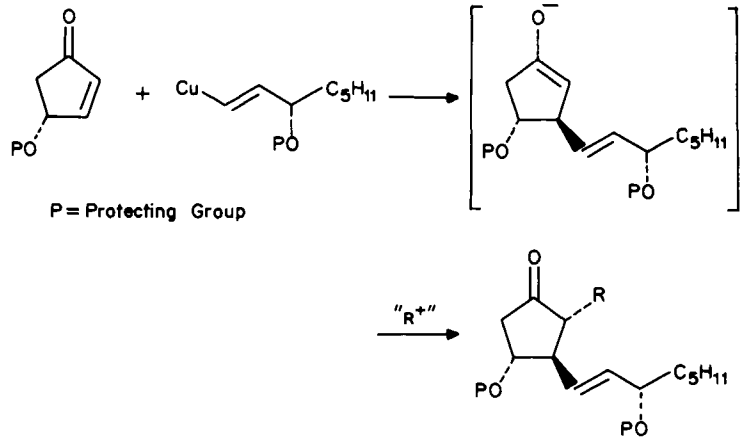
The α,β-unsaturated ketone (enone) functionality enjoys a pivotal position in organic chemistry. The ability to selectively functionalize up to five carbons by conjugate addition, alkylation, Diels–Alder reaction, etc. makes the enone function an attractive subunit for elaboration.



With such diverse chemistry available, the enone function has played a prominent role in the synthesis of many complex molecules in racemic or optically pure form. This chapter will review synthetic applications of enones possessing (non-racemic) chiral centers. Emphasis will be placed on commercially or otherwise readily available homochiral enones.

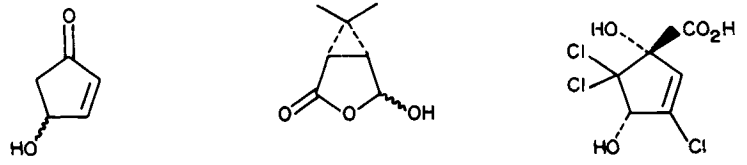
II. 2-CYCLOPENTENONES

The total synthesis of natural and unnatural prostaglandins has received much attention over the past twenty years[1]. Of the numerous synthetic approaches to the prostaglandins perhaps the most conceptually attractive route involves 'three component coupling'[2]. In such a route conjugate addition of an optically pure lower side-chain synthon to a protected, homochiral 4-hydroxy-2-cyclopenten-1-one is followed by treatment of the resulting enolate with a suitable electrophilic top-chain synthon to afford the basic prostaglandin skeleton in a single operation (Scheme 1).



SCHEME 1

This synthetic procedure is dependent on the ready availability of the enone **1** in optically pure form. A number of methods have been developed for preparation of the latter including resolution of the racemic hydroxycyclopentenone, preparation from optically pure natural products, asymmetric synthesis and microbial or enzymatic methods.

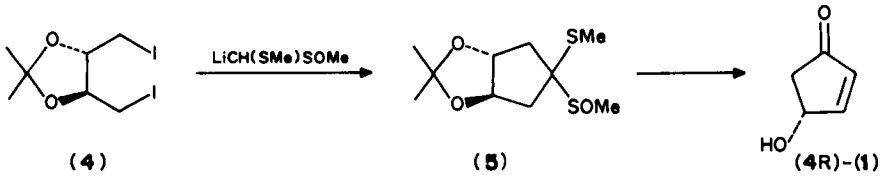


(1) (2) (3)

The racemic enone (±)-**1** has been prepared in a number of ways[3] from simple starting materials such as cyclopentadiene[4], 2-methylfuran[5], 2-(hydroxymethyl)furan[6], etc. Despite the sensitive nature of the compound, it has been efficiently resolved using the (1*S*,3*S*)-*trans*-chrysanthmic acid derivative **2**[7]. Resolution of the cyclopentenecarboxylic acid **3**, derived from phenol, using brucine followed by decarboxylation and removal of the chlorines also led to the optically pure (4*R*)-**1**[8].

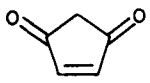
Optically pure natural products have served as precursors to (*R*)-**1** as demonstrated by Tsuchihashi and coworkers[9] (Scheme 2). The isopropylidene protected diol diiodide **4**, prepared in four steps from D-tartaric acid, on condensation with methyl methyl-

thiomethyl sulfoxide afforded the protected cyclopentanone **5**. Acid hydrolysis gave (*R*)-**1** in 22% overall yield (from D-tartaric acid) and 85% optical purity.

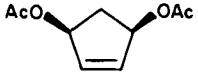


SCHEME 2

The enantioselective transformation of prochiral or meso compounds into optically pure products has recently received much attention since, in principle, a prochiral compound can be completely converted into a single enantiomer without the 50% 'waste' inherent in the resolution of a racemate[10]. The chiral 4-hydroxycyclopentenone is a prime candidate for preparation via this 'meso trick' since the prochiral cyclopentenes **6** and **7** are readily available from cyclopentadiene.



(6)



(7)

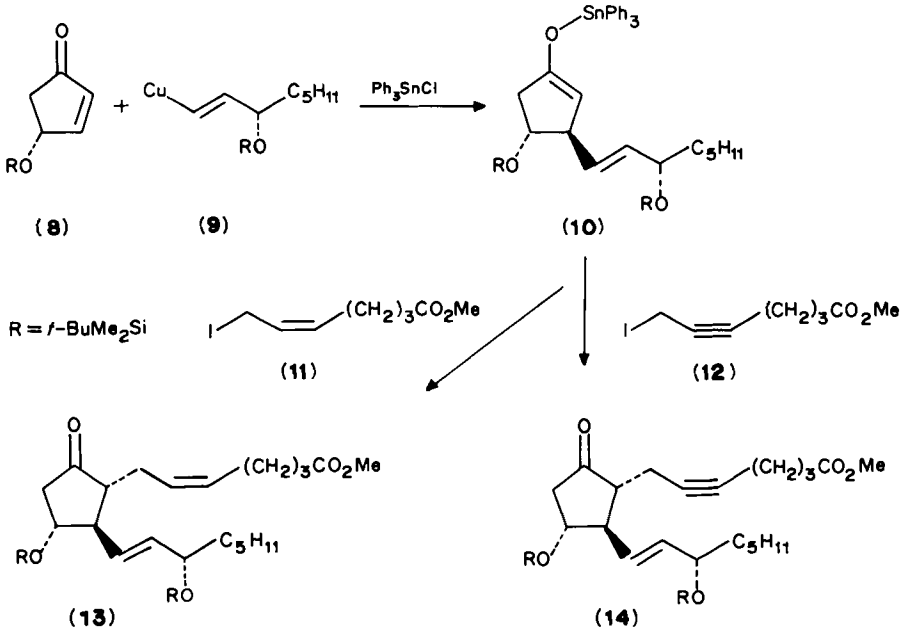
Noyori and coworkers found that reduction of cyclopentenedione (**6**) with the chiral reducing agent (*S*)-Binal-H gave (4*R*)-hydroxy-2-cyclopenten-1-one (**1**) in 65% yield and 94% ee[11].

The use of enzymes in organic synthesis is increasing in popularity, especially for the preparation of optically pure compounds. The enantioselective hydrolysis of diacetate **7** has been achieved using a variety of enzymes and microbes to give, ultimately, (4*R*)-hydroxy-2-cyclopenten-1-one with high purity[12].

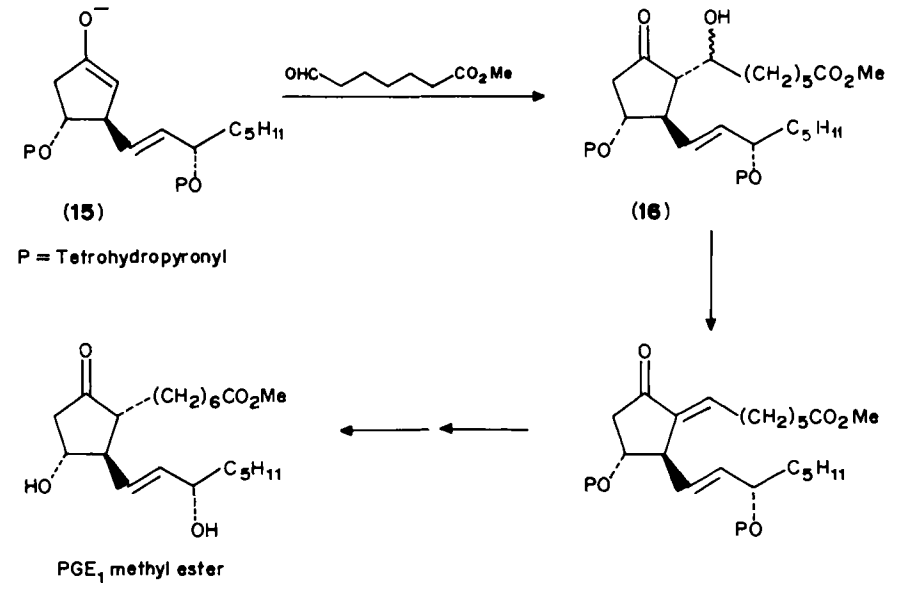
The use of organocopper chemistry to effect conjugate addition of nucleophiles to enone systems is well established and has been reviewed extensively[13]. In efforts directed towards the synthesis of prostaglandins, it was found that the ω chain could be introduced very efficiently in homochiral form via the appropriate cuprate; however, extreme difficulty was encountered during the direct alkylation of the intermediate enolate with organic halides. One solution to this problem was recently reported by Noyori and coworkers[14] who employed a lithium (or copper) to tin transmetallation at the enolate stage (Scheme 3). Addition of **9** to **8** followed by transmetallation to tin enolate **10** and reaction with the allylic or acetylenic iodide **11** or **12** afforded the PGE derivatives **13** and **14** in 78% and 82% yield, respectively. Removal of the silyl protecting groups and enzymatic hydrolyses of the esters would complete the shortest prostaglandin synthesis to date.

The problems associated with the direct alkylation of enolate **15** have also been circumvented by the use of more reactive electrophiles to give products which can be readily transformed into the natural prostaglandins. The enolate **15** could be condensed with aldehydes to afford aldol products in good yield[15]. This strategy was effectively employed by Noyori in the synthesis of PGE_1 and PGE_2 (Scheme 4). Condensation of enolate **15** with methyl 7-oxoheptanoate gave the aldol product **16** which was dehydrated and reduced to give PGE_1 (after removal of the protecting groups).

In a similar manner, the enolate **17** was condensed with methyl 7-oxo-5-heptynoate (Scheme 5) to give the aldol product **18**. This compound was efficiently deoxygenated to give the protected 5,6-dehydro-PGE_2 derivative which served as an intermediate for the

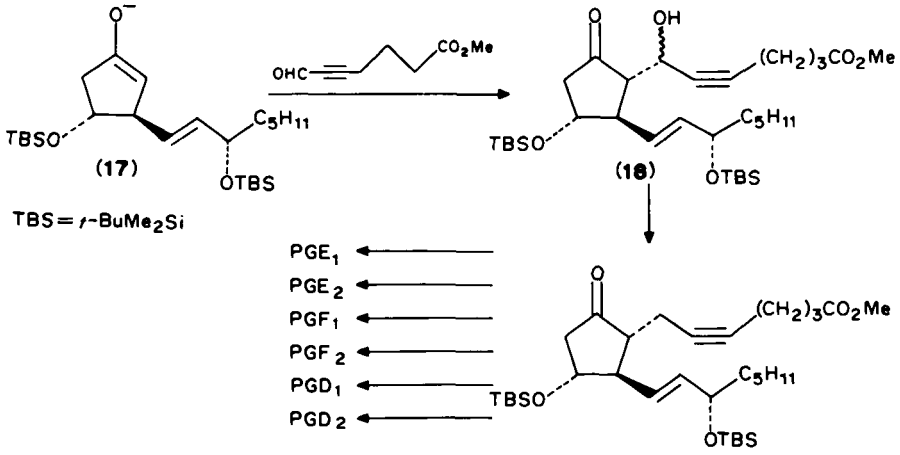


SCHEME 3



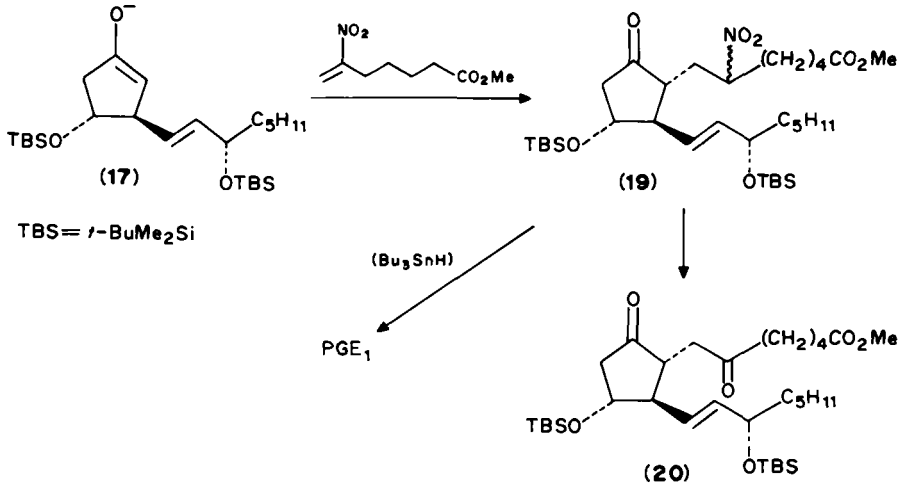
SCHEME 4

synthesis of a variety of primary PGs, e.g. PGE_2 (partial hydrogenation), $PGF_{2\alpha}$ (Bu_2AlH reduction, partial hydrogenation), PGE_1 (saturation of 5,6-triple bond), $PGF_{1\alpha}$ (Bu_2AlH reduction, hydrogenation), PGD_1 and PGD_2.



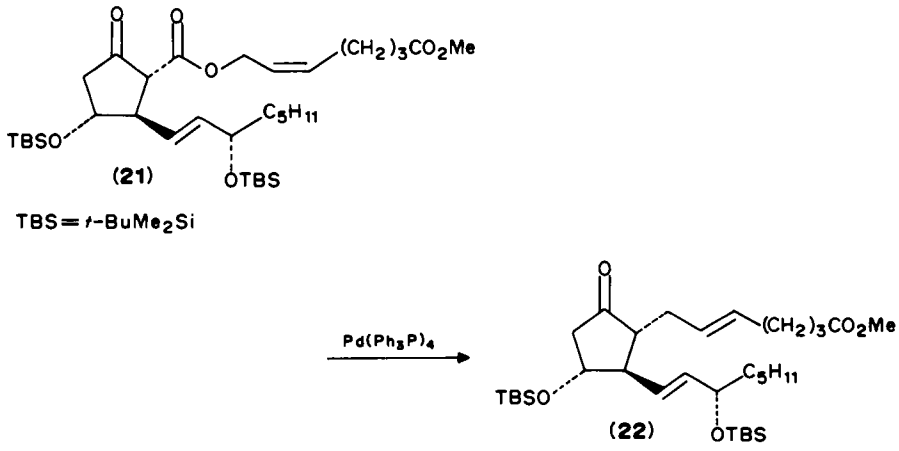
SCHEME 5

The enolate **17** can also be condensed with vinyl nitro compounds to give adducts such as **19** (Scheme 6), which are valuable intermediates in the preparation of both natural PGs and biologically important PG metabolites. For example, the nitro group in **19** is readily removed using tributyltin hydride to give the protected PGE_1 derivative[16]. Alternatively, the nitro group can be transformed into a keto functionality via a modified Nef reaction to give the 6-keto-PGE_1 derivative **20**, a metabolite of PGI_2 (prostacyclin), known to be a powerful vaso-active substance.



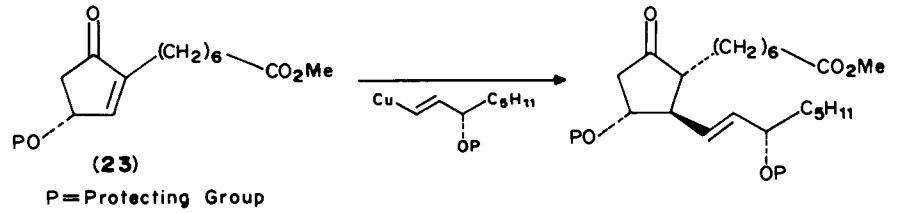
SCHEME 6

An interesting variant on the enolate trapping procedure was presented by Kurozumi and coworkers[17], who utilized a 2-alkenyloxycarbonylimidazole as the electrophile to give the alkenyloxycarbonylated product (**21**). Palladium-catalyzed decarboxylative allylation gave the PGE_2 derivative **22**, however, the 5,6-*cis* stereochemistry was completely lost during this operation (Scheme 7).



SCHEME 7

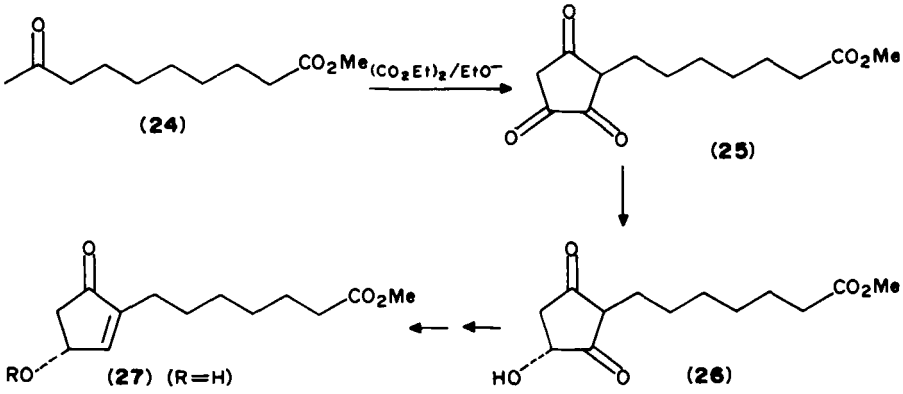
In addition to the synthesis of natural PGs, the three-component coupling procedure has been exploited for the preparation of a number of physiologically important PG analogues[18].



SCHEME 8

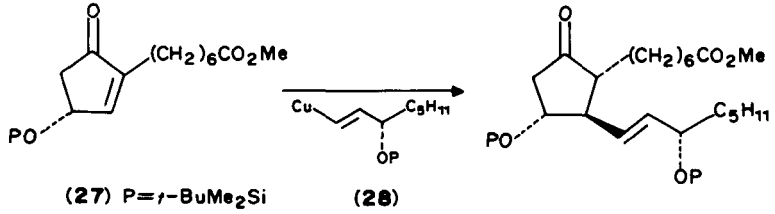
The problems associated with the alkylation of enolates such as **15** to introduce the PG α-chain can be avoided by use of a two-component coupling procedure in which the α-chain is already attached to the cyclopentenone system (Scheme 8). This approach has the advantage that a problematic operation, introduction of the α-chain via an enolate such as **15**, is avoided. One major drawback is that the α-chain is introduced early and must be carried through several manipulations. Clearly the success of such a procedure depends on the ready availability of substituted cyclopentenones such as **23** in optically pure form. A number of routes to **23** have been developed including resolution[19], synthesis using chiral starting materials[20] and asymmetric synthesis using chemical[21] and microbial techniques[22]. Much of the pioneering work in this area is due to Sih and coworkers, who found that the cyclopentanetrione **25**, available by condensation of ketone **24** with diethyl

oxalate, was enantioselectively reduced by the microbe *Dipodascus uninucleatus* to give the hydroxycyclopentanedione **26** (Scheme 9), which was transformed into the cyclopentenone **27**[22b,c,d].

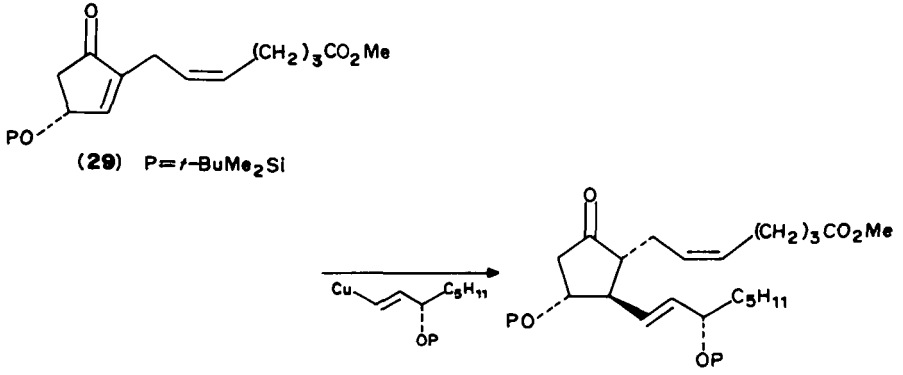


SCHEME 9

The synthesis of **27** has also been achieved via the asymmetric chemical reduction of **25** using lithium aluminum hydride partially decomposed by (−)-*N*-methylephedrine; the optical purity of the product is reported as 54(±6)%[21]. Compound **27** was prepared by Stork and Takahashi in homochiral form from D-glyceraldehyde[20].

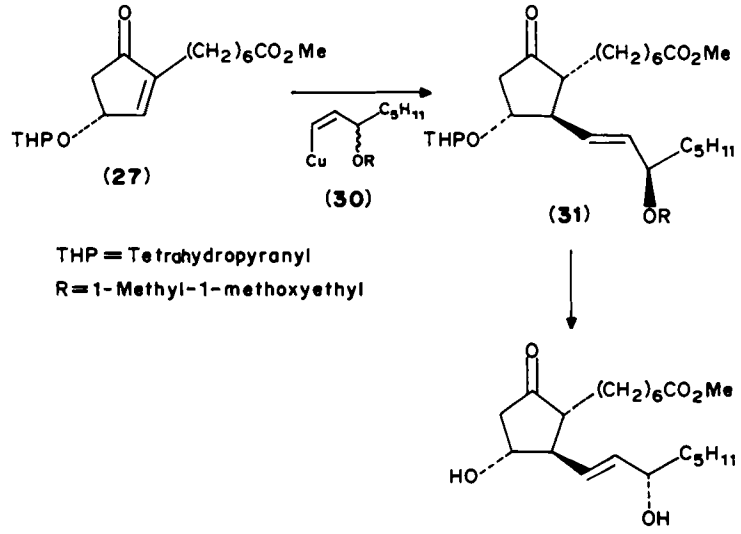


SCHEME 10



SCHEME 11

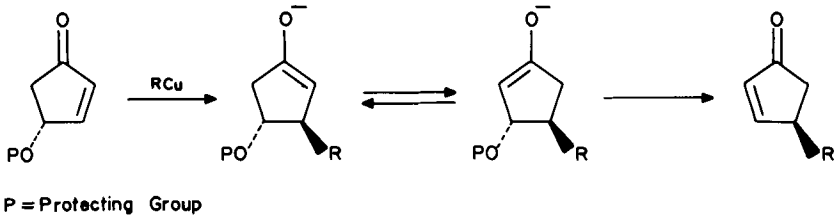
The conjugate addition of optically pure ω-chain **28** to suitably protected (+)-**27** to give the prostaglandin E_1 derivative (Scheme 10) was studied extensively by Sih. He found that the reaction was extremely dependent on the protecting groups on **27** and **28** and also on the type of copper reagent used. A combination of TBS-**27** and TBS-**28** (TBS = *t*-$BuMe_2Si$) was the most efficient for this conjugate addition when the vinyl anion was added as a divinyl cuprate reagent with *n*-Bu_3P as the solubilizing ligand. This approach was also effective for the preparation of PGE_2 from the cyclopentenone **29** (Scheme 11).[22b,c,d]



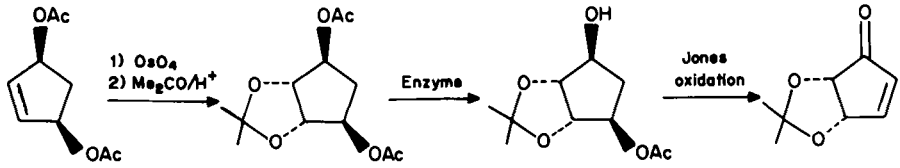
SCHEME 12

The syntheses above involved the use of allylic alcohol reagent **28** in homochiral form to achieve the preparation of optically pure PGs. Stork and Takahashi later showed that the racemic (*Z*)-cuprate **30** could be added to **27** to give exclusively the (15*R*)-PG derivative **31** through complete kinetic resolution (Scheme 12)[20]. Completion of the synthesis of PGE_1 involved the correction of the (13*Z*, 15*R*) side-chain of **31** to the (13*E*, 15*S*) arrangement which can be achieved via the Stork–Untch inversion sequence[23].

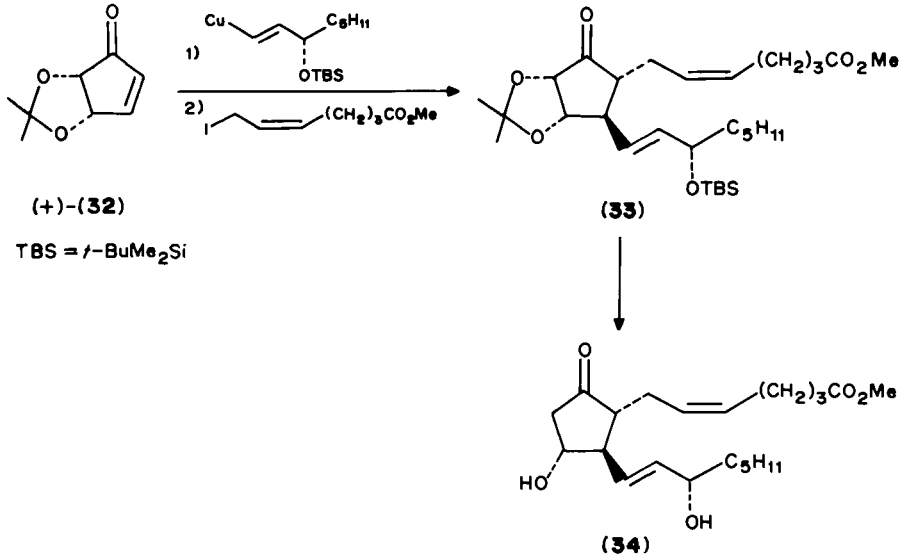
The problems associated with the three-component coupling process alluded to earlier have been attributed to equilibration of the intermediate enolate which results in elimination of the protected 4-hydroxy group (Scheme 13). In an attempt to overcome this problem,



SCHEME 13



SCHEME 14

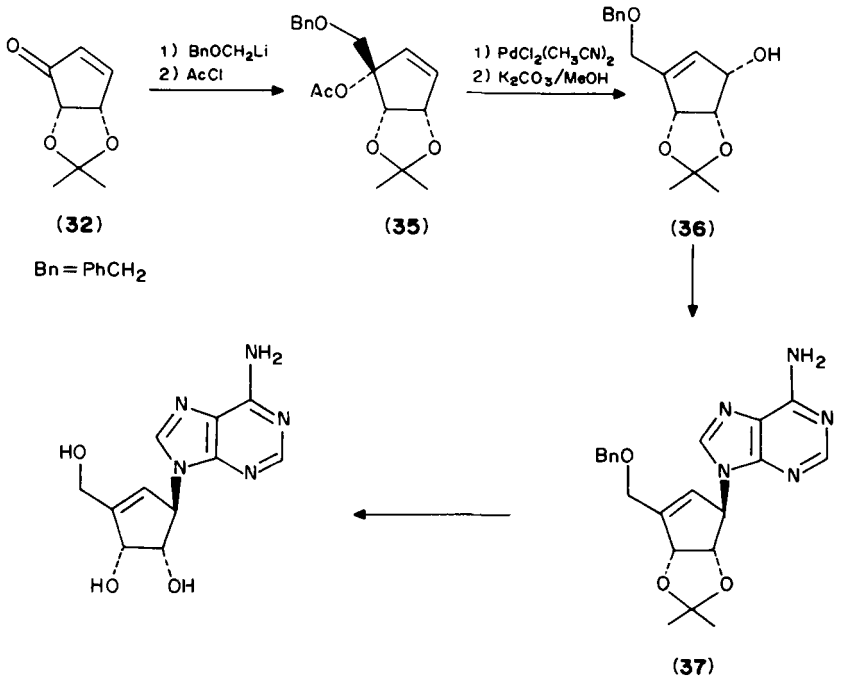


SCHEME 15

Johnson and Penning prepared the cyclopentenone **32** as outlined in Scheme 14; the key step in the sequence was the conversion of the *meso*-diacetate to the homochiral monoacetate using electric eel acetylcholinesterase. The overall yield of **32** (98% ee) by the sequence shown in Scheme 14 was 65%. Each carbon of the cyclopentenone framework of ketone **32** is differentially functionalized. The bicyclo[3.3.0] system ensured high or complete diastereoselectivity at the convex face. These factors, coupled with the ready availability of **32** in optically pure form, make it an attractive enone for elaboration to a variety of targets. It was proposed that the presence of the α-oxygen functionality, constrained in the second five-membered ring, would suppress enolate equilibration of the type shown in Scheme 13. Indeed, addition of the lower side-chain as a tributylphosphine stabilized copper reagent followed by alkylation with an allylic iodide gave the prostaglandin derivative (**33**) in 53% yield (Scheme 15). Deprotection of the 15-TBS protected alcohol was followed by reductive removal of the acetonide with Al(Hg) to give PGE_2 methyl ester (**34**)[24].

The enone (+)-**32** was also employed by Johnson and coworkers[25] as an intermediate in an efficient synthesis of neplanocin A, a carbocyclic nucleoside which shows significant

antitumor and antiviral activity. Addition of a benzyloxymethyllithium to the enone **32**, followed by acetylation, gave the acetate **35**, which was subjected to a palladium-catalyzed rearrangement to give **36** after hydrolysis (Scheme 16). Allylic alcohol **36** is an intermediate encountered in an earlier synthesis of neplanocin A[26]; however, in contrast to this earlier



SCHEME 16

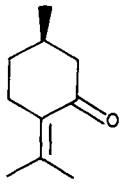
synthesis, Johnson found that the adenine base could be introduced intact by simple displacement of the mesylate derived from **36** to give **37**. Deprotection of **37** completed the synthesis of (−)-neplanocin A in 11% yield from cyclopentadiene.

III. 2-CYCLOHEXENONES

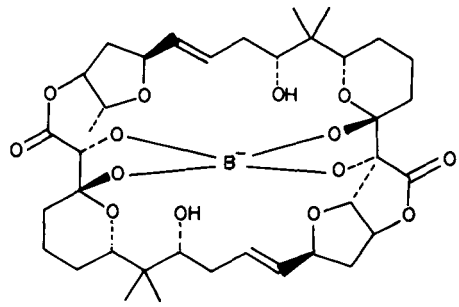
The optically pure monoterpene (+)-pulegone (**38**) has seen frequent and variable use in organic synthesis including: (i) the direct manipulation of the pulegone framework into the derived product; (ii) conversion of pulegone to another, non-enone, compound which is carried on in the synthesis; and (iii) transformation to a compound useful as a temporary chiral auxiliary for a wide variety of asymmetric processes.

The direct incorporation of the pulegone structure into a target molecule is probably the most efficient use of the chiral unit and several syntheses involving this procedure have been reported, most of which involve the exocyclic enone unit as a Michael acceptor.

Two independent approaches to the ionophoric antibiotic aplasmomycin (**39**) have been reported, both of which depend on (+)-pulegone as the basic starting material and also for the source of optical activity. Both groups recognized the C_2 symmetry present in the aplasmomycin skeleton and made similar initial bond disconnections, however, the subunits were prepared via different routes.

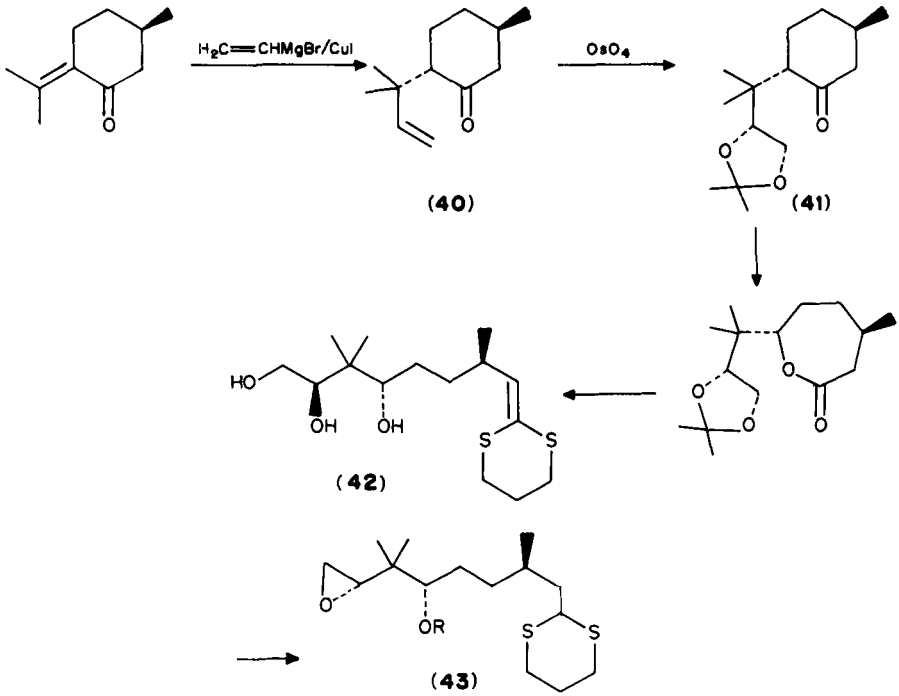


(38)



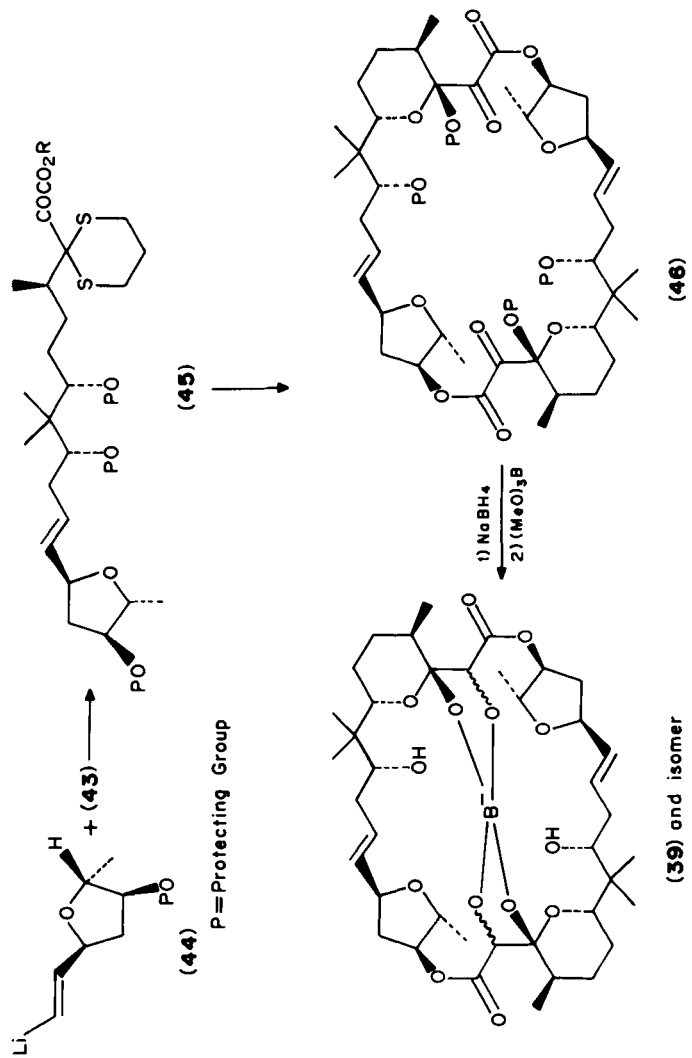
(39)

The initial step in the approach of Corey's group[27] to this molecule involved the conjugate addition of vinyl cuprate to (+)-pulegone to give **40** after equilibration (Scheme 17). An impressive stereoselective hydroxylation (OsO_4) of the vinyl moiety was carried out to give **41**, after suitable manipulation, which was oxidized to a lactone. Cleavage of the lactone using trimethylaluminum and propanedithiol gave ketenethioacetal **42** which was transformed to the key intermediate **43**.



SCHEME 17

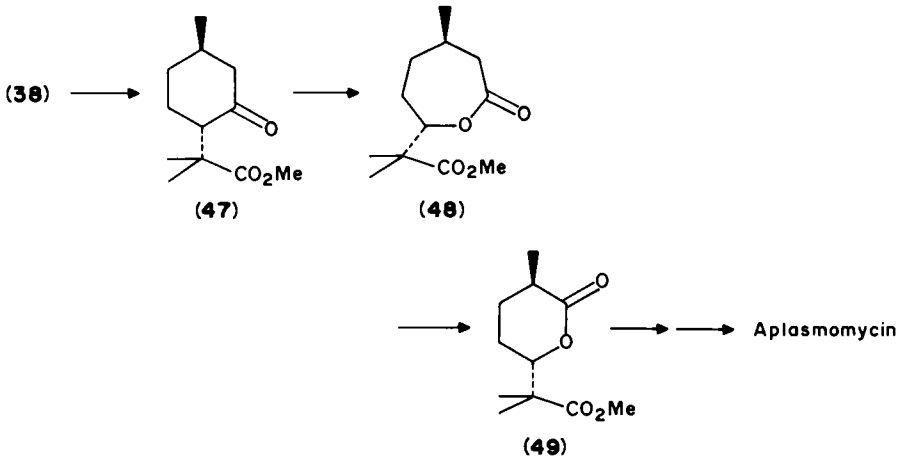
The vinyl lithium (**44**), derived from D-mannose, was coupled with epoxide **43** and the dithiane moiety was metallated and condensed with dimethyl oxalate to give **45**. The latter represents one half of the aplasmomycin skeleton in suitably protected form (Scheme 18).


COCO2R
S
S
PO
PO
PO
(45)
(46)
OP
1) NaBH4
2) (MeO)3B
OH
OH
B
(39) and isomer
Li
H
+ (43)
(44)
P=Protecting Group

SCHEME 18

Selective deprotection of **45** allowed coupling of two units of **45** to give the cyclic compound **46** with the key macrolactonization being achieved in 71% yield. Completion of the synthesis involved reduction and incorporation of the boron atom, however, no selectivity was achieved during the reduction step.

White and coworkers' approach[28] to aplasmomycin involved the chiral lactone **49**, which served as the C(3)–C(10) segment in each half of the macrocycle. This lactone was prepared either by resolution or, more efficiently, by manipulation of (+)-pulegone as outlined in Scheme 19[28b]. Keto ester **47** was prepared from (+)-pulegone via (i) hydrocyanation followed by hydrolysis or (ii) conjugate addition of vinyl cuprate followed by oxidative cleavage, and was subjected to Baeyer–Villiger oxidation to give lactone **48**. Ring contraction of **48** was achieved using conventional chemistry to give lactone (+)-**49** which was ultimately transformed into (+)-aplasmomycin and also served as an important building block in efforts directed towards a synthesis of boromycin.

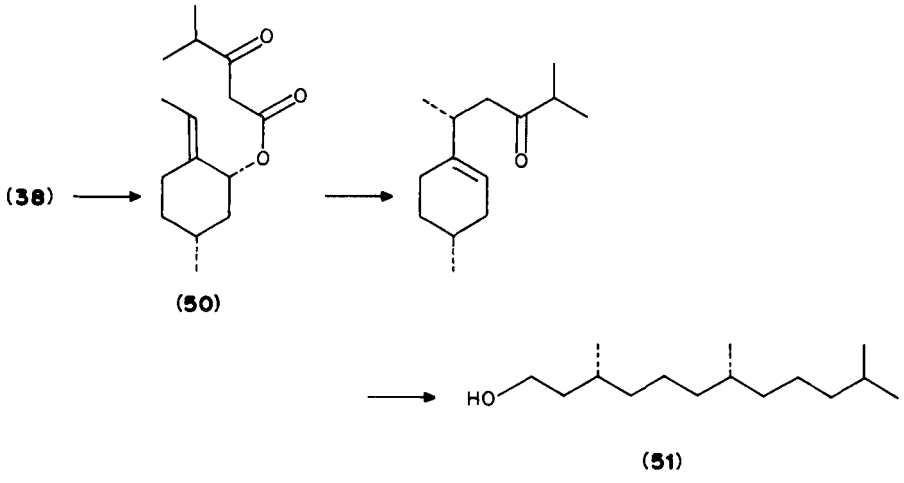


SCHEME 19

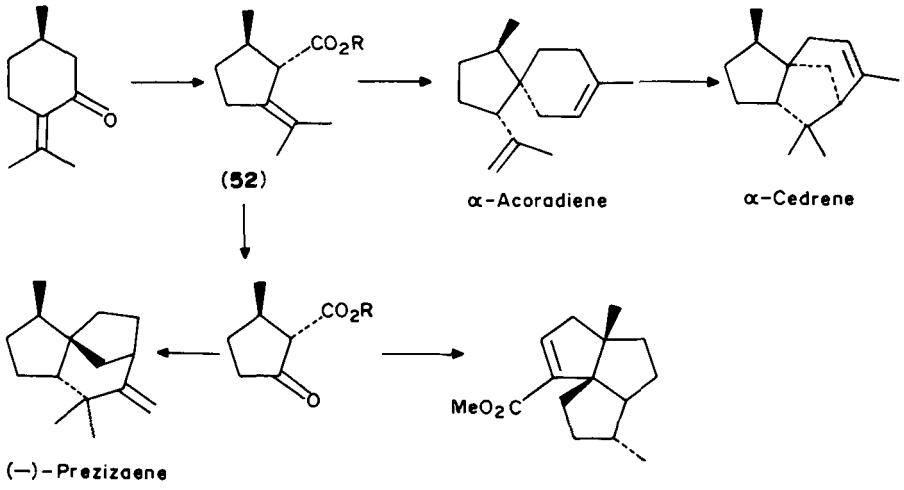
(+)-Pulegone has also found use in the synthesis of optically active acyclic compounds such as the vitamin E side-chain **51** as outlined in Scheme 20[29]. The key features of this synthesis involve the selective mono-demethylation of the isopropylidene moiety, via deconjugative ketalization and ozonolysis, and a highly stereoselective Carroll rearrangement of the β-keto ester **50** which serves to establish the stereochemistry at C-(7) of the final product. This example of 1,3-stereocontrol provides a highly efficient and completely stereocontrolled synthesis of the optically pure (3*R*, 7*R*) vitamin E side-chain.

Transformation of (+)-pulegone into the optically pure cyclopentane ester **52** can be readily achieved via the Favorskii rearrangement; this cyclopentane ester has found considerable use as a synthetic intermediate[30]. Since the enone functionality of (+)-pulegone plays no significant role in syntheses involving **52**, after the initial Favorskii rearrangement, this chemistry will not be covered in depth here. However, a notation of some syntheses involving cyclopentane **52** is given in Scheme 21.

The use of chiral auxiliaries to achieve asymmetric induction in a chemical transformation is an important process in organic chemistry, and one of the most widely used chiral auxiliaries is (−)-8-phenylmenthol (**53**)[31]. This chiral adjuvant is readily available from (+)-pulegone (Scheme 22) and has proved successful in achieving significant dias-



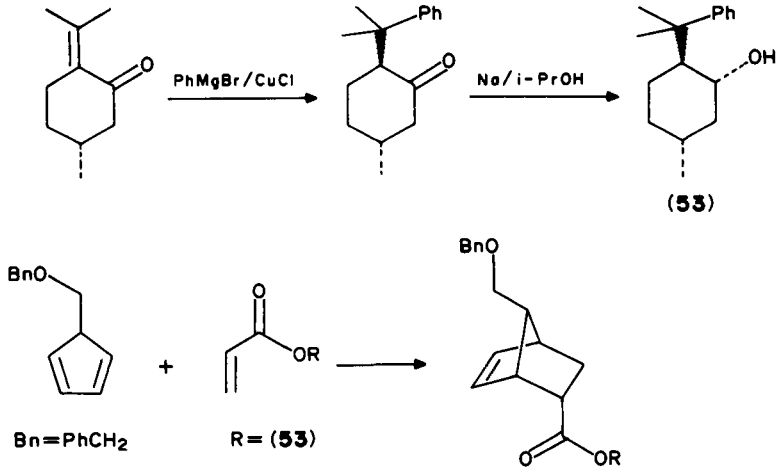
SCHEME 20



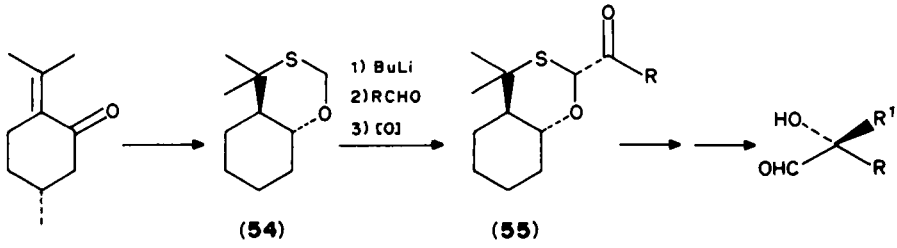
SCHEME 21

tereoselection in a number of reactions, including the Diels–Alder reaction, ene reactions, conjugate addition, alkylations, etc.[32]. The acrylate ester of (+)-8-phenylmenthol was employed by Corey and Ensley[31] as a dienophile for a highly diastereoselective Diels–Alder reaction. The bicyclic product was elaborated to an intermediate which was useful for prostaglandin syntheses.

The Michael acceptor property of (+)-pulegone was employed by Lynch and Eliel[33] to prepare the optically active 1,3-oxathiane **54** which was metallated, condensed with aldehydes and oxidized to give keto oxathianes **55** (Scheme 23). Addition of Grignard reagents to these keto oxathianes occurred with excellent diastereoselectivity and, after cleavage of the oxathiane, led to α-hydroxy aldehydes with a high degree of optical purity.



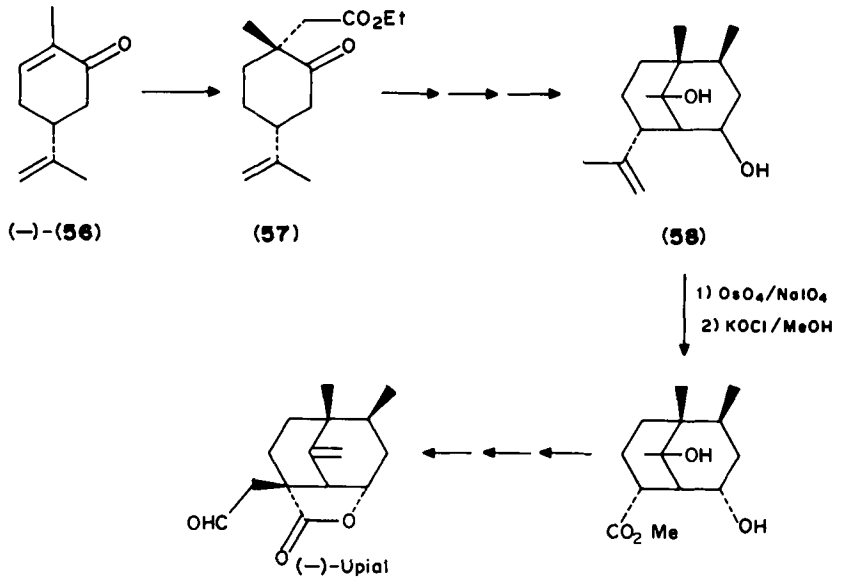
SCHEME 22



SCHEME 23

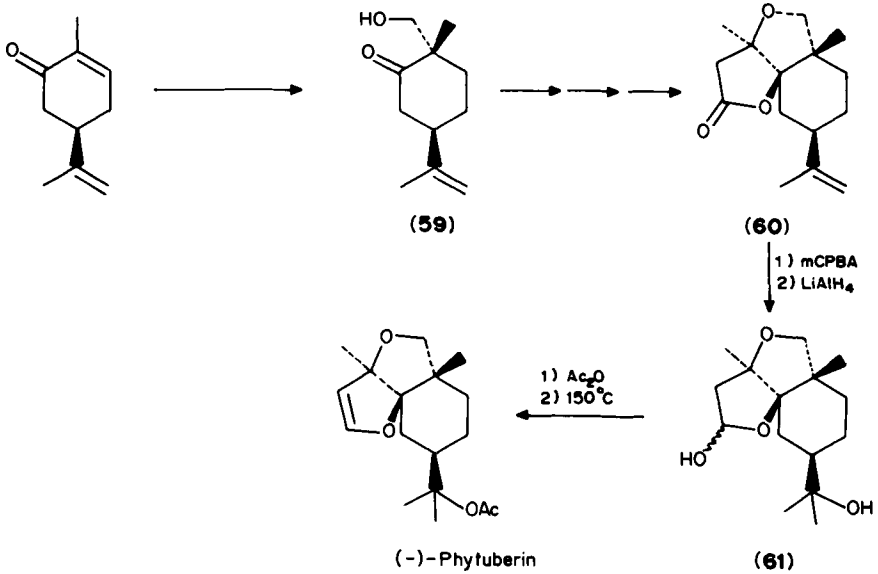
The availability of carvone, in either enantiomeric form, along with its diverse array of functionality has rendered this substance an attractive starting material for numerous synthetic endeavors. A classical method for the functionalization of α,β-unsaturated ketones involves a conjugate reduction/alkylation sequence and carvone has proved to be very amenable to this process. Alkylation of the enolate derived by conjugate reduction of (−)-carvone (**56**) with ethyl bromoacetate (Scheme 24) was the initial step in a recent synthesis of the non-isoprenoid sesquiterpene, upial, which served to establish the absolute configuration of this compound[34]. The keto ester **57** was elaborated to the bicyclic adduct **58**, whereupon the isopropenyl group was unmasked to give an ester function which was required for the final transformation.

The above synthesis of upial demonstrates the use of the isopropenyl group of carvone as a latent ester function; an example of the isopropenyl group acting as a dimethylcarbinol equivalent is outlined in Scheme 25, an elegant synthesis of (−)-phytuberin[35]. Condensation of the enolate derived by conjugate reduction of (−)-carvone with formaldehyde gave the hydroxymethylketone **59** as a mixture of diastereomers. Interestingly, the minor isomer could be re-equilibrated by simple thermolysis apparently via a retroaldolization/aldolization sequence. Elaboration of **59** to **60** was achieved via sequential ethynylation and hydration and the isopropenyl group was then converted to a



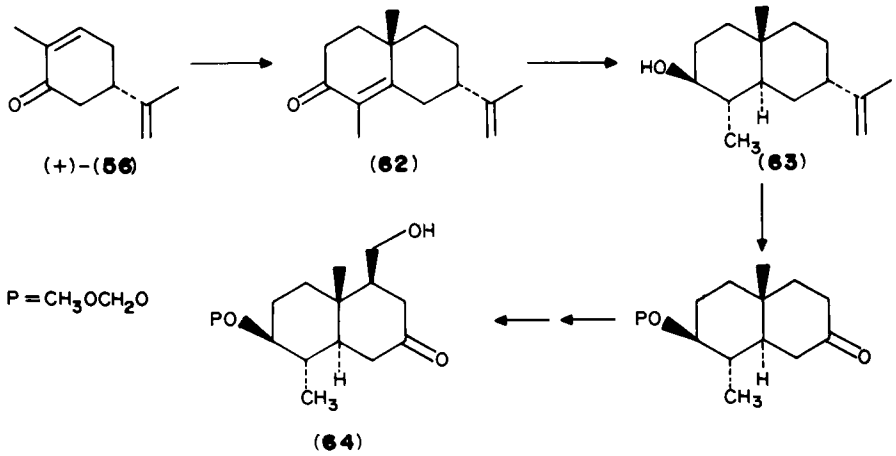
SCHEME 24

dimethyl carbinol by epoxidation followed by reduction to give **61**. Elimination of the lactol moiety completed the synthesis of (−)-phytuberin.



SCHEME 25

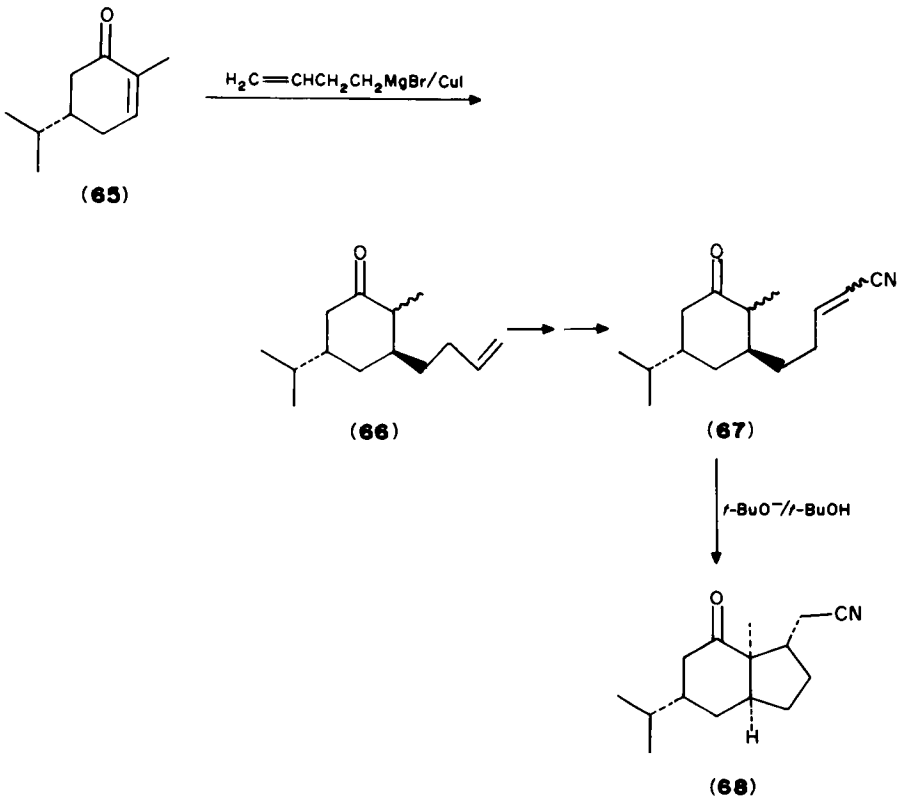
In studies directed towards a general synthesis of quassinoids, and in particular bruceatin, Ziegler required the keto alcohol **64** in chiral, non-racemic form. This compound could be effectively prepared from (+)-carvone [(+)-**56**] (2 mol scale) utilizing a reductive annelation sequence to give enone **62** (Scheme 26)[36]. Reduction of the enone **62** to alcohol **63** was followed by transformation of the isopropenyl group to a ketone by an ozonolysis, Baeyer–Villiger oxidation, oxidation sequence. Introduction of a hydroxymethyl group at C-9 was achieved through multiple transformations to give the desired product **64**. While this compound ultimately proved to be unsuitable for further transformation into bruceatin, the chemistry developed by Ziegler demonstrates that carvone can serve as a valuable precursor to highly functionalized decalins via the conjugative reduction/alkylation sequence.



SCHEME 26

The enone functionality in carvone can also serve as a Michael acceptor for carbon nucleophiles with the isopropenyl group serving to direct the approach of incoming nucleophiles. This methodology was employed by Brattesani and Heathcock to prepare the *cis* hydrindanone **68**, an intermediate in a proposed synthesis of the sesquiterpene alkaloid dendrobine[37]. Copper-catalyzed addition of 4-butenylmagnesium bromide to (+)-carvotanoacetone (**65**) occurred with complete diastereoselectivity, *trans* to the isopropyl group, to give adduct **66** (Scheme 27). Ozonolysis and chain extension gave the unsaturated nitrile **67** which, on treatment with base, underwent a stereoselective, intramolecular Michael addition reaction to give *cis* hydrindanone **68**. Unfortunately the stereochemistry of the cyanomethyl side-chain is the opposite of that required for elaboration into dendrobine, however, this approach using carvone allows rapid entry into optically pure hydrindanones.

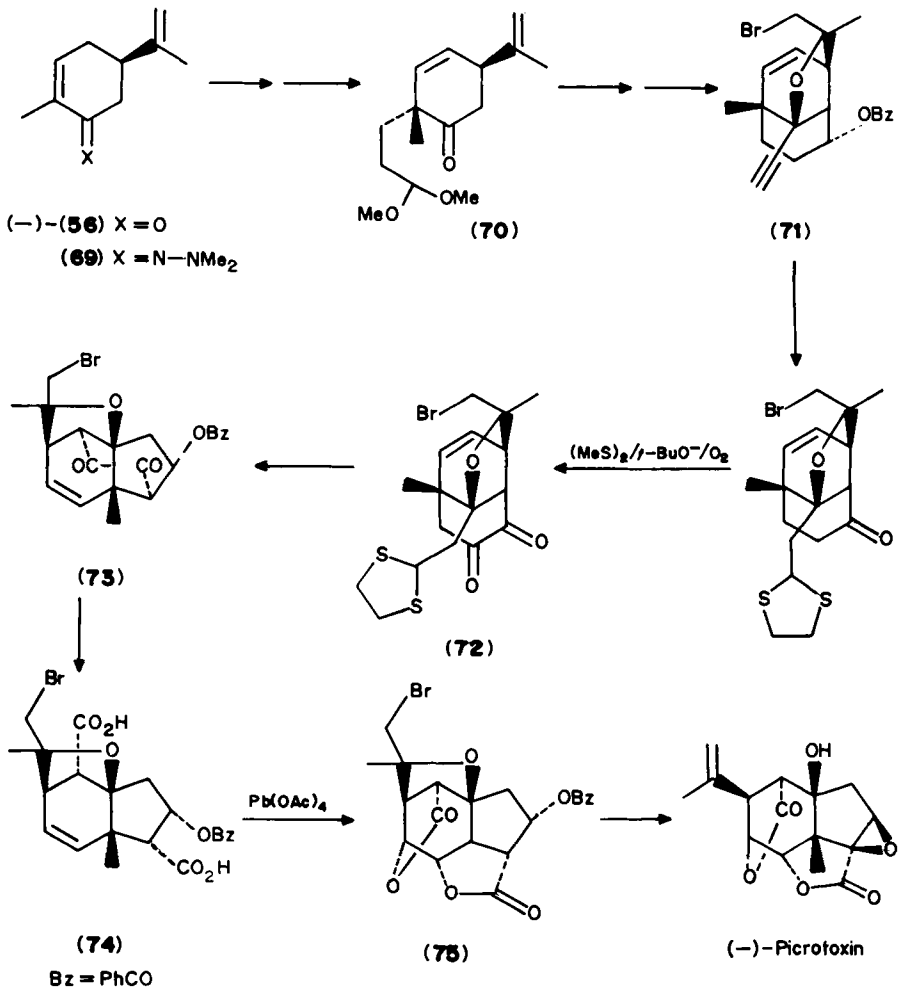
An impressive use of the complete carvone structure in the synthesis of a complex natural product is manifest in the first synthesis of picrotoxin by Corey and Pearce (Scheme 28)[38]. The first step in this synthesis involved α-alkylation of the anion derived by γ-deprotonation of the *N*,*N*-dimethylhydrazone derivative **69** of (−)-carvone to give **70**. Hydrolysis of **70** was followed by acid-catalyzed intramolecular aldol condensation, ethynylation and intramolecular bromoetherification to give **71**. The acetylene **71** was transformed into the corresponding protected aldehyde which was converted to diketone **72** using potassium *tert*-butoxide, dimethyl disulfide and oxygen, methodology developed



SCHEME 27

by Barton. Intramolecular aldol condensation of the aldehyde corresponding to **72** gave **73**, which established the hydroindene nucleus of picrotoxin. Oxidative cleavage of diketone **73** to diacid **74** was followed by double lactonization to give **75** which, on elimination of the benzoate, epoxidation and reductive removal of bromine, afforded (−)-picrotoxin. It is perhaps pertinent to note here that an inexpensive starting material with a single chiral center has been stereoselectively transformed into a complex product with eight contiguous chiral centers (three of them quaternary) in homochiral form.

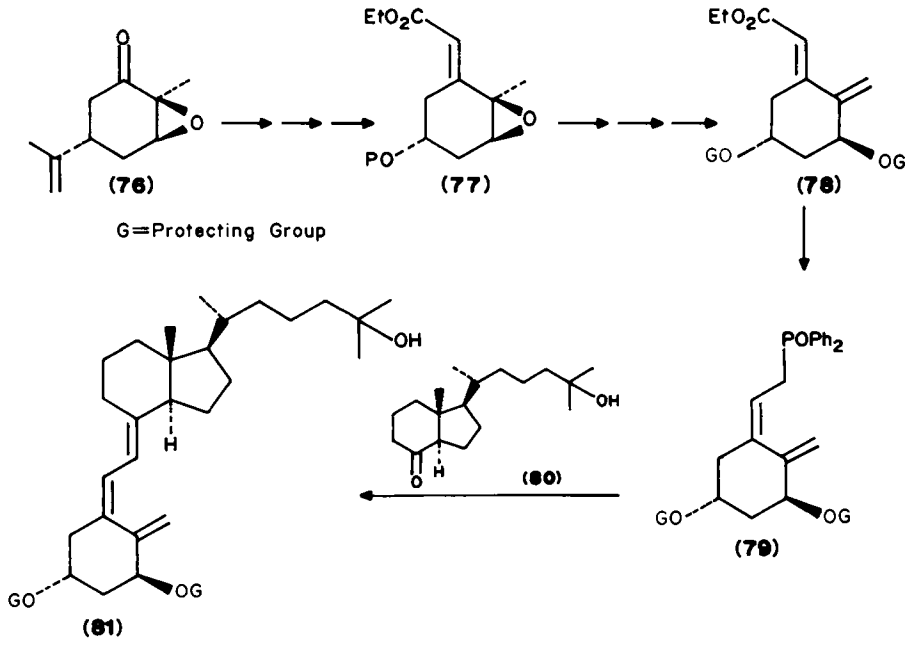
Stereoselective epoxidation of the enone group of carvone, or a carvone derivative, represents a convenient method for the introduction of two new asymmetric centers on carvone. This epoxidation, which occurs with complete selectivity, *trans* to the isopropenyl group, was exploited to establish the stereochemistry required in a total synthesis of a vitamin D metabolite, 1α,25-dihydroxycholecalciferol [**81** (P = H)] (Scheme 29)[39]. Epoxy ketone **76** was subjected to standard Horner–Emmons conditions and the isopropenyl group was transformed into an alcohol, via oxidative cleavage, Baeyer–Villiger oxidation and hydrolysis, to give **77**. Regioselective cleavage of the epoxide and elimination of the resulting tertiary alcohol gave **78** which was converted into the allylic phosphine oxide **79**. Wittig–Horner reaction between **79** and **80** (for the preparation of **80** see Scheme 46) gave **81**; the stereochemistry of the newly formed double bond was completely that shown.



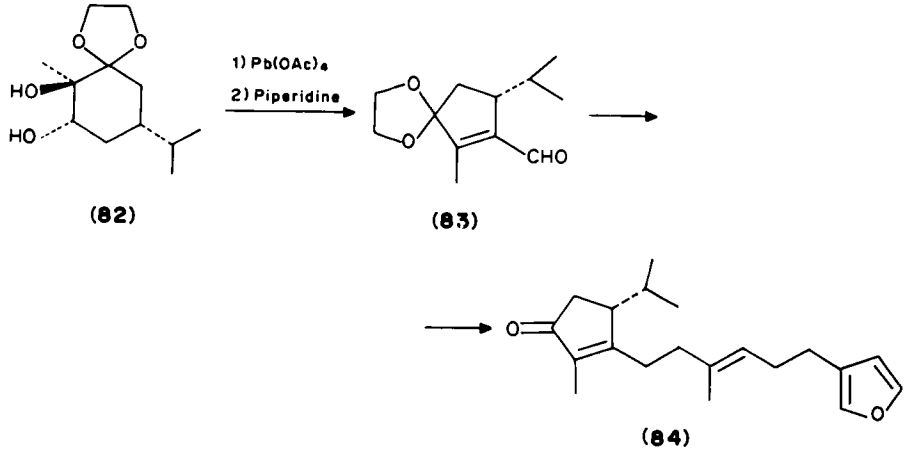
SCHEME 28

The enantiomer of **76**, prepared from (−)-carvone was employed by Yoshikoshi and coworkers as the key starting material in a short synthesis of the diterpene taonianone (**84**) (Scheme 30)[40]. The epoxide was transformed into cyclopentene **83** via protection, cleavage of the epoxide, hydrogenation, oxidative cleavage of diol **82** and intramolecular aldol condensation. Elaboration of the aldehyde group of **83** gave (+)-taonianone of known absolute configuration which allowed assignment of the stereochemistry of natural material.

An electrooxidative approach to the important pesticide (1*R*, 3*R*)-methyl chrysanthmate (**89**) reported by Torii and coworkers[41] used (+)-carvone as the starting material (Scheme 31). Stereoselective epoxidation of (+)-carvone hydrochloride (**85**) followed by methanolysis gave **86** which was oxidatively degraded using a MeOH–$LiClO_4$–Pt system

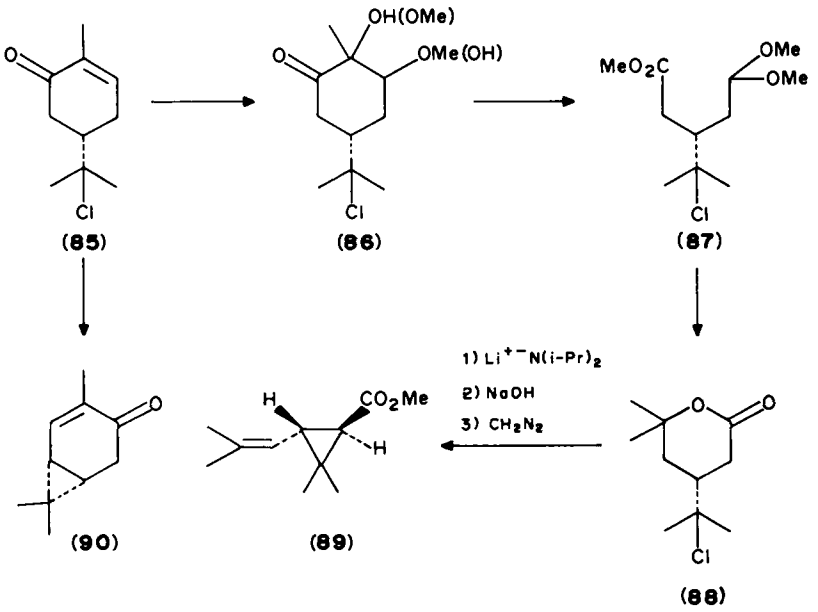


SCHEME 29



SCHEME 30

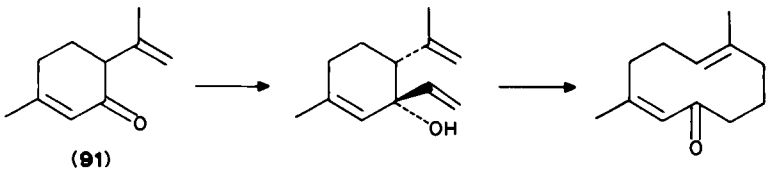
to give **87** in high yield. Ester **87** was treated with methyllithium followed by hydrolysis and oxidation to give the key intermediate **88** which is known to be a precursor of methyl chrysanthmate.



SCHEME 31

(+)-Carvone hydrochloride (**85**) was shown by Wiemer and coworkers[42] to be readily transformed into (−)-carenone (**90**) via intramolecular α-alkylation, Wharton rearrangement of the derived hydrazine and oxidation (Scheme 31). Since both enantiomers of **90** are readily available, simply by selecting (+)- or (−)-carvone, these compounds should prove useful in the preparation of a variety of natural products.

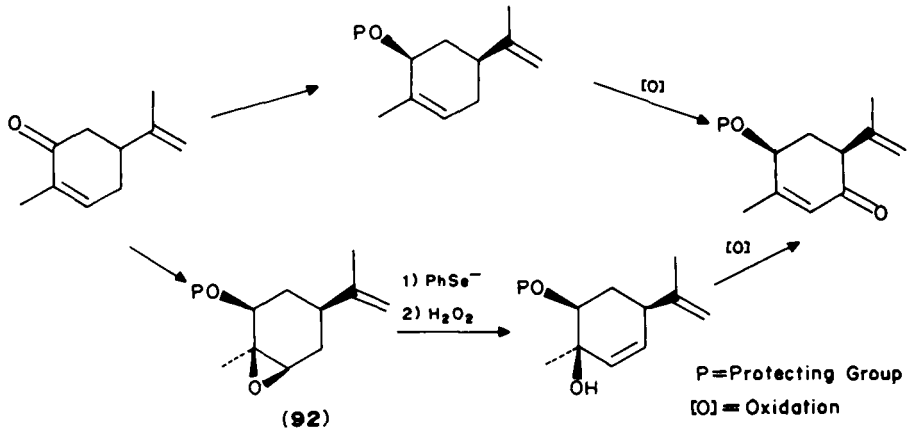
The addition of a vinyl nucleophile to the carbonyl of compounds such as **91** followed by Cope rearrangement provides a smooth method for the preparation of macrocyclic, germacrane-like intermediates (Scheme 32). Carvones have been found to be useful precursors to compounds such as **91** and ultimately to natural germacronolides.



SCHEME 32

The conversion of carvone into enones related to **91** has been accomplished via either a reduction, allylic oxidation sequence (Scheme 33), or a route involving selenide opening of epoxide **92** followed by selenoxide elimination and 1,3-oxidative rearrangement.

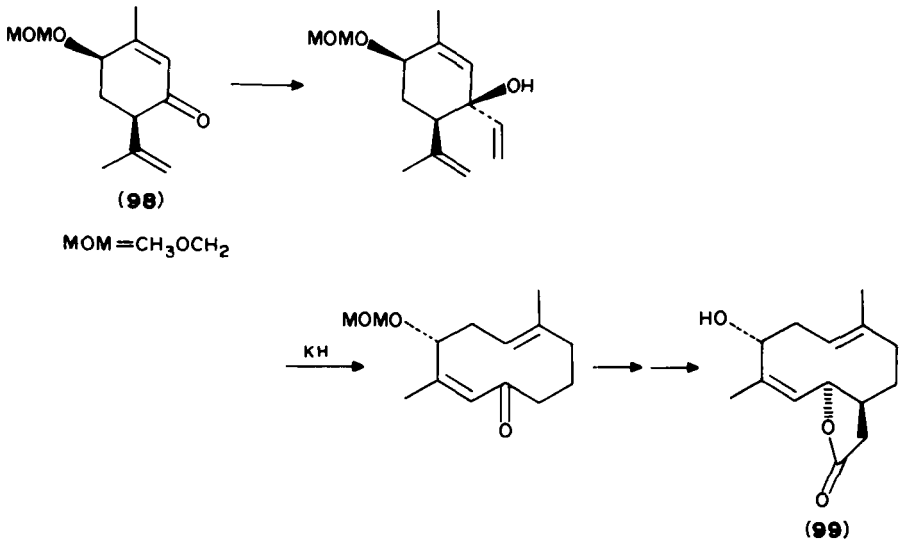
The enone **93**, derived from (+)-carvone, was employed by Still and coworkers[43] in a synthesis of eucannabinolide which featured an oxy-Cope rearrangement as the key step in the formation of the macrocycle. The cyclobutenyllithium **94** added to **93** with good



SCHEME 33

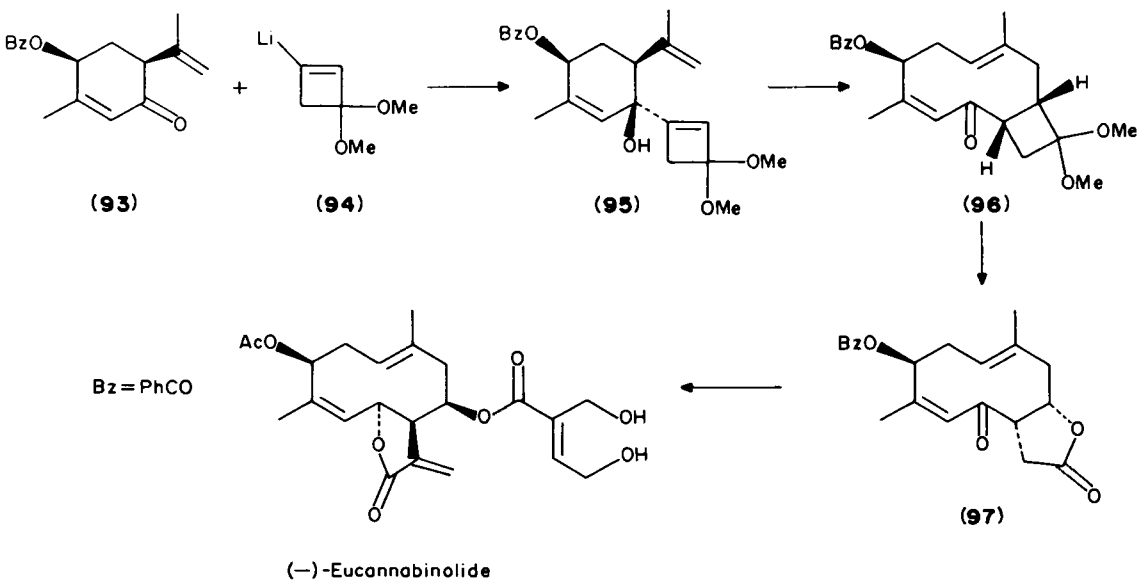
selectivity to give **95**, which was rearranged to the cyclodecenone **96** (Scheme 34). The cyclobutanone dimethylketal moiety of **96** was unmasked and subjected to Baeyer–Villiger oxidation to give **97**. Conversion of **97** into eucannabinolide involved selective reduction and lactone transformation; the stereo- and regiochemistry of these manipulations were effectively predicted on the basis of MM2 calculations.

A similar strategy was employed by Takahashi and coworkers[44] to prepare the heliangolide (**99**) from enone **98** (Scheme 35).



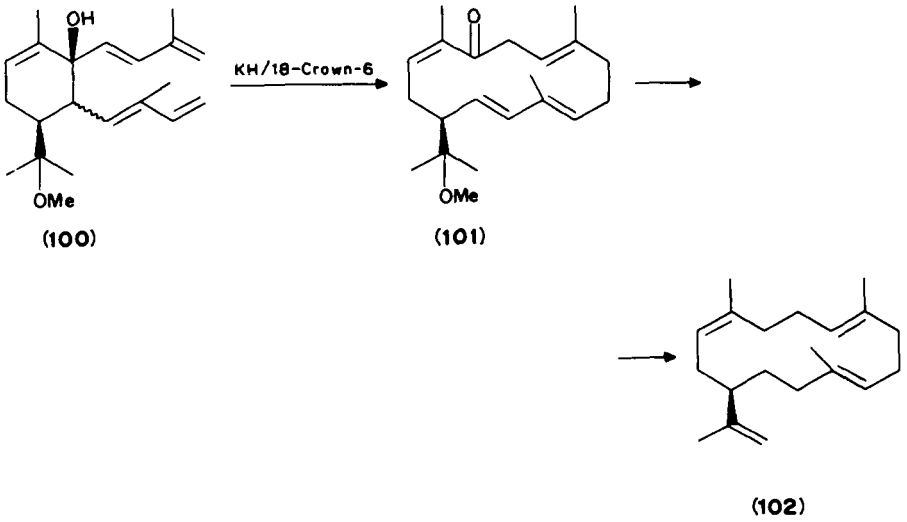
SCHEME 35

A novel variation of this oxy-Cope macro-expansion methodology was developed by Wender and Holt[45] to prepare 14-membered macrocycles as found in the cembrane series.


BzO
Li
OMe
OMe
OH
H
(93)
(94)
(95)
(96)
(97)
AcO
OH
Bz = PhCO
(—)-Eucannabinolide

SCHEME 34

The key step in this approach involves the rearrangement of **100**, prepared from (+)-carvone, to **101** (Scheme 36) which contains all 20 carbons required for elaboration into (−)-(3Z)-cembrane A (**102**). Reductive removal of the carbonyl in **101** was followed by selective hydrogenation of the least substituted double bond and elimination of the methoxy group to give **102**.



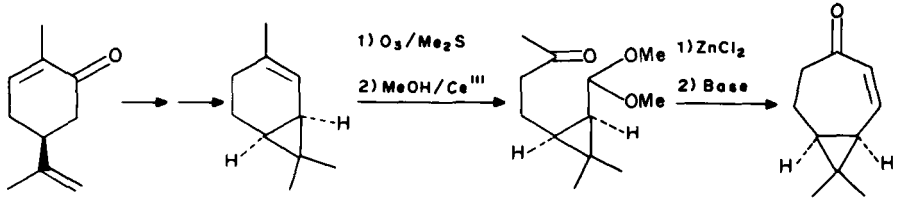
(100) (101) (102)

SCHEME 36

IV. 2-CYCLOHEPTENONES

The cycloheptane nucleus is found in a number of important natural products and, as a result, the preparation of functionalized cycloheptenones in homochiral form has become a desirable goal. While few, if any, optically pure cycloheptenones are commercially available, the preparation of these compounds has been achieved, either from the chiral pool or via asymmetric synthesis, and their use in total synthesis is expanding.

One of the more useful chiral cycloheptenones reported to date is the [5.1.0] bicyclic compound **103** prepared by Smith and coworkers[46]. This compounds can be prepared in both enantiomeric forms with the ultimate source of chirality being carvone. Conversion of (+)-carvone into (−)-2-carene (**104**) was readily accomplished via conjugate reduction, hydrochlorination-cyclization, and Shapiro reaction (Scheme 37). Ozonolysis of **104** and

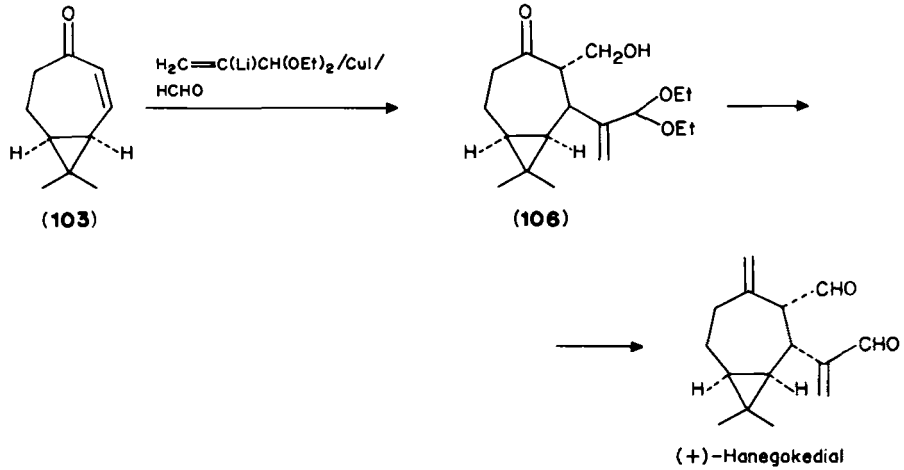


(104) (105) (103)

SCHEME 37

selective protection gave **105**, which was cyclized using the Mukaiyama protocol and eliminated to give homochiral **103** in good yield.

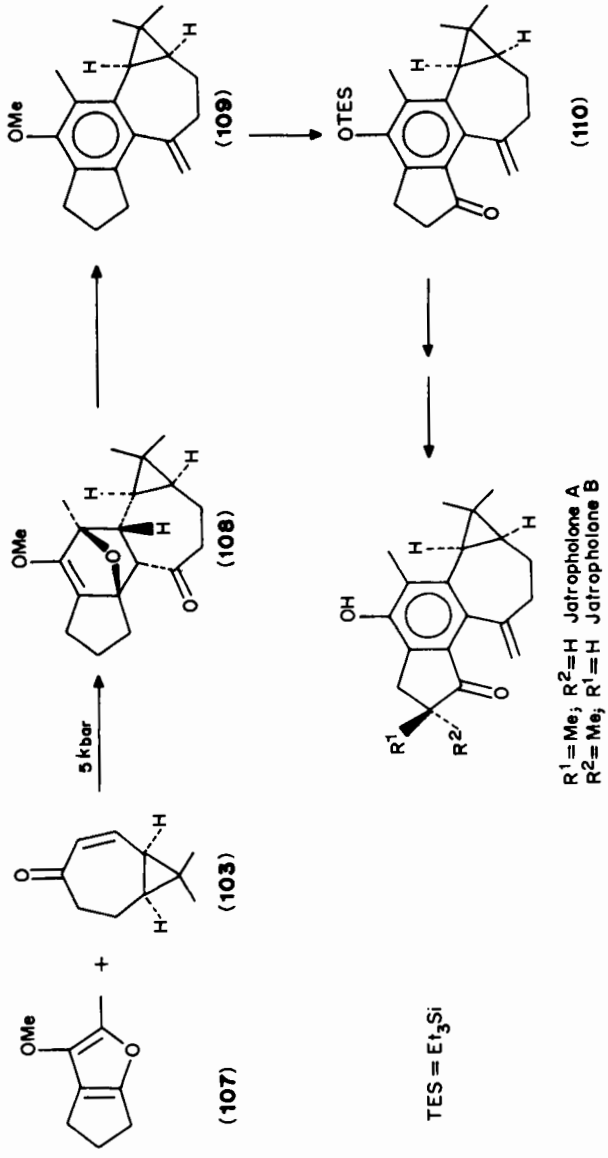
The enone functionality of **103** was exploited by Taylor and Smith in a short synthesis of the sesquiterpene (+)-hanegokedial as outlined in Scheme 38[47]. Sequential treatment of **103** with the cuprate prepared from bis(1,1-diethoxy-2-propenyl)lithium and formaldehyde gave **106** along with its C2 epimer, which was subjected to methylenation, oxidation and hydrolysis to give natural (+)-hanegokedial.



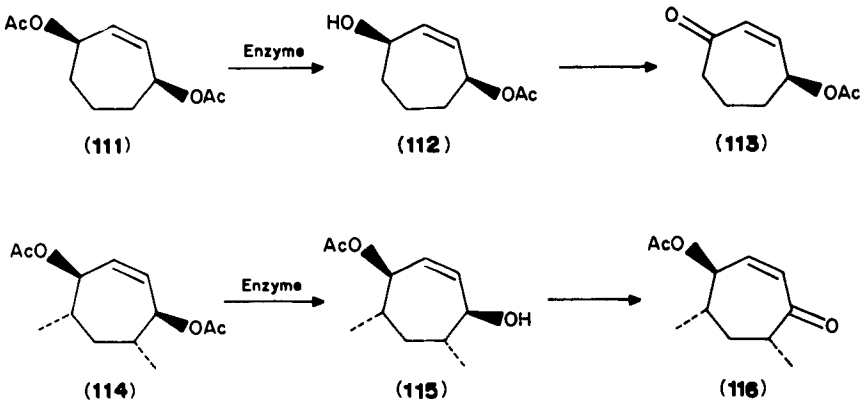
SCHEME 38

The enone **103** was also exploited by Smith and coworkers as a dienophile in a route to the jatropholone skeleton which featured a high-pressure Diels–Alder reactions[48]. The Diels–Alder reaction of **103** and furan **107** at 5 kbar occurred with complete diastereoselectivity and in high yield to give **108**. The ease of this reaction is significant, since cycloalkenones are known to be reluctant partners in Diels–Alder reactions and application of this process to more readily available chiral cyclohexenones and cyclopentenones may prove to be profitable. Aromatization of **108**, followed by methylenation, gave **109** which underwent regioselective oxidation to **110** after protecting group manipulation (Scheme 39). Methylation of **110**, followed by deprotection, gave (+)-jatropholones A and B in homochiral form, which established the absolute stereochemistry of these compounds.

The use of enzymes to prepare optically active cycloheptenones has recently been reported by Pearson and coworkers (Scheme 40)[49]. Enantioselective hydrolysis of **111** to give hydroxy acetate **112** could be achieved using electric eel acetylcholinesterase (39% yield, 100% ee) or the lipase from *Candida cyclindracea* (40% yield, 44% ee). Oxidation of **112** gave the optically pure cycloheptenone **113**, which should prove to be useful in natural product synthesis. In a similar manner the diacetate **114** was enantioselectively hydrolyzed using the lipase mentioned above to give **115** (61% yield, 100% ee). However, the direction of induced chirality was reversed. Oxidation of **115** afforded cycloheptenone **116**, which is related to enones known to be intermediates for the synthesis of the Prelog–Djerassi lactone.


OMe
(107)
(103)
5 kbar
(108)
(109)
OTES
(110)
OH
TES = Et3Si
R1 = Me; R2 = H Jatrophalone A
R2 = Me; R1 = H Jatrophalone B

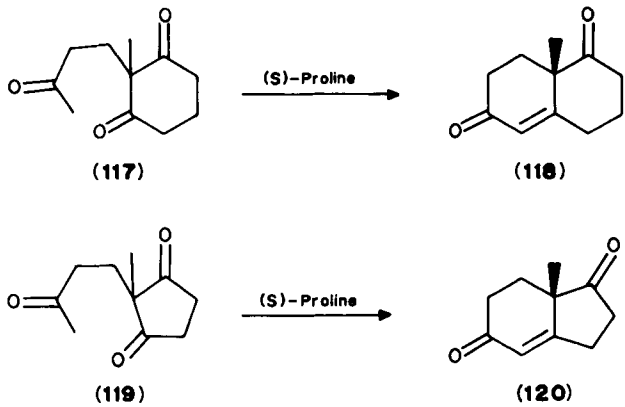
SCHEME 39



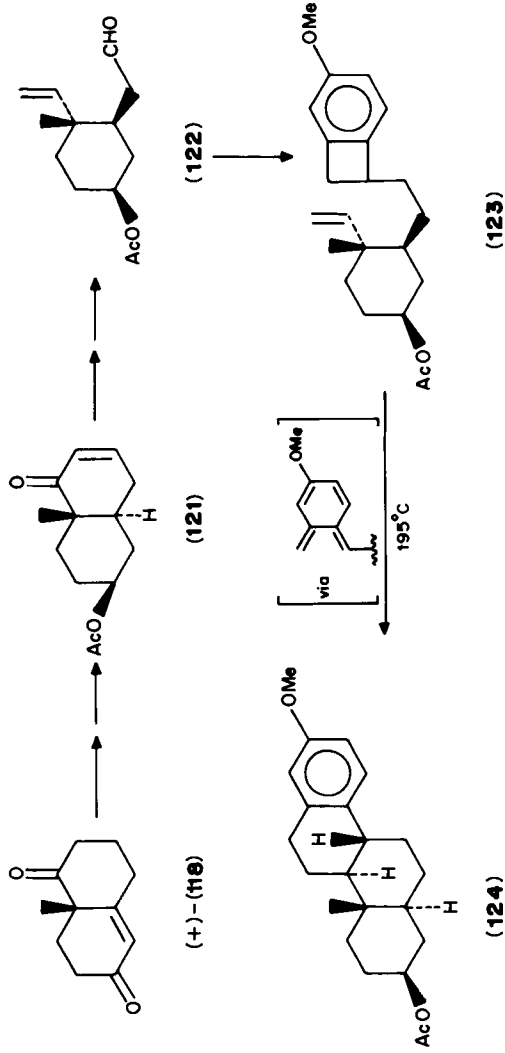
SCHEME 40

V. BICYCLIC ENONES

One of the most widely known bicyclic enones is the Wieland–Miescher ketone (**118**) which has been used in its racemic form as a versatile building block for the synthesis of steroids and terpenoids. Enone **120** became readily available in homochiral form as a result of independent work by the groups of Hajos[50] and Eder[51] who found that the intramolecular aldol condensation of triketone **119** could be rendered highly enantioselective through the use of a chiral catalyst, i.e. (*S*)-proline. Application of this process to the triketone **117** was reported by Furst and coworkers[52] to give the bicyclic enone **118** with 70% optical purity; however, alternate crystallization of optically pure **118** followed by racemic **118** allowed for the isolation of essentially optically pure **118** in reasonable yield. Clearly, either enantiomer of **118** or **120** is available simply by the appropriate choice of catalyst, (*S*)- or (*R*)-proline.



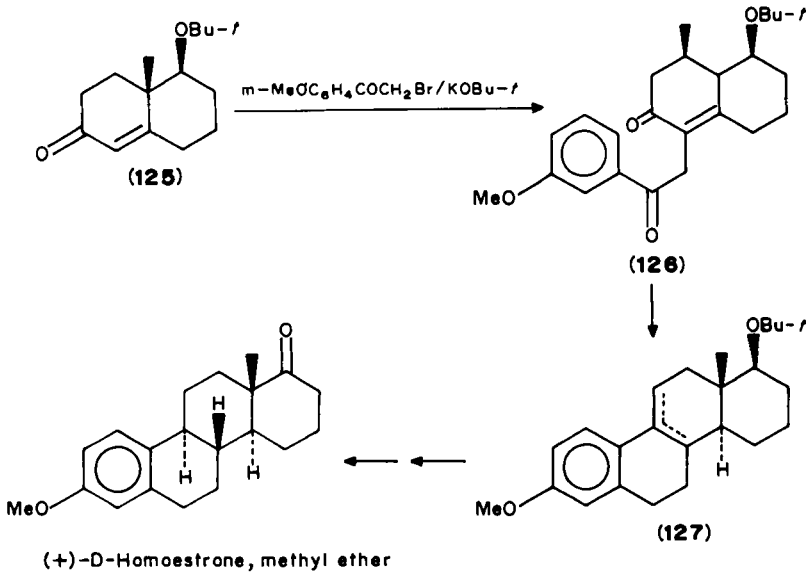
The total synthesis of natural and unnatural steroids continues to be an area of considerable synthetic interest[53] and the stereochemistry and functionality present in **118** makes it an attractive starting material for such endeavors. The (+)-D-homosteroid **124** is an important intermediate in the synthesis of several classes of steroid hormones. An elegant



SCHEME 41

approach to **124** was reported by Kametani and coworkers[54] based on the intramolecular Diels–Alder reaction of an *ortho*-quinodimethane (Scheme 41). The enone (+)-**118** was transformed into enone **121** using known chemistry. Enone **121** was epoxidized and cleaved via the Eschenmoser process to an acetylenic ketone which, upon partial hydrogenation, gave **122**, which was condensed with a benzocyclobutene to give the key intermediate **123** after reductive removal of the hydroxy and cyano groups. Thermolysis of **123** effected a completely stereoselective cyclization to give the D-homosteroid **124**.

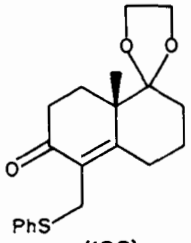
Enone (+)-**118** can also serve as a synthon for the CD ring system of homosteroids as demonstrated by Furst and coworkers in their synthesis of (+)-D-homoestrone (Scheme 42)[55]. Alkylation of enone **125**, readily prepared from (+)-**118**, with *m*-methoxyphenacyl bromide rapidly assembles all the carbons required for conversion into homoestrone. Hydrogenation of **126** was followed by treatment with acid to effect cyclization to **127**; hydrogenation, deprotection and oxidation gave D-homoestrone.



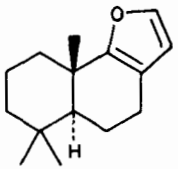
SCHEME 42

Ketone (+)-**118** has served as the starting point in a synthesis of (+)-pallescensin A (**129**), a furanosesquiterpene isolated from a marine sponge, by Smith and Mewshaw[56]. Transketalization of the ethylene ketal of 2-butanone and (+)-**118**, followed by treatment with aqueous formaldehyde, thiophenol and triethylamine, provided intermediate **128**. Conversion of **128** to the target **129** was achieved by a reductive methylation (Li/NH_3, then MeI), followed by Wolff–Kishner reduction and elaboration of the fused furan. Intermediate **128** offers possibilities for the synthesis of a variety of architecturally complex natural products containing *trans*-decalin units.

The transformation of (+)-**118** into optically active hydrindenones has been reported by Jung and Hatfield[57] in synthetic efforts directed towards steroid synthesis. Protection and epoxidation of (+)-**118** gave **130**, which underwent Eschenmoser fragmentation to acetylene **131**. Keto acetylene **131** was reductively cyclized to **132** using methodology developed by Stork and this allylic alcohol was rearranged and reduced to the

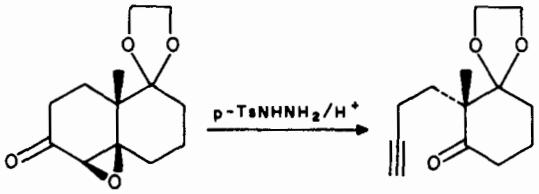


(128)

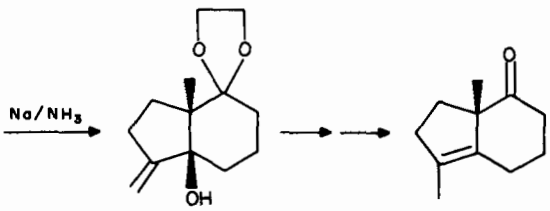


(129)

hydrindenone **133** (Scheme 43). This hydrindenone is a synthon for the AB ring portion of steroids via a sequence involving attachment of the C and D rings followed by ozonolysis and cyclization.



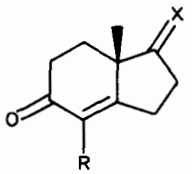
(130) (131)



(132) (133)

SCHEME 43

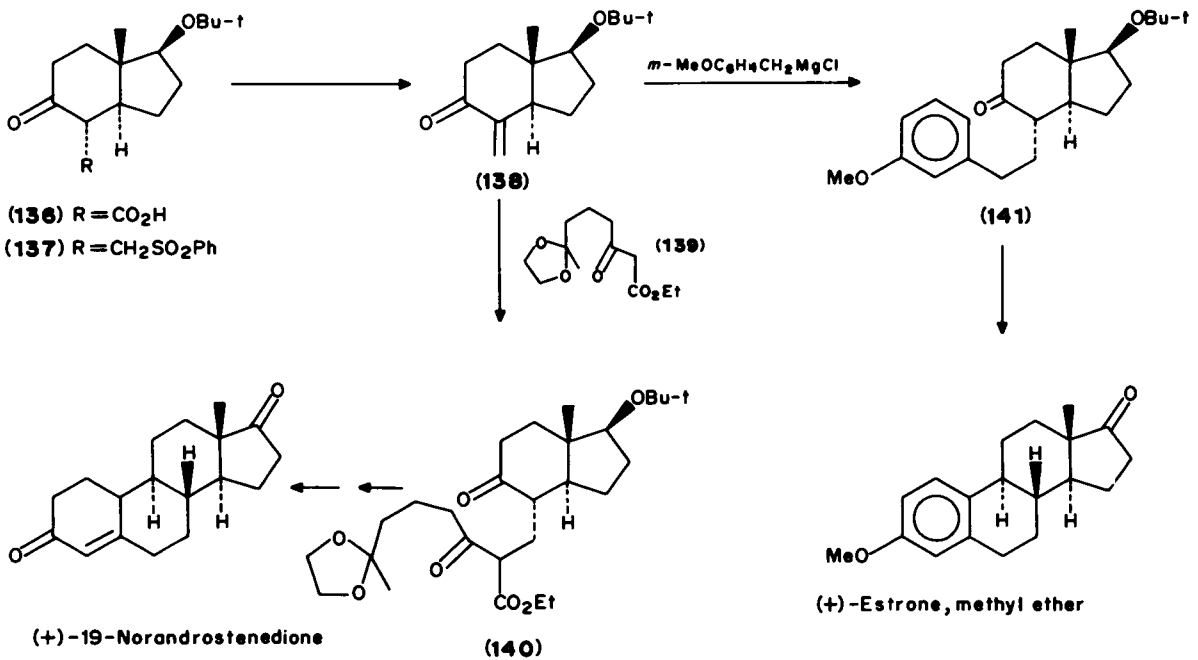
The preparation of hydrindenone **120** in optically pure form was outlined earlier in this section and this compound has found considerable use as a CD ring synthon in the synthesis of steroids, most notably in the preparation of estrones. The successful use of hydrindenones such as **120** in steroid total synthesis is dependent on their facile conversion



(120) R=H, X=O

(134) $R=CO_2H$, X=α-H,β-OBu-t

(135) $R=CH_2SO_2Ph$, X=α-H,β-OBu-t

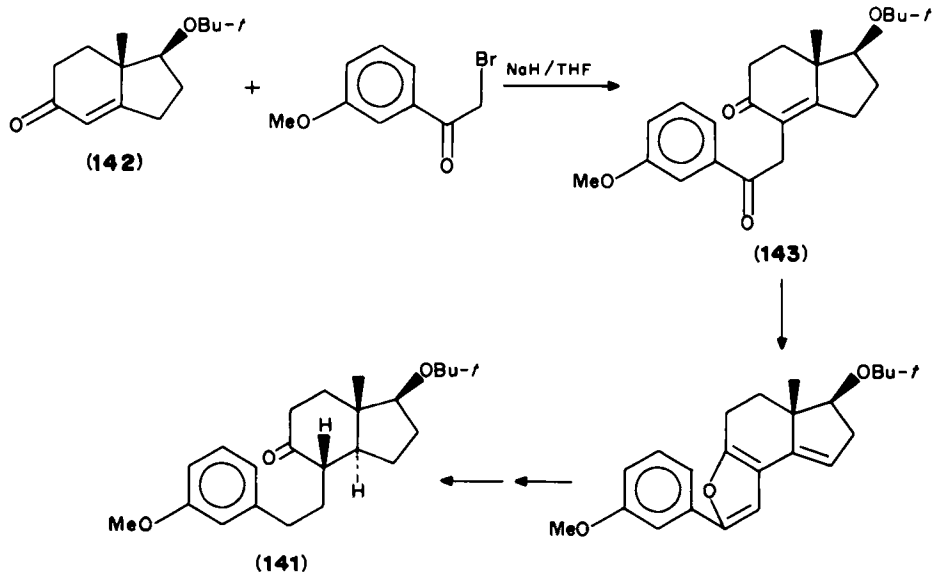

OBu-t
R
H
(136) R = CO2H
(137) R = CH2SO2Ph
(138)
m-MeOC6H4CH2MgCl
(139)
CO2Et
MeO
(141)
(+)-Estrone, methyl ether
(+)-19-Norandrostenedione
(140)

SCHEME 44

into intermediates possessing the required CD-*trans* ring fusion. Thus, the discovery that derivatives of **120**, such as **134** and **135**, undergo hydrogenation almost exclusively from the α face, to give the desired *trans* ring junction, was a significant breakthrough[58].

The elaboration of **136** and **137** into steroids can be achieved via a common intermediate, **138**, which is readily prepared by elimination of benzenesulfinate from **137** or via a decarboxylative Mannich reaction on **136**. The annelation of the AB rings onto **138** is achieved by exploiting the Michael acceptor nature of the exocyclic enone system in **138** (Scheme 44). The Hoffman–LaRoche approach to (+)-19-nortestosterone, and thence to (+)-19-norandrostenedione, involved the conjugate addition of β-ketoester **139** to **138** to give **140**, which was easily converted into the steroid nucleus by sequential aldol condensations[59]. Alternatively, Cohen and coworkers[60] treated **138** with the copper reagent derived from *m*-methoxybenzylmagnesium chloride to give **141** which, on cyclization, hydrogenation and D-ring manipulation, gave homochiral (+)-estrone methyl ether.

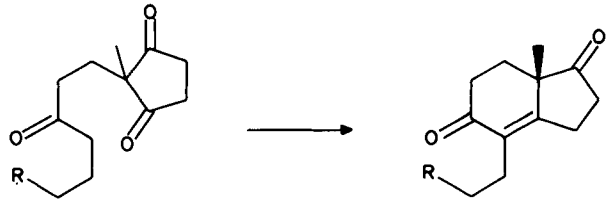
An alternative approach to optically pure (+)-estradiol was reported from the Schering A. G. laboratories[61]. Workers there found that the direct alkylation of **142** with *m*-methoxyphenacyl bromide could be achieved in high yield to give **143** (Scheme 45). Masking of the 1,4-dicarbonyl system as a furan was followed by hydrogenation and oxidation to give **141**, which could be transformed into estradiol, or estrone, using standard procedures.



SCHEME 45

The asymmetric aldol approach to **120** developed by Hajos and Eder was employed by Danishefsky and Tsuji and their coworkers to prepare analogues of **120** which contain masked 1,5-diketone units needed for elaboration into steroids. Danishefsky and Cain[62] found that the triketone **144** underwent asymmetric cyclization to give **145** (86% ee) on treatment with L-phenylalanine by the Hajos–Eder technique. Similarly, the triketone (**146**) was cyclized by Tsuji[63] to give **147** (76% ee) under identical conditions. These

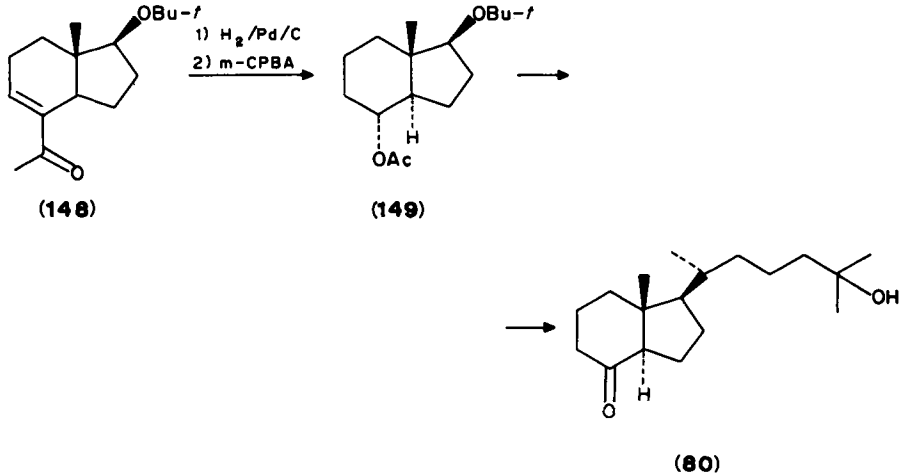
hydrindenones were further transformed into (+)-estrone and (+)-19-nortestosterone, respectively.



(144) R = 6-Methyl-2-pyridyl (145) R=6-Methyl-2-pyridyl

(146) R = CH_2=CH (147) R = CH_2=CH

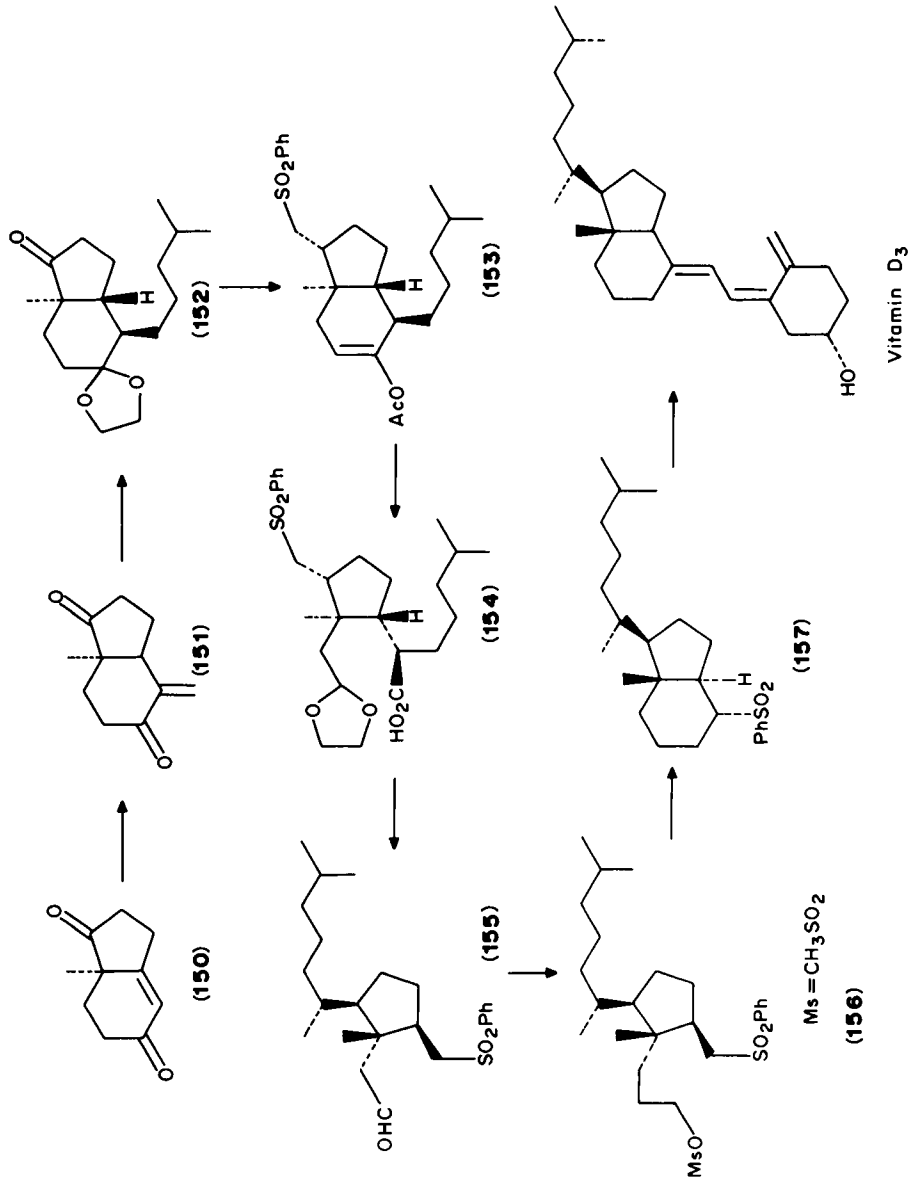
The structure and stereochemistry of the bicyclic unit present in the vitamin D series and some important metabolites have made them attractive targets for synthesis from hydrindenones derived from **120**. In the synthesis of 1α,25-dihydroxycholecalciferol reported by Baggiolini and coworkers[39] hydrogenation of **134** served to establish the *trans* hydrindane skeleton and reduction; carboxylate-methyl ketone transformation and elimination gave enone **148** (Scheme 46). Hydrogenation of **148** was followed by Baeyer–Villiger oxidation to give **149**, which was elaborated to the desired Windaus–Grundmann ketone (**80**) using chemistry described by Dauben based on the ene reaction. The Wittig–Horner reaction of **80** with an allylphosphine oxide prepared from (+)-carvone to give 1α,25-dihydroxycholecalciferol was outlined earlier (Scheme 29).



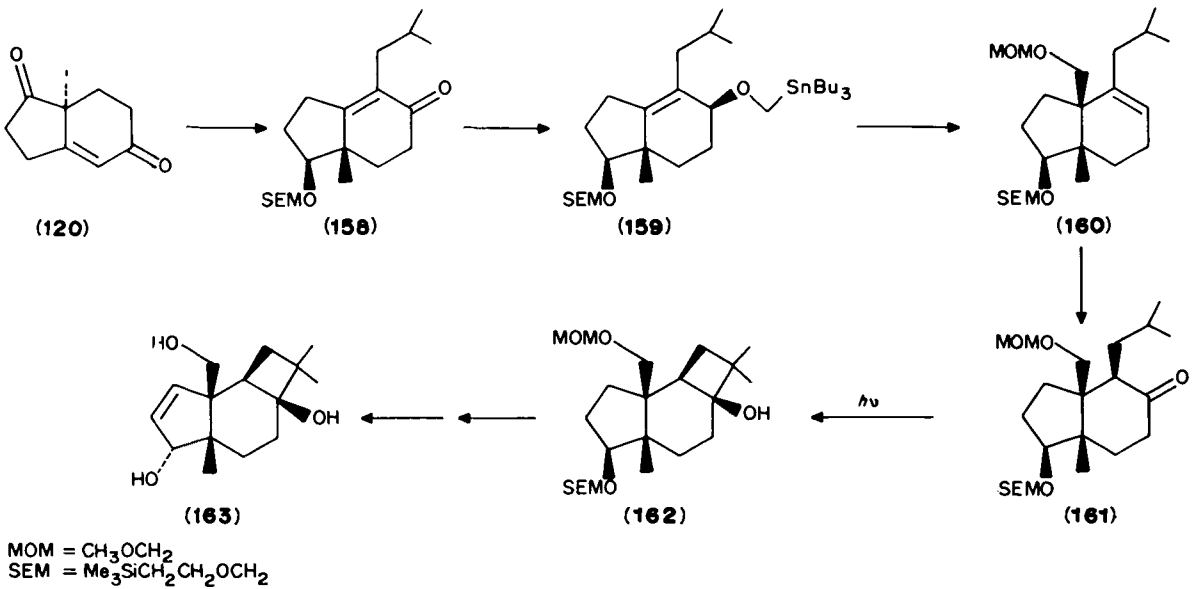
(148) (149) (80)

SCHEME 46

A synthesis of vitamin D_3 reported by Fukumoto and coworkers[64] utilized the hydrindenone **150** (the enantiomer of **120**) to establish the required stereochemistry in both the hydrindane skeleton and the side-chain. This synthesis exploits the equatorial nature of the 4-methylpentyl chain in **152**, prepared from **150** via **151**, which ultimately becomes the vitamin D_3 side-chain (Scheme 47). Conversion of **152** into enol acetate **153**


(150)
(151)
(152)
(153)
(154)
(155)
(156)
(157)
Vitamin D3
Ms = CH3SO2
SO2Ph
AcO
HO2C
OHC
MsO
PhSO2
HO

SCHEME 47

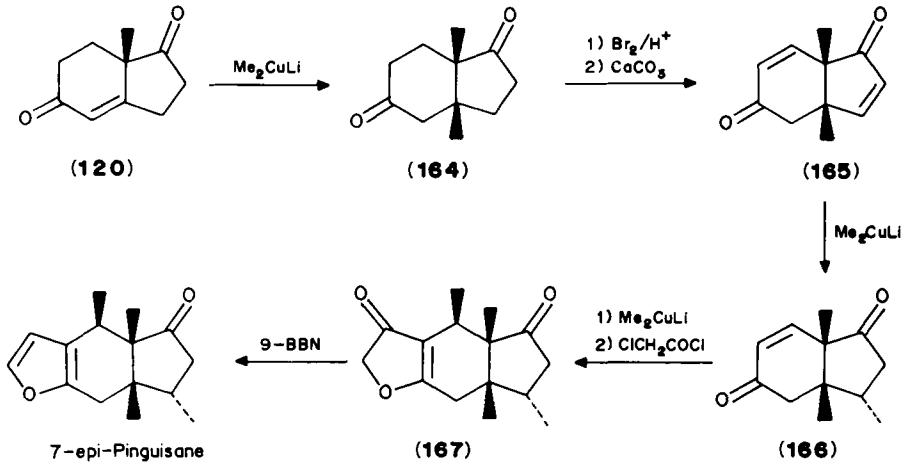

(120)
SEMO
(158)
SEMO
(159)
MOMO
SEMO
(160)
MOMO
SEMO
(161)
hν
MOMO
OH
SEMO
(162)
HO
OH
HO
(163)
MOM = CH_3OCH_2
SEM = $Me_3SiCH_2CH_2OCH_2$

SCHEME 48

was accomplished via Wittig reaction, hydrogenation and enol acetylation. Oxidative cleavage of **153** gave, after protection, the ketal acid **154** which was reduced to aldehyde **155**. This aldehyde was elaborated to mesylate **156** which was cyclized to give the hydrindone **157**. Coupling of **157** with a ring A component was achieved using Julia methodology to give, after deprotection, vitamin D_3.

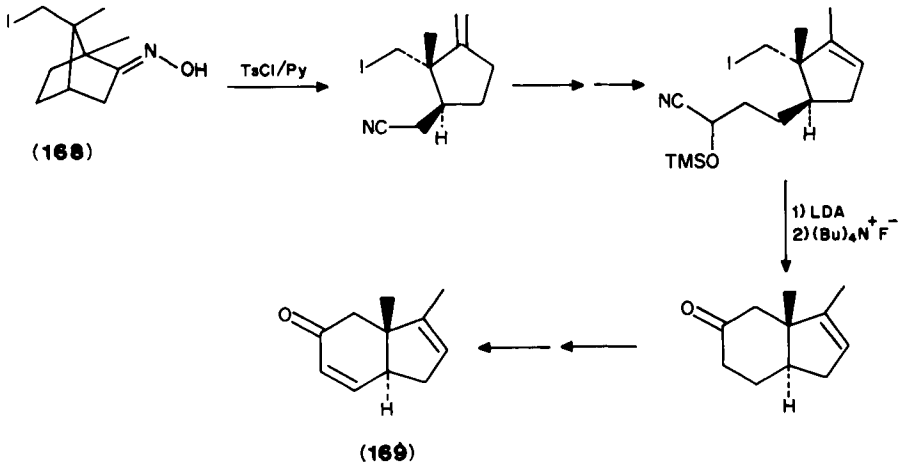
The application of hydrindenone **120** to the synthesis of optically pure terpenoids was recently demonstrated by Paquette and Sugimura in a synthesis of (−)-punctatin, a sesquiterpene with antibiotic properties[65]. This synthesis initially follows the protocol established for steroid synthesis to prepare the hydrindenone **158** which was reduced and converted to its tributylstannylmethyl ether **159** (Scheme 48). Transformation of **159** to **160** was accomplished using the Still modification of the vinylogous Wittig rearrangement. Hydroboration of **160** was followed by oxidation and equilibration to give the key intermediate **161**. Irradiation of **161** resulted in clean formation of the cyclobutane **162** as the product of a Norrish Type II reaction. Completion of the synthesis was achieved by introduction of the double bond, reduction and deprotection to give (−)-punctatin (**163**) of known absolute configuration.

The introduction of a methyl group to the angular position of **120** using copper chemistry establishes a *cis*-fused hydrindone framework and was a key step in the synthesis of pinguisane terpenoids reported by Jommi and coworkers (Scheme 49)[66]. Conjugate addition of lithium dimethylcuprate to **120** occurred with complete stereoselectivity to give **164**, which was subjected to double bromination–dehydrobromination to give dienone **165**. Addition of lithium dimethylcuprate to the cyclopentenone moiety of **165** occurred with complete chemo- and stereoselectivity to give **166**. A second conjugate addition of a methyl group, followed by trapping the resultant enolate with chloroacetyl chloride, gave β-furanone **167** which was easily transformed into 7-*epi*-pinguisane.



SCHEME 49

Hydrindenones structurally related to **120** have also found use in synthesis as exemplified by the enone **169** developed by Narula and Sethi (Scheme 50) as an intermediate for a proposed synthesis of steroids[67]. This hydrindenone was prepared from the oxime of (−)-π-iodocamphor (**168**) and features an intramolecular S_N2 displacement of a neopentylic iodide by an acyl anion equivalent.



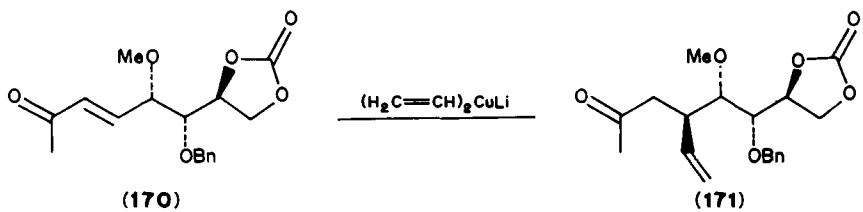
(168) (169)

SCHEME 50

VI. ACYCLIC ENONES

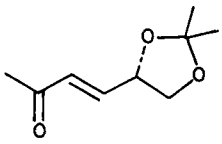
The diastereoselective addition of organometallic reagents to acyclic α-alkoxycarbonyl compounds is a powerful method in organic synthesis. The vinylogous addition of such reagents to γ-alkoxy-α,β-unsaturated carbonyl systems has received little attention. This is probably due to the relatively flexible nature of such enones, compared to the more rigidly defined cyclic analogues, which makes diastereoface differentiation much more difficult. Recently, however, some examples of conjugate addition to chiral acyclic enones which occur with modest to good selectivity have been reported.

In work directed towards the synthesis of olivin, Roush and Lesur[68] discovered that the addition of lithium divinylcuprate to enone **170** occurred with excellent selectivity (43:1) to give predominantly the *anti* product **171**. Similar results were noted by Cha and Lewis[69], who found that lithium dimethylcuprate added to enone **172** [readily prepared from (*R*)-glyceraldehyde] to give a 3.8:1 ratio of products **173a** and **174a**. Extensive investigation of enone **172** was carried out by Leonard and Ryan[70], who showed that isopropenylcopper reagents added to **172** to give **173b** in preference to **174b** (8:1). Further investigation by this group revealed a surprising dependence of this conjugate addition upon the counterion. Isopropenyllithium added highly selectively (1:36) to **172** in a 1,4 manner, instead of the expected 1,2 addition, and the direction of addition was opposite to that observed with the corresponding copper reagent.

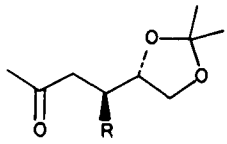


(170) (171)

Bn = $PhCH_2$



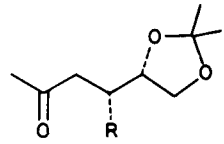
(172)



(173)

(a) R = Me

(b) R = $H_2C{=}C(Me)$

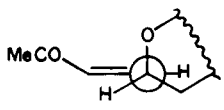


(174)

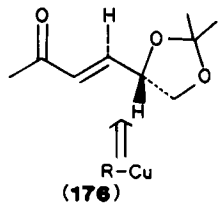
(a) R = Me

(b) R = $H_2C{=}C(Me)$

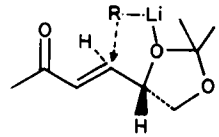
The stereoselectivities observed in these reactions can be accounted for by assuming that the reactions proceed via attack of the reagents on the conformer shown (**175**). The *anti* products, **171** and **173**, which are formed predominantly during the addition of copper reagents, could be formed by approach of the nucleophile from the face of the enone opposite to the electronegative oxygen, represented by the Felkin-type transition state **176**. The predominant formation of the *syn* isomer **174b** during the addition of isopropenyllithium to **172** may be explained by assuming chelation assisted delivery of the organometallic reagent to the enone from the same face as the oxygen atom as indicated in **177**.



(175)



(176)



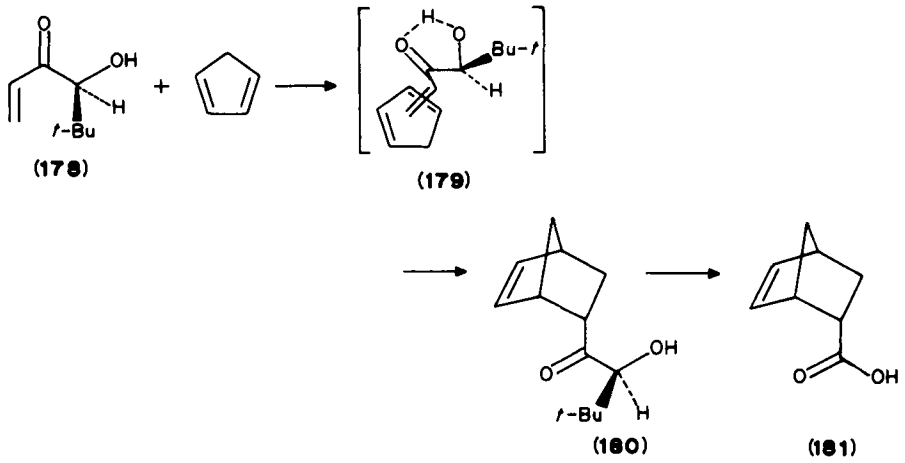
(177)

VII. ENONES BEARING CHIRAL AUXILIARIES

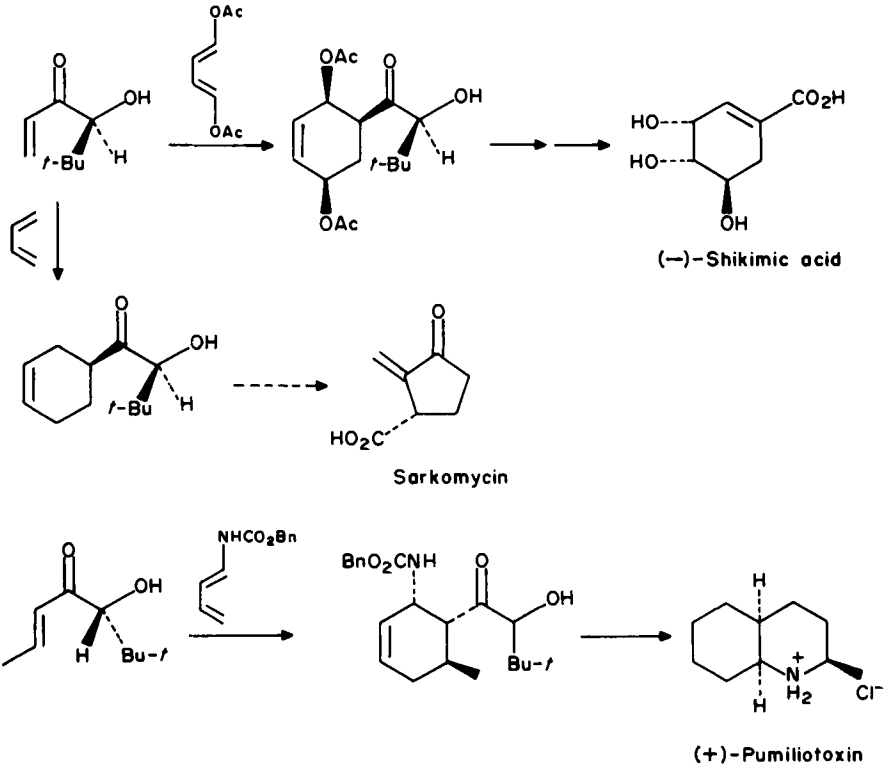
The use of chiral auxiliaries to effect diastereocontrol in a chemical reaction is an extremely powerful tool in organic synthesis. The Diels–Alder reaction[71], in particular, has proved to be amenable to this process with chiral acrylates, derived from optically pure alcohols, being widely used to prepare optically pure intermediates which are useful in synthesis. With such widespread use of chiral acrylates as partners for the Diels–Alder reaction, the lack of examples of chiral enones in such a process is surprising. This is particularly so in light of the impressive results achieved with the few known chiral enones.

Enone **178**, prepared by Masamune and coworkers[72], was found to undergo Diels–Alder reaction with cyclopentadiene with good selectivity (*endo*:*exo* 8:1), and excellent diastereoselectivity (99%). This level of diastereoselection is unprecedented in uncatalyzed in Diels–Alder reactions and is attributed to intramolecular hydrogen bonding, which locates the chiral center within a rigid five-membered ring. From the established absolute configuration of the products, it was inferred that the Diels–Alder reaction proceeded with the enone in its cisoid (syn planar) conformation as shown in **179**.

Application of Lewis acid catalysis [$ZnCl_2$, $Ti(PrO\text{-}i)_4$] to this Diels–Alder reaction served to increase the *endo*:*exo* ratio to 10–15:1 with no deterioration in the diastereoselectivity such that **180** was obtained as essentially the single product. Oxidative cleavage of the chiral auxiliary group gave the enantiomerically pure acid **181**.

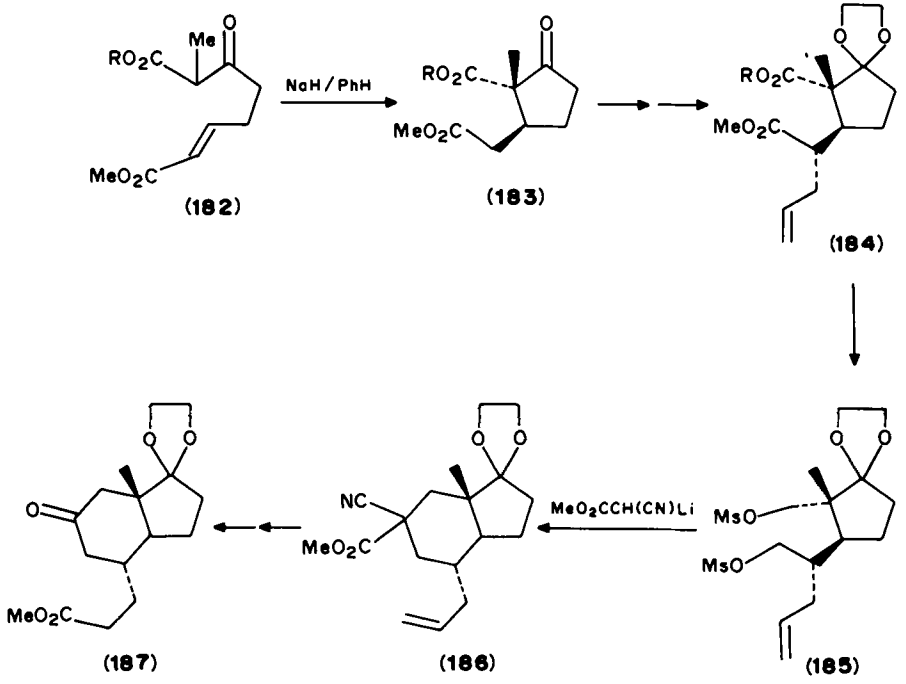


Masamune and coworkers extrapolated this process to a variety of dienes to give enantiomerically pure intermediates, which were useful for the synthesis of a number of natural products (Scheme 51)[73].



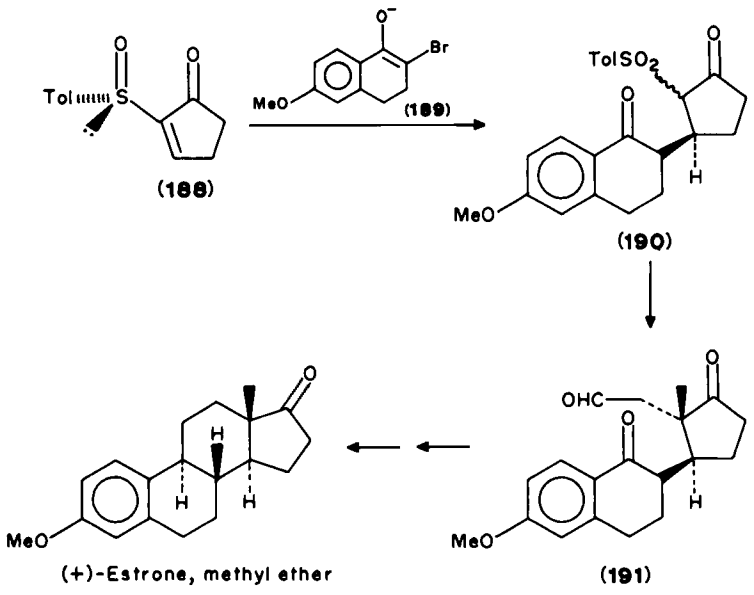
SCHEME 51

The intramolecular Michael reaction is a useful method to prepare carbon–carbon bonds and recently Stork and Saccomano demonstrated that this process can be rendered highly diastereoselective by the use of a chiral internal nucleophile[74]. Cyclization of the β-keto ester **182** occurred with high diastereoface selection to give the highly functionalized cyclopentanone **183**, which served as a valuable intermediate for the construction of 11-keto steroids as outlined in Scheme 52[75]. Alkylation of the ketal of **183** occurred with complete stereoselectivity to give **184**, which was reduced and converted to its dimesylate **185**. Double displacement of dimesylate **185** was achieved using methyl cyanoacetate to give **186**, which was readily transformed into indanone **187**. Conversion of **187** into the 11-keto steroid nucleus by way of an intramolecular Diels–Alder reaction proceeded via methodology developed previously by Stork.



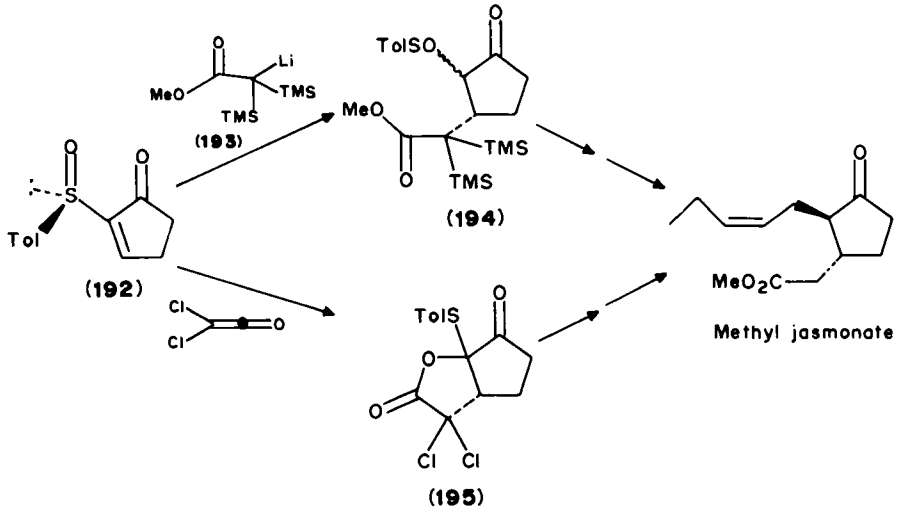
SCHEME 52

Optically pure, sulfoxide-substituted enones in organic synthesis have became important tools for the synthesis of homochiral compounds due primarily to the elegant work of Posner and coworkers[76]. The enone **188** acts as a Michael acceptor for a variety of nucleophiles and the direction of attack can be controlled by adding the nucleophile to a zinc chelated complex of **188**, which serves to position the aryl group of the sulfoxide over one diastereoface of the enone. Using this methodology, Posner and Switzer have prepared (+)-estrone methyl ether in extremely high enantiomeric purity (Scheme 53)[77]. Addition of the bromo enolate **189** to enone **188** occurred with high diastereoselection to give **190**, after oxidation and reductive removal of bromine. Sequential alkylation of **190** with methyl iodide and dimethylallyl bromide followed by ozonolysis afforded aldehyde **191**, which was reductively cyclized via the McMurry procedure and reduced to give (+)-estrone methyl ether.



SCHEME 53

Addition of enolate **193** to **192** (the antipode of **188**) served to establish the correct stereochemistry required in **194** for further manipulation into the perfume constituent methyl jasmonate (Scheme 54)[78]. An alternate synthesis of this product from the same precursor was also described by Posner and coworkers in which an additive Pummerer



SCHEME 54

rearrangement was employed to translate stereochemistry. Reaction of **192** with dichloroketene gave the lactone **195**, which was readily transformed into methyl jasmonate (20% ee)[79].

VIII. SUMMARY

The use of readily available, chiral (non-racemic) enones for the preparation of complex natural products is clearly a useful technique in organic synthesis. As more elaborate synthetic targets are pursued, the enone function will undoubtedly continue to play a prominant role. Continuing advances in asymmetric synthesis, including enzymatic and microbial based techniques, will undoubtedly expand the range of readily available, optically pure enones appropriate for such endeavors.

IX. ACKNOWLEDGEMENT

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The Chemistry of Enones
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CHAPTER **22**

Dimerization and polymerization of enones in the fluid and solid states

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I. INTRODUCTION[1]

The commonest polymerizable enone is methyl vinyl ketone ($MeCOCH{=}CH_2$, **1**) whose polymers have been known for a considerable time. Although the literature in this field is very extensive, recent reviews are not very abundant. Methyl vinyl ketone (MVK, 3-buten-2-one), as well as its polymers or copolymers, and those of its analogues, have been shown to be useful in a variety of practical applications. MVK has also found considerable use in graft polymerization. MVK itself will polymerize spontaneously and, in addition, a variety of catalysts have been used to initiate its polymerization, as well as photochemical means. Radical, anionic and cationic copolymerization is possible. Owing to the applicability of these polymers, many of the recent publications are in a patent form. In many of its applications, MVK appears to be used as a substitute of methyl methacrylate, which is considered, however, to be outside the scope of this review.

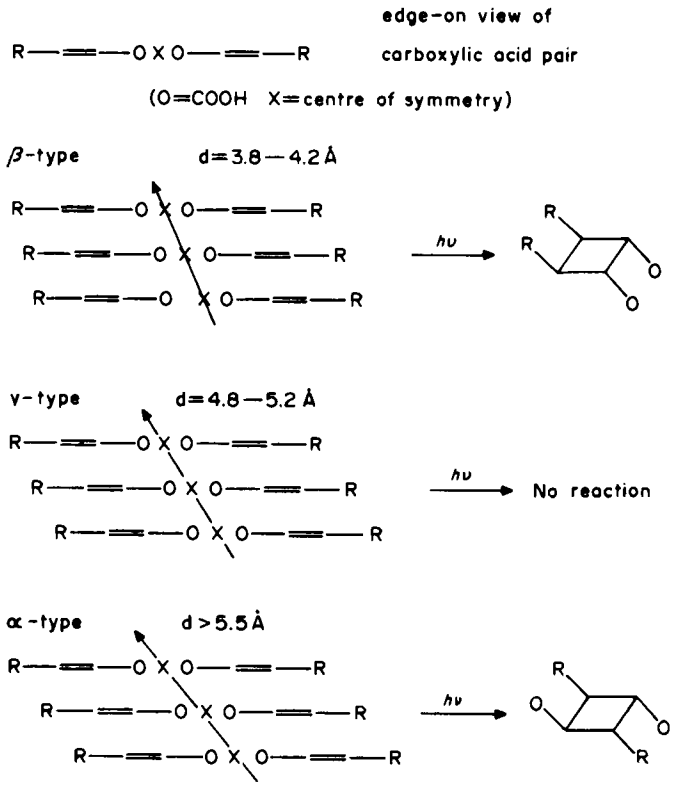
A large part of this chapter concentrates on the behaviour of enones upon irradiation with near-UV light, in the crystalline state. These reactions present some interesting features, and are of considerable fundamental and technological interest. A peculiarity of the solid-state reactivity of enones is that the predominant reaction is photochemically induced dimerization, although polymerization does occur and can be of a fairly complex nature. Other reactions such as hydride abstraction, decarboxylation and dehydration are also known, although they are outside the scope of this review. Enones have also been shown to be reversibly photochromic in the solid state.

The chapter has been divided into the following sections. First, a discussion of solid-state reactivity in general, second, sections on the solid-state reactivity of enones, covering both dimerization and polymerization, and finally, sections on fluid-state polymerization, dealing with homopolymerization and copolymerization, separately.

II. TOPOCHEMICAL REACTIONS

'Ein Kristal ist ein chemischer Friedhof'[2]; such was the widely held opinion among chemists during the first two thirds of this century. It was the development of chemical crystallography, and especially of direct methods, that made the systematic study of organic solid-state reactions possible. Several such reactions had been observed and reported, but no interpretation of the mechanism was attempted, or was possible at the time. Organic solid-state chemists consider, justly, that their subject was given birth in 1964 by G. M. J. Schmidt at the Weizmann Institute of Israel[3]. Schmidt, M. D. Cohen and their collaborators studied the solid-state photochemical behaviour of *trans* and *cis* cinnamic acids[4], which was first described by Liebermann in 1889[5]. Part of the reason why the Weizmann group succeeded in providing a consistent and logical interpretation for the behaviour of these solids where others had previously failed, lay in their recognition of the likely role of the crystal structure in the control of the reaction, and the availability of the so-called direct methods of structure solution, which do not require the presence of a 'heavy' atom in the molecule for success.

The Weizmann group observed that different crystalline modifications of *trans* cinnamic acid, obtained by changing the recrystallization solvents, behaved differently towards exposure to near-ultraviolet light (sunlight). They also studied a number of substituted *trans* cinnamic acids[6,7]. It was observed that some of these crystals were unchanged when under prolonged exposure to radiation, whereas others reacted to yield dimers, via opening of the exocyclic double bonds (see Scheme 1). It was found that any crystalline modification, irrespective of substituents, could be classified according to the length of the shortest unit cell axis into three classes, namely α, β and γ. For any substituent, or combination of them, an α crystal would always yield a dimer whose cyclobutane ring had a centre of symmetry, a β crystal would always yield a dimer with a mirror plane, and a



SCHEME 1

γ crystal would always be photostable. No *cis–trans* isomerization, which was known to occur in solution, was ever observed in crystalline *trans* cinnamic acids.

Schmidt and his coworkers determined the X-ray structures of some of these crystals (see for example Reference 8). They found that in an α crystal reactive double bonds were antiparallel, and in a β crystal parallel, to each other. In both cases the centre-to-centre distance of the bonds was between 3.6 and 4.2 Å. In γ crystals, the bond-to-bond distance was in excess of 4.6 Å. Changing the substituent pattern would clearly change the shape of the molecule and its intermolecular interactions, and thus change the crystal structure and hence photochemical behaviour. The ruse usually employed, before the advent of direct methods of introducing a heavy atom (e.g. Br) into the molecule in order to solve its crystal structure, could not be used here. This is because the introduction of an additional atom would change the crystal structure.

The observations on the photochemistry of *trans* cinnamic acid gave rise to the so-called Topochemical Principle, that reactions in the solid state occur with minimum molecular or atomic movement (reviews of this subject include References 4 and 9–20; the list includes mostly articles since 1980 and is not complete). The topochemical principle presupposes that no melting takes place, and no fluid acts as intermediate. The consequences of the principle are far reaching: reaction will only take place if the reactants are in the correct distance and geometry to do so. The nature of the product, if any, is

governed by the crystal geometry of the reactant. Thus, the geometry of the final product will reflect the crystallographic relationship between the parent molecules. For example, reactive double bonds related by a centre of symmetry in an α crystal result in a centrosymmetric cyclobutane ring, and in a β crystal translationally related double bonds yield a mirror-symmetric cyclobutane.

The topochemical dimerization of *trans* cinnamic acid does not involve diffusion either of the reactants to the reaction site, or of the products away from it. It can therefore occur at, or near, room temperature, unlike the vast majority of non-topochemical solid-state reactions. Most such reactions have to occur at elevated temperatures since diffusion through a solid (of reactants to the interface and, once product is formed, of reactants through this) is involved. Diffusion through a solid is a highly activated process. J. M. Thomas has therefore coined the phrase 'Diffusionless Reactions', as an alternative description of topochemistry[21].

Another consequence of the topochemical principle is that product formation does not lead to phase separation. The product, therefore, becomes part of the reacting lattice. This is so, because the reaction occurs randomly throughout all the crystal; reaction of one pair of molecules does not make reaction of a neighbouring pair any more or less likely than any other. If the shape and size of the product is such that it does not fit into the reacting lattice, stress is developed which is of a magnitude to lead to disruption of the structure, crystal fragmentation, and eventually to formation of an amorphous solid, containing both product and reactant molecules randomly distributed. Disruption of the lattice results in the cessation of the reaction, since it occurs in the first place because the reactant molecules are locked in a relative disposition conducive to reaction by the exigencies of the crystal structure. Dimer yield is consequently less than 100%. This is the case for cinnamic acid and a number of other solid-state reactions[22].

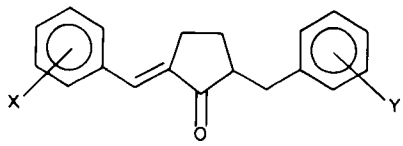
If the nature of the product is such that it occupies the same volume (both in size and shape) as its progenitors, then minimal disruption occurs and the crystallinity of the system is preserved. In such a case, reaction can proceed to 100% conversion[23]. If this system is allowed to react slowly, then the strains generated in the crystal are not large, and mechanical integrity of the crystal can be maintained. A single crystal of the reactant will therefore yield a single crystal of the product, and crystallography cannot only be used to study the structures of product and reactant and draw conclusions, but can also be used to study the path of the reaction. A whole chemical experiment can therefore be carried out in a single crystal. Examples of this were the reactions of 2-benzyl-5-benzylidenecyclopentanone (**2**), and its analogues, to be described in subsequent sections.

Since 1964, a number of systems in addition to the cinnamic acids have been found to be reactive in the solid state, including some which undergo polymerization. Apart from their academic interest, there is potential applicability of such systems in areas ranging from synthesis of chiral or regiospecific polymers to molecular and optoelectronics. Total asymmetric synthesis from achiral precursors has been shown to be possible through solid-state reactions. Probably the most striking use of solid-state reactions is in the preparation of large crystals of regular polymers. In this chapter, a wide interpretation of polymerization will be adopted to include dimerization reactions. Many of the molecules exhibiting solid-state topochemical activity contain conjugated double bonds, often as enones. Their reactivity pattern is very similar to that of the *trans* cinnamic acids.

III. SOLID-STATE CYCLOADDITIONS OF BENZYLIDENE CYCLOPENTANONES

A. Reactions of Benzyl Benzylidene Cyclopentanones

The solid-state reactivity of enones can be exemplified by the behaviour of 2-benzyl-5-benzylidenecyclopentanones[23,24,16] (BBCP, **2**). Crystalline **2** (see Scheme 2) assumes a



	X	Y
(2)	H	H
(3)	*p*-Br	H
(4)	H	*p*-Cl
(5)	H	*p*-Me
(6)	H	*p*-Br
(7)	*p*-Br	*p*-Cl
(8)	*p*-Br	*p*-Me
(9)	*m*-Br	H
(10)	*p*-Cl	H
(11)	*p*-Me	H
(12)	*o*-Cl	H

SCHEME 2

packing motif in which neighbouring molecules are related by a centre of symmetry, and are situated such that their exocyclic double bonds are antiparallel and separated by 4.1 Å (Figure 1). Further, this packing is conducive to single-crystal to single-crystal reactivity under topochemical control. This is so, because the product dimeric molecule occupies the same volume (Figure 2) and is roughly of the same shape as its two progenitors[25]. The dimer molecule can fit into the monomer lattice, thanks to the presence of the benzyl group. This is a bulky side-group which can change its conformation and relative orientation vis a vis the reacting part of the structure, i.e. the exocyclic double bond. As a result, the position of the benzyl phenyl ring remains unchanged in the dimer and compensates for the movement of other parts of the molecule (Figure 2). The strain produced within the lattice is minimal, and the mechanical integrity of the crystal is maintained throughout the reaction. In crystallographic terms, the change in volume and cell dimensions in going from monomer to dimer is very small. Single-crystal to single-crystal behaviour[26] is shown by molecules **2** to **6**. The fact that the product is crystalline means that there is a definite crystallographic relationship between parent and daughter phases. This is the definition of 'topotactic' process. Clearly, in cases such as that for *trans* cinnamic acid where the product is amorphous, no topotactic relationship is possible.

For all compounds described in this section, detection of reactivity was carried out using infrared spectroscopy. Reaction involves the conversion of a C—C double bond to a single bond, which can be observed with the collapse of a peak at 1640 cm^{-1}, which is characteristic of the former group[16].

The mechanism of the reaction is believed to be as follows[27]: on absorption of a photon of light ($\lambda > 360$ nm) one of the molecules in a closest-neighbour pair undergoes an $n \rightarrow \pi^*$ transition to an excited singlet state. This crosses over quickly to a vibrationally excited triplet state. This is the species which now reacts with a neighbouring ground-state molecule. The excited triplet state has a conformation which is similar to that of the monomeric residue in the dimer. As a result, the reacting atoms on the two molecules are now closer than the 4.1 Å separating them before photoexcitation. The product results

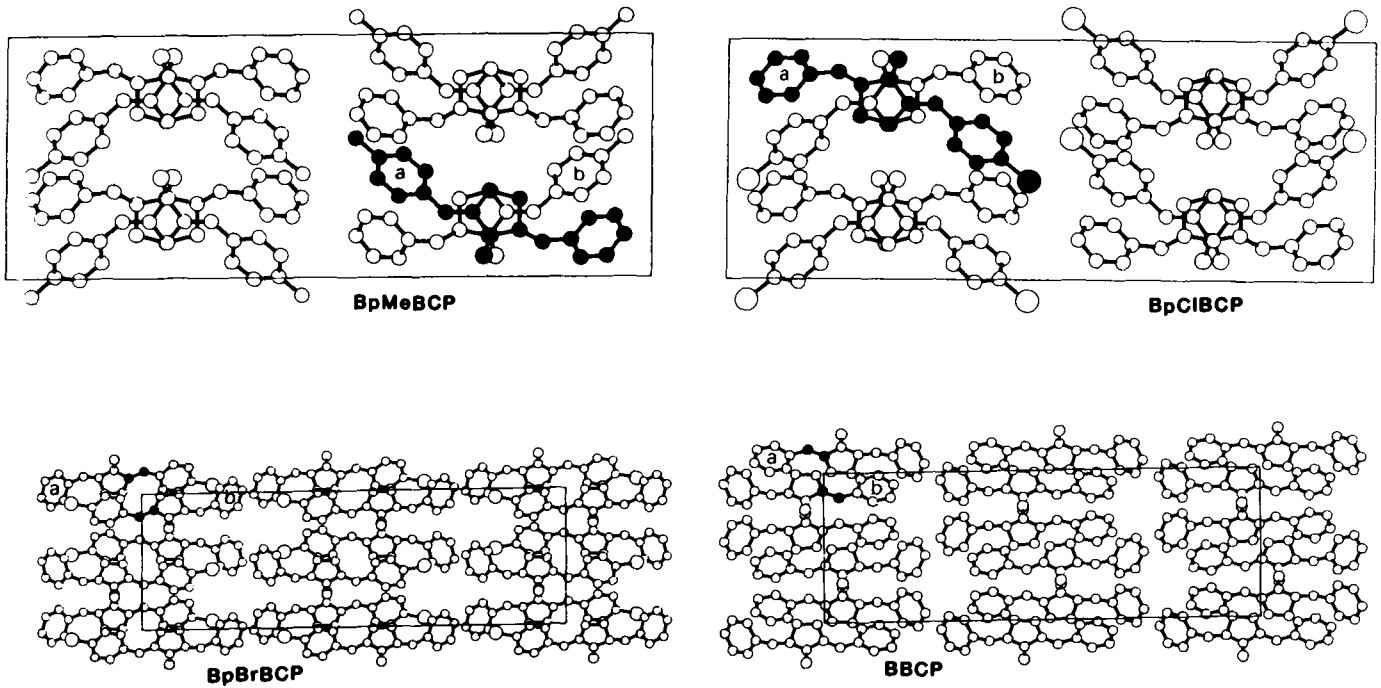


FIGURE 1. Packing diagrams for BpMeBCP (**11**), BpClBCP (**10**), BpBrBCP (**3**) and BBCP (**1**). Nearest neighbouring molecules in each structure are labeled as a and b.

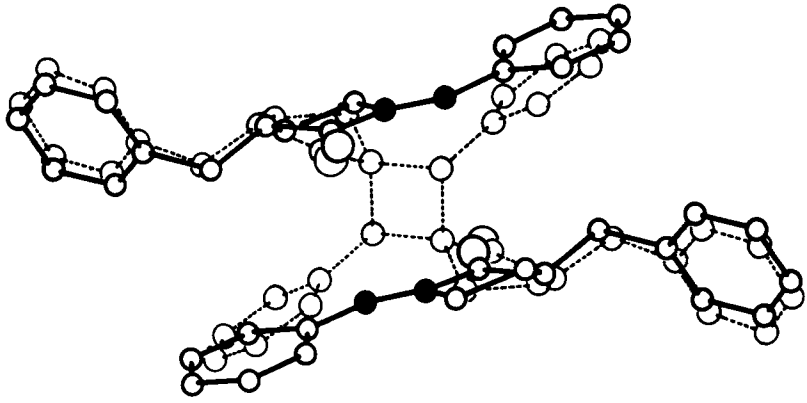
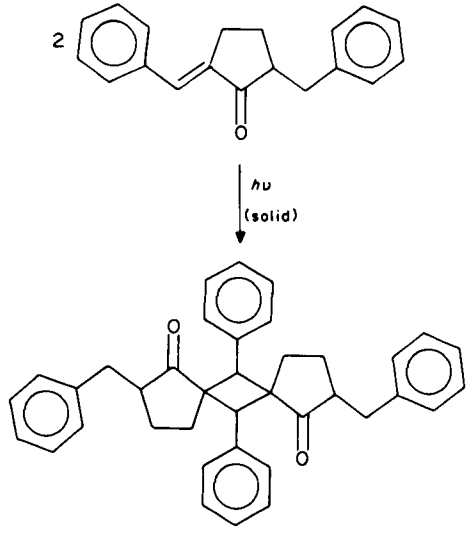


FIGURE 2. Incipient dimer pair and dimer molecule for **2**. The filled circles represent the reacting bonds for the monomer

from the opening-up of the two exocyclic double bonds to yield a centrosymmetric cyclobutane ring (Scheme 3). The source of excitation is usually either a low-pressure Hg lamp (100 or 500 W) with a pyrex filter to exclude low-wavelength radiation, or direct sunlight. The reason for filtering out the radiation with wavelengths shorter than 360 nm is that such UV radiation may cause the cleavage of single C—C bonds.

Substitution of a bromine atom at the *para* position of the benzylidene group (**3**) results in a packing motif which is very similar to that of the parent molecule (Figure 1). The difference in volume of the two cells is almost entirely due to the elongation of the *a* axis, which is necessary in order to incorporate the additional atom[28–30]: In this reactive motif, the long molecular axis is parallel to the long cell axis (i.e. *a*). However,



SCHEME 3

if Br is substituted by a Me or a Cl substituent, or if indeed a substituent is placed in any other position of the benzylidene group, the resulting packing motif is non-reactive and very different than that of **2** or **3** (Figure 1). This change in the packing means that the potentially reactive double bonds are no longer disposed in a way that will allow reaction[16,18].

For molecules analogous to BBCP (**2**), there appear to be two types of packing motif (Figure 1). For the first one, nearest-neighbour molecules are related by a centre of symmetry, and consequently have double bonds which are antiparallel to each other. In some of these, the bond-centre to bond-centre separation is between 3.6 and 4.2 Å. These crystals are expected to be photoreactive and they are found experimentally to be so. Some other crystals, however, have somewhat longer bond-to-bond separations than 4.6 Å and these are, as expected, photostable. The second type of packing motif is an unreactive one, in which nearest-neighbour molecules are related by a glide plane. The double bonds on these two molecules are no longer parallel, and are furthermore separated by distances in excess of 4.6 Å. The two types of unreactive packing mode have in common the fact that the long molecular axis is not parallel to any of the unit-cell axes. In contrast, in all the reactive crystals, the molecular axis and the longest cell axis are parallel. The relative disposition of the nearest-neighbour molecule pair in the reactive as compared with the unreactive packing mode is shown in Figure 3.

Examples of the first type of packing are molecules **2** and **3**. We have seen already that a single crystal of **2** can be converted to a single crystal of dimer[25]; the same is true for **3**, although the cell changes here are more significant[28]. To achieve a single-crystal to single-crystal change for the irradiation of **3**, a slower reaction is needed, which can be achieved by a lower UV dosage. Under these conditions, the mechanical integrity of the crystal can be preserved. Substitution in the benzyl group is also possible. Thus, substitution of Cl[31], Me[16] or Br[32] at the *para* position will yield compounds **4**, **5** and **6** respectively, which are isomorphous (i.e. have similar packing modes). The first two have unit cells with roughly equal volumes. This is in agreement with the proposition of Kitaigorodskii[34] that the packing of organic molecules in crystals can be understood as the close packing of spheres of various radii. Therefore, replacement of one substituent with another of similar van der Waals volume at the same position should leave the structure unchanged[33]. Cl and Me have similar van der Waals radii, and therefore **4** and **5** can be expected to be isomorphous. Kitaigorodskii[34] suggested that the interchange of Cl and Me substituents can be used as part of a crystal engineering strategy. The increase in cell volume for the third (**6**) reflects the larger size of the Br substituent. All three of these compounds pack in a photoreactive motif, and undergo a single-crystal to single-crystal transformation. These structures differ from those of **2** and **3** in that the length of the *a* axis has been halved, because of a change in spacegroup, from PbCa in BBCP to P21/c here, presumably in order to avoid short contacts of the substituents with surrounding molecules.

Since **3** and **4** have both been shown to be photoreactive, it was anticipated that **7** would also be photodimerizable. This was based on the fact that the substitution pattern in **7** is a combination of those in **3** and **4**. The crystals of **7**, however, were photostable[35], in spite of the nearest neighbours being related by a centre of symmetry. Stability is believed to be due to the double bonds being separated by 4.65 Å. The conformation of the benzyl group in this molecule is very different from that of any of the other analogues of **2**. This difference in conformation, and hence overall shape of the molecule of **7** (Figure 4), is made more striking when compared with its Me analogue, **8**, which shows a conformation of the benzyl group similar to that in **2**[34] (Figure 4). **8** packs in a photoreactive crystal similar to that for **4**. It is believed that the difference in the overall shape of the molecules is what gives rise to the differences in packing, and hence reactivity.

The conformational differences between **7** and **8** may be due to the electron-donating nature of the *p*-Me group as distinct from the electron-withdrawing ability of *p*-Cl[16,35].

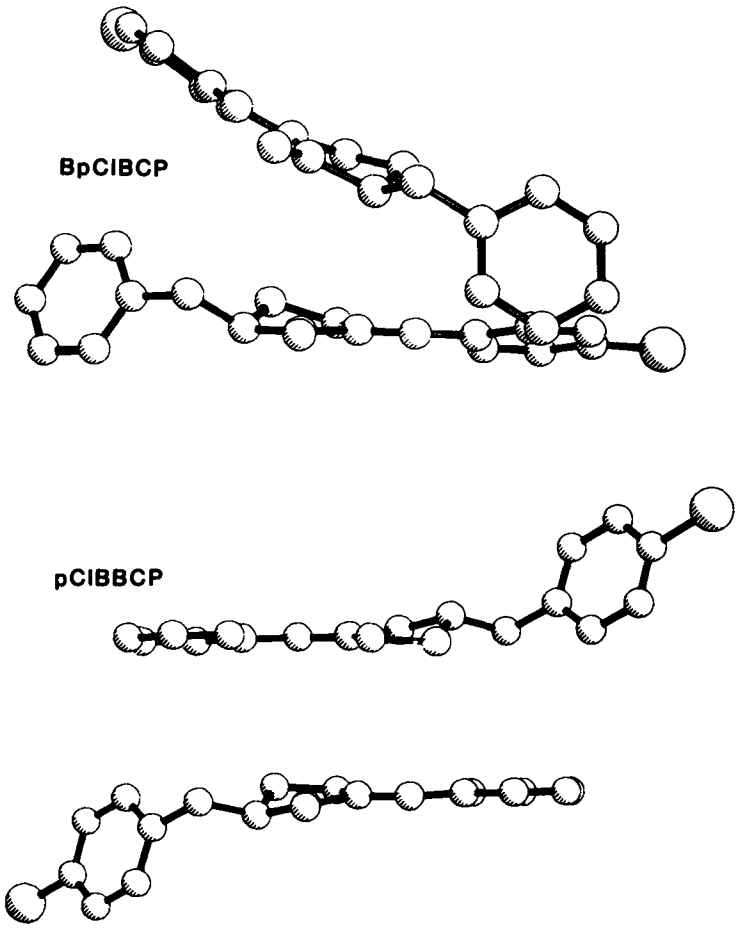


FIGURE 3. Nearest-neighbour molecules for a reactive crystal **4** (pClBBCP) and a photostable one **10** (BpClBCP)

Arguments solely based on the size of the substituent are insufficient to explain the packing adopted. The presence of the *p*-Br substituent on the benzylidene moiety means that any surplus or deficiency of charge on the carbon atoms of the benzyl group of neighbouring molecules will contribute significantly to the electrostatic interaction involving the *p*-Br atom of the benzylidene group. Me and Cl substituents differ electrostatically in the sense that the former would provide surplus charge to, and the latter extracts charge from, the carbon atoms of the benzyl group to which they are attached. The interaction between these benzyl carbon atoms and the surrounding Br atoms will differ depending on whether the substituent is chloro or methyl. This is reflected in the fact that the shortest contacts between the benzyl phenyl ring carbon atoms and bromine are considerably shorter in **7** than in **8**, as the electron-withdrawing ability of the Cl substituent in **7** will allow the bromine on a neighbouring molecule to form closer contacts (see

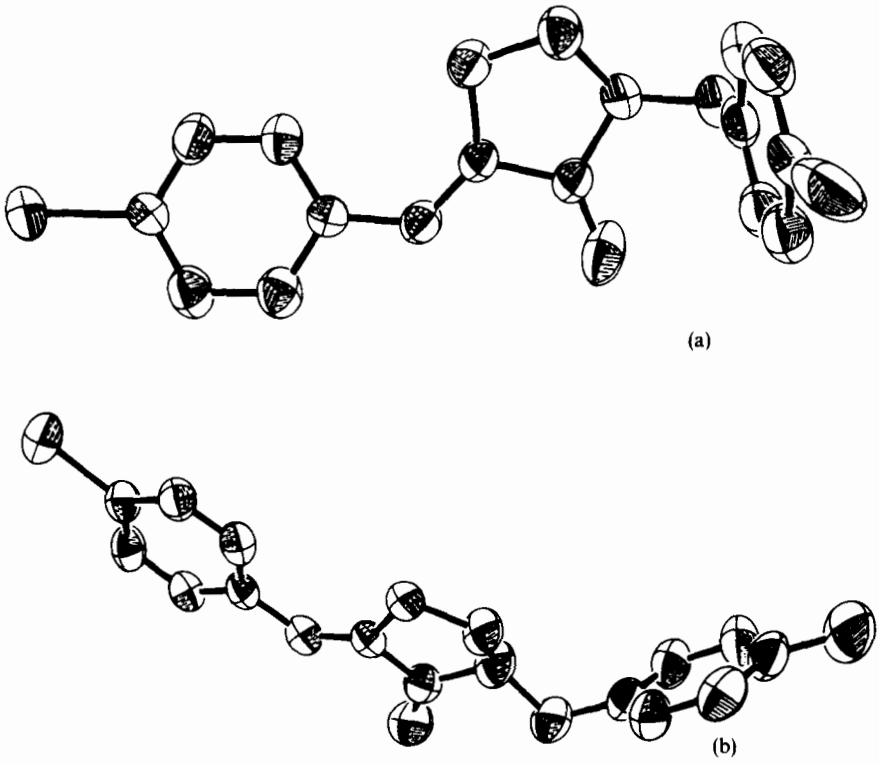


FIGURE 4. ORTEP plots for (a) **7** and (b) **8**

Table 1). The proposition, therefore, that the packing of organic molecules in the crystalline state is governed by size considerations only, is valid as long as electrostatic intermolecular interactions do not hold sway. Evidently, this is so in the case of **4** and **5**, but not **7** or **8**, where the presence of the polarizable Br substituent makes the electrostatic interactions dominant.

The centrosymmetric unreactive packing motif is represented by the structures of molecules **7** and **9**[18]. The crystal structure of **9** has two molecules in the asymmetric unit

TABLE 1. Shortest Br···C distances in the crystal structures of **7** and **8**[a]

	in molecule	
Br(1) to	**7** (Å)	**8** (Å)
C(7)	3.939	4.695
C(8)	3.868	4.244
C(9)	3.664	5.104
C(10)	3.544	6.228
C(11)	3.634	6.908
C(12)	3.824	5.868

related by a pseudo-centre of symmetry. The nearest double-bond to double-bond contact occurs between molecules related by a crystallographic centre of symmetry, and is 4.36 Å. This may be too long for reaction, but photostability may also be due to steric hindrance: the bromine atoms on each of the reacting benzylidene groups are relatively close to neighbouring benzyl groups; the two groups may clash with each other during the movement necessary for reaction, and thus cause photostability. The limit of 4.2 Å, normally accepted as the longest bond-to-bond distance conductive to [2 + 2] cycloaddition, is not an absolute limit but is based on experimental results. There appears to be a grey area between 4.2 and 4.7 Å, where in some crystals reaction occurs whereas in others it does not. The answer may lie either in the presence of steric hindrance to reaction in some structures and not others, or more detailed geometric requirements for topochemical control than that suggested by the formulation by Schmidt. This aspect of topochemistry will be discussed in later sections.

The packing motif where nearest neighbours are related by a glide plane is represented by **10**, **11** and **12**[16]. In the crystals of **10**, the nearest-neighbour molecules are related by a *b* glide (Figure 1), with a double-bond centre to double-bond centre separation of 5.40 Å, whilst for **12** they are related by a *c* glide, with a bond separation of 4.61 Å. In both cases, the double bonds are not parallel and no reaction occurs. The difference between these two molecules lies in the position of the Cl substituent in the benzylidene moiety, and they pack in a very similar packing motif. The closest Cl···Cl distance for **12** was 4.61 Å, for *c* glide related molecules, whereas for **10** the equivalent distance was 5.00 Å, for centrosymmetrically related molecules. Cl···Cl contacts are believed to have considerable influence on the mode of packing of aromatic compounds.

Crystals of **10** are isomorphous with those of **11** (Figure 1), indicating the interchangeability of chloro and methyl substituents in alkyl or aryl moieties, where volume considerations hold sway[16,18]. The reason why substitution at the *ortho* or *meta* position of the benzylidene group of **2** by Cl, Me or Br groups and by Cl and Me at the *para* position should result in a photostable packing mode, can be explained as follows. Substitution in the flat benzylidene moiety increases its effective size, compared with that it possesses in the unsubstituted **2**. This change has to be accommodated either by changing the molecular conformation, or by assuming a different packing. Given the rigidity of the benzylidene group, the only possibility available is the latter. This change of packing is also necessary in order to accommodate the non-bonded interactions in which the substituents take part. In the case of **3**, however, size considerations are presumably superseded by the tendency of the bromo substituent, which is a large polarizable atom, to partake in a large number of non-bonded short H···Br contacts, whose number is maximized by retaining the photoreactive motif[33,35]. If, however, substitution is carried out in the benzyl moiety of **2**, then a reactive structure is retained, but with a change in spacegroup. Compounds **4**, **5** and **6** can retain the same motif as **2** and **3**, because the increase in volume of the flexible benzyl moiety can be accommodated by a change in conformation.

In Section II, it was mentioned that the photochemical behaviour of *trans* cinnamic acid in the crystalline state can act as a good guide to the behaviour of enones. It has been seen that the acids can take up three distinct types of packing, namely α, β and γ. Enone **2** and its analogues can assume α- and γ-like packing, but not β. As a consequence, all dimers have a centrosymmetric cyclobutane ring, such as the dimer of **4** shown in Figure 5. It is believed that a molecule such as **2** cannot adopt a β-like structure. This is essentially a non-planar molecule, as the benzyl group always subtends a non-zero dihedral angle with the flat benzylidene moiety, for any substituent. Trying to stack such molecules parallel to each other rather than antiparallel or crossed would lead to a highly open, inefficient, and therefore unlikely crystal structure. Crossing of the molecular axes, such as occurs in some unreactive crystals, leads to non-reactivity, and a type of packing where closest neighbours are related by glide planes, a case not encountered in the cinnamic acid series.

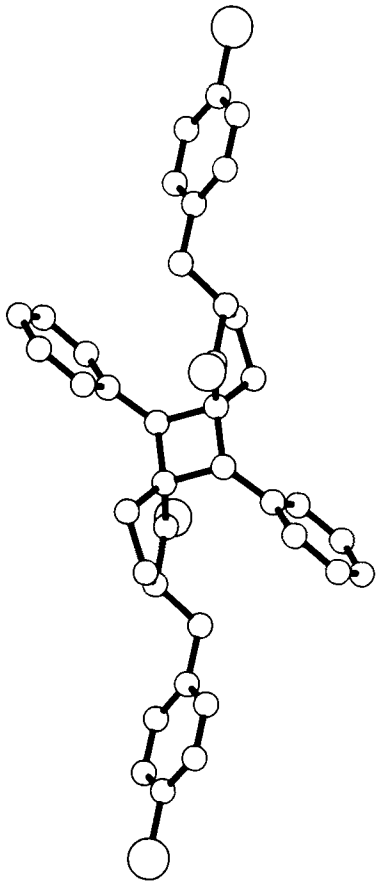
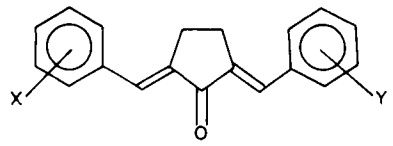


FIGURE 5. Dimer molecule of **4**

B. The Unusual Case of 2,5-Dibenzylidenecyclopentanone

2-Benzyl-5-benzylidenecyclopentanone (**2**) and 2, 5-dibenzylidenecyclopentanone (**13**, in Scheme 4), commonly abbreviated to DBCP, are closely related. The main difference between **2** and **13** is that the C(2)—C(6) single bond (see Figure 6) in **2** has been replaced by a double bond in **13**. DBCP is of interest for several reasons, all consequences of this change. First, the introduction of a second double bond creates additional, potentially reactive centres. Second, comparison of the solid-state photochemical behaviour of **2** and **13** can lead to an understanding of the consequences of rendering the monomer essentially planar and of imparting rigidity to the benzylbenzylidenecyclopentanone backbone. Third, the chiral centre at position 2 (the numbering scheme in Figure 6 is for both **2** and **13**) in the BBCP framework causes all members of this family to crystallize in racemic spacegroups. Racemic spacegroups are those capable of packing molecules of either handedness because they contain mirror planes, or centres of symmetry. The DBCP framework, however, does not contain any chiral centres and can therefore be expected to



	X	Y
(13)	H	H
(18)	*p*-Br	*p*-Br
(19)	*p*-Br	H
(20)	*p*-Me	H
(21)	H	*p*-NO_2
(22)	H	*p*-pyridyl
(25)	*p*-F	*p*-F

SCHEME 4

adopt packing arrangements conducive to topochemical reaction which cannot be adopted by either **2** or the cinnamic acids (cinnamic acids also adopt racemic spacegroups because they pack forming hydrogen-bonded centrosymmetric pairs of their carboxylic groups, as shown in Scheme 1). Finally, a racemic mixture of **2** cannot be resolved into optically pure fractions, because the C(2) hydrogen is acidic, and spontaneous racemization occurs in solution via a keto–enol tautomerism mechanism. A new chiral centre can be created at position 3 of the DBCP framework, which is not labile. An additional difference between **2** and **13** is that the former has a low molecular symmetry, whereas the latter can have either a mirror plane or a two-fold axis through its carbonyl, depending upon the substituents present. This symmetry can of course be destroyed by introducing a substituent on only one of the two phenyl groups, or by introducing different substituents.

13 itself has a two fold symmetry and packs in spacegroup $C222_1$, which is a chiral[36,37]. Irradiation with UV light of single crystals of **13** recrystallized from chloroform/methanol

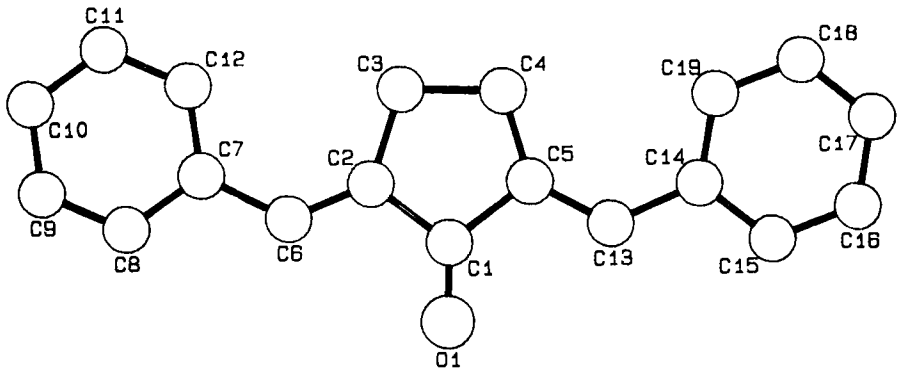


FIGURE 6. Numbering scheme for **13**. Note that the numbering scheme is the same in **2**, but for this latter molecule bond C(2)—C(6) is a single one

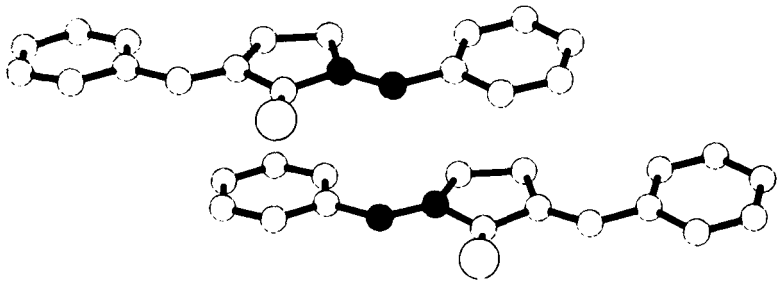
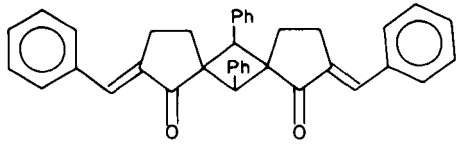


FIGURE 7. Incipient dimer pair for **13**. Filled circles are the two reacting moieties. Note that now they are not totally parallel

in the presence of nitrogen resulted in an amorphous crude product. Using TLC and recrystallization, a number of products were identified. The main product (**14**) is one whose formation can be explained in topochemical terms[38]. Packing in the parent crystal (see Figure 7) is such that nearest-neighbour molecules are parallel, since they are related by translation along the shortest cell axis, *b*. The double bonds on the two molecules closest to each other are shown as filled circles in Figure 7. From that figure, it can be seen that these bonds are in planes which are parallel to each other, but themselves subtend an angle of 56°. This is not a geometry generally considered conductive for a topochemical reaction, although the mean distance separating the potentially reactive centres is 3.71 Å, which is well within the limits previously deduced to be necessary for such reactions. However, comparison of the incipient dimer (Figure 7) and the molecular structure of the dimer (Figure 8) from its crystal structure indicates that **14** is the expected product of a reaction involving the pair in Figure 7, under topochemical control.



(**14**)

This apparent breakdown of the topochemical rule, which has been seen to hold sway in the cases of the cinnamic acid and BBCP families, can be explained as follows. The two reacting bonds are part of extended conjugation systems which are parallel to each other. The orbitals on each of the atoms, which are part of the double bond in the monomer and will overlap to form the cyclobutane ring in the product, are the p_z, which are by definition at right angles to the mean plane of the conjugation system, i.e. the molecule, since the DBCP backbone is virtually flat. Therefore, in **2**, where the double bonds are antiparallel, the p_z orbitals are directly above each other and can overlap upon excitation of one of the two molecules. In **13** the two orbitals are parts of parallel conjugation systems, and will therefore point in the general direction of each other[37]. Furthermore, one of the bonds is directly above the other. Overlap and cyclobutane ring formation is therefore still possible. Other examples of apparent breakdowns of the topochemical principle have been noticed before and since (see later sections). In the light of their observations on compound **13**, Thomas and coworkers suggested that the prerequisite for reactivity under topochemical control is the ability of the appropriate orbitals to overlap[37].

Compound **15** was identified among the products of the irradiation of **13**. Kaupp and

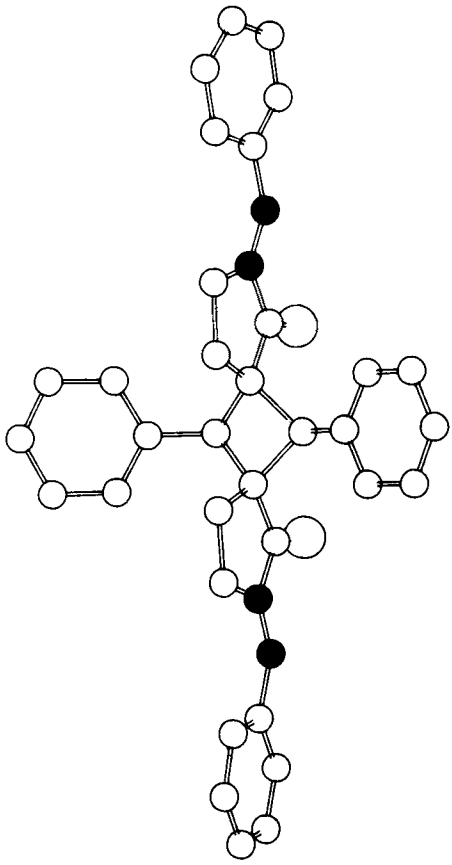
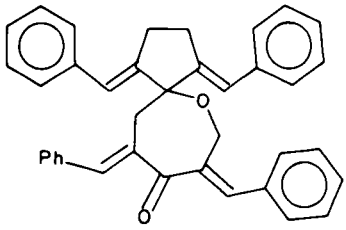


FIGURE 8. Dimer molecule for **13**

Zimmermann[38] suggested that **14** is the product of a reaction between an unreacted molecule of **13**, and the biradical **16**. The formation of this product can be explained in topochemical terms. Kaupp and Zimmermann used a different system than that used by Theocharis and coworkers, namely thin films grown from methylene chloride or methanol solutions. In addition to **14** and **15**, they reported a third product, **17**, no trace of which was detected from reactions in crystals grown from chloroform/methanol. The formation of **17** would not be allowed under topochemical rules from the structure of **13**, identified by Thomas' group. However, duplication of the routine used by Kaupp and Zimmermann did yield this product[39]. Powder XRD studies of **13**, recrystallized from methylene chloride, suggested that more than one phase is obtained, and TLC and NMR suggested that solids obtained by recrystallization from different solvents gave different ratios of products. It is therefore suggested that **13** exhibits polymorphism; one polymorph which is obtainable by recrystallization from chloroform/methanol gives rise upon irradiation to **14** and **15**, whereas other solvent systems yield at least one further polymorph, which is responsible for product **17**. This second polymorph is expected to be a minority component. Efforts to isolate this have so far failed.



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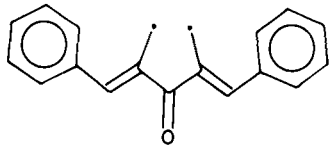
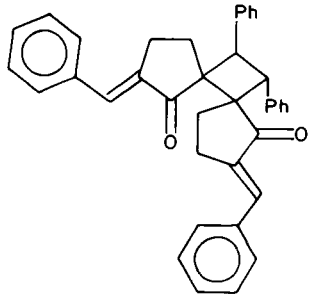


(16)

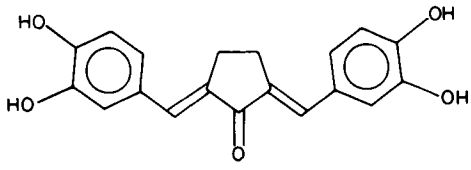


(17)

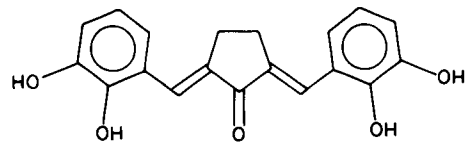
It is noteworthy that the crystal structure of **13** is of the β type, since nearest-neighbour molecules are parallel. However, the resulting dimer does not have mirror symmetry, but rather possesses a two-fold axis (Figure 8), at right angles to the cyclobutane ring. This is a consequence of the fact that the reactive double bonds are not the equivalent ones, i.e. the C(5)—C(13) double bond in one molecule reacts with C(2)—C(6) in the second. The change of molecular shape in going from the monomer to dimer is such that growth of the latter in the lattice of the former causes a lot of strain; this is not a single-crystal to single-crystal transformation. This change in shape also causes the second double bond in each molecule to move away from close contact with its neighbour. Therefore, oligomerization is not possible. Irradiation of crystals of **13** leads to an amorphous product. This is caused by the breakdown of the mechanical integrity of the crystals through strain, and the formation of more than one product; however, there is no phase separation. This is a further indication that although this reaction is not topotactic, it is topochemical. The difference in behaviour between **2** and **13** can be traced to the absence of a bulky, flexible anchoring group in **13**, and the rigidity of the whole molecule, caused by the π conjugation system extending over the whole molecule.

Various analogues of **13** have been studied, such as **18** and **19** (Scheme 4). Unlike the benzyl series, where **2** and **3** had very similar packing arrangements, **18**, unlike **13**, is photostable[40]. Crystals of **18** are of the Abm2 spacegroup, whilst the molecule is mirrorsymmetric. Nearest neighbours are related by a glide plane. In contrast, **19** is photoreactive[16], as are molecules **20**, **21** and **22**[41]. This led some workers to suggest that for the dibenzylidene series, photoreactivity is only possible for the parent molecule (**13**) and for non-symmetrically substituted analogues[41]. **20**, **21** and **22** yield dimers as well as oligomers on irradiation. Dimerization results in cyclobutane rings, whereas oligomerization may also involve oxetan formation, and should therefore involve the opening of the carbonyl carbon oxygen double bond in the reaction. This prediction is negated by compounds **23**[42], **24**[42], **25**[43] and **26**[44]. This can, however, be explained as follows. The

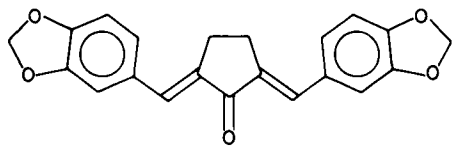
hydroxy substituents in **23** and **24** will probably be involved in hydrogen bonding; this type of interaction, which is not available in other benzylidenes, is likely to take over as the majority influence, from the $\pi-\pi$ interactions which would normally hold sway. The effect of the fluoro substituents in **25** onto the structure is likely to be complex. The size of the fluoro substituent should not be very different from that of H, but the atom–atom interactions favoured by each would be different. The study of a whole series of fluoro-substituted enones should help in elucidating the relative importance of size and electrostatic considerations, in determining packing patterns. As for **26**, methylenedioxy substitution has been shown to favour strong $\pi-\pi$ interactions, and hence β packing[45] **23** and **24** can act as chelating agents to appropriate transition-metal ions[42]. Coordination polymers (**27**) have been formed with Ni^{2+}, Cu^{2+} and Zn^{2+}. The Ni^{2+} and Cu^{2+} polymers are further photoreactive, but that for Zn^{2+} is photostable. The importance of these observations is that they show that the packing mode, and hence solid-state reactivity of the **13** framework, can be controlled by varying the coordinating metal ion, whilst leaving the substitution pattern intact.



(**23**)

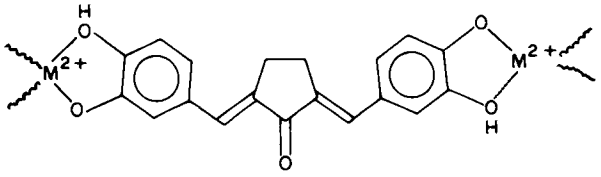


(**24**)



(**26**)

A chiral centre can be created in **13**, by introducing a substituent at position **3** of the cyclopentanone ring. The substituent which can be introduced most easily is Me, and since (+)3-Me cyclopentanone is commercially available, **28** was prepared[37]. These crystals belong to spacegroup $P2_1$, and nearest neighbours are related by the two-fold screw axis. The closest distance separating neighbouring double bonds is 3.87 Å. Although this distance is suitable for [2 + 2] cycloaddition, the crystal is photostable. This situation arises because the benzylidene groups, and therefore the conjugation systems to which these two bonds belong, are not parallel. This prevents the necessary overlap of potentially reactive orbitals. A malonic acid group can be introduced at position **3**, to yield the enone **29**, which does not dimerize on photoirradiation of its crystals, but undergoes dehydration. **29** can, in common with **23** and **24**, act as a chelating agent[43]. Complexation inhibits the dehydration process, which presumably involves the carboxylic group.



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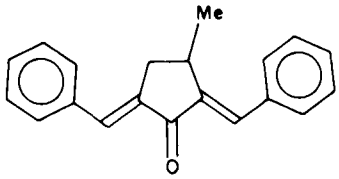

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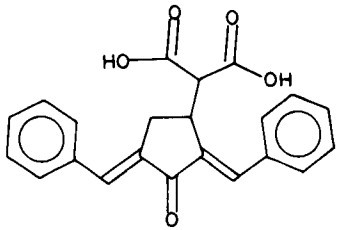


(29)

C. Properties of Mixed Crystals

The crystal structures of **4** and **5** are isomorphous, i.e. they have very similar cell dimensions. It is not therefore surprising that single crystals containing both compounds can be obtained from suitable solutions in chloroform/methanol[46]. The two components in such crystals are randomly distributed, forming ideal solid solutions. These crystals yield, upon UV irradiation, a number of dimers: some are the symmetric dimers containing either Cl or Me substituents but not both, as well as dimers which have one Cl and one Me substituent. The mixed dimer has chiral centres at each carbon atom of the cyclobutane ring. This reaction is of the single-crystal to single-crystal type[47]. When the two components **4** and **5** were mixed in varying amounts in a solution which was then allowed to evaporate to dryness, the melting points of the solid residues varied in a linear fashion with composition, between the values for the pure components. This is indicative of ideal-solution behaviour.

Crystal-structure determination on a number of single crystals showed that cell dimensions are intermediate between those of the pure components and dependent upon the Cl:Me ratio[47]. The ratios of dimers obtained upon irradiation was consistent with the Cl:Me ratio for the monomer crystal, as it was determined by crystallographic means. For a given mother solution, different single crystals contained different ratios of the two components, but the structure remained essentially the same, and similar to that of the single component crystals. The range of possible values for the Cl:Me ratio indicates that one can substitute continuously Cl for Me and *vice versa*, and retain the same, reactive packing motif.

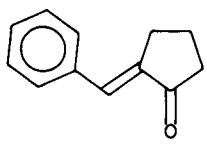
When compounds **7** and **8** were dissolved in chloroform/methanol and the solution slowly evaporated, single crystals were obtained with cell dimensions slightly but significantly different from those for **8**. X-ray intensity data were collected for such crystals, and their structure was solved to show that the benzyl benzylidene cyclopentanone framework exhibited a configuration very similar to that for **8**, rather than **7**. Further analysis revealed that both Me and Cl substituents were present, with the former being the majority component, and therefore that mixed crystals were obtained containing both compounds in a statistically averaged fashion[47]. This packing should be conducive to

topochemical dimerization, leading to a chiral product. This can be considered as an example of crystal engineering because **8**, which in its native crystal was unreactive, was forced to adopt a different conformation and a reactive packing motif, by incorporating in a lattice (provided by **7**) with those desired attributes. The relative concentrations of **7** and **8** in the solution, and therefore the crystals, was controlled by the low solubility of **8**. Thus, although it should have been possible, in theory, for crystals to be present where **8** was the majority component, thus forcing **7** into a photostable packing mode, none were detected.

Mixed crystals of **25** and **13** have also been studied[44]. The interest in this system is that it enables one to study the influence of the size of the fluoro substituent on the crystal packing: H and F have very similar sizes. Comparison of the rates of solid-state reaction for the two pure phases suggests that **25** reacts much faster than **13**, and that therefore the two crystal structures are likely to be different. The mixed crystals were found to be photoreactive, while mass spectroscopy indicated the presence of mixed dimer, suggesting that the two phases were intermingled. Contrary to the cases reported above, however, the melting points did not vary in a linear fashion with composition, but went through a maximum. This suggests that the solid solution was non-ideal. It is possible that these mixed crystals comprised domains of one compound in a matrix of the other. The presence of appreciable quantities of the mixed dimer is counterindicative to simple coprecipitation. If this had occurred, a mixed dimer would only be possible for reactions at interfaces, and would therefore be present in very small amounts.

D. Other Related Enones

2-Benzylidenecyclopentanone (**30**) has been found to be photostable, in spite of the closest double-bond to double-bond separation being 4.14 Å, for molecules related by a centre of symmetry[48]. This is a geometry which would normally be expected to lead to photoreactivity. However, closer examination of the crystal structure of **30** reveals that the two double bonds are situated in such a way that overlap of the appropriate p_z orbitals upon excitation would not be possible, as the double bonds are not directly above each other. To this extent, **30** is very similar to **7**, where the bonds are also not directly above each other; the presence of the benzyl group in **7**, however, causes the two molecules to be further apart, in which case for that structure the bond-to-bond separation was found to be 4.65 Å. Lactone **31**, however, assumes[49] a photoreactive packing motif, in which the double bonds are separated by 3.67 Å. **30** and **31** are isoelectronic, and might therefore be expected to assume similar packings[48]. It appears, however, that the crystallographic differences arise, at least in part, from the presence of C—H···O hydrogen bonds in **31**, but not **30**. What is surprising is that the hydrogen bonds in **31** involve the carbonyl oxygen, not the lactone one. Close examination of the crystal structure of **30** reveals that the six-membered and five-membered rings are not exactly coplanar, as is the case for **31**. This molecular puckering presumably contributes to **30** assuming a photostable packing motif. The presence of hydrogen bonding is reflected in the lower density of **31** and its higher melting point.



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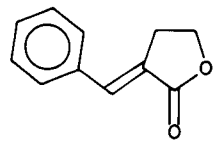
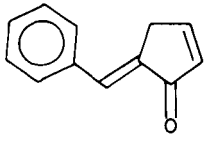


(31)

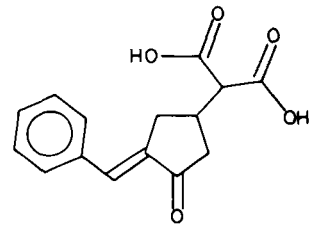
The dimerization of **31** is not of the single-crystal single-crystal type. In this, it is similar to the case for DBCP (**13**) which, however, poses the additional complication of the

generation of side-products. Single crystals of **31** begin to crack very quickly upon photoirradiation. This is due to the generation of strain caused by the mismatch of dimer molecules within the reacting monomer lattice. This behaviour may be traced to the absence of an anchoring group.

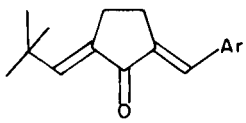
2-Benzylidenecyclopentenone[44] (**32**) was studied as a precursor to 3-malonic-2-benzylidene cyclopentanone[44] (**33**). **32** is of interest, because it is a much more rigid molecule than **30** and has a more extensive conjugation system. It has been found to be photoreactive. **33** was not only dimerizable upon irradiation, but also exhibited decarboxylation of the malonic group. Evolution of CO_2 was detected by Fourier-transform infrared spectroscopy of KBr pressed pellets. The CO_2 signal was a single peak, rather than possessing two branches. This would indicate that the product molecules remained trapped within the lattice. This reaction is probably intermolecular. The close chemical similarity of **33** with **29** leads to the assumption that both dehydration for **29** and decarboxylation for **33** are under topochemical control. The malonic acid group can act as a chelating ligand towards metals (e.g. Ni^{2+}). The complex has been shown to be photodimerizable, but the decarboxylation reaction was arrested.



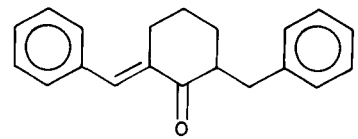
(**32**)



(**33**)



(**34**)



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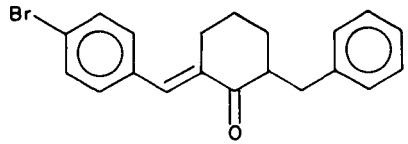


(**36**)

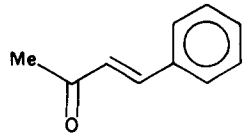
A series of 2-alkylidene-5-arylidenecyclopentanones[41] (**34**) have been studied, with 4-Me, 4-NO_2 or 4-pyridyl substituents on the aryl ring. These were found to be photoreactive, and yield dimers as well as oligomers. The oligomerization reaction appeared to involve the carbonyl group, as well as the exocyclic double bond, leading to oxetan formation.

The solid-state reactivity of the cyclohexanone analogue of 2-benzyl-6-benzylidenecyclohexanone (**35**) was studied, in order to determine the effect of additional molecular volume and flexibility, which is imparted by the extra methylene group[22]. Its

4-Br derivative **36** was also studied[16]. Both were found to be photoreactive. **35** crystallizes in spacegroup $P\bar{1}$, such that nearest neighbours are related by the centre of symmetry, with a bond-to-bond separation of 3.79 Å. Unlike that of the cyclopentanone analogue, the dimerization of **35** is not single-crystal to single-crystal. In fact, upon partial reaction the crystal melts. This may be due to two facts. First, the short bond separation may not allow the dimer molecule to relax after its formation, and second, the low melting point of **35** (69 °C) will be lowered by the presence of dimer. **36** adopts a packing totally different from that of the unsubstituted cyclohexanone, in spacegroup $P2_1/c$. The steering influence appears to be short Br···Br non-bonded contacts of 3.66 Å, across centres of symmetry. This contact is well short of the sum of the van der Waals radii of the two Br atoms. The shortest double-bond to double-bond separation was found to be 5.26 Å for centrosymmetric pairs. This is probably too long for reaction in the perfect lattice under topochemical control. Reactivity here is thought to arise because of defects: at the defects, molecules are correctly positioned for reaction (cf. the case for anthracenes). The hallmark of reaction at defects is that such reactions are inhomogeneous, i.e. they occur preferentially at some sites and not others. Evidence of inhomogeneity has been found with optical microscopy, where phase separation was observed during photoirradiation. Optical microscopic experiments were carried out under cross-polarized light. The reason for the role of the defects being seen in this reaction and not others may be as follows. Topochemical reactions occur in the perfect lattice when no transfer of energy can occur between an excited and a ground-state molecule, because of the brevity of the excited-state lifetime. Bromo substitution may lengthen the lifetime of the excited state long enough to allow energy hopping, and thus defect-controlled reactivity (see later sections). Defect-controlled reactions have been previously observed for a series of substituted anthracenes[50–52].

IV. THEORETICAL CONSIDERATIONS OF [2 + 2] CYCLOADDITIONS

Molecular-orbital calculations[53] within the MNDO approximation were performed on 1-phenyl-but-1-en-3-one (benzylidene methyl ketone (**37**)). This compound corresponds to the photochemically active portion of the benzyl benzylidene cyclopentanone molecule, and is quite close to those of **2** and **13**, and their analogues. It was therefore considered as an adequate model for the solid-state photodimerization of enones, as the nature and properties of the excited state should be the same, whether the reaction takes place in a fluid or solid environment. Some geometric constraints were imposed, however, on the conformation of the molecule, so as to model more closely the situation that obtains in the solid state. It was initially thought that the theoretical study of solid-state phenomena should involve the consideration of band structures. However, it is nowadays generally accepted that this is not necessary for molecular crystals, as electrons would be largely confined within a given molecule and would not be delocalized.



(37)

The ground state of **37** was found to have a heat of formation of 10.86 kcal mol^{-1}. The maximum electron density for the HOMO was on C(5), and for the LUMO on C(13), the two lobes having the same phase. The geometry, including bond lengths, angles and torsional angles, was close to that found for the benzylidene moiety in the crystal structure

of **2**. The lowest excited singlet state was found to have a heat of formation of 42.60 kcal mol^{-1}, with similar disposition of the HOMO and LUMO as the ground state.

The lowest excited state was found to be a triplet state with heat of formation 42.30 kcal mol^{-1}. Maximum electron density for the HOMO was located on C(5), and for the LUMO on C(13), but the two contributions had opposite phases.

The very similar energies of the lowest excited singlet and triplet states mean that transition from the former to the latter is extremely facile. The excited triplet state thus formed will be vibrationally excited. This can be correlated with the so-called 'phonon' assistance of solid-state [2 + 2] cycloaddition reactions previously reported[54]. The molecular-orbital symmetry is such that reaction between two ground-state molecules, or between one ground-state molecule and one in the singlet state, is not allowed. On the other hand, reaction between a ground-state molecule and one in the triplet excited state is allowed. Thus, the facility of energy transfer between states is crucial to the reaction occurring under topochemical control.

The lifetime of the triplet state for **13** as measured from the phosphorescence in emission spectra[55] at 77 K was only 200 μs. The brevity of the lifetime of the excited state means that the excited molecule cannot transfer its energy to a neighbouring one. This process is called energy hopping, and where it occurs the solid-state reaction is not homogeneous, as it is no longer random. Defects in the lattice act as energy traps and therefore such a reaction is more likely to occur at defects. The shapes of the two excited states are very similar to that of the monomeric residues in the dimer. The bond lengths and angles as determined from MNDO for the two excited states of **37** correspond well with those found crystallographically for the dimer of **2**.

The change in shape which accompanies excitation has two consequences: first, it makes energy hopping less likely, since this process is more probable between molecules closely related in structure. Second, this movement probably causes the reactive centres to move closer together, compared to the position they occupy when at the ground state. The speed of reaction is also related to the fact that the transition state is closer in structure to the product than to the reactant. The symmetry of the orbitals in the triplet and ground states indicates that both the head-to-head and head-to-tail reactions are intrinsically possible. Further, the cycloaddition has to be a non-concerted process, since only one pair of orbitals of the two involved are initially of the correct symmetry.

In other sections of this chapter, it will be seen that a number of reactions appear to occur under topochemical control, insofar as the geometry (nature) of the product can be rationalized in terms of the crystal structure of the reactant, yet they occur between double bonds either too far apart, or not totally parallel. A possible explanation for these discrepancies may be that parallel double bonds present the ideal geometry to enable a lobe with correct phase on the ground-state molecule to overlap with one on the excited state. This overlap is clearly possible for orientations other than parallel bonds. Furthermore, since in the present example the phases of the lobes are such that the reaction cannot be concerted, it may be that at the start of the reaction contact has to be favourable for only one atom on each molecule for reaction to be possible, and not for both atoms simultaneously. The term 'minimum movement' probably should only refer to the initial movement of the reacting atoms, and after that the consequent movement for the rest of the molecule may be larger (see, for example, the case for distyrylpyrazine)[91]. This movement will probably cause strain and the breakdown of the mechanical integrity of the crystal, and therefore stop any further reaction, as topochemical control would be lost.

Apparent breakdowns in the topochemical principle, because of separation, are more difficult to explain. There is a grey area consisting of bonds separated by distances between 4.25 and 4.7 Å where molecules, e.g. 4.7 Å apart, react and others separated by 4.3 Å do not, other things being equal. It is sometimes possible to explain stability, because bonds are not parallel (e.g. **27**) or because of steric hindrance to the movement necessary for reaction.

There are cases, however, whether no such clear explanations are possible[56]. It is suggested that in those cases, the reason for stability may be found in the geometric structure of the excited state.

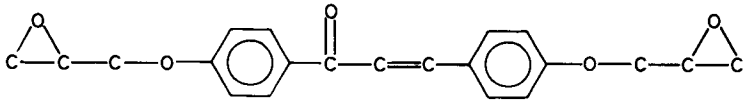
The topochemical principle is a very useful tool for the solid-state chemist, and is capable of application in a variety of situations. It does suffer, however, from the disadvantage that crystallography provides the structure of ground-state molecules when, in the case of photochemical reactions, excited states are involved.

V. SOLID-STATE DIMERIZATION AND POLYMERIZATION OF OTHER ENONES

A. Chalcones

The photochemistry of benzalacetophenone has been studied in solution and in the crystalline state[57,58]. In solution, it undergoes *trans–cis* isomerization. Photoirradiation of crystals leads to formation of both mirror-symmetric and centrosymmetric cyclobutane rings, as well as some resinous byproducts. Irradiation of a solution of *p*-anisal-acetophenone leads only to the formation of a resin. However, in addition to resin, dimers are formed in the solid state, of both the mirror-symmetric and centrosymmetric type.

The photochemistry of chalcones is of interest owing to their occurrence in the form of 4,4′-dioxychalcone functional groups in photo-crosslinkable epoxide resins[59]. In order to mimic their behaviour, the solid- and liquid-state photochemistry of the diglycidyl ether of 4,4′-dihydroxychalcone (**38**) has been studied[60]. The preferred solvent for the solution studies was acetonitrile. At least in solution, further reaction is preceded by *trans–cis* isomerization. Whether this occurs in the solid state before further reaction takes place is not clear from the paper. Prolonged irradiation with pyrex-filtered UV light (Hg vapour medium pressure lamp) led to 78% dimer and 22% low-molecular-weight polymer in solution, and 63% dimer with 37% polymer in the solid state. Gel permeation chromatography and mass spectroscopy was used to identify the nature of the dimers. It was found that both mirror-symmetric and centrosymmetric cyclobutane rings had been formed. Cleavage of the four-membered rings appears to take place. The olefins that result can either recombine to yield a dimer, or can be converted to a variety of radicals which then polymerize.



(38)

B. 2-Benzyl-5-cinnamylidenecyclopentanone

The enone **39** packs in spacegroup Pbca (Figure 9), with the asymmetric unit comprising two molecules (noted as A and B)[61]. Examination by IR spectroscopy before and after UV irradiation confirmed that reaction had taken place. Examination of the crystal structure indicates that although several double-bond to double-bond short (< 4.3 Å) contacts are present between at least two pairs of molecules (Figure 9), none is for precisely parallel double bonds. ^{13}C NMR spectroscopy indicates that oligomerization has occurred involving both the double bonds and the carbonyl groups. Four-membered rings in the polymer are of both the oxetan and cyclobutane kind. Oxetan formation has been encountered in other oligomerizable systems, such as **34**[49], and certain derivatives of **13**. In

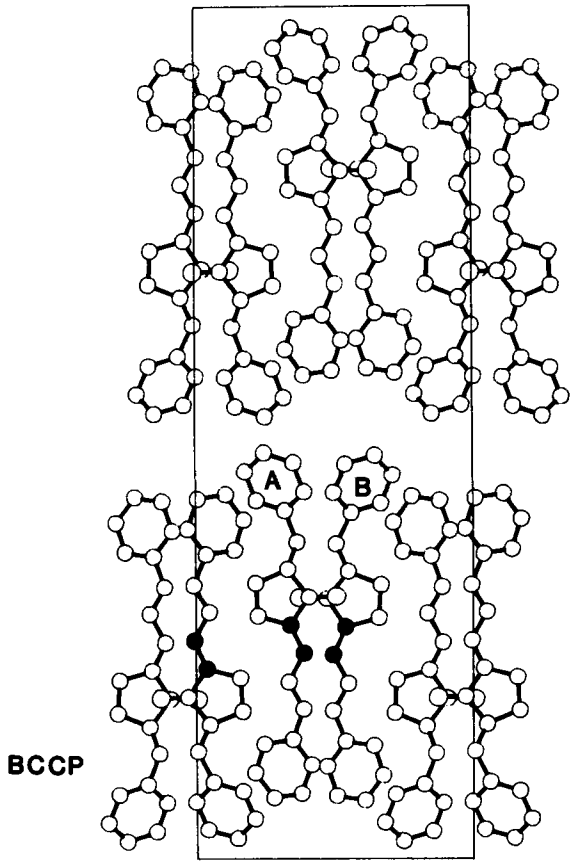
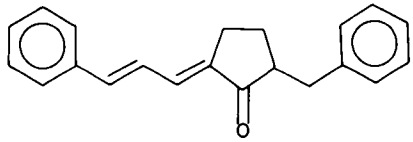


FIGURE 9. Packing diagram for **39**. Labeles A and B refer to the two independent molecules in the asymmetric unit. Filled circles indicate the closest bond-to-bond contacts

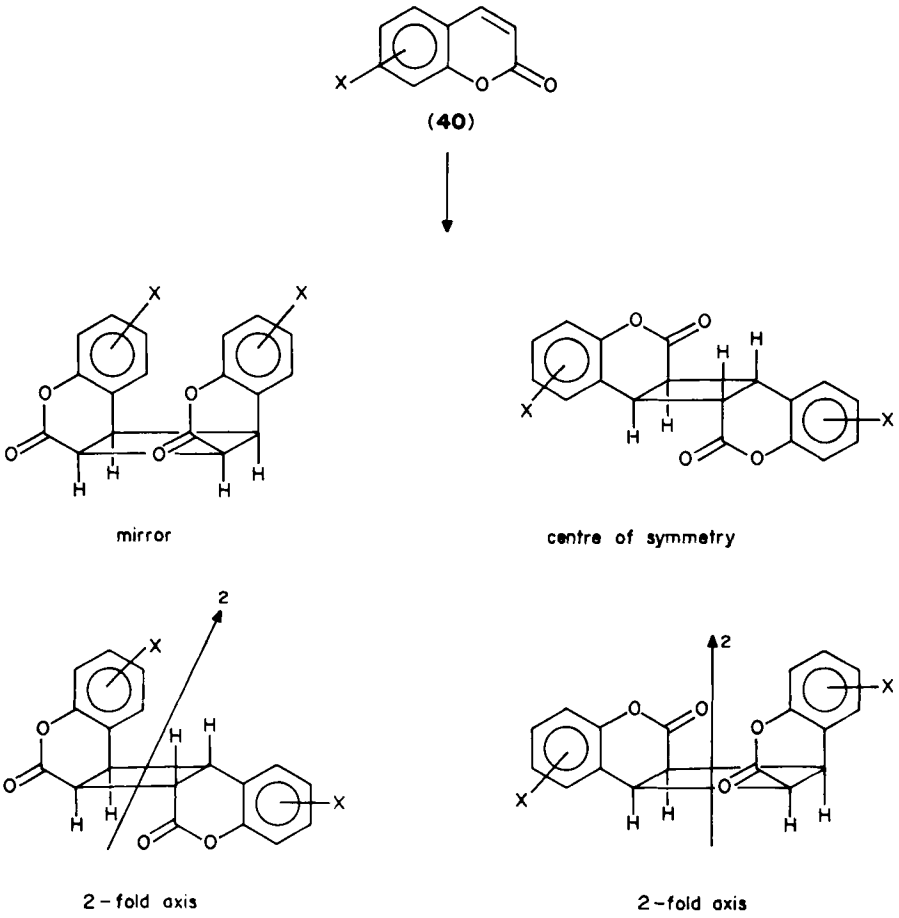
both **13** and **39**, the double bonds are, presumably, too close to each other in the molecular framework to allow them to react in the solid state simultaneously. In general, no case has been found in the solid state where polymerization occurs where only one double bond is involved. Polymerization occurs only where two widely spaced bonds are present suitably packed, or where the carbonyl is activated to such an extent that it is able to react and form an oxetan four-membered ring.



(39)

C. Coumarins

The solid-state photochemistry of a number of 4-, 6- and 7-substituted coumarins (**40**) has been studied[17]. Depending on the substituent, four different types of dimer have been found (Scheme 5). For example, 7-methoxycoumarin crystals[62] yield upon UV irradiation a dimer molecule with a centrosymmetric cyclobutane ring, and 7-chlorocoumarin yields a mirror-symmetric cyclobutane ring[63]. 4-Chlorocoumarin, on the other hand, yields two products, both with cyclobutane rings with two-fold symmetry; in one, the symmetry axis is in the plane of the four-membered ring, and in the other, at right angles (for the structures of these dimers, see Scheme 5).



SCHEME 5

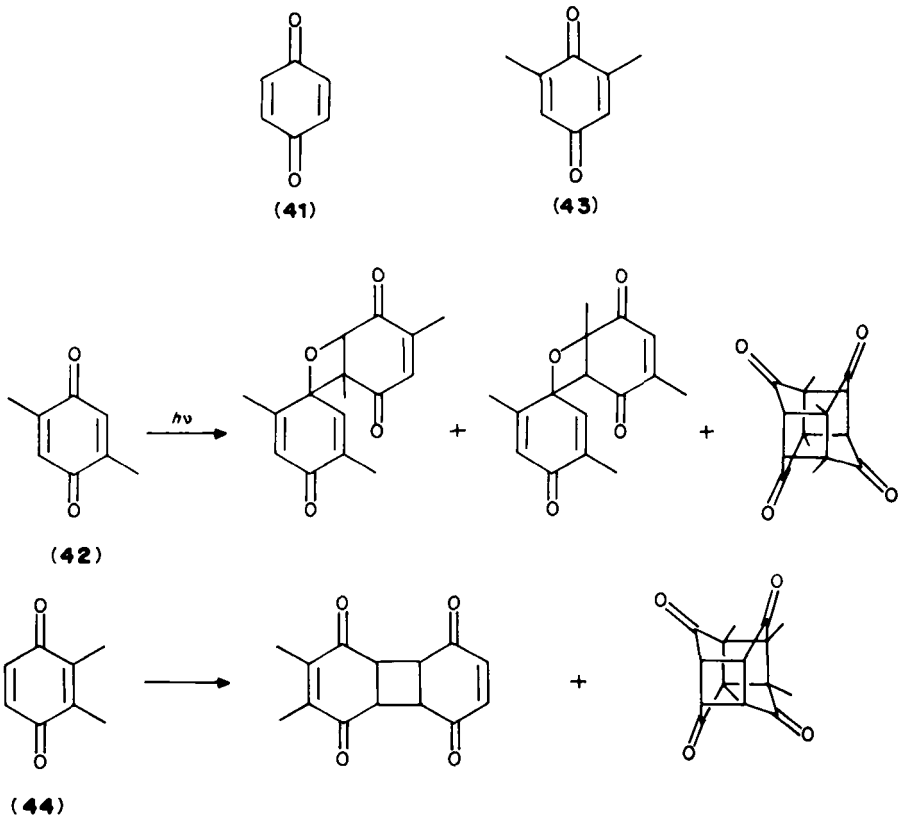
The crystal structures of these photodimerizable coumarins present several interesting points. For example, in 7-chlorocoumarin the molecules in the incipient dimer pair are related by translation, and the reactive groups are separated by 4.45 Å, a distance normally expected to be counterconductive to reaction. This is more striking given the presence of

centrosymmetrically positioned double bonds, separated by only 4.12 Å, which would normally be expected to lead to reaction. In 7-methoxycoumarin, the reactive double bonds are separated by 3.8 Å, but are not parallel, and subtend an angle of 65° between them. The explanation proposed for the reactivity of this compound is similar to that put forward for **13**.

It is noteworthy that the four types of dimer yielded by the different coumarins represent all the possible dimers obtainable by [2 + 2] cycloaddition of conjugated *trans* double bonds. Very few chemical systems which exhibit topochemical dimerization have shown such diversity to date: in the *trans* cinnamic acid family only two types of dimer are obtainable, and the same number are possible in the BBCP–DBCP complex. This versatility of the coumarins is probably due to the flatness of the coumarin carbon skeleton as opposed to the non-planar BBCP one, and the absence of the steering effect of hydrogen-bonding operative in the *trans* cinnamic acid system.

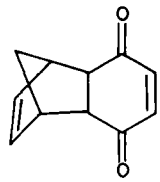
D. Quinones

The unsubstituted benzoquinone (**41**) and its 2,3,5,6-tetramethyl analogue are photostable[64,65]. This behaviour can be explained in topochemical terms. The dimethyl derivatives **42**, **43** and **44** (Scheme 6) are reactive in the solid state. Each of these quinones



SCHEME 6

yields in general two types of dimer, one cage dimer containing two cyclobutane rings, and an oxetan obtained by the reaction of a carbonyl group on one molecule with a double bond on a neighbour. The solid-state photoreactivity of **42** and **43** can easily be explained in topochemical terms. The crystal structures for these molecules are built up from asymmetric units consisting of two molecules. In both structures, each unique molecule in the asymmetric unit is part of its own stack. Contacts and orbital overlaps are favourable for oxetan formation in one of the two stacks, and for formation of the cage dimer in the other. The symmetry of the oxetan dimer is different for different monomers. In fact, **42** gives two oxetan dimers with different symmetries, whereas **43** yields only one oxetan, in addition to the cage dimer. The solid-state reactivity of **44**, however, cannot be explained easily. The cage dimer which is obtained has a mirror symmetry, whereas nearest neighbours are related by a centre of symmetry. It is possible that reaction in this crystal is controlled by, and occurs at, crystallographic defects. The second product from this crystal is not an oxetan, but contains a cyclobutane ring. Several benzoquinones (e.g. **45**) undergo intramolecular cycloaddition to yield a cage dimer[66,67].



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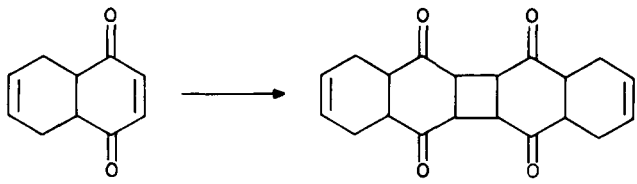

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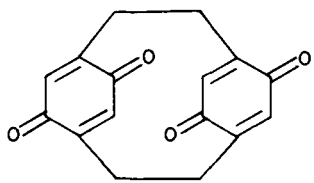

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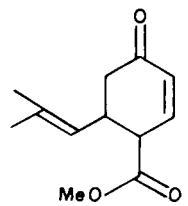
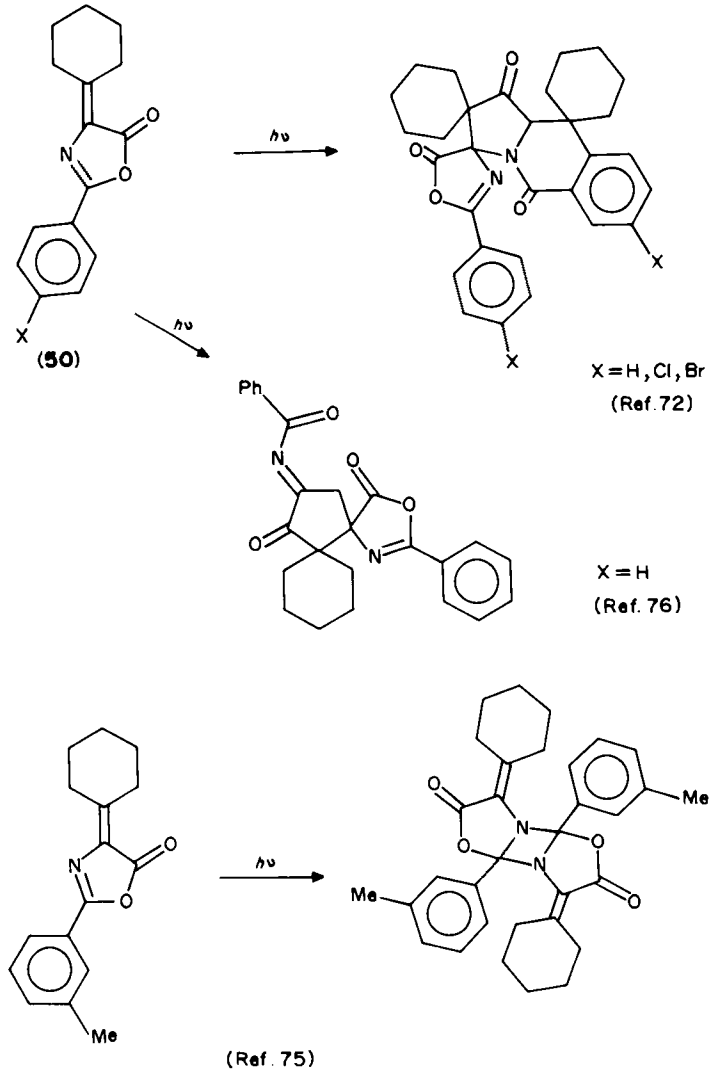


(49)

Scheffer, Trotter and other workers have studied the solid-state reactivity of substituted tetrahydronaphthoquinones extensively[11,15,68,69,148], over a number of years. Four different reactivity patterns can be discerned, which are correlated to the disposition of neighbouring molecules and the intermolecular distances. Reactions observed were intermolecular cycloaddition, intramolecular hydrogen abstraction by an oxygen or carbon, and intramolecular oxetan formation[66]. For example, **46** undergoes inter-

molecular cyclobutane formation to yield dimer **47**. Scheffer, Trotter and coworkers have shown that the variety of possible reactions is due to the fact that naphthoquinone is frozen into a single conformation in a crystal, irrespective of the substitution pattern. This series of compounds has been extensively reviewed in another volume of this series.

2, 5-Benzoquinonophane (**48**) is polymorphic[70]. In one of its crystal forms, the carbonyl groups of each six-membered ring in the molecule are parallel, and in the second crossed. The latter form is stable, whereas the first undergoes intramolecular cyclization. No intermolecular reactivity is observed. The enone **49** is a natural product, whose crystals are clear and needle-like. Exposure to light quickly changes the crystals into an opaque



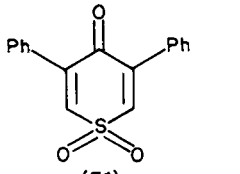
SCHEME 7

powder[71]. The product has a centrosymmetric cyclobutane ring. In the parent crystal, reactive molecules are antiparallel with a double-bond to double-bond separation of 3.86 Å. However the double bonds, although parallel, are not exactly on top of each other, so that a relatively large movement of *ca* 2.2 Å is needed from each carbon atom, to react.

E. Heterocyclic Compounds of Enones

4-Alkylidene-oxazol-5(4*H*)-ones (**50**) exhibit a variety of light-induced reactions, including asymmetric dimerization with[72] or without[73] H-shift, [2 + 2] dimerizations[74], dimerization reactions involving the C=N bonds[75] (Scheme 7) as well as Diels–Alder dimerizations and Norrish type II processes[75]. Some of these reactions involve opening of one of the lactone ring[76], in addition to ring formation.

3,5-Diphenyl-4-*H*-thiopyran-4-one-1,1-dioxide (**51**) undergoes a double Diels–Alder reaction[77] to yield the trimer **52**, with an attendant loss of SO_2. Other thiopyranone derivatives have been studied, and of these the 2,6-diphenyl derivative was reactive but the 3,5-dimethyl was photostable. *N*-Methyl-2-pyridone[78] (**53**) yields a centrosymmetric cyclobutane compound upon photoirradiation which reverts back to the monomer upon heating, whereas **54**[78] and **55**[79,80] yield mirror-symmetric cyclobutanes.



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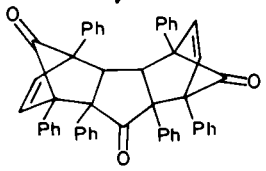
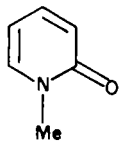
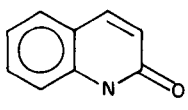


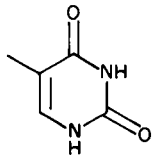
(**52**)



(**53**)



(**54**)



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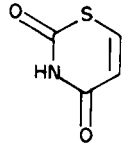
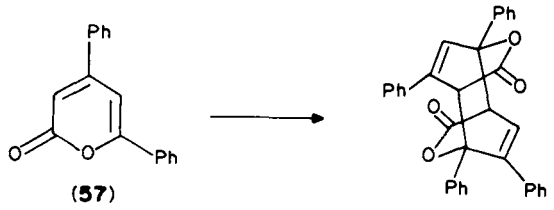


(**56**)

Photoirradiation of crystals of 1-thiouracil[81] (**56**) yields a dimeric molecule with a puckered, twisted, cyclobutane ring, which has a pseudo two-fold symmetry. Similar reactivity has been observed for uracil itself the dimer of which is obtained by the UV irradiation of RNA[82].

Two heterocycles which undergo [4 + 4] cycloaddition are the α-pyrone[83] (**57**) and the pyrazinone **58**[84], to yield centrosymmetric dimers **59** and **60**, respectively. The archetypal

[4 + 4] cycloadditions are those of the anthracenes[51]; a striking difference between **57** and **58** on the one hand and, for instance, 9-cyanoanthracene on the other is that the reactions described here are topochemical, whereas the anthracene one is defect controlled. In fact, the dimer yield for **57** is 100%.



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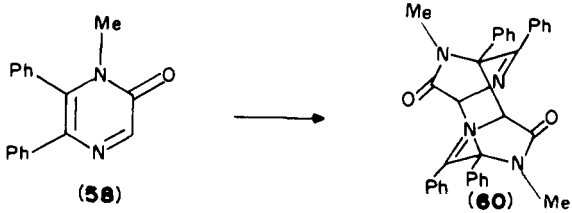
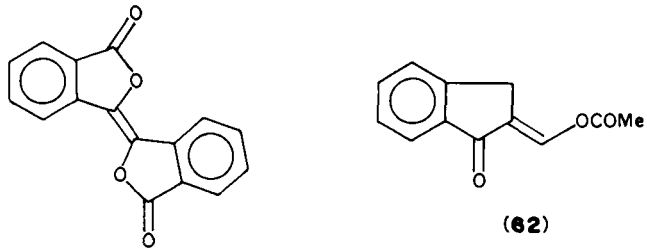


(58) (60)

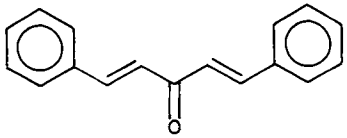
F. Miscellaneous Other Dimerizations

A number of other enones, such as **61**[85] and **62**[86], dimerize in the solid state to yield cyclobutane rings. Conjugated cyclopentadienones (**63**, R = H, Ph, *t*-Bu, Et, *p*-C_6H_4Me), on the other hand, undergo cyclization[87] to yield cage dimers (**64**). Dibenzylidene acetone (**65**) is photostable, but its dichloro analogue undergoes facile double cycloaddition to yield compound **66**, which contains two cyclobutane rings. This illustrates the usefulness of chloro substitution in crystal engineering: Cl···Cl close contacts are energetically very favourable and can be maximised by assuming β packing (cf. cinnamic acids).



(61) (62)

(63) (64)



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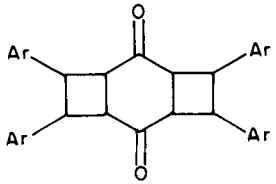


(66)

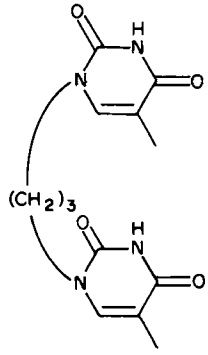
Mustafa has shown that compounds such as **65** containing[58] extended conjugated π-systems will form complexes with UO_2Cl_2 or $SnCl_4$. In the crystal of the 2:1 adduct of **65** to UO_2Cl_2, the metal ions are related by centres of symmetry with the organic parts of the complex in a packing motif in which they are related by that symmetry. The double bonds are then at the correct orientation and distance for reaction. This crystal-engineering strategy has been used by Moulden and Jones to steer **13** into a packing motif which yielded a centrosymmetric dimer[88].

G. Solid-state Polymerizations

1,7′-Trimethylenebisthymine (**67**) is packed in such a way that reactive double bonds subtend an angle of 4°, and are separated by 3.69 Å. Packing considerations suggest that both intra- and inter-molecular cyclobutane formation is possible, but the reaction actually occurring is the intermolecular one, leading to polymer formation[89].

The archetypal polymerizable dienone is **68**. In its crystals, molecules are arranged such that the reacting pair is skewed, and the intermolecular double-bond separations are 3.98 and 4.09 Å for one incipient cyclobutane, and 3.90 and 3.96 Å for the other[90]. In a single crystal of **68**, dimer **69** is obtained at the initial stages. This reacts further, either intramolecularly to yield the dimer **70** or it yields an oligomer as the minority product, via an intermolecular reaction (**71**).

In general, unsymmetric diolefins (i.e. those unlike **68** which have inequivalent double bonds) can adopt two types of packing conductive to polymerization (Scheme 8): one the so-called hetero-adduct and the other the homo-adduct motif[91]. The former yields chiral cyclobutane rings, and the latter symmetric ones. If a diolefin with a hetero-adduct packing motif crystallizes in a chiral spacegroup (i.e. one which does not contain mirror planes or centres of symmetry), then a single crystal of the monomer will yield a polymer chain of one chirality. If, however, the spacegroup is a racemic one, then polymer strands of



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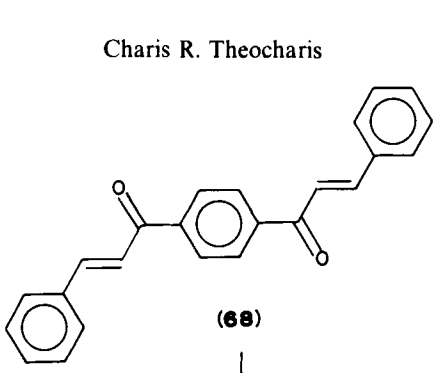

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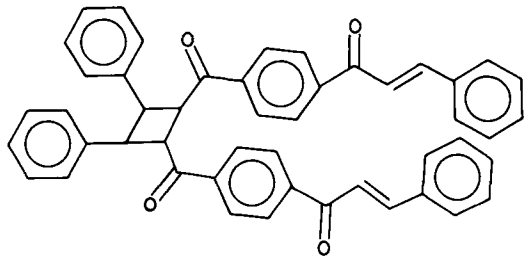

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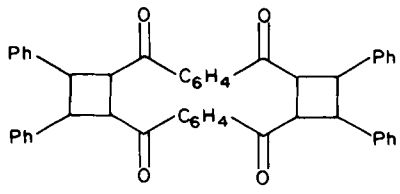

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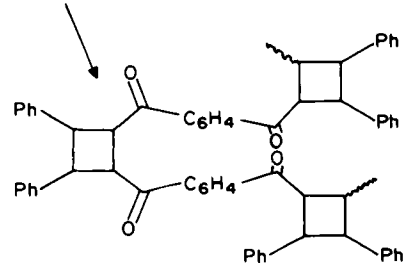

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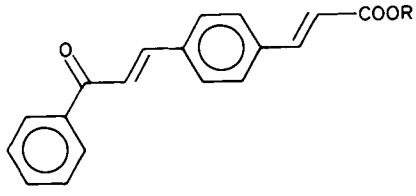
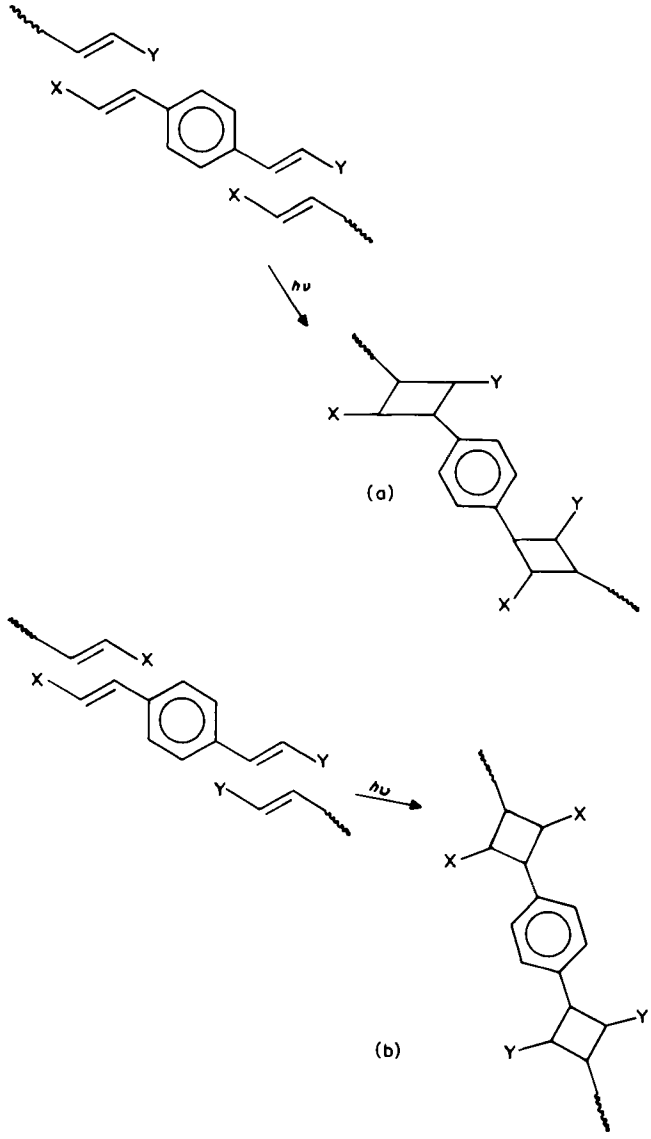


(72)

both chiralities will be obtained. The enone **72** has been successfully polymerized to yield a chiral polymer. Solid-state polymerization is particularly useful, because it can yield a product of very high crystallinity and relatively large crystals.



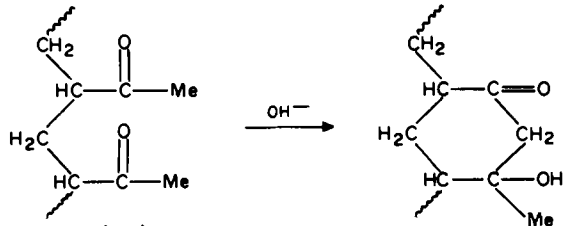
SCHEME 8. (a) Hetero-adduct polymer; (b) homo-adduct polymer

VI. FLUID-STATE HOMOPOLYMERIZATION OF ENONES

α, β-Unsaturated ketones are a particularly interesting class of monomer. At least some of the alkyl vinyl ketones, in addition to being spontaneously polymerizable, are susceptible to various types of initiation, including free radical, anionic and cationic initiation, and photochemical techniques[92,93].

A. Methyl Vinyl Ketone (MVK)

Methyl vinyl ketone (1), which is miscible with water, is among the most reactive monomers. When highly pure, MVK will spontaneously polymerize via a syrup to a solid mass on standing for a few hours in sunlight, or much faster on heating in the presence of peroxide catalysts[94]. The products, which contained some residual monomer, had a rubber-like consistency at room temperature. However, completely polymerized MVK was rigid and tough at room temperature, and became brittle on cooling down. The physical properties vary considerably with molecular weight. Thus, low-molecular-weight poly-MVKs prepared in the presence of inhibitors were soft adhesive solids, or even viscous liquids. Poly-MVK prepared in the presence of dibenzoyl peroxide as catalyst (0.5%) by heating at 50 °C for 5h was a yellow, clear and tough solid soluble in organic



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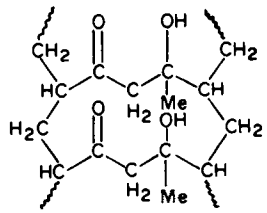

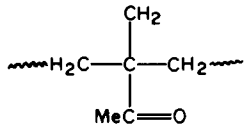

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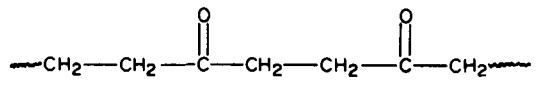

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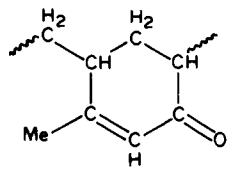
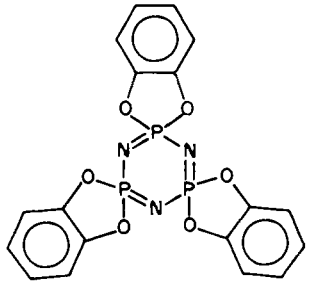


(76)

SCHEME 9

solvents such as acetone, acetic acid, dioxan and pyridine[95]. Reaction of this polymer with $ZnCl_2$ in pyridine at 60 °C did not result in dehydration. This was taken to mean that the structure of the polymer was essentially head-to-tail, i.e. it was a 1, 5-diketone (**73**). Most poly-MVKs are branched to some extent, to give structure **74**. This branching may give rise to the observed instability of some of these polymers[92]. Polymerization can also be induced in the gas phase, by UV light irradiation, with CO formed as a by-product[96].

Under certain reaction conditions, MVK undergoes hydrogen transfer polymerization rather than normal vinyl polymerization to yield **73**. For example, MVK dissolved in toluene was polymerized in the presence of *t*-butoxide, to yield a polymer at least in part made up of groups such as **75**, obtained via migration of a hydrogen from the methyl group adjacent to a carbonyl, to cause 1, 5 addition[97]. Crystalline, isotactic poly-MVK has been prepared with anionic catalysts, such as Sr or Ca—Zn tetraethyl at 0 °C in toluene[98], and was shown to have a helical structure; some amorphous material was also produced. Use of butyllithium catalyst or sodium naphthalene at − 70 °C yielded a non-crystallizable, red, soluble polymer, which had IR spectra characteristic of structure **76**. This is believed to arise from a reaction of **73** with the organometallic catalyst.



(**77**)

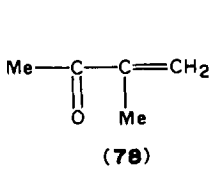
Poly-MVK can also be obtained by γ-ray irradiation of tunnel clathrates of MVK in cyclotriphosphazene (**77**)[99]. The poly-MVK obtained from this system has a high degree of stereoregularity and has no cross-linking, in contrast to bulk polymerization. Copolymers with random sequences can also be obtained via this route. The technique of group transfer has been used to control the structure of acrylic polymers, including poly-MVK[100]. For example, sequential addition of $Me_2C{=}C(OMe)OSiMe_3$ to **1** can be catalyzed by $(Me_2N)_3S^+\ HF_2^-$ (or, instead of HF_2^-, CN^-, N_3^- etc. can be used as counterions), or by Lewis acids such as $ZnCl_2$. This leads to poly-MVK with a variety of end groups, via a living polymer mechanism: the silyl group is transferred to the carbonyl oxygen of the monomer. Poly-MVK in common with many polymers containing acidic groups can undergo condensation reactions with mixtures of compounds of groups IIIb, VIIIa, Ia and Vb (e.g. $FeSO_4$). The products can be used as thickeners or retention agents[101].

The softening point of poly-MVK varies between 30 and 50 °C, depending on the mode of preparation. Self-condensation occurs in the presence of mineral bases (Scheme 9), leading to a brittle, insoluble polymer. Amines (e.g. aniline or aniline hydrochloride) react with solutions of poly-MVK to form eventually bright yellow cross-linked polymer, which contains some N function. In acetone solutions, poly-MVK can be reduced to a polymeric secondary alcohol, by reaction with HCHO in the presence of a small amount of mineral acid, which acts as a catalyst[92]. The same effect has been reported from reaction of $LiAlH_4$ with THF solutions of poly-MVK[102]. However, homogeneous reaction of $LiAlH_4$ with poly-MVK prepared by radical polymerization resulted in intramolecular cyclization[103].

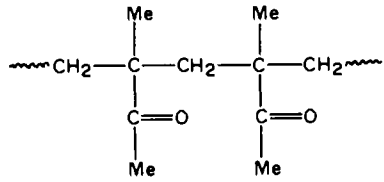
Irradiation of poly-MVK or of poly-isopropenyl ketone at room temperature resulted in depolymerization, but at elevated temperatures (80 °C) it resulted in degradation[104]. Heating of poly-MVK in vacuum at 250 °C led to random aldol condensation and a cyclic structure with variable conjugation length. The reaction mechanism is believed to involve $^{-}CH_2$ groups attacking neighbouring carbonyls[105].

B. Methyl Isopropenyl Ketone

Methyl isopropenyl ketone (**78**, α-methylvinyl methyl ketone) yields polymers with a higher softening temperature and clearer than those of MVK. **78** Polymerizes readily at room temperature, but less so than **1** under similar conditions. Storage of the monomer results in glass-clear polymer, or alternatively polymerization can be brought about by boiling, but only low molecular weights are achieved. Very high molecular weights can be obtained upon exclusion of oxygen. This polymer is believed to be of the head-to-tail type (**79**), and substantially uncross-linked. Coloured polymers can be achieved from aqueous emulsions.



(**78**)



(**79**)

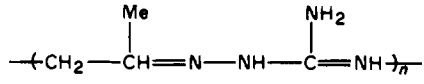
Catalysts used successfully in polymerizing **78** include dibenzoyl peroxide[106], azodiisobutyronitrile[107], and mixed metal alkyl-transition metal halides (e.g. $AlEt_3$–$FeCl_3$, or $MgEt_2$ with $CoCl_2$ or $MnCl_2$ in ether)[108,109]. Crystalline polymers have been obtained from these catalysts, in a series of hydrocarbon or ether solvents and at temperatures between −60 and 50 °C. For example, in the presence of a $AlEt_3$–$FeCl_3$ catalyst in methylcyclohexane at 18–22 °C, two types of crystalline polymer have been isolated, one isotactic and the other syndiotactic. In these reactions the polymer was precipitated upon addition of water.

Polymerization was also achieved in the presence of phenylmagnesium iodide in EtCl or chloroform solutions. Polymers prepared from radical initiators were not crystalline, whilst those prepared in the presence of BuLi were red in colour[93], the colour being probably due to a structure equivalent to **76**. Analogues of **78**, such as α-ethylvinyl methyl ketone, behave in ways similar to **78**, but propenyl methyl ketone is not polymerizable, presumably owing to its lack of a terminal $CH{=}CH_2$ group.

C. Uses of Methyl Vinyl Ketone and of Methyl Isopropenyl Ketone

The polymers of both **1** and **78** have been used in photographic or related processes. For example, the use of poly-MVK as an anion-exchange resin component in the manufacture of dye-receptive films has been patented by Kodak[109]. Poly-(methyl isopropenyl ketone) has been used as a component of dry developable resists for Si-wafer manufacture[110]. Poly-MVK obtained from MVK dissolved in dioxane in the presence of 1% Bz_2O_2 was dissolved in a mixture of acetic acid and dioxan with aminoguanidine[111]. Bicarbonate was added slowly under heat and, on addition of water and Zn dust with AcOH, a light amber colour was obtained. On addition of NaOH, **80** was obtained. An equivalent polymer was also obtained from poly-(ethyl vinyl ketone), and poly-(propyl vinyl ketone). **80** can be used in formulations of additives in light-sensitive emulsions for photography, as

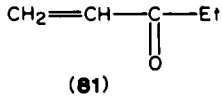
mordants. A recent patent application describes the use of various enone polymers reacted with cyano dyes as optical laser materials[112].



(80)

D. Other Alkyl or Aryl Vinyl Ketones

Ethyl vinyl ketone (**81**) polymerizes very readily in sealed tubes at 40 °C in the presence of diacetyl peroxide initiator, to a soft yellowish polymer[92]. Longer periods of reaction time can result in solid polymers. A variety of aryl vinyl ketones, including phenyl, 4-chlorophenyl and napthyl, have been polymerized using dibenzoyl peroxide initiator, yielding polymers of varied hardness[113]. Phenyl vinyl ketone can be polymerized in toluene, in the presence of several organometallic catalysts, at −70 °C[114]. This is not a crystallizable polymer, but a crystalline product has been obtained in the presence of initiators such as lithium dust, sodium hydride, BuLi, etc. The aryl vinyl ketone polymers obtained from this route have higher softening temperatures. Chlorinated monomers can also be used, e.g. **82**, which very readily yield solid polymers at room temperature[115].



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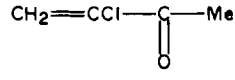
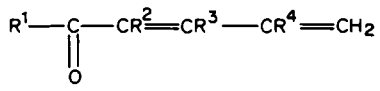


(82)

Two types of poly-(*t*-butyl vinyl ketone) have been produced[116]: the first, made at 25 °C with lithium or organolithium catalysts in hexane or toluene; the second, prepared in THF at 0 °C with lithium biphenyl, or with azobisisobutyronitrile in benzene at 60 °C. The first type is crystalline and much less soluble than the second, and it has been suggested that they are isotactic and moderately syndiotactic, respectively. It was found that with lithium dispersions, BuLi or lithium biphenyl initiators and a mixture of *t*-butyl vinyl ketone and methyl methacrylate in THF, only homopolymerization of the enone occurred, albeit at twice the rate than in the absence of the methacrylate[117]. Viscosity measurements suggested that chain transfer operated, which was thought to be the reaction of a growing enone chain with the carbonyl group of the methacrylate. The lithium methoxide thus produced would serve to terminate one chain and initiate another. The enhanced rate, however, is probably due to the preferential solvation of growing ion pairs by methyl methacrylate. Also, it is possible that the presence of methacrylate moderates the wasteage of initiator which would otherwise occur, owing to the formation of lithium methoxide, via a reaction of the organolithium compounds with the enone.

The dienone **83** can yield both homopolymers and copolymers[118]. A number of different substituents have been used, e.g., R^1 was cycloalkyl, alkenyl or phenyl, R^2 = H, alkyl, phenyl or a halogen, and R^3 or R^4 H, Me or a halogen. Copolymers with **78** have also been formed. For example, a solution of **83**, where R^1 = Me, R^2 = H, R^3 = H and R^4 = Me in toluene, yielded a *trans*-1,4 polymer in 1 day at 50 °C in the presence of $AlEt_3$. The product had a molecular weight of approximately 353,000. 2-Hydroxybut-1-en-3-one (**84**) yields brittle polymers[119]. Etherification with MeOH or EtOH of **84** yields a monomer, which can polymerize by heating at 30 °C for 4 days under nitrogen, to a strong transparent product. 2-Methoxymethyl-but-1-en-3-one was polymerized in the absence of oxygen to

a clear, hard resin, which was soluble in a variety of organic solvents[120]. Polymerization was initiated by heat, light or peroxides.



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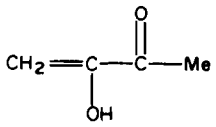
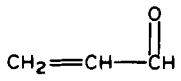


(84)

E. Acrolein

Acrolein, or prop-1-en-3-one (**85**), was first prepared over 150 years ago[121]. It polymerizes spontaneously to a white non-crystalline polymer. The polymerization reaction is complicated by condensations through the aldehyde group. Clear solid polymers can be obtained in the presence of basic catalysts and buffers. The presence of a little β-naphthol enables **85** to polymerize upon exposure to UV light. The spontaneous polymerization can be inhibited by the presence of hydroquinone.

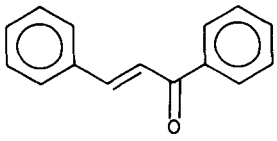


(85)

α-Methylacrolein (2-methylprop-1-en-3-one) polymerizes almost as readily as **85**. Freshly prepared and distilled, it begins polymerizing within a few hours of being left to stand in air, and polymerization may be complete in 4 days to a hard chalky resin. In the presence of hydroquinone, dimerization only occurs. This monomer can also be polymerized in the presence of *t*-Bu peroxide and $ZnCl_2$ in aqueous solution at room temperature, to an opaque gel. This can be converted to a hard polymer, by oxidation. The ethyl analogue only polymerizes rapidly on heating.

F. Exchange Polymerization

A novel polymerization route has recently been described involving the so-called carbonyl double-bond exchange mechanism. For example, homopolymerization of unsaturated ketones in the presence of WCl_6 yields polyacetylene[122]. Benzylidene acetophenone (**86**), or 1,3-diphenyl-2-buten-1-one (**87**) or 1,3,3-triphenyl-2-propen-1-one (**88**) in the presence of WCl_6 gave poly-phenylacetylene, with molecular weight in the region 1500–3000; increase in the amount of WCl_6 present led to an increase in the degree of polymerization[123]. This polymer was found to be paramagnetic. Reaction of 1,2,3-



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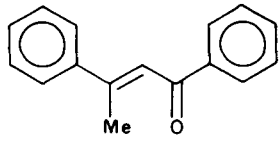
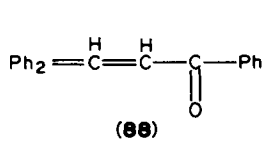
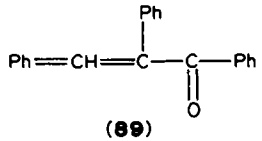


(87)

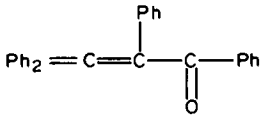
triphenyl-2-propen-1-one (**89**) or its 1,2,3,3-tetraphenyl analogue (**90**) led to poly-diphenylacetylene and 1,3-dimethyl-2-buten-1-one (**91**) yielded poly-methylacetylene. Polyacetylenes have generated a lot of excitement in recent years, because they exhibit semiconducting or metal-like conducting behaviour upon p- or n-type doping[124].



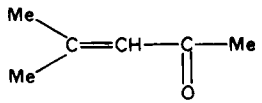
(**88**)



(**89**)



(**90**)



(**91**)

VII. COPOLYMERIZATION AND GRAFT POLYMERIZATION OF ENONES

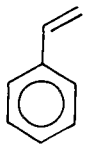
Enones undergo both copolymerization with a variety of monomers, and grafting on a number of polymers. Both processes have recently received considerable attention. Initiation of these reactions has been carried out by various radical, anionic and cationic catalysts. The usefulness of MVK and of its analogues in copolymerization is a relatively recent development. Copolymers of MVK initially reported tended to be rather water-sensitive, of limited stability and reactive. Products with acid-releasing comonomers tended to be discoloured.

One of the first comonomers that were employed was butadiene[92]. This formed an oil-resistant rubber with MVK which, however, tended to harden upon standing. Initiation was carried out by persulphate emulsions. Better results can be obtained if a small amount of inhibitor is added, which slows down the polymerization of MVK **78** also copolymerizes with butadiene, yielding a product with properties similar to the copolymer of MVK. The **78**–butadiene copolymers prepared in an emulsion medium were soluble in aromatic solvents, even at 80% monomer conversion. Terpolymerization of MVK with butadiene and styrene can also be brought about by the same route[125].

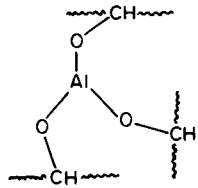
Radical mass suspension graft polymerization of methyl vinyl ketone and styrene (**92**) on polybutadiene results in high impact styrene copolymers with methyl vinyl ketone, which are photodegradable[126]. Copolymerization of **92** and highly pure MVK can also be brought about without the medium of polybutadiene, in the presence of radical initiators[127], such as Bz_2O_2. The reaction is carried out on a water bath in a methyl ethyl ketone solution, and under nitrogen. The polymer is a rubbery mass, which crystallizes to a white powder on stirring with MeOH[128]. In common with homopolymers of MVK, the **92**–MVK copolymer can react with $LiAlH_4$, to yield a poly-alcohol. Dienones such as dibenzylideneacetone (**65**) also form copolymers with **92**. These have molecular weights in the range of 20,000 to 30,000, and have thermal stability of form up to 130 °C[129].

Styrene also copolymerizes with a variety of other α,β-unsaturated ketones, including phenyl vinyl ketone, isopropenyl methyl ketone, propenal, 2-methyl propenal, 2-ethyl propenal and methyl methacrylate[127]. These polymers are photodegradable in solution and in the solid state. The reaction that occurs under irradiation is believed to be chain scission[130]. Solid **92**–MVK copolymers are susceptible to reaction with aluminium isopropoxide (*iso*-Pr—O)$_3$Al at 160 °C, which results in evolution of acetone[131]. The

reaction results in the elimination of carbonyl groups and the introduction of cross-linking of polymer chains via O—Al—O bridges (**93**).



(**92**)



(**93**)

Enones can also be copolymerized with ethylene. For example, MVK and ethylene react under γ-ray irradiation (Co^{60}) to yield uniquely copolymers; no homopolymerization occurs[132]. Graft copolymers of these two monomers have been used to immobilize Ni^{2+} ions on their surface. Such solids can be used to catalyze isomerization reactions of alkenes, and their dimerization[133]. One of the reactions catalyzed by this solid is ethylene conversion to butadiene. Graft copolymers of MVK on polyethylene can be used to immobolize Ti(IV) compounds, which are present on the polymer surface as clusters[134]. Such a solid is resistant to reduction and can be used as a catalyst.

MVK and other enones can be copolymerized with 2-hydroxymethyl methacrylate in the presence of $(NH_4)_2S_2O_8$ and $Na_2S_2O_3$ as redox catalysts and a small amount of *N*, *N'*-methylenediacrylamide, which can act as a cross-linking agent[135]. The product is a network polymer, which can act as an adsorbent of urea. Anionic or cationic copolymerization of MVK with 2, 5, 6-trisubstituted 3, 4-dihydro-2*H*-pyrans results in head-to-head alternating copolymers[136]. MVK copolymer with 4-vinylpyridine becomes dense and tough when cross-linked with malonyl dihydrazide. This polymer can be made into membranes, which perform well in reverse osmosis with NaCl and $CoCl_2$ containing feeds[137].

A number of vinyl monomers, including MVK, can enter into homogeneous anionic graft copolymerization on Nylon 6. Before reaction with the vinyl monomer, Nylon 6 is metallated in a solution using a variety of alkali metal compounds[138]. Graft copolymerization of MVK onto viscose or cotton fabrics can be carried out by immersing the polymers into an aqueous solution of MVK and irradiating with γ rays[139]. Cellulose can be modified by graft copolymerization of MVK[140]. The thermal stability of poly-(vinyl bromide) is increased if converted to copolymer with MVK. Stability increases with MVK concentration[141]. MVK and vinyl acetate can be copolymerized from ammonia-saturated MeOH solutions by heating at 80 °C for 4h in an autoclave. This polymer can be drawn into a fibre. Copolymerization with butadiene or acrylonitrile leads to fibres with improved dyeability[142].

MVK undergoes radical copolymerization with acrylamide and several of its derivatives[143]. Polymerization is carried out under vacuum at 60 °C, in the presence of dioxan as solvent. Other enone copolymers include those prepared with *p*-isopropenylphenol and its analogues. These comonomers undergo emulsion copolymerization with MVK at 60–80 °C, in the presence of $-MeC_6H_4SO_3H$ as catalyst[144]. Often, enone copolymers can have their properties changed, by subsequent reactions. For example, poly-MVK or MVK–divinylbenzene copolymers can react with dichlorophosphites (**94**), to yield poly-(α-OH α-Me-allyl phosphonic acid monoesters)[145]. 2, 4-Dinitrophenylhydrazine has also been shown to react with various MVK copolymers, e.g. with styrene as comonomer[146].

Acrolein can copolymerize with MVK or acrylamide by an anionic mechanism in THF solutions[147] in the presence of imidazole as initiator, at 0 °C. The acrolein–MVK

$$ROPCl_2$$

$$R=Me, Et, Pr, Bu$$

(94)

copolymer was a vinyl polymer with imidazo groups attached to the aldehyde or ketone side-chains. The acrolein–acrylamide copolymer resulted from both 1,2- and 1,4-addition polymerization.

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IX. REEFERENCES AND NOTES

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