Supplement A3: The Chemistry of Double-Bonded Functional Groups. Edited by Saul Patai

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Supplement A3

The chemistry of
double-bonded functional groups

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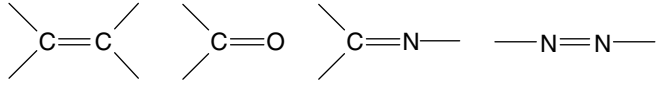

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The chemistry of **double-bonded functional groups**

Edited by

SAUL PATAI

The Hebrew University, Jerusalem

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Foreword

The first supplementary volume dealing with the chemistry of double-bonded functional groups was published in 1977 and contained thirteen chapters on C=C, C=O, C=N and N=N groups. The second supplementary volume was published in 1989 with eighteen chapters, some of them 'integrative' ones, i.e. giving a unified treatment of several double-bonded groups together.

I am happy to present now Supplementary A, Volume 3 — including again several 'integrative' chapters.

The literature coverage in most chapters is up to the end of 1994 and in many cases up to the middle of 1995 or later.

Jerusalem
January, 1997

SAUL PATAI

The Chemistry of Functional Groups Preface to the series

The series 'The Chemistry of Functional Groups' was originally 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 preparation, properties and reactions of the functional group treated and on the effects which it exerts both in the immediate vicinity of the group in question and in the whole molecule.

A voluntary restriction on 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 and in textbooks (i.e. in books which are usually found in the chemical libraries of most universities and research institutes), should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the topic. 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.

It is realized that no plan can be devised for a volume that would give a complete coverage of the field with no overlap between chapters, while at the same time preserving the readability of the text. The Editors set themselves the goal of attaining reasonable coverage with moderate overlap, with a minimum of cross-references between the chapters. In this manner, sufficient freedom is given to the authors to produce readable quasi-monographic chapters.

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

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

(b) Chapters discuss the characterization and characteristics of the functional groups, i.e. qualitative and quantitative methods of determination including chemical and physical methods, MS, UV, IR, NMR, ESR and PES — as well as activating and directive effects exerted by the group, and its basicity, acidity and complex-forming ability.

(c) One or more chapters deal with the formation of the functional group in question, either from other groups already present in the molecule or by introducing the new group directly or indirectly. This is usually followed by a description of the synthetic uses of the group, including its reactions, transformations and rearrangements.

(d) Additional chapters deal with special topics such as electrochemistry, photochemistry, radiation chemistry, thermochemistry, syntheses and uses of isotopically labelled compounds, as well as with biochemistry, pharmacology and toxicology. Whenever applicable, unique chapters relevant only to special functional groups are also included (e.g. 'Polyethers', 'Tetraaminoethylenes' or 'Siloxanes').

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the authors 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, some volumes may be published without giving consideration to the originally planned logical order of the chapters.

Since the beginning of the Series in 1964, two main developments have occurred. The first of these is the publication of supplementary volumes which contain material relating to several kindred functional groups (Supplements A, B, C, D, E, F and S). The second ramification is the publication of a series of 'Updates', which contain in each volume selected and related chapters, reprinted in the original form in which they were published, together with an extensive updating of the subjects, if possible, by the authors of the original chapters. A complete list of all above mentioned volumes published to date will be found on the page opposite the inner title page of this book. Unfortunately, the publication of the 'Updates' has been discontinued for economic reasons.

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

The publication of this series would never have been started, let alone continued, without the support of many persons in Israel and overseas, including colleagues, friends and family. The efficient and patient co-operation of staff-members of the publisher also rendered us invaluable aid. Our sincere thanks are due to all of them.

The Hebrew University
Jerusalem, Israel

SAUL PATAI
ZVI RAPPOPORT

Contents

List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
AIBN	azoisobutyronitrile
Alk	alkyl
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
Cp*	η^5-pentamethylcyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAH	diisobutylaluminium hydride
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	ferrocenyl
FD	field desorption
FI	field ionization
FT	Fourier transform
Fu	furyl(OC_4H_3)
GLC	gas liquid chromatography
Hex	hexyl(C_6H_{13})
c-Hex	cyclohexyl(C_6H_{11})
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
i-	iso
Ip	ionization potential
IR	infrared
ICR	ion cyclotron resonance
LAH	lithium aluminium hydride
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
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Pc	phthalocyanine
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 or phase transfer conditions
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
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thi	thienyl(SC_4H_3)
TLC	thin layer chromatography
TMEDA	tetramethylethylene diamine
TMS	trimethylsilyl or tetramethylsilane
Tol	tolyl(MeC_6H_4)
Tos or Ts	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, p. 305–322, will also be used in their unabbreviated forms, both in the text and in formulae instead of explicitly drawn structures.

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CHAPTER **1**

Heteropolar double bonds

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I. INTRODUCTION

This review will focus on heteropolar double bonds containing at least one carbon atom, where the other half of the bond is a group 14 carbene-type functional group [XH(A), where X = carbon, silicon germanium, tin and lead, and A is one of the substituents H, CH_3, F, OH, CN and NO]. The homopolar case complements the recent review by Trinquier and Malrieu[1]. The heteropolar systems have been nicely reviewed by Grev[2]. The emphasis in this review is on structure, both geometric and electronic. Bond dissociation energies will not be addressed, although bond strength is usually discussed within the framework of electronic structure considerations[3]. The focus here is on the series of compounds with the generic formulas $CH(A){=}XH_2$ and $CH_2{=}XH(A)$, where X is one of the group 14 atoms (C → Pb) and A is one of the substituents enumerated above. The objective is to probe and elucidate the effect of the substituents on the electronic and geometric structure description of the heteronuclear $\left(\diagdown\!\!\diagup C{=}X\diagdown\!\!\diagup\right)$ double bond involving main group atoms. Within this context isomerization energies will also be discussed.

The set of $CH(A){=}XH_2$ and $CH_2{=}XH(A)$ molecules allows a direct study of the effect of substitution (A) on the ground state geometry of the doubly-bonded systems. Both stability[3] and geometry[4] have been attributed to the singlet–triplet splitting of the carbenes (H_2X, HXA, H_2C and HCA) involved in the bond, although other factors have also been identified as important[5]. Historically, electronic structure effects have usually

been elucidated through a study of geometric structure and the effect of ligand substitution on geometry[6–9]. Therefore, the availability of a large number of equilibrium structures can contribute to an understanding of the electronic structure effects. In this context analogous analyses of transition metal carbenes are also relevant to such studies[10–12], although transition metal complexes themselves won't be discussed.

Besides the actual geometric structures and their information content with regard to local XH(A) electronic structure in the heteropolar double-bond systems, interest has centered on the degree of charge transfer between the two carbene-like ends of the double bond, individually and collectively in the π and the σ bonds. Representative examples of these types of studies are found in the recent literature[13,14]. These investigators use a multi-configuration self-consistent field method (MCSCF) of the complete active space (CAS) variety which distributes the four double-bond electrons (2 σ and 2 π) among the 4 molecular orbitals (MO): σ, σ^*, π and π^*. This MCSCF-type calculation is descriptively labeled CAS(4,4). The resultant MOs are then localized and a configuration interaction (CI) calculation carried out on the resultant carbene-localized σ and π orbitals. Although the localized MO (LMO) are still orthogonal, and therefore carry tail contributions from the other carbene fragment, this localized representation is probably sufficiently good to serve as a basis for a Valence Bond (VB) type analysis of trends in the CI configurations and their weights. Here, the open-shell spin coupled electron pairs in the σ and π spaces represent the double bond and other VB structures are formed by different occupancies of the localized carbene σ and π orbitals. The purely covalent structure puts two electrons on each local carbene fragment. Since any given orbital can be up to doubly occupied, additional structures can be constructed that represent electron transfer in both directions between the carbenes. These structures will have an unequal number of electrons on each carbene. The weight of each structure is simply the square of its coefficient in the orthogonal CI calculation. Such an analysis can also show the relative importance of the spin singlet and triplet character on each local carbene fragment. It should be noted that the carbene orbitals do not necessarily have to have pure σ and π character, but can also be equivalent, or nearly so, to form banana-type bonds between the carbene fragments. The nature of this orthogonal valence bond (OVB) analysis is not affected by the exact spatial orientation of the individual carbene orbitals.

However, using the newly developed nonorthogonal Valence Bond SCF (VBSCF) method these VB structures can be constructed directly from purely carbene localized orbitals, without the uncertainty introduced by the orthogonality tails[15,16]. The orthogonal LMO analysis described above (OVB) is more convenient computationally, but a limited number of real VB calculations need to be carried out on actual heteronuclear double-bond systems to compare with and to validate the LMO results. This analysis has been carried out here using *ab initio* VBSCF computer codes.

Density functional theory (DFT) using gradient or nonlocal corrected exchange and correlation functionals[17,18] has been shown to be a useful *ab initio* tool in computing geometric structures[19]. Mixing in a small amount of the actual Hartree–Fock exchange to the functional in a normalized fashion improves performance for a variety of properties[20,21]. These hybrid functionals seem to perform well because of a cancellation of errors due to spurious self-interaction intrinsic to DFT and the neglect of correlation in Hartree–Fock[22]. The DFT method has the major advantage of being considerably faster than conventional electronic structure methods at a level of accuracy variously estimated to be around MP2 (Moeller–Plesset to second order) for geometries[18,19]. Several DFT studies of heteronuclear double bonds have already been reported[5,23]. It would be useful to have overlapping studies of the same molecular systems by these different model theory levels for comparison and validation. Therefore, *ab initio* DFT has also been used for comparison with the OVB and VBSCF results.

The use of substituents to probe the electronic structure description of molecular systems has a long and successful history and has also been used for heteropolar double bonds[24]. The effect of substituent A on the geometric structures of $H_2C{=}XH(A)$ and $CH(A){=}XH_2$, and an analysis of resultant properties, could shed light on the different electronic factors that determine structure, in general. An understanding of the nature of the heteropolar double bond as a function of the group 14 atom X will also benefit from a comparison with the saturated systems that have only a single σ bond. This approach has been adopted by several researchers[5,25] and is also brought here for the VBSCF treatment. A great deal has already been written about the C−X (X = carbon → lead) single bond[26] and the O=X double bond[27]. The experience garnered from these and other studies will also be brought to bear here, where appropriate.

In this review we will discuss the optimized geometric structures of the $H_2C{=}XH(A)$ and $CH(A){=}XH_2$ sets of heteropolar double-bonded systems, where X is any of the group 14 atoms (carbon, silicon, germanium, tin and lead) and A is one of the substituents H, CH_3, F, OH, CN or NO. In this way the effect of substitution on each side of the double bond can be measured. The resulting MOs are analyzed for the electronic structure aspects and contributions using localized orbitals. Parallel DFT calculations are used to examine the geometries and bona fide nonorthogonal VBSCF orbitals are used selectively to probe the electronic structure description. The approach adopted here to analyze the electronic structure description of heteronuclear double bonds leans heavily on the previous work of Carter and Goddard[3], Trinquier and Malrieu[14], Windus and Gordon[13] and Jacobsen and Ziegler[5].

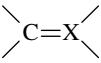
II. CALCULATIONAL METHODS

Ab initio MCSCF calculations were carried on the $CH_2{=}XH(A)$ and $CH(A){=}XH_2$ set of heteropolar double-bond compounds with substituents A = H, CH_3, F, OH, CN and NO on either the carbon or X atom, where X is one of the group 14 column series. The geometries of all these molecules were optimized at the *ab initio* CAS(4,4) level[11−13] using the GAMESS[28] set of computer programs. The CAS(4,4) MCSCF calculation takes into account all electronic configurations resulting from the distribution of 4 electrons among the $\diagdown\!\!\diagup C{=}X\diagdown\!\!\diagup$ σ, π, π^* and σ^* MOs, or their banana-bond equivalents, in a self-consistent field procedure. For all the atoms heavier than hydrogen a compact effective potential (CEP) was used to replace the core electrons[29], where for Si, Ge, Sn and Pb the relativistic CEP (RCEP) was used[30]. The valence electron basis sets were taken from the respective CEP[29] and RCEP[30] tabulations split double-zeta as published. A single d-type Gaussian polarization function was added to the post-hydrogen atoms and a single p-type function was added to hydrogen. The default polarization functions of GAMESS[28] for these atoms were used here. Overall, this basis set can be described as valence double-zeta plus polarization, CEP-N1(d,p), where $N = 3$ for the hydrogen, carbon and silicon atoms, and $N = 4$ for Ge, Sn and Pb. For brevity, the basis set will be identified as CEP-DZP.

The two HOMO (σ and π) and LUMO (π^* and σ^*) MCSCF MOs of the $\diagdown\!\!\diagup C{=}X\diagdown\!\!\diagup$ bond at the optimized geometric structure were subjected to the Boys localization procedure[31] to produce orthonormal localized carbene fragment molecular orbitals. The two LMO on each carbene can be either σ and π or $\sigma + \pi$ and $\sigma - \pi$. The latter couple with the other carbene LMO of the same form to produce banana bonds instead of the conventional σ and π $\diagdown\!\!\diagup C{=}X\diagdown\!\!\diagup$ bonds[32,33]. A complete CI calculation was then

carried out on the 4-electron/4-LMO set for the spin–singlet electronic ground state. This distribution generates 20 configurations having zero, 2 or 4 open shells, all coupled spin–singlet. The resulting CI coefficients and corresponding LMO occupancies can be interpreted in terms of the local carbene spin state (singlet or triplet) and the ionicity of each specific configuration[11–14]. This approach assumes, of course, that the LMO are well localized and that the orthogonality tails are small.

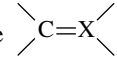
The orthogonal localized molecular orbitals produced thereby are intended to mimic the classical nonorthogonal Valence Bond orbitals. The OVB procedure has been followed in the past because of the great practical difficulty encountered in trying to produce real, nonorthogonal VB orbitals. This capability has recently become available using the VBSCF computer program system, TURTLE[15,16,34]. VBSCF is not yet the facile tool that is routinely available for the MO methods but rapid progress is being made. At this stage, the OVB method is still more convenient. However, for limited comparison purposes, *ab initio* VBSCF calculations were carried out on the heteronuclear double-bond series, $CH_2{=}XH_2$, where X = carbon, silicon, germanium, tin and lead. Compact effective core potentials were used for the chemically inert core electrons, just like for the CAS(4,4) calculations. The valence sp basis set consisted of the published CEP[29] and RCEP[30] bases

TABLE 1. VB structures for the four-electron  bond

Structure	Occupancy[a]			
	l1	l2	r1	r2
Covalent[b]				
I,II	1	1	1	1
III	2	0	1	1
IV	0	2	1	1
V	1	1	2	0
VI	1	1	0	2
VII	2	0	2	0
VIII	0	2	2	0
IX	2	0	0	2
X	0	2	0	2
$l \rightarrow r$ *CT*[c]				
XI	1	0	2	1
XII	1	0	1	2
XIII	0	1	2	1
XIV	0	1	1	2
XV	0	0	2	2
$r \rightarrow l$ *CT*[d]				
XVI	2	1	1	0
XVII	1	2	1	0
XVIII	2	1	0	1
XIX	1	2	0	1
XX	2	2	0	0

[a] l1 and l2 are the two participating orbitals on the left-side carbene, with the corresponding definitions for r1 and r2 and the right carbene.
[b] Two electrons on each carbene, irrespective of spin coupling.
[c] $l \rightarrow r$ *CT* = LRCT = Left to right charge transfer.
[d] $r \rightarrow l$ *CT* = RLCT = Right to left charge transfer.

contracted K111, where $K = 1$ for C and Si, $K = 2$ for Ge $\rightarrow$ Pb, augmented by the above-described d-type single Gaussian polarization functions on the nonhydrogen atoms. This basis set will be called CEP-5ZP. The hydrogen atom basis set was taken as the 311 split of the standard 5^s distribution[35].

For the OVB and VBSCF theory levels it remains to define the set of structures that comprise the wave function. If the two variably occupied orbitals on each carbene fragment [CH(A) and XH(A)] are labeled l1, l2, r1 and r2 (l = left and r = right), then Table 1 gives the orbital distribution of all the structures that can be composed by distributing 4 electrons among the 4 orbitals. These structures can be classified as covalent, with two electrons on each carbene irrespective of spin coupling, and charge transfer (CT) in either the l $\rightarrow$ r or r $\rightarrow$ l directions with an uneven number of electrons on each carbene fragment. In the σ, π representation of the  bond, l1 and l2 are the σ and π carbene orbitals on XH_2, respectively, for example. In the VBSCF calculations on the $CH_2{=}XH_2$ series, the geometries were taken from CAS(4,4) gradient optimization in the CEP-5ZP basis sets.

Ab initio density functional theory calculations were also carried out on the $CH_2{=}XH(A)$ and $CH(A){=}XH_2$ series of molecules. The basis set used was the CEP-TZDP+ described previously[26] and is more extensive than the DZP basis set used in the CAS(4,4)-OVB calculations. In TZDP+ the valence electron wave function is expanded in a triple-zeta sp set of functions plus a double set of polarization d-type functions plus a set of diffuse sp-type functions. The B3LYP exchange–correlation functional[20] as defined in the Gaussian 94 program set[35] was used in all the DFT calculations.

Finally, for correlation purposes, all the HXA carbenes (X = C $\rightarrow$ Pb, A = H, CH_3,F,OH,CN and NO) in their closed-shell singlet and lowest-energy open-shell triplet states were geometry optimized at both the CAS (CEP-DZP basis) and DFT (CEP-TZDP+) basis theory levels. The lowest-energy open-shell singlet state was also obtained by *ab initio* methods.

III. RESULTS AND DISCUSSION

A. $CH_2{=}XH_2$

The $CH_2{=}XH_2$ set with X = C $\rightarrow$ Pb are all calculated to be planar at the CAS(4,4) theory level in both the CEP-DZP and CEP-5ZP basis sets. This agrees with all previous work[5,13,36,37] except for the $CH_2{=}SnH_2$ results of Windus and Gordon[13]. The difference in geometry for the stanoethylene has been addressed by Jacobsen and Ziegler[5]. The calculated bond lengths and angles at the CAS(4,4)/CEP-DZP and DFT/CEP-TZDP+ levels are shown in Tables 2 and 3 for the most stable $CH_2{=}XH(A)$ and $CH(A){=}XH_2$ systems. A comparison with previous such work and with experiment where available for the $CH_2{=}XH_2$ molecules has been given by Jacobsen and Ziegler[5].

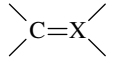
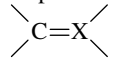
Table 1 shows the covalent and charge transfer (CT) structures (analogous to electronic configurations in MO theory parlance) that make up the VB wave function for the  bond. These can be further analyzed in terms of the separate carbene (HCA and HXA) states that represent the homolytic asymptotic dissociation limit for breaking the double bond in  . Each carbene is assumed to have two orbitals, $a_1(\sigma)$ and $b_1(\pi)$ in C_{2v} symmetry, in which are distributed two electrons. The resultant single configuration electronic states are $^3B_1$ and $^1B_1(a_1^1\ b_1^1)$, $^1A_1(a_1^2)$ and $^1A_1^*(b_1^2)$. For CH(A) (A = a substituent not hydrogen) in C_s symmetry the same distribution holds with

TABLE 2. CAS(4,4)/CEP-DZP optimized geometries of the $CH(A)=XH_2$ molecules[a]

X	A Y−Z	C=X	C−A C−Y	Y−Z	X−H[b]	∠ACX ∠YCX	∠H_bXC	∠CYZ	∠H_aCXH_b	∠ACXH_c ∠YCXH_a	∠ZYCX
C	H	1.390	1.093	—	1.093	121.1	121.1	—	0.	0.	—
Si	H	1.756	1.093	—	1.481	122.7	121.9	—	0.	0.	—
Ge	H	1.812	1.092	—	1.519	122.7	121.2	—	0.	0.	—
Sn	H	2.005	1.092	—	1.687	123.0	121.4	—	0.	0.	—
Pb	H	2.045	1.089	—	1.730	123.3	119.8	—	0.	0.	—
C	CH_3	1.388	1.516	1.098	1.516	124.4	120.9	111.3	0.1	0.	0.
Si	CH_3	1.760	1.523	1.099	1.477	122.8	121.9	111.1	0.	0.	0.
Ge	CH_3	1.816	1.517	1.099	1.519	122.7	122.1	111.2	0.	0.	0.
Sn	CH_3	2.008	1.523	1.104	1.686	127.3	122.2	111.2	0.	0.	0.7
Pb	CH_3	2.092	1.519	1.100	1.749	122.2	117.2	111.1	−39.4	38.5	−144.0
C	F	1.379	1.340	—	1.090	121.4	118.8	—	0.	0.	—
Si	F	1.770	1.349	—	1.473	123.2	117.9	—	0.	0.	—
Ge	F	1.844	1.345	—	1.517	121.9	114.9	—	−29.0	24.6	—
Sn	F	2.068	1.346	—	1.694	121.2	111.1	—	−43.6	35.9	—
Pb	F	2.128	1.341	—	1.751	117.1	111.1	—	−55.6	41.6	—
C	OH	1.384	1.369	0.952	1.091	121.9	119.2	109.7	0.	0.	180.
Si	OH	1.774	1.372	0.954	1.475	130.5	118.6	110.4	0.	0.	0.
Ge	OH	1.857	1.368	0.954	1.524	122.9	113.0	110.2	−33.9	27.3	142.8
Sn	OH	2.092	1.357	0.955	1.705	128.2	108.4	110.3	−47.0	41.2	−32.6
Pb	OH	2.171	1.342	0.956	1.775	124.3	106.8	110.0	−60.2	46.3	−40.2
C	CN	1.386	1.465	1.152	1.091	121.2	119.8	179.4	0.	0.	180.
Si	CN	1.758	1.456	1.154	1.472	123.2	120.5	179.7	0.	0.	0.
Ge	CN	1.815	1.454	1.154	1.512	122.4	120.4	179.8	0.	0.	0.
Sn	CN	2.002	1.452	1.155	1.679	123.1	120.4	179.6	0.	0.	1.0
Pb	CN	2.069	1.450	1.155	1.730	118.9	118.7	179.0	−29.7	28.5	−141.1
C	NO	1.388	1.436	1.197	1.091	117.6	120.8	113.1	0.	0.	180.
Si	NO	1.765	1.425	1.222	1.472	117.4	121.2	114.1	0.	0.	180.
Ge	NO	1.819	1.420	1.203	1.513	116.7	121.4	114.0	0.	0.	180.
Sn	NO	2.007	1.416	1.205	1.681	116.2	121.9	114.1	0.	0.	179.8
Pb	NO	2.045	1.403	1.208	1.726	112.0	123.3	114.5	0.	0.1	179.8

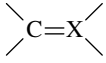
[a]Bond distances in Angstroms, angles in degrees. The labelling is: $CH_a(A)=XH_bH_c$, where for an A substituent that is diatomic, A = Y−Z. Bond lengths and nondihedral angles involving C−H are not listed unless part of A. For A = $C'H_3$, Y−Z is the C−H bond that is most nearly C−C′−H coplanar. H_a and H_c are *trans* to each other across the double bond.

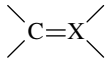
[b]Averaged for X = C.

TABLE 3. CAS(4,4)/CEP-DZP optimized geometries of the $CH_2{=}XH(A)$ molecules[a]

X	A Y−Z	C=X	X−A X−Y	Y−Z	X−H[b]	∠AXC ∠YXC	∠H_bCX	∠XYZ	∠H_aCXH_b	∠AXCH_b ∠YXCH_b	∠ZYCX
Si	CH_3	1.754	1.884	1.099	1.480	125.0	122.9	110.4	−0.2	0.3	−1.3
Ge	CH_3	1.811	1.952	1.098	1.523	124.6	121.8	109.7	−0.2	0.3	−1.4
Sn	CH_3	2.000	2.141	1.098	1.693	124.5	121.8	109.8	−0.3	0.3	−1.5
Pb	CH_3	2.047	2.175	1.095	1.741	125.4	120.3	108.4	−0.4	0.4	−1.5
Si	F	1.735	1.592	—	1.468	123.0	123.3	—	0.	0.	—
Ge	F	1.810	1.708	—	1.511	118.3	119.5	—	−32.7	22.1	—
Ge	F	1.792	1.705	—	1.507	119.9	121.2	—	0.	0.	—
Sn	F	2.034	1.893	—	1.687	113.2	117.0	—	−54.4	34.4	—
Sn	F	1.981	1.887	—	1.673	118.0	120.3	—	−0.1	0.1	—
Pb	F	2.100	2.016	—	1.744	109.4	112.3	—	−69.1	37.8	—
Si	OH	1.740	1.634	0.955	1.468	126.5	125.0	117.8	0.	0.	0.
Ge	OH	1.799	1.740	0.955	1.508	124.4	122.5	114.1	0.	−0.1	0.1
Sn	OH	2.032	1.936	0.954	1.685	119.0	118.2	116.7	46.7	−35.4	36.5
Pb	OH	2.100	2.047	0.956	1.740	115.7	113.3	111.8	59.0	−42.0	34.8
Si	CN	1.746	1.860	1.155	1.466	120.2	121.9	179.7	0.2	−0.1	−179.9
Ge	CN	1.800	1.924	1.155	1.503	119.1	120.7	179.6	0.	0.	−179.9
Sn	CN	2.023	2.119	1.156	1.680	113.9	118.4	178.5	43.5	32.5	−148.2
Pb	CN	2.088	2.191	1.156	1.732	111.4	114.1	178.1	−57.3	39.5	−148.3
Si	NO	1.749	1.828	1.205	1.471	117.2	121.2	113.6	0.	0.	−180.
Ge	NO	1.805	1.922	1.199	1.513	117.6	120.3	112.7	0.3	−0.2	−179.9
Sn	NO	2.029	2.151	1.198	1.691	113.7	118.8	112.9	41.4	−32.3	−156.8
Pb	NO	2.097	2.227	1.191	1.752	115.7	115.7	108.9	51.3	−42.9	−149.8

[a]Bond distances in Angstroms, angles in degrees. The labeling is: $CH_a(H_b){=}XH_c(A)$, where for an A substituent that is diatomic, A = Y−Z. Bond lengths and nondihedral angles involving C−H are not listed unless part of A. For $A = C'H_3$, Y−Z is the C−H bond that is most nearly C−C′−H coplanar. H_a and H_c are *trans* to each other across the double bond.
[b]Averaged for X = C.

$a_1 = a'$ and $b_1 = a''$. In CH_2, for example, $^3B_1$ is the electronic ground state with $^1A_1$ about 9 kcal mol^{-1} higher in energy. Referring to Table 1, it is clear that each of the ten covalent structures listed there can be related to some combination of these 4 electronic states on each carbene within the constraint of overall singlet state spin coupling. Thus structures I and II represent combinations of the $^3B_1$–$^3B_1$ and $^1B_1$–$^1B_1$ carbene states. All the other covalent structures (III → X) involve combinations of $^1B_1$, $^1A_1$ and $^1A_1^*$ carbene states. In a planar $CH_2{=}XH(A)$ or $CH(A){=}XH_2$ system, if the overall ground electronic state is $^1A_1$ then B_1 states, triplet or singlet, must appear in identical pairs, one on each carbene, in order to maintain overall A_1 spatial symmetry. For a nonplanar heteronuclear double-bonded system the symmetry combination constraints are relaxed but the spin combination constraints of the planar molecules still hold. Thus structures III → VI, as well as of course VII → X, involve only singlet carbene states. In the asymptotic dissociation limit each carbene goes to its electronic ground state. Thus the coefficients of most of the structures I → X are expected to decrease in magnitude as the  bond length increases.

Since the  systems dissociate to neutral carbenes, the coefficients of the charge transfer (CT) states also vanish in the asymptotic dissociation limit. There are 5 left → right CT states (LRCT), four being single electron transfers (XI → XIV) and one

double electron transfer (XV). The same situation is obtained for right → left electron transfer (RLCT), where XVI → XIX are one-electron processes and XX is a two-electron process.

In the VBSCF method the wave function is expanded as a linear combination of the 20 structures described in Table 1. Since the orbitals are nonorthogonal, the sum of the squares of the structure expansion coefficients (C_i) don't add up to one. However, a measure of the importance of each structure's wave function (Ψ_i) can be obtained from the formula in equation 1 for the weight, W_i[38]:

$$W_i = \sum_i C_i C_j S_{ij} \tag{1}$$

where S_{ij} is the overlap between structures i and j. The weights for the VBSCF results in the planar $CH_2{=}XH_2$ systems are tabulated in Table 4. In order to mimic the *trans*-bent (TB) structures that are so characteristic of the heavier heteronuclear

TABLE 4. VB structure weights (W_i) for the planar four-electron $\diagdown\!\!\diagup C{=}X\diagdown\!\!\diagup$ bond[a]

Structure i	W_i[b]				
	$CH_2{=}CH_2$	$CH_2{=}SiH_2$	$CH_2{=}GeH_2$	$CH_2{=}SnH_2$	$CH_2{=}PbH_2$
Covalent[c]					
I	0.220	0.214	0.218	0.215	0.215
II	0.269	0.285	0.296	0.314	0.319
III	0.	0.	0.	0.	0.
IV	0.	0.	0.	0.	0.
V	0.	0.	0.	0.	0.
VI	0.	0.	0.	0.	0.
VII	0.000	0.000	0.000	0.001	0.001
VIII	0.056	0.059	0.062	0.057	0.070
IX	0.056	0.047	0.045	0.043	0.035
X	0.000	0.000	0.000	0.000	0.000
Total	0.601	0.605	0.622	0.630	0.640
$CH_3{-}XH_3$[f]	0.674	0.654	0.676	0.675	0.685
$l \rightarrow r$ *CT*[d]					
XI	0.000	0.000	0.000	0.000	0.000
XII	0.074	0.033	0.034	0.023	0.021
XIII	0.126	0.083	0.102	0.083	0.099
XIV	0.000	0.000	0.000	0.000	0.000
XV	−0.001	−0.005	−0.005	−0.005	−0.004
Total	0.199	0.111	0.131	0.101	0.116
$CH_3{-}XH_3$[f]	0.163	0.080	0.123	0.095	0.116
$r \rightarrow l$ *CT*[e]					
XVI	0.000	0.000	0.000	0.000	0.000
XVII	0.074	0.107	0.094	0.094	0.098
XVIII	0.126	0.172	0.153	0.175	0.148
XIX	0.000	0.000	0.000	0.000	0.000
XX	−0.001	0.005	0.000	0.001	−0.001
Total	0.199	0.284	0.247	0.270	0.245
$CH_3{-}XH_3$[f]	0.163	0.266	0.200	0.229	0.199

[a] Planar geometric structure; from VBSCF calculations.
[b] See equation 1.
[c] Two electrons on each carbene, irrespective of spin coupling.
[d] Left to right charge transfer = LRCT.
[e] Right to left charge transfer = RLCT.
[f] See text.

double-bond systems[5,13,14], *trans*-bent structures for the $CH_2{=}XH_2$ molecules were produced by bending the CH_2 and XH_2 planes 45° away from the C=X bond in a *trans* configuration. All other geometric structural parameters were maintained at their optimized planar values. The resultant VBSCF structure weights for the TB geometries are shown in Table 5. The weights of the VB structures in Tables 4 and 5 are also summed into classes of covalent (equal numbers of electrons on each carbene) and ionic or charge transfer (unequal numbers of electrons on each carbene) contributions. In the covalent category the sum is taken irrespective of the closed- or open-shell nature of the contributing structures, as explained above.

Table 4 also contains an analogous analysis of the saturated $CH_3{-}XH_3$ systems for X = C → Pb, for comparison purposes. The optimized geometries were taken from CAS(2,2) calculations on $CH_3{-}XH_3$ using the CEP-DZP basis set. VBSCF calculations were then carried out on the $CH_3{-}XH_3$ set using the usual 3 VB structures: one covalent (CH_3:XH_3) and two ionic ($CH_3^+XH_3^-$ and $CH_3^-XH_3^+$)[39].

The summed weights, classified as covalent and ionic, show a consistent trend with the nature of the X atom. The value of the covalent contribution to the total VB wave function generally increases as X gets heavier from Si → Pb for the $CH_3{-}XH_3$ series, and from

TABLE 5. VB structure weights for the *trans*-bent four-electron $\diagdown\!\!\diagup C{=}X\diagdown\!\!\diagup$ bond[a]

Structure i	W_i[b]				
	$CH_2{=}CH_2$	$CH_2{=}SiH_2$	$CH_2{=}GeH_2$	$CH_2{=}SnH_2$	$CH_2{=}PbH_2$
Covalent[c]					
I	0.220	0.245	0.251	0.259	0.269
II	0.282	0.272	0.266	0.255	0.227
III	0.000	−0.002	0.001	0.003	0.008
IV	0.018	0.018	0.021	0.020	0.024
V	0.000	0.000	0.003	0.008	0.015
VI	0.018	0.018	0.021	0.019	0.026
VII	0.000	0.000	0.000	0.000	0.000
VIII	0.038	0.032	0.036	0.032	0.370
IX	0.038	0.038	0.033	0.033	0.034
X	0.000	0.001	0.001	0.001	0.001
Total	0.614	0.621	0.632	0.630	0.641
$l \rightarrow r$ *CT*[d]					
XI	0.000	−0.001	0.001	0.002	0.005
XII	0.050	0.023	0.024	0.016	0.019
XIII	0.134	0.080	0.099	0.073	0.084
XIV	0.011	0.008	0.009	0.006	0.009
XV	−0.001	−0.005	−0.005	−0.004	−0.004
Total	0.194	0.105	0.128	0.093	0.113
$r \rightarrow l$ *CT*[e]					
XVI	0.000	0.000	0.002	0.006	0.009
XVII	0.050	0.057	0.052	0.052	0.051
XVIII	0.134	0.199	0.169	0.198	0.165
XIX	0.011	0.017	0.019	0.022	0.023
XX	−0.001	0.002	0.000	0.001	0.000
Total	0.194	0.275	0.242	0.279	0.248

[a] *Trans*-bent (45°) geometric structure; from VBSCF calculations.
[b] See equation 1.
[c] Two electrons on each carbene, irrespective of spin coupling.
[d] Left to right charge transfer = LRCT.
[e] Right to left charge transfer = RLCT.

C → Pb for the $CH_2{=}XH_2$ set. The trend in the C−X single-bond group shows that the increase in covalent character in the $\diagdown\!\!\diagup C{=}X\diagdown\!\!\diagup$ bonding is not due to the double bond or to the π bond alone. The net charges on the CH_2 and XH_2 groups can be obtained as the difference between the total weights of the opposite direction (l → r and r → l) charge transfer contributions. These differences are seen to zigzag from zero for the symmetric X = C case to X = Pb. Such alternations and their possible cause have been discussed previously[26].

As noted above, the ground electronic states of the planar $H_2C{=}XH_2$ compounds can be most easily considered to be formed by the interaction of two triplet state carbenes CH_2 ($^3B_1$) and XH_2 ($^3B_1$). Not all the carbenes have a spin triplet electronic ground state and some are known or calculated to have $^1A_1$ (or $^1A'$) electronic ground states. The overall VB wave function contains contributions from all the possible (spin and symmetry-allowed) combinations of the $^3B_1$, $^1B_1$, $^1A_1$ and $^1A_1^*$ carbene states described above. The covalent structures I and II arise from the coupling of two $^3B_1$ and two $^1B_1$ state carbenes. As seen in the weights tabulated in Table 4, these are the major interaction modes of CH_2 and XH_2 (48–53%) to form the planar $CH_2{=}XH_2$ systems. The weights of the combinations of $^1A_1$ and $^1A_1^*$ states on each carbene (structures VII–X) are seen in Table 3 to be small for all X. This is surprising in light of the fact that, as will be subsequently discussed, the ground electronic state of the heavier XH_2 is $^1A_1$ and, therefore, $^3B_1$ is an excited state of those systems.

Steric interactions allowing, the interaction of two triplet-state carbenes is expected to lead to planar molecules, with ethylene as the prototypical model. The coupling of two $^1A_1$ carbenes is expected to lead to the familiar *trans*-bent structure[14] as the two electron pairs in the $a_1(\sigma)$ orbital avoid each other maximally and simultaneously try to maximize their interaction with the other-carbene empty b_1 orbital in the plane-perpendicular direction. The $a_1{}^2{-}a_1{}^2$ interaction is represented by structure VII and this is seen, in Table 4, not to contribute in a noticeable way to the planar ground state of the $CH_2{=}XH_2$ systems. However, the $CH_2{+}XH_2$ combinations of $a_1{}^2{+}b_1{}^2$ and $b_1{}^2{+}a_1{}^2$ (structures VIII and IX) do contribute somewhat (*ca* 10–11%) because of their overall $\sigma^2\pi^2$ configuration which is also expected to favor a planar geometry. The charge transfer (CT) structures contribute another 12–28% (XI → XX) of the total wave function. The geometric preference of the ionic structures is not clear, although those with equal numbers of σ and π electrons at least in single electron CT (XII, XIII, XVII, XVIII) should also tend to planarity. The double CT structures (XV and XX) don't contribute, as expected. Thus, the equilibrium geometries of the heteronuclear double-bonded systems can be considered to be related to the relative weights of the contributing carbene fragment state energies.

The energies and equilibrium geometric structures of the lowest-energy triplet and singlet electronic states of the simple HXA carbenes are easily calculated. The relative energies of the excited states are shown in Table 6 for the *ab initio* CEP-DZP and DFT/CEP-TZDP+ level theories. For Table 6 the $^3B_1$ ($^3A''$) state (denoted T) was optimized using the restricted open-shell Hartree–Fock method. The energy and equilibrium structure of the $^1A_1$ ($^1A'$) states were obtained as the lowest-energy solution of a one-pair GVB[40] calculation mixing the $a_1{}^2$ (a'^2) and $b_1{}^2$ (a''^2) configurations. This state is denoted S. For the DFT/CEP-TZDP+ calculations the B3LYP exchange-correlation functional was used with unrestricted Hartree–Fock (UHF) for the triplet state (T) and restricted HF (RHF) for the closed-shell singlet state (S). The $^1A_1^*$ ($^1A'^*$) and $^1B_1$ ($^1A''$) states are more difficult to calculate by *ab initio* or DFT methods. The $^1B_1$ state, denoted OS, was only *ab initio* optimized using the single excitation configuration interaction (CIS) option in Gaussian 94[35]. Using the UHF method for the $^3B_1$ state in DFT raises

the question of spin purity[41] of the resultant wave function. The calculated $\langle S^2 \rangle$ values are also tabulated in Table 6 and these are seen to be very close to the exact value of 2 for a spin triplet state, so that spin contamination here is not significant.

Table 6 shows the calculated singlet–triplet (S–T) and singlet–singlet (S–OS) splitting for all the HXA carbenes, with a limited comparison to experiment and other calculated results[5,42–48]. A negative value indicates T more stable than S. An interesting measure of the reliability of the calculated S–T splitting energies in the substituted carbenes where experimental data are not available is to compare their values between the two very different methods used to produce the results in Table 6. As described above, the *ab initio* results are obtained using a two-configuration CAS(2,2) wave function for the (S) $^1A_1$ ($^1A'$)

TABLE 6. Singlet–triplet (S–T) energy splitting in XH(A)[a]

A	X=	C	Si	Ge	Sn	Pb
H	S–T[b]	−11.4	17.4	23.5	23.4	34.1
	$\langle S^2 \rangle$[c]	2.006	2.002	2.002	2.002	2.003
	S–T[c]	−11.5	19.7	26.2	26.5	36.7
	Other	−9[d]	16.8[d]	23.1[g]	23.8[g]	34.2[e]
			17.7[e]	22.9[e]	23.2[e]	
			24.1[f]	24.1[h]		
	S–OS	32.5	59.8	60.8	59.4	63.3
CH_3	S–T[b]	−5.9	19.8	25.3	24.8	33.5
	$\langle S^2 \rangle$[c]	2.007	2.003	2.002	2.002	2.004
	S–T[c]	−5.6	22.1	27.8	27.6	35.5
	Other	−10.9[i]	19.8[i]			
	S–OS	37.4	64.4	63.9	61.0	62.8
F	S–T[b]	13.9	37.5	45.3	43.0	46.9
	$\langle S^2 \rangle$[c]	2.005	2.003	2.004	2.004	2.009
	S–T[c]	11.4	37.1	45.4	44.1	54.1
	Other	9.2[d]	37.7[d]			
	S–OS	65.4	88.4	88.4	84.6	86.1
OH	S–T[b,j]	14.5	36.3	42.9	39.8	51.2
	S–T[b,k]	16.5	38.6	44.7	41.1	52.7
	$\langle S^2 \rangle$[c]	2.006	2.003	2.004	2.005	2.010
	S–T[c,j]	22.8	39.8	46.6	44.2	52.6
	Other	23.3[i]	38.0[i]			
	S–OS	65.7	88.4	87.7	82.4	84.0
CN	S–T[b]	−5.9	25.0	36.3	33.7	47.9
	$\langle S^2 \rangle$[c]	2.066	2.011	2.008	2.005	2.007
	S–T[c]	−14.9	24.3	33.2	34.4	46.8
	S–OS	31.2	69.4	72.7	72.3	78.0

[a]Energies in kcal mol^{-1}. A positive S–T means that $^1A_1$ ($^1A'$) is below $^3B_1$ ($^3A''$). OS = $^1B_1$ ($^1A''$) state.
[b]*Ab initio* CEP-DZP theory level.
[c]DFT/CEP-TZDP+; B3LYP functional.
[d]See Reference 42.
[e]See Reference 5.
[f]See Reference 46.
[g]See Reference 43.
[h]See Reference 45.
[i]See Reference 47.
[j]Nonplanar geometry.
[k]*Trans* planar.

state and a single electronic configuration spin-restricted description of the (T) $^3B_1$ ($^3A''$) state. This approach has been shown to give a balanced description of the differential correlation effects between the two carbene states of different spin multiplicity[45]. The DFT method includes correlation effects in a direct manner for each of the spin states. As mentioned above, the specific B3LYP exchange-correlation potential used here apparently corrects for spurious self-interaction contributions in the local exchange term of the functional through cancellation with some of the correlation energy neglected in using a part of the Hartree–Fock potential[49].

Referring to Table 6, now, the XH_2 systems give very comparable S–T energy splittings for all X (C $\rightarrow$ Pb) between the two methods. The most extensively studied system, of course, is CH_2 and the experimental splitting there has been measured at *ca* 9 kcal mol^{-1}[50]. The calculated values in Table 6 are 11.4–11.5 kcal mol^{-1} and when zero-point energy (ZPE) differences are added the theoretical number is reduced towards the measured value. ZPE corrections have not been applied in Table 6 to the S–T splittings since these corrections are relatively small and not very important in examining trends. The other XH_2 S–T gaps (X = Si $\rightarrow$ Pb) generally agree well with previous work and experimental estimates. In the XH_2 series only CH_2 has a spin-triplet ground state and all the other group 14 carbenes have the closed-shell spin singlet electronic ground state. This situation has been attributed[42,44] to the s^2p^2 (^3P) ground-state electronic configuration of the group 14 atoms, which naturally combines with two doublet spin radicals (like the hydrogen atoms) to give the (S) $^1A_1$ ($^1A''$) carbene ground state. An s $\rightarrow$ p electron promotion ($s^2p^2 \rightarrow sp^3$) is needed to form the (T) triplet carbene state and this excitation energy, although difficult to define precisely for those purposes, is generally much larger for X = Si $\rightarrow$ Pb than for the carbon atom[44].

Looking at Table 6, methyl substitution [to form $XH(CH_3)$] doesn't change the sign of the S–T splitting for X = C and the triplet state is still lowest, although with a reduced magnitude for both the *ab initio* and DFT methods. Previous work has found the S–T splitting to be comparable in CH_2 and $CH(CH_3)$[47]. The opposite effect is found for the electronegative substituents F and OH, which preferentially stabilize the more available in-plane electron density in the (S) singlet state through electron withdrawal[42]. For these two substituents the (S) singlet state methylenes are the more stable electronic state for all the X atoms, including carbon. For XH(OH) the triplet state has a nonplanar electronic ground state[47] where the hydroxyl hydrogen atom is out-of-plane. The (S) singlet state is planar. The *ab initio* S–T gap in Table 5 for CH(OH) is smaller than both previous estimates and the DFT result, and the latter two are very close. The CN substituent to give CH(CN) again has a spin-triplet ground state. Presumably, the double interaction in the triplet state between the half occupied perpendicular $b_1(a'')$ orbital on the carbon atom with the π and π^* MO on the CN is the determining factor here. In the (S) singlet state only the $b_1(a'')$–π interaction is available and this is expected to be weaker than the $b_1(a'')$–π^* interaction in the triplet state since π^* is more localized on the carbon end of CN. The heavier (X = Si $\rightarrow$ Pb) cyanomethylenes all have spin (S) singlet electronic ground states. All the XH(CN) carbenes are planar.

XH(NO) is a difficult molecule. The closed-shell singlet state can also be written as H–X=N≡O[49] with a linear or quasi-linear geometry, as bent H–X–N=O (*cis* and *trans*), or even with a CNO ring group. The most relevant geometries to the homonuclear double-bond series [H_2C=XH(NO) and CH(NO)=XH_2] are the *cis* and *trans* bent structures, and between these two choices the *trans* structure was found to be preferred, wherever both conformers could be examined. However, the multiple-bonding possibilities in the HXNO fragment were too diverse to obtain consistent and definitive results for these carbenes within the framework and scope of this work. Therefore, the NO liganded carbenes are not included in Table 6.

We will now discuss the heteronuclear double-bonded systems in light of the carbene S–T gaps and the weight analysis of the contributing VB electronic structures to the total wave function. The VBSCF and OVB structure weights summed by category are set out in Tables 7 and 8. For a somewhat different approach, analysis and discussion of these aspects the reader is referred elsewhere[14].

B. $CH(A)=XH_2$

As noted above, all the $H_2C=XH_2$ species are calculated to be planar, in spite of the increasing S–T gap for the constituent carbene fragments with singlet at lower energy, as the X atom gets heavier (Table 6). Since the geometries of all the $H_2C=XH_2$ molecules are planar, it is difficult to attribute characteristic VB contributions to any geometry differences between them. In Table 7, for both the VBSCF and the orthogonal VB analyses, the combined covalent triplet–triplet W(T–T) and $^1B_1$–$^1B_1$ W(OS–OS) components increase as X gets heavier from Si $\rightarrow$ Pb, W(S–S) stays about constant and the CT components have a complementary, mildly zigzag behavior. Comparing the VBSCF and OVB structure weights, the outstanding difference is the tendency of the OVB method to give larger RLCT $XH_2 \rightarrow CH_2$ structure weights. This tendency has been noted previously[51]. As noted above, in perfectly C_s symmetry, the left–right W(S–OS) and W(OS–S) combinations don't contribute to the overall wave function for symmetry reasons. Because of the tendency of some of the localized orbital representations to form banana bond orbitals, a more detailed breakdown and discussion of the W(S–S) and CT contributions is not warranted.

Going from the planar (P) to the *trans*-bent (TB) conformation for all the $CH_2=XH_2$ set was examined at the VBSCF theory level by taking the optimized planar geometry and *trans*-bending the CH_2 and XH_2 hydrogen atoms out-of-plane by 45°. The *trans*-bending effect on the summed VB structure weights by category is shown in Table 7 and the individual weights are tabulated in Tables 4 and 5, respectively, for both the P and TB forms. *Trans*-bending is seen to affect the CT components to only a small degree. The covalent contributions become redistributed with an increased tendency for the left–right W(T–T), W(OS–OS) and W(S–S) summed weights to decrease, and the W(S–OS) + W(OS–S) weights to be larger as the X atom gets heavier. The individual carbene S–OS ($^1A_1$–$^1B_1$) energy splitting roughly correlates with the corresponding S–T ($^1A_1$–$^3B_1$) splitting, as can be seen numerically in Table 6, because the carbene $^3B_1$ and $^1B_1$ states have the same orbital configuration. This general redistribution among the covalent contributions upon *trans*-bending is found in all the $CH(A)=XH_2$ and $CH_2=XH(A)$ systems studied here.

Methyl substitution on the carbon atom [$CH(CH_3)=XH_2$] does not cause nonplanarity in the resultant heteronuclear double-bond system for X = C $\rightarrow$ Sn. However, $CH(CH_3)=PbH_2$ is calculated to have a *trans*-bent (TB) structure. If we compare in Table 7 the changes in the combined VB structure components in going from $CH_2=XH_2$ to $CH(CH_3)=XH_2$ for Si $\rightarrow$ Sn, then the following consistent trends are found: The W(T–T), W(OS–OS) and W(S–S) contributions increase, $l \rightarrow$ r CT (LRCT) increases and r $\rightarrow$ l CT (RLCT) decreases. These trends are understandable in terms of the accepted role of a methyl group as electron releasing. Thus, methyl substitution on the carbon atom tends to equalize the group electronegativities between the carbene partners. This leads to higher covalency and increased $CH(CH_3) \rightarrow XH_2$ charge transfer, and correspondingly decreased $XH_2 \rightarrow CH(CH_3)$ CT. The transition from a planar geometry to the *trans*-bent structure in going $CH_2=PbH_2 \rightarrow CH(CH_3)=PbH_2 \leftarrow CH(CH_3)=SnH_2$ correlates best with the combined carbene fragment S–T transition energies in Table 6. Thus, the destabilization of the $^3B_1(^3A'')$ triplet state in $CH(CH_3)$ relative to CH_2, and in $PbH(CH_3)$ relative to $SnH(CH_3)$, leads to decreased left–right covalent T–T [W(T–T)] contributions in going to $CH(CH_3)=PbH_2$ from both $CH_2=PbH_2$ and $CH(CH_3)=SnH_2$, respectively.

TABLE 7. Summed VB structure weights (W) by category[a]

CH(A)=XH$_2$		Conformation[d]		Covalent[b]				Charge transfer weights[c]	
X	A	A	total	W(T−T)+ W(OS−OS)	W(S−S)	W(S−OS)	W(OS−S)	LRCT	RLCT
VBSCF									
C	H	—	P	0.489	0.112	0.	0.	0.199	0.199
Si	H	—	P	0.499	0.106	0.	0.	0.111	0.284
Ge	H	—	P	0.514	0.107	0.	0.	0.131	0.247
Sn	H	—	P	0.529	0.101	0.	0.	0.101	0.270
Pb	H	—	P	0.534	0.106	0.	0.	0.116	0.245
C	H	—	TB[f]	0.502	0.076	0.018	0.018	0.194	0.194
Si	H	—	TB[f]	0.517	0.071	0.016	0.018	0.105	0.275
Ge	H	—	TB[f]	0.517	0.070	0.022	0.024	0.128	0.242
Sn	H	—	TB[f]	0.514	0.066	0.023	0.027	0.093	0.279
Pb	H	—	TB[f]	0.496	0.072	0.032	0.041	0.113	0.248
OVB[e]									
C	H	—	P	0.374	0.119	0.	0.	0.248	0.248
Si	H	—	P	0.338	0.092	0.	0.	0.078	0.486
Ge	H	—	P	0.361	0.096	0.	0.	0.089	0.447
Sn	H	—	P	0.378	0.090	0.	0.	0.077	0.450
Pb	H	—	P	0.401	0.096	0.	0.	0.089	0.409
C	CH$_3$[h]	T	P	0.373	0.041	0.003	0.003	0.288	0.288
Si	CH$_3$	T	P	0.350	0.095	0.	0.	0.089	0.456
Ge	CH$_3$	T	P	0.373	0.099	0.	0.	0.104	0.418
Sn	CH$_3$	T	P	0.394	0.092	0.	0.	0.089	0.418
Pb	CH$_3$	T	TB	0.372	0.044	0.055	0.064	0.120	0.343
C	F	—	P	0.374	0.116	0.	0.	0.263	0.243
Si	F	—	P	0.355	0.093	0.	0.	0.103	0.420
Ge	F	—	TB	0.335	0.058	0.047	0.046	0.107	0.406
Sn	F	—	TB	0.349	0.038	0.063	0.061	0.096	0.391
Pb	F	—	TB	0.389	0.051	0.044	0.060	0.119	0.333
C	OH	C	P	0.371	0.117	0.	0.	0.277	0.231
Si	OH[h]	T	P	0.359	0.099	0.010	0.007	0.110	0.414
Ge	OH	C	TB	0.324	0.054	0.061	0.062	0.124	0.373
Sn	OH	T	TB	0.354	0.056	0.055	0.070	0.134	0.328
Pb	OH	T	TB	0.381	0.086	0.032	0.069	0.181	0.244
C	CN	—	P	0.372	0.118	0.	0.	0.226	0.279
Si	CN	—	P	0.320	0.087	0.	0.	0.068	0.520
Ge	CN	—	P	0.339	0.091	0.	0.	0.074	0.493
Sn	CN	—	P	0.346	0.084	0.	0.	0.060	0.507
Pb	CN	—	TB	0.316	0.041	0.061	0.054	0.077	0.452
C	NO	C	P	0.371	0.119	0.	0.	0.227	0.278
Si	NO	C	P	0.320	0.088	0.	0.	0.065	0.520
Ge	NO	C	P	0.336	0.092	0.	0.	0.073	0.491
Sn	NO	*g*	P	0.341	0.085	0.	0.	0.060	0.507
Pb	NO	C	P	0.288	0.040	0.060	0.053	0.066	0.494

[a] See text. For the OVB method the weights add up to at least 0.990 because VB structure coefficients less than 0.05 have been neglected.
[b] S = $^1A_1$ ($^1A'$), T = $^3B_1$ ($^3B''$), OS = $^1B_1$ ($^1A''$).
[c] LRCT = l → r charge transfer; RLCT = r → l charge transfer.
[d] C = *cis*, T = *trans*, P = planar, TB = *trans*-bent. Conformation of A is with regard to the local carbene geometry.
[e] Orthogonalized VB from CAS(4,4)/CEP-DZP calculations; see text.
[f] Fixed 45° bend.
[g] Linear C−N=O.
[h] Not a perfect C_s symmetry.

TABLE 8. Summed VB structure weights (W) by category[a]

CH(A)=XH_2		Conformation[d]		Covalent[b]				Charge transfer weights[c]	
X	A	A	total	W(T–T)+ W(OS–OS)	W(S–S)	W(S–OS)	W(OS–S)	LRCT	RLCT
OVB[e]									
Si	CH_3	T	P	0.333	0.090	0.	0.	0.077	0.494
Ge	CH_3	T	P	0.356	0.095	0.	0.	0.087	0.457
Sn	CH_3	T	P	0.374	0.089	0.	0.	0.075	0.458
Pb	CH_3	T	P	0.396	0.095	0.	0.	0.086	0.415
Si	F	—	P	0.331	0.087	0.	0.	0.074	0.498
Ge	F	—	P	0.358	0.092	0.	0.	0.086	0.459
Ge	F	—	TB	0.310	0.046	0.058	0.049	0.092	0.443
Sn	F	—	P	0.378	0.086	0.	0.	0.075	0.457
Sn	F	—	TB	0.349	0.039	0.058	0.053	0.094	0.405
Pb	F	—	TB	0.393	0.059	0.034	0.051	0.124	0.336
Si	OH	T	P	0.323	0.087	0.	0.	0.073	0.514
Ge	OH	T	P	0.350	0.092	0.	0.	0.083	0.471
Sn	OH	T	TB	0.333	0.038	0.061	0.053	0.087	0.426
Pb	OH	T	TB	0.378	0.058	0.037	0.050	0.114	0.357
Si	CN	—	P	0.347	0.091	0.	0.	0.082	0.473
Ge	CN	—	P	0.371	0.096	0.	0.	0.094	0.434
Sn	CN	—	TB	0.341	0.036	0.065	0.056	0.092	0.406
Pb	CN	—	TB	0.382	0.052	0.045	0.055	0.120	0.342
Si	NO	C	P	0.343	0.092	0.	0.	0.081	0.477
Ge	NO	C	P	0.367	0.096	0.	0.	0.097	0.438
Sn	NO	C	TB	0.342	0.034	0.064	0.056	0.092	0.409
Pb	NO	C	TB	0.392	0.054	0.041	0.051	0.116	0.346

[a]See text. For the OVB method the weights add up to at least 0.990 because VB structure coefficients less than 0.05 have been neglected.
[b]S = $^1A_1$ ($^1A'$), T = $^3B_1$ ($^3B''$), OS = $^1B_1$ ($^1A''$).
[c]LRCT = l → r charge transfer; RLCT = r → l charge transfer.
[d]C = *cis*, T = *trans*, P = planar, TB = *trans*-bent. Conformation of A is with regard to the local carbenegeometry.
[e]Orthogonalized VB from CAS(4,4)/CEP-DZP calculations; see text.

It is well recognized that the left–right T–T interaction strongly favors the planar geometry. The left–right OS–OS interaction should not be a strong factor in determining planar–nonplanar geometric structure as X goes from Si to Pb since the individual carbene $^1A_1$–$^1B_1$ energy gap (Table 6) doesn't change much from SiH_2 to PbH_2. Although these components are shown together in Table 7, in fact, the covalent OS–OS interaction weight [W(OS–OS)] is relatively constant in CH(CH_3)=XH_2, X = Si → Pb, while it is the W(T–T) component that decreases. Thus, apparently, when the W(T–T) weight falls below a certain threshold, the distorting electronic structure components determine the geometric structure. Of course, as pointed out above, those other VB structures that maintain an equal number of σ and π electrons would also be expected to favor a planar geometry; but W(T–T) should be the most important of all.

The CH(F)=XH_2 series has planar equilibrium structures for X = C and Si, while for X = Ge, Si and Pb the optimized *trans*-bent geometry is more stable (Table 2). The planar forms for the last three X atoms are calculated to be 0.3, 2.3 and 5.4 kcal mol^{-1} higher in energy than the respective *trans*-bent forms. DFT/CEP-5ZP calculations using the B3LYP functional do not show stationary states in the planar geometry for the Sn and Pb compounds, while, as noted above, at the *ab initio* CAS(4,4)/CEP-DZP level

both planar and *trans*-bent structures are obtained for X = Ge → Pb. The $^3A''$ (T) state in CH(F) (Table 6) is calculated to be some 11–14 kcal mol^{-1} above the (S) $^1A'$ state, depending on theory level. Thus the combined T + T energies of the individual CH(F) and XH_2 carbenes is higher in CHF=XH_2 than in either CH_2=XH_2 or CH(CH_3)=XH_2 for all X, and the tendency to the *trans*-bent structure for A = F is found already for the lighter X = Ge and Sn atoms relative to the A=CH_3 set.

Comparing the planar and *trans*-bent structures in CH(F)=XH_2 for X = Ge, Sn and Pb, the trends show decreases in W(T–T) + W(OS–OS), W(S–S) and RLCT, and increases in LRCT, W(S–OS) and W(OS–S) (Table 7). The latter two are exactly zero in the planar geometry. Thus, in these cases, bending effectively decreases the electronegativity of the CH(F) to a small extent relative to XH_2. This may be related to changes in hybridization at the carbon atom due to, or accompanying, the bending process. Hybridization changes are expected to be less pronounced for the heavier X atoms (X = Si → Pb) because of the larger ns–np energy gap. This small effect was not found in the CH_2=XH_2 set. With increasing size of the X atom, within the CH(F)=XH_2 set the W(T–T), W(OS–OS) and LRCT contribution generally increases and the RLCT weight decreases. These trends can be traced separately for the planar and *trans*-bent geometric structures, and are in general agreement with the same trends for the other A group substituents.

As noted above, the more stable form of the planar XH(OH) carbenes is the *trans* isomer with a zigzag H–C–O–H arrangement. The global energy minimum belongs to the structure with the hydroxyl hydrogen atom almost perpendicularly out-of-plane. The CH(OH)=XH_2 structures here (Tables 7 and 8) were found to have essentially planar hydroxyl hydrogen atoms (H). Thus, a (H)*cis*-planar CH(OH)=CH_2 and a (H)*trans*-planar CH(OH)=SiH_2 were geometry optimized. For CH(OH)=GeH_2 a (H)*trans*-planar geometry was calculated but the (H)*cis* conformer optimized to a *trans*-bent structure, where the latter, of course, refers to the local conformation about the carbon and germanium atoms. The hydroxyl hydrogen atom here is also found to be out of the Ge=C(H)O plane, but to a much smaller degree than found for the free *trans*-HCOH carbene. Bending about the carbon atom is also found to be relatively mild. DFT/CEP-5ZP geometry optimizations also give the (H)*cis* nonplanar geometry for HC(OH)=GeH_2. Two different conformers were obtained for HC(OH)=SnH_2. The (H)*trans,trans*-bent structure is the more stable of the two and also the (H)*cis* is nonplanar (TB). DFT/CEP-5TZ calculations give similar results to those obtained by the CAS(4,4)/CEP-DZP method. For HC(OH)=PbH_2, results that are completely analogous to those of HC(OH)=SnH_2 were obtained. It should be noted that the tendency to stronger *trans*-bending about both the carbon and X atoms increases with the size of the X atom. However, the degree of out-of-plane bending of the hydroxyl hydrogen atom in HC(OH)=XH_2 remains small.

From Table 6, the CAS(2,2)/CEP-DZP results for CH(OH) show only a small increase in the S–T splitting energy compared to CH(F), where the $^1A'$ state is lower in both cases. Both conformers are described in Table 6. Compared to the nonplanar structure, the *trans*-planar geometry shows a somewhat larger S–T splitting by 1–2 kcal mol^{-1}. The DFT/CEP-5ZT calculations show a much larger S–T gap in the CH(OH) carbene compared to CAS(2,2)/CEP-DZP, but very similar S–T splittings for the heavier X atoms. It is therefore not surprising that the geometric structural preferences for CH(OH)=XH_2 should be very similar to that for CH(F)=XH_2, as described above, with allowances for small structural nuances due to the greater number of conformational arrangements in the hydroxyl series.

Comparing the CH(A)=XH_2, A=hydroxyl and fluorine series for a given X atom and consistent planar/nonplanar conformation in Table 7, the covalent weights add up to about the same numbers in both cases. Between W(T–T) and W(OS–OS) the latter seems to be somewhat larger in the hydroxyl series, with a concomitantly smaller W(T–T). A consistent difference between the two series is in the charge transfer weights, where

$XH_2 \rightarrow CH(OH)$ is smaller in the hydroxyl series than in the fluorine set. Correspondingly, $CH(OH) \rightarrow XH_2$ is larger in the hydroxyl series. These differences don't seem to have much effect on the geometric structures and can be attributed to the electronegativity difference between OH and F.

The $CH(CN)=XH_2$ sets are all calculated to have a linear C−C≡N bonding structure. The S–T gap in the CH(CN) carbene is CAS(2,2)/CEP-DZP predicted to be relatively small, with the triplet ($^3A''$) state lower. The other XH(CN) carbenes have a $^1A'$ ground state with a S–T splitting that is somewhere between the CH_2, $CH(CH_3)$ values and those for CH(F) and CH(OH). The $CH(CN)=XH_2$ geometric structures (Table 7) behave more like the $CH(CH_3)=XH_2$ series, as expected from the S–T splittings in the CH(CN) carbenes. Thus, X = C, Si, Ge and Sn are planar and $CH(CN)=PbH_2$ has the *trans*-bent conformation. DFT/CEP-5ZP calculations confirm the planarity of $CH(CN)=SnH_2$. These geometric structural results for the CN set strongly support the qualitative correlation between the combined carbene S–T splittings and the equilibrium conformation in the heteronuclear double bonds. Comparing the CN and F substituent groups for corresponding X atoms in Table 7 shows that the $CH(CN)=XH_2$ series is less covalent and has a larger $XH_2 \rightarrow CH(CN)$ charge transfer weight. The latter is undoubtedly due to the available π^* orbitals on the CN group.

As noted above, because of all the multiple-bonding possibilities and ring structures in CH(NO) or HCNO, at the level of theory applied here it was not possible to obtain clear-cut S–T energy differences in a consistent manner. The CAS(2,2) and DFT methods also tended to give very different results. Clearly, these carbenes need intensive study on a very high theoretical level, which is beyond the scope of this work. However, the $CH(NO)=XH_2$ systems seem to be better behaved. As with the OH substituent, the CH(NO) group can have both *cis* and *trans* conformations. For the $CH(NO)=XH_2$ both conformations were obtained with X = Si → Pb, while for X = C only the *cis* geometry was examined. All the equilibrium geometric structures calculated here were found to be planar. For X = Si → Sn the *cis* conformer was consistently more stable. $CH(NO)=PbH_2$ has the *trans* conformer as more stable; but this is apparently due to an extra Pb...O interaction in the *trans* structure that gives it extra stability. This tendency for lead compounds to form extra such interactions in a quasi-four-membered ring arrangement (Pb−C−N−O) has been noted previously[52]. Thus, as part of the heteronuclear double bond, CH(NO) prefers the *cis* structure, although this may not carry over to the isolated carbene. The fact that all the equilibrium geometries are planar, even for the heaviest X atoms, indicates that the S–T splitting in the XH(NO) carbenes must be small.

The distribution of VB structure weights among the different types of covalent and charge transfer contributions in Table 7 is remarkably similar between *cis*-$CH(NO)=XH_2$ and $XH(CN)=XH_2$ for a given X atom and the planar equilibrium geometries. This shows that the electronic structure description in terms of VB structures by itself does not seem to determine geometric structure and that the energy value of each component must be taken into account as part of the overall considerations in this regard.

C. CH_2=XH(A)

We now turn to the effect of substitution on the XH_2 carbene, when X is not the carbon atom. The four $CH_2=XH(CH_3)$ compounds, with X = Si → Pb, are all calculated to have planar equilibrium geometries (Table 3). As with their $CH(CH_3)=XH_2$ counterparts, the conformation of the in-plane hydrogen atom on the methyl group (C′−H) in $CH_2=XH(CH_3)$ is *trans* to X−H in the latter series across the X−C′ bond, or C−H in the former set across the C−C′ bond. The combined S–T energies of the $CH_2 + XH(CH_3)$ carbenes and the $CH(CH_3) + XH_2$ carbenes are very similar. As shown in Table 6, the

largest difference between the two combinations is due essentially to the larger S–T splitting in CH_2 compared to $CH(CH_3)$. Since for both these carbenes the triplet state is lower, the $CH_2{=}XH(CH_3)$ systems should show a slightly greater tendency to planarity. This might explain why, along with all the other members of its set, $CH_2{=}PbH(CH_3)$ is calculated planar while $CH(CH_3){=}PbH_2$ is predicted to have the *trans*-bent structure in the $CH(CH_3){=}XH_2$ series.

The VB structure weights for the $CH_2{=}XH(A)$ series are tabulated in Table 8. For $A = CH_3$ the trends for the covalent and charge transfer components behave as in the $CH(CH_3){=}XH_2$ series; with increasing weight of X the covalent component increases and the combined charge transfer weights (LRCT and RLCT) decrease. Comparing $CH_2{=}CH(CH_3)$ to $CH(CH_3){=}XH_2$, Table 8 shows that $XH(CH_3) \rightarrow CH_2$ charge transfer is generally larger than $XH_2 \rightarrow CH(CH_3)$ for $X = Si \rightarrow Pb$, as expected.

To anticipate the results for the $CH_2{=}XH(F)$ set of heteronuclear doubly-bonded systems we look at the combined S–T energy splitting of CH_2 and XH(F). Table 6 shows that simply adding the two individual carbene S–T gaps as X increases in size, keeping the minus sign for those carbenes that have a ground triplet state, gives resultant energies of 26.1, 33.9, 31.6 and 45.5 kcal mol^{-1} for $X = Si \rightarrow Pb$, using the *ab initio* values. For comparison, the analogous combined $CH(CH_3) + XH_2$ energies calculated from Table 6 are 31.3, 37.4, 37.3 and 48.0 kcal mol^{-1}. These results suggest that the $CH_2{=}CH(F)$ systems should have a somewhat greater tendency to planarity than $CH(F){=}XH_2$.

The calculated equilibrium geometric structures (Table 3) are somewhat interesting in this regard, $CH_2{=}SiH(F)$ is CAS(4,4)/CEP-DZP calculated to be planar. At this same theory level, $CH_2{=}GeH(F)$ is found both with a planar and a nonplanar, *trans*-bent structure, with an energy difference of only 0.2 kcal mol^{-1}. Both conformers are equilibrium geometries as indicated by the absence of imaginary frequencies in harmonic force-field frequency calculations. However, at the DFT/CEP-TZDP+ level with the B3LYP functional, only the planar structure is obtained, even when the *trans*-bent geometry is used as an initial guess; also with all real harmonic frequencies. An exactly analogous result is obtained for $CH_2{=}SnH(F)$. Both planar and *trans*-bent equilibrium structures are obtained at the CAS(4,4)/CEP-DZP level with all real harmonic frequencies, and only the planar equilibrium geometry is found at the DFT/CEP-TZDP+ level. Here, for $CH_2{=}SnH(F)$, the planar–nonplanar energy difference at the CAS(4,4)/CEP-DZP level is 1.9 kcal mol^{-1}. For $CH_2{=}PbH(F)$, again at the CAS(4,4)/CEP-DZP theory level, both the planar and *trans*-optimized planar structure are calculated, but with an energy difference of 5.8 kcal mol^{-1}. Here, the optimized planar structure has one imaginary harmonic frequency and the nonplanar geometry has none. The planar geometry is therefore a transition state and the TB form is the true equilibrium state. For $CH_2{=}PbH(F)$ the DFT/CEP-TZDP+ method gives only the *trans*-bent structure with all real harmonic frequencies. The Ge and Sn systems will need more intensive study in order to resolve the differences in calculated geometric structure, but the expected somewhat greater tendency of the $CH_2{=}XH(F)$ set to planarity compared to $CH(F){=}XH_2$ based on S–T energy splittings has been found.

As shown in Table 8, the $CH_2{=}XH(F)$ ($X = Si \rightarrow Sn$) planar structures have very similar summed VB weight distributions as the corresponding members of the $CH_2{=}XH(CH_3)$ series. This, in fact, can be seen to hold also for a comparison between $CH(F){=}XH_2$ and $CH(CH_3){=}XH_2$ (Table 7). The surprising aspect here is that the relative LRCT and RLCT components are so similar between $A = CH_3$ and $A = F$ for substitution on either the CH_2 or XH_2 carbenes. Given the large difference in behavior of the S–T energy splitting between the methyl and fluorine substituents and the electronegativity difference, the similarity in VB weight components separately within the $CH_2{=}XH(A)$ and $CH(A){=}XH_2$ sets is another indication that the OVB structure weights alone may not always be a sufficiently sensitive measure of the electronic structure description of these systems.

The HXOH carbene comes in two conformations: *trans* and *cis*. As noted above, the free carbene favors the *trans* structure in the planar geometry but the equilibrium geometry is nonplanar, energetically some 1–2 kcal mol^{-1} below the planar form (Table 6). In the CH(A)=XH_2 series discussed above the *trans* HCOH form was also energetically favored in the HC(OH)=XH_2 compounds. A similar situation is found for the CH_2=XH(OH) set. Thus, *trans*-CH_2=SiH(OH) is CAS(4,4)/CEP-DZP calculated to be more stable than *cis*-CH_2=XH(OH) by 1.4 kcal mol^{-1} while the same difference in the isolated H(OH) carbene (Table 6) is 2.3 kcal mol^{-1}. Analogously, for CH_2=GeH(OH) [HGeOH] the *trans* conformer is 1.3 [1.8] kcal mol^{-1} more stable than the *cis* geometry. It should be noted that the *trans*-CH_2=XH(OH) geometry has a lower dipole moment than the *cis* structure by *ca* 1.55D for both X = Si and Ge, and this would favor the *trans* conformer energetically. For CH_2=SnH(OH) three structures were examined at the CAS(4,4)/CEP-DZP theory level: the planar and (TB) nonplanar *trans* structures and the (TB) nonplanar *cis* conformer. The lowest-energy geometry was found for the overall *trans*-bent structure and a locally coplanar HSnOH arrangement of atoms with a *trans* conformation. The nonplanar *cis* structure is closer energetically to the nonplanar *trans* structure than to the planar *trans* geometry. Using the DFT/CEP-TZDP+ theory level with the B3LYP functional and the HSnOH *trans* conformer, only the nonplanar structure is obtained with all real harmonic frequencies. For CH_2=PbH(OH) both the planar and (TB) nonplanar structures were CAS(4,4)/CEP-DZP calculated in the HPbOH *trans* conformer with a 4.4 kcal mol^{-1} energy difference favoring the *trans*-bent form. At the DFT/CEP-TZDP+ level only the (TB) nonplanar structure is found with all real harmonic frequencies, just as for CH_2=SnH(OH).

The combined CH_2 + XH(OH) S–T energy splittings for X = Si → Pb are consistently smaller than the corresponding CH(OH)+XH_2 splittings at the CAS(2,2)/CEP-DZP level for the individual carbenes (Table 6). This difference even increases if the larger DFT/CEP-TZDP+ calculated S–T splitting energy for CH(OH) is adopted. The expectation, therefore, is that the CH_2=XH(OH) series would have a smaller tendency to the *trans*-bent distortion than the CH(OH)=XH_2 series. This, in fact, is what is found here, where the nonplanar equilibrium geometry is found for X = Sn and Pb in the former set whereas already CH(OH)=GeH_2 is also *trans*-bent, as described above.

CH_2=SiH(CN) and CH_2=GeH(CN) are CAS(4,4)/CEP-DZP calculated to be planar (Table 8). Both CH_2=SnH(CN) and CH_2=PbH(CN) have been obtained in both the planar and the lower-energy *trans*-bent structures at the same theory level. The energy differences between the planar and nonplanar forms are 1.2 and 3.7 kcal mol^{-1}, respectively for the Sn and Pb complexes. DFT/CEP-TZDP+ level theory with the B3LYP functional gives only (TB) nonplanar structures for both CH_2=SnH(CN) and CH_2=PbH(CN). As described above, in the CH(CN)=XH_2 series only the X = Pb member was calculated to be nonplanar. The combined individual carbene CH_2 + XH(CN) S–T energy splittings are consistently higher than the corresponding combined CH(CN) + XH_2 S–T gaps for a given X, for X = Si → Pb. This situation arises from the CAS(2,2)/CEP-DZP calculated S–T splittings in Table 6, where CH(CN) is 5.5 kcal mol^{-1} above CH_2 while the XH(CN) splittings are increasingly larger with the size of atom X, starting from 7.6 kcal mol^{-1} for X = Si to 13.8 kcal mol^{-1} for X = Pb. The result is that the CH_2=XH(CN) series is expected to have a stronger tendency to nonplanarity compared to CH(CN)=XH_2. This is the situation found here, where only CH_2=SnH(CN) and CH_2=PbH(CN) are nonplanar while in the CH(CN) + XH_2 set only the X = Pb member is calculated to have the *trans*-bent structure. These tendencies are only reinforced by the more negative S–T splitting energy for CH(CN) calculated by the DFT/CEP-TZDP+ method.

CH_2=XH(NO) can adopt two conformations for the HXNO carbene part: *trans* or *cis*. As with the CH(ON)=XH_2 series, all the members of the CH_2=XH(NO) set have

a *cis* HXNO carbene geometry in their lowest-energy equilibrium form (Table 8). For CH_2=SiH(NO) both the planar *cis* and *trans* structures were obtained. For X = Ge a nonplanar *trans* conformation was also calculated, but it was above the planar *cis* form in energy. DFT/CEP-TZDP+ level calculations with the B3LYP functional confirmed the *cis*-planar form for CH_2=GeH(NO) as the equilibrium ground state. For CH_2=SnH(NO) both the *cis*-planar, *cis*-nonplanar and *trans*-nonplanar geometries were found at the CAS(4,4)/CEP-DZP level, with the *cis*-(TB)nonplanar structure lowest in energy. Finally, for X = Pb both the *cis*- and *trans*-CH_2=PbH(NO) nonplanar structures were generated, with the *cis* conformer lowest. This latter structure was also obtained by DFT/CEP-TZDP+ calculation. In summary, whereas for the CH(NO)=XH_2 series all the equilibrium structures for all X are planar, in CH_2=XH(NO) the X = Sn and Pb geometries are found to be *trans*-bent. One simple conclusion from these differences in geometric structure within the framework of combined carbene S–T energy splittings is that there is a very large difference in this quantity between CH(NO) and the other XH(NO) carbenes.

D. Isomerization

Another indication of the possible role played by the individual carbene S–T energy splittings in determining energetics and structure in the heteronuclear doubly-bonded systems is obtained by examining the isomerization energies for the process,

$$CH(A)=XH_2 \longrightarrow CH_2=XH(A) \qquad (2)$$

Total energies are tabulated in Table 9. The energetics of this reaction for A = CH_3 is −7.3 (Si), −4.8 (Ge), −3.3 (Sn) and −8.0 (Pb) kcal mol^{-1}, where the minus sign signifies an exothermic process. Thus all the methyl substituted CH_2=XH_2 systems favor the CH_2=XH(CH_3) isomer. Analogously, the combined CAS(2,2)/CEP-DZP S–T energy splittings for CH_2 + XH(CH_3) are roughly below the combined S–T energy splittings of CH(CH_3) + XH_2 by about the same amount as the energetics of reaction 2. For A = F the isomerization or atom exchange reaction is exothermic by *ca* 49 kcal mol^{-1} (X = Si) to *ca* 36 kcal mol^{-1} (X = Pb). These reaction energies are pure electronic energy differences with no thermodynamic correction terms. The CH_2 + XH(F) combined *ab initio* S–T splitting energies from Table 6 are from 5 kcal mol^{-1} (Si) to 13 kcal mol^{-1} (Pb) lower than the corresponding CH(F) + XH_2 combination. Here, the general correlation is more qualitative and less quantitative. Analogously, the reaction 2 isomerization energy for A = OH ranges from *ca* 40 kcal mol^{-1} for Si to *ca* 19 kcal mol^{-1} for Pb, all exothermic, while the CH_2 + XH(OH) sum of S–T splitting energies (Table 6) is smaller than the corresponding CH(OH) + XH_2 total by *ca* 7 kcal mol^{-1} (Si) to *ca* 10 kcal mol^{-1} (Pb).

However, for A = CN the isomerization reaction favors CH_2=XH(CN) by *ca* 6 kcal mol^{-1} (Si) to *ca* 9 kcal mol^{-1} (Pb), whereas the combined CAS(2,2)/CEP-DZP S–T splitting energies are smaller for CH(CN) + XH_2 relative to CH_2 + XH(CN) by *ca* 3 kcal mol^{-1} (Se) to *ca* 9 kcal mol^{-1} (Pb). Here a correlation between the *ab initio* S–T splittings and isomerization reaction energies is not found to hold, although the qualitative geometric structure correlation described above was found to be valid.

The summary in Table 9 shows the correlation between the relative tendency away from a planar equilibrium geometric structure between the CH(A)=XH_2 and CH_2=XH(A) sets and the general exothermic direction of the isomerization reaction 2 for a given A substituent. Thus, even for the A = NO comparisons, where the HXNO S–T splitting energies are not known from these calculations, the consistently less stable isomer [CH_2=XH(A)] has the higher tendency to the *trans*-bent structure (X = Sn and Pb). This general correlation holds also for A = CH_3, F and OH, but not for A = CN. Also, except for A = CN,

TABLE 9. CAS(4,4)/CEP-DZP energies of $CH(A)=XH_2$ and $CH_2=XH(A)$

X	A	$CH(A)=XH_2$			$CH_2=XH(A)$		
		Conformation[a]		Energy	Conformation		Energy
		A	Total	(a.u.)	A	Total	(a.u.)
C	CH_3	T	P	−19.974071			
Si	CH_3	T	P	−18.194894	T	P	−18.206471
Ge	CH_3	T	P	−18.148716	T	P	−18.156259
Sn	CH_3	T	P	−17.702732	T	P	−17.707825
Pb	CH_3	T	TB	−17.754138	T	P	−17.766754
C	F	—	P	−36.597301			
Si	F	—	P	−34.808242	—	P	−34.886244
Ge	F	—	TB	−34.762843	—	P	−34.816868
						TB	−34.816562
Sn	F	—	TB	−34.320467	—	P	−34.373884
						TB	−34.370934
Pb	F	—	TB	−34.371716	—	TB	−34.428810
C	OH	C	P	−29.009014			
Si	OH	T	P	−27.221906	T	P	−27.285140
Ge	OH	C	TB	−27.177137	T	P	−27.216579
Sn	OH	T	TB	−26.737427	T	TB	−26.767659
Pb	OH	T	TB	−27.791738	T	TB	−26.821687
C	CN	—	P	−27.897308			
Si	CN	—	P	−26.124578	—	P	−26.134046
Ge	CN	—	P	−26.078417	—	P	−26.082600
Sn	CN	—	P	−25.634561	—	TB	−25.641678
Pb	CN	—	TB	−25.683015	—	TB	−25.697117
C	NO	C	P	−38.027269			
Si	NO	C	P	−36.250112	C	P	−36.247614
Ge	NO	C	P	−36.206408	C	P	−36.196001
Sn	NO	C	P	−35.762685	C	TB	−35.747911
Pb	NO	C	P	−35.813392	C	TB	−35.813049

[a] C = *cis*, T = *trans*, P = planar, TB = *trans*-bent. Conformation of A is with regard to the local carbene geometry.

the less stable isomer correlates with the higher combined carbene fragment S–T splitting energy. The electronic structure factors that make the CN substituent different must now be sought.

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CHAPTER **2**

Mass spectra of double-bonded groups

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I. ABBREVIATIONS

CI	chemical ionization
CID	collisional-induced dissociation
CR	charge reversal
CT	charge transfer
DA	Diels–Alder
EI	electron impact
FAB	fast atom bombardment
FI	field ionization
FIK	field ionization kinetics
ICR	ion cyclotron resonance

NRMS	neutralization–reionization mass spectrometry
PEPICO	photoelectron–photoion coincidence spectroscopy
PES	photoelectron spectrum
RDA	retro-Diels–Alder

II. AN INTRODUCTION, TO WARM UP

It is probably difficult to find a mass spectrometric fragmentation where neither a double-bonded nor a three-electron-bonded C=C, C=O or C=N group is present. In addition, in most ions, other functional groups containing a heteroatom may localize the charge; this might have a larger influence on the fragmentation pathway than a double bond. Thus it is not practicable to cover the whole field within a review of this size and the author has concentrated on a few fields that offer — in his view — a special interest and may serve as a *pars pro toto* in this field to guide the ideas. Whenever available, much weight is given to data including labeled compounds and the measurement of the time dependence over a wide range. It is the author's opinion that much information is hidden in such data that often invalidate conclusions drawn too hastily. Several new applications of mass spectrometry have been described by Splitter and Tureček[1].

Mass spectrometric fragmentation within the ion source covers roughly the time scale up to *ca* 1 μs. This might seem a short lapse of time, but is very long compared to the few hundred femtoseconds it takes for an elementary reaction to take place[2]. Many isomerizations will take place already within the ion source. Field ionization kinetics (FIK)[3–6] is a method that allows one to sample the time range from 10 ps to 1 μs. Unfortunately, the experimental difficulties are such that this interesting method cannot count on many adherents, but it is a field where unexpected surprises are programmed in advance. Infrared excitation can be used to excite additionally the neutral before field ionization takes place in order to get additional fragmentation. The time window around *ca* 10 μs is defined by flight time in magnetic and quadrupolar mass spectrometers and has received very much attention and delivered much new information about ions and short-lived neutrals. The metastable decay and the different modifications of collisional-induced dissociation (CID) fall in this field. However, it should not be forgotten that the structure of the ions whose properties and structure are elucidated during this time span rarely correspond to those of the ions initially produced. The time window for the study of reactions and properties of ions has been enlarged to *ca* 1 s by the ion cyclotron resonance (ICR) technique. This increase is of importance, e.g. for the study of reactions of vibrationally relaxed ions. The large majority of ions is being produced with much internal vibrational energy. It so happens that the time range of the ICR instruments falls within the range of vibrational emission[7–9]. A review has been given by Dunbar[10]. Even slow metastable decays can be observed within this time range[11,12]. The recent developments in the applications of the theoretical calculations by RRKM-QET have been reviewed by Lifshitz[13].

The dramatic increase in computing power has allowed one to calculate ions (and neutrals) containing many atoms. It can be estimated that semiempirical self-consistent field methods allow calculations of structures that contain about 100 atoms, whereas semiempirical methods increase this limit by a factor of ten[14–16]. A short review of the use of MINDO/3 in the field of ketones has been presented by Parker and collaborators[17]. The accuracy has reached a point where often it compares favorably with the experimental results. Many new structures have been confirmed or discovered. The price to pay is that many different isomeric structures may have energies that fall within the reach of internal energies of the ions and it is often an academic discussion to assign a given structure to a given intermediate.

Neutralization-reionization mass spectrometry (NRMS) is a new technique that has increased considerably our knowledge about the structure of intermediate cations, anions and neutrals[18–24]. It is based on the collisional-induced dissociation (CID), a technique of utmost importance in mass spectrometry[25]; it has recently been reviewed by Cooks[26] and Wesdemiotis and McLafferty[27]. In NRMS one seeks to neutralize an ion by a (soft) charge exchange without accompanying isomerization or isotopic scrambling[28,29] in the field-free region between two sectors. The efficiency of the process is governed by the Franck–Condon overlap between the projectile ion, its neutral counterpart and those of the target species[30]. The neutral will in principle keep its high kinetic energy and can — according to the instrumental conditions — be dissociated in a high-energy collision process. Reionization of the fragments then provides a mass spectrum — negative[31,32] and positive ions are feasible — that characterizes the original ion structure, but allows also conclusions about the structure of the neutral intermediate[33–43]. A special application introduced by Tureček and colleagues[44–46] is the survivor ion mass spectrometry which is based on the simultaneous neutralization and reionization of all stable ions produced in the ion source followed by selective monitoring of the nondissociating species. This procedure achieves isomer differentiation in a single spectrum while providing information on all stable isomers, as opposed to the conventional tandem mass spectrometry, where a matrix of spectra must be acquired in order to characterize two or more precursor ions[47]. These evolved applications necessitate multisector instruments[48–54]. The applications involving multisector instruments are summarized by Hoffmann[55].

III. THE LOCALIZATION OF THE C=C DOUBLE BOND: AN ANALYTICAL PROBLEM

The location of a C=C double bond in mass spectrometry is not an easy problem, because the energy for its delocalization within the ion is often not very high, as will be shown in later sections. This is particularly true for shorter chains. The problem is somewhat different, when other functional groups with a stronger tendency to localize the charge are present, such as acids, esters, alcohols etc. In this case a charge-remote fragmentation might yield fragments that are typical for the position of the C=C double bond (among other criteria). The analytical possibilities of charge-remote fragmentations have been reviewed up to 1989 by Adams[56,57]; some applications are summarized by Gross[58] and newer results resumed up to 1991 by the same author[59,60]. Jensen, Tomer and Gross demonstrated on several examples with negative ions (unsaturated[61] and polyunsaturated[62] fatty acids) the feasibility of the concept (see later). The collision-induced allylic cleavage reactions of deuterium-labeled $[M - H + 2Li]^+$ and $[M - H]^-$ ions were investigated by Adams, Gross and coworkers[63]. They demonstrated the usefulness of specific labeling for the elucidation of such processes; this fact of no visible H/D randomization is also an indirect proof that the charge is not involved in the fragmentation.

There are several possibilities to circumvent the problem of isomerization. Field ionization (FI) seems to be an ideal solution, since the fragmentation is faster than the isomerization. Effectively, it has been shown by Levsen and coworkers[64] for 19 olefins from C_4 to C_8 that the fragments thus obtained are typical for the location of the double bond. However, the difficulty to obtain reproducible results with the FI technique prevented widespread use. All methods that induce either a fragmentation that is faster than a shift of the double bond or use ionization energies at the threshold of the ionization energy are potentially useful candidates. One possibility is the secondary fragmentation of the ions that did not fragment after a few μs, as is done in NRMS and the related techniques. The possibility of a preceding isomerization of these ions is a problem, unless the excess of internal energy in ionization is very small. Photoionization at the lowest-energy

level is another method. For mixtures, it has the disadvantage that for best results the photon energy must be carefully adjusted. Negative ions often show a smaller tendency for fragmentation which can be an advantage for collisionally activated fragmentation without a preceding shift of the double bond. CI (chemical ionization) is a very soft ionization or derivatization method. In mixtures, practically all these methods have to be preceded by a separation either by gas or liquid chromatography. Analytically, the most promising method — where applicable — is the derivatization of the double bond in the neutral molecule before separation and fragmentation. A review of the mass spectrometric methods for the structural determination and analysis of fatty acids up to 1986 has been prepared by Jensen and Gross[65]. A particularly useful ionization method in this field is the fast atom bombardment (FAB), explained in the preceding review of this series by Mruzek[25], possibly coupled with collision-induced dissociation[66]. Positive ions, containing alkali metals, as well as negative ions are observed. Contado and Adams[67] elucidated the mechanism of the charge-remote fragmentations of the $[M + Li]^+$ ions of fatty esters; a detection limit of 25 ng of methyl palmitate is obtained. Gross and collaborators[68] studied a series of homoconjugated octadienoic acids with FAB. The carboxylate ion $[M - H]^-$, the dilithiated species $[M - H + 2Li]^+$ or the bariated species $[M - H + Ba]^+$ allow one to localize the charge. The Ba as metal has the additional advantage to shift the fragments into mass regions where only little overlap with other fragments, i.e. little 'chemical noise', is present. In addition, the Ba has a typical isotopic peak distribution. Other alkaline earth metals can also be used[69]. Electrospray ionization has been exploited by Wheelan, Zirrolli, and Murphy[70] for tandem mass spectrometry of polyhydroxy unsaturated fatty acids. Last but not least, it should be remembered that other methods such as infrared spectroscopy[71] or ^{13}C NMR[72] are often in competition with mass spectroscopy, albeit with less sensitivity.

The mass spectrometry of olefins is discussed in Sections V–VII. The possibility to distinguish geometrical (*E*)- and (*Z*)-isomers by different mass spectral methods has been reviewed up to 1990 by Vairamani and Saraswathi[73]. It is not possible to formulate general rules for the fragmentation of unsaturated compounds, but a mathematical treatment of the intensities of the different peaks can give some indication of the location of the double bond. Thus Brakstad[74] proposes the use of a least-squares correlation between the normalized spectral intensities of the electron impact mass spectrum as the independent variable and the C=C bond position as the response. Using 12 straight-chain monounsaturated fatty methyl esters, ranging in double-bond position from C(5) to C(11), incorporating both *cis*- and *trans*-isomers and chain lengths from C_{16} to C_{20}, the author obtained the true position with a reproducibility of ± 0.46 at a 95% confidence interval. Sanchez and Kowalski[75] use the advantage of the tandem mass spectrometry, thus obtaining two matrices to optimize. The method works, at least for lower olefins. An extended and modern use of the possibilities of the computer is the application of the fuzzy logic for the interpretation of the spectra, as has been done by Yuan, Horiike and coworkers. The procedure has been tested, partly in mixtures separated by gas chromatography, with tetradecenols[76,77], hexadecenols[78], dodecenols[79,80], unsaturated acetates[81–83] and in a practical application on insect pheronomes[84].

For the separate determination of — at least — high boiling alkenes, a gas chromatographic separation before identification by mass spectrometry is necessary. With this combination Ramnäs, Oestermark, and Petersson separated 52 acyclic and 11 cyclic C_5–C_7 alkenes either in petrol[85] or in the air emitted from petrol[86]. Different complex hydrocarbon mixtures were analyzed by Revill, Carr, and Rowland[87]. In such problems a heavy load is taken by the gas chromatographic separation, in particular by the choice and the quality of its column. Soják, Kraus and collaborators managed to separate

C_{17} and C_{18} alkanes and alkenes[88] and finally all 17 (*cis*- and *trans*-) isomers of nonadecenes on a mesogenic stationary phase and to identify them by mass and infrared (*cis*/*trans*!) spectroscopy[89]. The separation between two peaks in the gas chromatogram was often barely more than one Kováts index unit. The determination of monounsaturated C_{12} to C_{18} acetates, aldehydes, alcohols and carboxylic acids was performed after gas chromatographic separation by Leonhardt, DeVilbiss, and Klun[90] and Lanne, Appelgren, Bergström and Löfstedt[91]. In both cases the correlation with certain mass fragment ratios was necessary to determine the position of the double bond within a certain probability. Polyunsaturated fatty acids from microalgae in the C_{16} to C_{22} range with up to six double bonds were determined by Bousquet, Sellier and Goffic[92]. Hori, Sahashi, and Koike[93] separated polyunsaturated fatty acids in triglycerides. In all these investigations, the main importance of the mass spectrometer is its high sensitivity and the possibility to determine the molecular weight. The combination of gas chromatography with tandem mass spectrometry (MS/MS) was used to analyze pentacyclic triterpenes by Hazai, Galvez-Sinibaldi, and Philp[94]. In this work a library search enabled the components to be identified.

CI as a soft ionization tool, also capable of producing characteristic adducts, possibly coupled with a preceding gas chromatographic separation, is an efficient tool to produce specific ions that can be characterized by collisional activation. Early reviews have been given by Ferrer-Correia, Jennings and Sen Sharma[95] and Budzikiewicz[96]. Vairamani, Mirza and Srinivas[97] reviewed up to 1988 unusual positive ion reagents in CI. The use of acetone as reagent ion by Vairamani and collaborators[98] is described in Section VIII. A simple method is to let the molecular ion react with its neutral, a method not always possible in an analytical application. Ferrer-Correia, Jennings and Sen Sharma[99] applied this technique to determine the position of double bonds. Einhorn, Kenttämaa and Cooks[100] enlarged the method for linear alkenes with 6 to 23 carbon atoms. Budzikiewicz and Busker[101] studied various reactant gases (CH_4, i-C_4H_{10}, NO, N_2O, amines, ethers, Me_2Si) for their usefulness in localizing double bonds, but only isobutane, NO and $MeNH_2$ proved to be useful. Isobutane has been a reagent for CI of long standing. Doolittle, Tumlinson and Proveaux[102] demonstrated that it can be used in different functionalized conjugated dienes in the C_{12} to C_{18} range, as long as the double bonds are not near or conjugated to the functional groups such as aldehydes, alcohols, formates and acetates. Einhorn and coworkers[103] enlarged the series in the C_{12} to C_{16} range. Munson and coworkers[104] concentrated on molecules of smaller molecular weight and formulated rules concerning the type of ions formed. The optimal conditions for the use of methyl vinyl ether have been studied by Jennings and collaborators[95,105,106]. A mixture of methyl vinyl ether (and N_2) has been proposed by Chai and Harrison[107], giving cleaner spectra and well defined adducts. DiMe ether was employed by Keough[108] for the characterization of alkanes and alkenes. Formaldehyde and diethyl ether were found to be less useful. Dichlorocarbene, $:CCl_2$, produced by pyrolysis from sodium trichloroacetate directly in the methane CI source, proved to be a good reagent to determine the geometric configuration of an added unsaturated compound such as stilbene, furmaric and maleic acid (Yang and coworkers[109]). It was found that the *E*-isomer of the alkene formed a more stable *E*-substituted dichlorocyclopropane ion than that of the corresponding *Z*-isomer, which more easily gives fragment ions. Acetonitrile, proposed by Traldi and coworkers[110], has the advantage, that the $[M + CH_2CN]^+$ cation seems to be very stable, independent of the manifold temperature, allowing one to obtain very reproducible results.

Nitric oxide as a reagent gas for the CI has been proposed by Hunt and Harvey[111]. The ions *m*/*z* 30 (NO^+) and *m*/*z* 60 ($[NO \cdot NO]^+$) react with internal olefins and dienes to produce $(M + NO)^+$, M^+ and $(M - 1)^+$. Terminal olefins produce in addition a series of fragments derived from the Markownikoff addition of NO^+ to the olefin linkage. This

system has been studied in detail by Einhorn, Malosse and collaborators: in long-chain alcohols, acetates and aldehydes[112] the double bond assignment is mostly provided by the presence of an acylium ion $C_{x+2}H_{2x+3}O^+$ formed from the alkyl side of the molecule. Similar to isobutane as reagent gas mentioned above, the fragmentation scheme changes when the double bond is located near a functional group. The study has been extended to alkenoic acids, esters and alkenes[113]. The reproducibility of the results is influenced by instrumental conditions. Not only the position of a double bond, but also the location of a cyclopropane ring is possible by this method[114]. However, according to Budzikiewicz and coworkers[115] the reaction of aliphatic double bonds with NO^+ can be governed in a wide range by the remote functional group. This may explain certain discrepancies observed by other authors (compare Traldi[110] cited above). The mechanism of the cleavage of the C=C double bond after the insertion of NO^+ is a complex process, as is demonstrated by Bukovits and Budzikiewicz[116] by deuterium labeling. Homoconjugated dienoic acids do not give characteristic fragmentation patterns with NO^+, as found by Brauner, Budzikiewicz and Francke[117]. Budzikiewicz, Blech and Schneider[118] showed that also the position of the double bond close to the hydrocarbon end of an aliphatic diene functionalized at C(1) can readily be determined by CI with NO^+, but the localization of the other double bond may be difficult owing to low abundance of characteristic fragments.

The use of Fe(I) CI has been explored by Peake and Gross. The authors[60,119] propose the formation of an Fe–olefin (or alkyne) intermediate complex, followed by the insertion of Fe^+ into the allylic C–C bond, followed by β-H transfer to produce bis(olefin) complexes. The collisional-induced spectra allow the determination of the double or triple bond. The procedure has been extended to mixtures of olefins and alkynes, separated by gas chromatography[120,121]. The approach is successful over a 1:10 dynamic concentration range. Hydrocarbons with more than twelve carbon atoms pose problems because of successive fragmentations. Ni and Harrison[122] studied the singly charged transition metal ions from Sc^+ through Cu^+ with six acyclic C_5H_8 isomers. Sc^+, Ti^+ and V^+, produced by FAB ionization of the solid metal chlorides, give distinctly different spectra for all isomers investigated. CI spectra with $MeNH_2$ as reagent gas have been studied by Budzikiewicz, Laufenberg and Brauner[123]. The use of $MeNH_2$ as reagent gas is not limited (as, e.g., i-C_4H_{10} or NO) to straight-chain Z-alkenes. Addition to the double bond occurs also with E-di-, tri- and tetra-substituted and cyclic olefins. Isomers differing in their double bond position do in most cases give distinguishable spectra.

The concept of a charge-remote fragmentation is also useful in the domain of negative ions, especially coupled with collision-induced fragmentations, and contains practical structural information. The loss of C_nH_{2n+2} from the alkyl terminus of unsaturated fatty acid carboxylate anions is such a case, as is demonstrated by Gross and coworkers[61,124]. Even the double bonds in polyunsaturated fatty acids were located by combination of FAB with MS/MS by these authors[62]. Bambagliotti, Traldi and collaborators[125] produce $[M-H]^-$ anions from six C_{18} fatty acid methyl esters CI with OH^- as reagent gas. The positions of chain branching and the double bond are clearly recognized. The collision-induced fragmentation of $[M-H]^-$ ions of isomeric decenyl and dodecenyl acetates were systematically studied by Takeuchi, Weiss and Harrison[126]. With the exception of double bonds in the 3 and 4 positions, the spectra are characteristic for the position of the double bond. This might be another example of the above-mentioned proximity effect of the charged functional end group. Stearic, oleic, linoleic and arachidonic acids have been recorded by Griffiths and coworkers[127], using electrospray ionization and collision of the pseudomolecular $[M-H]^-$ parent ion with Xe, using a new type of combined mass spectrometer. The double bonds are clearly characterized. The collision-induced spectra of hydrogenated cyclic fatty acids, analyzed as their pentafluorobenzyl esters by

Le Quéré and colleagues[128], furnish again characteristic fragmentations. The resonance electron capture furnishes an additional parameter for the analysis of different systems and is studied by Vionov, Elkin and Boguslavskiy[129,130]. The capture of electrons by fatty acids, their methyl esters and pyrrolides takes place in three electron energy regions: *ca* 0 eV, 1–2.5 eV and 7 eV. It was established that at low energy, fatty acids form carboxylate anions and ester carbanions by the loss of an H from C(2). In the high energy region neither of these ions is generated, but the fragment spectra contain the information about the structure of the neutrals[131]. A molecular orbital study for some of the measured ions gives some information about the mechanism[132].

Photodissociation is also used to differentiate among different isomeric alkenes. C_5H_{10}[133] and C_5H_8[134] isomers as examples are detailed in Section V. Photodissociation–photoionization mass spectrometry is used to determine the sites of branching and unsaturation in small (C_5–C_8) aliphatic compounds, as is shown by van Bramer and Johnson[135]. The same group extend this research also to higher olefins[136]. Van der Hart[137] and Tecklenburg and Russell[138] reviewed some aspects of the field up to 1988 and 1989, respectively.

Derivatization, i.e. the transformation of the double bond (or the terminal functional group), can be due to two reasons: Either it substitutes the double bond by a group that is more easily recognizable in the mass spectrometric fragmentation, or/and it makes the transfer into the gas phase easier. The price to pay are additional chemical reactions on the neutral and, coupled with it, probably some loss of sensitivity. An overview of the different possible strategies up to 1987 was presented by Anderegg[139]. A comparison with ^{13}C NMR is given by Schmitquiles, Nicole and Lauer[140]. DiMe disulfide seems to be a very favorable choice. The addition reaction of disulfides to alkenes was studied by Caserio, Fisher and Kim[141]. Francis and Veland[142] worked with alkenes between C_{11} and C_{16}, Bhatt, Ali and Prasad[143] with mixtures of dehydrogenated paraffins between undecenes and tetradecenes, but containing many aromatic compounds, only partly separated by GC-MS. Hexa-, hepta- and octadienes were studied by Pepe and coworkers[144]. Carlson and collaborators[145] derivatized natural and synthetic long-chain alkenes, alkadienes and alkatrienes (C_{25}–C_{37}) and investigated the problem of their separation and identification in mixtures by GC-MS. Attygalle, Jham and Meinwald[146] determined the double-bond position in unsaturated terpenes and other compounds branched at the double bond. In contrast to the spectra of the derivatives containing initially the CH=CH double bond, which show two predominant fragment ions, most of the branched compounds showed only one predominant fragment ion, arising from that part of the molecule which possesses the more substituted carbon of the double bond. A few nanograms furnished already good spectra. Long-chain acetates (C_{11}–C_{18}) were investigated by the groups of Buser[147] and of Vincenti[148]. The double-bond locations in fatty acid esters were determined by Pepe and coworkers[149,150]. The separation and double-bond determination on nanogram quantities of aliphatic mono-unsaturated alcohols, aldehydes and carboxylic acid methyl ester were effectuated by Leonhardt and DeVilbiss[151]. Beside the position of the double bond, also *cis–trans* isomers are distinguished. The use of oxazoline derivatives of unsaturated fatty acid esters is compared (and combined) with an infrared technique by Wahl and coworkers[152]. The infrared spectrum is less sensitive, but allows an easy distinction between *cis*/*trans* isomers. A combination of both techniques seems to be very useful. The same derivatives were use by Řezanka[153] to identify polyunsaturated fatty acids from slime moulds. The derivatization of olefins by cycloaddition of halocarbenes seems to be a promising method, studied by Schlunegger, Schuerch and collaborators[154]; the use of bromofluorocarbene offers some advantages[155]. A flow-chart type procedure of analysis is proposed.

IV. ETHYLENE: AN OLD FAITHFUL

Ethylene is a relatively simple ion that allows measurements and comparison with calculations that are not possible for more complex ions. The ground state configuration of ethylene is $1a_g^2 1b_{1u}^2 2a_g^2 2b_{1u}^2 1b_{3u}^2 3a_g^2 1b_{2g}^2 1b_{2u}^2$. The highest occupied orbital is of the σ_{CC} type and therefore concentrated in the carbon p orbitals. Several electronic levels of ethylene have been determined by Ohno and collaborators[156] by Penning ionization by collision with He* in the 2^3S state. They improved the resolution compared with their earlier work[157] (see also Kimura and colleagues[158]) and measured five bands (in parentheses the orbital character and the state): 10.51 eV (π_{CC}, $1b_{2u}$); 12.85 eV (σ_{CH}, $1b_{2g}$); 14.66 eV (σ_{CC}, $3a_g$); 15.87 eV (σ_{CH}, $1b_{3u}$); 9.10 eV (C_{2s}, $2b_{1u}$). The cross section for the first state decreases with increasing collision energy, indicating that the interaction potential between the He atom and the π-orbital of ethylene is attractive. This could have been expected, since the π-orbital behaves as a Lewis acid to form hydrogen bonds with electron acceptors[159], but the authors put a question mark to this explanation. However, this decrease seems to be a general trend for unsaturated hydrocarbons[157]. The cross section of the other bands increases with increasing collision energy (contrary to the isoelectronic HCHO molecule), which is explained as a repulsive potential between these orbitals and He. Higher energy levels have been determined and compared with theoretical *ab initio* calculations with the help of the Auger spectra up to 64 eV by Liegener[160]. Two of the vibrational levels of ethylene ion and its completely deuterated isotopomer have been reviewed and calculated by Somasundram and Handy[161]. Both are lowered compared to the neutral molecules. *Ab initio* molecular orbital calculations on the 1,2-H shift on ethylene, allene and propyne by van der Hart[162] show that $CH_3CH^{+\bullet}$ is not a stable structure, whereas $CH_2CHCH^{+\bullet}$ obtained from the two other ions is only stable because the ion can relax to a more stable form, which could be described as an allyl cation with one of the terminal hydrogen atoms removed.

The photoelectron–photoion coincidence mass spectrometry has allowed one to elaborate the fragmentation mechanism at the lower energy limit. Stockbauer and Inghram[163] determined the ionization potential (10.517/10.528 eV), the appearance energy for the loss of H/D (13.22/13.41 eV), of H_2/D_2 (13.14/13.24 eV), of 2H/2D (17.86/17.91 eV) and of CH_2/CD_2 (18.04/18.13 eV), where the second energy refers to the deuterated compound. Bombach, Dannacher and Stadelmann[164] calculated the breakdown diagram for energies up to 18 eV and compared it with the experimental values of Stockbauer and Inghram. A very good coincidence was found. Tsuji and collaborators[165] used the charge-transfer reaction from Ar^+ to measure the branching fraction at an energy of 15.76 eV and obtained 4% $C_2H_4^{+\bullet}$, 76% $C_2H_3^+$ and 20% $C_2H_2^{+\bullet}$. The fraction of available energy deposited into internal energy of the ions is estimated to be 85–95%. They obtained similar results for CH_4, C_2H_6, C_3H_6 and C_3H_8, but a much smaller value (38%) for C_2H_2. The Balmer emission of the hydrogen atom from ethylene, ionized by 70-eV electron ionization, allowed Beenakker and de Heer[166] to draw conclusions about the ionization process at this energy. The investigation of the nonresonant multiphoton ionization at two wavelengths (532 nm and 355 nm) allowed Martin and O'Malley[167] to study the fragmentation of acetylene, ethylene, ethane, propene, propane, isobutene and *cis*-2-butene as a function of the laser energy. The values for the bond dissociation energies have been reviewed by Berkowitz and collaborators[168,169]. An experimental and theoretical study of the photoionization of vinyl chloride allowed Li and collaborators[170] to draw conclusions about possible isomeric structures for the polyatomic fragments. The gas phase acidity of ethylene has been determined by Graul and Squires[171] and DePuy, Bierbaum and collaborators[172]. Both groups arrived at an identical value of 1703 ± 4 kJ mol^{-1}.

The isotope effect of the fragmentation of the ethylene ion has been treated experimentally and theoretically by several authors. Gordon, Krige and Reid[173] observed a strong isotope effect and an H/D scrambling for *trans* CHDCHD and C_2HD_3. Hvistendahl and Williams[174] deduced from the isotopic substitution for molecular hydrogen elimination that the two C−H bonds in the transition state must be synchronously stretched. All possible isotopomers of ethylene have been synthesized and studied by Vial, Nenner and Botter for dissociation within the source as a function of the electron energy[175] or in the metastable range[176]. They can explain their results with the quasi-equilibrium theory by allowing for the difference in zero-point energies; no tunneling was needed.

The concentration of doubly charged ions in the 70-eV mass spectrum of ethylene is only *ca* 1% of all ions, making their study difficult. A theoretical investigation of the outer valence doubly ionized states of ethylene was undertaken by Ohrendorf, Sgamellotti and coworkers[177], who showed that the ground state of the dication is nonplanar with a torsional angle of 90°. Auger spectroscopy permitted the authors to determine many double ionization potentials from 29.46 eV up to 47 eV and to attribute the orbitals involved[178]. The ionization and appearance energies of several doubly charged ions of ethylene, difluoroethylene and a few other compounds was the subject of a study of Brehm, Fröbe and Neitzke[179]. For ethylene they measured the following energies: $C_2H_4^{++}$: 31.4 eV; $C_2H_3^{++}$ 35.7 eV; $C_2H_2^{++}$ 36.8 eV; C_2H^{++} 50.1 eV; for difluoroethylene $C_2H_2F_2^{++}$ 28.5 eV; $C_2H_2F^{++}$ 33.4 eV; C_2HF^{++} 35.5 eV; $C_2H_2^{++}$ 42.0 eV; C_2H^{++} 51.8 eV. The dissociation of doubly charged CH_2CD_2 and CH_2CF_2 ions by single photon excitation of the valence electrons with photons of 37 and 75 eV was evaluated by Ibuki and collaborators[180]. The branching ratios for a large number of fragments were determined. It seems that the double ionization releasing at least one π_{CC} electron seems to give a large contribution to the central C=C bond cleavage, while the double ionization of σ_{CC}, σ_{CH} and C_{2s} orbital electrons occurring at photon energies above 37 eV results in bond fission to form two smaller fragment ions. By using OH^+ as projectiles, Griffiths and Harris[181] populated mainly triplet electronic states, thus sorting out the values of 31.4, 34.9, 38.2, 40.3 and 42.9 eV from the large number of values determined or calculated by the authors cited above. A theoretical and experimental study on tetrafluoroethylene dication has been undertaken by Schwarz and coworkers[182]. It is accessible by charge stripping from $C_2F_4^{+\bullet}$. According to the calculations the planar (D_{2h}) form is 15 kJ mol^{-1} more stable than the perpendicular (D_{2d}) isomer, in distinct contrast to the analogous ethylene dication (see above).

Ethylene cation forms easily clusters with neutral ethylene. The question if the ethylene cation preserves its structure in such a polymer or whether it undergoes an 'internal' ion–molecule reaction to form ions of higher molecular weight has found much interest; e.g. Ono and collaborators[183] cited, in 1983, 30 references on the subject without being complete. The basic question is under which conditions does an ion–molecule reaction take place, because the reverse reaction, the loss of an ethylene neutral, is one of the main fragmentations of alkenes, at least in the metastable range (see later). The cluster properties can be regarded from two sides: either the ethylene cation collects its neutrals by some sort of ion–molecule reaction, which demands a minimum pressure that can also collisionally stabilize the freshly formed clusters, or the clusters are preformed, preferentially in a molecular beam, and subsequently ionized. In this case the problem consists of separating the neutral clusters of different size. This can be done by elastically scattering with He and using angular-dependent mass spectra. Buck and collaborators[184] showed that ionization of the neutral dimer yields the fragmentation spectrum of the monomer: the internal energy is redistributed and results in the evaporation of the second ethylene. A small contribution of higher masses than *m/z* 28 is attributed to internal ion–molecule reaction. For trimers

and tetramers again a large probability to form the monomer ion is observed. However, $C_3H_5^+$ and $C_4H_8^{+\bullet}$ are now becoming the prominent ions. The structure of the latter ion forms one of the main problems in this kind of research. It can be concluded that the fragmentation of such clusters is dominated by ion–molecule reaction of a single ionized $C_2H_4^{+\bullet}$ ion within the cluster. In field ionization conditions Beckey and coworkers[3,185] showed that $C_2H_5^+$ is the main reaction product of ethylene. Since the protonation of ethylene cannot be achieved by a field reaction of ethylene ions, the reaction must take place in a physically adsorbed layer.

The current interest in clusters stems from their unique position as an aggregate state of matter between the gas and the condensed phase. Photoionization is probably one of the best methods to investigate the behavior of neutral van der Waal clusters. Ceyer and coworkers[186] chose their expansion conditions in a way to produce mainly the neutral dimer, which is subsequently photoionized by removing an electron from the $1b_{3u}$ (π-bond) of the ethylene, the vibrational fine-structure near the threshold serving as evidence. They determine a well depth of 76 ± 2 kJ mol^{-1} for the dimer and of 18 ± 3 kJ mol^{-1} for the trimer ionic complex. The authors propose structures and energy diagrams for the solvation of the fragments. The molecular beam photoionization method was also used by Tzeng and collaborators to study the behavior of ethylene dimers[183] and trimers[187]. They made the observation that at nozzle expansion conditions, where the trimer and heavier clusters produced in the beam are higher, the appearance energies for the $C_3H_5^+$ and $C_4H_7^+$ fragments from the dimer are shifted from 10.21 ± 0.04 eV and 10.05 ± 0.04 eV, respectively, to lower values, indicating that trimers and tetramers can give rise to the same product ions, confirming earlier values[183]. The ionization energy of the dimer is found to be 9.84 ± 0.04 eV. The group of Sieck and Ausloos[188] photoionized different isotopomers of ethylene containing two D atoms and determined the distribution of the deuterium in the $C_3(H,D)_5^+$ ion as $C_3HD_4^+$ 8%, $C_3H_2D_3^+$ 39%, $C_3H_3D_2^+$ 40% and $C_3H_4D^+$ 11% a nearly random distribution, independent of the initial position of the D atoms. Tzeng and coworkers[187] observed several fragmentation pathways for the trimer, yielding the following product ions: $C_3H_6^+$, $C_3H_7^+$, $C_4H_7^+$, $C_4H_8^{+\bullet}$, $C_5H_9^+$ and $C_6H_{11}^+$. The fact that these channels are similar to those observed in the unimolecular decomposition of $(C_3H_6)_2^+$ and $(c\text{-}C_3H_6)_2^+$ is consistent with the interpretation that these loose complexes rearrange to similar stable $C_6H_{12}^+$ ions prior to fragmenting. The ionization energies of the trimer and the tetramer were determined as 9.46 ± 0.04 and 9.29 ± 0.03 eV and the binding energies for successive ethylene units for $(C_2H_4)_2^+ - C_2H_4$ and $(C_2H_4)_3^+ - C_2H_4$ as 38 ± 4 and 19 ± 4 kJ mol^{-1}, respectively. The precision of some of these values has been questioned by Baer and collaborators[189] because of the gradual onset of the photoionization efficiency curves. Meisels and coworkers[190] stated that the angular momentum can have an influence in ion–molecule reactions and can affect the branching ratios when the products are selected by an angle-sensitive method. Electron ionization is used by the group of Garvey[191] to investigate clusters of ethylene, 1,1-difluoroethylene and propene as a function of expansion and ionization conditions. For ethylene and difluoroethylene, a peaking is observed for clusters containing four molecules. For propene, it changes from three to four and then to six, with increasing expansion pressure and lowering of the electron energy. This is explained by intracluster ion–molecule reactions, i.e. the formation of covalent bonds between the single units.

The structures and isomerization of $C_4H_8^{+\bullet}$ ions in connection with the problem of ethylene clusters has been the subject of many studies. Doepker and Ausloos[192] studied the photolysis of cyclobutane, its deuterated isotopomer and mixtures thereof, and in their detailed product analysis they found *cis*-2-butene, *trans*-2-butene and 1-butene as major ionic products in the approximate ratio of 1:1:2. Lias and Ausloos[193] determined

by product analysis that at low pressures the $C_4H_8^{+\bullet}$ ions which are initially formed in ethylene, cyclobutane and methylcyclopropane isomerize to the thermodynamically most stable configurations, namely *i*-butene$^{+\bullet}$ and 2-butene$^{+\bullet}$, with the latter structure predominating. At higher pressures, 1-butene$^{+\bullet}$ could be intercepted, indicating a complex isomerization scheme. In a later work, the same group[194] studied these isomerizations in detail. They stated that to supplement mass spectrometric studies by photochemical (and possibly radiolytical) experiments can often help to simplify a complex situation. Jungwirth and Bally[195,196] summarized the situation up to 1992 and studied the reaction of ethylene and its radical cation theoretically by *ab initio* methods. Their calculated binding energy for the dimer compares favorably with the above-mentioned value. They locate two transition states, one leading to cyclobutane and the other to 1-butene cations, thus confirming the observations of the Ausloos group. 1-Butene$^{+\bullet}$ can either dissociate or isomerize to 2-butene$^{+\bullet}$. Booze, Feinberg, Keister and Baer[189] investigated in detail the dissociative ionization of ethylene dimers, trimers and tetramers by a photoelectron photoion coincidence technique using a time-of-flight spectrometer that allowed one to study the metastable decay of the ions. They showed that the neutral ethylene dimer can be photoionized to produce a stable $C_4H_8^{+\bullet}$ ion, contrary to trimers and tetramers, and that the dissociation starts from the 2-butene$^{+\bullet}$ structure. The dissociative ionization step for trimers and tetramers involves the evaporation of an ethylene monomer with the remaining $C_nH_{2n}^{+\bullet}$ ion being a straight-chain olefin.

Ion–molecule reactions of the ethylene cation in the gas phase are of interest, because polymerization chain reactions set in at higher pressures. However, already Wexler and Marshall[197] demonstrated that fragmentation products are mainly responsible for these secondary reactions under electron impact. Myher and Harrison[198] and Tiernan and Futrell[199] discussed these reactions in detail and tried to distinguish between secondary and tertiary reactions. Henis proposed[200] intermediate structures. Sieck and Ausloos[201] measured the rate coefficients for the disappearance of the ethylene cation as a function of the photon energy used to ionize the neutral. The rate decreases with increasing energy. The dependence of the rate on deuteration and kinetic energy of the ions was determined by Huntress[202] who gave a summary of the rate constants obtained for ionization by electrons and photons up to 1977[203] with the following product distributions (average values; ΔH_r in kJ mol^{-1}):

$$C_2H_4^{+\bullet} + C_2H_4 \longrightarrow C_3H_4^{+\bullet} + CH_4 \qquad (1\%; -3) \qquad (1)$$

$$C_2H_4^{+\bullet} + C_2H_4 \longrightarrow C_3H_5^{+} + CH_3 \qquad (90\%; -17) \qquad (2)$$

$$C_2H_4^{+\bullet} + C_2H_4 \longrightarrow C_4H_6^{+\bullet} + H_2 \qquad (0.2\%; -29) \qquad (3)$$

$$C_2H_4^{+\bullet} + C_2H_4 \longrightarrow C_4H_7^{+} + H\bullet \qquad (9\%; -11) \qquad (4)$$

$$C_2H_4^{+\bullet} + C_2H_6 \longrightarrow C_3H_6^{+\bullet} + CH_4 \qquad (7\%; -22) \qquad (5)$$

$$C_2H_4^{+\bullet} + C_2H_6 \longrightarrow C_3H_7^{+} + CH_3\bullet \qquad (93\%; -9) \qquad (6)$$

There is strong disagreement concerning the product distribution with C_2H_6 between these authors and Dunbar and collaborators[204]. The reason is not clear, but is probably due to impurities. This list has been enlarged by Lindinger, Ferguson and coworkers[205] for reactions of interstellar interest, in particular with H·. Bowers and collaborators[206] performed a study on different ion–molecule reactions of interest in interstellar clouds. CH_3^+ associates with methanol to yield $MeOHMe^+$; H_3O^+ and C_2H_4 yield $CH_3CH_2OH_2^+$ while NH_4^+ and C_2H_4 give $CH_3CH_2NH_3^+$. They conclude that CH_3^+ infrared radiative association should not contribute to the formation of $C_2H_5O^+$, $C_2H_7O^+$ and $C_2H_8N^+$

ions in interstellar clouds, but reactions with H_3O^+ and NH_4^+ may well do. It is interesting to realize that Cao, George and Holmes[207] tried a reverse experiment: but they failed to produce evidence of an involvement of the complex ions $[C_2H_4^{+\bullet}/HOCH_3]$ and $[C_2H_4^{+\bullet}/HOC_2H_5]$ in a variety of $C_3H_8O^{+\bullet}$ and $C_4H_{10}O^{+\bullet}$ isomeric ions. McAdoo and collaborators[208] compared the energy dependence of H-exchange vs C−C bond formation in the complex $[C_2H_4^{+\bullet}/HOCH_3]$. They came to the conclusion that a distonic $[CH_3OH^+ C_2H_4\bullet]$ isomerizes to $CH_3CH_2CH_2OH^{+\bullet}$ via the internal ion–molecule reaction:

$$[C_2H_4^{+\bullet}/HOCH_3] \longrightarrow [C_2H_5^{\bullet\ +}HOCH_2] \tag{7}$$

followed by C−C bond formation. About 60 kJ mol^{-1} higher (attained by CID and reaction of $C_2H_4^{+\bullet}$ with methanol) $CH_2{=}OH^+$ and $CH_3OH_2^+$ are formed. Hydrogen exchange between oxygen and ethylene occurs at this energy. Jung and coworkers[209,210] studied the electron impact ionization of ethylene–methanol clusters and looked for stable configurations. It seems that $(C_2H_4)_n(CH_3OH)_mH^+$ ions with $n + m \leqslant 3$ have a particularly stable structure, again interpreted as the result of intracluster ion–molecule reactions. The probability for protonation, expressed as the ratio $[(C_2H_4)_n(CH_3OH)_mH^+]/[(C_2H_4)_n(CH_3OH)_m^+]$, increases with increasing ethylene/methanol mixing ratio, indicating that the proton is preferentially bound to methanol. The occurrence of H/D within the cluster is also studied.

The reactions of ethylenes substituted with fluorine and chlorine were determined by Anicich, Bowers and coworkers[211–216]. Su and collaborators[217] tested several reactions of fluoroalkyl radical anions with C_2F_4:

$$CF_3^- + C_2F_4 \longrightarrow C_2F_5^- + CF_2 \quad (3.4\times10^{-10}\ \text{cm}^3\ \text{molecule}^{-1}\text{s}^{-1};\ -8.8\ \text{kJ mol}^{-1}) \tag{8}$$

$$C_2F_5^-, C_3F_7^-, C_4F_9^- \longrightarrow \text{no reaction} \tag{9}$$

The reactions of CH_5^+ with ethylene, C_2H_2, C_3H_6 and *c*-C_3H_6 have been measured by Fiaux, Smith and Futrell[218] in a tandem mass spectrometer. The total rates of reaction are independent of the excitation energy of CH_5^+. Isotope labeling studies suggest that reaction occurs by simple proton transfer to the neutral species which — if energetically feasible — undergoes fragmentation. This study was enlarged by the same authors[219] to cover the reactions of CH_3^+, $C_2H_5^+$, $C_3H_5^+$ and $C_3H_7^+$ with C_2, C_3 and C_4 hydrocarbons. Again the internal energy of the reactants was varied and the effect of deuteration studied. Most of the major reaction channels are best described as proceeding through a short-lived intermediate complex. The reactions of $C_2H_5^+$ with propene and cyclopropene are particularly interesting since the major reaction product, $C_4H_9^+$, is produced through both direct proton transfer and complex formation. Abernathy and Lampe[220] performed a similar study of the reaction of CH_3^+ with C_2H_4. No $C_3H_7^+$ is observed, but isotopic variants of the reaction using C_2D_4 and $^{13}CH_3^+$ as reactants strongly suggest that the reaction proceeds via $(CH_3)_2CH^+$ and $(c\text{-}C_3H_6)H^+$ intermediates of short lifetimes.

The ion–molecule reactions of CF_3^+ with C_2H_2, C_2H_4 and C_3H_6 have been studied at near-thermal energy. The following reactions are found (in parentheses, the branching ratios):

$$CF_3^+ + C_2H_2 \longrightarrow C_3H_2F_3^+ \qquad (100\%) \tag{10}$$

$$CF_3^+ + C_2H_4 \longrightarrow C_3H_3F_2^+ + HF \qquad (62\%) \tag{11}$$

$$CF_3^+ + C_2H_4 \longrightarrow C_3H_3^+ + CF_3H + 0.35\ \text{eV} \qquad (29\%) \tag{12}$$

$$CF_3^+ + C_2H_4 \longrightarrow CHF_2^+ + C_3H_3F \qquad (7\%) \tag{13}$$

$$CF_3^+ + C_2H_4 \longrightarrow CH_2F^+ + C_2H_2F_2 \qquad (2\%) \tag{14}$$

$$CF_3^+ + C_3H_6 \longrightarrow C_2H_4F^+ + C_2H_2F_2 + 1.1\ \text{eV} \qquad (58\%) \tag{15}$$

$$CF_3^+ + C_3H_6 \longrightarrow C_2H_5F_2^+ + HF \qquad (26\%) \tag{16}$$

$$CF_3^+ + C_3H_6 \longrightarrow C_4H_4F^+ + 2HF \qquad (9\%) \tag{17}$$

$$CF_3^+ + C_3H_6 \longrightarrow C_3H_5^+ + CF_3H + 1.7\ \text{eV} \qquad (7\%) \tag{18}$$

Several reaction schemes and intermediate structures are proposed. Similar distributions are found by Morris and coworkers[221], who studied in addition also the reactions of CF_2Br^+. Their intention was to check if ion–molecule reactions of the fire suppressant Halon 1301 in hydrocarbon flames could produce free radicals that could interfere with pyrolytic processes in flames, but no evidence is to be found. Stanney and collaborators[222] also detected large amounts of CHF_2^+ and CH_2F^+ in their beam experiments. The possibility of the collisional deactivation of some long-lived intermediates leading to these two ions cannot be ruled out. Ion–molecule reactions in vinyl chloride are rather complex. A summary has been given by Herman, Herman and McMahon[223]. They suggest on the basis of collision-induced dissociation mass spectra a 'butadiene-like' structure for the product ions $C_4H_5Cl^{+\bullet}$ and $C_4H_6Cl^+$, and a nonbenzenium structure for $C_6H_7^+$, formed in a two-step mechanism involving $C_4H_5^+$ as an intermediate ion. El-Shall and Schriver[224] constructed a reaction scheme for the clustering of vinyl chloride that goes up to seven C_2H_3Cl units. Five types of reactions are distinguished: addition of C_2H_3Cl, addition + elimination of HCl, addition + elimination of Cl_2, loss of HCl, loss of Cl·. Gable and collaborators[225] performed the gas-phase ionization of ethylene with positive ions generated from molecular I_2. They assign to *m/z* 155 the only ion formed, an iodiranium structure. No H/D scrambling, but an isotope effect of 1.41 ± 0.02, is observed in a C_2H_4/C_2D_4 mixture.

Gross and coworkers[226] formed the β-distonic ion from the reaction of pyridine radical action and ethylene and studied its collision-induced fragmentation that is different from the isomeric ethylpyridine ion. The reactive site of attachment of C_2H_4 is the nitrogen atom of pyridine, giving rise to the β-distonic ion adduct $C_5H_5N^+–CH_2C^{\bullet}H_2$, which can be differentiated from the α-distonic ion $C_5H_5N^+–C^{\bullet}HCH_3$. It is of interest in this connection that Bally, Roth and Straub[227] observed and defined spectroscopically the π-complex benzene–ethylene cation radical with a strong absorption band at 680 nm. Schwarz and coworkers[228] performed an *ab initio* calculation of the reaction between ketene radical cation and ethylene. They propose that this reaction should not be classified as a cycloaddition, but rather as a nucleophilic addition of ethylene to the ketene ion. $CO_2^{+\bullet}$ reacts with CH_4, C_2H_n ($n = 2, 4, 6$) and C_3H_n ($n = 6, 8$) as has been demonstrated by Tsuji and coworkers[229]. The product ion distributions and rate constants are determined. Except for methane, only charge-transfer channels leading to parent ions and/or fragment ions thereof are found. All rate constants are a little smaller than the calculated values from Langevin's theory. The reactions of the disilicon carbide $Si_2C_2^+$ with benzene and unsaturated hydrocarbons was the subject of work by Parent[230]. The C_3H_4 isomers appear to react by insertion into the single bond. The reaction sequence with ethylene seems to be rather simple:

$$Si_2C_2^+ + C_2H_4 \longrightarrow Si_2C_2H_2^+ + C_2H_2 \tag{19}$$

$$Si_2C_2H_2^+ + C_2H_4 \longrightarrow Si_2C_4H_5^+ + H\cdot \tag{20}$$

However, labeling the carbide ion with $^{13}C_2$ reveals a complexity that is hidden in the reaction sequence. 16% of the reactant ions in equation 19 undergo carbon exchange in a

statistical 4:1 ratio. It seems that an intermediate complex $Si_2C_4H_4^+$ is formed, where all C atoms are in equivalent positions. Lindinger and collaborators[231] studied the reaction of Si^+ in the ^2P ground state with ethylene. $SiC_2H_3^+$ and $SiC_2H_4^+$ are observed in the pressure range from 0.14 to 0.52 Torr in a drift tube. In this pressure range these products are formed in binary and ternary reactions. The pressure dependence led the authors to propose that both the binary and the ternary channels are proceeding via the same rate-determining process before they separate into two channels.

V. THE PENTENE STORY

Duffy, Keister and Baer[232] published under the above-mentioned title a study where they discuss the competition between isomerization and dissociation, seen by photoelectron–photoion coincidence. $C_5H_{10}^{+\bullet}$ has many isomers and the problem, whether they are distinct isomers or whether they fragment from a common intermediate ion, has generated much interest. Millard and Shaw[233] came to the conclusion that C_2H_4 is mainly lost from the unsaturated end of 1-pentene. Doepker and Ausloos[192] studied the ion–molecular reactions of cyclo-$C_5D_{10}^{+\bullet}$ and its main fragment $C_3D_6^{+\bullet}$ both in mass spectrometry and in radiolysis. They were particularly interested in the ratio of H^- and H_2^- transfer from alkanes of different structure. Their conclusion is that at a pressure of 20 Torr, *ca* 20% of the parent ions undergo ring-opening prior to the charge-transfer process to NO or $(Me)_3N$. Gross and Wilkins[234] use an ICR mass spectrometer to determine the ionization potentials and the appearance energies for the main fragments $[M - Me]^{+\bullet}$ and $[M-C_2H_4]^{+\bullet}$ for seven $C_5H_{10}^{+\bullet}$ isomers. Their main purpose was to demonstrate the feasibility and the advantages of a computer-coupled instrument. In a later publication Gross and coworkers[235] use the possibilities of this instrumental method to distinguish among the different neutral isomers by the reactions of the C_5H_{10} isomers with the 1,3-butadiene radical cation. All isomers undergo characteristic ion–molecule reactions except 2-Me-2-butene, where only charge transfer is observed, and cyclopentane, where no reaction is observed. Koyano, Suzuki and Tanaka[236] studied the ion–molecule reactions of the parent ions of five isomeric pentenes and cyclopentene with their corresponding neutral molecules at 1.7 eV exit energy using a photoionization mass spectrometer. 1-Pentene is the most and 3-Me-butene-1 and 2-Me-butene-2 the least reactive parent ions, confirming earlier conclusions by Henis[200,237] that, with the exception of 2-Me-butene-2, no rearrangement occurs before fragmentation. Dimeric ions were detected in all systems.

According to Bowen and Williams[238] the metastable fragmentations of olefin ions are largely determined by the relative energetics of the possible product combinations. They derive rules from C_{2-}, C_{3-}, C_{4-} and C_6-olefins, which they apply successfully to predict fragmentations of $C_5H_{10}^{+\bullet}$ isomers. In particular, they reach the very important conclusion that for the ions $C_nH_{2n}^{+\bullet}$ up to $n = 5$ the different isomers should behave very similarly, whereas for $n > 5$ the fragmentation of isomers should become increasingly divergent with n increasing. This parallels somehow the observation of Gäumann[239] for alkyl radicals. In either case a well-founded explanation for this behavior is missing. The advent of collisionally activated fragmentation led Nishishita and McLafferty[240] to test this possibility to differentiate between isomers of pentene and hexene molecular ions. They confirmed the above-mentioned observations by realizing that the decomposition of the (metastable) ions of the pentenes were nearly identical, but those of the hexenes showed some differences. Levsen and Heimbrecht[241], using the same technique, reached the same conclusion. Again an onset of nonisomerization was noted at $n = 6$. However, this is not true when the time-scale is shortened to nano- and picoseconds by field-ionization kinetics (FIK). In this time domain, explored by Levsen and collegues[64], even isomeric butenes

are clearly distinguishable at short fragmentation times. In 1-pentene the most important fragment loss is that of $C_2H_5^{\bullet}$ (≡100), followed by $-C_2H_4$ (=65) and $-Me^{\bullet}$ (=23), whereas for 2-pentene the main fragmentation is $-Me^{\bullet}$ (≡100), some $-C_2H_4$ (=15) and no loss of ethyl. Thus the double bond retains its original location up to *ca* 100 ps. The fragmentation of saturated cycloalkanes is compared with that of alkenes of the same composition by van Dishoeck, van Velzen and van der Hart[242,243]. Photoionization and charge transfer allow the conclusion that cyclobutane and cyclopentane rings open upon ionization, whereas cyclohexane and cycloheptane remain cyclic. Alkenes form two isomeric molecular ions with strongly different reactivity in ionization and photodissociation spectra. 1- and 2-pentene are also studied by Herman, Podgórtsky and Lalonde[244] using photoionized ions for ion–molecule reactions with their neutrals. With increasing pressure (up to 3 Torr) the reaction sequences are getting complicated by the presence of many condensed species, up to $(C_5H_{10})_4^{+\bullet}$, confirming earlier results by the group of Koyano[236] cited above. 1-Pentene is more reactive; 70% of the total intensity at 3 Torr is accounted for by the formation of $C_8H_{15}^{+}$ and $C_8H_{14}^{+\bullet}$, ions that are unreactive toward the neutral parent. The clusters for 2-pentene are smaller in size and less reactive. Lunell and coworkers[245] studied the electronic ground state of 1- and 2-pentene by *ab initio* calculations at high levels, together with the ESR spectra, recorded in halocarbon matrices at low temperatures. The 1-pentene radical cation is described as a rigid, nonplanar structure where the two terminal aliphatic carbons are rotated out of the plane. The singly occupied highest molecular orbital is found to be partially delocalized over the whole allylic fragment, contrary to 2-pentene, where a localized π-bond ionization is present, as one would expect in an alkene radical ion. Miller and Gross[246] tried to distinguish ten different $C_5H_{10}^{+\bullet}$ isomers by CID, charge stripping and low-energy ion–molecule reactions. For the latter, beside a proton transfer from NH_4^{+}, the formation of the immonium ion $CH_3CH{=}NH_2^{+}$ through a reactive collision is also observed. According to these authors, cyclopentane, Me-cyclobutane and substituted cyclopropanes retain their cyclic structure for at least a few μs. Charge stripping proved to be the best method to distinguish all isomers, CID and ion–molecule reactions being less informative. The positive results of the charge-stripping method are not confirmed by Sozzi, Audier and Milliet[247] nor by Holmes and coworkers[248]. It might be that the instrumental conditions are rather critical. The latter authors are, however, able to suggest by charge-stripping and appearance energy measurements that pentan-1-ol and 1-chloropentane form ethylcyclopropane when losing H_2O or HCl, respectively. Ingemann, Nibbering and coworkers[249,250] studied under ICR conditions in detail the formation of the immonium ion $CH_3CH{=}NH_2^{+}$ mentioned above. Only proton transfer to ammonia is observed for $[4\text{-octene}]^{+\bullet}$, $[2\text{-nonene}]^{+\bullet}$ and $[4\text{-decene}]^{+\bullet}$, leading to the conclusion that the intramolecular hydrogen transfer preventing the immediate dissociation of the collision complex is not sufficiently rapid. Reaction of $[1\text{-hexene}]^{+\bullet}$ with ND_3 leads to the incorporation of up to ten D atoms in the hexene ion. Nonterminal alkenes do not undergo H/D exchange; thus, this exchange could be used for an estimation of the presence of alkenes with a terminal double bond.

Brand and Baer[133] studied the dissociation dynamics of six isomeric energy-selected $C_5H_{10}^{+\bullet}$ ions in a first publication using the photoelectron–photoion coincidence method. With the exception of 2-Me-2-butene all parent ions exhibit a two-component decay, indicating a dissociation from at least two distinct forms of the molecular ion. This is interpreted as a competition between the fragmentation of the original structure of the parent ion and an isomerization to a common intermediate, identified as 2-Me-2-butene, the ion with the lowest ΔH_f. In a later study Baer and collaborators[232] repeated this work, but this time using a molecular beam to cool the isomers before ionization, arriving at a vibrational temperature of 180 K. By this procedure, multicomponent rates are well resolved. All parent ions decompose by loosing $Me^{\bullet}$ and C_2H_4 in different proportions.

Six rate constants are measured, namely for isomerizations and two dissociation rates, and fitted by RRKM theory. The rate constants for the direct dissociation (of the original ion) are too fast to be determined by this method. In all cases, the slowest rates correspond again to the fragmentation of 2-Me-2-butene ion. The metastable time range is around a few μs, whereas the infrared photodissociation in an ICR instrument takes place between ten milliseconds and one second. The fragmentations of cyclopentane and six pentene isomers are compared for these time windows by Bensimon, Rapin and Gäumann[251]. All $C_5H_{10}^{+\bullet}$ ions fragment similarly (2-Me-2-butene and cyclopentane showing slight deviations), but different in the different times scales (metastable/infrared): $[MCH_3^{\bullet}]^+$: 76%/70%; $[M-CH_4]^{+\bullet}$: 3%/19%; $[M-C_2H_4]^{+\bullet}$: 19%; $[M-C_2H_5]^+$: 2%/0%. Apparently a small evolution, i.e. stabilization of the final structure, is still visible over this time range. This is no more true for the $C_6H_{12}^{+\bullet}$ and even less for $C_7H_{14}^{+\bullet}$ ions.

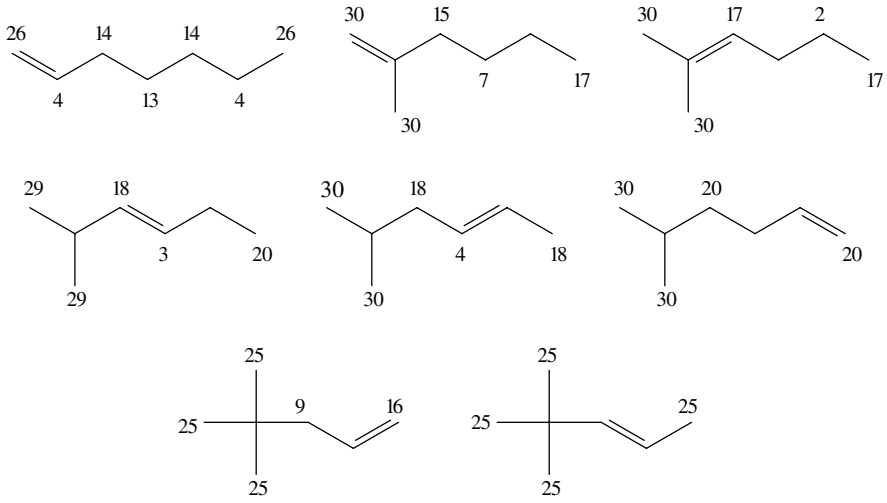
Van Bramer and Johnston[135,136] use a totally different scheme to identify alkene isomers: the neutral molecules are first photodissociated with an ultraviolet laser and the resulting fragments subsequently ionized with coherent ultraviolet radiation. 14 isomeric alkenes of five to eight carbon atoms and four isomeric hexadienes were tested. The primary and secondary product distributions are predictable and usually occur without isomerization, allowing one to use the method to determine the sites of branching and unsaturation in aliphatic hydrocarbons. The main photodissociation reaction is the cleavage of the β-C−C bond in the neutral. Products of α- or γ-cleavage are typically less than 20% as abundant. Secondary fragmentations occur as well in the neutral as in the fragment ions. Usypchuk, Harrison and Wang[252] studied the possibility of the ion−molecule reaction of $CH_3NH_2^{+\bullet}$ with isomeric butenes and pentenes to distinguish different structures; it is moderately successful, since in many cases only charge exchange is being observed. Also, Vollmer and Gross[253] used the reverse way to study $C_5H_{10}^{+\bullet}$ ions: the gas-phase reaction of propene and cyclopropane with ethylene. They find an efficiency of one out of five collisions to produce 2-Me-2-butene as a final product, formed over ethylcyclopropane as an intermediate, defined by its charge-stripping spectrum. It is probably fair to summarize this story by saying that isomeric pentenes can be characterized by different methods, that they fragment initially characteristically for the structure of the neutral, but isomerize rather rapidly to the most stable isomer, 2-Me-2-butene, the dissociation of which depends on its internal energy, i.e. changing somewhat over the whole time range available in mass spectrometers.

VI. HEPTENE: THE OTHER STORY

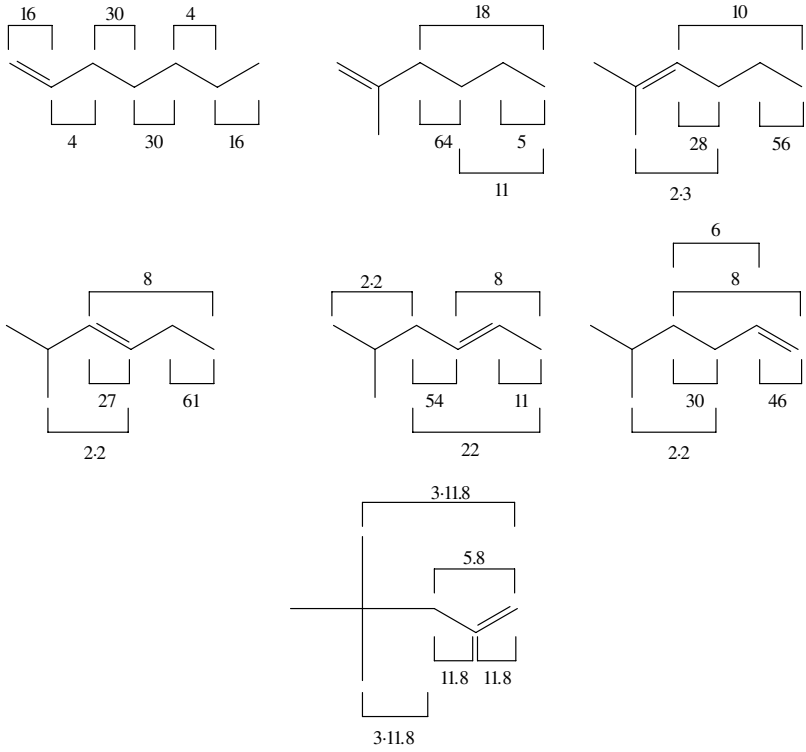
The story of the heptenes is partially reviewed by Gäumann[239]. Stefani[254] was probably the first author to realize that the fragmentations of $C_7H_{14}^{+\bullet}$ might present some surprises. While measuring the electron impact spectra of three specifically deuterated 2,4-diMe-1-pentenes at 70 eV and at low voltages, he realized that the loss of C_3H_6 by a McLafferty rearrangement was not only a fragmentation that occurred with little or no H/D scrambling, but that the C_2H_4 seemed to originate from positions 3 and 5 coupled with a transfer of an H atom from position 5 to another, unknown position, again without much scrambling. Houriet and Gäumann[255] studied the CI of linear alkenes with six to nine carbon atoms using CD_4, D_2O, CD_3OD as reagent gas and realized a pronounced scrambling in the alkyl ions formed. This research has been enlarged by using ^{13}C- and D-labeled heptenes by Parisod and Gäumann[256]. The protonation of 1-heptene by CH_5^+ appears not to occur solely at the first carbon of the chain or scrambling takes place. The peculiarity of the scrambling of alkyl radicals has been discussed in detail elsewhere[239]. The competing metastable decompositions of 14 isomeric $C_7H_{14}^{+\bullet}$ ions is compared by Falick, Tecon and Gäumann[257] and confirmed by Harrison and Li[258]. The most important metastable

losses are either $Me^{\bullet}$ or C_2H_4; however, it is concluded that the molecular ions of these compounds probably do not isomerize to a common structure prior to metastable decay. The presence of a terminal bond strongly enhances the metastable loss of C_2H_4; the presence of a 2-Me substituent favors this reaction. The metastable decomposition of labeled 1-heptene and 5-Me-1-hexene has been studied in detail by Antunes Marques, Stahl and Gäumann[259]. Part of the results are shown in Schemes 1 and 2.

Falick and Gäumann[260] undertook a study on source and metastable fragmentations of 1-heptene where all positions were partially multiply-labeled with ^{13}C and/or D. Loss of $Me^{\bullet}$ and $C_2H_5^{\bullet}$ occurs mainly from the two ends of the molecule, loss of C_2H_4 partly from positions 1 and 2, but also from any other position, coupled with some H/D scrambling (see Schemes 1 and 2 for the metastable fragmentations). Bowen and Williams[238] and Levsen and Heimbrecht[241] realized that the tendency to isomerize to a common structure diminishes with increasing size of the olefin (see above). Levsen and coworkers[64] show that for heptenes also the fragmentation in the FI range is very structure-specific. Tecon, Stahl and Gäumann[261,262] examined the time dependence of the fragmentation of 1-heptene. Below 0.1 ns, 80% of C_2H_4 is lost from positions $1 + 2$, decreasing to 55% and 22% for ionization within the source with 17-eV and 10-eV electrons, respectively. In the metastable range this value decreases to 17%[259]. The values for the losses from positions $6 + 7$ do not exceed 10–15%, since at longer times the majority of the ethylene is eliminated from inside the chain. The effect is similar, but less accentuated, for the loss of $C_3H_5^{\bullet}$. At short fragmentation times C_2H_5 elimination occurs from the saturated end, but again mixing sets in at longer times. It is evident that fragmentations in the short time window, i.e. at high internal energies, correspond to a simple C–C cleavage. When the internal energy is lower, an internal elimination of ethylene, possibly coupled with a shift of the double bond position, sets in. However, no skeletal isomerization, but H/D scrambling, is perceived, since only accompanying positions are lost as C_2H_4. Gäumann and collaborators[255–257,259–268] started work on the fragmentation of branched $C_7H_{14}^{+\bullet}$, labeled in all positions with one or several ^{13}C and D. Some of the results for the metastable decay — partly unpublished — are shown in Schemes 1 and 2. The fragmentation of labeled 2-Me-1-hexene in the time range



SCHEME 1. Positional loss of CH_3. Probability in %



SCHEME 2. Positional loss of C_2H_4. Probability in %

between 10 ps and the metastable range was measured by Gäumann and coworkers[263]; they compared also its CID spectrum with the spectrum of 2-Me-2-hexene. No shift of the double bond to the more stable 2-position was noticeable except in the metastable time range, but even at the shortest observed fragmentation times (10 ps) the Me- and the 1-position are identical. The charge-exchange spectra and the break-down graphs were measured by Harrison and coworkers[258,269]. These charge-exchange spectra, measured with $14\,C_7H_{14}{}^{+\bullet}$ ions, complement in many respects the results obtained with labeled compounds. Multiply labeled 1-heptenes formed the bases of a publication by Tecon, Stahl and Gäumann[265]. If most of the fragmentation can be explained by a shift of the double bond, the loss of ethylene that is mainly expelled from the interior of the ion (see Scheme 2) remains unexplained. A particularly interesting ion is 4,4-diMe-1-pentene, studied *in extenso* by Falick, Tecon and Gäumann[264,266]. The loss of Me is for fragmentation almost exclusively from positions 5; positions 1 and 4 gain in importance in the metastable time window. The loss of C_2H_4 is rather complex for fragmentation within the source, but gets surprisingly simple — but hard to understand — in the metastable range: a CH_2 group from position 1 or 3 is eliminated with exactly equal probability from positions 2 or 5 and with half the probability from position 3 or 1, respectively. The time scale for fragmentation of heptenes was enlarged by Bensimon, Rapin and Gäumann[251,268] using excitation of long-lived ions by infrared photons in an ICR instrument. The structure of the molecular ion after *ca* 100 ms could thus be probed. Beside a dependence of the infrared photodissociation spectrum that is structure-dependent, less fragments than in the

metastable decay are seen. Betts, Park and Schweikert[270] used plasma desorption mass spectrometry to study, among other compounds, the fragmentation of 1-heptene. Dimeric and trimeric ions are also seen, but not enough data are known to judge whether this technique gives additional information about specific reactions beside its use as a general analytic method. The situation may be summarized as follows: (i) linear heptenes may isomerize, since at short fragmentation time neutrals are expelled from different positions; (ii) for linear heptenes and 1-Me-2- and 2-Me-2-hexene the double bond is shifted, at least after 1 μs; (iii) most $C_7H_{14}^{+\bullet}$ ions loose their neutral fragments in a characteristic, but so far unexplained way; (iv) there is no evidence for a general isomerization to a common — minimum energy — structure.

Doubly charged ions of 1-heptene were observed in its field ionization mass spectrum by Tecon, Stahl and Gäumann[267]. By using ^{13}C-labeled compounds they were able to prove that these ions are formed in an absorption process on the emitter surface, partly by ion–molecule reactions.

VII. ALKENES: TO FILL SOME GAPS

Methods to distinguish different $C_3H_6^{+\bullet}$ have been sought since the beginning of organic mass spectrometry. One possibility consists of ion–molecule reactions. Sieck and Ausloos[201] used photoionization to study the effect of internal energy on the bimolecular reactions of propene and cyclopropane with their neutrals. The latter react much slower. Bowers and coworkers[271] proposed a four-center mechanism for the formation of the dimers of the two isomers with their neutrals, making use of specifically deuterated compounds. The results for the ethylene loss from the dimer can be predicted with the quasi-equilibrium theory. Gross and McLafferty[272] noted distinct variations in both the rate and modes of reaction of $C_3H_6^{+\bullet}$ ions formed by ionization of propylene and cyclopropane. Sieck, Gordon and Ausloos[273] presented evidence that ring-opening of the cyclopropane ion depends on the internal energy content of the ion, an observation confirmed by a photoionization study by van Velzen and van der Hart[243]. Barbalas, Tureček and McLafferty[274] ascertained the observation by Maccoll and Mathur[275] that 1-chloropropane forms exclusively cyclopropane when losing HCl, but the authors demonstrated that HCl elimination from 2-chloropropane yields cyclopropane and propene as well. Other precursors were also studied by CID. Gross[276], producing labeled $C_3(H,D)_6^{+\bullet}$ ions from tetrahydrofuran, concludes that a cyclic structure is being formed; however, he cannot rule out a ring opening before the following reaction with ammonia:

$$C_3H_6^{+\bullet} + NH_3 \longrightarrow {\bullet}CH_2NH_3^+ + C_2H_4 \qquad (21)$$

$$C_3H_6^{+\bullet} + NH_3 \longrightarrow CH_2NH_2^+ + C_2H_5{\cdot} \qquad (22)$$

This reaction has been discussed in detail by Sack, Cerny and Gross[277]. Lias and Buckley[278] generated $C_3H_6^{+\bullet}$ ions by charge transfer to cyclopropane from several ions, thus producing $C_3H_6^{+\bullet}$ ions with different internal energy. In addition to the characteristic reactions (equations 21 and 22) with ammonia, they observed for ions that are produced with zero internal energy a proton transfer to ammonia. *c*-$C_3H_6^{+\bullet}$ reacts with PH_3 to give $CH_2PH_3^{+\bullet}$ and PH_4^+ as products. Rusli and Schwarz[279] demonstrated that the $C_3H_6^{+\bullet}$ ions produced either from cyclopropane or from tetrahydrofuran consist, under their experimental conditions, of a mixture of 80% propene and 20% cyclopropane ions. Morgues, Hammerum and coworkers[280] came to the conclusion that the ring-opening reaction of $C_3H_6^{+\bullet}$ ions produced from cyclopropane is slower than the hydrogen exchange between propene and D_2O on the time scale of an ICR mass spectrometer.

McLafferty, Barbalas and Tureček[281] exclude a low isomerization barrier on the grounds of their collisionally activated dissociation data. They propose that the observed (low energy) isomerizations in ion–molecule reactions should be explained by an intermediate association product. They showed also that the reactions of cyclopropane$^{+\bullet}$ with methanol resemble its reaction with ammonia in that addition takes place. The predominant product ions on the ICR time-scale (*ca* 1 s) are $CH_3OH_2^+$ and $C_2H_5O^+$ ions. The latter ion is proposed as indicator for the presence of cyclopropane$^{+\bullet}$. It is interesting to note that these authors also find 20% ring structure in ionized cylopropane. Methanol exchanges its hydroxyl hydrogen with deuterium in ionized propene according to McAdoo and coworkers[282]. They explain the reaction as an exchange within an ion/neutral complex:

$$[CH_3CH{=}CH_2{}^{+\bullet}\ HOCH_3] \longleftrightarrow [CH_2{}^{\bullet}CHCH_2\ {}^{+}H_2OCH_3] \qquad (23)$$

From the speed of the H/D exchange the authors estimate a lifetime of the complex of 10–30 ps. Propanol and tetrahydrofuran yield 48% and 35% of the cyclic $C_3H_6^{+\bullet}$, respectively, but 1-pentene and *i*-Bu alcohol none, confirming earlier estimations by Bowen, Colburn and Derrick[283], Holmes and coworkers[284], and Gross and Lin[285]. Holmes and Terlouw[286] were unable to distinguish in the metastable time range different $C_3H_6^{+\bullet}$ formed from several precursors. This is also true for collisional activated spectra performed by Bowen and coworkers[287] and Maquestiau and collaborators[288] and charge-stripping experiments by the latter authors. A somewhat reverse way was chosen by Ono and collaborators[289] in expanding neutral propene and cyclopropane in a supersonic beam, where also dimers of the neutral could be formed and observed. The photoionization efficiency of the neutrals and their dimers is measured with high optical resolution; an ionization energy of 9.738 ± 0.003 eV for propene, 9.33 ± 0.04 eV for its dimer, 9.721 ± 0.011 eV for cyclopropane and 9.61 ± 0.04 eV for its dimer is measured, respectively. The appearance energies for several fragments are also obtained.

First *ab initio* calculations on cyclopropane were conducted by Haselbach[290] which reveal that the low-energy form is an isosceles triangle. Collins and Gallup[291] calculated the two lowest-energy surfaces of the cyclopropane ion. The surface of the ground state possesses a series of relatively flat minima, whereas the upper surface corresponds to a ring-opened trimethylene radical ion isomer. The calculations give a difference of 1.3 eV (127 kJ mol^{-1}) between the upper-energy and the lower-energy minima, confirming the conclusions of the group of McLafferty[281] cited above. They estimated correctly the two adiabatic onset positions of the first two peaks in the PES (photoelectron spectrum) of cyclopropane. Du, Hrovat and Borden[292] calculate a very small barrier height (0.8 kJ mol^{-1}) for the hydrogen migration from trimethylene to form propene. Skancke[293] uses improved *ab initio* techniques to estimate the isomerization of cyclopropane$^{+\bullet}$ to propene$^{+\bullet}$. For this process she found an asynchronous one-step mechanism with an activation energy of about 125 kJ mol^{-1}, confirming earlier calculations cited above. It can be concluded that ion–molecule reactions cannot be used to estimate the concentration of cyclopropane radical cation, since these reactions apparently pass over intermediate adducts with low activation energies.

Isomeric C_6H_{12} radical ions fragment not very differently by the different mass spectrometric methods. The metastable decays are nearly identical, but the collisionally activated spectra of 14 isomeric hexenes, measured by Nishishita and McLafferty[240], exhibit some quantitative differences. Bensimon, Rapin and Gäumann[251] compared the metastable decay and the photoinduced fragmentation by infrared photons of long-lived parent ions of six hexene isomers and cyclohexane. If the linear isomers are practically identical, some notable differences are observed for branched isomers. Cyclohexane behaves similar to *n*-hexenes. The metastable fragmentation of H/D-labeled 4-Me-2-pentene, 2-Me-2-pentene

and 1,1,2-triMe-cyclopropane are, according to Laderoute and Harrison[294], also identical. Me is lost from the terminal end groups as well as from internal positions, explained by isomerization. Very little difference is also observed in Me loss, when the molecular ions are produced by charge transfer. According to Fura, Tureček and McLafferty[19] angle-resolved NRMS does not allow one to distinguish between isomeric *n*-hexenes, but the survivor ion mass spectrometry granted the characterization of all C_6 dienes and cyclohexene[47]. The ring-opening reaction was studied by Levsen, Schwarz and collaborators[295] by field ionization kinetics and collisional activation. The authors reach the conclusion that three-, four- and five-membered substituted cycloalkanes form with *ca* 1 ns the 1-alkene molecular ions, preceding a shift of the double bond. However, six-, seven- and eight-membered rings remain intact prior to decomposition. Wolkoff and Holmes[296] estimate an activation barrier of *ca* 1 eV for the ring opening in cyclohexene, based on appearance energies, shapes and kinetic energy releases of metastable peaks. Derrick, Falick and Burlingame[297] fix the time scale for H/D randomization in cyclohexene between 10 ps and 1 ns. Ethylene is being expulsed by a Diels — Alder reaction (see Section X). The survivor ion mass spectra (see Section II) of the nondissociating molecular ions of three hexadienes and cyclohexene differ considerably from the electron impact and NRMS spectra. The isomers can be distinguished by the ions containing six carbon atoms. This study, using the same technique, was extended by Tureček and Gu[46] to eight C_6H_{10} isomers. Its seems that, generally, isomers of low internal energy content can be identified, using an appropriate method.

The various rotamers of the hexatriene cation have been calculated by *ab initio* methods by Cave and Johnson[298]. Photodissociation allowed Wagner-Redecker and Levsen[134] to distinguish 2-pentyne, 1,2-pentadiene, 1,3-pentadiene and cyclopentene. Boyd, Beynon and collaborators[299] compared CID, metastable spectra and dissociative charge stripping to distinguish among seven $C_5H_8^{+\bullet}$ isomers and D- and L-limonene as standard. The greatest degree of structure differentiation was possible using the dissociative charge-stripping. The ΔH_f of the neutral, the ion and the adiabatic ionization energy obtained by MNDO semiempirical calculations for the $C_5H_8^{+\bullet}$ ions were compared with experimental results. The electron ionization mass spectra of 19 monoterpenes are reported at 70 eV, 500 K and 12 eV, 350 K by Brophy and Maccoll[300]. The influence of electron energy and temperature is very different for the different terpenes. Dunbar, Faulk and So[301,302] studied the photodissociation of nine Me-substituted butadiene cations and of 2-Me-1-penten-3-yne ion with high optical resolution. This allowed them to study the Me-substituent band shift and to make molecular orbital attributions.

Levsen and coworkers[64] demonstrated that also in *n*-octene radical cations (see above) the location of the double bond can be clearly seen in the field ionization spectrum, contrary to the metastable fragmentation. This does not hold for 2,4,4-triMe-pentenes with the double bond in the 1- or 2-position. The FIK technique permits one to follow the progress of hydrogen migration in 4-octene[303] and isomerization in all four *n*-octene ions[304]; it seems to be complete after *ca* 1 ns. ^{13}C labeling allowed one to realize that up to 0.1 ns the ions decompose predominantly by specific mechanism. At longer lifetimes the fragmentations become more complex, being explained by isomerization reactions by the authors. Levsen[305] demonstrates that collisional activation spectra also allow some distinction of six isomeric octenes. By multiple labeling with ^{13}C and D, Gäumann, Stahl and Tecon[306] showed analogous fragmentation reactions for 1-nonene as for 1-heptene indicated in Schemes 1 and 2.

The mass spectra of eleven doubly charged alkenes between C_5 and C_{10} and 12 alkadienes and cyclic olefins have been measured by Appling, Musier and Moran[307]. In general, the spectra are rather different from the spectra of the monocharged analogues; they are

dominated by fragments which result from extensive hydrogen loss. Not enough isomers were measured to allow a judgment about the isomerization of the doubly charged molecular ion, but at least $C_6H_{10}^{2+}$ ions indicate some differences among isomers. The fragmentation due to unimolecular charge separations of the doubly charged ions $C_2H_2^{2+}$, C_2HD^{2+}, $C_4H_2^{2+}$ and $C_4H_3^{2+}$ are reported by March, Macmillan and Young[308]. From the charge separation the authors come to the conclusion of a three-membered ring structure for the C_4 ions. Harris and coworkers measured and calculated triplet[309] and singlet[310] energies of the allene dication. The triplet states were created by double charge-transfer from OH^+ and F^+. The singlet states were populated by double charge-transfer from H^+ projectiles. The ionization energies to the triplet states start at 27.2 eV, to the singlet at 28.7 eV. Values up to 40 eV are measured.

The O^- CI mass spectra of thirteen acyclic C_6H_{10} isomers and cyclohexadienes have been determined by Bosma, Young and Harrison[311]. Beside the common $[M-H]^-$ base peak, some isomer distinction is possible from the intensity of the fragments and the ions resulting from the addition of O to the base peak; in particular, the alkynes can be identified. The corresponding mass spectra of 1,3- and 1,4-cyclohexadiene are easily distinguishable. The authors assume a common structure for the base peak of the hexadienes and methylpentadiene. The use of N_2O in a mixture with either H_2 or CH_4 by Smit and Field[312] gives similar results, with the exception that instead of an O-addition the $[M-H+NO]^-$ ion is being formed. The π^* anion state of 1,4-cyclohexadiene has been calculated and earlier results reviewed by Juang and Chao[313]. The chemical properties of butadienyl anions are the subject of a study by van der Hart, Nibbering and collaborators[314]. Proton abstraction from 1,3-butadiene yields an isomeric mixture of 1- and 2-butadienyl anions, the former being *ca* 10 kJ mol^{-1} less stable and having a very different structure, as confirmed by *ab initio* calculations. The acidity of 1,3-butadiene, leading to the more stable 2-butadienyl anion, is determined to be 1637 ± 2 kJ mol^{-1}. Bond dissociation energies, gas-phase acidities and ion–molecule chemistry of allene, Me-acetylene and the propargyl radical $CH_2{=}C{=}C^{\bullet}{-}H$ is compared by Bierbaum, DePuy, Lineberger and coworkers[315]. The reactions of perfluoroisobutene with anions possible in air (from H_2O, CO_2, O_2) were determined by Watts and coworkers[316] in view of pollution problems in air, perfluoroisobutene (a potential industrial hazard) being highly toxic. NRMS can also produce anions from collision of neutrals with Xe[31]. This technique is used by Wesdemiotis and Feng[317] to gain information about anions produced from $C_3H_n^+$ ions ($n = 0$–6). Reionization efficiencies decrease by two orders of magnitude from $n = 0$ to 6. All C_3H_n radicals ($n = 1, 3, 5$) can be transferred collisionally to stable even-electron anions. For $n = 0, 2, 4$ and 6 the stability of the radical anion increases with decreasing n.

Normal and cyclic alkenes form stable gas-phase ions in air at atmospheric pressure, when the moisture is below 1 ppm, as has been proven by Bell, Karpas and colleagues[318,319]. The reactions, including those of alkanes, with H_3O^+ and $N_2^{+\bullet}$ were also studied. High-pressure (0.1–2 Torr) photoionization of isobutene allowed Nagase and Herman[320] to study the kinetics, and the deactivation by different neutrals, of clusters of the type $C_4H_9^+(C_4H_8)_n$ and $C_8H_{14}^+(C_4H_8)_m$. The stabilization of the clusters, compared with the dissociation of an excited dimer to form $C_4H_9^+$, increases tenfold from a rare gas to a polyatomic hydrocarbon as neutral. Correlations of the deactivation efficiency with the potential well depth and the heat of vaporization are made. According to Vairamani[321], nitromethane can be used as a substitute for NO in the CI of alkynes, alkenes and alcohols. Terminal olefins yield fairly abundant $[M+NO]^+$ peaks, contrary to nonterminal olefins. Bouchoux and Penaud-Berruyer[322] studied the competition of hydrogen atom abstraction and the cycloaddition–cycloreversion reactions by vinylamine radical

cation with various neutral olefins and compared it with the reactivity of the nucleophilic attack of an olefin by a free radical. A close parallelism was found and substantiated by *ab initio* calculations. Conjugated dienes lead to the elimination of NH_3 or of a hydrocarbon radical from the adduct $[M + CH_2{=}CHNH_2]^{+}$[323]. With the same idea in mind the reactions of the charged radical $(Me)_2S^+{-}CH_2^{\bullet}$ with cyclic alkenes was studied by Chyall, Byrd and Kenttämaa[324]. Again, the competition between hydrogen abstraction and addition to the double bond is compared to the reactivity of neutral radicals and supported by *ab initio* calculations. This distonic ion is 74 kJ mol^{-1} higher than the radical cation $CH_3CH_2SCH_3^{+\bullet}$, but it is stable against isomerization. The gas-phase reactions of $(Me)_2S^+CH_2^{\bullet}$ were also studied by Nibbering and collaborators[325] who compared the reaction rate with the (faster) Et Me thioether $CH_3CH_2S^{+\bullet}CH_3$. A reaction mechanism is proposed for the reaction with 1,4-cyclohexadiene, based on the use of labeled substrates. The ion–molecule reactions of fullerene cations C_n^+ and dications C_n^{2+} (n = 54, 56, 58, 60, 70) with propene, 1-butene and isobutene is the subject of a study by Stry and Garvey[326]. The isomeric form of the butene as well as the size of the fullerene ion affects the reactions observed. The numerous new reactions discovered still await explanation. The reactions of monocyclic carbon cluster ions $C_n^{+\bullet}$ (n = 10–20) with allyl chloride and 2-chloropropene were investigated by ICR mass spectrometry by Sun, Grützmacher and Lifshitz[327]. The chloropropenes add to the carbon cluster by loss of Cl. Exceptionally large reaction rates are found for the antiaromatic clusters $C_{13}^{+\bullet}$ and $C_{17}^{+\bullet}$, i.e. $n = 4r + 1$. The collisional-induced fragmentation of the products from even $C_n^{+\bullet}$ yield exclusively $C_3H_3^+$, while ions from odd $C_n^{+\bullet}$ generate several fragment ions. A reaction model is proposed.

VIII. ACETONE, SEEMINGLY SIMPLE

Neutral alkane molecules are eliminated in the low-energy reactions of many ketones, low molecular weight secondary alcohols (e.g. 3-pentanol[328]) and *s*-alkyl primary amines[329]. Even [2,2,6,6]-tetramethylcyclohexanone yields acetone. In this case Schwarz and collaborators[330] discovered two pathways for its formation. McLafferty and colleagues[331] and Holmes and collaborators[328] have shown that the enolic form — the most stable isomer — is being formed in this process. However, the former authors were able to demonstrate that the main fragmentation of the resulting $C_3H_6O^{+\bullet}$ ion, the loss of Me to yield *m/z* 43 ($MeCO^+$), originates from the keto form. By labeling the ketones, they made the unusual observation that the two methyl groups are lost from this intermediate acetone at unequal rates, probably due to an incomplete randomization of energy before fragmentation, considered to be a nonergodic behavior of the intermediate acetone. The problem of the α-cleavage is reviewed by Bouchoux[332]. Lifshitz, Schwarz and colleagues[333] labeled 2-hexanone with ^{13}C either in the 1- or the 3-position. By a McLafferty rearrangement the enol form of acetone is produced with the label either in the Me or in the methylene position. The probability for losing Me within the metastable time window range from the original methylene in hexanone is 56% instead of 50% and the half-width $T_{0.5}$ value in the MIKE spectrum is 72 meV against 59 meV for the loss of the original Me group. Similar results were obtained by Heyer and Russell[334]. They produced $[^{13}CH_3C(OH){=}CH_2]^{+\bullet}$ ions starting from 1-^{13}C-Me cyclobutanol and found for the neutral loss ratio $CH_3/^{13}CH_3$ a value of 1.38. A statistical model used by Lifshitz[335] confirmed the findings. In neutral molecules (and probably in most ions) the equilibration of the internal vibrational energy is reached within a few picoseconds[336–338] and a violation of the ergodic theorem is a rare event[339]. Tureček and McLafferty[32] made the interesting observation that the Me loss from the isomeric propene oxide and Me vinyl ether is also nonergodic. They

concluded from this observation that also for these ions this loss passes through the keto form of acetone. Hrušák and Tkaczyk[340] predict the parallel existence of the keto and the enol structure of the acetone cation on the basis of MNDO calculations. They enlarged their calculations to a series of MeCOR compounds (R=H, F, Cl, Me, NH_2, OH, OMe, NHMe)[341]. The keto–enol tautomers and their relation to distonic ions is the subject of reviews by Bouchoux[342,343] and by Holmes[344].

It is thus not astonishing that the fragmentation of acetone has roused much interest in spite of the fact that it presents one of the simplest mass spectra, *m/z* 43, $[M-Me]^+$ being the base peak with >70% of the total ion current. But of the fragmentation reactions,

$$Me_2CO^{+\bullet} \longrightarrow MeCO^+ + Me\bullet \quad (24)$$

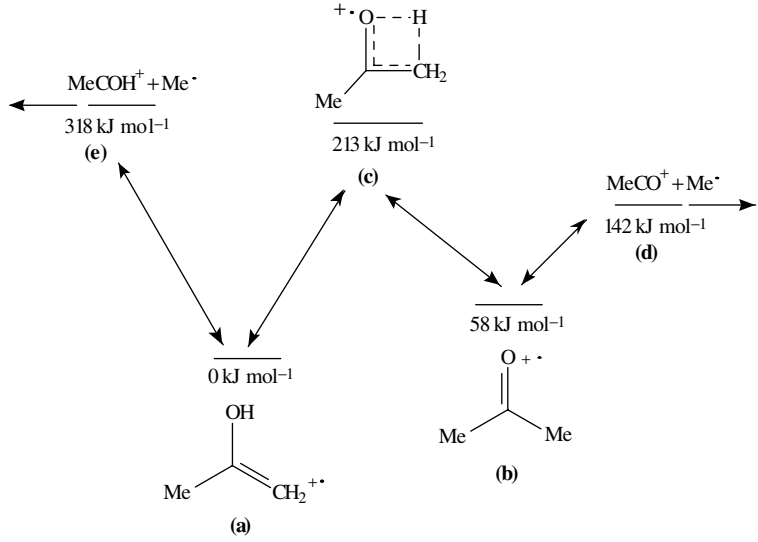
$$Me_2CO^{+\bullet} \longrightarrow CH_2CO^{+\bullet} + CH_4 \quad (25)$$

$$Me_2CO^{+\bullet} \longrightarrow C_2H_3{}^+ + MeCO\bullet \quad (26)$$

$$Me_2CO^{+\bullet} \longrightarrow CH_3{}^+ + (Me\bullet + C{=}O) \quad (27)$$

only the first two have been carefully studied over the twenty years since McLafferty and colleagues[331,345] proposed that the loss of Me from the acetone molecular cation also constitutes an example of nonergodicity. This behavior and its explanation has been confirmed with acetone labeled with ^{13}C by Tureček and McLafferty[346] and by labeling with D by Lifshitz and her colleagues[347], McLafferty and collaborators[331] and Beynon and collaborators[348], although the explanation is seriously questioned (for a résumé see elsewhere[346]). They assume that Me is not lost from the more stable enol cation, but from the re-isomerized keto form[331], Hudson and McAdoo[349] (among others, see later) proposed the formation of ion-radical complexes. It is particularly intriguing that in the metastable time scale only loss of Me (reaction 24) and in the CID spectrum only loss of methane (reaction 25) is observed [350–352].

The problem can be best visualized by looking at Scheme 3[333,353]. $C_3H_6O^{+\bullet}$ ions produced as intermediates will in most cases have the enol structure **a**. Its heat of formation has been determined by Holmes and Lossing[354] as 660 kJ mol^{-1}. By choosing a suitable precursor, the Me and the methylene groups correspond to defined positions in the precursor neutral. Ionized acetone **b** will either lose Me in a fast reaction or isomerize to **b**. The enol has a direct way to lose Me by **e**, but the isomerization via **c** to the keto form **b** offers a pathway much lower in energy for the same loss. The enol **a** 'discriminates' between the two Me groups of acetone, whatever the detailed structure of the intermediate **c** may be. The loss of CH_4 from acetone has an appearance energy that is about 4 kJ mol^{-1} lower than the loss of Me; the probability to lose CH_4 compared to Me loss in the metastable time window is at least 10^4 times higher when acetone is formed by direct ionization as **b**; but the reverse is true when the $C_3H_6O^{+\bullet}$ is produced as the enol form **a**, e.g. from heptan-2-one[350]. Lifshitz, Schwarz and collaborators[355] performed RRKM-QET calculations on an *ab initio* potential energy surface in order to explain the difference in speed of the two eliminations. They assumed tunneling in the methane elimination path. The existence of a hydrogen-bridged intermediate complex **c** leading to a loose transition structure was proven. However, the idea of a tunneling is contested by Osterheld and Brauman[356] on the basis of infrared multiphoton dissociation experiments in an ICR spectrometer. They studied the fragmentation of $CH_3COCH_3{}^{+\bullet}$ and $CD_3COCD_3{}^{+\bullet}$, excited by a continuous wave (CW) CO_2 laser with a wavelength of 10.6 μm . The branching ratio (Me)/(methane) for H_6-acetone was 2,4 and 2.2 ± 0.1 for D_6-acetone respectively. The ions were irradiated for about 300 ms. When irradiated with a high-power pulsed CO_2 laser of 2 μs half-width, this ratio increased with the fluence



SCHEME 3

of the irradiation from 4.0 to 5.3, independent of the isotopic substitution. When doing the same experiments with CH_3COCD_3, some complications arise since acetone can easily exchange within the inlet system which the authors tried to minimize and to correct for. The loss of the following isotopomer neutrals is measured: $\cdot CD_3$, CD_3H, $\cdot CH_3$ and CH_3D. For the methane loss they obtained a ratio $CD_3H/CH_3D > 8$. Because of the above mentioned corrections this is to be taken as a lower limit; the ratio approaches probably about 70, the value obtained for the metastable decay by Lifshitz and Tzidony[357]. When neglecting the CH_3D loss, they obtain for the branching ratio $\cdot CH_3/\cdot CD_3/CD_3H$ the values of $0.61/0.21/0.18 \pm 0.02$. Since the difference in energy for the loss of methane and Me is only 4 kJ mol^{-1}, the influence of the differences of the zero-point energies of the vibrations C−H and C−D can strongly influence the branching ratios. Because of the isotope effect for a C−D abstraction, the pathway for CH_3D cannot compete with the other reactions. However, the same amount of CH_4 and CD_4 in the pulsed laser experiments is not consistent with a tunneling mechanism; the tunneling of a deuterium atom would only compete with the pumping rate at energies significantly higher than those necessary for hydrogen. In a subsequent publication Osterheld and Brauman[353] made similar photofragmentation studies with $^{13}CH_3COCH_3^+$, produced from 1-$^{13}CH_3$-cyclobutanol; in this case the enol produced has the structure $^{13}CH_3C(OH^+)=CH_2$. CW laser photolysis gave a ratio of 1.16 ± 0.08 in favor of the loss of CH_3, i.e. 7.6% of the acetone decomposes nonrandomly. With pulsed irradiation this ratio increases with intensity to a limiting value of 1.6, corresponding to 22% nonrandom fragmentation. This can be interpreted that the nonrandom part increases with increasing energy, i.e. shorter fragmentation time, as is the case with the pulsed laser. How far this augmentation is due to excitation of nonreacting vibrations[358] remains an open question. The increase in importance of the 'nonrandom' part of the fragmentation is also derived from the kinetic release distributions from metastable peaks[357]. The authors find a 'bimodal' distribution in the sense that it consists of a narrow, low translational component and a much broader high-energy component. For a review see McAdoo and Morton[359]. It is of interest that

Iraqi, Lifshitz and Reuben[360] were unable to observe the reverse reaction between ketene ion and methane: $CH_2{=}C{=}O^{+\bullet} + CH_4 \rightarrow [CH_2{=}C{=}O^{+\bullet} + CH_4]$. The reaction is with 1.6 kJ mol^{-1} only slightly uphill[355].

Several studies of the unimolecular fragmentation of energy-selected acetone, either by photoelectron–photoion coincidence spectroscopy (PEPICO) or high resolution photoionization, have been published. In an early work Cant, Danby and Eland[361,362] measured the decay of acetone by the PEPICO method over an energy range of 10 eV. Both the product translational energy distributions and the branching ratios show deviations at high internal energies. The authors point out that electronically excited Me radicals could be produced in some of the decompositions. Mintz and Baer[363] investigated also CD_3COCD_3. Although they disagree partially with the findings of the former authors, they also realize that the theoretical predictions underestimate the kinetic energy release, again for higher values of the excess energy above the fragmentation threshold. Johnson, Powis and Danby[364] treat the problem from a more theoretical standpoint. A breakthrough came from the PEPICO work of Bombach, Stadelmann and Vogt[365] on the unimolecular fragmentation of internal energy selected fragmentation of 1,2-epoxy propane. They realized that epoxy propane cations initially formed in the electronic ground state with little vibrational energy do not dissociate. This is used to explain the comparable slow dissociation process of acetone ion that is initially ionized to the electronic excited $\tilde{A}$ state of the enol that coincides with the one obtained from the epoxide. By internal conversion, the ion will decay to the electronic ground state, followed by rapid fragmentation. In a subsequent publication Stadelmann[366] demonstrates that CH_3^+ is not formed directly from the acetone molecular ion in a violation of Stevenson's rule[367], but in a secondary fragmentation from CH_3CO^+ fragment. Compare also the *ab initio* calculations of the structures and stabilities of the $C_2H_3O^+$ ions by Nobes, Bouma and Radom[368] and the MNDO calculations on acetone and its enol by Hrušák and Tkaczyk[340].

Further progress was attained by scattering studies with the acetone molecular ion. Futrell and collaborators[369,370] determined the scattering contour maps for the fragment ion $MeCO^+$. They show that this ion is predominantly backward scattered with intensity maxima for the two center-of-mass collision energies studied (0.65 and 0.45 eV) that are lying well outside the elastic scattering circle. This can occur only by the conversion of internal energy into translational energy, demonstrating the presence of long-lived ($t > 30$ μs) excited states of the acetone molecular ion. It must be mentioned that this lifetime of an excited state exceeds by far the microsecond time scale of metastable and CID experiments in the mass spectrometer. The authors infer from their results that on collision the ion releases all the excess energy into recoil energy of the resulting internally excited ground state which rapidly fragments into $MeCO^+$ and Me· without allowing equilibration of the internal energy. This idea was ensued by subsequent work of the group of Futrell[371–373] where they investigated the collision-induced dissociation of acetone molecular ion activated by He and Ar. The released energy measured matches the X ← A electronic excitation energy difference, suggesting a very efficient transfer of electronic excitation in translation energy. At collision energies $\geqslant$6 eV the superelastic scattering is no longer observed. The dynamics is consistent with the hypothesis that the reverse process, namely transfer of translational energy of the ground state acetone ion to an excited state, can take place under these conditions. This interconversion of translational and electronic energy was further studied by these authors[374]. They were able to demonstrate that two populations of collisionally excited ions are formed, one long-lived and the other dissociating into $MeCO^+$ and Me·. The interconversion of translational and electronic energy seems to be unexpectedly facile in low-energy collisions. A triple-cell ICR spectrometer has been used by Futrell and collaborators[375] to measure the

lifetime of electronically excited acetone molecular ions that were collisionally excited. The threshold energy for CID is around 0.15 eV; this is consistent with a small barrier to curve-crossing into the ground state. The lifetime depends on the experimental conditions: two values, 4 and 14 ms, are obtained for collisions with He and O_2, respectively. Martinez and Ganguli[376] confirmed, enlarged and refined the above-mentioned results. Their work resumes the state of our understanding of the acetone fragmentation under collision, presenting branching ratios and cross sections as a function of the collision energy with argon.

The energy necessary for the double ionization of acetone has been determined with the help of the Auger spectrum 28.0 eV by Correia and coworkers[377]. They determined also the energies necessary for the double ionization of formaldehyde (33.8 eV), acetaldehyde (30.3 eV) and formamide (30 eV). The assignment of the spectra has been made by using *ab initio* calculations; similarities and differences among the four neutrals are stressed. In a later publication Harris and collaborators[378] measure the triplet electronic states of the doubly charged ion of acetone with the help of a double-charge-transfer spectrum with multisector mass spectrometers. They determine a vertical ground state energy for the doubly charged triplet of 29.6 eV together with the energies, the state configurations and the state designation for 27 higher-lying states up to 40 eV. The same group[379] determined a series of double ionization potentials of acetaldehyde for the triplet electronic state between 31.2 and 40 eV and for the singlet state from 30.4 to 42 eV.

Acetone has been detected in the stratosphere as a trace component, together with acetonitrile and nitric acid[380], although acetonitrile is the component of major interest[381]. The concentration of acetone decreases steeply above the tropopause due to increasing photolysis and decreasing production from nonmethane hydrocarbons (mainly propane). The lifetime of acetone in the lower stratosphere is only about ten days. The presence of acetone can interfere with the detection of vinyl acetate traces as pollutant in the air[382]. However, it can easily be determined by soft ionization methods in ppb levels[383]. Ion/molecule reactions of protonated bases of atmospheric importance were studied by Lifshitz and collaborators[384]. Exothermic proton transfers, e.g. from $(MeCN)H^+$ to Me_2CO, are observed to be fast. Hoshika, Nikei and Muto[385] developed a method to determine trace amounts of acetone in air by atmospheric pressure ionization. A series of peaks, including clustering with water, is used and a sensitivity better than 0.01 ppm is obtained.

The vertical electron affinity (EA) of acetone is given as −1.51 eV by Jordan and Burrow[386]. Lifshitz, Wu and Tiernan[387] determine — among other compounds — the excitation function and rate constants of the slow proton transfer reactions between acetone-H_6, acetone-D_6 and other ketones. The acetone enolate anion has been produced in a CO_2 laser induced alkane elimination from alkoxide anions by Brauman and collaborators[388–390]. These show, e.g. that the methane elimination from *t*-butoxide anion is a stepwise process:

$$(Me)_3CO^- \longrightarrow [(Me)_2C^{\bullet}O^- \cdots {}^{\bullet}CH_3 \text{ or } (Me)_2CO \cdots {}^-CH_3]$$

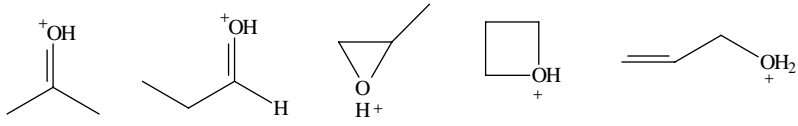
$$(Me)_3CO^- \longrightarrow MeC(O^-){=}CH_2 + CH_4 \qquad (28)$$

This reaction was further studied by the same group[391] using several D-labeled butoxide anions with CW and high-power pulsed CO_2 lasers. Relatively small primary, but large secondary isotope effects were found, pointing again to a stepwise process that has been modeled by using RRKM theory. The gas-phase ion/molecule reaction of nitric oxide anion with several ketones (among other substances) has been examined with the flowing afterglow technique by Grabowski and collaborators[392]. The reaction of NO^- with acetone is very slow; the only primary reaction observed is cluster addition:

$$NO^- + Me_2CO \xrightarrow{Ar} (Me_2CO)NO^- \qquad (29)$$

A large series of nucleophilic displacement reactions has been determined by Olmstead and Brauman[393], including different fluorinated and deuterated acetone molecules and anions. Rate constants and reaction affinities are determined and the results compared with theoretical calculations using the RRKM theory. Klass and Bowie[394] studied the reactions of methoxide anions with different ketones, supported by a theoretical *ab initio* study with acetone as ketone by Sheldon[395]. Three different adduct complexes were distinguished and their energies calculated. A tetrahedral adduct at the carbonyl carbon seems to be the most favorable. The same authors[396] enlarged their study on the reactions of alkoxide-alkanol negative ions with carbonyl compounds. The condensation of the carbanion of acetone with acetone neutral formed the basis of a study by Bouchoux and Hoppilliard[397]. They noted the analogies with the above-mentioned measurements of Brauman and coworkers[390]. The gas-phase base-catalyzed Claisen–Schmidt reaction of the acetone enolate anion with various *p*-substituted benzaldehydes and its correlation with the Hammett constant was investigated in detail by Haas and Gross[398]. The structure of acetone anion in a solid argon matrix at 4 K has been determined by Köppe and Kasai[399] in an ESR study. It is surmised that the acetone anion is pyramidal and each methyl group is locked into a staggered conformation, the C- and O-atom of the C=O group sharing the electron in a 1:2 ratio. The state-of-art of the electron transfer as a possible initial step in nucleophilic addition–elimination reactions between (radical) anions and acetone, fluorinated acetone, CF_3CO_2Et and CF_3CO_2Ph has been investigated and résuméd in a thesis by Stanecke[400]. Much work remains to be done in this field.

Many isomers having the composition $[C_3H_7O]^+$ of protonated acetone are possible. Some are presented in Scheme 4. A partial potential energy profile had been proposed by Bowen and collaborators[401,402] for the isomers proposed in this Scheme. McLafferty and Sakai[403] determined stable structures for **a** and **b**. Harrison, Gäumann and Stahl[404] studied the isomers of Scheme 4 using metastable and collision-induced fragmentation. The CID studies show that protonation of acetone **(a)** and allyl alcohol **(e)** yield different metastable ions with distinct structures while protonation of propanal **(b)** or propylene oxide **(c)** yields ions of the same structure. The main fragmentation reactions are loss of H_2O, C_2H_4 and CH_2O. Protonated oxetane **(d)** rearranges less readily to give the same structure(s) as protonated propanal and propylene oxide. The ions fragmenting as metastable ions after formation by *i*-butane or methane CI have a higher internal energy than the same ions fragmenting after formation by EI (electron impacts)[402]. Deuteration of the C_3H_6O isomers using CD_4 reagent gas shows that loss of C_2H_3D proceeds by a different mechanism than loss of C_2H_4. These findings were confirmed by Curtis and Harrison[405]. Tsang and Harrison[406] showed experimentally and theoretically that the relative metastable fragmentation of **a** and **b** are rather independent of the internal energy. It may be mentioned that the structures of $C_3H_7O^+$ ions formed from alcohols are also relatively well defined, as has been shown by labeling with D and ^{13}C[407]. The same labels were used to get information about the loss of ethylene from ions of the structure **b**[408]. Propylene oxide is depicted to exist in a very shallow potential energy (*ca* 15–20 kJ mol^{-1})[409]. Lin and Kenttämaa[410] measured the relative stabilities of different



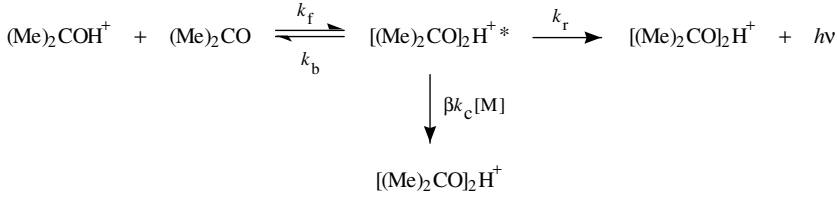
(a) **(b)** **(c)** **(d)** **(e)**

SCHEME 4

protonated C_3H_6O isomers by using proton transfer reactions with different exothermicities and then probing the structure by using energy-resolved mass spectrometry. In contrast to the results mentioned above, it is demonstrated conclusively that protonated propylene oxide is not only thermodynamically but also kinetically stable towards ring opening in the gas phase. McAdoo and Hudson[411] concentrate on the question of how $CH_3CH_2{}^+O{=}CH_2$ **(f)** and **b** fragment, since Bowen and coworkers[402] in their potential energy scheme mentioned above suggested that these two ions reach a common region with an ion-neutral complex as a transition state. McAdoo and Hudson present evidence that **b** forms a complex of the structure $[CH_2{=}CH_2\ {}^+HO{=}CH_2]$ **(g)** and **f** $[CH_3CH_2{}^+\ O{=}CH_2]$ **(h)**. **g** and **h** are distinct in their chemistry, in particular for losing C_2H_4, and **h** $\rightarrow$ **g** is irreversible. Bowen, Suh and Terlouw[412] investigated the alkene elimination of metastable ^{13}C-labeled oxonium ions with five and seven carbon atoms. Several pathways for isomerization are proposed, but the preference to retain the initial C−O connection is general, leading to a very high selectivity for elimination of propene and butene. $C_3H_7O^+$ ions of different structures have also been prepared by Eyler and coworkers[413] from oxygen-containing hydrocarbons with infrared multiphoton dissociation.

Using supersonic cooling of a molecular beam, Trott, Blais and Walters[414] obtained the dimer, trimer and tetramer of acetone and its hexadeuteroisotopomers $((Me)_2CO)_n$ and measured their ionization potentials and the appearance potential of the main fragment $MeCO^+$. The measured ionization energies are found to decrease linearly with $1/n$ from 9.694 ± 0.006 eV for $n = 1$ to 9.02 ± 0.03 eV for $n = 4$. By consideration of appropriate thermodynamic cycles, a lower limit for the acetone dimer ion binding energy is calculated to be 52 kJ mol^{-1} and the desolvation energy of $((Me)_2CO) \cdot MeCO^+$ is estimated to be also 52 kJ mol^{-1}. No appreciable isotope effect is found. Parker and coworkers[415] use also photoionization to produce ground electronic state molecular ions with little internal or translational energy. Ion/molecule reactions occurring under thermal energy conditions lead to the formation of the proton-bound dimer of acetone at mTorr pressures.

Protonated acetone has the possibility of adding a second acetone neutral to form a dimer with a rate constant k_f (see Scheme 5). Since this is an exothermic reaction, the dimer has to be stabilized either by collision with a third body of collision rate k_c and probability for stabilization β, or by radiating part of its excess energy as infrared emission with a rate constant k_r. The lifetime of vibrationally excited states is in the millisecond range (see, e.g., Dunbar[10,416,417]), thus the determination of k_r can only be done at very low pressures in order to avoid the competition by collision or by reverse fragmentation. This experiment has been done by Kofel and McMahon[418]. They observed the formation of $((Me)_2CO)_2H^+$ in an ion cyclotron mass spectrometer at a pressure of 3.4×10^{-10} mbar for over 3 h. Only the dimer is formed (as the main peak), and no trimers or higher polymers are detected[419]. By measuring the overall rate over a range of pressures and by taking $k_f = 2.2 \times 20^{-9}$ cm^3 molecule^{-1} s^{-1}, as measured at high



SCHEME 5

pressures by Parker and collaborators[415], and with some (reasonable) assumptions about collision rate and efficiency, Kofel and McMahon obtain for the dimer a radiative lifetime of 10 ms and the rate constant $k_b = 2.4 \times 10^4$ s^{-1}, corresponding to a 'lifetime' of 43 μs. McMahon and coworkers[420] determined also the threshold energy for the decomposition of the 'stable' dimer by measuring the collision-induced fragmentation 5–10 ms after formation. They evaluate a bond dissociation energy for loss of Me_2CO from the proton bound dimer of 140 ± 10 kJ mol^{-1}. Fisher and McMahon[421] extended this work to include dimethyl ether, diethyl ether and acetonitrile. Parker and collaborators[17] confirm that in high- and low-energy collision-induced dissociations and in multiphoton-infrared dissociation spectra, the only observable fragment of the proton-bound dimer of acetone is the protonated monomer. By model calculation using MINDO/3 they propose three possible isomeric ion-neutral complexes for the proton-bound dimer of acetone, two of which may interconvert. Thus there is disagreement with earlier calculations by Yamabe and coworkers[422] about the structure of the dimer (and trimer). The thermodynamic quantities for polymers of protonated acetone have been measured by Lau, Saluja and Kebarle[423], Hiraoka and Takimoto[424] and Parker and collaborators[17]. Their results for the clustering reaction $B_nH^+ + B \rightarrow B_{n+1}H^+$ (B = acetone, water, several alcohols, acetic acid, ammonia, different amines, pyridine) are tabulated together with his own data by Meot-Ner[425]: $\Delta H^\circ = -126$ and -60 kJ mol^{-1} and $\Delta S^\circ = -123$ and -96 J mol^{-1} K^{-1} for $n = 1$ and 2, respectively. He is not able to confirm a general trend observed by Hiraoka and collaborators[424] between the proton affinity of the base and the bond energies for proton-held dimers. The reaction of proton-bound dimers is reviewed and enlarged by a series of dimers of acetonitrile, acetone and dimethyl ether with many neutrals by the group of Lifshitz[426]. The comparison of the rate constant for reactions of the protonated dimer of acetone with a calculated collision rate for a series of bases is near unity for bases with a higher proton affinity than acetone. The high rate constant for acetone with the proton-bound dimer of acetonitrile is also remarkable and explains some of the problems encountered in the understanding of stratospheric reactions[380,381]. Radiative lifetime measurements were also made for a series of ion complexes, e.g. of NO^+ with acetone and 2-butanone by Weddle and Dunbar[427]. The latter author provided also a review of the field[9].

MacNeil and Futrell[428] demonstrated that several fragments of acetone, in particular CH_3^+ and CH_3CO^+, are also able to form polymers with acetone. A considerable temperature effect is noted which results in a shift towards higher polymers as the reaction temperature is lowered. Łuczynskí and Wincel[429] photoionized acetone at 150 and 320 K. They produce polymers up to $n = 6$, some containing water, others losing water in a fragmentation reaction. A complicated fragmentation pattern for clusters of protonated acetone is also observed by Stace and Shukla[430]. The study of the photophysics of acetone clusters has been continued by the group of Castleman[431,432]. The most striking finding is that the presence of water in a cluster suppresses the above-mentioned dehydration reaction, yielding evidence for the influence of a solvent on ion/molecule reactions. They confirmed also the above-mentioned presence of acetone clusters formed with the fragments of acetone. The stability of $C_7H_{10}^+$ and $C_6H_7O^+$ cyclic ions in the acetylene/acetone heteroclusters is the subject of a study by Garvey and coworkers[433]. Clusters with two C_2H_2 units seem to be particularly stable. This is explained by intracluster ion/molecule polymerization reactions forming covalently bonded cyclic ions.

The domain of ion/molecule reactions with acetone and ketones in general is very large and only a sketchy overview of the field can be given. Eyler, Ausloos and Lias[434] showed that the C=O bond in ketones can be split by CF_3^+, $C_2F_5^+$ and CCl_3^+, e.g. the reaction

$$CF_3^+ + CH_3COCH_3 \longrightarrow C_3H_6F^+ + (CF_2O) \quad (30)$$

which is endothermic. The product ion reacts with carbonyl compounds to form the protonated ketone or aldehyde as the final product. In a field ionization experiment, Beckey and coworkers[3,435] demonstrate a somewhat similar reaction of acetone surface ions and CCl_4 in the high electric field strength of the field emitting surface:

$$^*OC(CH_3)_2^+ + CCl_4 \longrightarrow {}^+OC(CH_3)_2Cl + CCl_3^+ \quad (31)$$

$$^*OC(CH_3)_2Cl + H\cdot - e^- \longrightarrow {}^+OH + C_3H_6Cl^+ \quad (32)$$

(* signifies an adsorbed species). The electron impact ionization of a mixture of acetone and iodomethane in a high-pressure ion source induces the protonation of acetone and a methylation yielding an ion $C_4H_9O^+$, as has been shown by Maquestiau and colleagues[436]. By labeling experiments and *ab initio* MO calculations, most of the ions of this composition are shown to have the structure of a dimethylmethoxycarbenium ion $C^+(Me)_2OMe$; but depending upon the experimental conditions, the isomeric Me-2-propenyloxonium ion $CH_2{=}C(Me)O^+(H)Me$ is also detected. Ionized acetone reacts with ketene by abstraction of a methylene group to form a distonic ion *m/z* 72 (Kenttämaa and collaborators[437]):

$$(Me)_2CO^{+\bullet} + CH_2CO \longrightarrow (Me)_2{}^+COCH_2{}^\bullet + CO \quad (33)$$

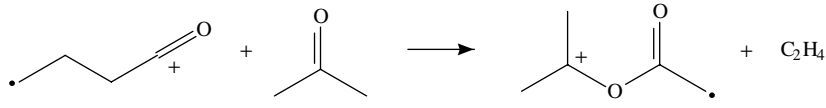
$$(Me)_2{}^+COCH_2{}^\bullet + CH_2CO \longrightarrow (Me)_2{}^+COCH_2CH_2{}^\bullet + CO \quad (34)$$

This ion reacts further with ketene to form the γ-distonic ion $C_5H_{10}O^{+\bullet}$ (*m/z* 86). The primary products *m/z* 43 and 59 are also observed.

The ammonia CI of ketones has been the subject of considerable work. It has been reviewed by Harrison[438,439] and by Westmore and Alauddin[440]. Maquestiau, Flammang and Nielsen[441] investigated the adducts of thirteen aliphatic and aromatic ketones K by mass analyzed ion kinetic energy spectrometry. Three main peaks were found: $[K + NH_3 + H]^+$ **(a)**, $[K + (NH_3)_2 + H]^+$ **(b)**, and $[K_2 + NH_3 + H]^+$ **(c)** ($K = RR'CO$). They assign the structure of a protonated carbinolamine $R(R')C(OH)NH_3{}^+$ to the ion **a**. No metastable fragmentation is observed, but on high-energy collision-induced dissociation NH_3 and H_2O is lost. The proposal is in contradiction with earlier suggestions where a hydrogen bridged structure $R(R')C{=}O\cdots H^+\cdots NH_3$ between the ketone and ammonia was assumed[442]. The question is of some importance, since Cooks and Kruger[443] proposed to use the adduct ion **a** to determine relative proton affinities of their component neutral bases. The ion **a** was also observed as a metastable fragment of **b** and **c**. They suggest that the additional ammonia (ion **b**) or ketone (ion **c**) are weakly bonded to the protonated amino group of **a** and form a hydrogen-bonded cyclic structure with the OH group. Tzeng, Wei and Castleman[444] formed neutral acetone-ammonia clusters they subsequently photoionized in a multiphoton process. Clusters of the general composition $[(NH_3)_n\cdot(C_3H_6O)_m]H^+$, $n = 1$–18, $m = 1$–5, were observed. For $n = 1$ the cluster loses an acetone moiety, whereas for $n = 2$–18 ammonia is eliminated. The authors propose a structure with a central $NH_4{}^+$, around which the additional molecules are clustered. They assume that the different source conditions for formation of the clusters in the work of Maquestiau could explain the different findings. Castleman and coworkers[445], using photoionization, realized that clusters prepared by different methods have different composition. Li and Harrison[446] repeat the work of Maquestiau with acetone and 3-pentanone as ketones including D-labeling products, using in addition to ammonia Me-, diMe- and triMe-amine as ionizing gas. They are unable to find any dependence on the source conditions, but they propose a severe discrimination against detection of low-energy fragments

in the technique used by Maquestiau (see Cooks and colleagues[447]). All results point in the direction of a proton-bound cluster, as expected since, in each case, the proton affinity of the amine is greater than the proton affinity of the carbonyl compound.

Terlouw, Schwarz and collaborators[448] propose that β-ketocarbenium ion $(Me)_2C^+CH_2COOH$ rearranges to the proton-bound acetone–ketene ion $[(Me)_2C{=}O\cdots H\cdots CH_2{=}C{=}O]^+$ prior to its dissociation into $(MeCO^+ + Me_2CO)$ or $(Me_2COH^+ + CH_2CO)$. Collision-induced experiments on D- and ^{13}C-labeled isotopomers indicate that this rearrangement is characterized by two consecutive [1,5]proton migrations. Stirk and Kenttämaa[449] studied an inverse reaction, the transfer of an ionized ketene to acetone. They base their findings on the theoretical calculations and predictions of Schwarz and colleagues[228] and Dass and Gross[450] that ionized cyclobutanone should have a γ-distonic, open-chain structure, $\bullet CH_2CH_2CH_2C{=}O^+$. Stirk and Kenttämaa[451] prove this structure experimentally. The authors realize that this ion transfers an ion of *m/z* 42, corresponding in mass to trimethylene, to acetone[449], forming an ion *m/z* 100. However, accurate mass measurement proves the transferred fragment to contain an oxygen atom, yielding the γ-distonic ion shown in Scheme 6. The reaction scheme is in addition confirmed by labeling experiments. The only reaction of this ion *m/z* 100 with $(CD_3)_2CO$ gives an ion *m/z* 106 with a collision efficiency of about 50%. As would be expected, the lower homologue β-distonic ion, $\cdot CH_2CH_2C{\equiv}O^+$, does not react with acetone. These findings were enlarged by Kenttämaa and coworkers[437] by showing that the reaction of neutral ketene with oxygen- or sulfur-containing ions can be used to produce a variety of stable distonic radical cations.



SCHEME 6

Acetone is not only an interesting substance in the field of kinetics of ion/molecule reactions, it can also be used as a reagent for analytical use in CI. An overview up to 1988 of its use in this field is given by Vairamani, Mirza and Srinivas[97] in a review about the use of unusual positive ion reagents in CI. Wang and coworkers[452] found that acetone can be used as reagent to detect distinct features in the spectra of stereoisomers of monosaccharides which do not appear in the corresponding CI with isobutane and ammonia. Hass, Nixon and Bursey[453] use the acetyl fragment of acetone for CI studies of a variety of substances, including a series of ketones. Vairamani and his colleagues explore the many characteristics of the CI with acetone. Acyclic, cyclic and bicyclic olefins are found to undergo acetylation, giving rise to diagnostic ions 98. Terminal olefins show enhanced loss of water from the $[M + 43]^+$ adduct. The adducts with other olefins give characteristic CID spectra. Acyclic, cyclic and bicyclic alkyl acetates show characteristic displacement reactions[454]. The authors propose an S_N1-like mechanism. Vairamani and Kumar[455] explored in more detail the reaction with hexenyl acetates. With aromatic compounds, often only charge exchange can be observed[456]. Substances with a higher proton affinity than acetone will react by proton transfer. Phenols and anilines will acetylate. A complex formation between phenol and acetone is observed[457]. Acetone CI of many acyclic, cyclic alcohols and diols were studied[458]. Comparison with reported isobutane CI mass spectra of these compounds suggests close similarity in the case of acyclic alcohols. Cyclic alcohols undergo different kinds of ion–molecule reactions under acetone CI.

Overall, the diagnostic adduct ions such as $[M+43]^+$, $[M+59]^+$ and $[M+101]^+$ are highly abundant. Vainiotalo and coworkers[459] found that acetone is a nondiscriminating agent for the characterization of fourteen 4-substituted camphors, the same as ammonia and isobutane, but contrary to methane. The same authors studied the electron impact mass spectra and, among other reagents, the CI of acetone of 33 differently substituted oxazolidines[460]. Mainly acetyl adducts are observed. This is also true in a series of 1,3-dioxolanes and their sulfur-substituted analogues[461]. Because stereoisomeric trinorbornane-2,3- and -2,5-diols cannot be distinguished under electron ionization, their differentiation was investigated under CI conditions by Vainitalo and collaborators[462], using ammonia, isobutane, methane, acetone and trimethyl borate as reagent gas. Although all the stereoisomers can be identified, the differences between the *cis*-2,3-diols are minor. Isobutane and trimethyl borate give results similar to acetone.

Harrison and Jennings[463] studied the reactions of the negative oxygen ion $O^{-\bullet}$ with methyl-, dialkyl- and some cyclic ketones. The main reactions are:

$$O^{-\bullet} + RCH_2COCH_2R' \longrightarrow OH^- + [M-H] \tag{35}$$

$$O^{-\bullet} + RCH_2COCH_2R' \longrightarrow [M-H]^- + OH\cdot \tag{36}$$

$$O^{-\bullet} + RCH_2COCH_2R' \longrightarrow H_2O + RC^{-\bullet}COCH_2R' \longrightarrow RCCO^- + R'CH_2 \tag{37}$$

$$O^{-\bullet} + RCH_2COCH_2R' \longrightarrow H_2O + R'C^-COCH_2R \longrightarrow R'CCO^- + RCH_2 \tag{38}$$

$$O^{-\bullet} + RCH_2COCH_2R' \longrightarrow RCH_2COO^- + \cdot CH_2R' \tag{39}$$

$$OH^- + RCH_2COCH_2R' \longrightarrow [M-H]^- + H_2O \tag{40}$$

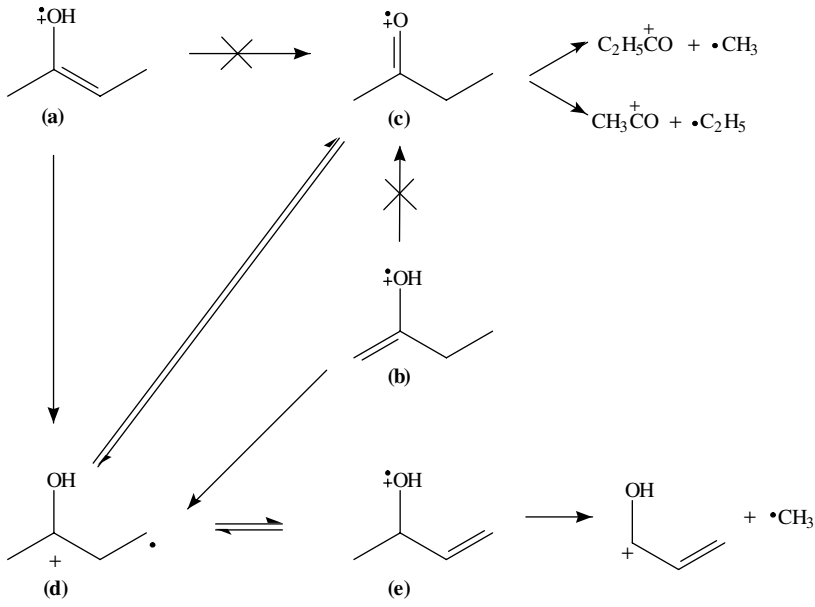
The H_2^+ abstraction stems exclusively from a single carbon atom in α-position (equations 37 and 38). In contrast to the specific abstraction of H^+ from the α-position by $O^{-\bullet}$ and OH^- in forming $(M-H)^-$ ions (equations 36 and 40), the reaction of $O^{-\bullet}$ ions to produce OH^- ions (equation 35) is much less specific and other positions may also be involved, although to a lesser extent. Sürig and Grützmacher[464] demonstrated that collisional charge-reversal NRMS spectra allow the distinction of heptanal and ten isomeric heptanones, cyclanones and several monoterpene ketones. In a later work, Marshall, Tkaczyk and Harrison[465] use these reactions in order to characterize twenty-eight C_4 to C_7 carbonyl compounds. In addition to the above-mentioned reactions they use the fact that the $[M-2H]^{-\bullet}$ ions (equations 37 and 38) fragment further by alkyl radical elimination. The relative importance of the reactions depends strongly on the molecular structure. For isomeric aldehydes, charge reversal spectra were needed in addition to distinguish among all isomers.

IX. OTHER KETONES: THE MORE IT CHANGES, THE MORE IT IS THE SAME

The fragmentation of ketone cations $RCOR'^{+\bullet}$ other than $[acetone]^{+\bullet}$ follow similar patterns insofar as the loss of the alkyl side chains R· and R′· and of alkanes RH and R′H are again observed in most cases, although in different proportions. Both reactions can be fast, since ketones deuterated in the α-positions show no H/D scrambling when ionized by 70-eV electrons[466], contrary to ionization by 10-eV electrons[467], metastable decays or collision-induced dissociation. This indicates that the speed of the keto–enol equilibration is slower than the fast decomposition. Cooks, Yeo and Williams[468] realized that in the metastable fragmentations of ketones of the general formula $R_sR_lC{=}O$ (where R_s is the shorter and R_l the longer alkyl group), R_s is usually lost with the lower activation energy. The relative probability for the loss of the two alkyl neutrals

seems to depend, however, on the internal energy of the molecular ion. In addition to the alkyl and alkane losses, McLafferty eliminations of olefins and γ-eliminations of radicals are observed when the conditions for such reactions are favorable. Yeo and Williams[466] show that also with 70-eV electron ionization for these reactions scrambling is observed for deuterated ketones, pointing to relatively slow rearrangement reactions. Methyl ketones other than acetone have little or no tendency to lose an alkane moiety, as has been shown by Hammerum, Donchi and Derrick[329]; they may lose Me from other than the α-position (Bouchoux and Hoppilliard[469]). Maccoll[470] finds an approximately linear relationship between the intensity ratios $[RCO^+]/[CH_3CO^+]$ and the appearance energy differences $AE(CH_3CO^+) - AE(RCO^+)$. As mentioned above, 2-pentanone is an exception, probably because of the McLafferty rearrangement that interferes in this case. Abbatt and Harrison[471] demonstrate the use of charge-exchange spectra with $CS_2^{+\bullet}$, $COS^{+\bullet}$ and $N_2O^{+\bullet}$ for identification of isomers. The energy transfer from $N_2O^{+\bullet}$ is sufficiently high for producing spectra that resemble EI spectra. The two fragmentation reactions were explored by Traeger, Hudson and McAdoo[352] by measuring the photoionization curves. The results are discussed in the framework of ion-neutral complexes proposed and reviewed by Longevialle and Botter[472–476]. The energy range over which alkane eliminations are significant increases substantially with the size of the alkane eliminated. This is attributed to an increasing polarizability of the radicals in the intermediate ion-neutral complex $[R''C{\bullet}HCO^+ \cdots R'H]$. A review of the fragmentations of ketones up to 1986 has been given by Bouchoux[342,477], on ion-neutral complexes by McAdoo[478]. The problems become rather involved when more than one functional group is present, as is often the case with enols, since the two functional groups in their combination may react differently than when they are separate. This problem is reviewed by Záhorsky[479].

The two major fragmentations of butanone are losses of Me and Et, also for low-voltage, low-temperature spectra[470]. Loss of CH_4 and C_2H_6 are of little importance. This is also true for fragmentation within the metastable time window, where the ratio of $[M - Me]^+/[M - CH_4]^+ > 10$[352], but in contrast to collisional-induced dissociation, where the loss of methane is the main fragmentation, increasing even for 'metastable' selected ions[480]. As with the fragmentation of acetone, the (main) loss of alkyl radical originates from the keto form of butanone[481]. With photoionization mass spectrometry it has been demonstrated by Traeger and his collaborators[482–484] that the two fragmentations occur at the thermochemical threshold for production of acylium ions $C_2H_5CO^+$ and CH_3CO^+. Many different isomers $C_4H_8O^{+\bullet}$ have been produced from suitable precursors (for an exhaustive list see McAdoo, Hudson and Witiak[485]) and their thermochemical data measured (see e.g., elsewhere[484,486,487]). The thermochemical data of some neutral and ionized $C_4H_8O^+$ species has been tabulated by Bouchoux[342]. The rather complicated way for explaining the alkyl loss from the different isomers is presented in Scheme 7, following a proposition by Bouchoux[342,488]. It might be mentioned that isomers having the oxygen in position 1, such as butanal, 2-Me-propanal, 2-Me-2-propen-1-ol, 2- and 3-buten-1-ol, form hydroxycarbenium $[CH_2CHCHOH]^+$ ions[480]. 3-Buten-2-ol is an exception, since it seems to produce both $C_3H_5O^+$ isomers. Bouchoux, Flament and Hoppilliard[489] performed a theoretical and experimental study on a series of $C_4H_8O^{+\bullet}$ isomers. The seemingly complicated way for losing Me had already been realized by McAdoo and collaborators[485,490] who propose a rearrangement sequence that shifts the oxygen from position 1 to position 2 in order to explain the results, including the scrambling of deuterium atoms. For an *ab initio* calculation of the competing pathway of the loss of ethylene in a McLafferty reaction for a system with the oxygen in the 1-position, see Bouchoux, Hoppilliard and Tortajada[491,492] and Hudson, Griffin and McAdoo[493]. The



SCHEME 7

latter authors performed RRKM calculations to estimate rates of reaction of the McLafferty rearrangement and concluded that this reaction must be stepwise.

The (small) loss of methane from metastable butanone **c** has an associated average translational energy of 13.5 kJ mol^{-1}[352]. Hudson, McAdoo and collaborators[494] investigated in detail, experimentally and theoretically, the barrier to methane elimination from ionized butanone. The authors compute a threshold energy of 50 kJ mol^{-1} for Me loss. They try to produce butanone by a CT (charge transfer) reaction in order to see if at very low excess internal energy content the methane loss might gain in importance. With $CS_2^{+\bullet}$ (54 kJ mol^{-1} above threshold) no fragmentation is observed. $NH_3^{+\bullet}$ (63 kJ mol^{-1} above threshold) yields 11% $MeCO^+$, 4% $MeCH{=}C{=}O^{+\bullet}$ ($[M-CH_4]^{+\bullet}$) and 35% $MeCH_2CO^+$ relative to the abundance of **c**. These figures are very close to the distribution observed by Maccoll[470] for low-temperature, low-voltage fragmentation of **c**. In another attempt to generate **c** at low internal energies, the authors let ketene ion react with C_2H_6 and C_2D_6 in an ion/molecule reaction. It is interesting that **c** can be formed by the reaction of ethane with $CH_2{=}C{=}O^{+\bullet}$, since $MeCO^+$ is not found as a dissociation product of the reaction with CH_4 with ketene by Iraqi, Lifshitz and Reuben[360]. Although **c** could not be detected, the fragmentation products demonstrate clearly the formation of the complex $[CH_3CO^+ \ {}^\bullet CH_2CH_3]$ and fragments without isotopic scrambling with approximately the same distribution as observed CT (100:3:15 for $-Et^\bullet$, $-CH_4$, $-Me^\bullet$ respectively). All *ab initio* calculations placed the transition state for H-transfer in **c** 6–7 kJ mol^{-1} above the combined heats of formation of $Me^\bullet + MeCH_2CO^+$. It is hard to understand why such a small difference can be so discriminating, in particular because tunneling was already excluded for acetone with its higher difference in energy of the TS (in favor of the Me elimination) and of the final products (in favor of the methane elimination) (see above, Brauman[356]). Hoppilliard and Bouchoux[495] advance the explanation that the rate constant for methane elimination is too large for the reaction to be observed in the metastable time

window. However, this explanation is refuted by Derrick and Hammerum[496]. Hammerum, Vulpius and Audier[497] argue that one or several isomerization mechanisms in competition with slow fragmentation can create a bimodal distribution of the internal energy that can falsify the relative distribution among competing dissociation channels allowed by a breakdown diagram, i.e. the fragmentation as a function of the internal energy. They explain the metastable Me· loss as an isomerization **d** ↔ **c**, the distonic ion **d** being about 30 kJ mol^{-1} lower in energy. The internal energy of the back-isomerizing ion would be sufficiently high for the predominant fragmentation to be the loss of Me· rather than methane.

The research on the isomerization and fragmentation of 2-pentanone, 3-pentanone and 3-Me-butan-2-one up to 1986 is summarized by Bouchoux[343], who also gives thermochemical data for the $C_5H_{10}O^{\bullet+}$ ions. The main fragmentations of 2-pentanone in the ion source are the loss of Me and ethylene. The same dissociations are also found in the metastable range and in the CT spectrum with $COS^{\bullet+}$[471], where in addition, as with higher electron energies, loss of $C_3H_7^{\bullet}$ and $C_2H_3O^{\bullet}$ is becoming important. Again the thermodynamically most stable products, corresponding to the methane elimination, is not observed. McAdoo and colleagues[498] studied the reactions of metastable $C_5H_{10}O^{\bullet+}$ ions with the oxygen on the second carbon atom. Nearly all of them seem to interconvert with each other and lose Me and ethylene at the threshold for dissociation. The loss of ethylene is explained by McLafferty and collaborators[498,499] and the reaction is named after him. The authors propose a stepwise and not a concerted reaction with the formation of a γ-distonic ion $CH_3C^+(OH)CH_2CH_2CH_2^{\bullet}$ as an intermediate product. It should be remembered that Dewar[500] questions the possibility of truly synchronous reactions. The intermediate ion is in equilibrium with $CH_2{=}C(OH^{\bullet+})CH_2CH_2CH_3$, demonstrated by the exchange of deuterium between positions 1 and 5, as several authors have shown[348,498,501]. Already in their classical paper on the photoionization of ketones, Murad and Inghram[502] have shown that the loss of Me must correspond to several different reaction mechanism, since they observe for 2-pentanone-1,1,1,3,3-D_5 a loss of $CH_3^{\bullet}$ and $CD_3^{\bullet}$ in a ratio of about 1:5, whereas the ethylene lost was practically pure C_2H_4. This is confirmed by Beynon, Caprioli and Cooks[348] and Krenmayr[503]. Harrison and coworkers[504] were able to demonstrate that the loss of a methyl from position 1 leads to the formation of the acyl ion $CH_3CH_2CH_2C{\equiv}O^+$ and from position 5 to the protonated vinyl ketone $CH_2{=}CHC(=OH^+)CH_3$. These findings were independently confirmed by Bouchoux and colleagues[501]. McLafferty and collaborators[498] and Hudson and McAdoo[505] found also evidence for a small loss of Me from position 3, which can be explained by an isomerization of the Pr side chain. It has been mentioned above that 3-penten-2-ol fragments similarly to 2-pentanone in the metastable range. Nibbering, Harrison and colleagues[506] found the same $T_{0.5}$ value of 18 meV for the ethylene loss from both isomers. Therefore, we can assume that the time behavior for Me loss for the former isomer has also some meaning for 2-pentanone. When studying the time dependence of the methyl loss from 3-penten-2-ol-1,1,1-D_3 with field ionization, they realized that $CH_3^{\bullet}$ and $CD_3^{\bullet}$ are lost already at times <30 ps, with a prevailing loss of the latter. After 30 ps, loss of $CH_3^{\bullet}$ is preponderant, but in the metastable window of *ca* 1 µs it decreases again to an intensity ratio $[M^+ - CH_3]/[M^+ - CD_3]$ of 3/2, confirmed by others[498,501,506]. This demonstrates only how difficult it is to draw valid conclusions for fragmentation pathways, realizing that mass spectrometry allows one to observe fragmentation between 0.1 ps (FIK) and 100 ms (ICR), a time window of twelve orders of magnitude.

Although the elimination of C_2H_6 is the lowest energy process for 3-pentanone, Et is the main fragment eliminated in the source, in the CAD[352] and in the charge-transfer

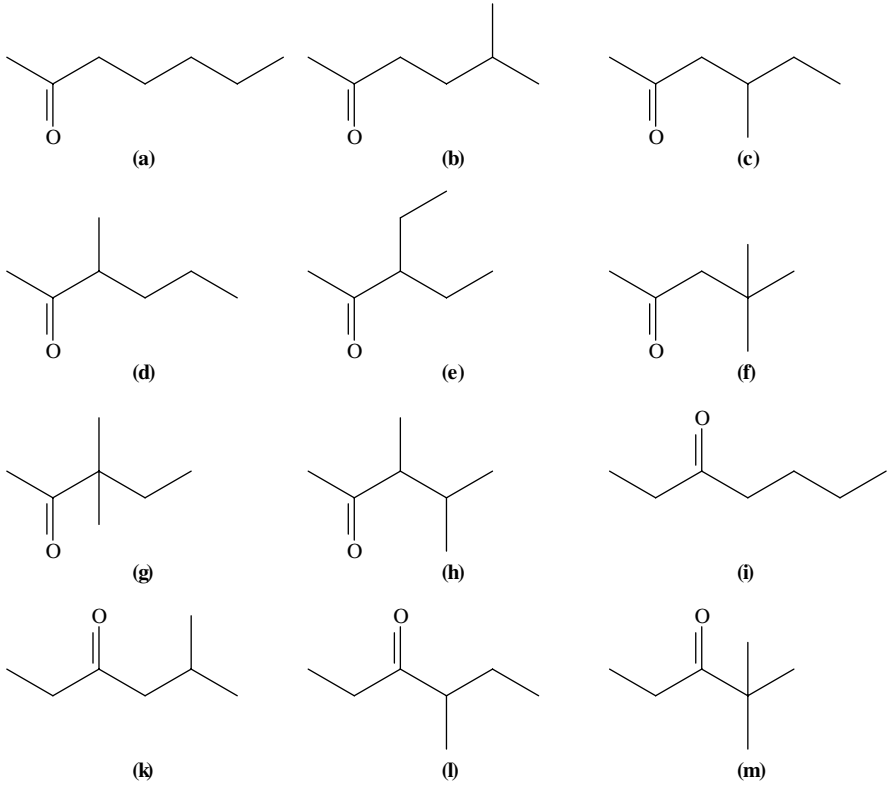
spectra[471]. It is lost from the keto form, as has been proven with ^{13}C labeling by Depke and Schwarz[507]. They show also that the keto form of 3-pentanone fragments after complete energy randomization, i.e. ergodically, contrary to acetone (see above). The prevailing Et loss within the ion source is explained by a *cul-de-sac* isomerization reaction by Hammerum, Vulpius and Audier[497] as mentioned above for butanone. From the photoionization curves obtained by Traeger, Hudson and McAdoo[352], one realizes that ethane is lost only in a rather narrow energy range, confirming the finding that in the metastable range only the loss of ethane is important. A study by Cooks and coworkers[468] indicates that metastable 3-pentanone-2,2,4,4-D_4 loses practically only CH_3CD_3. However, some isotope effect is seen, since Traeger, Hudson and McAdoo[508] measure a ratio $[M^+ - C_2H_3D_3]/[M^+ - C_2H_6]$ of 6/10 with a $T_{0.5}$ value of 17.2 and 16.2 meV, respectively. 3-Pentanone-2,2-D_2 loses overwhelmingly $C_2H_4D_2$, 3-pentanone-2,2,4,4-D_4 C_2H_5D/C_2H_6 in a ratio 2/1. The authors propose rather elaborated isomerization schemes.

3-Methylbutanone loses in the source mainly the two alkyl groups, Me and $C_3H_7^\bullet$ (isobar with $CH_3CO^\bullet$). This is also true when the ketone is ionized by low-energy charge transfer from $COS^{+\bullet}$[471], at low voltage and low temperature[470] or by photoionization[502], whereas in the metastable range loss of Me and of some C_2H_4 is observed. Bouchoux, Hoppilliard and Jaudon[509] studied labeled 3-methylbutanone-1,1,1,3-D_4 and found the following numbers for the metastable loss of Me: $CD_3^\bullet \equiv 100$, $CH_3^\bullet$: 16(29), $CH_2D^\bullet$: 4 (9), and $CHD_2^\bullet$: 3 (7); the corresponding values for ethylene are C_2H_4: 10 (10), C_2H_3D: 13 (13), $C_2H_2D_2$: 6 (6) and C_2HD_3: 1 (—), respectively. The numbers in parentheses are the values given by McAdoo and colleagues[498]. The kinetic energy releases for CD_3 and CH_3 differ only slightly: $T_{0.5} = 10$ meV and 12 meV, respectively[509]. The loss of ethylene with $T_{0.5} = 10$ meV exhibits an important scrambling. The totally different metastable decomposition pathways of the ions $[M^+ - CH_3]$ and $[M^+ - CD_3]$ produced in the source prove their different structure that has also been studied by collisional-induced dissociation[501]. The time dependence of the Me loss from 2-CD_3-3-buten-2-ol was studied by Nibbering, Harrison and colleagues[506]. The similarity of the $CH_3^\bullet/CD_3^\bullet$ ratio in the metastable range (among other considerations) led the authors to the proposal that the ion is isomerized to the 3-Me-butanone ion. Below 30 ps the loss of $CD_3^\bullet$ amounts to 90%. When the enol form of the 1,1,1,-D_3 ketone is produced from a suitable precursor, the ratio $CH_3^\bullet/CD_3^\bullet$ is inverse[498]. The isomerization of the different enol form is discussed by Bouchoux[343].

The thermochemical data for $C_6H_{10}O$ isomers are also tabulated by Bouchoux[343]. The fragmentations of isomeric 2-hexanones, i.e. 2-hexanone **(a)**, 3-Me-pentan-2-one **(b)**, 4-Me-pentan-2-one **(c)** and 3,3-diMe-butanone **(d)**, were measured by Abbatt and Harrison[471] and Maccoll[470]. Although the EI and the CT spectra of all isomers are different, **a**, **c** and **d** present identical metastable decay: loss of Me. **b** loses only little Me beside C_2H_4. The metastable loss of 1,1,1,3,3,-D_5-hexan-2-one consists of two competing losses, leading to a major $[M^+ - CD_3]$ and a minor $[M^+ - CH_3]$ loss[466,510], shown to have different structures by McLafferty and collaborators[511]. Bouchoux and collaborators[512] proved by ^{13}C labeling that Me loss **a** in the metastable range stems mainly from positions 4 and 6. In the elimination of ethylene and Et (in the ratio 7:1) considerable 'scrambling' of the carbon atoms (with the exception of position 1 and possibly 2) is observed. The necessary skeletal rearrangement of the Bu group is interpreted in terms of a 1,2-[enol-olefin]$^{\bullet+}$ shift. Loss of Pr and propene is also measured by these authors. Again, considerable mixing of the carbon positions is observed that is explained by ion-neutral complexes[332]. The loss of a methyl group not coming from the position 1 is also seen for other isomers by the research groups of Bouchoux[343,513,514] and Grützmacher[515]. In photoionization, i.e. at the

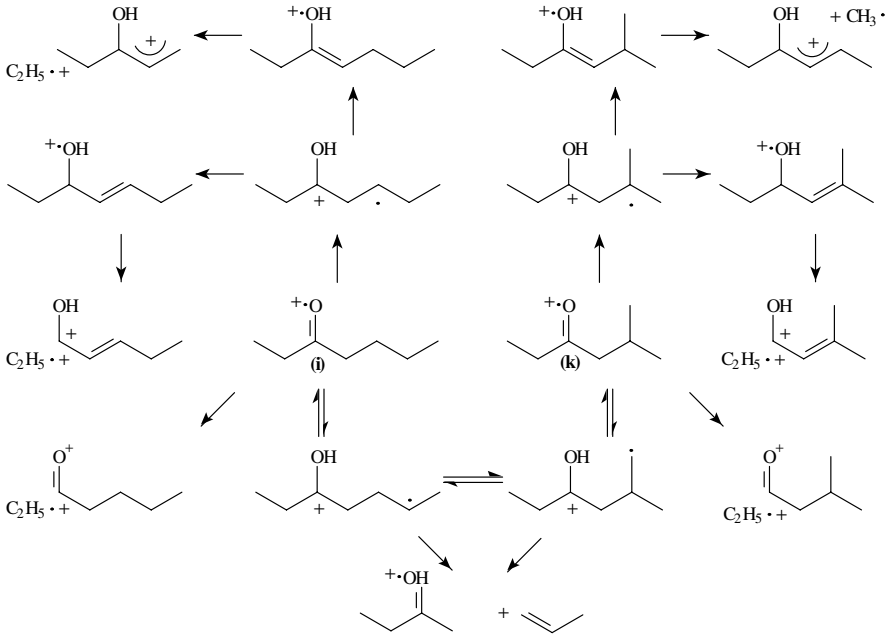
ionization limit, **a** and **c** lose mainly $Me^{\bullet}$ and propene[502]. This corresponds to the CT spectra observed by Abbatt and Harrison[471]. Loss of C_2H_6 and C_3H_8 in the ratio 5:1 with $T_{0.5}$ values of 15 and 9 meV, respectively, is observed for 2-Me-pentan-3-one (Et *i*-Pr ketone) **(e)**[352,469]. The photoionization ion efficiencies are given by Traeger, Hudson and McAdoo[352]. When deuterated in positions 2 and 4, $C_2H_3D_3$ and $C_3H_5D_3$ are lost with little or no scrambling. In 3-hexanone **(f)** ethylene is lost in a McLafferty reaction beside Et in an α-cleavage (Yeo and Williams[466]). When deuterated in the 2 and 4 positions, $C_2H_3D_2^{\bullet}$ and C_2H_4 are lost without scrambling at 70 eV. This is no longer true with low ionization energies and even less in the metastable range. This study is enlarged for metastable fragmentations, including the enol forms produced from suitable precursors and CID spectra of the main products by McAdoo and his collaborators[516]. The authors base their interpretation on the assumption that all isomerizations take place in stepwise processes, explaining the fragmentations of the deuterated ions.

Many different isomers are possible for ions of the composition $[C_7H_{14}O]^{+\bullet}$, some of them being shown in Scheme 8. Beside the fact that the elucidation of reasonable fragmentation pathways is always difficult and often not without ambiguity or some wishful thinking, the unequivocal differentiation between the different isomers is not a simple task. This problem has been addressed by several research group using different methods. Yeo and Williams[466] demonstrate for deuterated 3-heptanone (Scheme 8: **i**) that for ionization with 70-eV electrons little scrambling of the deuterium atoms could be observed; this

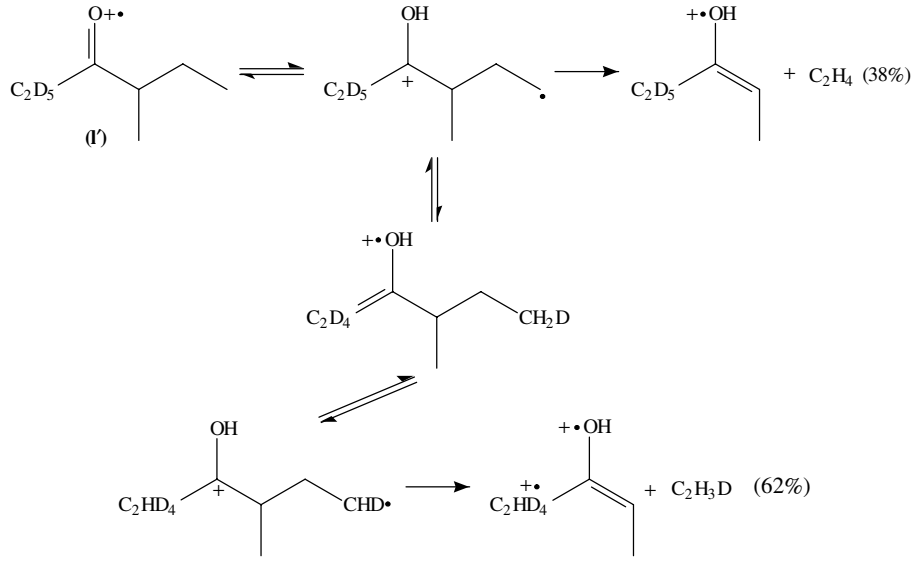


SCHEME 8

changes already for ionization with 10-eV electrons, where the lower energy increases the reaction time for fragmentation. In the metastable range, the scrambling for the loss of Et or ethylene is rather complete. This is also evident from the work of Abbatt and Harrison[471], where the impact, charge transfer and metastable spectra of the ions **a**, **c**, **d**, **f** and **i** are compared. The metastable fragmentation of 2-heptanone **(a)** is completely different from the corresponding 70-eV spectrum[517]. Since most of the methods utilizing special techniques to elucidate the structure of an ion work with ions having a lifetime of 1 μs or longer, the (eternal) question may be asked: how significant are such results for the structure of the initial ion (or molecule)? Bouchoux and collaborators[518] enlarged their above-mentioned study on the metastable fragmentation of ^{13}C-labeled 2-hexanone[512] on isomeric hexanals and the heptanones **b**, **f** and **g**. Surprisingly enough, the main fragmentation of the ions **f** and **g** consists in the loss of neutrals containing two carbon atoms, in particular ethylene (see also elsewhere[471]). By studying several deuterated isotopomers of the ions **i**, **k**, **l** and **m**, Bouchoux and coworkers[519] try to draw the fragmentation pathways presented in Schemes 9 and 10. The structure of the fragment ions produced from precursors of both high and low internal energy are identified by collision experiments in a six-sector mass spectrometer[48]. They reach the conclusion that a complete isomerization of 3-heptanone **i** and its Me isomer **k** takes place (Scheme 9), whereas **l** and **m** give essentially ethylene and Et loss, respectively. 4-Methyl-3-one **l** undergoes an isomerization to the enol distonic ion, that exchanges D atoms with the deuterated Et group before losing an ethylene by a McLafferty reaction (Scheme 10). The ion **m** loses only its Et side chain. The intramolecular ^{13}C and D isotope effect of the McLafferty reaction of 4-heptanone and 3-ethylpentan-2-one **e** is measured and interpreted by Bowie, Derrick and collaborators[520]. They assume a stepwise mechanism in which more than one



SCHEME 9



SCHEME 10

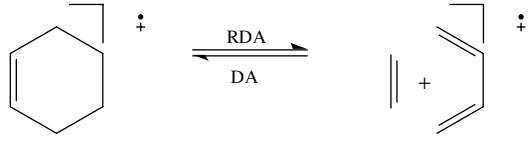
step is rate-determining. They use two mass spectrometers of different dimensions, thus having different flight times for the metastable time window. The isotope effects increase with increasing lifetime, i.e. decreasing internal energy, of the precursor ion. Traeger, Hudson and McAdoo[352] studied the alkane and alkyl elimination in the photoionization of 2,4-dimethylpentan-3-one. This ion loses exclusively propane in the metastable and Pr in the collisionally activated dissociation. They explained their results by the formation of ion-neutral complexes mentioned above. Masur, Sprafke and Grützmacher[521] come to the same conclusion for the ions **a**, **b**, **c**, **d**, **e**, **f**, **g** and **h**. They study the collision-induced dissociation. The main question they address is whether the different isomers could be distinguished by this technique. Since only in a few cases is the result unequivocal, they use the 'similarity index' introduced by the group of Nibbering[522] to distinguish between the different spectra. This index corresponds in principle to the variance of the summed difference over all peak intensities between the spectra of two isomers. It is compared with the index obtained for repetitive measurements of the same isomer, i.e. the reproducibility of the measurements. As with all statistical calculations, a confidence limit has to be defined which creates a 'gray zone' that is always open to question. The authors conclude that the isomer pairs **b/f** and **d/h** are indistinguishable in the CID range, **a/f**, **a/c** and **c/f** are limiting cases (gray zone), but the other pairs have definitely different precursors (or precursor mixtures). In a later publication Sürig and Grützmacher[464] study the charge-reversal (CR-NRMS) spectra of the negative enolate ions. Such CR mass spectra of linear heptanones differing in the position of the carbonyl group can be easily correlated with the structure of the parent ketone. For the isomeric 2-heptanones **a**–**h** of Scheme 8, the pairs **a/d**, **a/h** and **c/e** lay in the gray zone; all the other combinations are clearly distinguishable. Isomeric Me-cyclohexanones cannot be distinguished, but cycloheptanone is clearly different. A series of monoterpene ketones yield also rather identical similarity indices by this technique.

2-, 3- and 4-octanone can be distinguished by their reaction intermediate spectra, necessitating the use of a multisector instrument, as is shown by the group of Cooks[523]. Different

reaction pathways can be recognized, such as α-, γ- and δ-cleavage, simple and double McLafferty rearrangements, Et and Pr loss, cyclizations, etc. The same authors also use these substances to demonstrate the superiority of a pentaquadrupole instrument[52]. The combination of the different ion manipulations necessary for the reaction intermediate scans hide pitfalls and can produce errors that are not always immediately visible, as is demonstrated with 2-octanone by Eller and Drewello[524]. It is of interest that in the time window of FIK 7-methyl-octan-4-one-7-D_1 **a** the H/D isomerization competes with even the fastest fragmentation, whereas this is not the case for 2-octanone-1,1,1,3,3-D_5 **b**, as is shown by Derrick and collaborators[525,526]. Partial H–D randomization occurs prior to the McLafferty rearrangement. This behavior contrasts sharply with that of the straight-chain ketone **b** in which no such randomization occurs prior to the McLafferty rearrangement at times <0.7 ns. At times of 10–100 ps following field ionization (FI) the rate of the McLafferty rearrangement is an order of magnitude smaller in **a** than in **b**, but at *ca* 1 µs the situation is reversed with the rate being an order of magnitude smaller in the straight-chain ketone. The difference in kinetics is consistent with the McLafferty rearrangement at times $>$ a few 10^{-11} s following FI being a stepwise rather than a concerted process. It is proposed that H–D randomization in **a** involves γ-transfer to the oxygen forming a tertiary radical, followed by reverse D transfer from the oxygen to the alkyl chain. The reverse transfer is facilitated by the stability of the tertiary radical.

X. DIELS–ALDER AND RETRO-DIELS–ALDER REACTIONS

The Diels–Alder (DA) reaction is in its simplest form a [4+2] cyclization between a diene and a dienophile. The retro-Diels–Alder (RDA) reaction is the opening — in the simplest case — of a substituted cyclohexene as is shown in Scheme 11. According to Winters and Collins[527], the energy required to produce $C_4H_6^{+\bullet} + C_2H_4$ from $[\text{cyclohexene}]^{+\bullet}$ lies with 169 kJ mol^{-1} near the thermochemical threshold. Although not many pericyclic reactions of doublet (spin) species are symmetry-allowed[528], the DA is such a reaction (for a discussion see elsewhere[529,530]): The orbital correlation diagram reveals that cycloaddition of the ethylene cation radical to s-*cis*-1,3-butadiene is symmetry-allowed[531]. However, the reactions are not limited to six-membered rings[532]. They are of considerable importance in organic chemistry, especially because of their stereoselectivity. Since they are in addition much faster for cations than for neutrals[533], products or fragments of DA or RDA are of analytic interest in mass spectrometry. However, care has to be taken that the reaction does not already take place with the neutral substance in the inlet system, as has been demonstrated e.g. by Veith and Hesse[534] for different classes of compounds. It will be shown later that this can also be used for producing new, unstable compounds by pyrolysis.



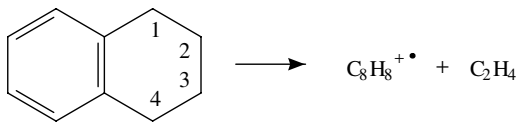
SCHEME 11

It is not astonishing that a series of reviews covers this interesting field. After a first review by Kuhne and Hesse[535] on RDA reactions of tetralin and its derivatives, a 'classical' overlook of the field was given in 1984 by Tureček and Hanuš[529]. A chapter in this series by Mruzek[25] covers the field up to 1988. The literature in the field of mass

spectrometry of large oligonucleides, primarily by electrospray and laser desorption methods, is summarized for the period 1988 through mid-1991 by McCloskey and Crain[536]. Mandelbaum[537] treated in 1993 the stereochemical effects of the RDA fragmentation in a book about the applications of mass spectrometry in organic stereochemistry[538]. Many cases of RDA fragmentations are cited in the review by Vairamani and Saraswathi[73] on a mass spectral study of geometrical *E*- and *Z*-isomers. The DA reaction of 'neutral' molecules has been reviewed by Fringuelli and Taticchi[539].

Bouchoux and Salpin[540] studied the simplest DA reaction in detail: [1,3-butadiene]$^{+\bullet}$ + ethylene, using also labeled compounds. Because of the low pressure in the ion cyclotron resonance instrument no stable adduct $[C_6(H/D)_{10}]^{+\bullet}$ is seen, only ions corresponding to the loss of Me and ethylene. Measurements of the deprotonation enthalpies indicate that the $[C_5H_7]^+$ ions have the cyclopentadienyl structure. The distribution of the deuterium atoms in the products is nearly random, contrary to the loss of ethylene, where very little scrambling is observed. The ethylene contains one terminal CH_2 group of butadiene and one CH_2 from ethylene. Since the two fragmentations have about the same time dependence, it can be assumed that they originate from the same adduct, which the authors propose to have the structure of the distonic ion $CH_2{=}CHC^+HCH_2CH_2CH_2^\bullet$. That this reaction occurs without critical energy is concluded by Bauld[541] from a MO calculation. This ion either isomerizes to a vinycyclobutene that can split off an ethylene, or it undergoes several hydrogen shifts causing the H/D scrambling and finally leading to a Me-cyclopentadiene that loses the methyl group. The complex addition–dissociation of 1,3-butadiene cation and ethylene precludes a synchronous character for the DA reaction.

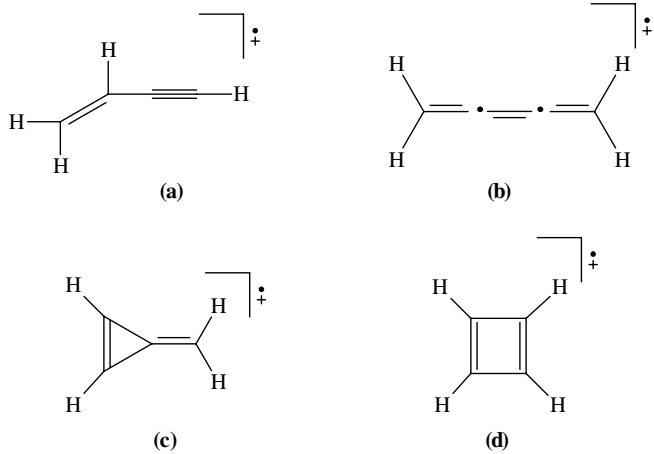
The RDA reaction is a high-energy process that is in competition with other processes that need less activation energy, albeit with higher steric hindrance. Even if one limits the RDA process as an elimination of a dienophile that contains two consecutive carbon atoms from the ring (in the correct initial position), there is still the possibility of a concerted or a two-step process, possibly in competition. In the latter case, the stereospecific characteristic of the RDA fragmentation may be lost. Several reactions yielding the same products may compete with each other, asking for much experimental ingenuity in order to get a clear-cut answer. This may be illustrated by the classic elimination of ethylene from tetralin that had been studied by Budzikiewicz, Levsen and collaborators[542,543]; see also Mruzek[25] (Scheme 12). The time dependence of the reaction is studied with the help of field ionization kinetics, using ^{13}C- and D-labeled compounds. It results that ethylene is not only lost in a RDA reaction from position 3 + 4, but also from 1 + 4 and 2 + 3 and after complete scrambling of all C and D atoms of the saturated ring. The time dependence demonstrates that the high-energy RDA process prevails at short times, giving way after 1 ns to the process that eliminates ethylene from positions 1 + 2 and 3 + 4, which is still the main process in the metastable window (>1 μs), although an important scrambling sets in after 1 μs. Therefore, it can be concluded that the metastable decomposition and the structure of the molecular ion that is used for the study of fragmentation by collisional activation do not necessarily correspond to the structure of the initial molecular



SCHEME 12

ion after ionization. It can be assumed that the resulting $C_8H_8^{+\bullet}$ ion consists of a mixture of structures. The RDA fragmentation might yield the *o*-quinodimethane ion, the 1,2-elimination may yield styrene. CID experiments give a spectrum that is somewhere midway between the corresponding spectra of styrene and the $C_8H_8^{+\bullet}$ ion formed from tetrahydroisoquinoline. The latter fragments in a pure RDA reaction. The ideal case for such a study is the 'symmetric' molecule 5,6,6*a*,7,12,12*a*-hexahydrobenzo[*a*]anthracene, studied by Bobenrieth, Levy and Hass[544] and amply discussed by Mruzek[25].

$C_4H_4^{+\bullet}$ is an interesting candidate for a study of the DA reaction, since in spite of its simple formula it exists in several isomeric forms that can be prepared separately. Its rate of formation as a function of the internal energy of benzene, one of its precursors, has been measured by Andlauer and Ottinger[545,546]. Rosenstock and collaborators[547,548] propose the existence of linear and cyclic forms. Several attempts to elucidate the structure of $C_4H_4^{+\bullet}$ are summarized by Baer and collaborators[549] who studied its formation, together with that of $C_3H_3^+$, as a function of the internal energy of 2,4- and 1,5-hexadiyne as precursors. They suggest the structure of a methylene-cyclopropene cation (**c** in Scheme 13) for $C_4H_4^{+\bullet}$. Benzene and pyridine as precursors were studied by Ausloos[550]. In the fragmentations two $C_4H_4^{+\bullet}$ are formed, only one of them reacting with benzene. On the basis of CT reactions he attributes the structure of 3-butene-1-yne **(a)** to the reactive form and methylenecyclopropene **(c)** to the unreactive form. Bowers and collaborators[551] confirm the findings by Ausloos and show that the linear form can be isomerized with acetylene to the cyclic form over a long-lived $C_6H_6^{+\bullet}$ intermediate. Van der Hart[137], studying the photofragmentation of benzene and 1,5-hexadiyne, determined that in these fragmentations 60% **a**, 10% **b**, and 30% **d** are formed, measured on the time scale (milliseconds) of an ion cyclotron resonance spectrometer. When studying the ion/molecule reactions, unimolecular dissociations and CID spectra of a series of precursors, the group of Lifshitz and Levsen[552] adds cyclobutadiene **(d)** as an additional structure to the list. Kohn and Chen[553] measured the photoelectron spectrum of cyclobutadiene, determined an ionization energy of 8.16 ± 0.03 eV and confirmed the rectangular structure for the neutral and the ion. The spectrum confirms that correlation between σ and π electrons is needed in an *ab initio* calculation for the ion to obtain even a qualitative correct geometry for the Jahn-Teller distorted ion. The group of McLafferty[554–556] confirms all four structures with



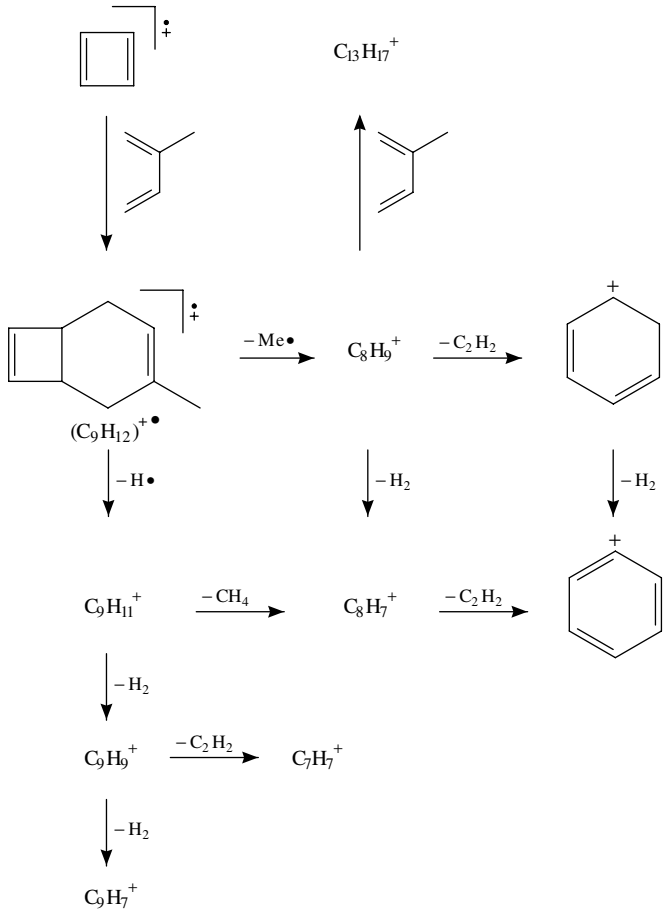
SCHEME 13

the help of the newly developed NRMS technique. The four isomers **a–d** can be produced from vinylacetylene, butatriene, 6,7-benzo-3-methylenetricyclo[3.2.2.0^{24}]nona-6,8-diene and 7,8-benzotricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene, respectively[49]. Cyclobutadiene radical cation is also obtained directly from *cis*-3,4-dichlorocyclobutene[557]; its potential surface is calculated by Borden, Davidson and Feller[558]. McLafferty and collaborators[554] show that neutrals that correspond formally to the condensation products of cyclobutadiene or methylenecyclopropene with benzene or naphthalene yield, on electron impact, $C_4H_4^{+\bullet}$ ions with a structure that corresponds to the C_4H_4 in the neutral. A summarizing overview is given by Zhang, Carpenter and McLafferty[559].

The possibility of a DA reaction by the four isomers **a–d** in Scheme 13 is studied in detail by Shay, Eberlin, Cooks and Wesdemiotis[49]. They use a pentaquadrupole instrument, where the first (Q1), third (Q3) and fifth (Q5) quadrupole are used as mass analyzers and the second (Q2) and fourth (Q4) as 'reaction chambers'. Different combinations of the mass analyzing quadrupoles allow experiments that give answers to rather specific questions such as sequential product and reaction intermediate scans. Although for none of the isomers is the DA-reaction product with isoprene detected at *m/z* 120, the authors are able to show that only cyclobutadiene **d** yields fragments that could be derived from the unstable intermediate product $C_9H_{12}^{+\bullet}$. The authors formulate this ion as derived from a cycloaddition yielding the 2-methylcyclo[4.2.0]octa-2,5-diene (Scheme 14). The ions *m/z* 119 (loss of $H^\bullet$) and *m/z* 105 (loss of $Me^\bullet$) form the basis of this conclusion. The latter ion can add an additional isoprene neutral in a second DA reaction to yield the ion *m/z* 173 ($C_{13}H_{17}^+$). In Scheme 14 a series of consecutive reaction products that are observed from these 'primary' fragments of the DA product reinforce this conclusion. The origin of many of these ions is proven by using the multiple possibilities the pentaquadrupole instrument offers. The ion–molecular reactions of the other ions **a–c** with isoprene are dominated by charge exchange with the neutral, forming products starting from the isoprene cation (*m/z* 68), subsequently reacting with isoprene neutrals. The product spectra differ only slightly from the results of the ion/molecule reaction between isoprene ion with the isoprene neutral . These results show that the DA reaction has little chance in cases where competing reactions exist. The competition by the CT was confirmed when the isomeric ions were allowed to react with allene.

The correctness of these conclusions was proven by the fact that only cyclobutadiene underwent a DA reaction (series) with thiophene and furan[49]. Again the primary addition product is unstable, but the fragmentation products (loss of $H^\bullet$ and of Me) from the unstable precursor could again be identified, in addition to the loss of $C_3H_3^\bullet$, yielding the aromatic six-membered heterocyclic ring. In the reaction with the thiophene neutral the elimination of acetylene yielding an odd-electron ion is observed, necessitating a preceding rearrangement to a thiocyclohexadiene or thiocycloheptadiene structure before fragmenting. Other candidates as precursors (e.g. a substituted tiophenol) could be ruled out with the help of sequential product scans, showing again the possibilities of a multiquadrupole instrument. The authors[49] conclude that it is difficult to distinguish the isomeric $C_4H_4^{+\bullet}$ ions on the basis of their ion/molecule reactions (a possibility offered by multisector instruments), whereas it is even more difficult to do so by conventional CID methods. This is both because of the milder conditions used to perform ion/molecule reactions and because bond-forming processes allow a greater variety of products than the (often) brute-force conditions of CID. To determine the set of four $C_4H_4^{+\bullet}$ isomers one needs simply to apply the allene and thiophene reactions. The yields of $C_4H_4^{+\bullet}$ addition products to electron–rich dienes decrease in the order **d** > **a**, **b** > **c**.

An important question is when the DA reaction is a concerted or a two-step cycloaddition. This question is answered experimentally by Groenewold and Gross[560] and theoretically by Bauld and collaborators[530,531] for the reaction of butadiene neutral with



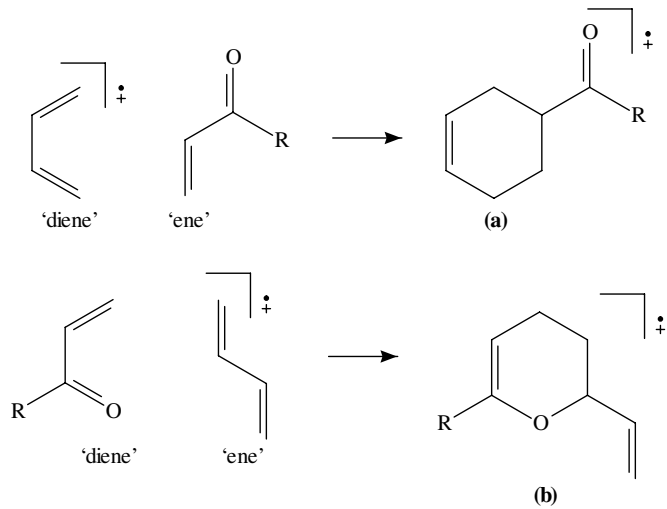
SCHEME 14

1,3-butadiene cation radical, and by Holman, Rozeboom, Gross and Warner[561] with benzene ion in favor of the two-step process. In the former reaction the resulting $C_8H_{12}^{+\bullet}$ is decomposed by collision-induced fragmentation. If this ion is stabilized by collisions before CID, the resulting spectrum corresponds closely to the spectrum of vinylcyclohexene, but without collisional stabilization, a branched acyclic cation radical was found. Therefore the cyclization must proceed in two steps. CS_2 is used as a stabilizing gas because of its high ionization energy and in order to avoid further reactions of neutral butadiene with the adduct. Slight deviations between the CID spectra of vinylcyclohexene and the collisionally stabilized product are explained by small amounts of [2 + 2] and/or [4 + 4] additions. The results with benzene are analogous: With collisional stabilization, the CID spectrum corresponds to a 2-phenyl-2-butene radical cation and without prior stabilization to 1-methylindan.

Chen and Williams[562] demonstrated by ESR the rearrangement of 4-vinylcyclohexene to bicyclo[3.2.1]oct-2-ene in a $CFCl_3$ matrix when irradiated by γ-rays and then

allowed to warm from 77 K to 140 K. Semiempirical AM1 calculations by Dewar and coworkers[563] have shown this rearrangement to be exothermic by 59 kJ mol^{-1}. As an intermediate structure Chen and Williams propose either a bicyclo[3.2.1]oct-2-yl-6-ylium or a bicyclo[2.2.2]oct-2-yl5-ylium distonic ion. Vollmer, Rempel, Gross and Williams[564] demonstrated the occurrence of this isomerization in the gas phase by use of MS/MS and ion cyclotron resonance spectrometry, using a specially developed technique to collisionally cool the ions[565]. When vinylcyclohexene and bicylo[3.2.1]oct-2-ene were separately ionized by electron impact, they had identical CID spectra. However, when they are ionized by charge transfer from CS_2 and collisionally cooled, their CID fragmentation is different in the intensity ratio of the $[M^+ - Me]/[M^+ - C_3H_6]$ peaks produced. Since the FT instrument allows a controlled excitation of the collisionally cooled ion, this peak ratio is measured as a function of the excitation energy. Since it passes through a maximum before decreasing to the small value corresponding to bicylo[3.2.1]oct-2-ene, the existence of an additional unstable and unknown intermediate ion is postulated.

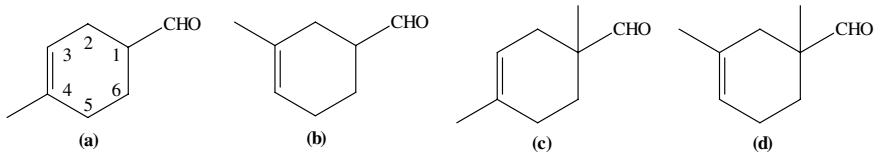
1,3-Butadiene cation reacts with acrolein and methyl vinyl ketone to produce products that can be stabilized by collisions. The question arises as to whether the butadiene ion reacts as a dienophile or as an 'ene' in these reactions? This problem has been attacked by Castle and Gross[566]. The two possible pathways are given in Scheme 15 (acrolein: R = H, **a1**, **b1**; Me vinyl ketone: R = Me, **a2**, **b2**). The authors use an ion cyclotron mass spectrometer at low pressures and a triple-sector instrument for CID studies at high pressures. Since they did not dispose of pulsed multiple inlet systems for their instruments, the simultaneous ionization of both components of the mixtures poses some problems. By measuring the time dependence of the product formation and disappearance and using the feature of double resonance in the FTICR instrument, they are able to circumvent some of the problems. An additional complication is the isomerization of the substituted pyran **b1** to the aldehyde **a1** by a Claisen rearrangement; the metastable decay of these two products are practically identical, as has been shown by Sarraf, Audier and Morizur[567]. Thus the two possible adducts **a** and **b**, that are not detectable at the low pressure of the FT instrument, are difficult to be characterized according to their CID spectra in the high



SCHEME 15

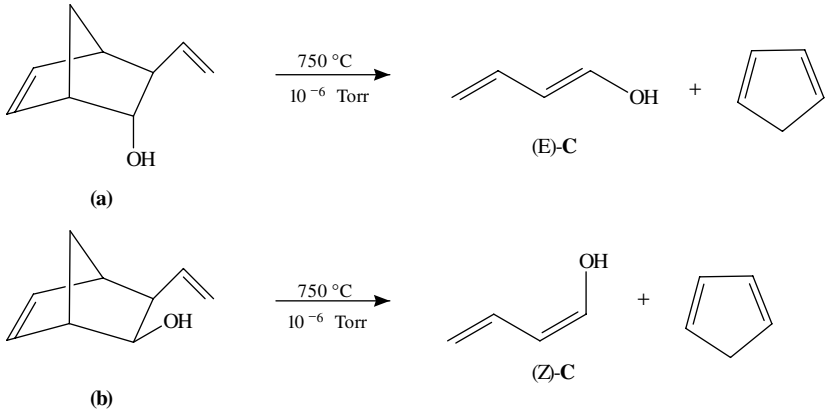
pressure instrument. However, by a series of experiments the authors are able to advance arguments that the butadiene cation serves as the 'ene' and the acrolein and methyl vinyl ketone react as dienes, forming adducts that have the pyran structure **b**. This is supported by the finding that a substituted pyran does undergo the corresponding RDA reaction in a metastable decay[567].

At least in solution this does not seem to be the case, because Mayoral and collaborators[568] performed the reactions between isoprene and acrolein and methacrolein in toluene solution and got only products that had the structure of a substituted cyclohexene carbaldehyde (**a**, **b** for acrolein; **c**, **d** for methacrolein in Scheme 16). Their aim was to study the RDA reaction of these products. The experimental results are complemented by semiempiric AM1 MO calculations, since it has been shown by Camaioni[569] for the through-bond delocalization in bibenzylic systems and by Wiest, Steckhan and Grein[570] for the calculations of the selectivity of the DA reactions in indoles and electron-rich dienes, that this method is perfectly useful for such systems. This is of importance for the decision, if — under the assumption of a stepwise reaction — the C(1)−C(2) or the C(5)−C(6) bond is opened, On the basis of these calculations, the authors could show that in the case of **a** the former and of **b** the latter case is energetically more favourable. This allows one to explain the observed differences in the electron impact and the metastable spectra of **a** and **b**: **a** → $[M - Me]^+$, $[M - H_2O]^{\bullet +}$, $[M - CO]^{\bullet +}$; **b** → $[M - CHO]^+$, as main peaks in the metastable decay. The case of **c** and **d** is slightly more complex. The calculations for this case show that the scission of C(1)−C(2) is energetically more favorable than C(5)−C(6) for both ions. This is consistent with the H_2O loss for both isomers in the metastable fragmentation. By simplifying the results of the calculations one can say that a metastable loss of H_2O is characteristic for a scission of the C(1)−C(2) bond, whereas loss of ·CHO is typical for an opening of the C(5)−C(6) bond. Since $[M - HCO]^+$ is much more important for **d** than for **c**, it is to be concluded that the opening of C(5)−C(6) is more important for the former in spite of the calculations that predict a difference in heats of formation between C(1)−C(2) and C(5)−C(6) scission of 95 and 54 kJ mol^{-1} for **c** and **d**, respectively. Since the spectra are rather different, an isomerization of one form in another does not seem to be important, the problem remains to be definitively resolved.



SCHEME 16

The stereospecificity of the RDA reaction can be used to produce unstable species and to determine their thermodynamic properties with the mass spectrometer. Such a project was undertaken by Tureček and collaborators[571] to distinguish the *Z*- and *E*-form of the dienol **c** given in Scheme 17. The 3-*exo*-vinylbicyclo[2.2.1]hept-5-en-2-ol is flash-pyrolized in the inlet system of a mass spectrometer and ionized within a few ms after decomposition. The mass spectra and the ionization energies of **E-c** and **Z-c** were determined. The electron impact spectra are similar, although some reproducible differences can be seen; the CID spectra are identical. The same ions are produced by dissociative ionization of the precursors **a** and **b**. Their CID spectra are identical, however different from the isomeric aldehyde[572]. The ionization energies of the neutral dienols were measured as IE(*E* - **c**) = 8.51±0.03 and IE(*Z* - **c**) = 8.47±0.03 eV, respectively. Since the activation

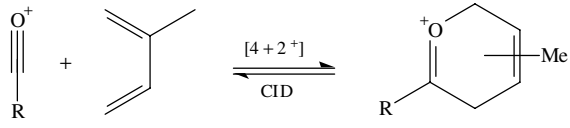


SCHEME 17

energy for thermal $Z-E$ isomerization has been estimated by Rabinovitch and Michel[573] to be about 200–250 kJ mol^{-1}, it is improbable that the two forms isomerize. The authors obtain $\Delta H_f^\circ([E\text{ - }\mathbf{c}]^{+\bullet}) = 733 \pm 5$ kJ mol^{-1} and $\Delta H_f^\circ([Z\text{ - }\mathbf{c}]^{+\bullet}) = 728 \pm 6$ kJ mol^{-1}.

A possible isomerization before or during a RDA reaction must be taken into account. With this question in mind Buchs and collaborators[574] prepared a large number of D- and ^{13}C-labeled 2-cyclohexen-1-ols and studied the loss of ethylene from the molecular ion which corresponds to the base peak in the EI spectrum. The mass shift for the different D-labeled compounds indicated no H/D scrambling, but the presence of (at least) two different RDA processes; 35% correspond to the elimination of C(5) + C(6) as neutral ethylene, in 65% C(4) + C(5) are lost. The latter route requires that the molecular ion undergoes an allylic isomerization either via a 1,3 shift of the C(1) hydrogen (shift of the double bond in position 1), or of the OH group. Similar isomerizations have been observed before, e.g. in cyclohexene[297], menthene[575] or methylcyclohexene[576]. The elimination of Me is not straightforward in 2-cyclohexen-1-ol. Labeling studies prove that the carbon of the Me group comes from position 2, whereas in the metastable time scale a complete scrambling of H/D is observed. Since Derrick, Falick and Burlingame[297] have shown that on the *ca* 10 ps time scale of a field ionization kinetics experiment, an All group of cyclohexene is eliminated without any scrambling, together with an additional H-atom, some sort of reversible isomerization between a six- and five-membered ring could be assumed. This has been shown to be the case for (even electron) *c*-Hex ions by Wesdemiotis, Wolfschütz and Schwarz[577]. However, no definitive conclusion could be reached for cyclohexenol.

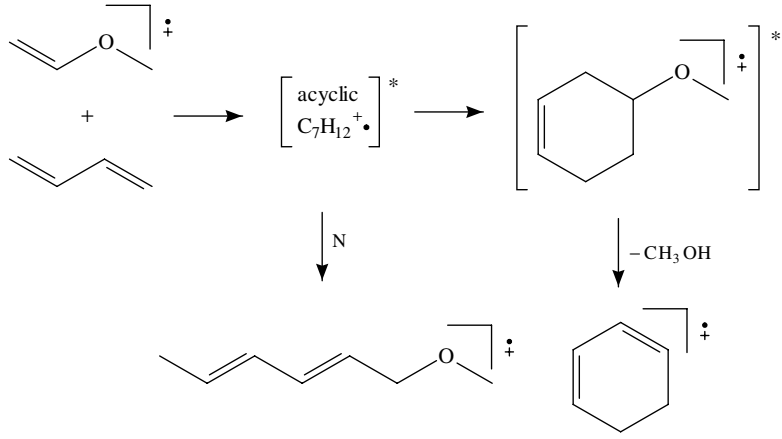
Eberlin and Cooks[578] discovered that acylium ions react with neutral isoprene and other 1,3-dienes in the gas phase to form covalently bound adducts by polar [4 + 2$^+$] Diels–alder cycloadditions. The general reaction is given in Scheme 18, where R may range from H and alkyl to unsaturated, aromatic and polar substituents. The formation



SCHEME 18

of stable adducts occurs for the acetyl ion, but not for its $C_2H_3O^+$ isomers, as was also shown by the groups of Cooks[579]. Isoprene is used as neutral to check if a DA reaction (yielding a stable adduct or its fragments) or a charge or proton transfer takes place with the acyl ion. R = Me, Ph, Me_2N, $H_2C{=}C(i\text{-Pr})$, PhHC=N yielded stable adducts in at least tenfold excess compared to the proton-transfer product; for R = H, MeNH, HO, Cl only the CT product could be observed. Some substituents show comparable probabilities for both reactions. A second question is the necessary structure of the neutral indispensable for a stable adduct. The acetyl ion is used as probe. Only isoprene, 1,3-butadiene and cyclopentadiene give a stable adduct whose structure seems to correspond to a $[4 + 2^+]$ addition. When 3-methylenecyclohexadiene is used, with a diene which is locked in the *trans* configuration, the adduct is not generated and the product spectrum is dominated by proton transfer. It seems that a *cis*-diene conformation is needed for the DA reaction. In order to discriminate against a $[2 + 2^+]$ addition, the reaction of 1,3-butadiene is compared with that of limonene, a nonconjugated diene. The latter yields very little adduct products. Similarly, the acetyl cation fails to show substantial adduct formation with benzene, benzonitrile and Et vinyl ether. Thus, ample evidence is produced to show that a $[4+2^+]$ addition takes place. MS^3 spectra (see above) give additional evidence for such an addition.

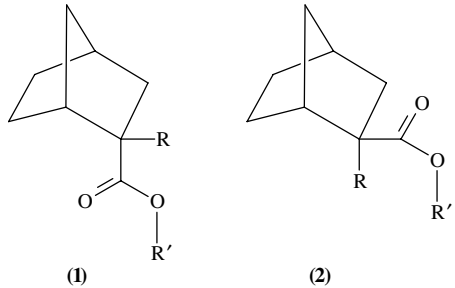
The reaction of vinyl Me ether cation radical with 1,3-butadiene forms another case where the reaction scheme seems to be rather complicated, as is demonstrated by Groenewold and Gross[580]. When the reaction is being conducted at low pressure, no adduct is observed. Since the ether as well as the diene is ionized by electron impact, both molecular ions and their fragmentation products are observed in the ion source. The time revolution in the ICR spectrometer shows a rapid transfer from the butadiene ion to vinyl Me ether. At the same time $C_6H_8^{+\bullet}$ (*m/z* 80) and $C_6H_9O^+$ (*m/z* 97) rise in a ratio of about 10:1. The fragment *m/z* 80 corresponds to a loss of methanol, typical for a 4-methoxycyclohexene, as is shown by deuterium labeling by van Doorn, Nibbering, Ferrer-Correia and Jennings[581]. These observations are strong evidence for a cyclic adduct at low pressures. In a high-pressure ion source the adduct ion is stabilized by collisions; it can be isolated and studied by CID. There is no resemblance with any cyclic product, but a nearly 1:1 correspondence with the spectrum of 2,4-pentadienyl Me ether. Therefore the authors propose the reaction sequence of Scheme 19, where an acyclic unstable



SCHEME 19

intermediate adduct either undergoes ring closure to the unstable substituted cyclohexene or is stabilized by collisions to the stable pentadienyl Me ether. Sequential and not two parallel reactions are preferred, because in the latter case, as well as in the low- as in the high-pressure spectra, evidence of both structures should be evident, which is definitely not the case.

The influence of stereochemistry on the mass spectrum in the RDA reaction can be well studied with substituted norbornanes (bicylo[2.2.1]heptane). Traldi, Cativiela and collaborators[582] studied the case of mono- and disubstituted norbornanes (see Scheme 20). For the carboxylic acids **1a** and **2a**, there is a clear difference in the spectra produced by electron impact: e.g. the *endo*-form **1a** having $[M - C_2H_3O_2R]^{+\bullet}$ as the base peak, whereas the *exo*-form **2a** had a much stronger tendency to lose the carboxylic group. However, this is not the case for the slow metastable decay, where spectra of both ions are indistinguishable. The isomerization of the two forms, although slow compared to the larger part of the decay (which takes place in <1 ns), is faster than the metastable time window (>1 μs). Clear differences are also observed for the two isomers **1b** and **2b**, but in contrast to **1a** and **2a**, also the metastable spectra are different, e.g. the intensity of $[M - ROH]^{+\bullet}$ is more important for the *exo*-isomer. **1c** and **2c** are again different in the electron impact and the metastable spectra, but for **1d** and **2d** only minor differences can be seen in both kinds of spectra. Different substituents may change the fragmentation pathways and with this a stereoisomeric difference may manifest itself or not. Of special interest is the dependence on the time scale of fragmentation; isomerization may precede the relatively long time needed for a collisional excitation experiment. However, the fact that the RDA reactions of differently D-labeled 5-norbornenols have been used by Tureček and Hanuš[583,584] to prepare by flash pyrolysis differently labeled unstable ethenols and to obtain their mass spectra proves that usually the fast fragmentations proceed without too much isomerization.



(1) **(2)**

(a) R=R′=H
(b) R=H;R′=CH_3
(c) R=$NHCOCH_3$;R′=H
(d) R=$NHCOCH_3$;R′=CH_3

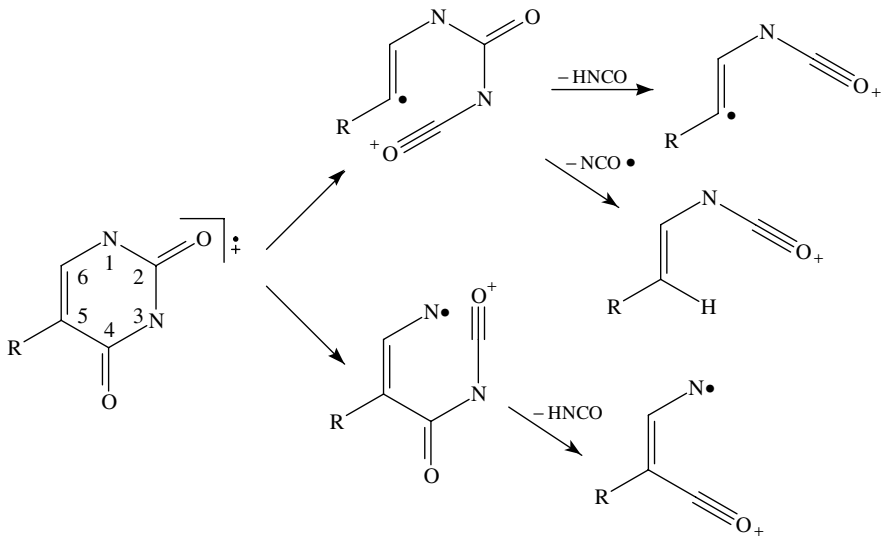
SCHEME 20

Vainiotalo and collaborators[585] measured the electron impact spectra of several either di-*exo*- or di-*endo*-norbornane/ene-fused 2-*N*–phenyl iminoperhydro-1,3-oxazines. Whereas the stereoisomeric unsaturated compounds cannot be distinguished on the basis of their electron impact spectra, the spectra of the stereoisomeric saturated compounds are sufficiently different to allow differentiation of the stereoisomers. The N-substituents were either H or Me. The difference is due to the fact that the unsaturated compounds fragment mainly by two RDA reactions with first a loss of cyclopentadiene and then yielding

phenylisocyanate O=C=NPh$^{+\bullet}$ as the base peak. *N*–Me substitution changes the base peak to the diene fragment *N*-(2-propenylidene)methylamine, probably because of a shift of the ionization potentials. The fragmentation of the saturated compounds is more complex and allows the differentiation of the stereoisomers. The same authors[586] study also the fragmentation of four norbornane/ene di-*exo*- and di-*endo*-fused 1,3-oxazin 2(1*H*)-ones and four 1,3-oxazines-2(1*H*)-thiones. The results are so far similar in that it is again possible to differentiate among the saturated compounds, whereas the unsaturated molecules allow no distinction. The use of CI as a softer ionization technique reveals some differences. It might well be that initially the difference in structure is maintained, but the small barrier to isomerization asks for especially mild ionization techniques. Hints in this direction may be taken from the work of the group of Vainiotalo[587], where four diastereoisomeric camphane-2,3-diols were synthesized and their mass spectrometric behavior studied. Electron impact ionization spectra are within reasonable limits identical and stereochemical effects are weak when NH_3, *i*-C_4H_{10} or CH_4 are used as CI reagents. The situation is much more favorable when the CID spectrum of the ammonium adduct $[M + NH_4]^+$ is measured. The study of this adduct, possible with the CID spectra for its main fragment $[M - H_2 + NH_4]^+$, may allow a differentiation of the stereoisomers. Labeling experiments show that the two hydrogen atoms come from the hydroxyl groups.

Rice, Dudek and Barber[588] were the first to show that the major fragmentation in the electron impact spectrum of uracil was the RDA reaction with a loss of HNCO (or RNCO) from positions 2 and 3. Reiser[589] proved this not to be always the case, depending on the substitution. An alkyl group with two or more carbon atoms in position 2 gives rise to a $[M - C_4H_7]^+$ ion that often forms the base peak. The RDA reaction can be used to differentiate between 2- and 4-thiouracils, and between 1- and 3-Me and Ph substituted uracils. Traldi and coworkers[590] studied the influence of different substituents R in position 5 of uracil on the metastable spectrum (R = H, F, Cl, Br, I, OH, CF_3, Me). For all substituents except R = OH the 'RDA' peak $[M - HNCO]^{+\bullet}$ forms the base peak with >80% of the total intensity. For OH as substituent, $[M - HN(CO)_2]^{+\bullet}$ is of comparable intensity. They assume the reaction sequence given in Scheme 21, where positions 3 and 4 as well as 2 and 3 are eliminated in the RDA reaction, contrary to the proposition of the authors cited above. The reason is that the metastable spectra of the $[M - HNCO]^{+\bullet}$ fragments are different for the different neutral precursors: for R = OH and CH_3, exclusively CO is eliminated; for R = Cl and Br, HCN is the neutral fragment lost; for R = F and CF_3, the loss of both of these fragments is observed; this is also true for R = I, but in addition I^+ and CI^+ are formed, probably because of their low ionization energy; with R = H, $[(M - HNCO) - H]^+$, $[(M - HNCO) - HCO]^+$ and $CO^{+\bullet}$ are additional fragments of comparable intensity. Therefore several $[M - HNCO]^{+\bullet}$ and/or mixtures thereof must be formed according to the substituent of the uracil. This is underlined by the very different values of $T_{0.5}$ that vary between 50 and 1100 meV according to the substituent.

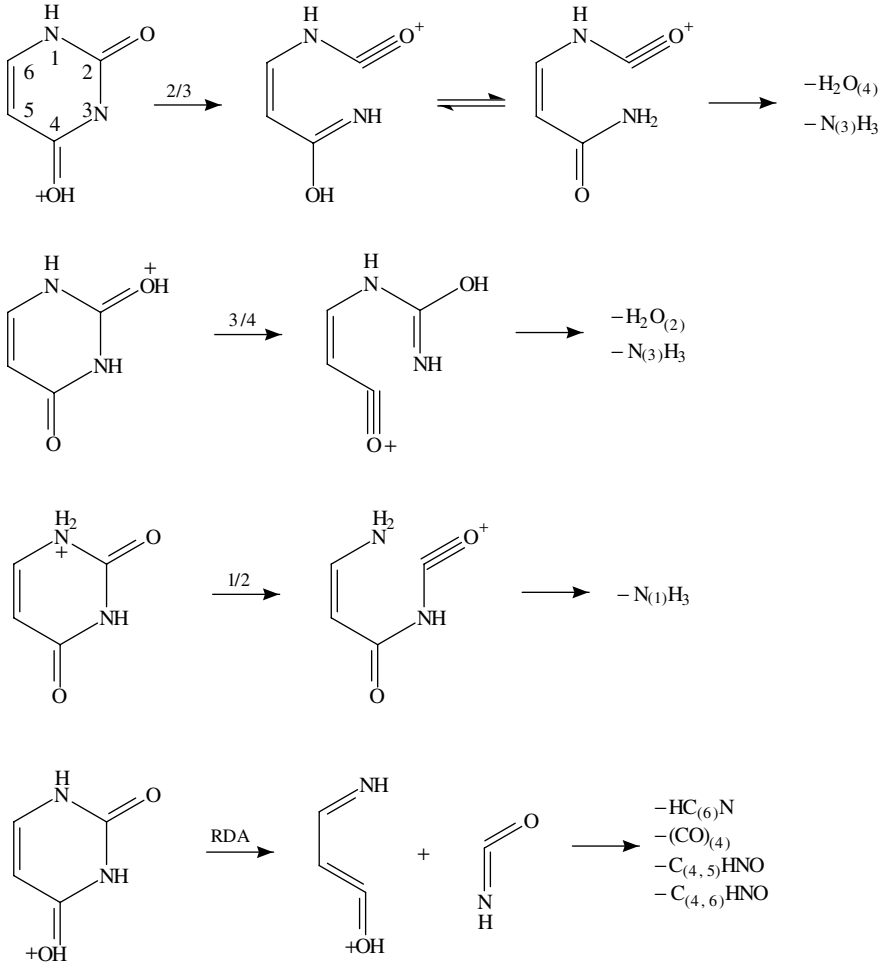
Nelson and McCloskey[591] studied the collision-induced dissociation of protonated uracil and some of its derivatives using extensive isotopic labeling with D, ^{13}C, ^{15}N and ^{18}O. The principal fragment in the CID spectrum of the protonated uracil molecular ion MH^+ is again the ion resulting from a RDA reaction, $[MH - HNCO]^+$, followed in importance by $[MH - NH_3]^+$, but the spectra of the labeled uracils confirm the suspicion advanced in the paragraph above that several pathways for the RDA reaction are possible even for the unsubstituted molecule. For the principal fragments the following pathways are determined (for the numbering see Scheme 22): $[MH - NH_3]^+$: 7% N(1), 95% N(3); $[MH - H_2O]^+$: 50% O^2, 50% O^4; $[MH - HNCO]^+$: 10% (N(1) + CO(2)), 87% (N(3) + CO(2)), 3% (N(3) + CO(4)); $[MH - NH_3 - CO]^+$: 90% (N(3) + CO(4)), 10% (N(3) + CO(2)); $[MH - H_2O - CO]^+$: 100% (CO(2) + O^4). Most of the minor fragments are also formed



SCHEME 21

in highly site-specific processes. The first question to answer is where the protonation takes place. Hass, Mezey and Ladik[592] calculate that the two oxygen atoms should have about the same probability to be protonated. This seems to be a general feature[593]. However, an observation by Kenttämaa[594], that in the moment of the collision process isomerizations may take place, makes the question somewhat academic. The findings of Nelson and McCloskey[591] are summarized in Scheme 22: Several initial isomers are assumed; in three of them a ring opening (*k*/*l*) between two consecutive atoms *k* and *l* takes place before fragmentation sets in. This explains the loss of H_2O and NH_3 as primary fragmentation, whose sum amounts to about 80% of the RDA reaction. A small percentage of the primary ions fragments further in often clean processes, coupled with hydrogen transfer, but deuteration of positions 5 and 6 indicated that some hydrogen exchange between these positions and the heteroatoms takes place before elimination of the neutral fragments. The authors studied also the influence of substitution in the pyrimidine ring: 2-thiouracil, 4-thiouracil, 2-thiothymine, as well as 3-methyluracil and a series of C-5-substituted uracils (Me−, −OH, CH_3O−). The results, taken *cum grano salis*, are similar. It may be mentioned that the mass spectrum of the deprotonated negative ion of uracil (*m*/*z* 111) seems to be simpler, consisting of only two ions, *m*/*z* 67 and *m*/*z* 42, as is demonstrated by Sakurai, Matsuo, Kusai and Nojima[595].

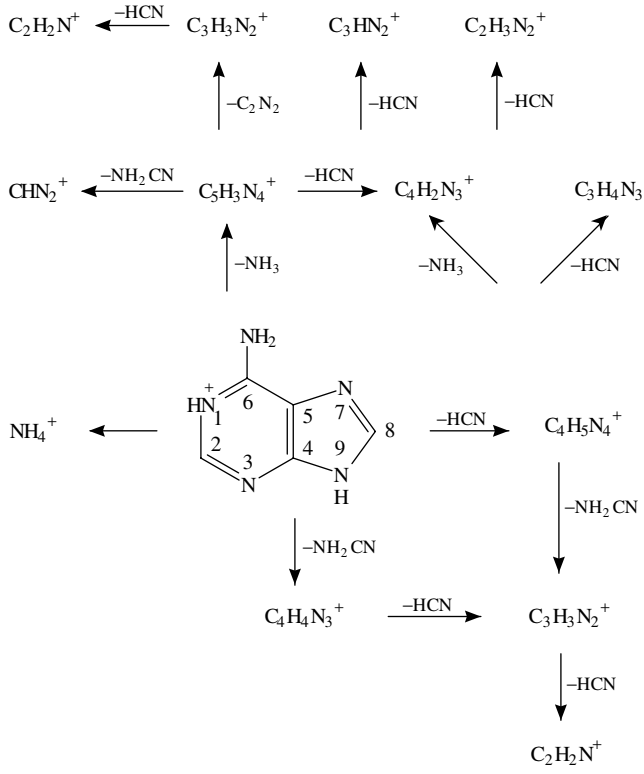
Nelson and McCloskey[596] studied also the collision-induced fragmentation of protonated adenine (Scheme 23), again labeled with ^{15}N, ^{13}C and D. Four main primary reactions are determined: $[MH - NH_3]^+$: 55% N(1), 45% N(6); $[MH - NH_2CN]^+$: 100% N(1) + N(6); $[MH - HCN]^+$: 90% N(1) + C(2); NH_4^+: 90% N(1) retained in the ion. There are many secondary reactions; this makes it uncertain to determine the fragmentation paths. Up to three consecutive losses of HCN from MH^+ and two from $[MH - NH_3]^+$ are observed. This is rather typical in nitrogen heterocycles[597]. The latter ion loses also C_2N_2 and NH_2CN, but the isotopic distribution of the fragment ions is complicated, indicating different possible reaction pathways. The CID spectra for 1-,



SCHEME 22

2-, 7- and N^6-Me adenine were also studied. These are analogous to adenine except for the loss of Me, which however is a minor process for 7-Me-adenine. A review of the mass spectrometry of nucleic acid constituents up to 1992 is given by McCloskey and Crain[536].

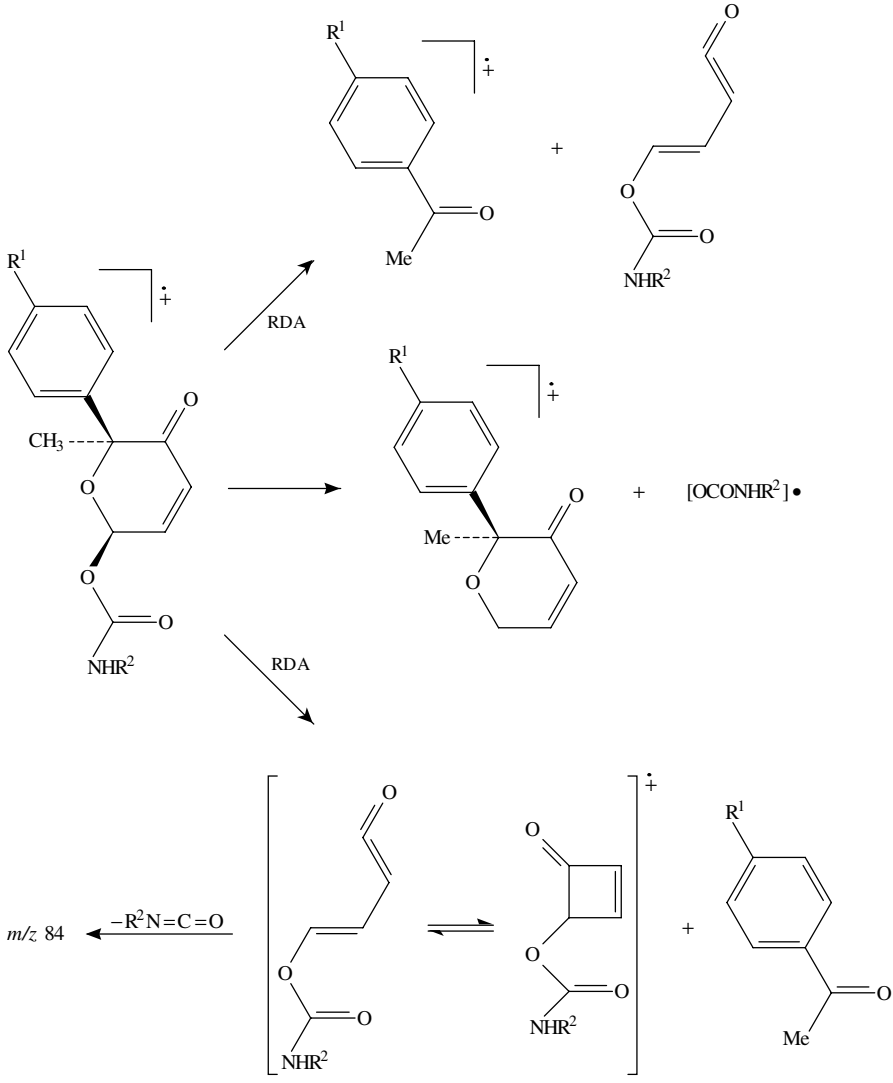
The RDA fragmentation can also be of diagnostic value in more complex molecules. Couladouros and Haroutounian[598] demonstrate that the electron impact ionization mass spectra of 6-carbamoyloxy-3-oxo-3,6-dihydro-2*H*-pyrans show a weak molecular peak, but a base peak of *m/z* 84 resulting from a RDA reaction and a subsequent fragmentation. The three main fragmentation pathways are given in Scheme 24 (R^1 = Ph−S, Ph−S(O), Ph−SO_2; R^2 = Me, Et). The fragmentation for oxazoendiones is similar, but three fragments are formed, shown in Scheme 25; their relative intensity is a function of the substituents (same R^1 and R^2; in addition R^2 = OMe).



SCHEME 23

The fragmentation of negative organic ions is reviewed by Bowie[599,600]. It turns out that negative ions do not easily undergo a RDA reaction. For example, substituted cyclohexenes, the classical case for positive ion RDA, will not undergo this fragmentation. Since in negative ion spectroscopy the main reaction is the cleavage to an oxygen atom, dioxin containing 1,3- and 1,4-oxygen atoms do undergo a RDA fragmentation. This is shown by Bowie and Ho[601] for nitro-2*H*, 4*H*-1,3- and -2,3-dihydro-1,4-benzodioxins. The relative abundance of peaks produced by the RDA reaction shows that the extent of the reaction is largely dependent upon the position of the nitro group. The order observed is 7-NO_2 > 5-NO_2 ≫ 6-NO_2 ∼ 8-NO_2. It seems that the importance of the reaction is mainly determined by the relative ease of cleavage of the second bond.

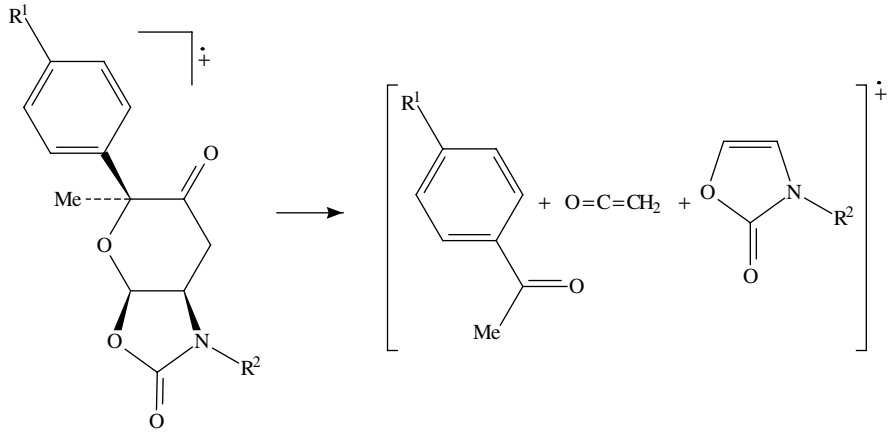
Ofloxacin, 9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo 2,3-dihydro-7*H*H-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid, is a DNA gyrase inhibitor that displays potent antibacterial activity. Routine molecular mass determination of ofloxacin by negative chemical ionization mass spectrometry with methane as reagent gas by Burinsky, Dunphy, Alves-Santana and Cotter[602] revealed the astonishing fact that only two ions, the molecular anion *m/z* 361 and a fragment *m/z* 319, are present. MS/MS experiments confirmed that the fragment must result from a RDA reaction where C−N and C−O bonds are cleaved (Scheme 26). CID showed only one additional fragment, $[M - C_3H_6 - C_2H_5F]^{-\bullet}$, resulting from an additional loss from the piperidine ring. Both the NCI mass



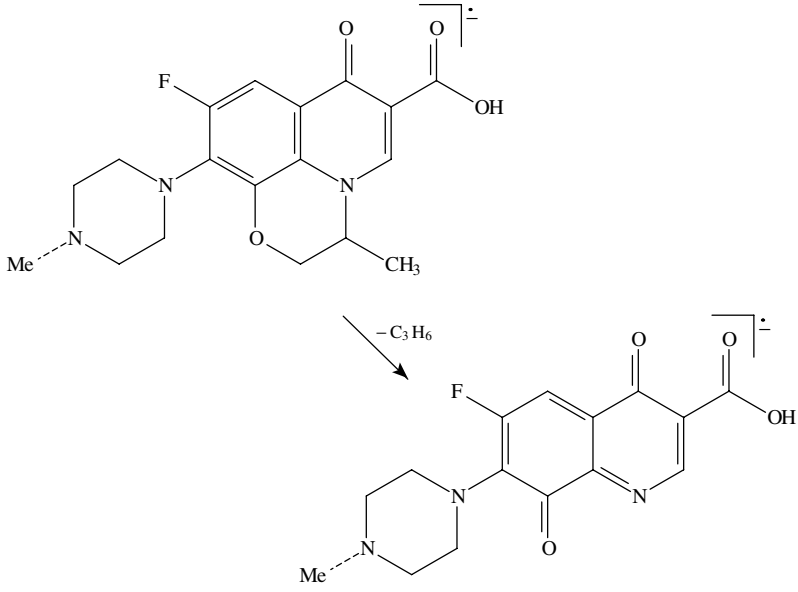
SCHEME 24

spectrum and the daughter ion MS/MS spectrum for the molecular anion of des-fluoro-ofloxacin exhibit a fragment that corresponds to the RDA reaction. This shows that the presence of fluorine is not necessary for this fragmentation behavior, although the fluorine-substituted ring possesses a considerable positive electron affinity.

Etinger and Mandelbaum[603] report what they call the first examples of negative-ion RDA fragmentation in a carbocyclic system. The diones Z-1, Z-2 and Z-3 shown in Scheme 27 exhibit highly stereospecific RDA reactions in positive ion electron ionization and in chemical ionization mass spectra[537]. The negative chemical ionization of Z-1 exhibits practically no fragmentation. The same is true for CID with Ar as collision gas

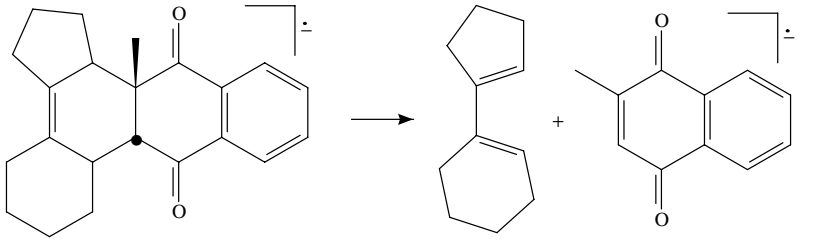


SCHEME 25

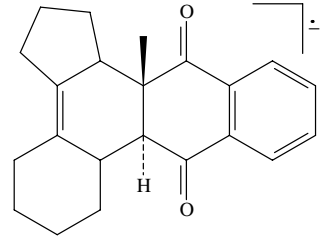


SCHEME 26

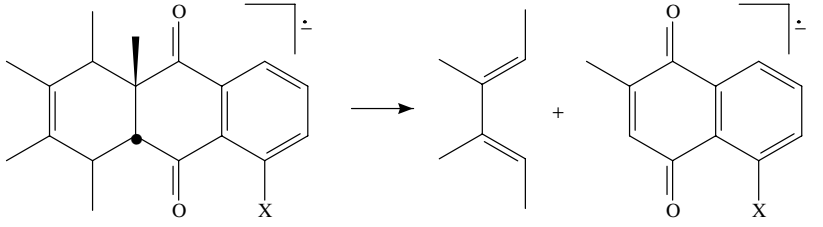
for energies below 60 eV. At higher energies, *m/z* 172 is the most abundant fragment beside $[M - Me]^-$. The epimeric E-1 exhibits an even higher CID stability and only $[M - Me]^-$ can be observed. The same is true for Z-2 and E-2. In the spectra of the nitro-substituted diones Z-3 and E-3 more fragments can be seen in the negative chemical ionization spectra, but the RDA fragment is only observed in the *cis*-isomer Z-3. Because of the high stereospecificity the authors assume a concerted mechanism for the RDA reaction.



Z–1 *m/z* 172

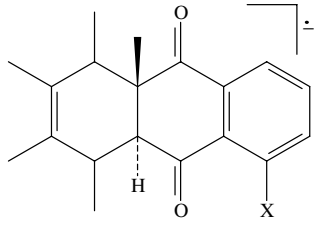


E–1



Z–2 X=NH_2
Z–3 X=NO_2

X=NH_2 *m/z* 187
X=NO_2 *m/z* 217



E–2
E–3

SCHEME 27

XI. ACKNOWLEDGMENTS

It is a pleasure for the author to dedicate this review to Hs. H. Günthard on the occasion of his 80th birthday and to Daniel Stahl on his 55th birthday as recognition of lifelong friendship and encouragement. I wish to thank my collaborators mentioned in the text for many fruitful discussions and help.

XII. REFERENCES

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CHAPTER **3**

Electronic effects of groups containing carbon–carbon or carbon–oxygen double bonds

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I. INTRODUCTION: THE SCOPE OF THIS CHAPTER

Previous articles by the present contributor in *The Chemistry of Functional Groups* series have dealt with the electronic effects of the sulphonio group[1], of the sulphinyl and sulphonyl groups[2], of SOOH and related groups[3], of amidino, guanidino and related groups[4], of ether and hydroxyl groups[5], of cyano, isocyano, acetylenic and diazonio groups[6] and of nitro, nitroso, amino and related groups[7]. In the first two cases[1,2] there was copious information from which to draw, but fairly comprehensive surveys were practicable. In the third and fourth contributions[3,4] the amount of information available was very restricted. In the fifth and sixth cases[5,6] the amount of available material was enormous and the treatment was highly selective both in the topics covered and in the illustrative examples provided. This was the situation *a fortiori* for the seventh case, because the nitro group and the amino group and closely related groups are extremely popular substituents. In the space available it was not possible to give detailed accounts of all the substituents of interest. The contributor therefore decided to give a fairly thorough account of the nitro group and to deal with the other relevant substituents much more concisely.

The writing of a chapter on electronic effects in a volume devoted to the chemistry of groups containing carbon linked by a double bond to other atoms presents its own problems. There is a fair amount of material on the effects of substituents containing C=C and C=O, but very little on the effects of groups containing other double bonds, in particular C=N and C=S. Such experimental data regarding substituent constants as are available for groups containing C=N or C=S would not form the basis of substantial coherent accounts. Thus it has been decided to concentrate exclusively on groups containing C=C or C=O.

The general arrangement of this chapter differs in some respects from that adopted in recent chapters on electronic effects[5–7]. There is no specifically historical section in the present Introduction, but as in the earlier accounts, notice is often taken of classical papers and texts whose importance has been overlaid by more recent work. The quantitative study of the electronic effects of C=C and C=O groups is naturally much concerned with the Hammett equation and its extensions. Section II therefore contains a summary of the salient features of the Hammett equation and cognate linear free-energy relationships, along the general lines of corresponding sections in certain of the contributor's articles in the series[1,2,5–7]. This section also includes general material on the determination of substituent constants from the application of modern experimental and theoretical techniques.

In Section III the electronic effects of olefinic groups are discussed. The vinyl group is treated in detail, followed by accounts of structural effect in aliphatic acids containing C=C and of the transmission of substituent effects through C=C. Section IV deals with groups containing C=O under the headings of alkoxycarbonyl groups, the carboxy group, acyl groups, various groups containing C=O and the *ortho*-effects of these groups. The last-mentioned involves the moderation of the electronic effects of the groups by steric effects and hydrogen-bonding.

Multiparameter treatments such as the Yukawa–Tsuno equation and the dual substituent–parameter equation have long been important and further treatments have been devised in recent years. As in some of the earlier contributions to the series[5–7] a final section is devoted to some of the newer multiparameter treatments, with an indication of the place of C=C and C=O groups in those treatments.

An account of directing and activating effects of doubly bonded groups was previously contributed to the series by Marvin Charton[8]. This article notes the paucity of experimental information for C=N and C=S groups.

This chapter is dedicated to the memory of Robert Wheaton Taft (1922–1996). The contributor enjoyed friendship with Bob Taft for some thirty years. The present chapter, like the corresponding chapters in earlier volumes[1–7], contains much discussion of Taft's work in linear free-energy relationships. Since the 1950s he had always been at the forefront of progress in this field.

II. THE HAMMETT EQUATION[9]

A. Introduction

The Hammett equation is the best-known example of a linear free-energy relationship (LFER), that is an equation which implies a linear relationship between free energies (Gibbs energies) of reaction or activation for two related processes[10]. It describes the influence of polar *meta*- or *para*-substituents on reactivity for side-chain reactions of benzene derivatives.

The Hammett equation (1937)[11–16] takes the form of equation 1 or 2:

$$\log k = \log k^0 + \rho\sigma \tag{1}$$

$$\log K = \log K^0 + \rho\sigma \tag{2}$$

The symbol k or K is the rate or equilibrium constant, respectively, for a side-chain reaction of a *meta*- or *para*-substituted benzene derivative, and k^0 or K^0 denotes the statistical quantity (intercept term) approximating to k or K for the 'parent' or 'unsubstituted' compound. The *substituent constant* σ measures the polar (electronic) effect of replacing H by a given substituent (in the *meta*- or *para*-position) and is, in principle, independent of the nature of the reaction. The *reaction constant* ρ depends on the nature of the reaction (including conditions such as solvent and temperature) and measures the susceptibility of the reaction to polar effects. Hammett chose the ionization of benzoic acids in water at 25 °C as a standard process. For this ρ is defined as 1.000, and the value of σ for a given substituent is then $\log(K_a/K_a^0)$, where K_a is the ionization constant of the substituted benzoic acid and K_a^0 that of benzoic acid itself. Selected values of σ for well-known substituents are given in Table 1. They are readily interpreted qualitatively in simple electronic terms, i.e. through the inductive (I) effect and the resonance or conjugative (R) effect.

Jaffé (1953)[19] showed that while many rate or equilibrium data conform well to the Hammett equation (as indicated by the correlation coefficient), many such data are outside the scope of the equation in its original form and mode of application. Deviations are commonly shown by *para*-substituents with considerable $+R$ or $-R$ effect[20]. Hammett himself found that *p*-NO_2 ($+R$) showed deviations in the correlation of reactions of anilines or phenols. The deviations were systematic in that a σ value of *ca* 1.27 seemed to apply, compared with 0.78 based on the ionization of *p*-nitrobenzoic acid. Other examples were soon discovered and it became conventional to treat them similarly in terms of a 'duality of substituent constants'.

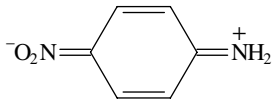
When σ values based on the ionization of benzoic acids are used, deviations may occur with $+R$ *para*-substituents for reactions involving $-R$ electron-rich reaction centres, and with $-R$ *para*-substituents for reactions involving $+R$ electron-poor reaction centres. The explanation of these deviations is in terms of 'cross-conjugation', i.e. conjugation involving substituent and reaction centre.

TABLE 1. Selected values[a] of σ, σ^+ and σ^- constants

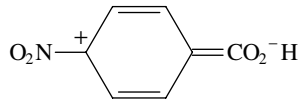
Substituent	σ_m	σ_p	σ_p^+	σ_p^-
Me	−0.07	−0.17	−0.31	—
OMe	0.12	−0.27	−0.78	—
SMe	0.15	0.00	−0.60	0.21
OH	0.12	−0.37	−0.92	—
SH	0.25	0.15	—	—
NMe_2	−0.15	−0.63	−1.7	—
F	0.34	0.06	−0.07	—
Cl	0.37	0.23	0.11	—
CF_3	0.43	0.54	—	0.65
CN	0.61	0.65	—	0.88
NO_2	0.71	0.78	—	1.24
CO_2H	0.37	0.45	—	0.73

[a]These values, drawn from various sources, are presented solely for illustration. The table should not itself be used uncritically as a source of σ values for correlations. See rather References 13, 17 and 18. The values for CO_2H will be discussed later in this chapter.

In the ionization of the *p*-nitroanilinium ion, the free base is stabilized by delocalization of electrons involving the canonical structure **1**. An analogous structure is not possible for the *p*-nitroanilinium ion. In the ionization of *p*-nitrophenol, analogous delocalization is possible in both phenol and phenate species, but is more marked in the ion. Thus, in both the aniline and the phenol system *p*-NO_2 is effectively more electron-attracting than in the ionization of benzoic acid, where the reaction centre is incapable of a $-R$ effect, and indeed shows a small $+R$ effect (**2**).

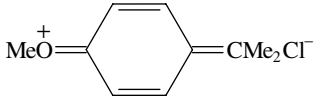


(1)

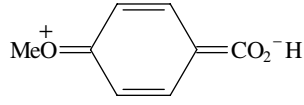


(2)

An example of a reaction series in which large deviations are shown by $-R$ *para*-substituents is provided by the rate constants for the solvolysis of substituted *t*-cumyl chlorides, $ArCMe_2Cl$[21]. This reaction follows an S_N1 mechanism, with intermediate formation of the cation $ArCMe_2^+$. A $-R$ *para*-substituent such as OMe may stabilize the activated complex, which resembles the carbocation–chloride ion pair, through delocalization involving structure **3**. Such delocalization will clearly be more pronounced than in the species involved in the ionization of *p*-methoxybenzoic acid, which has a reaction centre of feeble $+R$ type (**4**). The effective σ value for *p*-OMe in the solvolysis of *t*-cumyl chloride is thus −0.78, compared with the value of −0.27 based on the ionization of benzoic acids.



(3)



(4)

The special substituent constants for $+R$ *para*-substituents are denoted by σ^-, and those for $-R$ *para*-substituents are denoted by σ^+[21]. They are based respectively on the

reaction series discussed above. Selected values are given in Table 1. Characteristic σ^- or σ^+ values are sometimes distinguished for *meta*-substituents also, but only for a minority of substituents which show very marked $+R$ or $-R$ effects do these differ significantly from ordinary σ values. The range of applicability of the Hammett equation is greatly extended by means of σ^- and σ^+, notably to nucleophilic (by σ^-) and to electrophilic (by σ^+) aromatic substitution.

However, the 'duality of substituent constants' and the attempt to deal with cross-conjugation by selecting σ^+, σ or σ^- in any given case is somewhat artificial. The contribution of the resonance effect of a substituent relative to its inductive effect must in principle vary continuously as the electron-demanding quality of the reaction centre is varied, i.e. the extent to which it is electron-rich or electron-poor. A 'sliding scale' of substituent constants would be expected for each substituent having a resonance effect and not just a pair of discrete values: σ^+ and σ for $-R$, or σ^- and σ for $+R$ substituents[22].

B. Multiparameter Extensions[14,15,23]

There are two main types of treatment, both involving multiparameter extensions of the Hammett equation, which essentially express the 'sliding scale' idea.

In the Yukawa–Tsuno equation (1959)[24] (equation 3), the sliding scale is provided by multiple regression on σ and $(\sigma^+ - \sigma)$ or $(\sigma^- - \sigma)$, depending on whether the reaction is more or is less electron-demanding than the ionization of benzoic acid. (There is a corresponding equation for equilibria.) The quantity $r^{\pm}$ gives the contribution of the enhanced $\pm R$ effect in a given reaction. (The equation was modified in 1966[25] to use σ^0 instead of σ values, see below, but the essential principles are unaltered.)

$$\log k = \log k^0 + \rho[\sigma + r^{\pm}(\sigma^{\pm} - \sigma)] \tag{3}$$

In the form of treatment developed by Taft and his colleagues since 1956[26–28], the Hammett constants are analysed into inductive and resonance parameters, and the sliding scale is then provided by multiple regression on these. Equations 4 and 5 show the basic relationships, the suffix BA signifying benzoic acid. The σ_I scale is based on alicyclic and aliphatic reactivities (see below),

$$\sigma_m = \sigma_I + 0.33\sigma_R(\mathrm{BA}) \tag{4}$$

$$\sigma_p = \sigma_I + \sigma_R(\mathrm{BA}) \tag{5}$$

and the factor 0.33 in equation 4 is the value of a 'relay coefficient', α, giving the indirect contribution of the resonance effect to σ_m. However, the ionization of benzoic acids is not regarded as an entirely satisfactory standard process, since it is subject to some slight effect of cross-conjugation (see structure **4** above). Consideration of 'insulated series', not subject to this effect, e.g. the ionization of phenylacetic acids, is used as the basis of a σ^0 scale, which can be analysed by equations 6 and 7[29]. (Note the different value of α.) By a different procedure Wepster and colleagues[22] devised an analogous σ^n (n = normal, i.e. free from the effects of cross-conjugation). Analysis of σ^+ and σ^- constants correspondingly involves ${\sigma_R}^+$ and ${\sigma_R}^-$.

$$\sigma_m^0 = \sigma_I + 0.5\sigma_R^0 \tag{6}$$

$$\sigma_p^0 = \sigma_I + \sigma_R^0 \tag{7}$$

Multiple regression on σ_I and σ_R-type parameters employs the 'dual substituent-parameter' equation, which may be written as in equation 8[30].

$$\log(k/k^0) = \rho_I\sigma_I + \rho_R\sigma_R \tag{8}$$

TABLE 2. Selected values[a] of σ^0, σ_I and σ_R-type constants

Substituent	σ_m^0	σ_p^0	σ_I	σ_R(BA)	σ_R^0	σ_R^+	σ_R^-
Me	−0.07	−0.15	−0.05	−0.12	−0.10	−0.25	—
OMe	0.06	−0.16	0.26	−0.53	−0.41	−1.02	—
NO_2	0.70	0.82	0.63	0.15	0.19	—	0.61
F	0.35	0.17	0.52	−0.46	−0.35	−0.57	—
Cl	0.37	0.27	0.47	−0.24	−0.20	−0.36	—

[a]See footnote to Table 1.

The combining of the k and k^0 terms implies that there is no intercept term allowed, and k^0 is now the actual value for the parent system, *cf* below. For any given reaction series the equation is applied to *meta*- and *para*-substituents separately, and so values of ρ_I and ρ_R characteristic both of reaction and of substituent position are obtained. The various σ_R-type scales are linearly related to each other only approximately. In any given application the scale which gives the best correlation must be found[31].

Values of σ^0, σ_I and σ_R-type parameters for certain substituents are given in Table 2. It should be mentioned that Exner has developed a slightly different procedure for analysing sigma values[32] into inductive and resonance components (Section V.B)[15,16,33].

A slightly different procedure for carrying out multiple regression on σ_I and σ_R-type parameters employs the 'extended Hammett equation' of Charton[34], which may be written as in equation 9.

$$Q = \alpha\sigma_{I,\mathrm{X}} + \beta\sigma_{R,\mathrm{X}} + h \tag{9}$$

For the substituent X, Q is the absolute value of the property to be correlated ($\log k$ or $\log K$ in the case of reactivity), i.e. not expressed relative to X = H, h is introduced as the appropriate intercept term, and the regression coefficients are α and β. (Charton has used various symbols at various times.)

The correlation analysis of spectroscopic properties in terms of σ_I and σ_R-type parameters has been very important. Substituent effects on ^{19}F NMR shielding in fluorobenzenes have been studied in great detail by Taft and colleagues[29,35,36]. For δ_m^{F} linear regression on σ_I is on the whole satisfactory, but a term in σ_R^0 with a small coefficient is sometimes introduced. The correlation analysis of δ_p^{F}, however, requires terms in both σ_I and σ_R-type parameters, with σ_R^0 being widely applicable. Many new values of these parameters have been assigned from fluorine chemical shifts. In recent years there has also been extensive use of correlation analysis of ^{13}C NMR data[37,38].

The correlation analysis of infrared data has been much examined by Katritzky, Topsom and colleagues[39,40]. Thus the intensities of the ν_{16} ring-stretching bands of some mono- and di-substituted benzenes may be correlated with the σ_R^0 values of the substituents and these correlations may be used to find new σ_R^0 values. A more detailed discussion of the correlation analysis of spectroscopic properties is given in Section II.C.

Finally, in this account of multiparameter extensions of the Hammett equation, we comment briefly on the origins of the σ_I scale. This had its beginnings around 1956[28] in the σ' scale of Roberts and Moreland[41] for substituents X in the reactions of 4-X-bicyclo[2.2.2]octane-1 derivatives. However, at that time few values of σ' were available. A more practical basis for a scale of inductive substituent constants lay in the σ^* values for XCH_2 derived from Taft's analysis of the reactivities of aliphatic esters into polar, steric and resonance effects[28,42–44]. For the few σ' values available it was shown that σ' for X was related to σ^* for XCH_2 by the equation $\sigma' = 0.45\sigma^*$. Thereafter the factor

0.45 was used to calculate σ_I values of X from σ^* values of XCH_2[45]. These matters will be referred to again later in this chapter, and other methods of determining σ_I values will also be mentioned. Taft's analysis of ester reactivities was also important because it led to the definition of the E_s scale of substituent steric parameters, thereby permitting the development of multiparameter extensions of the Hammett equation involving steric as well as electronic terms.

C. The Determination of Substituent Constants from the Application of Modern Experimental and Theoretical Techniques

1. Experimental techniques

In Section II.B brief reference was made to the use of substituent constants in the correlation analysis of spectroscopic data, particularly ^{19}F and ^{13}C substituent chemical shifts and infrared frequencies and intensities. These matters must now be explored in greater detail as background to later discussions of individual substituents relevant to the present chapter.

Attempts were made to apply benzoic acid-based σ_m and σ_p constants to the correlation analysis of spectroscopic data. Some significant correlations were obtained, but many of the correlations were rather poor, trends rather than precise relationships. Success in this area was found to involve the separation of inductive and resonance effects and the application of the dual substituent–parameter (DSP) equation (Section II.B). Indeed the development of the DSP equation became closely associated with the correlation analysis of ^{19}F NMR shielding of substituted fluorobenzenes at an early stage, around 1957[45]. σ_I and σ_R^0 were applied extensively to ^{19}F NMR data[29], and within a few years the correlations were being used to investigate 'the effect of structure and solvent on the inductive order'[35], and 'the effect of structure and solvent on resonance effects'[36]. New σ_I and σ_R^0 values were based on the correlations. What happened with ^{19}F NMR set a pattern which was followed by later work. Established σ_I and σ_R^0 values for substituents which were expected to be 'well-behaved' were used to set up regression equations. In the very early days the established substituent constants were all based on chemical reactivity (rate or equilibrium constants). ^{19}F NMR data for groups for which no appropriate substituent constants were available were then substituted in the regression equations to obtain '^{19}F NMR-based values' of the substituent constants. Further, for the substituents which had been used to establish the regression equations, back-calculation from the NMR data led to '^{19}F NMR-based values' for those substituents as well. Thus, for many substituents both 'reactivity-based' and '^{19}F NMR-based' values of σ_I and σ_R^0 became available. For certain substituents there was a proliferation of values based on reactivity under various conditions or on ^{19}F NMR in different solvents. Slightly later, correlation analysis of infrared data led in particular to new σ_R^0 values and, to a lesser extent, new σ_I values, which were described as 'IR-based'[39,40,46]. Somewhat later the same development occurred in connection with ^{13}C NMR, leading to '^{13}C NMR-based values'[37,38].

There is a continual tendency for the values of σ_I and σ_R^0 (and other σ_R-type constants) to be adjusted in the light of new measurements. Thus measurements in 1979[47] of *para* ^{13}C substituent chemical shifts for a series of mono-substituted benzenes in very dilute solution in cyclohexane, carbon tetrachloride or deuteriochloroform were the basis for a redefinition of the σ_R^0 scale and some amendment of σ_R^0 values.

Reynolds and coworkers[48] based a similar operation on ^{13}C substituent chemical shifts of *meta*- and *para*-substituted styrenes. Iterative multiple regression was used for the redefinition of the σ_I and σ_R^0 scales. The authors also took the opportunity to replace the

symbol σ_I by σ_F, having become convinced that the so-called inductive effect was entirely a field effect (see the present author's discussion of this matter[15]). The authors presented an extensive table in which their values of the substituent parameters are compared with those obtained by other authors.

Happer[49] determined ^{13}C substituent chemical shifts for *meta*- and *para*-substituted styrenes in seven different solvents. Data for the side-chain carbons, and in the *meta* series for the ring carbon *para* to the substituent, were analysed as a basis for assessing solvent effects on σ_I, σ_R^0, σ_R(BA) and σ_R^-.

The influence of solvent on the inductive order of substituents was studied by Laurence and collaborators through infrared measurements on 4-substituted camphors[50]. From these Laurence[51] has tabulated new σ_F values applicable to solutions in carbon tetrachloride or other solvents of low dielectric constant.

Mention must also be made of the use of studies of chemical reactions in the gas phase as a means of determining substituent constants. The investigation of substituent effects and LFERs in the gas phase has become an enormous subject with which we can deal only briefly. Part of this subject was established a long time ago and consists in the study of such reactions as the pyrolysis of esters by the techniques of gas kinetics (see the review by Smith and Kelly[52]). One purpose of such work is to see how far substituent constants based on processes in solution may be applied successfully in the gas phase. This leads to the possibility of determining substituent constants in the complete absence of solvent. Work of this nature continues today; see the recent review by Holbrook in this Series[53], which updates the earlier review by Taylor[54].

The major activity in gas phase studies now depends on the use of modern techniques such as ion cyclotron resonance (ICR). Thus Fujio, McIver and Taft[55] measured the gas-phase acidities, relative to phenol, of 38 *meta*- and *para*-substituted phenols by the ICR equilibrium constant method, and their results for $+R$ substituents led them to suggest that such substituents in aqueous solution exerted solvation-assisted resonance effects. It was later[56] shown by comparison of gas-phase acidities of phenols with acidities in solution in DMSO that solvation-assisted resonance effects could also occur even when the solvent did not have hydrogen-bond donor properties.

Taft and Topsom[57] have written an extensive review of the electronic effects of substituents in the gas phase. This article includes a tabulation of substituent inductive and resonance parameters. The inductive parameters (designated σ_F) are based on measured spectroscopic properties in either the gas phase or in hydrocarbon or similar solvents. The resonance parameters were arrived at through the treatment of 38 gas-phase reactivity series by iterative multiple regression, using the σ_R^0 values of Bromilow and coworkers[47] as the starting point. The column heading in Taft and Topsom's table is simply σ_R, but inspection shows that the values must be regarded as being those of σ_R^0 when the distinction matters, i.e. with $-R$ substituents.

2. Theoretical techniques

The application of *ab initio* molecular orbital theory to suitable model systems has led to theoretical scales of substituent parameters, which may be compared with the experimental scales. Calculations (3-21G or 4-31G level) of energies or electron populations were made by Marriott and Topsom in 1984[58]. The results are well correlated with σ_F (i.e. σ_I) for a small number of substituents whose σ_F values on the various experimental scales (gas phase, non-polar solvents, polar solvents) are concordant. The regression equations are the basis of theoretical σ_F values for about fifty substituents.

A theoretical scale of substituent resonance effects was based on calculations of electron populations in substituted ethylenes[59]. A suitable regression equation was again set up

by using standard substituents, but in this case the quantum-mechanical quantity was correlated with infrared-based σ_R^0 values. The equation was the basis of theoretical σ_R^0 values for more than forty substituents. A further redefinition of the theoretical scale was later made as a result of a change of view as to the most suitable level of MO approximation[60]. Other recent theoretical papers by Topsom are on a scale of variable π-electron transfer[61], the influence of water on substituent field effects[62], the influence of water on substituent resonance effects[63], the acidities of *ortho*-substituted phenols[64] and theoretical studies of the effects of hydration on organic equilibria[65]. There is also an extensive review of theoretical studies of electronic substituent effects[66]. It seems rash, however, to regard theoretical substituent parameters as in any way replacing those founded on experimental results.

Fairly recently there have been various other treatments of substituent effects, e.g. the correlation analysis of substituent effects on the acidity of benzoic acid by the AM1 method[67] and direct prediction of linear free-energy substituent effects from 3D structures using comparative molecular field analysis, the relevant data set being 49 substituted benzoic acids[68]. Very recently Russian workers have presented a new model for the inductive effect, in an extremely detailed communication in three parts[69]. The approach appears to be successful in rationalizing a large amount of relevant experimental data.

Although the term 'theoretical techniques' in relation to electronic effects may commonly be taken to refer to quantum-mechanical methods, it is appropriate also to mention the application of chemometric procedures to the analysis of large data matrices. This is in a way complementary to analysis through substituent constants based on taking certain systems as standards and applying simple or multiple linear regression. Chemometrics involves the analysis of suitable data matrices through elaborate statistical procedures, such as principal component analysis and factor analysis. The parameters characterizing substituents and processes emerge from the data analysis. As an example of this kind of work, the recent contributions of the group of Ludwig and Pytela will be mentioned briefly. These authors determined the dissociation constants of a large number of substituted benzoic acids in different solvents[70]. The results were treated as a data matrix by the chemometric methods referred to above, and various sets of Hammett σ values were derived for the 35 substituents involved[71]. More recently these authors have augmented their own experimental results with other information from the literature to construct a data matrix of 46 sets of measurements on substituted benzoic acids in various solvents; a total of 51 *meta*- or *para*-substituents was involved[72,73]. 'Optimized' σ values were tabulated[73]. Other papers in the series 'Chemometrical Analysis of Substituent Effects' are on additivity of substituent effects in dissociation of 3,4-[74] or 3,5-[75] disubstituted benzoic acids in organic solvents and on the *ortho*-effect[76]. In the last-mentioned, data for the dissociation of *ortho*-substituted benzoic acids in 23 solvents are combined with data on the reactions of the acids with diazodiphenylmethane (Section IV.E) and with other rate and equilibrium data bearing on the behaviour of *ortho*-substituents to form a matrix involving data for 69 processes and 29 substituents.

III. THE ELECTRONIC EFFECTS OF OLEFINIC GROUPS

A. The Characteristics of the Vinyl Group

The pronounced electronegative character of the carbon–carbon triple bond has long been recognized. It is indicated by the acidity of terminal acetylenes, RC≡CH, and by the effect of C≡C on the strengths of carboxylic acids[6]. This electronegative or electron-attracting character is commonly attributed to the sp hybridization of the carbon atoms involved. The electronegativity of a carbon atom increases with the percentage of s

character in the hybrid orbitals, thus in the order: $sp^3 < sp^2 < sp$, the percentage of s character being 25%, 33% and 50%, respectively. The behaviour of the carbon–carbon double bond might thus be expected to lie between that of the triple bond and the single bond in this respect. Terminal olefins, $R_2C{=}CH_2$, are not acidic, but the acid-strengthening effect of C=C has long been known. In 1889 Ostwald determined pK_a values for propanoic acid and propenoic acid in water at 25 °C as 4.87 and 4.25, respectively[77], *cf* 1.89 for propynoic acid. The behaviour of C=C in this respect thus appears to be much closer to that of C−C than to that of C≡C. Ingold[78] classified both acetylenic groups and olefinic groups as $-I$ in character (his sign convention[20]), with the inductive effects of the former being greater than those of the latter. He also recognized that the mesomeric effects of olefinic groups could be in either direction with respect to an attached benzene ring, depending on the nature of any other groups attached to the double bond, so that olefinic groups in general should be classified as $\pm M$ in Ingold's system.

The $+I$ character of the vinyl group (sign convention being used in this article[20]) is most simply shown by its effect on the acidity of acetic acid. The pK_a value of vinylacetic acid is 4.352 (water, 25 °C). The pK_a value of acetic acid being 4.756[79], $\Delta pK_a = 0.404$. [The change in acid strength produced by a substituent X is conveniently expressed as ΔpK_a, defined as $(pK_a)_H - (pK_a)_X$, so that an increase in acid strength is associated with a positive value of ΔpK_a.] This may be compared with $\Delta pK_a = -0.064$ for butanoic acid and 1.316 for ethynylacetic acid.

In Charton's work pK_a data for 4-X-substituted-bicyclo[2.2.2.]octane-1-carboxylic acids in 50% w/w $EtOH–H_2O$ are the basis for primary σ_I values of the substituents X (Section II.B)[80]. (The bicyclooctane system is considered to have the ideal features that the 4-X and 1-COOH are not conjugated with the molecular skeleton, the substituent is somewhat remote from the acidic centre and the geometry for 4-X and 1-COOH closely resembles that for groups in a 1,4-disubstituted benzene)[81]. However, the pK_a value for the vinyl-substituted acid in this solvent was not available, so the σ_I value for the vinyl group was calculated by substituting the pK_a value for vinylacetic acid in water at 25 °C (4.352) in the regression equation 10:

$$pK_a = -4.05\sigma_I + 4.791 \tag{10}$$

which had been established for the acids XCH_2CO_2H by using data for groups X whose σ_I values were available from data for the bicyclooctane system. This procedure gave the value of 0.108 for σ_I of vinyl, which was rounded to 0.11.

Values of σ_I for vinyl in the neighbourhood of 0.10 have also been obtained by using other procedures involving pK_a data. Thus earlier calculations by Charton based on the substituted acetic acid system found a value of 0.09[82]. Exner[17] used data from Grob's studies of the ionization of 4-substituted-quinuclidinium ions[83] to calculate a σ_I value of 0.08 for vinyl. Back-calculation from Charton's[80] regression based on Grob's data yields a σ_I value of 0.09 for vinyl. A similar calculation from his regression based on Grob's data[84] for the rates of quaternization of 4-substituted quinuclidines with methyl iodide in methanol at 10 °C gives 0.10.

For our present purposes we shall accept a value of 0.10 as a reactivity-based value to characterize the inductive effect of a vinyl group in aqueous solutions, and probably also applicable in other hydroxylic solvents.

It should be mentioned that the compilation of Hansch and Leo[85] (1979) and the recently published updated version by Hansch, Leo and Hoekman[86] (1995) provide four and six values, respectively, of σ^* for vinyl, ranging from 0.4 to 0.65. The values are mainly reactivity-based. They may be converted into σ_I values for the vinyl group by dividing by the methylene group decremental factor of 2.7 to give σ^* values for 2-propenyl[28] and then

multiplying by 0.45 (see Section II.B[45]), thus giving a range from 0.07 to 0.11, in fair agreement with the values discussed above. Similarly, the same sources[85,86] give several σ^* values for 2-propenyl ranging from 0.12 to 0.26 (excluding one or two obviously eccentric values). When multiplied by 0.45 these give σ_I values for the vinyl group ranging from 0.05 to 0.12, again in fair agreement with the values previously discussed.

Ellam and Johnson[87] measured the pK_a values of *m*- and *p*-vinylbenzoic acids in water at 25 °C as 4.13 and 4.28, respectively. Taking the value for benzoic acid as 4.205, the corresponding σ_m and σ_p values are 0.08 and −0.08, respectively (rounded to two places of decimals). These values have recently been recommended in a I.U.P.A.C. technical report on 'Values of σ_m and σ_p based on the ionization of substituted benzoic acids in water at 25 °C'[18]. Ellam and Johnson's work appears to have been carefully done. However, the results of a simple analysis of these σ values into inductive and resonance components indicate that all is not well. The application of equations 4 and 5 of Section II.B as simultaneous equations gives σ_I and σ_R(BA) values as 0.16 and −0.24, respectively. The former is far higher than any value suggested above for σ_I; the latter is much more negative than any value indicated by any other method for a σ_R-type parameter for vinyl (see below). The only other experimental result which can help with this problem is a pK_a value for *p*-vinylbenzoic acid in 50% ethanol−water determined by Hoefnagel and Wepster[88]. (See note[89] for a more precise specification of this solvent.) The ΔpK_a value is −0.03, and since the ρ value for the dissociation of substituted benzoic acids in this solvent is about 1.5[90], a value of −0.02 is indicated for σ_p of vinyl. If the above analysis into inductive and resonance components is repeated with this value for σ_p and Ellam and Johnson's value of 0.08 for σ_m, the calculated values of σ_I and σ_R(BA) are 0.13 and −0.15, respectively. These values are much more reasonable than those based solely on Ellam and Johnson's σ values. The use of 0.06 for σ_m would lead to even more reasonable values of σ_I and σ_R(BA), 0.10 and −0.12, respectively.

The present situation regarding the σ values of the vinyl group is obviously unsatisfactory. Pending the carrying out of further experimental work, values of σ_m and σ_p may be suggested tentatively as 0.06 and −0.02, respectively. Charton has also proposed $\sigma_m = 0.06$, along with $\sigma_p = -0.04$[80]. The latter is said to be based on a pK_a value privately communicated by Wepster. This was presumably the value for *p*-vinylbenzoic acid referred to above. Either Wepster had second thoughts about the value before publication[88], or an error has crept in somewhere. Charton had suggested much earlier[91] the values $\sigma_m = 0.05$ and $\sigma_p = -0.02$ for vinyl, *c f* above. In any event it is clear that in the position *para* to a carboxy group, vinyl behaves as a $-R$ group. Such character should of course be enhanced in the effect of this substituent on an electron-poor reaction centre (see Section II.A), but there appears to be little reliable information on this matter. Hansch and colleagues[86] quote a σ_p^+ value of −0.16 for vinyl, said to be based on solvolysis studies. In processes involving electron-rich reaction centres, such as the ionization of phenols or anilinium ions, indications of $+R$ behaviour of vinyl might be expected, but there appears to be no information available about this.

We turn now to characterizing the electronic effects of the vinyl group through spectroscopic studies.

Laurence[51] has derived σ_I values (he uses the symbol σ_F; see Section II.C.1) from the correlation analysis of the carbonyl stretching frequencies of 4-substituted camphors in carbon tetrachloride. The value of 0.11 is given for the vinyl group, in good agreement with the reactivity-based values discussed above, in spite of the use of a non-polar medium. Laurence compares this with a 'statistical value' of 0.06 from Taft and Topsom[57], said to refer to effects on physical properties in either the gas phase or in hydrocarbon or similar solvents.

The classical spectroscopic method of determining σ_I values is from ^{19}F NMR shielding effects in *meta*-substituted fluorobenzenes (see Section II.C.1). Taft and colleagues[35] applied this method to the vinyl group and tabulated a value of 0.01, independent of whether the solvent used was a 'normal solvent', dioxan, or a 'weakly protonic solvent'. However, a detailed inspection of their results reveals a rather complicated situation. The shielding parameters for *m*-vinylfluorobenzene in the various solvents vary from 0.30 to 0.68 ppm, but are mainly 0.60 ± 0.05. The regression equation relating the substituent shielding effect to σ_I has a gradient of -7.10 and an intercept of $+0.60$, of no particular physical significance. The consequence is that a shielding parameter of 0.60 ppm corresponds to $\sigma_I = 0.00$. Values slightly greater than 0.60 correspond to a small negative value of σ_I, while values slightly less than 0.60 correspond to a small positive value thereof. The method is therefore not suitable for the precise study of substituents of fairly small inductive effect. In the case of vinyl, however, it certainly appears that the inductive effect as probed by ^{19}F NMR is rather smaller than would correspond to the σ_I value of about 0.10 derived by reactivity-based methods or from the camphor infrared model, but no particular significance should be attached to the tabulated value 0.01.

A recent re-examination of the ^{19}F NMR data for *meta*-substituted fluorobenzenes in hydrocarbon solvents by Hansch, Leo and Taft[92] led to a slightly different regression equation. When this was applied to the vinyl group, σ_I was found to be 0.07, in fair agreement with the reactivity-based value of 0.10.

The ^{19}F NMR shielding parameters of *para*-substituted fluorobenzenes are governed mainly by the σ_R^0 values of $-R$ substituents, with a small contribution from a σ_I term. In the classical work of Taft and colleagues[36] a value of -0.03 for σ_R^0 of the vinyl group was derived. In the re-examination[92] of the work of Taft and colleagues[35,36] the value was changed to -0.01. A value for σ_R^0 of vinyl has also been determined from ^{13}C substituent chemical shifts as -0.04 (quoted by Hansch and colleagues[86]). Correlation analysis of the infrared intensities of the ν_{16} ring bands of monosubstituted benzenes involves the squares of σ_R^0 constants. Thus it is capable of leading to new numerical values of such substituent constants, but the signs must be inferred from other evidence[46]. In the case of vinyl the numerical value is 0.05, to which is added a negative sign in accord with the well-recognized behaviour of vinyl as a $-R$ substituent. Thus the values suggested for σ_R^0 are all much less negative than the values tentatively indicated above for σ_R(BA) at around -0.12 to -0.15. This is of course as it should be, in view of the nature of COOH as a weakly $+R$ group (see Section II.A).

The vinyl group has been included in the work of Topsom and colleagues on theoretical scales of field (inductive) and resonance parameters (see Section II.C.2). A value of 0.04 was derived for σ_F[58], in fair agreement with the values of σ_I determined spectroscopically as discussed above, but rather lower than most of the reactivity-based values. The first attempt at establishing a theoretical scale of resonance parameters found $\sigma_R^0 = -0.05$[59], in good agreement with the spectroscopic values discussed above. However, the later redefinition of the theoretical scale of resonance parameters[60] produced a value of 0.04 for vinyl, which the authors tabulate alongside the infrared-based value of 0.05, i.e. the $+$ option of $\pm$ has now been chosen, *c f* above.

B. Structural Effects in Aliphatic Acids Containing C=C

The pK_a values (water, 25 °C) in the series of acids $H_2C{=}CH(CH_2)_n{-}COOH$ are as follows: $n = 0$, 4.25; $n = 1$, 4.352; $n = 2$, 4.678; $n = 3$, 4.721. The direct attachment of the vinyl group to COOH, rather than through CH_2, will greatly enhance the $+I$ effect, but now the $-R$ effect will be a factor tending to weaken the acidity by stabilizing the

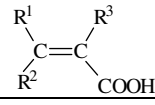
undissociated acid relative to the ionized form (*cf* the $-R$ effect of Ph in benzoic acid). In the result the pK_a value is decreased by only about 0.10, which is in marked contrast to the analogous situation for the ethynyl group, when the $-R$ effect of HC≡C is completely swamped by the $+I$ effect[6].

The introduction of successive methylene groups in the series $n = 1, 2, 3$ produces a marked damping of the acid-strengthening effect of the vinyl group. However, even when $n = 3$, the acid is appreciably stronger than the corresponding saturated acid, AmCOOH, which has a pK_a value of 4.88.

The effect on the acidity of substituting the H atoms of the vinyl group in $H_2C{=}CHCOOH$ by various alkyl groups is of interest for several matters, in particular the behaviour of stereoisomers. Pertinent data are collected in Table 3. The methyl group in *trans*-crotonic acid (entry 2) is markedly acid-weakening and this is attributed to the electron-releasing properties ($-I$, $-R$) of the group. *cis*-Crotonic acid (entry 3) is, however, only 0.17 units weaker than acrylic acid (entry 1); various factors have been suggested as being in competition with the electron-releasing effect of the methyl group. The traditional explanation is based on a structural analogy between this acid and *o*-methylbenzoic acid. The apparent acid-strengthening effect of the *o*-methyl group in the latter is usually attributed to the methyl preventing coplanarity of phenyl and carboxy groups and thus introducing steric inhibition of resonance involving these groups, which is normally a factor stabilizing the undissociated form of the acid relative to the ionized form, *cf* above for acrylic acid.

The concept of steric inhibition of resonance has, however, recently been criticized by Exner, Gal and their coworkers[93], who consider that it has often been invoked for molecules in which it is unlikely to occur. These include *o*-methylbenzoic acid. Substantial evidence was assembled in support of this view. The authors suggest that a primary steric effect may be involved, which is greater in the undissociated molecule than in the ion and is therefore acid-strengthening. This idea would presumably be applicable to *cis*-crotonic

TABLE 3. The pK_a values (water, 25 °C) of various alkyl-substituted acrylic acids



	R^2	R^2	R^3	pK_a
1.	H	H	H	4.25
2.	Me	H	H	4.70
3.	H	Me	H	4.42
4.	H	H	Me	4.65 (18 °C)
5.	Me	Me	H	5.12
6.	Me	H	Me	4.96 (18 °C)
7.	H	Me	Me	4.29 (18 °C)
8.	Me	Me	Me	4.41
9.	Et	H	H	4.74
10.	Pr^i	H	H	4.75
11.	Bu^t	H	H	4.88
12.	H	Et	H	4.70
13.	H	Pr^i	H	4.63
14.	H	Bu^t	H	4.12
15.	Et	Me	H	5.15
16.	Me	Et	H	5.13

acid. We may also recall that about thirty years ago Bowden[94] suggested that all *cis*-3-substituted acrylic acids were strengthened relative to their *trans* isomers by about 0.30 pK_a units, through the operation of a factor which was not steric in nature, but was somehow associated with *cis* substitution. The nature of the factor could not be definitely established. This matter will be referred to again below.

The introduction of a *cis*-3-methyl group when a *trans*-3-methyl group is already there produces an acid-weakening effect of 0.42 units (entry 5 compared with entry 2). This is similar to the effect of the *trans*-3-methyl group (entry 2 compared with entry 1), so no special effect of *cis* substitution is manifested here. One or the other of the methyl groups can be replaced by an ethyl group without affecting the acidity to any great extent; compare entries 5, 15 and 16.

It is perhaps surprising that the introduction of a 2-methyl group into acrylic acid (entry 4) does not have as strong an acid-weakening effect as a the 3-methyl group (entry 2). Competition with an acid-strengthening effect could be responsible, possibly a primary steric effect of the type suggested by Exner, Gal and coworkers[93]. The introduction of a 3-methyl group *trans* to the carboxy group in 2-methylacrylic acid (entry 6) or of a 3-methyl group *cis* to the carboxy group in 2-methylacrylic acid (entry 7) produces an acid-weakening or acid-strengthening effect, respectively, which is fairly similar to the corresponding effect in the case of acrylic acid. It appears from entry 8 that when three methyl groups are present very complicated interactions occur; no approach to additive behaviour in substituent effects can be discerned. However, it should be pointed out that entry 8 relates to work done about one hundred years ago[95].

Entries 2, 9, 10 and 11 show the effect of branching at the α-carbon atom of the 3-alkyl group in the *trans* disposition with respect to COOH. This is in accord with the order of electron-release Me < Et < Pr^i < Bu^t. For the effect of such branching of the 3-alkyl group in the *cis* disposition: entries 3, 12, 13 and 14, the situation is more complicated. There is an apparent marked decrease in acidity of 0.28 pK_a units when Me is replaced by Et. This is difficult to understand, *c f* entries 15 and 16. The values for entries 12, 13 and 14 were all determined by the same authors[96], who also found a pK_a value of 4.70 for *cis*-crotonic acid, compared with the value of 4.42, or thereabouts (entry 3), which has been found by several different authors. (In Reference 79b the work of Reference 96 is classified as 'approximate', rather than 'reliable'.) We shall therefore not attribute any particular significance to the difference in values between entries 3 and 12, but will assume that the entries 12, 13 and 14 constitute a self-consistent series worthy of comment. The increase in acidity through this series would traditionally be ascribed to steric inhibition of resonance destabilizing the undissociated acid relative to the ionized form. This may certainly be true for the Bu^t compound, but an increase in a primary steric effect, as suggested by Exner, Gal and their coworkers[93] (see above), is also a possible explanation.

Extending the conjugated system of acrylic acid by introducing another C=C has a somewhat acid-weakening effect. Values of pK_a for *cis,cis*-Me−CH=CH−CH=CH−COOH and *trans,trans*-Me−CH=CH−CH=CH−COOH at an ionic strength $I = 0.10$ are 4.49 and 4.50, respectively. For comparison with the proper thermodynamic pK_a value of 4.25 for acrylic acid, a correction of about 0.12 is required[97], changing the values to 4.61, and 4.62, respectively. Presumably the introduction of the second C=C should enhance the electron-attracting influence of the vinyl group, but the effect of this is apparently swamped by the extension of the conjugation stabilizing the undissociated acid relative to the ionized form. The stereochemistry of the molecule seems not to matter. The introduction of a second C=C directly into the vinyl group as in CH_2=C=CH−COOH has a markedly acid-strengthening effect; this acid has a pK_a value of 3.685 at $I = 0.10$, giving a corrected value of 3.805, compared with 4.25 for acrylic acid.

TABLE 4. Values of σ_I for substituted vinyl groups[80]

Group[a]	σ_I
$H_2C{=}CH$	0.11
$MeCH{=}CH$	0.07
$H_2C{=}CMe$	0.10
$H_2C{=}CHCH_2$	0.02
$Me_2C{=}CH$	0.05
$EtCH{=}CH$	0.07
$MeCH{=}CHCH_2$	0.02
$H_2C{=}CHCH_2CH_2$	0.02
$Me_2C{=}CHCH_2$	0.00
Z-ClCH=CH	0.18
E-ClCH=CH	0.17

[a]Charton[80] also tabulates values for $Cl_2C{=}CH$, $CH_2{=}CCl$ and $Cl_2C{=}CHCH_2$, but the present contributor has been unable to trace in the literature the experimental data on which they are said to be based.

With a pK_a value of 4.42 (water, 25 °C) *trans*-cinnamic acid clearly shows the acid-weakening effect of extending the conjugated system by introducing the phenyl group. *cis*-Cinnamic acid, however, with a pK_a value of 3.93, is a considerably stronger acid than its *trans* isomer, and is even somewhat stronger than acrylic acid. The traditional explanation of this behaviour would be in terms of the $+I$ effect of Ph and steric inhibition of resonance, but we may recall the suggestions of Exner, Gal and coworkers[93] and of Bowden[94] discussed above.

Charton[80] tabulates σ_I values for several of the alkyl-substituted vinyl groups which are components of the acids discussed in the present section, as well as values for other substituted vinyl groups, such as chloro-substituted groups. A selection is shown in Table 4.

C. The Transmission of Substituent Effects through C=C

C=C may be used as the connective G in the acids PhGCOOH, and so its transmission of the effects of substituents in Ph may be studied, When G = CH_2 or $(CH_2)_2$ the Hammett ρ values for ionization in water at 25 °C are 0.56 and 0.24, respectively, compared to 1.00 for benzoic acid[98]. Transmission by CH=CH is, however, greater than that by $CH_2{-}CH_2$, the ρ value for the ionization of *trans*-cinnamic acids being 0.42. In a simple way it may be imagined that the π-bond component makes the C=C double bond more polarizable than the C−C single bond and this facilitates the transmission of substituent effects. The ρ values for the rate coefficients of reaction of the acids with diazodiphenylmethane in ethanol at 30 °C show much the same pattern: CH_2, 0.40; $(CH_2)_2$, 0.22; CH=CH, 0.42, compared with 0.95 for benzoic acid. The necessary data for estimating the transmission of substituent effects through C=C in *cis*-cinnamic acid do not appear to exist. Bowden[98] and Bowden, Chapman and Shorter[99] tried to develop a simple theory of the relative transmitting powers of various groups G. The theory achieved a modest success.

Bowden[94] studied the transmission of substituent effects through C=C in the esterification of 3-substituted acrylic acids with diazodiphenylmethane (DDM) and in the ionization of the same acids. The σ_p values of the substituents were used to characterize their electronic effects for Hammett-type correlations. In esterification with DDM at 30 °C, the ρ values of the *trans* acids and the *cis* acids were 1.682 and 1.772, respectively, in ethanol

as solvent, corresponding results in *t*-butanol being 2.065 and 2.16, and in ethyl acetate, 2.960 and 3.042. Thus the transmission of the substituent effect through the *cis* acids is slightly greater than through the *trans* acids, and there is a considerable solvent effect, which enhances transmission is the less polar solvents. The ρ values for the ionization of the acids in water at 25 °C were 2.249 for the *trans* acids and 2.452 for the *cis* acids. There was a linear free-energy relationship between log *k* values for the *trans* acids reacting with DDM in ethanol and the pK_a values in water. The data for the *cis* acids were correlated by a different line, approximately parallel to the first and separated from it by about 0.3 pK_a units. This behaviour was the basis for Bowden's suggestion that the *cis*-3-substituted acids were all strengthened relative to their *trans* isomers by 0.3 units (see Section III.B). An analogous effect had previously been detected for *ortho*-substituted benzoic acids[100]. The nature of this effect seems not to have been satisfactorily explained, although reference to it is made from time to time[6,7].

In a review article on substituent effects in non-aromatic unsaturated systems. Charton[101] treats many systems by means of his extended Hammett equation (Section II.B). There is much information on the transmission of the inductive and resonance components of substituent effects through C=C.

IV. THE ELECTRONIC EFFECTS OF GROUPS CONTAINING CARBON–OXYGEN DOUBLE BONDS

A. Alkoxycarbonyl Groups

Alkoxycarbonyl groups are classified as $+I$, $+R$ substituents in their electronic effects. Most of the available information concerns CO_2Me and CO_2Et and these groups are often regarded as having essentially identical electronic effects, within the usual limits of experimental error of reactivity and spectroscopic studies and within the precision of correlation equations. Thus in the absence of relevant information about one of these groups, information about the other may be used. Indeed Exner's compilations of substituent constants[16,17] do not distinguish individual alkoxycarbonyl groups and tabulate values simply for CO_2R. It seems probable that the electronic effects of, for example, CO_2Bu^t would differ appreciably from those of CO_2Me or CO_2Et, but there is little information about such matters. Our discussion will be restricted to CO_2Me and CO_2Et, but it will be made clear whether a particular piece of information relates to CO_2Me or CO_2Et.

The pK_a value of 4-ethoxycarbonylbicyclo[2.2.2]octane-1-carboxylic acid in 50% w/w EtOH–H_2O at 25 °C is 6.40, compared with 6.87 for the parent compound, i.e. $\Delta pK_a = 0.47$. These values are used by Charton[80] to define a primary σ_I value for CO_2Et through equation 11:

$$\sigma_I = \Delta pK_a/1.56 \tag{11}$$

the value being 0.301, which was rounded to 0.30. A secondary value for CO_2Me was based on the ionization of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids in 50% v/v MeOH–H_2O at 25 °C, which conforms to equation 12.

$$pK_a = -1.14\sigma_I + 6.230 \tag{12}$$

The σ_I value for CO_2Me was found to be 0.318, which was rounded to 0.32.

The above values of σ_I for CO_2Me and CO_2Et are found to be widely applicable to the effects of these substituents on processes in aqueous, aqueous organic or other protic solvents. To illustrate this point we show in Table 5 the back-calculated values of σ_I for CO_2Me and/or CO_2Et from some of the regressions in Charton's article[80].

TABLE 5. The influence of alkoxycarbonyl groups on reactivity in various aliphatic and alicyclic systems

Process	Solvent	Temp. (°C)	Group	σ_I[a] (calc)
Ionization of 3-substituted adamantane-1-carboxylic acids	50% v/v EtOH–H_2O	25	CO_2Me	0.302
Ionization of substituted methylamines	H_2O	25	CO_2Me CO_2Et	0.314 0.309
Ionization of 4-substituted quinuclidinium ions	H_2O	25	CO_2Me CO_2Et	0.305 0.305
Rate of reaction of 4-substituted quinuclidines with MeI	MeOH	10	CO_2Et	0.282
Rate of reaction of *trans*-4-substituted cyclohexane carboxylic acids with diazodiphenylmethane	EtOH	30	CO_2Me	0.320
Rate of reaction of ethyl 4-substituted bicyclo[2.2.2]octane-1-carboxylates with OH^-	87.83% w/w EtOH–H_2O	30	CO_2Et	0.303

[a]From regression equations by Charton[80].

In the establishing of the σ_I scale about forty years ago CO_2Et played an important part because it was one of the substituents for which Roberts and Moreland[41] determined a σ' value from the bicyclooctane system (see Section II.B). The value was 0.30 and in conjunction with the value of 0.78 for the σ^* value of CH_2CO_2Me[28] it contributed to determining the factor 0.45 for the interrelationship of the σ^* and σ_I scales (see again Section II.B).

The situation regarding the benzoic acid-based σ values of CO_2Me or CO_2Et is not straightforward. The necessary pK_a values have not become available until recent years. No value appears to exist for either of the *meta* acids in water, but there is a value for *m*-methoxycarbonylbenzoic acid in 10% v/v EtOH–H_2O[90]. From this value and the ρ value for the ionization of benzoic acids in this solvent, $\sigma_m = 0.33$. However, Charton[80], by using what appear to be the same data communicated to him privately before publication, calculated $\sigma_m = 0.38$. For the *para* acid a pK_a in water is cited by Hoefnagel and Wepster[102], from which σ_p may be calculated to be 0.46. The recent I.U.P.A.C. compilation[18] recommends the slightly different value 0.45, data for ionization in 10% EtOH–H_2O[88] having also been taken into account. Charton[80] appears to have had access to the latter data before publication and calculates σ_p as 0.43.

If $\sigma_m = 0.33$ and $\sigma_p = 0.46$ are analysed in a simple way into inductive and resonance components, as in Section II.B, we obtain values of σ_I and σ_R(BA) as 0.27 and 0.19, respectively. The former value is slightly lower than the reactivity-based value discussed above. Charton considers that his σ_m and σ_p values for CO_2Me are consistent with $\sigma_I = 0.32$ (as above) and $\sigma_R(BA) = 0.11$. For CO_2Et he proposes $\sigma_m = 0.36$ and $\sigma_p = 0.41$, consistent with $\sigma_I = 0.30$ and $\sigma_R(BA) = 0.11$.

Since these substituents are $+R$ groups, there will be no important distinction between σ and σ^0, or between σ_R(BA) and σ_R^0 (see Section II.B). There is, however, a distinctive σ_p^- value (see Section II.A). The recent compilation by Hansch and coworkers[86] presents several values of this substituent constant for both CO_2Me and CO_2Et. Quite a range of values is given in each case and this situation is one in which to take notice of the authors' own *caveat*[86]. We will content ourselves with following Exner[17] on this occasion and

dealing with the general substituent CO_2R. Exner[17] quotes 0.74 based on the ionization of anilinium ions and 0.64 based on the ionization of phenols. The present contributor has pointed out previously that there are often discrepancies between the phenol and anilinium scales and the most significant are usually in the sense that the enhancement of the $+R$ effect is smaller for the ionization of phenol than for the ionization of the anilinium ion[6]. This provides a warning that values based on the two systems should not be mixed in correlations. Ideally only one of these systems should be chosen as the basis for the σ^- scale. The other should be regarded as a system for treatment by the Yukawa–Tsuno equation[24,25] or other multiparameter extensions[23] of the Hammett equation (Section II.B).

The $+I$ effect of alkoxycarbonyl groups has been studied by several spectroscopic techniques. The infrared method using the camphor model[51] (see Section III.A) found a value of 0.31 for σ_I of CO_2Me in carbon tetrachloride, in good agreement with the value based on reactivity in aqueous organic solvents. However, the work of Taft and collaborators in 1963 on ^{19}F substituent chemical shifts[35] found that the shift for *m*-ethoxycarbonylfluorobenzene varied considerably with solvent, the extreme values for the shielding parameter being -0.13 ppm in benzene and -1.80 in trifluoroacetic acid. The derived values of σ_I were 0.11 in 'normal solvents', 0.13 in dioxan, 0.21 in 'weakly protonic solvents' and 0.35 in trifluoroacetic acid. The last-mentioned high value was attributed to the effect of the hydrogen-bonding of CF_3COOH to one or the other or both oxygen atoms of CO_2Et. With the exception of the value determined in trifluoroacetic acid, all the other values are well below the value of 0.30 determined from reactivities in protonic solvents, as already discussed. It thus appears that this value is for an ester group that is extensively solvated by hydrogen-bonding. According to the shielding parameters, even methanol and formic acid, the 'weakly protonic solvents', do not produce as pronounced a hydrogen-bonding effect as the aqueous organic solvents involved in the determination or application of the reactivity values of σ_I. (Note, however, that in one example in Table 5 methanol is the solvent. The back-calculated value of σ_I is the lowest in the Table at 0.282, but the deviation is not particularly serious.) As already mentioned (Section III.A) a recent re-examination of the ^{19}F NMR data for *meta* substituted fluorobenzenes in hydrocarbon solvents[92] led to a slightly different regression equation. The value of σ_I (the symbol σ_F is preferred by the authors concerned) is now given as 0.19. If the new regression equation is applied to the shielding parameter formerly obtained using methanol as solvent[35], σ_I for CO_2Et comes out at 0.26, which is at least approaching the value based on reactivity in aqueous organic solvents. In trifluoroacetic acid the value would now be 0.42.

For *para*-substituted fluorobenzenes containing $-R$ substituents the ^{19}F substituent chemical shift is considered to depend on $\sigma_R^{0\,36}$, but for $+R$ groups the resonance effect is slightly enhanced by cross-conjugation between the substituent and the F atom. In the recent re-examination of ^{19}F shielding by Hansch, Leo and Taft[92], the resonance effect of CO_2Et is described simply with the symbol σ_R and given a value of 0.16. Measurements of infrared intensities do, however, give information about σ_R^0 values for $+R$ groups (Section II.C). Katritzky and colleagues[46] give values of 0.155 and 0.180 for CO_2Me and CO_2Et, respectively. As already mentioned (Section III.A) the sign is not given by the correlation, but must be inferred from other evidence, which gives no trouble for these ester groups. It is interesting that these values are rather greater than the 0.11 suggested by Charton[80] for the resonance parameter of CO_2Me and CO_2Et, but not too far from the value 0.19 obtained by simple analysis of $\sigma_m = 0.33$ and $\sigma_p = 0.46$.

Other estimates of inductive and resonance parameters for these groups have been based on the correlation analysis of ^{13}C substituent chemical shifts, e.g. in the work of Reynolds

and colleagues[48] (see Section II.C). In the case of CO_2Me they favour a fairly low value for σ_F, that is σ_I, at 0.21, and a value of 0.16 for σ_R^0.

It must finally be said that the recent compilation of Hansch and coworkers[86] records for these ester groups a very wide numerical range of inductive and resonance parameters determined by physical methods. These values must be viewed very critically and the situation raises the fundamental question: 'Do the various probes really 'see' the same aspects of the substituent?'

The CO_2Me group was included in the work of Topsom and colleagues on theoretical scales of field (inductive) and resonance parameters (see Section II.C.2). A value of 0.23 was derived for σ_F[58], in only fair agreement with the experimental value of 0.17 which they quote as applicable to the gas phase[55]. However, Taft and Topsom[57] quote the quite different value of 0.24 for this purpose. Both the earlier[59] and the later[60] attempt to establish a theoretical scale of resonance parameters produced a value of 0.17 for σ_R^0 of CO_2Me, in good agreement with the experimental value of 0.16 quoted from the literature (see above).

B. The Carboxy Group

Charton bases a primary σ_I value for CO_2H on the ionization of the bicyclooctane carboxylic acids in 50% w/w EtOH−H_2O at 25 °C, as described in Section IV.A for the corresponding methyl ester group[80]. The value is 0.30, very close to the values for the ester groups. This is not unreasonable, although CO_2H might be expected to be slightly more electron-attracting than CO_2R. The determination of σ_I in this way involves the titration of the 1,4-dicarboxylic acid. The apparent pK_a values for the first and second ionizations are 6.10 and 6.87, respectively. The difference of 0.77 is not really sufficient to give a clearcut separation of the two stages of ionization. Thus the determination of σ_I for COOH must in principle be subject to the same problems that are involved in determining σ_m and σ_p for CO_2H (see below). Too much stress should therefore not be laid on the exact numerical value of σ_I for this substituent. The value 0.30 has not been widely applied, but it seems to be approximately valid for other alicyclic carboxylic acids[80], although it must be pointed out that in these series also there may be overlapping of the first and second stages of ionization of the dicarboxylic acids. It should also be pointed out that the pK_a value of the bicyclooctane carboxylic acid requires correction by a statistical factor of 0.5 in calculating σ_I, i.e. 0.301 must be added to give 6.40, which is the same as that of the ethoxycarbonyl-substituted acid (see Section IV.A).

The difficulty of determining benzoic acid-based σ values for CO_2H has recently been examined in a technical report of IUPAC[18], and we will essentially follow the discussion as presented therein.

The determination of accurate pK_a values for the first ionization of isophthalic and of terephthalic acid is very difficult, because the second ionization overlaps with the first. Elaborate treatment of results is required.

Probably the most reliable value for the first ionization constant of isophthalic acid is that determined by Ang in 1958[103]. When the pK_a value of 3.70 (water, 25 °C) is combined with a value of 4.205 for benzoic acid and a statistical correction is applied for the presence of two ionizable groups, the value of 0.204 for σ_m is obtained. It is generally believed among physical organic chemists that CO_2H should differ but little from CO_2Me in net electron-attracting ability and therefore the above σ_m value is anomalously low by at least 0.1 unit (see Section IV.A). The explanation of this is not clear. There does not appear to be any information available for the first ionization of terephthalic acid of reliability comparable with that for isophthalic acid.

However, Exner[104] has directed attention to the work of Thamer and Voigt[105], which is mentioned by Kortüm and coworkers[79a] but classified by them as *unsicher*. This work involved a combination of spectrometric and electrometric methods for both isophthalic and terephthalic acids and a treatment of results which was claimed to separate K_1 and K_2. Exner has re-examined the work and suggests that it yields values for 10^4K_1 of 2.78 ($\pm$0.25) and 3.4 ($\pm$1) mol dm^{-1} for isophthalic and terephthalic acids, respectively. When the corresponding pK_a values of 3.556 and 3.469 are combined with a value of 4.205 for benzoic acid and the statistical correction of 0.301 is applied, the values of 0.348 and 0.435 are obtained for σ_m and σ_p, respectively, which may be rounded to 0.35 and 0.44, respectively. These seem reasonable values by comparison with the corresponding values for CO_2Me (see Section IV.A). This part of the report concludes, 'Nevertheless it would be unwise to tabulate 'recommended' values for CO_2H'.

For CO_2H Charton[80] gives 0.36 and 0.41 for σ_m and σ_p, respectively. These are exactly the same as for CO_2Et and are approximately in accord with $\sigma_I = 0.30$ and $\sigma_R(BA) = 0.11$. Exner's values[104] as above are approximately in accord with $\sigma_I = 0.30$ and $\sigma_R(BA) = 0.14$.

Hansch and collaborators[86] give nine pairs of σ values for this substituent, determined in a wide variety of ways. Most of them are around 0.35 for σ_m and 0.43 for σ_p, but there are some eccentric values. They also provide some four values for σ_p^-. These are mainly in the range 0.73 to 0.78.

The infrared method using the camphor model[51] (see Section III.A) found a value of 0.36 for σ_I of CO_2H in carbon tetrachloride. It is interesting that this is slightly larger than the value for CO_2Me at 0.31. This could be an indication that the acid group is actually slightly more electron-attracting than the ester group, but see below. Little attention seems to have been paid to using the carboxy group as a substituent in studies of ^{19}F or ^{13}C NMR. The main information about the σ_R^0 value of CO_2H comes from infrared intensities. Katritzky and colleagues[46] find 0.29 for this quantity, which is far greater than the indication of the resonance effect from dissociation of the substituted benzoic acids at 0.11 to 0.14. These authors[46] quote for comparison a value of 0.21 based on ^{19}F substituent chemical shifts and communicated to them by Taft and Sheppard. There appears to be an anomaly here. It seems possible that dimerization of benzoic acid in carbon tetrachloride, the solvent used in the infrared intensity studies, leads to an erroneous indication of the resonance effect of CO_2H. The measurement of σ_I by the infrared camphor model may also be affected by the dimerization of the substrate.

On the theoretical scale of field parameters[58] CO_2H acquires a value of 0.27 and on the theoretical resonance scales[59,60] a value of 0.17. The authors quote for comparison the infrared intensity-based σ_R^0 of 0.29 and imply that there must be something wrong with it and that their theoretical value of 0.17 is more reliable[59]. It is still somewhat greater than the indications from the dissociation of the substituted benzoic acids.

C. Acyl Groups

The largest amount of information is available for the acetyl group. Charton[80] bases the σ_I value for acetyl on the effect of this group on the ionization of the quinuclidinium ion, there being no data available for this group as a substituent in the bicyclooctane system. The value is 0.30, essentially the same as that for CO_2R. This is perhaps surprising since it might well be supposed that the $+I$ effect of the ester group would be reduced relative to that of COR by internal conjugation involving the canonical form $C(O^-)=O^+R$. Such internal conjugation is not possible in COR, although in $COCH_3$, for example, hyperconjugation involving the methyl group would be possible, i.e. $C(O^-)=CH_2H^+$.

This value of σ_I for acetyl is essentially confirmed by other reactivity-based methods. In 1956 Taft[28] gave a value of 0.60 for the σ^* constant of CH_3COCH_2, which was based on his analysis of ester reactivity. When the factor of 0.45 is applied, σ_I for acetyl comes out at 0.27 (Section II.B). In 1964 Charton[82] derived a value of 0.29, based on a pK_a value of 3.58 for acetylacetic acid (water, 25 °C). Substitution of this pK_a value into Charton's later regression equation for substituted acetic acids[80] gives 0.299 for the σ_I value of acetyl.

The σ_m and σ_p values for acetyl are well-established as based on the determination of the pK_a values of the substituted benzoic acids by many authors; various experimental techniques have been used for measurements in water and in several aqueous organic solvents. The recent IUPAC report[18] considers four independent determinations of σ_m ranging from 0.35 to 0.38, with a mean value of 0.368, rounded to 0.37 as the recommended value. For σ_p five independent determinations were considered, ranging from 0.47 to 0.503, with a mean value of 0.486, rounded to 0.49 as the recommended value. These values are consistent with $\sigma_I = 0.31$ and $\sigma_R(\mathrm{BA}) = 0.18$. The values of 0.37 for σ_m and of 0.49 for σ_p of acetyl are both higher than the corresponding values for CO_2Me, 0.33 and 0.46, respectively (Section IV.A). This suggests that in fact the $+I$ and $+R$ effects of acetyl are slightly greater than the corresponding effects of methoxycarbonyl, but it is difficult to quantify the individual differences within the limits of experimental error and the limitations of the simple separation of inductive and resonance effects in the ionization of the substituted benzoic acids (Section II.B). Charton[80] gives almost the same values as the above for σ_m and σ_p of acetyl, 0.38 and 0.50, respectively.

The $+R$ effect of acetyl is subject to considerable enhancement in processes involving electron-rich reaction sites (Section II.A). Thus values of σ_p^+ are tabulated by Exner[17] as 0.82 from the ionization of anilinium ions, 0.84 from the ionization of phenols and 0.87 from nucleophilic aromatic substitution. These values are greater than the corresponding values for CO_2R (see Section IV.A), confirming that in identical circumstances, the resonance effect of acetyl is greater than that of alkoxycarbonyl. Presumably this difference is due to the internal conjugation of the ester group diminishing its ability to conjugate with the benzene ring.

We turn now to the study of the inductive effect of the acetyl group by spectroscopic techniques. The infrared method using the camphor model[51] (see Section III.A) found a value of 0.25 for σ_I of COMe in carbon tetrachloride. The agreement with the value based on reactivity in water or aqueous organic solvents is not quite so good as was noted for CO_2Me, but perhaps the surprising fact is that the agreement was so good in the latter case. Much more serious indications of solvent-dependence of the inductive effect of the acetyl come from ^{19}F NMR studies. The work of Taft and coworkers in 1963[35] found that the substituent chemical shift for *m*-acetylfluorobenzene varied considerably with solvent, the extreme values of the shielding parameter being −0.35 ppm in dioxan and −2.65 in trifluoroacetic acid. The derived values of σ_I were 0.18 in 'normal solvents', 0.15 in dioxan, 0.23 in 'weakly protonic solvents' and 0.46 in trifluoroacetic acid. The last-mentioned high value is of course attributed to the effect of hydrogen-bonding of CF_3COOH to the *CO* of acetyl. The slightly reduced value in dioxan is attributed to Lewis acid bonding. (No effect of this nature was observed for CO_2Et, see Section IV.A.) The values determined in the 'weakly protonic solvents' methanol and formic acid are still somewhat below the reactivity-based value of 0.30. In the recent re-examination of the ^{19}F NMR data for *meta*-substituted fluorobenzenes in hydrocarbon solvents[92], the use of a slightly different regression equation led to a value of 0.25 for σ_I of acetyl in hydrocarbon solvents. If the new regression equation is applied to the shielding parameter formerly obtained using methanol as solvent[35], σ_I now comes out at 0.30, in good agreement with the reactivity-based values. In trifluoroacetic acid the value would now be 0.52.

For *para*-substituted fluorobenzenes containing $-R$ substituents the ^{19}F substituent chemical shift is considered to depend on σ_R^0[36], but for $+R$ groups the resonance effect is slightly enhanced by cross-conjugation between the substituent and the F atom. In the recent re-examination of ^{19}F shielding by Hansch, Leo and Taft[92], the resonance effect of the acetyl group is described simply with the symbol σ_R and given a value of 0.16. Measurements of infrared intensities do, however, give information about σ_R^0 values for $+R$ groups, although they do not give the sign (Section II.C). Katritzky and colleagues[46] give a value of 0.219. This is in reasonable agreement with the value of 0.18 obtained above from the simple analysis of the Hammett σ values. Charton[80] suggests 0.20. In the ^{13}C NMR work Reynolds and colleagues[48] (see Section II.C) a fairly low value of σ_F, that is σ_I, is favoured, at 0.229, and a value of 0.161 for σ_R^0.

The recent compilation of substituent constants by Hansch, Leo and Hoekman[86] records for acetyl twelve values of σ_I covering a wide numerical range, and mainly determined by physical methods. We repeat that this kind of situation raises the fundamental question: 'Do the various probes really 'see' the same aspects of the substituent?'

On the theoretical scale of field parameters[58] COMe acquires a value of 0.19 (for comparison the authors quote a gas-phase value of 0.22) and on the theoretical resonance scales values of 0.20[59] and 0.15[60]. The authors quote for comparison a literature value of 0.22 for σ_R^0, which is probably the value based on infrared intensity measurements.

We will add a few comments on the behavior of the formyl group CHO. In water or aqueous organic solutions this substituent exists as an equilibrium of CHO and $CH(OH)_2$. Charton does not attempt to determine a value of σ_I for CHO by his usual methods[80]. The apparent pK_a value of the 4-formylquinuclidinium ion is 9.89 (water, 25 °C)[83]. When this value is inserted into Charton's regression equation for this system[80], an apparent σ_I value of 0.216 is obtained. This certainly relates mainly to $CH(OH)_2$. Indeed the value is almost exactly twice the value for CH_2OH calculated from the data for the quinuclidinium system.

The situation for the ordinary Hammett σ values based on measurements of the dissociation constants is unsatisfactory. The experimental results do not seem to be very reproducible as between one set of authors and another[18]. The value of σ_m appears to be about 0.40, and that of σ_p to be about 0.5 (see also Hansch and coworkers[86]). These are certainly in the region expected for CHO rather than $CH(OH)_2$, so it may well be that the hydration equilibrium is more in favour of CHO in aromatic aldehydes than in compounds in which the group is attached to a saturated carbon atom.

The recent re-examination[92] of ^{19}F substituent chemical shifts for *meta*-substituted fluorobenzenes finds a σ_I value of 0.35 for CHO in hydrocarbon solvents, greater by 0.10 units than the corresponding value for COMe. In view of the electron-releasing nature of the methyl group, relative to the hydrogen atom, such a difference is not unreasonable. The corresponding σ_R values are 0.23 for CHO and 0.16 for COMe, again a reasonable difference. The infrared intensity method[46] yields a σ_R^0 value of 0.244.

On the theoretical scale of field parameters[58] CHO acquires a value of 0.22, rather lower than the value based on ^{19}F NMR, and very close to that of COMe. On the theoretical resonance scales the values are 0.18[59] and 0.17[60], again rather lower than the value based on ^{19}F NMR and close to that of COMe.

D. Various Groups Containing Carbon–Oxygen Double Bonds

The electronic effects of the groups already discussed in Section IV have attracted the most study, but some quantitative information is available for various other groups COX.

TABLE 6. The inductive and resonance constants of COX groups as determined through ^{19}F NMR measurements[92]

X of COX	σ_I	σ_R
OEt	0.19	0.16
NH_2	0.23	0.12
Me	0.25	0.16
OPh	0.25	0.20
Ph	0.29	0.16
H	0.35	0.23
F	0.45	0.26
Cl	0.45	0.26
CF_3	0.52	0.27
CN	0.62	0.31

This information is rather patchy and this discussion will be restricted to the data for σ_I and σ_R based on ^{19}F NMR measurements of *m*- and *p*-substituted fluorobenzenes in hydrocarbon solvents, as compiled and re-examined by Hansch, Leo and Taft[92]. Most of the available data are in Table 6. Data for some groups already discussed are included for comparison.

It has already been suggested that the $+I$ and $+R$ effects of the alkoxycarbonyl groups are reduced relative to those of the corresponding acyl groups by internal conjugation in the former (see Section IV.C). No doubt the electronic effect of the amide group is similarly affected by internal conjugation. The slightly enhanced electron-attracting power of phenoxycarbonyl compared with ethoxycarbonyl is due to the $+I$ and $+R$ effects of phenyl. In the case of the benzoyl group the slightly greater value of σ_I compared with that of acetyl is also due to the $+I$ and $+R$ character of phenyl, but this is not apparent in the σ_R values. The electronic effects of acetyl and formyl have already been compared (Section IV.C). The remaining entries in Table 6 involve highly electronegative moieties X and the increasingly positive values of σ_I and, to a less marked extent, those of σ_R, clearly reflect this. Probably the behaviour of COF and COCl is also affected by internal conjugation, as in the CO_2Et group.

Another type of substituent involving a carbon–oxygen double bond is −G−COX, in which the linking to the molecular skeleton is through the connective G. Possible groups G include NH, O and CH_2. In such substituents COX essentially serves to modify the electronic effects of GH, that is NH_2, OH and CH_3, respectively. For illustration we take COX as COMe and base a comparison on the σ_I and σ_R values determined through ^{19}F NMR measurements[92]. The relevant values are as follows: NHAc, 0.34, −0.21; NH_2, 0.09, −0.48; OAc, 0.34, −0.19; OH, 0.32, −0.43; CH_2Ac, 0.11, −0.08; Me, −0.01, −0.13. These figures are in accord with the electron-attracting effect of the introduced acetyl group making the inductive effect of GH more positive and the resonance effect less negative.

E. The *ortho*-Effects of Various Groups Containing Carbon–Oxygen Double Bonds

The term *ortho*-effect has long been used to cover the peculiar influence of a substituent in the position *ortho* to a reaction centre, which often differs markedly from that of the same substituent in the *meta*- or *para*-position[43,106,107]. Steric phenomena have long been recognized as playing a major part in the *ortho*-effect. Primary steric effects of various kinds, including steric hindrance to the approach of the reagent or to solvation, and

secondary steric effects have been invoked. In certain systems hydrogen-bonding and other intramolecular interactions have been postulated.

One of the main difficulties in understanding the *ortho*-effect, however, lies in adequately specifying the electronic effects of *ortho*-substituents. The relative contributions of I and R effects to the influence of *ortho*-substituents are liable to be very different from those operating at the *meta*- or *para*-position. There have been many attempts to develop scales of 'sigma-*ortho*' constants analogous to σ, σ^0, σ^+, σ^-, etc. (Section II) for the *meta*- and *para*-positions, but such scales are never found to be of very general application[43,107]. The composition of the electronic influence of *ortho*-substituents with respect to I and R effects seems greatly subject to variation with the nature of the reaction, the side-chain, the solvent etc. The inductive effect of an *ortho*-substituent operates at much shorter range than that of a *meta*- or *para*-substituent, but the orientations of substituent dipoles with respect to the reaction centre are very different from those of *meta*- or *para*-substituents. It is sometimes supposed that the resonance effect of an *ortho*-substituent tends to be inherently weaker than that of the same substituent in the *para*-position, because *ortho*-quinonoid instead of *para*-quinonoid structures may be involved in its operation. However, the resonance effect also is being delivered at rather short range from the *ortho*-position.

The most fruitful treatment of the electronic effects of *ortho*-substituents involves the use of the same σ_I and σ_R-type constants as may be employed in correlation analysis for *meta*- and *para*-substituents by means of the 'dual substituent-parameter equation'[30] or the 'extended Hammett equation'[34] (Section II.B). Obviously it is a considerable assumption that these are valid for *ortho*-substituents and the implication is that in the correlation analysis any peculiarities may be adequately expressed through the coefficients of the inductive and resonance terms. Really satisfactory correlation analysis for any given reaction system requires a large amount of data and can only rarely be accomplished.

One system for which this can be done is the reactions of *ortho*-substituted benzoic acids with diazodiphenylmethane (DDM), which were studied by the present contributor and his colleagues some years ago[108,109]. Rate coefficients (l mol^{-1} min^{-1}) at 30 °C were measured for the reactions of benzoic and 32 *ortho*-substituted benzoic acids in 11 alcohols (including 2-methoxyethanol) as solvents[108]. The reaction involves a rate-determining proton transfer from the carboxylic acid to the DDM to form a diphenylmethanediazonium carboxylate ion-pair. Subsequent fast product-governing stages have been variously formulated[108]. A more restricted study was carried out for reaction at 30 °C of the substituted benzoic acids in 7 aprotic solvents[109], in which the proton transfer is believed to be rate-limiting rather than rate-determining.

The correlation analysis employed the extended Hammett equation in the form of equation 13:

$$\log k = \alpha\sigma_I + \beta\sigma_R + \varphi\upsilon + h \tag{13}$$

where σ_I and σ_R are, respectively, the inductive and resonance constants of Taft's analysis of ordinary Hammett σ constants (see Section II.B) and υ is the steric substituent constant developed by Charton[110–112]. A full discussion of the *ortho*-effect as revealed in this work would be inappropriate here. We must restrict ourselves to the more limited task of indicating the role of certain substituents containing carbon–oxygen double bonds. We discuss first the work involving alcohols as solvents. To apply the extended Hammett equation, i.e. to determine the regression coefficients α, β and φ and the intercept term h, it is first necessary to select a set of substituents which can be expected to be 'well-behaved'. Particular problems for σ_R and υ may be caused by conformational effects, and internal hydrogen-bonding may occur as a further factor governing reactivity, for which parametrization is not included in equation 13.

Nine substituents (Set A: H, Me, Bu^t, F, Cl, Br, I, CF_3 and CN) were selected as a basic set for the following qualities[108]: (i) symmetry and simplicity, (ii) freedom from conformational effects, (iii) lack of a large resonance effect, (iv) lack of any marked tendency to form hydrogen-bonds with the reaction centre. It proved possible to expand the list from 9 to 18 by making reasonable assumptions about the conformations of certain substituents, thus enabling them to be placed on the σ_R and υ scales [Set B: Set A + Et, Pr^i, OMe, OEt, OPh, SMe, SO_2Me, CH_2Ph, $(CH_2)_2Ph$). Correlations based on Set B turned out to be superior to those based on Set A.

The regression equations were established for data in 11 alcohols as solvents and were used to assess the peculiar behaviour of another 15 *ortho*-substituents in respect of conformational effect and intra-molecular hydrogen-bonding[108,113]. Here we are concerned with assessing the situation for several *ortho*-substituents containing carbon–oxygen double bonds. We first give as an example the regression for 2-methoxyethanol as solvent:

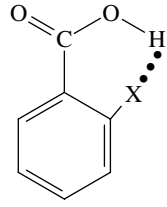
$$\log k = \underset{(\pm 0.074)}{1.624\sigma_I} + \underset{(\pm 0.082)}{0.964\sigma_R} + \underset{(\pm 0.060)}{0.346\upsilon} - 0.305 \qquad (14)$$

$$n = 18, \quad R = 0.990, \quad s = 0.070$$

(n = number of data points, R = multiple correlation coefficient, s = standard deviation of the estimate)

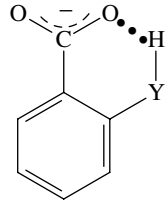
The regression coefficients are positive for the σ_I and σ_R terms because electron-attracting groups accelerate the reaction and electron-releasing groups retard it. The positive regression coefficient for the υ term corresponds to the reaction being subject to steric acceleration by *ortho*-substituents through deconjugation of COOH with the benzene ring.

Before we discuss the results for individual substituents containing carbon–oxygen double bonds, it is necessary to describe the possible role of hydrogen-bonding of substituent to reaction centre. If *o*-X bonds to the H of CO_2H, the reaction will be retarded ('unfavourable' hydrogen-bonding), while if *o*-YH bonds to a negatively charged O in the nascent carboxylate ion, the reaction will be accelerated ('favourable' hydrogen bonding); see **5** and **6**[108].



Unfavourable

(5)



Favourable

(6)

For CO_2Me there are two sets of substituent parameters: $\sigma_I = 0.32$, $\sigma_R = 0.10$ and $\upsilon = 1.51$ for the group when coplanar with the benzene ring, and $\sigma_I = 0.32$, $\sigma_R = 0.0$ and $\upsilon = 0.50$ for the group when orthogonal to the benzene ring. Thus the inductive effect is considered to be unaffected by twisting the CO_2Me group, the resonance effect is eliminated by twisting to the orthogonal conformation and the steric effect is much greater for the coplanar conformation than for the orthogonal. We may now substitute these parameters in equation 14 and analogous equations for the reactions in the

other solvents to obtain values of $\log k$(calc, coplanar) and $\log k$(calc, orthogonal), which may be compared with $\log k$(obs). For equation 14, $\log k$(calc, coplanar) = 0.834 and $\log k$(calc, orthogonal) = 0.388. $\log k$(obs) = 0.441, i.e. between the values calculated for the two conformations, but rather closer to the value for the orthogonal conformation. Without quoting the regression equations[108,114], we give the results of similar calculations for the reactions in various alcohols [solvent, $\log k$(calc, coplanar), $\log k$(calc, orthogonal), $\log k$(obs)]: methanol, 1.510, 0.958, 1.156; ethanol, 1.135, 0.586, 0.763; 2-methylbutan-2-ol, 0.415, −0.129, 0.093; benzyl alcohol, 1.966, 1.502, 1.650. In every case the observed value lies between the two extremes, indicating that an intermediate conformation of the methoxycarbonyl group is preferred, probably somewhat closer to the orthogonal than to the coplanar. No evidence of unfavourable hydrogen-bonding is apparent.

The results for other groups of interest to the present chapter are briefly as follows. *o*-CO_2H also adopts an intermediate conformation, but for the reaction in several of the alcohols (particularly phenyl-substituted alcohols) $\log k$(obs) is much closer to the value calculated for the coplanar conformation than to that calculated for the orthogonal. There is no clear evidence for the favourable hydrogen-bonding effect which might be expected to occur. For *o*-$CONH_2$, $\log k$(obs) is always near to the value of $\log k$(calc, orthogonal) and for some solvent alcohols is actually below it. This may be an indication of a role for unfavourable hydrogen-bonding. In the case of *o*-COPh the $\log k$(obs) values are intermediate between the $\log k$(calc) values for the conformational extremes, and there is no evidence for any hydrogen-bonding effect. The substituent constants of the remaining three groups do not show conformational dependence, but deviations of $\log k$(obs) from $\log k$(calc) may indicate the role of hydrogen-bonding between substituent and reaction centre. For *o*-NHCOMe there are indications of a small favourable hydrogen-bonding effect, although *o*-NH_2 does not show any significant deviation from the regression equations. Presumably the electron-attracting influence of COMe promotes such hydrogen-bonding. In the case of *o*-OCOMe and *o*-CH_2CO_2Me the $\log k$(obs) values are always below those of $\log k$(calc), probably indicating the occurrence of unfavourable hydrogen-bonding.

The more limited study of the reactions of *ortho*-substituted benzoic acids with DDM in aprotic solvents[109] revealed some differences in the *ortho*-effects, compared with the reactions in alcohols. Thus *o*-CO_2Me appears to adopt an essentially orthogonal conformation in most of the solvents, and this is also the case for *o*-CO_2H in DMA, DMF and DMSO. However, for the reactions of the *o*-CO_2H acid in acetone or ethyl acetate, $\log k$(obs) is considerably greater than $\log k$(calc, coplanar), certainly indicating the occurrence of favourable hydrogen-bonding, which was not observed for the reactions in alcohols. The favourable hydrogen-bonding shown in a small degree by *o*-NHCOMe in the reactions in alcohols is very marked for the reactions in acetone, ethyl acetate, DMA, DMF and DMSO. *o*-COPh appears to adopt a coplanar conformation in DMA, DMF and DMSO, but in nitrobenzene, chlorobenzene, acetone and ethyl acetate an intermediate conformation appears to be shown. There is no evidence for unfavourable hydrogen-bonding. Finally, *o*-OCOMe and *o*-CH_2CO_2Me conform to the regressions for aprotic solvents rather better than they do to the regressions for alcohols. This behaviour is anomalous because the unfavourable hydrogen-bonding effect, which appears to be indicated from the reactions in alcohols (see above), would be expected to be enhanced in aprotic solvents.

Intramolecular catalysis by the carbonyl group is important in some reaction systems and can sometimes be a component of the *ortho*-effect. Bowden has recently reviewed intramolecular catalysis by carbonyl groups in ester hydrolysis[115].

V. SOME FURTHER MULTIPARAMETER TREATMENTS OF SUBSTITUENT EFFECTS

A. Introduction

Earlier sections of this chapter contain accounts of the Yukawa–Tsuno equation[24,25], the Dual Substituent-Parameter (DSP) equation[30,31] and the Extended Hammett (EH) equation[34] (see Section II.B), with the particular intention of showing how these may be applied to data sets involving the substituents of particular interest for this chapter. These equations are not now the only possibilities for multiparameter treatment. In this section we shall give accounts of some of the other approaches. The accounts will necessarily be brief, but key references will be given, with indications as to how the substituents of interest for this chapter fit into the various treatments.

B. Exner's Analysis

This is essentially a method of providing an alternative set of σ_I and σ_R parameters for use in the DSP equation or EH equation. In the mid-1960s Exner[33] found evidence that the inductive effect from the *para* position of benzoic acid was stronger than that from the *meta* position by a factor of 1.14. He also suggested that σ_I values current at that time and based on alicyclic and aliphatic reactivities were out of scale with σ_m and σ_p by a factor of 1.10, and should be multiplied by this to introduce the π-inductive component. This led Exner to a revised analysis of σ_m and σ_p in terms of inductive and resonance components. He calculated revised σ_I values by multiplying the alicyclic/aliphatic values by 1.10, and then multiplying these further by 1.14 before subtracting from σ_p values to obtain revised values of σ_R.

The most dramatic changes were for some $+R$ substituents, such as NO_2 and CN, whose σ_R values dropped to zero. The implication of this is that such substituents are normally not conjugated with the benzene ring and only become so in the presence of a $-R$ *para*-substituent with which cross-conjugation is possible (Section II.A). For $+R$ substituents containing a carbon–oxygen double bond there is a small residual σ_R value, thus: COMe, 0.05; COPh, 0.04; CO_2R, 0.03; CO_2H, 0.03. Exner's recalculation of σ_R values imposes less dramatic changes on $-R$ substitutents, although these are still appreciable.

The status of Exner's revised σ_I and σ_R values has been debated for thirty years. A number of prominent workers in the field are rather critical of Exner's approach. For a fairly recent appraisal of the situation, see an article by the present author[15]. Exner has continued to propagate his view on this matter in his book published in 1988[16]. Some of his papers in the past few years indicate that he is developing further criticisms of aspects of the 'traditional' separation of inductive and resonance effects and of the ways in which correlation analysis of substituent effects is generally carried out[93,116–118].

C. C.G. Swain's Treatments

These began with a paper by Swain and Lupton[119] in 1968. The approach was slightly modified and greatly extended by Hansch's group in 1973[120]. During the first 15 years or so of its life, the Swain–Lupton treatment was applied extensively, but was also severely criticized. A revised version appeared in 1983 in a paper by Swain and coworkers[121]. This version was in its turn severely criticized, but also applied. The Swain–Lupton treatment was reviewed by the present author in 1978[23] and again more briefly in 1982[14]. A more

recent review[15] covers also the revised version and an account of a mini-symposium in print in which several of Swain's critics set forth their views, and Swain replied[122–125].

The Swain–Lupton treatment[119] was a reaction against the proliferation of scales of polar substituent constants. The authors maintained that the polar effect of any given substituent could be adequately expressed in terms of just two basic characteristics: a field constant $\mathcal{F}$ and a fixed resonance constant $\mathcal{R}$. Swain and Lupton maintained that the correlation analysis of chemical reactivity data and spectroscopic data of aromatic systems could be carried out satisfactorily in terms of $\mathcal{F}$ and $\mathcal{R}$ (*cf* the four σ_R-type parameters introduced for the DSP equation), *meta* and *para* series being dealt with separately, as in the case of the DSP equation. The assumptions involved in establishing the $\mathcal{F}$ and $\mathcal{R}$ scales provoked much criticism. Nevertheless, the treatment achieved fair success when applied to chemical reactivity data and some spectroscopic data, particularly NMR[14,23]. The most notable success, however, was in the correlation analysis of biological activity data[126].

The revised version[121] developed new scales of field and resonance parameters, the awkward symbols $\mathcal{F}$ and $\mathcal{R}$ being replaced by the more straightforward F and R. Some of the criticism made of the earlier form of the treatment had been met by the modifications, but the critics were still not satisfied[122–124].

A compilation of F and R constants, as revised by Hansch, appeared in a book by Hansch and Leo[85]. A more recent compilation of substituent constants includes F and R values, revised again by Hansch[92]. See also Hansch, Leo and Hoekman[86]. Values are provided for numerous substituents of interest in this chapter.

D. The Poly Substituent-Parameter (PSP) Equation

This equation is an elaboration of the dual substituent-parameter (DSP) equation. Its development has been relatively recent, but Taft and Topsom, who were closely associated with it, have written a long review article[57] involving the equation, and this article will probably acquire the status in respect of the PSP equation that the article of Ehrenson, Brownlee and Taft[31] has in connection with the DSP equation. The name Poly Substituent-Parameter Equation was devised by the present author in a short account thereof[15]. Hopefully, that account and the present briefer one will encourage study of Taft and Topsom's article[57].

The new treatment had its origins partly in *ab initio* molecular orbital calculations of substituent effects and partly in extensive studies of gas-phase proton transfer reactions since about 1980 (Section II.C.1). Various aspects of this work essentially drew attention to the importance of substituent polarizability. In 1986 Taft, Topsom and their colleagues[127] developed a scale of 'directional substituent polarizability parameters', σ_α, by *ab initio* calculations of directional electrostatic polarization potentials at the 3-21G//3-31G level for a large set of CH_3X molecules. The σ_α values were shown to be useful in the correlation analysis of gas-phase acidities of several series of substrates[127], and such work has subsequently been extended by Taft and Topsom[57].

Values of σ_α are available for over thirty substituents. H is the standard at 0.00 and the values range from +0.13 for F to −0.81 for Ph. The values for $CH_2{=}CH$, CO_2Me, COMe, CHO and $COCF_3$ are −0.50, −0.49, −0.55, −0.46 and −0.51, respectively. To set these values in context we mention that the σ_α values for Me, Cl, CN and SO_2Me are −0.35, −0.43, −0.46 and −0.62, respectively.

The PSP equation is written by Taft and Topsom[57] in various forms. Equation 15 is a convenient form with which to begin this discussion:

$$-\delta\Delta G^\circ = \rho_F\sigma_F + \rho_R\sigma_R + \rho_\alpha\sigma_\alpha + \rho_\chi\sigma_\chi \qquad (15)$$

The equation is written in terms of Gibbs energy changes, rather than $\log K$ or $\log k$, because much of its application initially was to gas-phase reactions for which the use of Gibbs energies is conventional. Corresponding equations in terms of $-\delta\Delta E^\circ$ or $-\delta\Delta H^\circ$ have also been used. The negative sign is introduced to make the signs of ρ values correspond to the conventions of the Hammett equation. σ_F is Taft and Topsom's preferred symbol for the inductive constant σ_I (see Section II.C.1), σ_R is a resonance constant closely related to σ_R^0, σ_α the substituent polarizability parameter as above and σ_χ is the substituent electronegativity parameter.

The inclusion of σ_χ is to deal with the possibility that consideration of electronegativity may be helpful in understanding substituent effects. Values of σ_χ come from *ab initio* calculations. On this scale H is taken as a standard at $\sigma_\chi = 0.00$, and the values range from −0.15 for SMe to +0.70 for F. CH_2=CH, CO_2Me, COMe, CHO and $COCF_3$ are at 0.00, 0.04, −0.04, −0.05 and 0.03, respectively. To set these values in context we mention that the σ_χ values for Me, Cl, CF_3 and CN are 0.00, 0.16, 0.02 and 0.30, respectively. However, except at very short range, electronegativity effects of substituents are found not to be important, and the PSP equation may be simplified to equation 16:

$$-\delta\Delta G^\circ = \rho_F\sigma_F + \rho_R\sigma_R + \rho_\alpha\sigma_\alpha \tag{16}$$

Taft and Topsom's article[57] and also Topsom's[66] should be consulted for details of the setting up of the scales of substituent parameters. The equation has been applied to a wide range of gas-phase reactivities. (In the multiple regressions an intercept term is often permitted, but usually this turns out to be indistinguishable from zero, as it should be if equation 16 is valid.) For aliphatic and alicyclic saturated systems the resonance term is duly negligible. The roles of field, resonance and polarizability effects are discussed and the interpretation of the various ρ values is attempted.

When the equation is applied to reactions in solution, it is found that polarizability effects tend to be much smaller than in the gas phase, but the PSP equation has to be adapted to include Substituent Solvation Assisted Resonance (SSAR). The PSP equation then assumes the form of equation 17:

$$-\delta\Delta G^\circ(\text{soln.}) = \rho_F\sigma_F + \rho_R\sigma_R + \rho_S\Delta\sigma_R \tag{17}$$

where $\Delta\sigma_R$ is the SSAR parameter. A scale of $\Delta\sigma_R$ values has been established. It is also necessary to use special σ_F(aq.) values for some hydrogen-bond acceptor substituents in aqueous solution.

The SSAR phenomenon affects only $+R$ substituents. The $\Delta\sigma_R$ value of H is 0.00. Values for several $+R$ substituents are as follows[57]: SO_2Me, 0.02; CN, 0.07; CO_2Me, 0.08; COMe, COPh, 0.10; NO_2, 0.18; CHO, 0.18. Several of the substituents for which enhanced σ_F(aq.) values are tabulated are $+R$ substituents, including: COMe, 0.29; CO_2Me, 0.31; CHO, 0.34. The 'enhancement' of these values is, of course, with respect to the gas phase. The values correspond closely to the 'reactivity' values discussed in Sections IV.A and C.

A fairly recent study applied the PSP equation to good effect in discussing the gas-phase and aqueous solution basicities of about fifty 2-, 3- or 4-substituted pyridines and some 2,6-disubstituted compounds[128]. The substituents studied included 3- and 4-COMe, and 3- and 4-CO_2Me, and these conformed fairly well to various relations and graphical plots. Various groups containing carbon–oxygen double bonds also feature extensively in another study on the inherent dependence of resonance effects of strongly conjugated substituents on electron demand[129].

E. Charton's LDR Equation

This has been developed since 1986. The title letters stand for *L*ocalized *D*elocalized *R*esponse. The localized effect is Charton's preferred name for the inductive effect and

delocalized effect is his preferred name for the resonance effect. Indeed, he would like to change the usual symbols from σ_I to σ_L and σ_R to σ_D for the purposes of the Extended Hammett (EH or LD) equation[80]. The response referred to is that of the substituent to the electronic demand of the site (i.e. reaction site in the correlation analysis of reactivity). Thus this equation, like the PSP equation, is concerned with the parametrization of substituent polarizability.

We shall describe the treatment only rather briefly, because a detailed article[130] and a useful introductory account[131] have already appeared. (The latter includes a table of substituent constants for about thirty common substituents.)

The LDR equation may be written as in equation 18:

$$Q_X = L\sigma_l + D\sigma_d + R\sigma_e + h \tag{18}$$

where Q_X is the property influenced by the substituent X, σ_l is the localized effect parameter, identical to σ_I, σ_d is the intrinsic delocalized effect parameter for minimal electronic demand of the active site and σ_e gives the sensitivity of X to changes in electronic demand of the active site; h is the intercept term. Quantities σ_d and σ_e are defined by equation 19:

$$\sigma_D = \sigma_e\eta + \sigma_d \tag{19}$$

where η expresses the electronic demand of the active site and σ_D (i.e. σ_R) is the relevant delocalized electronic parameter which would be used in the EH treatment of the system, i.e. a σ_R-type quantity. The main article mentioned above[130] should be consulted for the methods whereby the substituent parameter scales were established. Several hundred data sets have been treated by means of the LDR equation, and the various sigma parameters have been tabulated for more than 120 substituents.

As already mentioned, the σ_l values correspond to those of σ_I as derived by Charton[80], while the values of σ_d are broadly similar to Charton's values of σ_R[80]. However, individual values may sometimes differ by a few units in the second place of decimals, consequent upon σ_d being derived from σ_D (i.e. σ_R) in equation 19 by subtracting an electronic response term. For substituents of interest for this chapter, values of σ_l and σ_d, respectively, are as follows: CH_2=CH, 0.11, −0.08; CO_2Me, 0.32, 0.16; CHO, 0.30, 0.27. H is the standard for σ_e at 0.00, and the scale runs from +0.041 for F to −0.29 for PPh_2. The values for CH_2=CH and CO_2Me are −0.12 and −0.07, respectively. To set these values in context we mention the values for a few selected substituents: Me, −0.030; Cl, −0.011; OMe, −0.064; NO_2, −0.077.

The electronic demand parameter η, characteristic of a given process, is equal to the ratio of the coefficients R/D and has been shown to depend on the nature of the active site, skeletal group and medium. Contrary to the general view, electronic demand is roughly the same in magnitude for σ_R (based on benzoic acid ionization) and σ_R^0 scales, but is positive for the former and negative for the latter.

It is claimed that, 'The LDR equation is the first successful model for electronic effects of substituents bonded to carbon in all substrates'[132].

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(b) E. P. Serjeant and B. Dempsey, *Ionisation Constants of Organic Acids in Aqueous Solution*, Pergamon Press, Oxford, 1979 (I.U.P.A.C. Chemical Data Series, No. 23).
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pK_a values determined in aqueous organic or purely organic solvents. Detailed references may be found in the above sources. Some use has also been made of Tables in Charton's review[80], where detailed references are also given. Reference 79c has also been used as a source of rate constants in the present chapter, where no more specific reference is given.

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CHAPTER **4**

The chiroptical properties of the carbon–carbon double bond

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I. INTRODUCTION

This chapter is not an update of a previous chapter and will therefore try to review the reported chiroptical data on the carbon–carbon double bond, starting from 1968. It will refer only to the available literature on the C=C chromophore itself. It will analyze the available data of molecules which contain only one chromophore, the carbon–carbon double bond. It will not dwell on molecules which have the C=C bond as one of the chromophores which are responsible for its optical activity. It will cover the literature in the field of electronic excitations and will not provide information on vibrational CD (VCD) or Raman optical activity. The chiroptical properties provide information regarding the spectroscopy of the chromophore, as well as its absolute configuration. The latter is usually done with the help of sector rules around the chromophore of interest. In this review both aspects will be discussed.

A. History

CD instruments became available commercially at the beginning of the sixties[1]. Since the olefinic moiety is absorbing in the wavelength range below 220 nm, it was not among

the first measured chromophores, because the first instruments could not reach this wavelength region. It took a few more years for the first report to be published[2]. The amount of data available for olefins was still limited, due to the lower wavelength limit of 195 nm imposed by the commercially available instrumentation. In 1970 two new instruments[3,4] were built, capable of extending CD measurements down to 140 nm. This breakthrough enabled the study of higher valence and Rydberg states of the olefinic chromophore.

II. THE SPECTROSCOPY OF THE OLEFINIC CHROMOPHORE

A. General Remarks

The most comprehensive review of the excited states of ethylene, the symmetric chromophore, was written by Merer and Mulliken[5]. According to their ordering of the excited states, the lowest singlet state, lower than the first N → V ($\pi \rightarrow \pi^*$) valence state, is a transition from the π orbital to a 3s Rydberg orbital (N → R). This ordering was not accepted by Scott and Wrixon[6], who advocated the lower-lying transition, having an opposite-sign CD signal to that of the $\pi \rightarrow \pi^*$ transition, as the $\sigma \rightarrow \pi^*$ absorption. This transition, the $\sigma \rightarrow \pi^*$, has a predictable nonzero rotational strength. It is worth mentioning that another state, the so-called 'mystery band', was also detected at lower energies than the N–V valence band. However, this band, which was recorded mostly in solution, was assigned as a $\pi \rightarrow \sigma^*$ transition having an almost-zero magnetic moment and thus a vanishingly small rotational strength. While dealing with the lower excited states, the $\pi \rightarrow$ 3s Rydberg transition and the $\pi \rightarrow \pi^*$ valence transition, we should introduce the other notations used for these states. The first transition can be represented by the Merer and Mulliken notation[5] as the $1b_{3u} \rightarrow 4a_g$ or as $A_g \rightarrow B_{3u}$; here, the lower-case symbols denote one-electron orbitals and the capitals refer to molecular states in the symmetric chromophore. The corresponding notations for the $\pi \rightarrow \pi^*$ are $1b_{3u} \rightarrow 1b_{2g}$ or $A_g \rightarrow B_{1u}$. These symbols, which are used in the assignment of the excited states of ethylene, are adopted also for the substituted optically active molecule whose symmetry is lower than that of ethylene. The use of the ethylenic symbols is justified, because the excited states of the symmetric chromophore are only slightly perturbed by the introduction of the substituents. This is true when substituents such as a hydrogen atom or an alkyl group are creating the asymmetry. The excited states of these substituents are higher in energy than the excited states of the chromophore of interest, and the previous assumption is therefore justified. Among the higher excited states, the one that will be mentioned quite often in this review is the $\pi \rightarrow 3p_y$ Rydberg transition, known also as $\pi_x \rightarrow \pi_y^*$. This state, whose symmetry in the symmetric chromophore is B_{2g}, is an electric-dipole forbidden and magnetic-dipole allowed transition from the ground state[7]. It will therefore show a weak absorption band and a strong CD signal.

This review will use the terminology of differentiating between valence and Rydberg transitions. We will therefore devote some explanation to clarify the subject. A Rydberg orbital is an orbital in which the principal quantum number, n, is higher than the n of the ground-state molecular orbitals. For example, the ground-state π orbital is composed of 2p atomic orbitals of the carbon atoms. The Rydberg orbitals (for the alkene moiety) will have its $n > 2$. The lowest Rydberg in the alkene chromophore will be the 3s orbital. The π^* orbital, which is also an unoccupied orbital in the ground-state configuration, is a valence orbital because it is generated only from 2p atomic orbitals. Several techniques are known to be used for the identification of Rydberg states. They are all summarized in Robin's book[32] and will be mentioned later in this review.

This review will start with *trans*-cyclooctene for reasons that will become clear later.

B. *trans*-Cyclooctene

The molecule that has been investigated more than any other olefin is the *trans*-cyclooctene. This molecule, which is a twisted olefin, served as a model compound for the olefinic chromophore, the main reason being that chromophores in general can be divided into two types: those which are asymmetric (inherently asymmetric) by nature and those which become asymmetric as a result of chiral centers in their vicinity.

Chromophores which are asymmetric by nature are characterized by the absence of a center and plane of symmetry in the group of atoms participating in the optical transition. The rotational strength of these are usually larger when compared with chromophores that become optically active due to substitution. This is demonstrated in Mason and Schnepp's[8] study of *trans*-cyclooctene, α-pinene and β-pinene. They pointed out that the g (anisotropy factor, $g = \Delta\varepsilon/\varepsilon$) value of the major bands in *trans*-cyclooctene is 'relatively high as expected for an intrinsically asymmetric chromophore' when compared with the other two olefins.

The earliest work on *trans*-cyclooctene, in the time period which this review is covering, is by Yaris, Moskowitz and Berry[9]. They have measured the absorption and CD of (+)-*trans*-cyclooctene in a cyclohexane solution, as well as the ORD in heptane solution. They have also presented the temperature dependence of the absorption spectra of vapors of *trans*-cylcooctene and *trans*-cyclononene. The solution spectrum reveals one intense and very broad absorption band peaked at around 195 nm. Yaris and coworkers[9] have also carried out semiempirical calculations of energies, oscillator strengths and rotational strengths for a number of singlet–singlet transitions of ethylene and of *trans*-cyclooctene. The analysis showed that a minimum of three low-lying singlet states are required to explain the CD and absorption data which have been scanned in the 225–190 nm region. The states were the aforementioned states, namely the $\pi \rightarrow 3s$ Rydberg, the $\pi \rightarrow \pi^*$ valence transition and the $\pi \rightarrow 3p_y$ magnetic-dipole allowed transition. The latter is the only transition which could conceivably account for the absolute sign and magnitude of the observed rotational strength of *trans*-cyclooctene, because the other transitions had a reasonable magnitude for the measured rotational strength, but the wrong sign. The $\pi \rightarrow \pi^*$ was responsible for the strong absorption.

Scott and Wrixon[10] have also calculated the transition energies and rotational strengths of ethylene and *trans*-cyclooctene. The energies of the latter were measured at two twisting angles, $\delta = 0^0$ (planar) and $\delta = 15^0$. The energy of the $\pi \rightarrow \pi^*$ transition was 6.31 eV for the 'planar' *trans*-cyclooctene and 5.81 eV for the twisted ($\delta = 15^0$) *trans*-cyclooctene. The experimental value is 6.32 eV. For the same transition the rotational strength was calculated[9] as +71.39, while the observed experimental value was -130 (10^{-40} cm g s) at $\delta = 10^0$. The results showed that the *planar trans*-cyclooctene gave better energies for the π–π^* state and that an opposite sign was calculated for the CD of the same transition in the *twisted trans*-cyclooctene. These results led the authors to claim that an alternative, dissymmerically-perturbed chromophore model approach should be examined side by side with the twisted olefin calculations as a basis for chirality assignment and transition energy allocations for chiral olefins.

Two back-to-back papers[11,12] have reported the CD spectrum of (+)-*trans*-cyclooctene in the vapor phase. The first, by Bach[11], scanned the 225–185 nm region using a CARY 60 spectropolarimeter. The second (see Figure 1), by Schnepp and coworkers[12], measured the same enantiomer, employing their home-made instrument down to 160 nm. In both cases a broad positive CD band was observed peaked at 197 nm. A distinct break in the slope of the CD contour at 207 nm was detected in the two spectra, indicating the existence of a weaker CD system. The differences between the two measurements were observed only in the magnitude of the CD band, where Bach[11] reports 16×10^4 for the

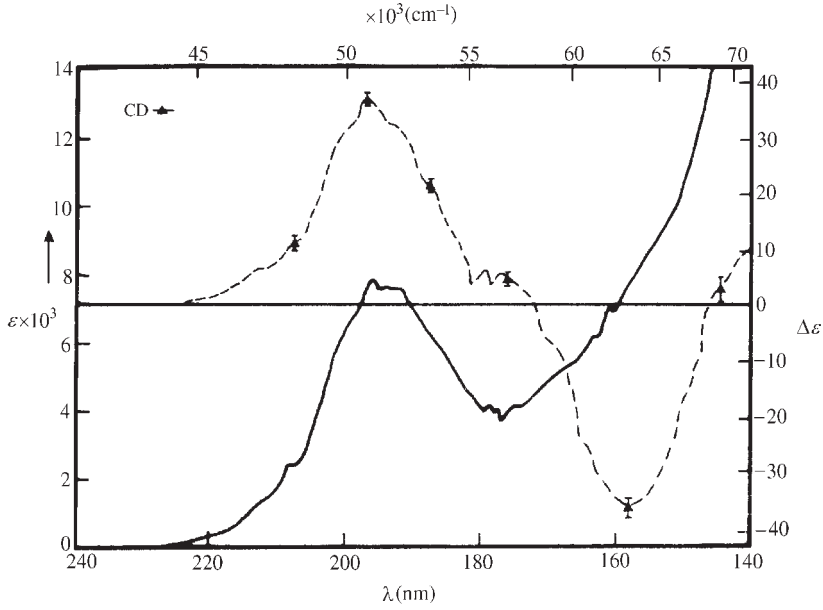
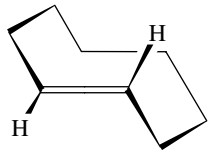


FIGURE 1. The absorption and CD spectra of (+)-*trans*-cyclooctene in the gas phase. CD resolution is 0.8 nm

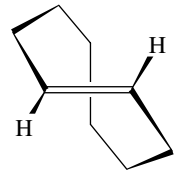
[θ] value at the maximum, while for Schnepp's group the measured value of [θ] was 9×10^4.

We have already mentioned that *trans*-cyclooctene has attracted the attention of a few theoreticians, and various calculations were applied to calculate the sign and magnitude of the rotational strength of the $\pi \rightarrow \pi^*$ transition in this molecule. Two other calculations will be mentioned at this stage: they are the *ab initio* calculation by Robin and coworkers[13] which included configuration interaction, and another by Levin and Hoffmann[14] which employed extended Huckel and CNDO/2 methods to calculate two conformations of *trans*-cyclooctene, as well as some other model compounds. Robin and his coworkers[13] concentrated on a twisted ethylene prototype as a model for the *trans*-cyclooctene. The ethylene in their calculations was twisted so as to form a 10° dihedral angle between methylene groups, with all bond distances remaining as for planar ethylene. The twisting about the C=C axis has the effect of mixing $\pi \rightarrow \pi^*$ electric dipole intensity into both the $\sigma \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*$ excitations. They argue that for a large twisting angle, the oscillator strengths of these forbidden states might reach 0.2, but for a 10° dihedral angle, they are of the same order of magnitude of vibronically allowed bands. Their calculated energy levels placed four excitations at energies lower than the $\pi \rightarrow \pi^*$ transition. The oscillator strengths and rotational strengths for these and some higher excited states were also calculated. According to their results, the rotational strengths of $\pi \rightarrow \sigma^*$ excitations are smaller than those for $\sigma \rightarrow \pi^*$ transitions.

Levin and Hoffmann[14] carried out their calculations on two *trans*-cyclooctene conformations, **1** and **2**. To introduce the two conformations here and also on a number of simpler prototypes, one of them was twisted ethylene, using 29°, 20° and 10° torsion angles. They have suggested three possible sources for the optical activity of *trans*-cyclooctene: the chirally disposed allylic substituents, the transannular portion of the methylene chain



(1)
chair form



(2)
twist form

and the double-bond torsion. For the twist conformation, **2**, the third parameter is the most important factor, and the others are only minor perturbers. As the angle of twist is decreased, the magnitude of the rotatory strength is decreased. For the chair conformation the transannular methylene contribution is more important. The explanation provided for the major role of the twisting angle in determining the rotational strength (magnitude and sign) of the twisted double bond is as follows: the rotational strength of a transition between ground state **g** and the excited state **e** is

$$\mathbf{R}_{ge} = \mathrm{Im}\langle g|\mu|e\rangle \cdot \langle e|m|g\rangle \tag{1}$$

where μ and m are the electric and magnetic transition moment operators, respectively, and Im is the imaginary part of the following expression. The scalar product dictates that the electric and magnetic transition moments should be allowed along the same axis. For a molecule like ethylene, having a D_{2h} symmetry, this cannot happen, because if the electric transition moment is allowed along the internuclear distance (which is the case for the $\pi \rightarrow \pi^*$ transition), the magnetic transition moment along this axis is zero. Twisting the double bond out of planarity reduces the local symmetry from D_{2h} to D_2, where the magnetic transition moment along the internuclear axis is nonzero. In cases where the chirality is due to substitution, the local D_{2h} symmetry is preserved and other mechanisms are used to explain the optical activity. The authors speculate that the chiral disposition of substituents around the double bond uniquely define its sense of twist or, in other words, that on a time-average basis all chiral olefins are nonplanar. A similar case was reported by Charney and coworkers[15,16], who found this speculation to be true for a number of steroidal dienes.

The absorption and CD spectra of gaseous *trans*-cyclooctene in the wavelength region of 230–140 nm was measured and assigned by Mason and Schnepp[17]. The spectra are presented in Figure 1. They have assigned the first electronic transition, which appears as a weak shoulder at 208 nm (48077 cm^{-1}), to be a $\pi \rightarrow$ 3s Rydberg transition. This assignment was based on some extensive theoretical calculations[18]. The intense absorption peak at 196 nm (51020 cm^{-1}) was assigned as the valence $\pi \rightarrow \pi^*$ transition. As for the CD, two options were mentioned. The first, which is based on the observation that the CD and the absorption have almost the same contour and therefore represent only one transition, is the valence $\pi \rightarrow \pi^*$ transition. The second option is that the spectra correspond to a superposition of two states, both of which contribute similarly to the absorption and have the same CD sign. In this case the two transitions would be the $\pi \rightarrow \pi^*$ and the $\pi \rightarrow \sigma^*$.

The weak system consisting of two peaks at 178 nm (56180 cm^{-1}) and at 175.5 nm (56923 cm^{-1}) was not well characterized. The interpretation suggested by Mason and Schnepp[17] was to assign the bands to the second Rydberg transition, the $\pi \rightarrow$ 4s. The spacing between the two peaks (740 cm^{-1}) was interpreted as a twisting vibration

about the double bond. This assignment is in accordance with the expectation[5] that the angle of twist would change upon excitation to a Rydberg state. The intense negative CD system peaking at 156.5 nm (63898 cm^{-1}) was attributed to a $\sigma \rightarrow \pi^*$ transition. Both Yaris[9] and Robin[13] predicted a negative CD sign for this transition. The absorption strength according to Yaris[9] should be somewhat less than half that of the $\pi \rightarrow \pi^*$, and this was indeed consistent with the observed experimental results. The g values of both major bands were relatively high, as expected for an intrinsically asymmetric chromophore.

Bouman and Hansen[19] have reported the results of *ab initio* calculations of absorption, as well as CD intensities using a particular version of the equations-of-motion method called the random-phase approximation (RPA). The molecular system they have considered comprised chiral conformations of ethylene and *trans*-2-butene. These molecules were chosen to mimic the twisted mono-olefin chromophore. Their paper[19] also contains three other *ab initio* approaches, which are added for comparison with the RPA results. The calculations do not include Rydberg orbitals, and the spectra[17] are assigned as based only on valence transitions. The agreement between the computed ethylene and *trans*-2-butene results, on the one hand, and the overall agreement between the prominent experimental features and the computed excitations, on the other, indicate that the low-energy excitations of the twisted C=C chromophore can be accounted for by a twisted ethylene[19]. The two opposite-sign main CD signals[17] were assigned as the $\pi \rightarrow \pi^*$ and $\sigma_{C-H} \rightarrow \pi^*$ valence transitions, respectively, and the magnitude of the calculated CD signal agrees with the experimental results in sign and magnitude. The calculated excitation energies were about 2 eV higher than the experimental transitions energies. The calculated separation of these two transitions (1.5–2.0 eV), on the other hand, was in better agreement with the experimental splitting of 1.6 eV. They concluded that the prominent features of the low-energy excitation properties of twisted mono-olefins can be accounted for on the basis of a localized, twisted ethylenic chromophore. As for the two weak negative CD transitions at 5.8 and 6.9 eV, which were previously assigned as $\pi \rightarrow 3s$ and $\pi \rightarrow 4s$[17] Rydbergs, they[19] offer a different characterization. The double-zeta basis set leads to two excitations of about the right rotatory strength, namely a $\pi \rightarrow \sigma_{C-C}$ (having a B_1 symmetry) and a $\pi \rightarrow \sigma^*_{C-H}$ (having a B_3 symmetry). They reject the idea that Rydberg transitions[13] play any role in these excitations, because 'such Rydberg-type excitations would not be expected to show up in the CD spectrum with appreciable intensity'.

In another theoretical study[20], rotatory strengths of twisted ethylene were computed directly from wavefunctions obtained by the following molecular orbital methods: CNDO/2, INDO, ODIN and RHF-LCAO-MO-SCF. Several approaches, including limited single-excitation CI and the electron-hole potential method, were used to improve the description of the excited state. Despite the fact that all the semiempirical methods yielded the same signs as obtained from the most rigorous *ab initio* study for all transitions, the authors concluded that the semiempirical (CNDO/2 and INDO) and the nonempirical (ODIN) methods yield unreliable results for rotatory strength computations. The results contain information regarding Rydberg and valence transitions. The lowest-energy excitation is the $\pi \rightarrow 3s$ Rydberg transition, for which the right CD sign and magnitude were also obtained. The couplet of the two strong oppositely signed CD bands observed in the CD spectrum of *trans*-cycooctene is assigned as the $\pi \rightarrow \pi^*$ and $\sigma \rightarrow \pi^*$ valence excitations, respectively.

In a later study Rauk and Barriel[7] have recalculated the twisted ethylene molecule. The approach they took in this calculation, to overcome the difficulty of configuration interaction of a large set, made use of perturbation theory. Their method was recommended for small and medium-size molecules. The excitation energies for ethylene twisted 10°

were uniformly lower than the planar excitation energies by only 0.07 eV, with three exceptions: the first was the $\pi \rightarrow \pi^*$ state, which was lowered by 0.21 eV upon twisting; the $\sigma_{CH} \rightarrow \pi^*$, which was raised by 0.09 eV; and the $\pi \rightarrow 3p_\pi$, which was lowered by 0.12 eV. The main features of the CD spectrum of *trans*-cyclooctene were reproduced[7]. The lowest-energy transition was the $\pi \rightarrow 3s$, which occurred at lower energy than the $\pi \rightarrow \pi^*$ transition, but had a significant rotational strength and the same sign as the $\pi \rightarrow \pi^*$. At higher energies they have calculated[7] a strong CD signal of opposite sign to that of the $\pi \rightarrow \pi^*$, the $\sigma_{CH} \rightarrow \pi^*$ transition. The experimentally observed separation of these two states was approximately 1.6 eV, which was close to the calculated value of 1.5 eV.

Liskow and Segal[21] reported on a series of extensive CI calculations directed towards the complete elucidation of the *trans*-cyclooctene CD spectrum. These calculations dealt with CI problems ranging up to 23322 configurations, utilizing a partition approach. The calculations were carried out in ethylene in the planar form, 10° twisted (D_2) and in the *trans*-cyclooctene (C_2) double-bond geometry. The energy of the first negative CD band is 6.32 eV, and it was assigned unequivocally as a $\pi \rightarrow \pi^*$ transition. The computed excitation energies (Table III, Reference 21) for this state were 8.80, 7.54 and 8.14 eV for the planar ethylene, the *trans*-cyclooctene and the 10° twisted ethylene, respectively. This trend, where the *trans*-cyclooctene is lower by 1.0–1.5 eV than the planar ethylene, is the same for the calculated excited states. This was explained[21] as due to effects of the *trans*-substitution on ethylene. In reality, the absorption maximum of the $\pi \rightarrow \pi^*$ transition in planar ethylene lies at 7.66 eV. The second major dichroic band in *trans*-cyclooctene is observed at 7.95 eV. The calculated value for the $\sigma \rightarrow \pi^*$ is 7.98 eV. The calculated rotatory strength for this state was found positive, opposite in sign to the V state. In order to make this comparison more quantitative, and to analyze the effect of the saturated hydrocarbon substituents on the excitation energies, additional calculations on *trans*-substituted ethylene were performed. These calculations used a minimal STO-4G basis set. Although a more extensive basis set is necessary to calculate the excitation energies of twisted ethylenes, this lower-level basis is adequate for the calculations of the shifts in the state energies due to the presence of a saturated hydrocarbon moiety. The results (presented in Table IV of Reference 21) indeed improve dramatically the excitation energies. For the $\pi \rightarrow \pi^*$ the calculated energy was 6.15 eV, as compared with 6.32 eV observed experimentally. The $\pi \rightarrow 3s$ Rydberg transition was calculated[21] to lie at 5.94 eV and to have the same CD sign as the $\pi \rightarrow \pi^*$ (V state). This is in good agreement with the shoulder observed in *trans*-cyclooctene in both CD and absorption at 5.92 eV, the CD being the same sign as the 6.32 eV band. The experimental CD and absorption spectra of *trans*-cyclooctene exhibit structure to the blue of the V state from 6.95 to 7.08 eV. The rotation of at least one of these three features is of the same sign as the V state, but smaller in magnitude. The $\pi \rightarrow 3d\sigma$ transition is calculated[21] to lie at 7.09 eV, and the rotatory strength is calculated to be negative (as the V state) and to be one-ninth of that of the V state. Liskow and Segal could not rule out, however, that the transition is a $\pi \rightarrow 4s$ because 4s Rydberg basis functions were not incorporated in the calculations.

At that time these calculations[21] provided a comprehensive based assignment to the absorption and CD spectra of *trans*-cyclooctene. Hansen and Bauman have revisited the *trans*-cyclooctene[22–24] calculations several times over the last 25 years. In each visit they have used another computational technique to calculate energies, oscillator strengths and rotatory strengths, carrying out the calculations either directly or on distorted ethylene. In 1979[22] they imposed off-diagonal hypervirial relations upon two approximate configuration interaction representations of the ground and excited states. It was shown that if the ground state is approximated by the Hartree–Fock function, correlated by double excitations, and the excited state is represented by mono-excited CI, the hypervirial constraint

leads directly to the RPA equations[19]. The geometry of the ethylene group was adopted from Traetteberg[25], where the only element of symmetry in the chosen geometry was a C_2 axis. The excitations under considerations were the $\pi \rightarrow \pi^*$ and $\sigma \rightarrow \pi^*$, having both a B symmetry. The results show that agreement with the experimental results for the two excited states is somewhat better than what is obtained in the large-scale perturbative CI calculations[21]. The authors argue that further improvement of the results can be achieved, recalling that the saturated surroundings of the ethylenic chromophore tend to lower the transition energies as well as rotatory strengths.

In their third calculation, Hansen and Bouman[23] carried out an *ab initio* random-phase approximation study, using an extended basis set to account for Rydberg as well as valence excitations. They computed the excited states of two examples: a planar olefin, (3*R*)-3-methylcyclopentene, and a twisted olefin, (−)-*trans*-cyclooctene. The work[23] also presents calculations on the fragment molecules ethylene and *trans*-2-butene distorted as in *trans*-cyclooctene. The results were analyzed using various techniques. The excitation analyses were conducted in terms of transition and rearrangement densities and by the study of improved virtual orbitals. The use of localized orbitals allowed the RPA expression for the rotatory strength to be cast into a form containing all three contributions in Kirkwood's theory of optical activity[26,27]. The results are exhibited in contour plots of occupied orbitals, improved virtual orbitals, transition densities and charge rearrangement densities. All the plots are presented for the *trans*-cyclooctene molecule. When the intensities of the various transitions in *trans*-cyclooctene are compared to their intensities in the fragments, the following results are observed: in all three fragments, the $\pi-\pi^*$ showed a considerable oscillator strength and the same sign of the calculated CD signal; the $\pi-3s$ and $\sigma-\pi^*$ transitions also retain their respective negative and positive CD signs in all three fragments. Beyond that, little regularity was found when the intensities and signs of the fragments were compared with the *trans*-cyclooctene. The decomposition of the rotatory strength to Kirkwood's three mechanisms (the one-electron model; the electric dipole–magnetic dipole coupling, $\mu-m$; and the polarizability theory, $\mu-\mu$) were also presented. The three mechanisms contribute to all the transitions, even for the $\pi-\pi^*$ and $\sigma-\pi^*$, which in zeroth order would be thought of as dominated by the one-electron model. The assignment of the various bands in *trans*-cyclooctene followed the previous suggestion with some minor modifications. The main absorption band at 6.32 eV is assigned as a superposition of the $\pi-\pi^*$ and a $\pi-3p_{\parallel}$ Rydberg calculated to lie at about the same energy. In the same way the shoulder at 6.07 eV is also assigned as being composed of the $\pi \rightarrow 3s$ Rydberg transition and the $\pi \rightarrow 3p_{\div}$ state[23], which have the same CD sign and almost the same energy.

Recently Hansen and collaborators[24] have revisited the *trans*-cyclooctene molecule, carrying out *ab initio* calculations using London atomic orbitals. The calculations were carried out on *trans*-cyclooctene, as well as on various fragments. The results demonstrated that the absorption and CD spectra of *trans*-cyclooctene could not be generated from any of the fragment molecules. The rotatory and oscillator strengths, as well as energies, were computed for the 16 lowest transitions in *trans*-cyclooctene. The calculations in general reproduce successfully the $\pi \rightarrow \pi^*$ and fail to account for the observed spectra in the $\sigma \rightarrow \pi^*$ region.

III. THE PLANAR C=C CHROMOPHORE

The discussion of the planar C=C chromophore will be divided into two classes: in the first, substituted cyclic alkenes will be discussed, while the second class will present the aliphatic planar moiety. In the first class, we will concentrate mostly on small cyclic compounds rather than on steroidal compounds containing a double bond. Among the first cycloalkenes studied was 3-methylcyclobutene[28]. Its absorption was reported in the

gas phase, while its CD spectrum was measured in a *n*-heptane solution. The absorption spectrum was measured with a CARY 14 spectrophotometer, which was limited in its wavelength scanning ability. It has revealed the beginning of a strong and broad absorption band peaked at about 189 nm.

Three shoulders at 192, 195 and 208 nm were also observed. When the absorption of 3-methylcyclobutene (MCB) was measured in *n*-heptane solution, the 192 and 195 nm bands remained untouched while the 208 nm band disappeared. This was indicated on the valence nature of the 192 and 195 nm bands and on the 208 nm band as being a Rydberg 3s transition. The CD of the (*R*) enantiomer showed a negative maximum at 191 followed by a negative shoulder at 193 nm. The negative CD was assigned as the $\pi \rightarrow \pi^*$ valence transition. This assignment was questioned by few groups. In a detailed investigation of the chiroptical properties of (*R*)-3-methylcyclopentene (MCP)[29] a positive CD band was measured and calculated for the $\pi \rightarrow \pi^*$ transition. The question was raised whether the addition of one ring carbon caused a change in the CD sign, or whether it was a result of the solution study which shifts the Rydberg state to the blue and caused the overlap with the $\pi \rightarrow \pi^*$ and the change of sign. Chabalowsky and coworkers[30] carried out an *ab initio* calculation including CI of MCB. They reasoned their choice as follows: (1) MCB possesses a relatively rigid ring with no large groups or side chains whose orientation might be difficult to determine; (2) it is small enough to treat within an *ab initio* framework and still use a variety of basis sets; (3) experimental data are available for direct comparison with calculated results; (4) the MCB is a molecule in which the methyl group gives rise to the CD spectrum, because of its asymmetric perturbation of an otherwise inherently symmetric chromophore. In all five basis sets in which the calculations were carried out, a positive CD signal was obtained for the π–π^* transition.

This is again opposite to the sign reported by Rossi and Diversi[28]. Their attempt[30] to associate the broad negative band observed by Levi and coworkers[29] as being composed of three transitions still resulted in a positive sign, and they remained in disagreement with the experimental results[28].

The CD and absorption spectra of (*R*)-3-methylcyclopentene (MCP) was measured[29] in the gas phase down to 140 nm. The spectra are presented in Figure 2. Four distinct CD bands with alternating sign were observed. *Ab initio* self-consistent field wavefunctions obtained for the ground and excited states of MCP were used to calculate the optical rotatory strengths of the lowest-lying electronic excited states. The assignment of the measured spectra, based on the computations, showed that the first three observed bands can be identified with $\pi \rightarrow \pi^*$ and $\pi \rightarrow$ Rydberg-type excitations of the olefin chromophore and $\sigma \rightarrow$ Rydberg transitions of the skeletal frame. In Table 1, we present a comparison between experimental data and calculated values. The calculations predicted the correct sign for the various transitions, though the magnitude is systematically small by an order of magnitude. The first excited state, which was assigned as the $\pi \rightarrow$ 3s Rydberg transition, showed a relatively large g value of 4×10^{-3}, which was the largest for the MCP molecule. Taking into consideration that it is a magnetic-dipole forbidden transition, the g value was surprisingly large. The unexpected g value was explained[29] by evoking the computational results which calculated a $\sigma \rightarrow$ 3s Rydberg transition to contribute appreciably to the CD of the 202-nm band. It was mentioned earlier that the MCP spectra was also reproduced theoretically by Hansen and Bouman's[23] RPA calculations. They have calculated two conformers of the MCP, the equatorial MCPE and the axial MCPA. The SCF energies make the equatorial more stable by 2.2 kcal, while using the second-order Moller–Plesset correction the axial is favored by 1.0 kcal. The results are given therefore for 1:1 mixtures of the two conformers. In Table 2 we present their data and compare their results with those of Reference 29 and the experimental data. The result common to the two calculations is that the $\sigma \rightarrow \pi^*$ transition, which plays

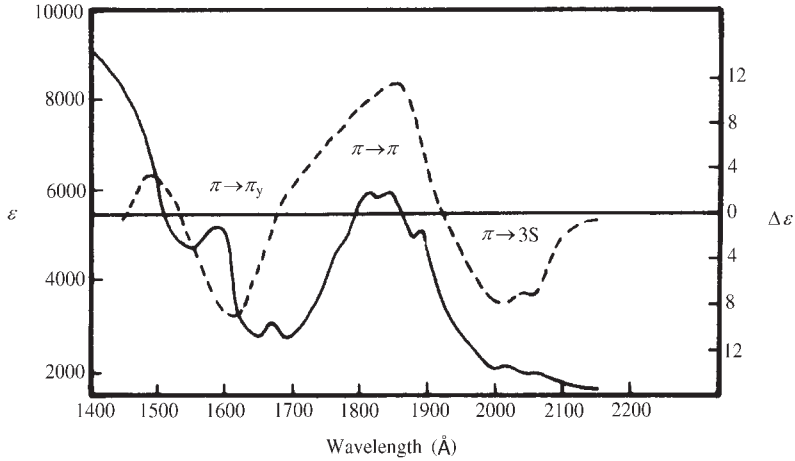


FIGURE 2. The absorption (———) and CD (- - - - -) spectra of (*R*)-3-methylcyclopentene in the gas phase. The spectral resolution of the absorption spectrum is 0.8 nm and that of the CD is 3.2 nm

TABLE 1. Assignment of the observed spectrum of MCP

Band	Description	Energy[a]		*Rs*[b]		*f*[d]	
		Obsd	Calcd	Obsd	Calcd[c]	Obsd	Calcd
1		6.05		−16		0.03	
	$\pi \rightarrow$ R(3s)		6.04		−2.03		0.014
	$\sigma \rightarrow$ R(3s)				−6.01		0.006
2		6.7		+26		0.16	
	$\pi \rightarrow \pi^*$		7.4		+2.74		0.504
3		7.0					
	$\pi \rightarrow$ R($3p_x$)				+3.17		0.006
	$\sigma \rightarrow$ R($3p_x$)				+0.75		0.006
4		7.7		−16		0.09	
	$\pi \rightarrow$ R($3p_{y,z}$)				−1.36		0.005
	$\pi \rightarrow$ R($3p_{z,y}$)				−4.24		0.007

[a] In eV.
[b] In 10^{-40} cgs.
[c] Average of RS (∇) and RS(r) in Table III.
[d] $f = [f(r) \cdot f(\nabla)]^{1/2}$.

a major role in *trans*-cyclooctene, is pushed to very high energies (>9.5 eV) in planar olefins. The location and sign of the $\pi \rightarrow \pi^*$ transition is also in agreement in the two calculations[23,29]. The differences are as follows: (1) Hansen and Bouman have not found any evidence for low-lying excitations out of σ orbitals; and (2) the asymmetric tail on the blue side of the $\pi \rightarrow \pi^*$ transition was assigned in Reference 23 as a $\pi \rightarrow 3p_y$ excitation of the axial conformer, while Levi and coworkers[29] assign it as $\pi \rightarrow 3p_x$ and $\sigma \rightarrow 3p_x$.

Mason and Schnepp[17] were mentioned already as being responsible for the first gas-phase VUVCD measurement of *trans*-cyclooctene. In the same study they also reported the absorption and CD spectra of α- and β-pinene in the gas phase[17]. In

TABLE 2. Association of computed excitations with observed bands in MCP, assuming a 1:1 mixture of MCPE + MCPA

Band	Present			Levi and coworkers[29]			Experimental[29]	
	Assign	f	R	Assign	f	R	f	R
I	$\pi \rightarrow 3s$	0.02	−4	$\pi \rightarrow 3s$ $\sigma \rightarrow 3s$	0.02	−8	0.03	−16
IIa	$\pi \rightarrow 3p_x$ $\pi \rightarrow 3p_z$ $\pi \rightarrow \pi^*$	−0.28	+33	$\pi \rightarrow \pi^*$	0.50	+3	0.16	+26
IIb	$\pi \rightarrow 3p_y$	0.01	+15	$\pi \rightarrow 3p_x$ $\sigma \rightarrow 3p$		+4	shoulder	shoulder
III	$\pi \rightarrow 3d$	0.05	−4	$\pi \rightarrow 3p_y$ $\pi \rightarrow 3p_z$	0.01	−16	0.09	−16

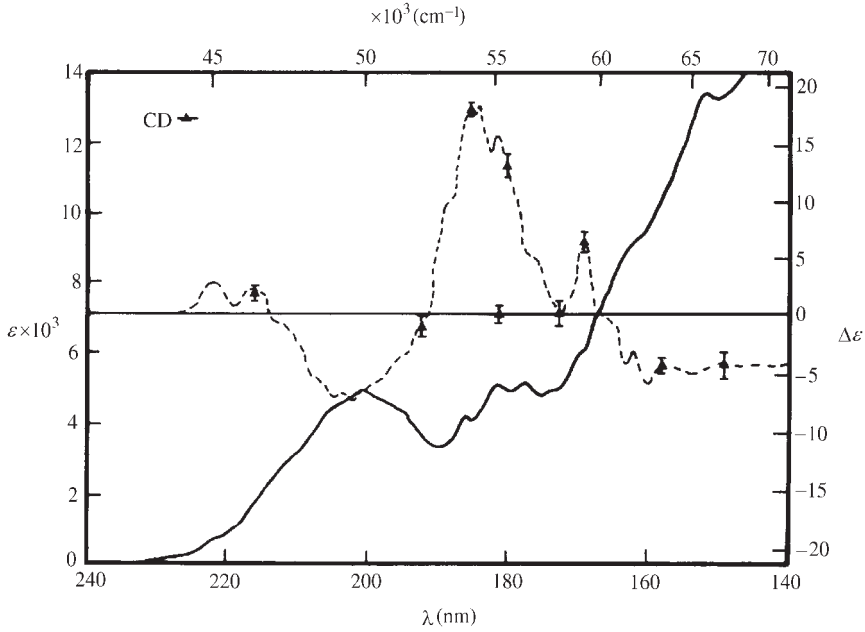


FIGURE 3. The absorption and CD spectra of (−)-α-pinene in the gas phase. CD resolution is 0.4 nm

Figure 3 we present the results of Schnepp and Mason[17] for the CD also the absorption spectra of α-pinene in the gas phase. The first CD band in α-pinene was observed at 222 nm (45045 cm^{-1}). It was followed by a band at 216 nm (46300 cm^{-1}), having the same-sign CD signal. The two bands are assigned as the $\pi \rightarrow 3s$ Rydberg transition. The spacing between the two peaks was 1250 cm^{-1}, which is similar to the interval observed in the corresponding absorption in ethylene. There it was interpreted as some combination of the C−C stretch and twist. In α-pinene the frequency may be expected to be at higher energies due to the rigid skeleton in which the double bond is held. The corresponding absorptions for these two peaks were not observed, either because

the absorption was underlying the rise to the intense band, or because of the higher sensitivity of the CD measurement as compared with absorption study. The negative CD[17] band at 202 nm (40500 cm^{-1}), which corresponded to the intense absorption band at 201 nm (49750 cm^{-1}), is assigned as the $\pi \rightarrow \pi^*$ valence transition. The assignment is based on the high absorption intensity and its low g value. This transition is an electric-dipole allowed magnetic-dipole forbidden transition. The following CD system to higher frequencies is positive and exhibited a large peak at 184 nm (54350 cm^{-1}). The relatively large g value provided evidence for its character as a magnetic-dipole allowed transition in the symmetric chromophore. The proposed assignment was a $\pi \rightarrow \sigma^*$ or, if we consider the calculations of Buenker and collaborators[18], this state is largely composed of $n = 3$ basis functions and as such should be assigned as a $\pi \rightarrow 3p_y$ Rydberg transition. A vibrational structure is observed as superimposed on the envelope of this system. The vibrational spacing was 700 cm^{-1} and attributed to the twisting vibration. The weak positive band at 169 nm which corresponded to the shoulder in the absorption spectrum was assigned as $\pi \rightarrow$ 4s Rydberg transition. The spectra of β-pinene[17] was assigned similarly to that of α-pinene, the only difference being the absence of the $\pi \rightarrow$ 3s Rydberg transition from the CD spectrum while it appeared clearly in the absorption spectrum.

Drake and Mason[33] have also measured the CD and absorption spectra of α-pinene. The measurements were carried out in the gas phase as well as in 2,2,2-trifluoroethanol and 3-methylpentane solutions. In the latter, CD measurements were taken at room temperature and also at lower temperatures. The enantiomer that was measured was the (−)-α-pinene and, as in Reference 17, a positive CD signal was obtained for the $\pi \rightarrow$ 3s transition at 222 nm in the gas phase. A negative CD signal peaked at 200 nm was ascribed to a $\pi \rightarrow \pi^*$ transition. In the solution, the positive CD was shifted strongly to the blue. In 3-methylpentane at room temperature the Rydberg is shifted to 204 nm, at −95 °C it is peaked at 198 nm and at −182 °C it was found at 192 nm. The blue shift that a Rydberg transition undergoes is a well known phenomenon[34–36]. The absorption spectrum in the gas phase is dominated by the valence $\pi \rightarrow \pi^*$ transition and the Rydberg is not resolved. When the molecule was embedded in the solvent, the $\pi \rightarrow \pi^*$ transition underwent a red shift which is typical for valence states[36]. That has raised the question of the g factor of the $\pi \rightarrow$ 3s Rydberg, which was estimated by Drake and Mason as being as large as 10^{-2}. This has been compared with the g value of the $\pi \rightarrow \pi^*$, which was only 6×10^{-4}. The large g value for the Rydberg state was attributed to the configuration of the molecule in the Rydberg state, which has an equilibrium torsion angle of 25°. The rotational strength of this transition is derived from the π-bond torsion. The authors[33] also pointed out that the large g factor indicated that caution is required in the application of a sector rule to the $\pi \rightarrow \pi^*$ transition of the CD spectra of olefins. This is due to the assumption that only the $\pi \rightarrow \pi^*$ and the higher transitions contribute to the CD, while they[33] show that the Rydberg–Cotton effect is detectable even in nonvolatile chiral alkenes through the marked blue shift observed in their report.

Gross and Schnepp[31] have measured the absorption and CD and absorption spectra in the gas phase of three aliphatic olefins. These three molecules were: (*S*)-3-methyl-1-pentene, (*S*)-4-methyl-1-hexene and (*S*)-5-methyl-1-heptene. The measurements were carried out over the wavelength range of 200–140 nm. The general features common to all three olefins were as follows: (1) The lowest transition was the $\pi \rightarrow$ 3s, whose CD sign was opposite to that of the $\pi \rightarrow \pi^*$, the next higher excited state. (2) The g value for the $\pi \rightarrow \pi^*$ is lower by an order of magnitude when compared with the g value of the same transition in planar cycloalkenes or twisted cycloalkenes. This drop in

g value is due to the decrease in the CD signal. It is hardly detected in (*S*)-5-methyl-1-heptene, while the absorption has almost the same ε as in the other chromophores. The explanation that we propose for this small CD value is based on work by Hansen and Bouman[23], who showed that at least two additional excited states lie close to the $\pi \rightarrow \pi^*$ transition and might have opposite-sign signal. The flexibility of the molecule is also contributing to the small CD signal. (3) At higher energies two distinct CD signals of opposite sign were observed. The first, at 160–170 nm, does not have a corresponding absorption band. It reveals a positive CD signal in all three olefins and it was assigned as the $\pi \rightarrow \sigma^*$, also assigned as the $\pi \rightarrow 3p_y$, whose symmetry in the symmetric chromophore is $A_g \rightarrow B_{1g}$, which justifies the relatively large g value being a magnetic-dipole allowed electric-dipole forbidden transition. (4) The highest-energy transition was observed in the wavelength region of 145–155 nm (a red shift is observed with the lengthening of the alkyl chain) having a negative CD band. The corresponding absorption in this case is also hardly observed. It was assigned as the $\sigma \rightarrow \pi^*$ which is also a $g \rightarrow g$ transition. This state is next to the $\pi \rightarrow \pi^*$ transition in the twisted olefins and is pushed to higher energies in the planar olefins[23]. In fact, it has not been detected in the planar cycloalkenes.

Drake and Mason[37] have measured the CD and absorption spectra of 17 chiral olefins under various conditions. Of the 17 molecules, few were measured in the gas phase as well as in solution at various temperatures. The less volatile molecules were investigated only in solution at various temperatures. We have already presented their[33] results of α-pinene. Three other six-membered rings were studied in the gas phase: (+)-camphene, (−)-bornene and (−)-β-pinene. The CD of camphene and bornene were similar to that of α-pinene in revealing a CD signal of the $\pi \rightarrow 3s$ Rydberg transition, opposite in its sign to that of the $\pi \rightarrow \pi^*$, which disappeared in an alkane solution due to either a large blue shift or to a severe broadening. In contrast, neither the gas-phase CD nor the solution of β-pinene exhibit the features distinctive of a Rydberg band. The reader is, however, reminded that Mason and Schnepp[17] have detected in the absorption spectrum (not in the CD) two vibronic bands at 230 and 219 nm assigned as the 3s Rydbergs. The explanation provided was that the $\pi \rightarrow 3s$ and the adjacent $\pi \rightarrow \pi^*$ have the same sign and the intrinsically weaker Rydberg is not evident in the CD spectrum. On the other hand, when the Rydberg and adjacent valence state have opposite-sign CD signals, the weaker Rydberg is more readily detected in the gas phase and the solution. With respect to all the olefins studied by them and by others, they concluded that there is no relationship between the signs of the CD signals of the Rydberg $\pi \rightarrow 3s$ and that of the adjacent $\pi \rightarrow \pi^*$. The authors[37] have offered a different mechanism based on higher-energy opposite-sign signals that will be discussed later. It should, however, be noted that since 1977 some other 20 olefins were studied in the gas phase and all of them showed opposite-sign CD signals for the $\pi \rightarrow 3s$ and the $\pi \rightarrow \pi^*$. On the other hand, in a few cases the mechanism proposed[37] 'does not hold water' because of similar CD signs or the disappearance of one component (see Reference 31). The detection of the lower Rydberg was not limited to the volatile molecules mentioned above. It was found indirectly also in Δ^5-cholestene in n-pentane solution (see Figure 4). The positive CD band lying at 213 nm (47000 cm^{-1}) at +70 °C blue-shifted progressively through 4700 cm^{-1} as the temperature is reduced to −190 °C. The major negative CD band (Figure 4) is less temperature-sensitive and at low temperatures it began to appear at the lower frequency. They[37] concluded that only two excitations were operative in the CD spectrum, the lowest in energy being a Rydberg transition. In the same manner Drake and Mason[37] have introduced a new mechanism for explaining the CD spectra of olefins, namely *the olefin CD couplet*. The spectra of a number of chiral alkenes exhibited two major CD bands and comparable areas, in addition to the low-frequency Rydberg CD band in the cases

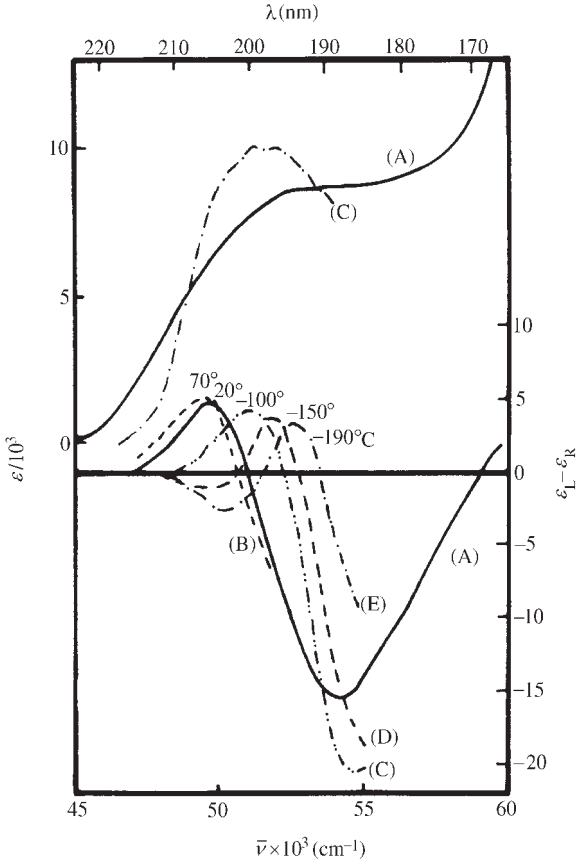


FIGURE 4. The absorption spectra (upper curves) and CD spectra (lower curves) of Δ^5-cholestene, (A) in *n*-pentane at $+20\,^{\circ}$C, (B) in iso-octane at $+70\,^{\circ}$C, and in 3-methylpentane, (C) at $-100\,^{\circ}$C, (D) at $-150\,^{\circ}$C and (E) at $-190\,^{\circ}$C

where the latter was observed[17,29,31]. Each major CD band of the couplet is associated with an isotropic absorption band which, for a given chiral olefin, has similar intensities. For one of the compounds, cyclohexylidene-cyclohexane, the polarized single crystal has been investigated[38]. This study showed that both the 208 (48000 cm^{-1}) and 182 nm (55000 cm^{-1}) bands are strictly *z*-polarized along the direction of the C=C bond. The 208 and 182 nm bands were ascribed, respectively, to the $\pi \rightarrow \pi^*$ and $\sigma_z \rightarrow \sigma_z^*$ transitions, each having individually a *z*-polarized electric dipole moment. This assignment was, however, questioned and found improbable because an oppositely-signed CD couplet is generated by the interaction of two electric transition dipoles only if the two moments have a finite separation in the molecule and are *noncoplanar*, having orthogonal components[39]. A couplet originated only from the interaction of two collinear transition moments if one is an electric dipole and the other a magnetic dipole. The proposed assignment[37] was therefore a $\pi \rightarrow \pi^*$ transition, with a *z*-polarized electric dipole moment and a $\pi \rightarrow \pi_y^*$

having a z-component magnetic dipole. These two states were represented as the linear combination

$$\psi_+ = C_1|xx^*\rangle + C_2|xy^*\rangle \tag{2}$$

and

$$\psi_- = C_2|xx^*\rangle - C_1|xy^*\rangle \tag{3}$$

where

$$|xx^*\rangle = 1/\sqrt{2}\{\pi_x(1)\pi_x^*(2) - \pi_x^*(1)\pi_x(2)\} \tag{4}$$

The energy of the transition from the ground state to the olefin excited states, ψ_+ and ψ_-, are given by the expression

$$E_{0\pm} = 0.5(E_{xx^*} + E_{xy^*}) \pm \langle xx^*|V|xy^*\rangle/2C_1C_2 \tag{5}$$

where $\langle xx^*|V|xy^*\rangle$ is the matrix element of the coulombic potential between the charge distributions of the configurational excitations.

A chiral deformation mechanism for optical activity in the olefin chromophore requires a nonzero torsional angle at the equilibrium configuration, or equivalent turning points in each level of the torsional vibration, υ_4. For a π-bond torsion angle in the range $0 < \theta < \pi/2$ and for the $\pi \rightarrow \pi^*$ excitation, they concluded that if the electric dipole moment μ_{xx^*} is parallel to the magnetic dipole moment m_{xy^*}, then for a negative angle of the π-bond torsion a positive CD will be obtained for the lower-frequency component of the CD couplet. The π-bond negative angle is defined in Figure 11 of Reference 37.

The low-frequency $\pi \rightarrow$ 3s Rydberg transition develops an intrinsic rotatory strength when the olefin becomes inherently dissymmetric. For a negative π-bond torsion angle the $\pi \rightarrow$ 3s transition acquires an x-polarized magnetic moment parallel to the zero-order electric moment. The resulting positive rotatory strength has the same sign as the lower-frequency component of the CD couplet. Having the same sign as the adjacent and stronger CD band, the Rydberg CD band is not readily detected in the spectra of chiral alkenes owing their optical activity to π-bond torsion. This was indeed the case for *trans*-cyclooctene and (+)-twistene. For the pinenes, camphene, bornene and many others in which the CD sign of the $\pi \rightarrow$ 3s Rydberg is opposite to that of the $\pi \rightarrow \pi^*$ transition, their optical activity is clearly not due to a π-bond torsion. This was indeed the result of an electron diffraction study of α-pinene[40].

For the planar olefins, the case in which the symmetric chromophore is embedded in a dissymmetric molecular environment, two approaches were proposed[37]. The first, the static field mechanism, is concerned with the substituent-induced mixing of chromophore transitions, namely the $\pi \rightarrow \pi^*$ and the $\pi \rightarrow \pi_y^*$. They were mixed by a Coulombic potential due to the ground-state distribution of the substituents. The result was that if a substituent bearing a positive charge is placed in an octant region defined by $+XYZ$, the rotatory strength is positive for the lower-energy part of the couplet, the $\pi \rightarrow \pi^*$. The second theoretical treatment[37] was based on a second-order dynamic coupling mechanism. This mechanism resulted in a $+XYZ$ sector rule, namely if a substituent is located in an octant for which the coordinate product XYZ is positive, the $\pi \rightarrow \pi^*$ will have a positive CD signal and an opposite sign signal will be observed for the $\pi \rightarrow \pi_y^*$, the higher-energy part of the couplet.

Our next section will deal with symmetry rules for chiral olefins. Before introducing these rules we would like to present another molecule whose spectra will serve later as a warning for the use of chirality rules. This molecule is limonene, whose absorption and CD spectra were measured[41] in the VUV region in the gas phase. In addition, the

photoelectron spectrum of limonene was also recorded. Prior to the $\pi \rightarrow \pi^*$ transition a rich vibrational structure of the $\pi \rightarrow$ 3s Rydberg was observed. It consisted of three bands separated by about 1500 cm^{-1} and located at 217.5, 210.6 and 204.9 nm. They represent the excitation of one and two quanta of the C=C stretching vibration. We have assigned the broad feature at 190 nm to the $\pi \rightarrow \pi^*$ valence transition arising from the double bond of the ring. The other transitions were assigned as Rydbergs converging to either the first or the second ionization potentials.

IV. SECTOR RULES FOR CHIRAL OLEFINS

In this section we will present the various sector rules that have been proposed for chiral olefins. Historically, the earliest attempt to correlate the CD and the absolute configuration of the olefin was suggested by Yogev and his coworkers[52]. We will, however, start with Scott and Wrixon[42], who have proposed an octant rule for the olefinic chromophore. This rule, whose octants are depicted in Figure 5 (also known as 'left-handed' octant rule or reversed octant rule), was based on Schellman's theory[43]. His theory, which was based on the static field perturbation model, claimed that from group theoretical consideration, the planar olefinic chromophore (D_{2h} point group) should obey a regional octant rule. Scott and Wrixon have shown[42] that an octant rule with a left-handed coordinate frame has predicted correctly the sign of the CD signal of the $\pi \rightarrow \pi^*$ transition in the vicinity of the 200-nm region. Sixty-eight molecules were examined in their study and only in three cases was the observed sign opposite to the predicted sign. In six other cases, however, the predicted sign was not determined. It is worth mentioning that in all 68 cases the CD spectra were measured in solution. As an example we will introduce a monocyclic olefin, such as *R*-(+)-4-methylcyclohexene (see Figure 6). The assumption for all the alkyl substituents on the cycloalkene ring was that they adopt equatorial or pseudo-equatorial positions. This assumption included *S*-(−)-limonene that will be discussed later. The antioctant behavior of a cyclopropyl moiety which was detected for ketones[44] was examined also for olefins by studying[42] the CD of (+)-sabinene. The spectrum exhibited a normal octant behavior for the $\pi \rightarrow \pi^*$ transition. It did show, however, a red shift of the peak greater than in normally disubstituted olefins. This red shift was accounted for in terms of conjugation between the olefin and the cyclopropane function. The wrong CD signs were obtained for α- and β-pinenes. The explanation offered was that the existence of the cyclobutyl ring, which is known to possess a low refractivity constant[45,46], was causing the antioctant behavior.

Levin and Hoffmann[14], who were mostly interested in twisted olefins, have formulated the correlation between the twisting angle and the CD sign for these molecules. They have predicted correctly the CD sign of *trans*-cyclooctene, but failed to predict the CD sign of twistene(tricyclo[4,4,0,$0^{3,8}$]dec-4-ene), which was recently shown to have its absolute configuration incorrectly assigned in the first instance[58]. For the planar olefins they have examined two hypothetical conformations of *cis*-2-pentene and concluded[14] that their considerations for the torsion angle and the CD sign that resulted from it concurred with the olefin octant rule[42].

A number of exceptions to this octant rule have been observed and reported[47–50]. For example, Fetizon and Hanna[47] have studied 18 methylene-steroids, mostly androstane, where one *exo*-methylene or two methylene groups were substituted at various ring places. Yogev and coworkers[49] have found that the two CD maxima which are usually observed in the C=C spectrum are resolved mostly in endocyclic olefins, while in exocyclic olefins the two maxima were very close, making the assignment of signs difficult. They have used linear dichroism as a tool for resolving the absorption spectrum into its components. This[49] procedure helped in resolving the CD spectrum as well.

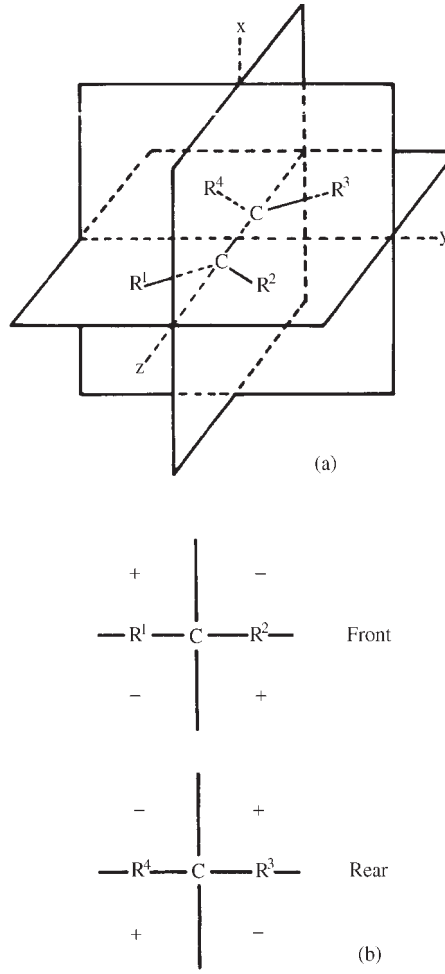


FIGURE 5. Octant diagram for chiral olefins showing (a) intersecting symmetry planes *xy*, *yz*, *xz*, and (b) the corresponding front and rear octants viewed along the *z*-axis

The CD spectra of the *exo*-methylene compounds which revealed an antioctant behavior were reexamined[51] and measured more carefully. It was observed that the lowest-energy band, assigned as the $\pi \rightarrow \pi^*$, is almost obscured by the higher-energy transition of opposite sign. Thus, in many cases, the anomalous olefins display a shoulder near the position expected for the lowest-energy transition and, in fact, the principal CD maximum frequently occurred at a wavelength considerably lower than that found for regular olefins. While solving, perhaps, the question of the octant rule, the remaining problem, according to this explanation, was why the $\pi \rightarrow \pi^*$ is so diminished relative to the $\pi \rightarrow \pi_y^*$. This interpretation, arguing that the $\pi \rightarrow \pi^*$ and the $\pi \rightarrow \pi_y^*$ have an opposite-sign CD signal in which the former is obscured by the latter, was not detected for all the exomethylene compounds, certainly not for β-pinene[17].

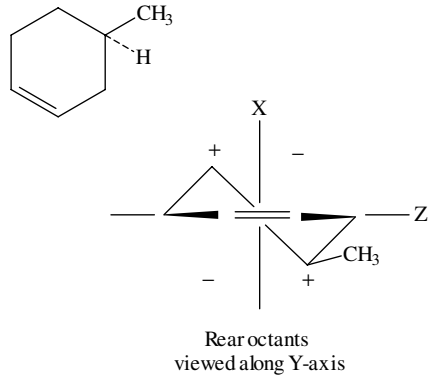


FIGURE 6. Rear octants of (+)-*R*-4-methylcyclohexene as viewed along the *Y*-axis

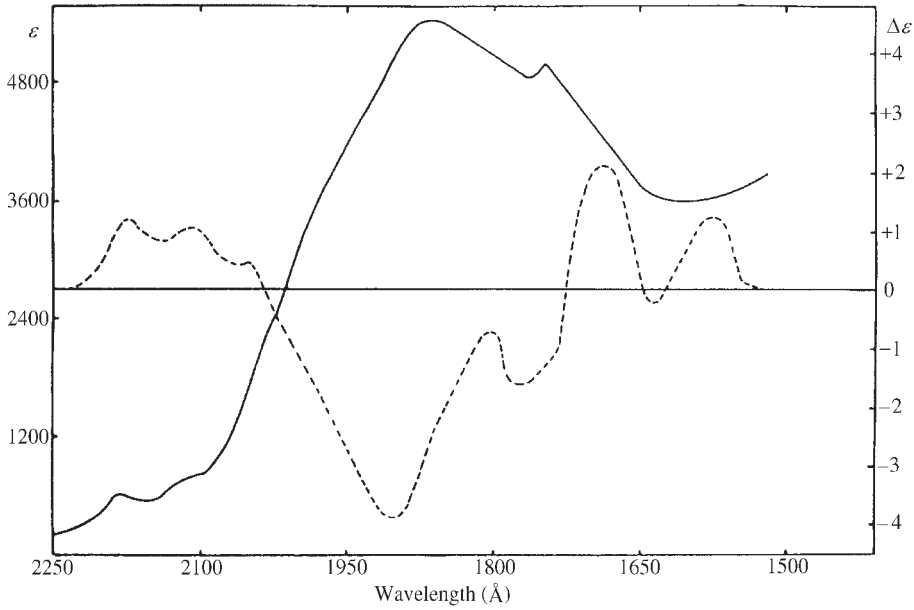


FIGURE 7. Absorption (———) and CD (- - - - -) of (+)-d-limonene in the gas phase. The spectral resolution of the absorption and CD spectra is 16 Å

Limonene, which was molecule number 63 on the Scott–Wrixon list[42], was also measured[41] in the gas phase over the VUV wavelength range. The studied enantiomer[42] was the (−)-1-limonene, which revealed a negative CD signal for the $\pi \rightarrow \pi^*$ in a solution study[42]. This was also the predicted sign according to the octant rule. However, the gas-phase measurements[41] of the (+)-d-limonene, depicted in Figure 7, also showed a negative CD signal for this transition. This result contradicted the octant rule. We have not introduced the limonene case to point out that antioctant behaviors existed, but rather

to call the attention of the reader to the opposite signs obtained for the CD signal of the $\pi \rightarrow \pi^*$ transition in solution and in the gas phase. This issue and the importance of the gas-phase measurements have already been discussed in this review and were also mentioned by Drake and Mason[37].

A few other attempts to correlate the CD sign with the structure of the molecules were made. The first was suggested by Yogev's group[52], who claimed that both the double bond and its neighboring σ-bonds should be regarded as a dissymmetric chromophore. Similar ideas were also suggested by other groups[53–55]. The axial bond chirality signs are in direct variance with the octant rule proposed by Scott and Wrixon[42]. In fact, only by ascribing a dominant role to the allylic C−H bonds can it be applied to endocyclic olefins with any success. The second attempt, which was based on the allylic bond polarization model, was developed by Anderson and coworkers[56,57]. Their model suggested that the $\pi \rightarrow \pi^*$ CD sign was dominated by the rotatory contribution of more polarizable allylic bonds (C−CH, C−O, C−X). The sign depended on the sense of polarization of the bond and its chiral relationship to the π orbital. The magnitude is maximal, with optimum overlap ($\phi = 90^\circ$, negative; 270°, positive); thus the contributions of axial substituents dominated. They analyzed these contributions for endocyclic and exocyclic olefins. Figure 8 compares the three sector rules which correlated the CD sign with the absolute configuration of the optically active molecule. In their later paper[57] they have provided the first experimental evidence for establishing the characteristics of torsion-induced olefin CD, and presented the first observation suggesting an additional active CD transition in the $\pi \rightarrow \pi^*$ region. To define the characteristic features of the twisting of the π bond they measured the CD of a series of 1,3-dialkylcyclohexanes and compared it with the CD of a series of 1,4-dialkylcyclohexenes. In the first series a couplet CD was observed with a positive CD for the lower-energy transition; the $\Delta\varepsilon$ was larger for a heavier alkyl group at position 1. For the 1,4-dialkylcyclohexenes only one positive CD band was observed; the magnitude of the CD signal was independent of the alkyl size. The explanation provided was as follows: the CD couplet is an outcome of the twisting of the π bond. By steric arguments this torsion was particularly favorable when a C-3 pseudo-equatorial group was present. The 1,4 series, which lacked a pseudo-equatorial group at C-3, displayed only a single CD band. For the same reason the increase of the vinylic substitution did not increase the rotatory power. They have[57] also provided evidence for the existence of a fourth transition, which played a role in the CD spectra of olefins in the 185–225 nm wavelength span. The sequence of transitions for trisubstituted olefins was as follows: (1) the $\pi \rightarrow$ 3s Rydberg transition at 225–190 nm whose wavelength was solvent-dependent, (2) the $\pi \rightarrow \pi^*$ at 200–210 nm, (3) the $\sigma \rightarrow \pi^*$ at 195–205 nm and (4) the $\pi \rightarrow \pi_y^*$ at 185–200 nm. The

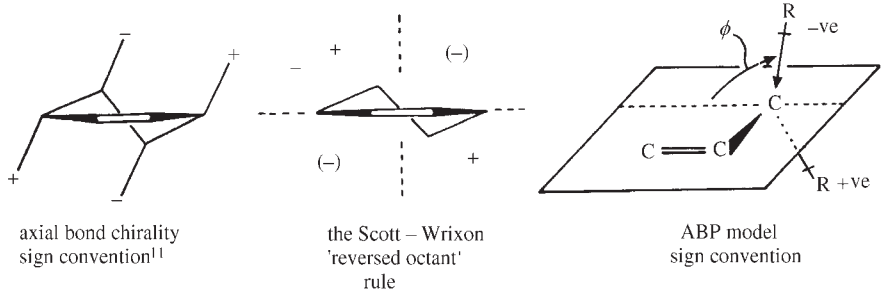


FIGURE 8. Comparison between the sector rules proposed by the three models

author of this review does agree with their comment that *the extreme complexity of this spectral region argues against strict use of any simple rule*.

A very detailed study, which included 228 olefinic compounds, was carried out by Hudec and Kirk[59]. The CD spectra were measured in a hexane solution, enabling the extension of the measurements to shorter wavelengths (183 nm). Most of the compounds examined were cyclohexene or methylenecyclohexane derivatives. Some were among those reported earlier by other authors.

The olefinic compounds were divided into four classes, according to their substitution patterns when considered as alkylated ethylene derivatives. *Class A: 1,1-Disubstituted ethylenes*. Exocyclic methylene compounds for the most part follow a carbonyl-like octant rule, the main point of difference being a large consignate octant contribution from a β-axial methyl group, which can outweigh effects of carbocyclic rings. *Class B: cis-1,2-Disubstituted ethylenes*. Cyclohexene analogues which give a CD band with sign corresponding to a consignate effect of the allylic axial C−H bonds. *Class C: Trisubstituted ethylenes*. Compounds of the 1-methylcyclohexene type follow those of class B fairly closely, but trisubstituted ethylene fragments of the ethylidenecyclohexane type, including $\Delta^{1(19)}$-octalin analogues, gave strong CD bands with signs determined by chirality of the ethylidenecyclohexane unit. An additional feature of the $\Delta^{1(19)}$-octalin analogues was a very large dissignate effect accompanying axial alkyl substitution at the allylic carbon atom *trans* to the olefinic C−H bond. Alkyl substitution at the other allylic centers had relatively little effect. *Class D: Tetrasubstituted ethylenes*. These compounds generally showed rather weak CD curves, but axial-allylic methyl substituents produce dissignate effects. This classification and the nature of the regularities found were based on the assumption that their so-called λ_1 is the same transition for all the compounds studied. They assigned this transition as the $\pi \rightarrow \pi^*$ state. They claimed[59] that any attempt at similar correlations with the $\pi \rightarrow \pi_y^*$ state (λ_2 in their notation) would be tentative.

Scott and Wrixon[60] have also compared the relation between their octant rule[42] and the Mills rule[61], which was refined by Brewster[62]. In analyzing 25 alkyl cycloalkenes and 49 oxygenated cycloalkenes, they have found a satisfactory correlation between the two oppositely signed $\pi \rightarrow \pi^*$ transitions and the resultant sign of the D line rotation. In every case the olefin octant rule (or its inverse for oxygen substitution) predicted the sign of the longest-wavelength transition. In most, but not in all cases, the $\Delta[M]_D$ values followed the Mills–Brewster[61,62] rules. The correlation by the CD method, however, was found to be most useful in several examples which cannot be treated by molecular rotation differences.

Another system in which an attempt was made to correlate the CD sign of the $\pi \rightarrow \pi^*$ transition and the absolute configuration of the molecule was the methylenecyclohexane chromophore[63]. The CD of 12 different olefins all having a basic moiety, the (4-methylcyclohexylidene)methane structure, were studied in the gas phase over the VUV region. The absorption spectra of all the 12 molecules showed a striking similarity to the spectrum of the symmetric methylenecyclohexane which was studied previously by Robin[64] and Demo[65].

The first transition[63] was assigned as the $\pi \rightarrow 3s$ Rydberg transition. It usually showed one symmetric stretching vibration built on its origin. The second transition was assigned as the $\pi \rightarrow \pi^*$ valence transition. It has exhibited a richer vibrational structure. The active vibration was also the symmetric stretching, and since the absorption maximum usually appeared at the $v = 3$ vibration in the progression, it is believed that the configuration of the molecule in the excited state is stretched, as compared with the ground state. In all 12 molecules, opposite CD signs were observed for the $\pi \rightarrow 3s$ and $\pi \rightarrow \pi^*$ transitions[63].

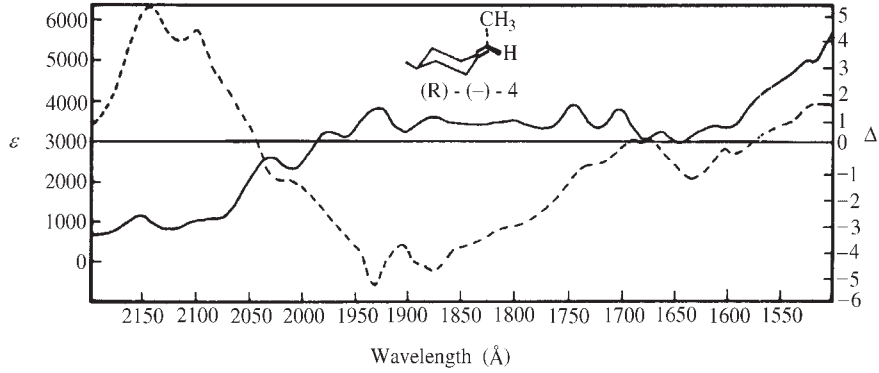


FIGURE 9. The absorption (———) and CD (- - - - -) spectra of (*R*)-(−)-(4-methylcyclohexylidene) ethane in the gas phase

Unlike the olefins mentioned so far, the spectrum of 4-methylcyclohexylidene chromophore showed a rich structure, even at higher energies than the $\pi \rightarrow \pi^*$ transition. The transitions were assigned as belonging to higher Rydberg transitions. For example, for the *n*s Rydberg series, bands were detected with members up to $n = 7$. In Figure 9 we present the absorption and CD spectra of (4-methylcyclohexylidene)ethane in the gas phase. The second purpose of the study[63] was to determine whether, and in what manner, a substituent lying in the nodal plane of the π orbital contributed to the CD. Deuterium[66,67] and fluorine[68,69] substituents, which are known to exhibit an antioctant effect on the $n \rightarrow \pi^*$ of carbonyls, were of special interest in our system, in which the molecular asymmetry was due to having both a substituent other than hydrogen in the 4-position of the cyclohexane ring and a situation in which X did not equal Y in Figure 8. Any contribution of allylic axial bond in Figure 8 would, of course, cancel each other out. In all our compounds the methyl substituent in the 4-position is kept constant and only the X and Y attached to the double bond are varied. It is therefore the effect of the X and Y substituents that will determine the sign of the $\pi \rightarrow \pi^*$ CD signal. In particular, we have explored the effect of the deuterium and fluorine atoms on the $\pi \rightarrow \pi^*$ transition. The results presenting the sign of the $\pi \rightarrow \pi^*$ transition for the *R* configuration are summarized in Table 3. It can be seen that, with the exception of deuterium, when Y = H a negative CD sign is observed for the $\pi \rightarrow \pi^*$ transition. The alkyl substituents, as well as the halogens, including fluorine, exhibited the same consignate effect. Attempts to correlate the sign of the CD spectra of the fluorine derivatives with mass or polarizability[70] of the substituents failed. The results were rationalized in terms of the C−X vs C−Y bond lengths. When the covalent radius of X > Y, then the CD sign of the $\pi \rightarrow \pi^*$ transition will be negative, and when Y > X it will be positive, as long as the substituent X or Y does not possess a π delocalizing system at the point of attachment to C. The dependence of the CD sign on $R_{C-X}{}^{-n}$, where R_{C-X} is the distance between the chromophore and a substituent X, is common to all three semiempirical mechanisms (static perturbation, dynamic coupling and the coupled oscillator[71]) explaining optical activity. These relations were raised in an attempt to account for the experimental results.

A more serious explanation was offered recently[72]. The independent systems perturbation (ISP) approach was used to calculate the CD of the $\pi \rightarrow 3s$ and $\pi \rightarrow \pi^*$ transitions. The ISP approach is interested in a particular transition belonging to an achiral chromophore A; the other chromophores in the molecule interact with this transition giving it

TABLE 3. Configuration, atomic radii and sign of $\pi \rightarrow \pi^*$ CD of **1** substituted by various X and Y groups

Configuration	Substituent (radii, Å)		CD ($\pi \rightarrow \pi^*$)	
	X	Y	Predicted	Found
(*R*)-(−)·**3**	Br (1.14)	H (0.37)	(−)	(−)
(*R*)-(−)·**4**	CH_3 (0.77)	H (0.37)	(−)	(−)
(*R*)-(−)·**5**	CD_3 (0.77)	H (0.37)	(−)	(−)
(*R*)-(+)·**7**	D (0.371)	H (0.373)	(+)	(+)
(*R*)-(−)·**8**	Cl (0.99)	H (0.37)	(−)	(−)
(*R*)-(−)·**9**	CH_2CH_3 (0.77)	H (0.37)	(−)	(−)
(*R*)-(−)·**6**	*t*-Bu (0.77)	H (0.37)	(−)	(−)
(*R*)-(−)·**13**	F (0.72)	D (0.371)	(−)	(−)
(*R*)-(−)·**14**	F (0.72)	H (0.373)	(−)	(−)
(*R*)-(−)·**11**	Br (1.14)	F (0.72)	(−)	(−)
(*R*)-(−)·**12**	F (0.72)	CH_3 (0.77)	(+)	(+)

a helical character. A perturbing chromophore that lies on the reflection plane of A gave on helical character. Two identical chromophores symmetrically placed with respect to a reflection plane have no net effect. Thus one might expect the ethylene chromophore transitions of Figure 9 to have no CD since the substituents lie on reflection planes of the chromophore framework. In fact, small CD were observed for these transitions as a result of the concerted coupling of both substituents to the transitions of A. The final explanation for the deuterium dissignate behavior is that it is a reflection of the fact that the C−D bond length is less than the C−H one.

A theoretical attempt that has provided the basis for the octant rule[42] was developed by Scott and Yeh[73]. They have considered the intensity of the CD band from the ground state to an excited state as consisting of three components:

$$R = R^{\text{inherent}} + R^{\text{static}} + R^{\text{dynamic}} \tag{6}$$

For olefins, the first term has been studied in terms of the symmetry D_2 independently by two groups[9,13]. The second term, which was also called the one-electron term, is usually neglected in cases of electronically allowed transitions because it is small compared with the other two terms. It is even smaller in the olefinic case, where the molecules contain mainly nonpolar bonds. Scott and Yeh[73] have therefore concentrated on the third term, which arises from the coupling of a considered transition **a** with all the transitions of different chromophores within the molecule. If transition **a** falls energetically below all the transitions of the other chromophores, the latter can be viewed as polarizable groups and their anisotropies β determine the dynamic coupling[74]. The final expression obtained was

$$R^{\text{dynamic}}{}_{\pi\rightarrow\pi^*} = 208.7\ \Sigma\beta_b\Gamma_b 10^{-40}\ \text{cgs}\cdot\text{esu}$$

where β is the anisotropy for which three sets of values were introduced and tried in their[73] calculations. The Γ factor contained, besides, a directional factor, an expression that is inversely proportional to the square of the distance of the polarizable group and the double bond. Thus the allylic bond is expected to have a dominant effect because it is close to the double bond, and also because other groups may be sufficiently flexible for their effects to be canceled by virtue of random orientation. Among the three sets of anisotropies, two yielded the same signs as the Scott–Wrixon rule[42] and Anderson's model[56] as well. The authors admitted that too many assumptions were made to justify

the above-mentioned rules and that the negative C−C single-bond anisotropies which they have used represent only a minority viewpoint.

A second theoretical study, which was also based on the dynamic coupling mechanism, was developed by Weigang[75]. The formalism was developed for electric-dipole allowed transitions. Unlike most sector rules, Weigang's formalism required[75] careful observation of the orientation as well as the location of bonds placed dissymmetrically with respect to the chromophore. The expression representing the rotatory strength consists of two sector rules. In the first the space is divided into eight octants, while the second has a conical distribution which is depicted in Figure 10. In addition, the expression contained the averaged polarizability and the anisotropy of the perturber's polarizability. This treatment was applied to the ethylenic chromophore, and (+)-*trans*-cyclooctene as well as twistene were examined in light of the two sector rules. The contributions to the sign of the $\pi \rightarrow \pi^*$ signal in (+)-*trans*-cyclooctene, from the conical and the octant sector rules, were both positive, which was the measured sign for this transition[8]. The predicted

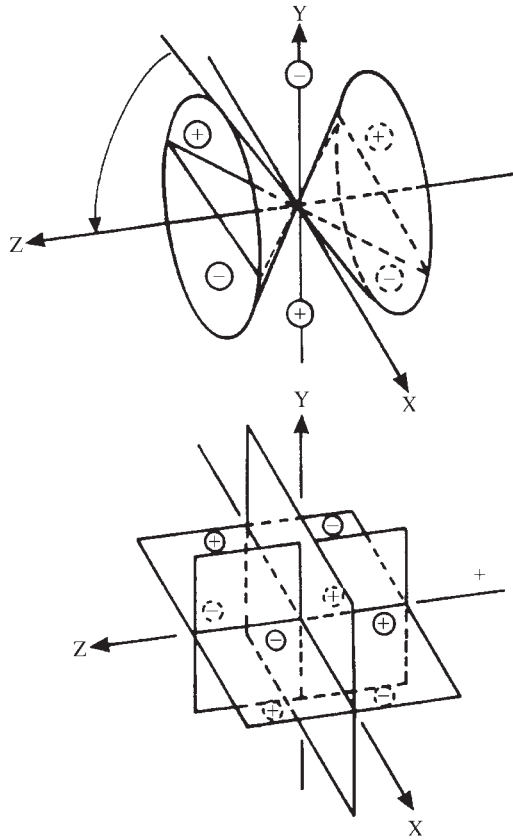
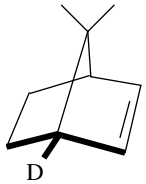


FIGURE 10. Sectors and nodal surfaces for the two terms developed in Weigang's theory. The signs refer to the absolute sign of the rotatory strength when the trigonometric functions and the $\alpha\beta$ are all positive. The chromophore and perturber must be oriented in a manner discussed in Weigang's paper and depicted in his Figure 1[75]

sign[75] for the same transition in (−)-α-pinene is positive, while a negative sign was measured[8].

V. ISOTOPE EFFECT

Since the discovery of deuterium, many chiral compounds owing their optical activity to the presence of this isotope have been prepared[76]. In the early days of optical activity it was thought that such a small effect would not be amenable to experimental observation. Over the years it became clear that, for many chromophores, optical activity which is due solely to the introduction of a deuterium atom can be measured. In fact, the anisotropy factor, *g*, for the oxirane chromophore, for example, was a factor of 2 smaller when the deuterium was replaced by a methyl and almost the same as for a hydroxyl replacement[77]. The first report of CD measurements of olefins which owed their chirality solely to isotopic substitution was by Paquette and coworkers[78]. Four such compounds were prepared and measured in pentane solution at 20 °C. They were (1*R*)-[1-^{2}H]-apobornene **11**, (1*R*)-[1,2-^{2}H]-apobornene **13**, (1*R*)-[2-^{2}H]-apobornene **16** and (1*R*)-[2-^{2}H]-norbornene **21**. For two compounds, **13** and **21**, gas-phase measurements were also performed and yielded the same results as in the pentane solution. The only exception was that the gas-phase absorption of compound **21** revealed[78] two vibrational shoulders at 48600 and 49900 cm^{-1}. The frequency interval between the two shoulders and their position on the red side of the main absorption band indicated that they arise from the $\pi \rightarrow$ 3s Rydberg transition. This Rydberg is overlaid by the $\pi \rightarrow \pi^*$ transition. The Rydberg has not been detected in the CD spectra of all the four compounds. The specific rotation of compounds **11** and **13** were negative, opposite to the CD sign of the lowest-energy band. The negative specific rotation was attributed to the higher excited states such as the $\pi \rightarrow \pi_y^*$, which indeed has a negative CD signal. The two isotopic perturbations in compound **13**, which confer chirality upon the otherwise achiral apobornene structure, are different in kind. A comparison of the CD spectra of **11** and **22** (which has a methyl group in position 1) showed that the contributions of the C−D and C−CH_3 in 1-position to the optical activity of the $\pi \rightarrow \pi^*$ are *dissignate*. This is similar to what was observed for carbonyls and other chromophores[76]. The comparison of two other compounds (**21** and **23**) which have a deuterium vs CH_3 at the 2-position of norbornene showed *consignate* contributions to the $\pi \rightarrow \pi^*$ transition. The chiral perturbations introduced by C-1 and by C-2 in the chiral parent structure are of a different kind. The explanation was[78] that for the dissignate effect of C-1, in addition to the usual common explanations — the polarizability and the bond-length changes — the steric compression factor in the H/D isotopic replacement is also of importance. In other words the lighter isotope effectively acts like a larger atom in repulsive interactions with its neighbors, so that the bridgehead C−C−C bond angles are less compressed sterically in the 1-deuterio derivatives.



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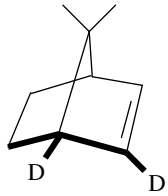

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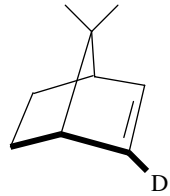

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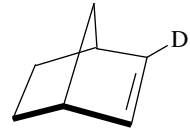

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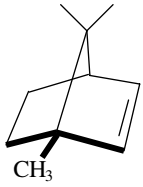

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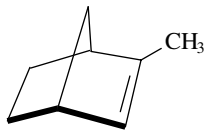

(23)

For the 2-position in which the deuterium showed a *consignate* signal with the CH_3 group, the explanation was centered on the displacement of the carbon atom of the olefin chromophore. Although the amplitude of the vibrational motion of a C−H bond is larger than that of the corresponding C−D bond, the displacement of the carbon atom in the motion is smaller for the lighter isotope. The mass of the methyl group is still larger, and the consignate effect of the C−D and the C−CH_3 is thus dependent on the displacement of the carbon atom, which was related to the mass of the substituent.

We have already discussed another example[63] of an isotope effect related to the C=C chromophore and the theoretical explanation[72] which was proposed for the experimental results. It is worth mentioning that the $\Delta\varepsilon/\varepsilon$ for the $\pi \rightarrow \pi^*$ transition of the deuterio-substituted 4-methylcyclohexylidene was 4.4×10^{-4}, whereas for a methyl replacing a vinylic hydrogen a value of 1.6×10^{-3} was obtained.

VI. LINEAR DICHROISM MEASUREMENTS

The spectroscopic properties of isolated double bonds were measured through their linear dichroism. The molecules were oriented in stretched films, and their UV spectra were measured using polarized light in the direction of stretching and orthogonal to it[79]. The instrumentation and the method by which these experiments were carried out was described in an early paper[80]. The molecules subjected to these measurements included symmetrically substituted and unsymmetrically substituted olefins. The symmetric molecule was bicyclohexylidene and among the optically active olefins were Δ^4- and Δ^5-cholestenes. While the first showed two bands at 208 and 185 nm, the latter revealed only one band peaked at 190 nm. The latter exhibited a wavelength-dependent linear dichroic spectrum, while bicyclohexylidene's spectrum was wavelength-independent over the absorption bands. The two transitions were assigned as being polarized along the double bond. The broad and structureless band was resolved into two overlapping bands, λ_1 and λ_2, at shorter and longer wavelengths, respectively. The polarization of the shorter-wavelength component, λ_1, was along the double-bond axis. The λ_2 transition formed an angle of 17° with the plane of the double bond; the projection of this transition on the double-bond plane falls at an angle of 10° with the axis of the double bond. The shorter-wavelength band, λ_1, was assigned as the valence $\pi \rightarrow \pi^*$ transition. The other band was assigned as the Rydberg $\pi \rightarrow 3p_y$, which is also known as the $\pi \rightarrow \pi_y^*$. The reader is, however, reminded that the order of these excited states in Mason and Schnepps' paper was reversed[8].

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CHAPTER **5**

Chiroptical properties of compounds containing C=O groups

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I. INTRODUCTION

Chiroptical properties of compounds containing a carbonyl group are among the most studied in organic chemistry. Among the many different carbonyl-containing functional

groups, in this series chiroptical properties of carboxylic acids and their simple derivatives (esters, lactones, amides, lactams) and thio analogues have been reviewed most recently in 1992[1]. This review also included a section on exciton chirality. Chiroptical properties of ketones and aldehydes, on the other hand, have not been reviewed in this series, except for α,β-unsaturated ketones[2]. Since Djerassi's book on optical rotatory dispersion (ORD) appeared in 1960[3], many monographs have appeared covering chiroptical properties of organic chromophores[4–15]. Most of these appeared in the 1960s and 1970s, whereas from 1982[13] until 1994[14,15] none appeared. Since the mid-1960s the most studied chiroptical property of ketones and aldehydes has been circular dichroism (CD), and while books on CD have appeared periodically, they have covered many different aspects of CD spectroscopy.

Since the chiroptical properties of most compounds containing C=O groups have been reviewed recently in this series, in the following we focus on CD of ketones and the relatively few aldehydes that have been studied by CD spectroscopy. Because most studies of saturated ketones have focussed on their octant rule behavior, a description of the octant rule and how to apply it appears early in this chapter. This is followed by an easy-to-read graphic compilation of the published work on saturated aldehydes and ketones since 1977, the date of the most recent comprehensive review[10] with many literature references. Conjugated ketones implicitly do not obey the octant rule. We discuss rules for interpreting the CD spectra of α,β-and β,γ- unsaturated ketones. This discussion is also followed by a graphical updating of their CD spectra. Finally, we attempt to update the reader on applications of the exciton chirality rule to ketones.

II. THE OCTANT RULE

The octant rule remains the most successful and longest serving chirality rule for interpreting ORD and CD spectra. It was formulated by Djerassi and colleagues[3,16,17] more than 35 years ago and provided a way to determine (i) the absolute configuration of a saturated alkyl ketone or aldehyde when its conformation is known, or (ii) the conformation when the absolute configuration is known. It is doubtless the most important of the many chirality sector rules proposed for various chromophores[10,18]. Sector rules focus on the chromophore in a molecule and relate the CD spectrum to the chirality of the extra chromophoric environment, to the chirality of the chromophore, or to both[19]. The octant rule relates the $n \rightarrow \pi^*$ CD spectrum of a saturated ketone or aldehyde to the extra chromophoric environment, to the molecule's structure surrounding the C=O group. In chirality rules for unsaturated ketones, considerations of the chirality of the extended chromophore become important.

The octant rule is probably best summarized by the graphics of Figure 1. The ketone or aldehyde carbonyl chromophore is oriented along the Z axis while its oxygen and carbon and atoms conjoined lie in the *YZ* plane. The two local symmetry planes, *XZ* and *YZ* of the C=O, divide all surrounding space into quadrants, and a nonsymmetry-derived third nodal surface (A or B) divides quadrant space into octants. In the classical octant rule[16], the third nodal surface was approximated as a plane (A). Subsequent theoretical and experimental studies defined it as a concave surface (B) in the revised octant rule[20,21]. To apply the octant rule, the observer looks down the C=O axis, from O to C. Front octants are nearer the observer; back octants are farther away, behind A or B. Groups or atoms lying on or near the octant surfaces make essentially no contribution to the octant rule and the CD of ketone or aldehyde. Groups or atoms lying off the octant surfaces make signed contributions according to the sign ascribed to each octant (Figure 1). These contributions are summed and weighted to predict the CD of the saturated ketone or aldehyde.

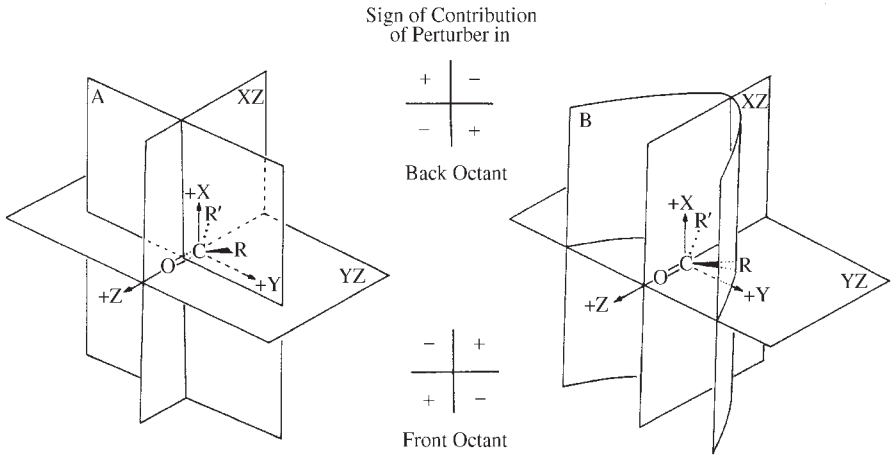


FIGURE 1. (Left) Classical octant rule diagram (Reference 16) for the carbonyl n $\rightarrow \pi^*$ transition of ketones and aldehydes. Local symmetry-derived, orthogonal octant planes *XZ* and *YZ* divide all space into quadrants, and a nonsymmetry-derived third nodal surface (A) is approximated by an orthogonal plane bisecting the C=O bond. To apply the octant rule, the observer looks down the C=O bond from O to C. 'Front' octants lie in the $+Z$ direction and are those nearer and observer. 'Back' octants lie in the $-Z$ direction and are farther away from an observer. (Middle) Octant contribution signs from perturbers in back and in front octants. (Right) Revised octant rule (Reference 20) with octant planes *XZ* and *YZ* unchanged and the third nodal surface defined theoretically as a concave surface (B). Reprinted with permission from Reference 21. Copyright (1986) American Chemical Society

In order to use the octant rule to determine the absolute configuration of a ketone, its conformation must be known. With cyclohexanones, for example, one may assume a predominance of the chair conformation and orient the cyclohexanone so that the local symmetry planes of its carbonyl chromophore are coincident with those shown on the octant diagram of Figure 1. As illustrated in Figure 2, the preferred chair conformation of (3*R*)-methylcyclohexanone has an equatorial methyl. On the octant diagram, its methyl group lies in an upper left (+) back octant, whereas ring atoms 1, 2, 4 and 6 lie in symmetry planes and thus make no contributions. Carbons 3 and 5 lie in upper left (+) and upper right (−) back octants, equally disposed across the *XZ* symmetry plane and thus make no net contribution. Consequently, the net contribution to the CD is *positive*, and a positive n $\rightarrow \pi^*$ CD is predicted. Rotation of the molecule about the C=O (*Z*) axis by 180° would position the methyl group in a lower right (+) back octant, with the same conclusion. Strictly speaking, one weighs the contribution of the equatorial methyl carbon and its three hydrogens lying in the upper left (+) back octant vs an equatorial hydrogen lying in an upper right (−) back octant. More 'weight' is given to the larger group, and hence a net *positive* n $\rightarrow \pi^*$ CD Cotton effect is predicted. The experimentally *observed* CD is positive. If absolute configuration of 3-methylcyclohexanone had not been known, the observed positive Cotton effect would be interpreted by the octant rule to correspond to 3*R*. If the absolute configuration were known, the observed positive Cotton effect would fit best an equatorial chair conformation.

The possibility of ring conformational flexibility such as inversion (to afford the axial methyl isomer) or the intrusion of twist-boat isomers can be dismissed in (3*R*)-methylcyclohexanone because its n $\rightarrow \pi^*$ Cotton effect sign and magnitude ($\Delta\varepsilon_{284}^{\max}$ +0.57)

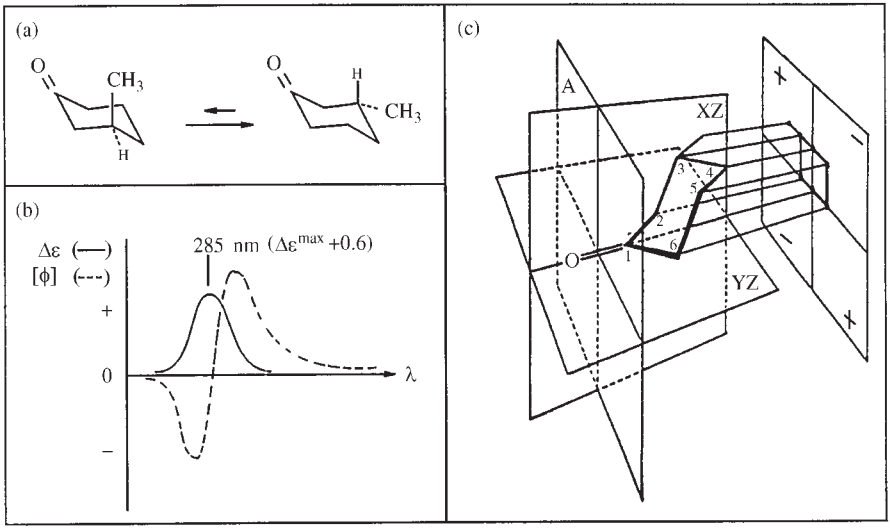


FIGURE 2. (a) Interconverting chair conformers of (3*R*)-methylcyclohexanone with axial (left) and equatorial (right) methyls. (b) CD and ORD spectra of (3*R*)-methylcyclohexanone showing positive CD and ORD Cotton effects. (c) Octant rule (Figure 1) applied to an octant projection diagram for (3*R*)-methylcyclohexanone with an equatorial methyl configuration. [(c) is modified from J. F. King, in *Elucidation of Structures by Physical and Chemical Methods*, Part One (Ed. K. W. Bentley), Chap. VI, Wiley, New York, 1963 Reproduced by permission of John Wiley & Sons, Inc]

is very close to that observed of a rigid analog, (1*S*,3*R*)-4(e)-methyladamantan-2-one ($\Delta\varepsilon_{284}^{max} + 0.67$), where the cyclohexanone is locked into a chair conformation and the methyl perturber is equatorial (Figure 3)[21]. Adamantanone is highly symmetric. All ring atoms lie on the *XZ* or *YZ* symmetry octant planes (Figure 1) or are equi-disposed across them. Only groups attached at ring carbons β to the C=O make octant contributions. As such it is an ideal system for isolating and evaluating octant contributions. Significantly, replacing the methyl perturber with larger alkyl substituents (ethyl, isopropyl, *tert*-butyl or neohexyl) on the rigid and symmetric adamantanone framework causes relatively little change in the n $\rightarrow \pi^*$ Cotton effect magnitude. These results indicated that the major octant contribution is made by the first carbon in the alkyl perturber chain, and the magnitude of octant contributions falls off rapidly with distance, as predicted much earlier[3,16].

In general, octant contributions fall off with increasing distance of perturbers from the carbonyl chromophore. This is further illustrated by comparing the n $\rightarrow \pi^*$ Cotton effects from α-axial methyl and β-equatorial methyl perturbers on chair cyclohexanones as found in Table 1. Both methyl perturbers lie far from octant nodal planes (Figure 1), but the α-axial methyl lies closer to the carbonyl chromophore and thus makes a larger octant contribution. When the perturber lies close to an octant symmetry plane, as in an α-equatorial methylcyclohexanone, even if it also lies close to the carbonyl chromophore, the magnitude of the octant contribution is significantly diminished. With β-methyls, neither the equatorial nor the axial lie near an octant symmetry plane. However, since the β-axial lies closer to the carbonyl group than β-equatorial, it was predicted[16] to be an ordinary octant perturber with a strong positive n $\rightarrow \pi^*$ Cotton effect. It was thus quite surprising when Snatzke and colleagues[22] showed that a *β-axial* methyl perturber not only did not

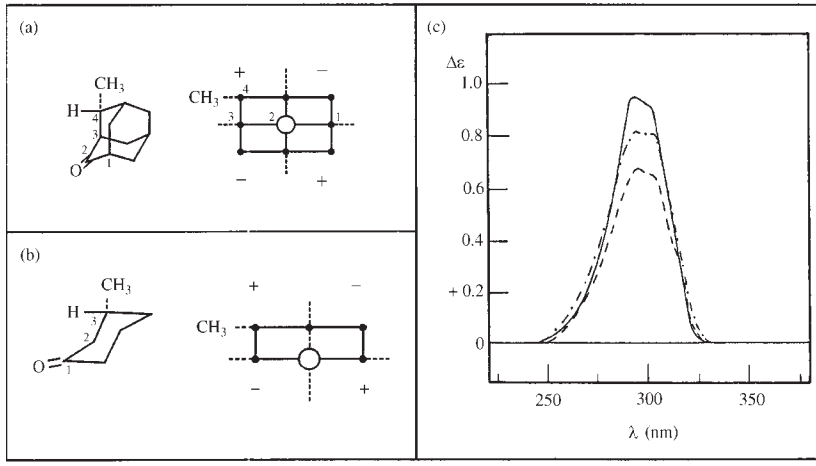
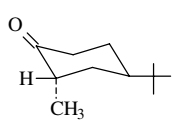
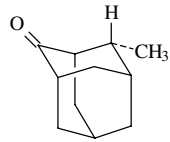
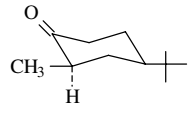
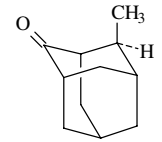
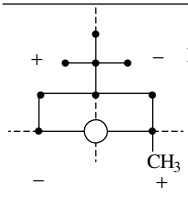
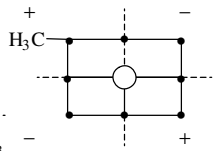
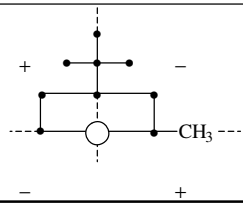
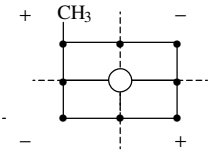


FIGURE 3. (a) (1*S*,3*R*)-4(*e*)-Methyladamantan-2-one and its octant projection diagram. (b) (3*R*)-Methylcyclohexanone and its octant projection diagram. (c) CD spectra of (1*S*,3*R*)-4(*e*)-substituted adamantan-2-ones in EPA (ether–isopentane–ethanol, 5:5:2, v/v/v) run at 25 °C and corrected to 100% e.e. The equatorial substituents are methyl (- - - - -), $\Delta\varepsilon_{295}^{max} = +0.67$; ethyl (- · - · -), $\Delta\varepsilon_{295}^{max} = +0.81$; isopropyl (approx. - · - · -), $\Delta\varepsilon_{295}^{max} = +0.80$; *tert*-butyl (approx. - - - - -), $\Delta\varepsilon_{295}^{max} = +0.771$; neohexyl (———), $\Delta\varepsilon_{295}^{max} = +0.92$. [(c) is reprinted with permission from Reference 21 Copyright (1986) American Chemical Society]

TABLE 1. Axial and equatorial α-methyl and β-methylcyclohexanone units and their associated Cotton effects and octant diagrams

α-Axial CH_3	β-Equatorial CH_3	α-Equatorial CH_3	β-Axial CH_3
			
Δε ≃ +1.4	Δε ≃ +0.6	Δε ≃ −0.3	Δε ≃ −0.1
			

obey the octant rule but also gave only a very weak Cotton effect, much smaller than α-equatorial. Since the β-axial methyl does not lie near a C=O nodal plane (Figure 1), this observed 'anti-octant' behavior was astonishing. It was a source of much concern and led to a re-consideration of the octant rule that led to a better definition of the third nodal surface as concave (Figure 1)[20,21].

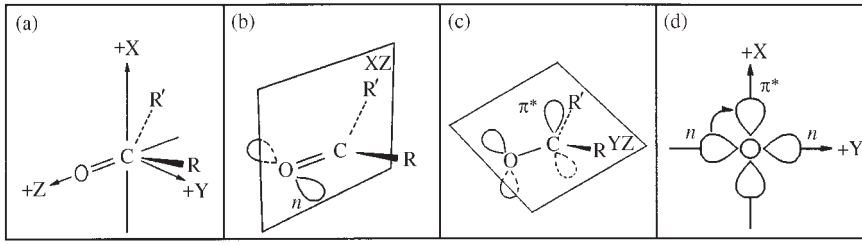


FIGURE 4. (a) Coordinate system for C=O group. (b) Relevant n-orbital of ketone carbonyl n $\rightarrow \pi^*$ transition. The vertical XZ plane is a nodal plane for the n-orbital that bisects the R−C−R′ angle and lies perpendicular to the R(R′)C=O local symmetry plane. (c) Relevant π^*-orbital of ketone n $\rightarrow \pi^*$ transition. The horizontal YZ plane is a nodal plane for the π^* orbital and lies on the R(R′)C=O local symmetry plane. (d) Carbonyl oxygen, as viewed looking down the Z-axis from O to C, showing circular movement of electron from the n to the π^* orbital

A. The Ketone C=O n $\rightarrow \pi^*$ Transition in Ketones and Aldehydes

The n $\rightarrow \pi^*$ transition of ketones and aldehydes lies near 300 nm in the UV-visible spectrum. The relevant orbitals of n $\rightarrow \pi^*$ transition are shown in Figure 4. The transition involves movement of an electron from an oxygen nonbonding (n) orbital (p_y) to a π^* anti-bonding orbital comprising a linear combination of oxygen and carbon p_x orbitals. This rotation of charges leads to a large induced magnetic dipole moment ($\vec{\mu}_m = 1$ Bohr magneton) oriented along the C=O bond (Z-axis), but it does not induce an electric dipole moment ($\vec{\mu}_e = 0$) in the same direction. Therefore, on the basis of local symmetry, the n $\rightarrow \pi^*$ transition is a magnetic dipole-allowed ($\vec{\mu}_m \neq 0$), electric dipole-forbidden ($\vec{\mu}_e = 0$) transition. Thus, to a first approximation, the n $\rightarrow \pi^*$ should not be observed. However, a weak UV absorbance ($\varepsilon \simeq 10$–100) near 300 nm is typically observed for ketones because electric dipole intensity is 'borrowed' through vibronic coupling from higher energy electric dipole-allowed transitions such as the $\pi \rightarrow \pi^*$, which is polarized along the Z-axis (Figure 4). Although intensity borrowing provides a mechanism to observe n $\rightarrow \pi^*$ absorption, it does not lead to optical activity of the chromophore, which still possesses a plane of symmetry. When the carbonyl group is located in a chiral environment, however, dissymmetric perturbations on the n $\rightarrow \pi^*$ transition lead to a nonzero rotatory strength, $R = \vec{\mu}_e \cdot \vec{\mu}_m$, and thus a nonzero CD.

B. C=O Symmetry Planes, Quadrants and The Third Nodal Surface

In the octant rule, all space surrounding the carbonyl chromophore is divided up into eight octants (Figure 1), and the octant occupied by a particular perturber determines the sign of its contribution to observed n $\rightarrow \pi^*$ CD, to the rotatory strength of the n $\rightarrow \pi^*$ transition. The octants are derived primarily from the local symmetry (C_{2v}) of the carbonyl chromophore and the relevant orbitals of the n $\rightarrow \pi^*$ transition. The two well-defined carbonyl symmetry planes (XZ and YZ, Figure 5a) coincide with the symmetry-derived nodal planes of the n and π^* electronic wavefunctions (Figure 4). They divide all space about the C=O group into quadrants. Quadrants are the minimum number of spatial subdivisions based on the intersecting symmetry planes of the isolated C=O chromophore. Using group theory, Schellman[23] showed that a quadrant rule is the minimum sector rule for ketones. However, there may be additional nonsymmetry-derived nodal surfaces. Bouman and Moscowitz[24] showed that if only n $\rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ states are mixed by incomplete coulombic screening, a quadrant rule is obtained for a localized n-orbital. However, if the n-orbital is delocalized, an incorrect octant rule is predicted. On the

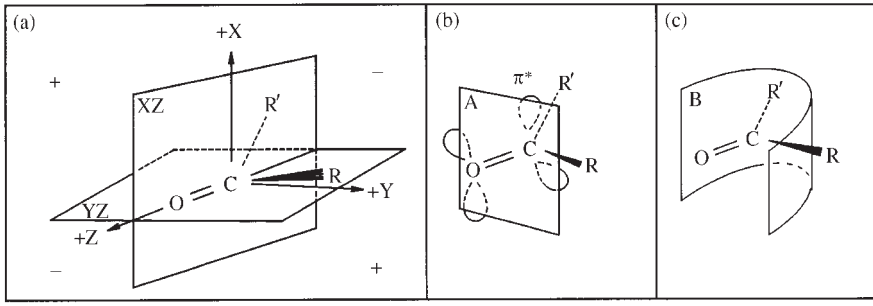


FIGURE 5. (a) C=O symmetry (C_{2v}) planes that divide all space surrounding the carbonyl group into quadrants. The + or − signed contributions that perturbers make are denoted: upper right and lower left, negative; lower right and upper left, positive. (b) The third nodal surface associated with the π^* orbital and approximated by a plane (A) that lies midway between the C and O. (c) Concave third nodal surface (B) derived by theory and experiment

other hand, mixing of the n $\rightarrow$ π^* state with *D* states generated from 3d-orbitals leads to the octant rule behavior with the correct sign for hydrogen and carbon perturbers. In either case, the contribution to the CD intensity from the *D* states is in most instances about an order of magnitude greater than that obtained from mixing with the $\pi \rightarrow \pi^*$ states. Thus, whatever 'quadrant' contributions come into play are suppressed by 'octant' contributions.

Moffitt and colleagues[16] took the third surface to be a plane bisecting the C=O bond (Figure 5b) purely for convenience rather than on any theoretical basis. Indeed they specifically cautioned that this surface was very probably *not* a plane. Subsequently, Bouman and Lightner[20] showed by theory and experiment that the shape of the third nodal surface is closer to concave, cutting behind the carbonyl carbon (Figure 5c).

Reflection of a perturber across either of the symmetry planes (*XZ* and *YZ*, Figures 4 and 5) leads to a mirror image molecular fragment, and hence one with oppositely-signed rotatory strength. Since the third nodal surface does not follow from symmetry, 'reflection' across it does not correspond to a mirror image situation, and hence the weight given to a perturber in a front octant is not the same as for a like position in a back octant. Each atom or group surrounding the C=O chromophore makes a signed contribution to the observed n $\rightarrow$ π^* CD. The signs for atoms such as C, H, Cl, Br and I are shown in Figure 5. Atoms lying in symmetry planes offer no contribution, and atoms symmetrically located across the carbonyl symmetry planes will exert no effect on the CD, due to cancellation. In general, the *sign* made by an octant perturber to the observed CD of the n $\rightarrow$ π^* transition varies as the *sign* of the product, $X \cdot Y \cdot Z$ of the atomic coordinates, as defined in Figures 1, 4 and 5. Contributions are assumed to be additive, and the magnitudes of the contributions vary according to the nature of the perturber while falling off rapidly with increasing distance from the carbonyl chromophore or closeness to the nodal surfaces. Broadly speaking, the octant rule, a geometrical rule so simple and straightforward to apply, has served well in establishing the absolute configuration and in elucidating the conformation of a large number of compounds[3–20].

C. Front Octants and Anti-Octant Effects

The validity of the octant rule is supported largely and convincingly by ORD and CD spectra from numerous examples where the dissymmetric perturbers (the groups perturbing the carbonyl chromophore in a nonsymmetric way), such as the methyl group of

3(*R*)-methylcyclohexanone, are invariably located in back octants — behind the carbon of the carbonyl group. There are extremely few examples in which dissymmetric perturbers are found in front of the carbonyl carbon or oxygen. And in most of these few examples there are also dissymmetric perturbers in back octants. Although there was some doubt over the existence of or need for front octants, it was quite obvious at an early stage in the development of the octant rule that ketones could be found where some atoms would lie in front octants, e.g. in 1-oxo, 7-oxo- and 11-oxosteroids. Here, however, octant contributions from atoms lying in back octants always appeared to dominate the sign of the Cotton effect[3,16]. Examples of contributors entering front octants were discussed by Djerassi and Klyne[25], but their examples also had back octant as well as front octant contributions and thus did not clearly test the existence of front octants. Kirk, Klyne and Mose[26] prepared structurally related D-homo and D-nor 7-ketosteroids and subtracted Cotton effect of the D-norsteroid from that of the D-homosteroid to estimate its front octant contributions. The authors concluded in favor of an octant rather than a quadrant rule. At the same time, CD spectra of potentially cleaner examples, *cis*- and *trans*-6-methylspiro[4.4]nonan-1-ones, supported the notion of front octants, but the analysis was complicated by ring conformational changes[27]. With the lack of unambiguous proof for the existence of front octants, the octant rule remained incompletely proved by experiment until 1974, when the existence of front octants was shown unequivocally by the synthesis and CD[28] of two spiroketones, *syn*-(1′R)-spiro[cyclobutan-2-one-1,2′-(4′(*a*)-methyladamantane)] and its *anti* isomer (Figure 6), prepared from (−)-(1*R*,3*S*)-4(*R*)(*a*)-methyladamantan-2-one (Table 1). In the former the methyl group lies in *front* of the carbonyl oxygen; in the

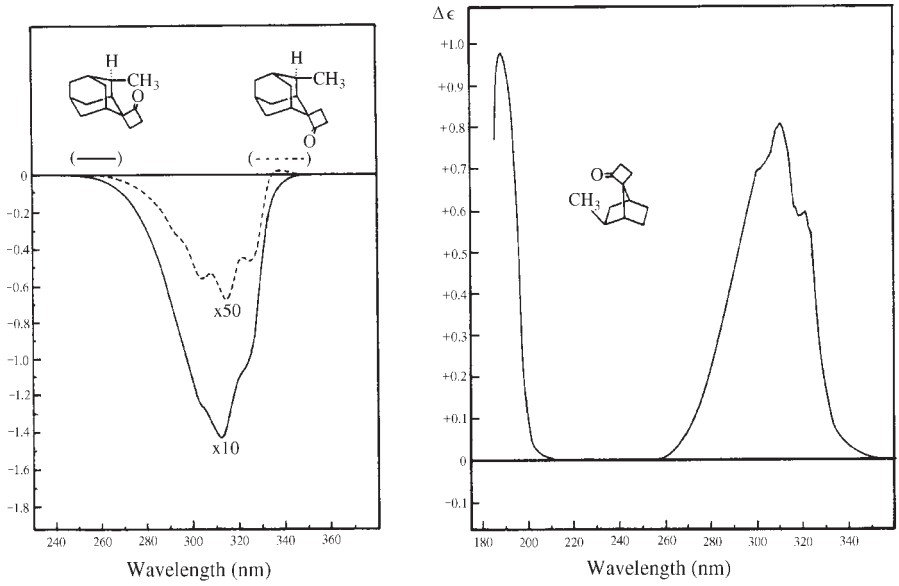


FIGURE 6. (Left) CD spectra of *syn*-(1′*R*)-spiro[cyclobutan-2-one-1,2′-(4′(*a*)-methyladamantane)] (———) *anti*-(1′*R*)-spiro[cyclobutan-2-one-1,2′-(4′(*a*)-methyladamantane (- - - - -) in isopentane at 20°. (Right) CD spectra of *syn*-(1′*R*)-spiro[cyclobutan-2-one-1,7′-(2′-*exo*-methylnorbornane)] in isopentane at 20 °C Corrections are made to 100% optical purity. [(Right) Reproduced by permission of The Royal Society of Chemistry from Reference 29; (Left) Reprinted with permission from Reference 28. Copyright (1974) American Chemical Society]

latter it lies well behind. With a time-average planar cyclobutanone conformation, the plane of the cyclobutanone ring bisects the spiro-fused adamantane skeleton. That is, in the absence of the methyl group, the plane of the cyclobutanone ring would lie on an octant symmetry plane (*YZ*, Figure 1). Thus, the methyl group, which does not lie on a symmetry or nodal plane, represents the lone dissymmetric perturber of the ketone carbonyl chromophore. In a quadrant rule, the methyl perturbers of both spiro-adamantyl cyclobutanones would lie in oppositely-signed quadrants: upper left or lower right positive for the *syn* and upper right or lower left negative for the *anti* (Figure 5a). However, the observed n $\rightarrow \pi^*$ CD Cotton effect signs are the same for the *syn* and the *anti*. The negative sign of the *anti* is in agreement with both a quadrant rule and the octant rule, but the negative sign of the *syn* is in agreement only with the octant rule. The methyl group of the *syn* lies in an upper left or lower right (−) *front* octant. Additional support for front octants comes from the positive n $\rightarrow \pi^*$ Cotton effect of spiro-bornylcyclobutanone[29] (Figure 6b), which has a different carbocyclic framework, but one where the lone dissymmetric methyl perturber lies in front of the carbonyl oxygen in an upper right or lower left positive front octant. Even considering puckering of the cyclobutanone ring and attendant changes in octant locations of the perturbers, the n $\rightarrow \pi^*$ Cotton effect is still dominated by a methyl perturber in a *front octant*[30]. The *syn* spiroketones of Figure 6 thus provided the previously missing unequivocal experimental proof for the existence of front octants.

Instances where octant rule behavior was predicted and not observed, the problem of 'anti-octant' effects, emerged shortly after the octant rule was first postulated[3,16], e.g. in a theoretical derivation of the octant rule in 1966, where Pao and Santry[31] calculated the n $\rightarrow \pi^*$ Cotton effects of various methyl-substituted chair cyclohexanones. Their results from Gaussian orbital calculations for *all* methyl configurations except 3-axial agreed with those predicted by Moscowitz in his theoretical derivation of the octant rule[32]. Later calculations using an extended Hückel treatment[33] agreed with the new prediction for axial 3-methylcyclohexanone. (It is important to note that Moscowitz did not include this structure in his calculations.) These findings suggested that the third nodal surface might be curved. At nearly the same time, Snatzke and coworkers[34,35] published the first experimental verification that the 3-axial substituents on chair cyclohexanone gave anti-octant contributions to the octant rule. (1*R*,3*S*)-4(*R*)(*a*)-methyladamantan-2-one (mirror image shown in Table 1) gave a weak, *positive* CD Cotton effect in ethanol or dioxane solvent[36], opposite to the predicted *negative* Cotton effect for the methyl perturber in a lower left or upper right back octant. The significance of this surprising observation was obscured by the fact that a weak negative Cotton effect was seen when the solvent was changed to isooctane for the same ketone. Yet adamantanones with other β-axial perturbers were found to exhibit 'anti-octant' CD Cotton effects which did not change sign: Cl, Br, I, N_3[22,36] and SCN, ONO_2, OAc, OCO_2CH_3[35].

Other apparent 'anti-octant' effects were found shortly thereafter[37–41]. The most perceptive of these is the work of Coulombeau and Rassat[37], who analyzed CD and ORD data for a number of ketones and made the proposal that the third nodal surface was convex, curving sharply *away* from the carbonyl oxygen. They thus explained 'anti-octant' behavior in terms of the perturber actually lying in *front* of the third nodal surface as they defined it. Tocanne drew a similar conclusion from his cyclopropylketone work[41]. Although other anti-octant effects had been noted prior to 1974[42,43], at that time there was no unambiguous experimental demonstration from carbon and hydrogen as static, dissymmetric perturbers — except the work of Snatzke and Eckhardt[36] in which a peculiar solvent effect had been noted. In 1974 it was shown that the stereochemically rigid and well-defined (1*R*)-*exo*-2-methyl-7-norbornanone and (1*R*)-*endo*-2-methyl-7-norbornanone gave negative and positive n $\rightarrow \pi^*$ CD Cotton effects, respectively, in isopentane[42]

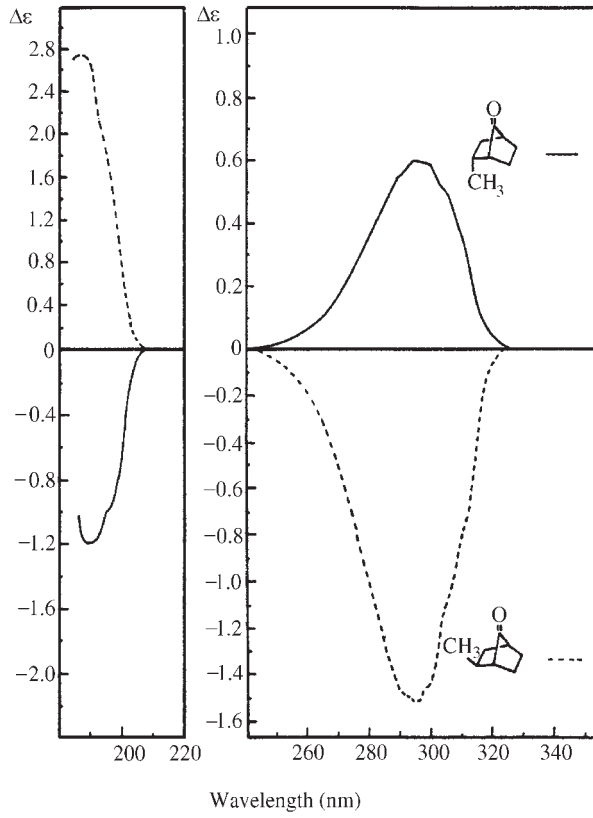


FIGURE 7. CD spectra of (1*R*)-*exo*-2-methylbicyclo[2.2.1]heptan-7-one (- - - - -) and (1*R*)-*endo*-2-methylbicyclo[2.2.1]heptan-7-one (———) in isopentane at 20 °C Corrections are made to 100% optical purity. [Reprinted with permission from Reference 42. Copyright (1974) American Chemical Society]

(Figure 7). Since 7-norbornanone is achiral, the methyl perturbers represent the lone dissymmetric octant perturbers, which in both compounds lie behind the third nodal surface (A, Figure 1) in a positive upper left or lower right octant. It thus appeared that the apparent 'anti-octant' effect should not be interpreted as such but rather as a *front octant* effect, with the *exo* methyl perturber lying in a negative front octant. And it was becoming likely that other so-named 'anti-octant' effects for alkyl and other perturbers[36–38] could be attributed to the perturbers lying in front octants[42].

In 1976, Bouman and Lightner[20], in a detailed theoretical analysis and CNDO/S calculations of the known 'anti-octant' compounds and a series of decalones, updated the octant rule by defining the third, nonsymmetry-derived nodal surface as concave (from the perspective of a viewer looking down the C=O bond, from O to C, as in B of Figure 1). The third nodal surface thus bends outward in the $+Z$ direction. Although this might appear to contradict the empirical results, surface B cuts just behind the 3-axial position, which locates the 'anti-octant' β-axial methyl group of adamantanone and the 2-*exo*-methyl group of 7-norbornanone in front octants. Replacing the methyl perturber with larger groups that project even farther into front octants, as in (1*S*,3*R*)-4(*a*)-ethyl or

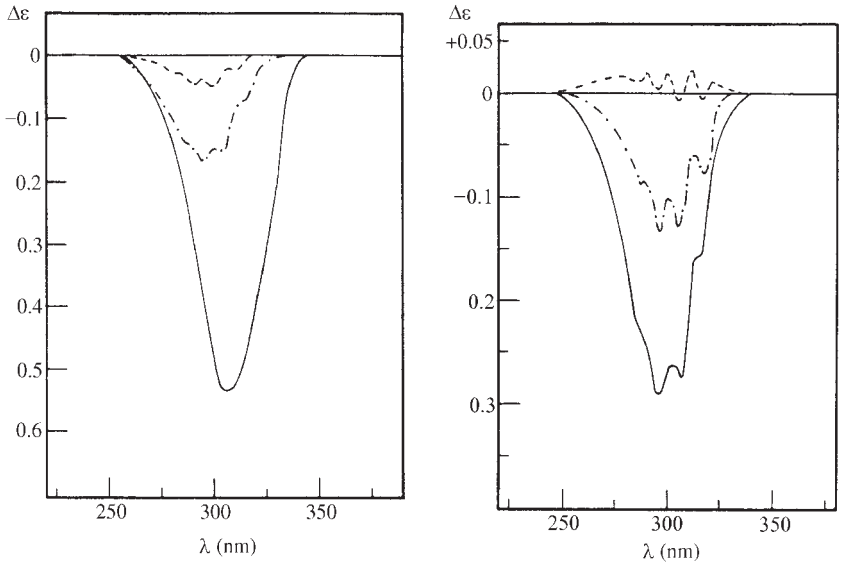


FIGURE 8. CD spectra of 10^{-3} M (1*S*,3*R*)-4(*a*)-substituted adamantan-2-ones (left) in EPA (ether–isopentane–ethanol, 5:5:2, v/v/v): (Left) run at 25 °C and corrected to 100% e.e. methyl (- - - - -), $\Delta\varepsilon_{306}^{max} = -0.046$; ethyl (approx. - · - · -), $\Delta\varepsilon_{296}^{max} = -0.15$; isopropyl (- · - · -), $\Delta\varepsilon_{297}^{max} = -0.17$; *tert*-butyl (———), $\Delta\varepsilon_{296}^{max} = -0.54$; neohexyl (- · - · -), $\Delta\varepsilon_{296}^{max} = -0.17$. (Right) In MI (methylcyclohexane–isopentane, 4:1, v/v): methyl (- - - - -), $\Delta\varepsilon_{313}^{max} = +0.025$; ethyl (approx. - · - · -), $\Delta\varepsilon_{301}^{max} = -0.10$; isopropyl (- · - · -), $\Delta\varepsilon_{297}^{max} = -0.15$; *tert*-butyl (———), $\Delta\varepsilon_{296}^{max} = -0.29$; neohexyl (approx. - · - · -), $\Delta\varepsilon_{297}^{max} = -0.10$. [Reprinted with permission from Reference 21. Copyright© 1986 American Chemical Society]

tert-butyladamantan-2-one, gives relatively stronger Cotton effects (Figure 8)[21]. Application of the octant rule places the perturbers in an upper left (or lower right) *negative* front octant. Although an axial methyl perturber sometimes makes a negative contribution and sometimes a positive at 25 °C, the Cotton effects are uniformly strongly *negative* at low temperatures[21]. The temperature and solvent effects seen for the β-axial-methyl group, which lies close to the third nodal surface, have been ascribed to restricted rotation and solvent perturbation of the C=O chromophore or vibronic effects[21].

D. Octant Consignate and Dissignate Perturbations

Kirk and Klyne assigned the term octant 'consignate' to apply to those groups or locations obeying the octant rule, and octant 'dissignate' where the octant rule is not obeyed[44]. Following an extensive analysis of decalones and analogues[43], they also proposed a somewhat different model to use in predicting Cotton effect signs and magnitudes, adopting the view espoused by Hudec and colleagues[45–48] that interactions from the hydrocarbon chains outside the chromophore (rather than direct perturbative action on the carbonyl group) dominate the contributions to Cotton effect. They believed that the 'through-bond' interactions are quite sensitive to chain conformations and reach appreciable values only when a planar (W-*zig-zag*) path can be traced along the bonds from the carbonyl group to the dissymmetrically placed substituent. Using this approach, Kirk and Klyne integrated

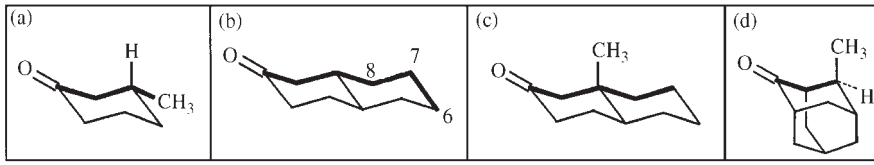


FIGURE 9. Carbon W-coupling (zigzag) paths shown in heavy lines for octant consignate perturbers: CH_3 of (a) and C-6, C-7, C-8 of (b). Octant dissignate perturbers [the angular CH_3 of (c) and axial CH_3 of (d)] do not lie on a primary zigzag coupling path. [Modified from Figure 10.11 in D. A. Lightner, Chap. 10 in Reference 15. Reproduced by permission of VCH Publishers, Inc., Deerfield Beach, FL]

data for *cis*- and *trans*-decalones and the 'anti-octant' compounds of Snatzke[22,36] into a single empirical scheme, but the shape of the third nodal surface was more difficult to assess[49].

Perturbers lying on a primary zig-zag (Figure 9) are said to make octant consignate contributions to the ketone n $\rightarrow \pi^*$ Cotton effect and obey the octant rule[43,49]. Perturbers not lying on a primary zig-zag make octant dissignate contributions and give front octant or 'anti-octant' effects. This analysis places considerable importance on bond couplings in the framework and a lesser importance on octant 'perturbers' and therefore offers a complementary perspective to that expressed in the octant rule. Recently a qualitative MO analysis was developed to explain both the enhancement of magnitude and the bathochromic shift of n $\rightarrow \pi^*$ transitions of carbonyl compounds which adopt a planar zig-zag as 'W' conformation[50].

E. Qualitative Completeness

One of the basic tenets of the octant rule is that atoms or groups lying in the symmetry planes do not contribute to the Cotton effect. Among the problems recognized quite early by Moffitt and colleagues[16] in applying the rule included the undefined shape of the third nodal surface (approximated as a plane) and the effect of unforeseen distortions from the 'idealized' geometries typically employed. The shape of the nonsymmetry-derived third nodal surface was described by theory[20] and experiment[51] as concave and cutting behind the carbonyl carbon (B, Figure 1)—a surface which divides quadrant space into octant space and explains many previously noted dissignate (or 'anti-octant') contributions of normal perturbers. Problems associated with distortion from the 'idealized' geometry were less well recognized or investigated. For example, it may be noted that the octant symmetry planes (*XZ* and *YZ*, Figures 1 and 4) are derived from the local symmetry (C_{2v}) of the C=O chromophore and are therefore only approximations when the molecular symmetry does not coincide with the local symmetry of the chromophore. Thus, for chair cyclohexanone only the *XZ* octant plane coincides with both a C=O local symmetry plane and the molecular symmetry plane. In contrast, the *YZ* octant plane is no longer a molecular symmetry plane. Consequently, the C=O local symmetry breaks and the *YZ* surface is only *approximately* a plane. In 3(e)-methylcyclohexanone, which has no planes of symmetry (and therefore no molecular symmetry coincident with the local symmetry of the C=O group), the *XZ* octant surface is also only approximately a plane (Figure 2). In fact, distortion from planarity of the C=O local symmetry-derived octant surfaces (*XZ* and *YZ*, Figures 1 and 4) will follow for all chiral molecules; yet the octant rule still works because most perturbers lie far from the octant 'planes'. However, when a perturber lies close to an octant surface, anomalous behavior may be anticipated[51]. A good example is (1*S*,5*S*)-dimethyladamantan-2-one (Figure 10), which has both methyl

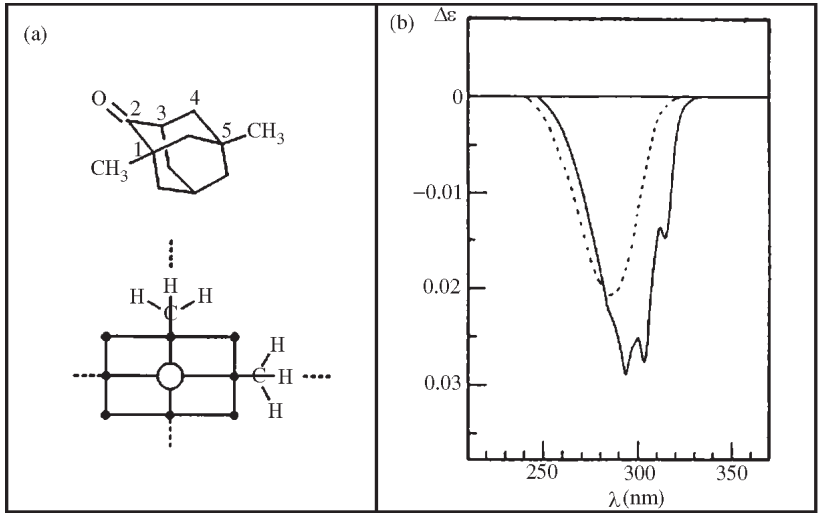


FIGURE 10. (a) (1*S*,5*S*)-Dimethyladamantan-2-one and its octant projection diagram. (b) CD spectra in cyclopentane (———) and 2,2,2-trifluoroethanol (- - - - -) at 18 °C; the $\Delta\varepsilon = 0$ baseline is the CD of the racemic ketone. Data are corrected to 100% e.e. [Modified from Figure 10.17 in D. A. Lightner, Chap. 10 in Reference 15. Reproduced by permission of VCH Publishers, Inc., Deerfield Beach, FL]

perturbers lying in octant symmetry planes. Although optically active, the n $\rightarrow \pi^*$ Cotton effect predicted by the octant rule is zero[52,53]. Despite the octant rule prediction, the CD data clearly reveal a weak monosignate negative Cotton effect. The Cotton effect remains negative, and its intensity is essentially invariant down to −150 °C.

The apparent discrepancy with the octant rule predictions was anticipated ten years previously in a theoretical paper of Yeh and Richardson[54], who explained how a dimethyladamantanone CD might be reconciled with the octant rule. Although the one-electron perturbation model of n $\rightarrow \pi^*$ optical activity in chiral ketones provides the simplest and most direct rationalization for the octant rule, it may be insufficient to account for optical activity when carried out only to first order. That is, in first-order perturbation only (*additive*) pairwise interactions between the C=O group and dissymmetric perturbers are considered. At this level the octant rule lacks qualitative completeness, but when the one-electron model is carried to higher-order perturbation, *multiplicative* terms contribute to the n $\rightarrow \pi^*$ Cotton effect. Thus, a ketone such as the dimethyladamantanone of Figure 10 are predicted in first-order one-electron perturbation theory (octant rule) to have zero optical activity. However, it is predicted to be optically active in second-order perturbation, which accounts for three-way interactions among the two CH_3 perturbers and the C=O chromophore. Qualitatively, this means that each CH_3 group of the dimethyladamantanone destroys each of the two planes of symmetry (octant symmetry planes) in the C_{2v} local symmetry of the C=O chromophore. One way to understand the octant or quadrant symmetry planes is that they are only approximately planes, except for molecules with C_{2v} symmetry, e.g. adamantanone. Any deviation from planarity will depend on the nature and location of the perturbing group. And while such deviations are *not important for more qualitative applications of the octant rule*, they can in fact be detected and analyzed in carefully chosen molecules.

F. Isotopic Perturbers

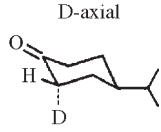
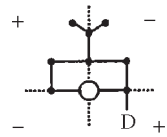
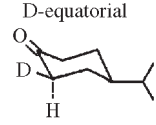
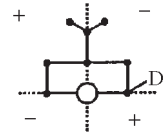
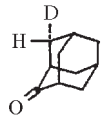
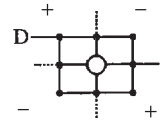
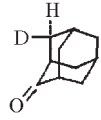
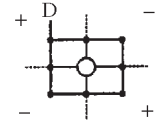
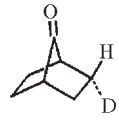
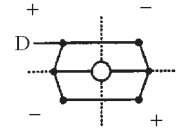
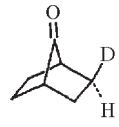
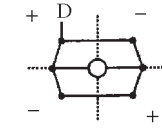
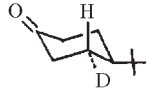
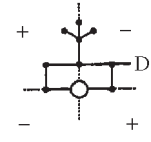
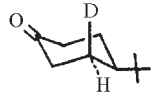
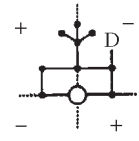
Prior to about 20 years ago, there were very few examples where the octant rule had been applied to interpret the n $\rightarrow \pi^*$ Cotton effects of chiral ketones with isotopic perturbers. Then for a period of about 10 years a significant effort was brought to bear on this aspect of isotopic stereochemistry. By the mid-1980s research efforts in this area essentially ceased but left behind a large body of CD data[55]. The first attempt to study the influence of isotopic substitution focussed on deuterium as a perturber of the ketone carbonyl n $\rightarrow \pi^*$ Cotton effect[56]; however, no difference could be detected between the ORD spectra of 3β-acetoxy-6β-deuteriocholestan-7-one and its protio analogue. (Results derived by difference measurements of large values are not entirely satisfactory, especially since the two systems measured must be of the same concentration and optical purity, and they must have identical geometries.) Subsequently, Djerassi and Tursch[57] attempted the first direct measurement of a ketone Cotton effect where chirality was due to a single deuterium perturber, viz. where the protio analogue is achiral. They prepared (3*S*)-deuteriocyclopentanone of known absolute configuration and measured its ORD spectrum but found no rotation ($<42°$) down to 280 nm. Subsequently, Meyer and Lobo[58] determined that (+)-camphor-9,9,9-d_3 had a molecular amplitude 3% smaller than that of the protio analogue. From this observation and the fact that deuterium has an atomic refractivity less than hydrogen, the authors concluded that deuterium, like fluorine[24,59], makes an octant-dissignate contribution.

The first monoketone n $\rightarrow \pi^*$ Cotton effect due solely to deuterium was observed in a later reinvestigation of (3*R*)-deuteriocyclopentanone which showed it to have a weak negative circular dichroism CD n $\rightarrow \pi^*$ Cotton effect, $\Delta\varepsilon_{304} = -0.019$ (25 °C) and $\Delta\varepsilon_{302} = -0.021$ (−196 °C)[60]. This result indicated that deuterium is an octant-dissignate perturber and led to a flowering of interest in the CD Cotton effects of conformationally mobile[61–63] and locked[64] cyclic deuterio ketones. In those papers, deuterium was typically but not always[64,65] found to exhibit an octant-dissignate effect and also to prefer the more hindered (axial) configuration relative to hydrogen[62].

Investigations of the CD of α-axial and α-equatorial deuteriocyclohexanones on the chair conformation anchored by a 4-isopropyl group (Table 2) indicate that an α-axial D is a *dissignate* perturber and an α-equatorial D is a *consignate* octant perturber[55]. Although both are very weak perturbers, the magnitude of the octant contribution from an α-axial deuterium is an order of magnitude larger than that from an α-equatorial.

Similarly, studies on α-axial and β-equatorial deuteriocyclohexanones couched in the rigid adamantanone framework (Table 2)[21,66] indicate that a β-equatorial deuterium makes an octant-dissignate contribution. A β-axial deuterium is found to be an octant-dissignate perturber, with reference to the original octant rule. CD data on the deuterioadamantanones were confirmed in *endo*-and *exo*-deuterio-7-norbornanones[67] (Table 2). *Endo*- and *exo*-deuterium atoms in norbornanones lie in octant positions very similar to those occupied by β-equatorial and β-axial deuterium atoms (respectively) in adamantanone. The octant dissignate contribution from β-equatorial deuterium was confirmed in 4-*tert*-butylcyclohexanone. However, opposite to that of adamantanones, a β-axial deuterium behaves as a weak consignate octant perturber in 4-*tert*-butylcyclohexanone[64,68]. A β-equatorial or *endo* deuterium gave a much larger octant contribution than β-axial or *exo*, and a theoretical explanation for the dissignate contributions has been offered[67]. Although deuterium is generally a dissignate octant perturber, the most notable exception to this trend is the consignate contribution of an α-equatorial deuterium[55,68], which is located close to an octant nodal plane, a region of sign change. These investigations of deuterium octant contributions in conformationally immobile ketones provided reliable estimates of the sign and magnitude of the perturber's contribution to the n $\rightarrow \pi^*$ CD

TABLE 2. Chair conformations, octant projection diagrams and n → π^* CD Cotton effects of β- and α-deuteriocyclohexanones as found in adamantanones and 4-isopropylcyclohexanones

	Octant projection diagram	Observed $n \longrightarrow \pi^*$ Cotton effect
D-axial 		$\Delta\varepsilon \simeq -0.090$
D-equatorial 		$\Delta\varepsilon \simeq -0.0091$
D-equatorial 		$\Delta\varepsilon \simeq -0.11$
D-axial 		$\Delta\varepsilon \simeq -0.01$
endo-D 		$\Delta\varepsilon \simeq -0.13$
exo-D 		$\Delta\varepsilon \simeq -0.03$
equatorial-D 		$\Delta\varepsilon \simeq +0.088$
axial-D 		$\Delta\varepsilon \simeq -0.0085$

Cotton effect for deuterium α and β positions of chair cyclohexanone. And application of those data to conformationally mobile systems led to the interesting stereochemical conclusion that deuterium prefers the more sterically crowded axial configuration in 3-deuteriocyclohexanone[55,69].

Octant contributions from an α-deuterium were explored further in conformationally rigid, symmetric ketones: bicyclo[3.2.1]octan-3-one and bicyclo[3.1.1]heptan-3-one. Substitution of ring hydrogen by deuterium is not expected to lead to skeletal distortions from their C_s symmetry. Thus the deuterium atom may be viewed as the lone dissymmetric octant perturber that controls the sign and magnitude of the CD Cotton effect. α-Axial deuterioketones (entries 6 and 7) show negative $n \rightarrow \pi^*$ Cotton effects (Table 3). Even a quasi-axial deuterium (entry 5) lying in an upper left or lower right back octant makes an octant-dissignate contribution, albeit with a smaller magnitude. Similarly, in entry 4 where the deuterium perturber lies in a negative back octant, an octant-dissignate positive CD is observed. Even as the α-deuterium tilts toward an equatorial location (as in entry 3)[72], it still makes an octant-dissignate contribution. However, as the D−C$_\alpha$−C=O torsion angle closes to 20° (entry 2)[71] and adopts the characteristic smaller angle associated with an equatorial position, the deuterium perturber becomes octant consignate. Therefore, it would appear that an 'equatorial' deuterium is an octant-consignate perturber up to D−C$_\alpha$−C=O torsion angles lying between 20° and 37°, at which point it becomes an octant-dissignate perturber. The reason for this is not entirely clear.

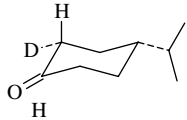
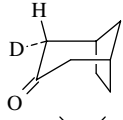
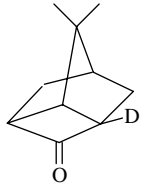
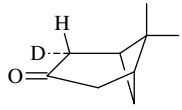
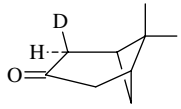
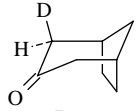
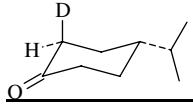
G. Applications of the Octant Rule

The octant rule has been invaluable to the determination of absolute configuration[3−15]. Illustrations of its utility may be found in a wide variety of ketones, from monocyclic to polycyclic. In the following, applications to decalones illustrate its usefulness and the concept of additivity of octant contributions. For example, (5*S*)-*trans*-1-decalone, (a) of Table 4, is predicted to have a negative $n \rightarrow \pi^*$ CD Cotton effect. According to its octant projection diagram, carbons 1, 2, 4, 8, 9 and 10 all lie on carbonyl symmetry planes (Figure 1), and carbons 3 and 5 lie equally disposed across a symmetry plane. These atoms are predicted by the octant rule to make no contribution to the Cotton effect, leaving atoms 6 and 7 to determine its sign. Since both lie in an upper right (or lower left) negative octant, a net negative Cotton effect is predicted — in agreement with that observed ($\Delta\varepsilon \simeq -1.0$). The presence of an angular methyl at C (10), as in (b) of Table 4, leads to a positive Cotton effect. Since the ring atoms of decalone (b) make the same contribution as in those of (a), it is the angular methyl group that causes the sign reversal. The angular methyl is close to the carbonyl group, much closer than carbons 6 or 7, and in an α-axial position. It can therefore be expected to act as a stronger octant perturber. An α-axial methyl group on cyclohexanone probably contributes $\Delta\varepsilon \simeq +1.7$ when the α-axial methyl lies in a positive octant, as in (b).

Octant projection diagrams for the 2- and 3-ketodecalins, (c) and (d) of Table 4, are very similar. The octant locations of the ring atoms are identical, with carbons 7, 8 and 9 in (c) and carbons 6, 7 and 8 in (d) lying in a positive back octant. Since the other ring atoms lie on octant planes, or have counterparts across an octant plane, they make no contribution to the Cotton effect. One would therefore expect a net positive $n \rightarrow \pi^*$ CD coming from both carbocyclic skeletons. The methyl perturbers either lie in an octant plane, as in the angular methyl of (d); or they lie (barely) in a front octant, as in the angular methyl of (c); or they lie distant from the C=O but still in a positive back octant, as in the C(9) methyl of (c). Thus the net CD Cotton effect contributions in decalones (c) and (d) are positive and nearly identical in magnitude, as is observed.

The ring carbons of the *trans*-4-oxodecalin, (e) of Table 4, lie in the same back octants as those of *trans*-1-decalone (a): These perturbers should thus sum to a negative CD. The

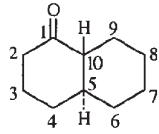
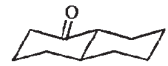
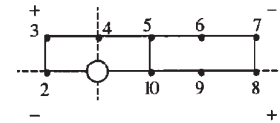
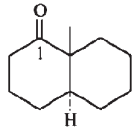
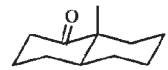
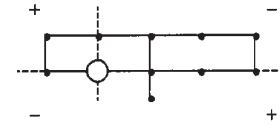
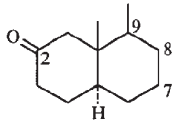
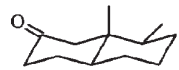
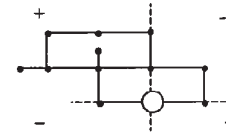
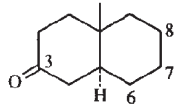
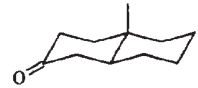
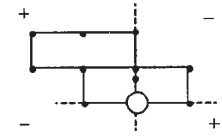
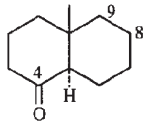
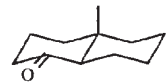
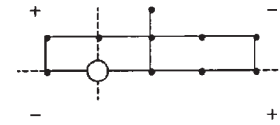
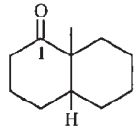
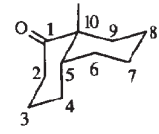
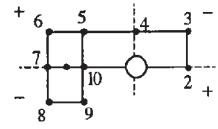
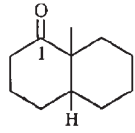
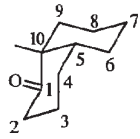
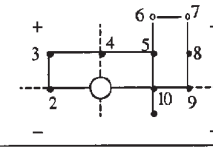
TABLE 3. Reduced rotatory strengths [R] and D−C_α−C=O torsion angles for the n → π^* transition of α-deuterioketones

Compound	[R][a]	Octant dissignate or consignate	Torsion angle
	−0.03[b,c]	Consignate	−9°
	−0.29[d]	Consignate	−20°
	+0.078[e,f]	Dissignate	−37°
	+0.037[d,f]	Dissignate	—
	−0.029[d,f]	Dissignate	60°
	−0.14[d,g]	Dissignate	96°
	−0.25[c,d,h]	Dissignate	108°

[a] [R] = rotatory strength × 1.08 × 10^{-40}, corrected to 100% ee. and α 100% D and measured at 25 °C.
[b] Values from Reference 69.
[c] Measured in isooctane solvent.
[d] Value from Reference 71.
[e] Value from Reference 70.
[f] Measured in CF_3CH_2OH solvent.
[g] Measured in EPA (ether:isopentane:ethanol, 5:5:2, v/v/v) solvent.
[h] The value in EPA (−0.3) is thought to be low due to H exchange for D occurring during isolation (Reference 64).

only difference between (e) and (a) is the presence of a β-axial methyl in the former. β-Axial methyls are known from earlier work on adamantanones to be weak dissignate perturbers. Consequently, the Cotton effect in (e) is predicted to have the same negative sign as (a), with a slightly smaller magnitude. The observed CD Cotton effect of (e) is negative and only slightly smaller than that of (a).

TABLE 4. Decalones, conformational representations, octant projection diagrams and predicted and observed n → π^* CD Cotton effects

	Decalone[a]	Conformation	Octant projection diagram[b]	Cotton effect pred.	Δε obs.
(a)				−	−1.0
(b)				+	+0.7
(c)				+	+1.3
(d)				+	+1.2
(e)				−	−0.8
(f)				−	+1.3
(g)				+	+1.3

[a] Steroid numbering system.
[b] See Figure 1. Back octant contributors are denoted by filled circles (•), front octant contributors or suspected front octant contributors are denoted by open circles (○).

In *cis*-fused decalones, two different conformations are possible, as in the steroid (f) and nonsteroid (g) conformers of Table 4. The octant rule predicts a strong negative Cotton effect for (f) and a strong positive Cotton effect for (g). Assuming chair conformations, nearly all of the ring atoms of (f) lie in octant symmetry planes (carbons 1, 2, 4, 7, 10 and the angular methyl) or have counterparts across the octant planes (carbons 3 and 5,

6 and 8), leaving only carbon 9 to make an α-axial contribution in a negative octant. In the nonsteroid conformer (g), most of the ring atoms are cancelling, as in (f). Carbons 1, 2, 4, 9 and 10 lie in an octant plane, and carbons 3 and 5 lie equally disposed across an octant plane and are thus cancelling. The angular methyl lies close to the C=O, in an α-axial position in a positive octant. Carbon 8 lies distant in a negative octant, and its contribution is probably weak. Carbons 6 and 7 lie in positive front octants similar to β-axial methyl on 3-methylcyclohexanone. The predicted net Cotton effect for (g) is thus positive. Since a strong positive Cotton effect is observed, the *cis*-decalone probably adopts conformation (g).

When the absolute configuration of the ketone is known, the conformation can often be determined by applying the octant rule — as in (f) and (g) of Table 4. In other examples, low-temperature CD measurements have been used to extract conformational information when the absolute configuration is known. Although a wide variety of ketones have been investigated, several classical examples are worthy of note.

The most stable conformation of (−)-menthone is almost certainly one where both the α-isopropyl and β-methyl groups are equatorial (Figure 11). The diaxial conformer might relax into a lower-energy twist-boat conformation, but that is still a higher-energy state. The CD spectrum in hydrocarbon solvent at 25 °C consists of a mainly negative CD with a weak positive component[72]. At lower temperatures, the Cotton effect becomes increasingly

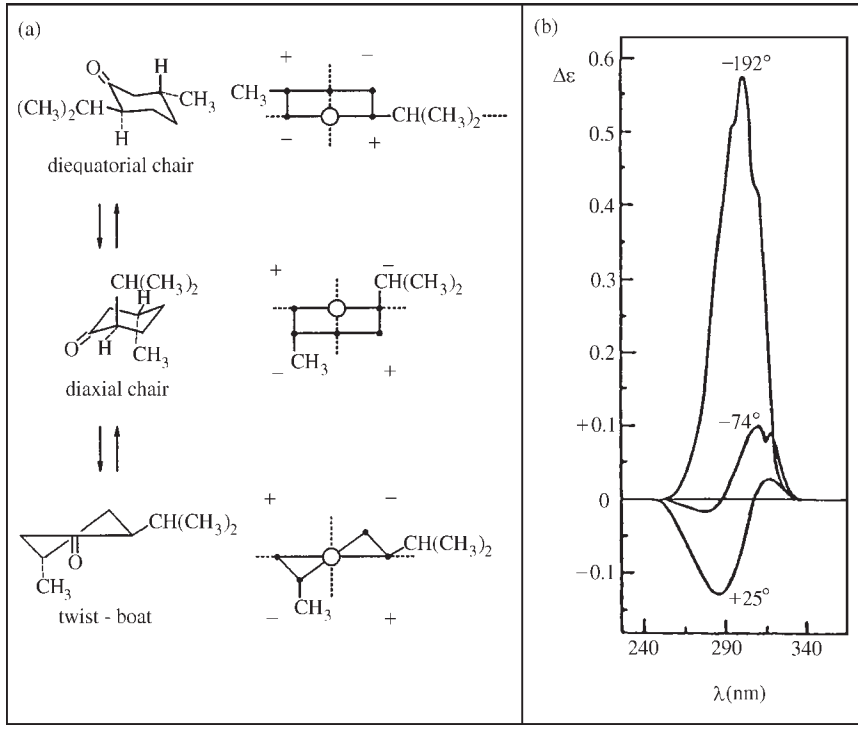


FIGURE 11. (a) (−)-Menthone conformations and octant projection diagrams. (b) Variable-temperature CD spectra of (−)-menthone in hydrocarbon solvents: +25 °C and 74 °C in decalin; −192 °C in isopentane-methylcyclohexane. [Modified from D. A. Lightner, Chap. 5 in Reference 14 and reproduced by permission of Elsevier Science Publishers, Amsterdam]

positive, indicating that the lowest-energy conformer has a strong positive CD. According to the octant rule, the diequatorial conformer is predicted to have a moderate positive Cotton effect, but the diaxial and twist boat conformers are predicted to exhibit strong negative Cotton effects. Although a small population of either the diaxial or twist-boat conformers at room temperature might overwhelm the positive CD due from the major diequatorial conformer, as the temperature is lowered the population is shifted more toward the more stable conformer. Then the positive Cotton effect becomes dominant.

(+)-*trans*-6-Chloro-3-methylcyclohexanone can adopt diequatorial or diaxial chair conformations, or a twist-boat conformation as in (−)-menthone. In isooctane solvent a negative n $\rightarrow$ π^* Cotton effect is observed, but in methanol a positive Cotton effect is found (Figure 12)[73]. Octant projection diagrams for the two chair conformations predict a weak to moderate positive Cotton effect for the diequatorial isomer and a strong negative Cotton effect for the diaxial isomer. In methanol a positive Cotton effect is found, suggesting a preponderance of the diequatorial isomer. However, in isooctane a negative Cotton effect is observed, corresponding to a significant percent of the diaxial isomer. The red-shifted CD spectrum in isooctane is consistent with an α-axial chlorine, indicating a significant contribution from the diaxial conformer in this nonpolar solvent (where the C=O, C−Cl dipole–dipole repulsion is minimized).

For 2-oxo-*p*-menthanol (Table 5) the octant rule predicts a positive Cotton effect for the equatorial isopropyl isomer and a negative Cotton effect for the axial isopropyl isomer. A positive Cotton effect is observed in methanol, and a negative Cotton effect is observed in isopentane-methylcyclohexane[74]. These results suggest that the axial isopropyl isomer, which is stabilized by intramolecular hydrogen bonding between the α-equatorial OH and the C=O, is present to a much greater extent in the hydrocarbon solvent than in methanol.

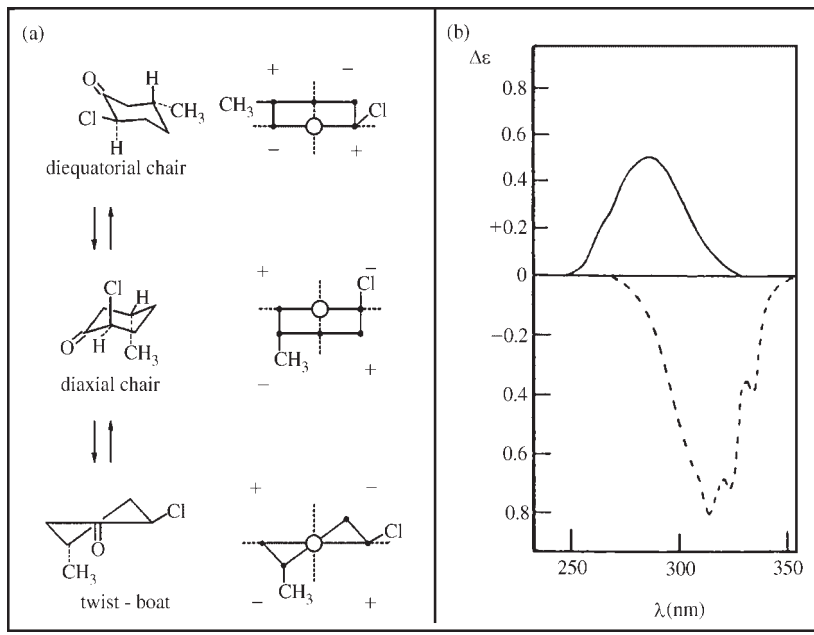
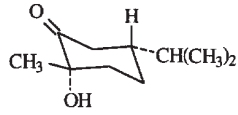
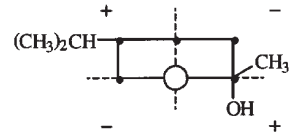
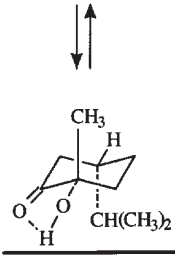
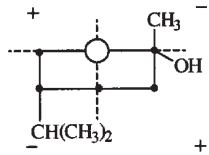


FIGURE 12. (a) (+)-*trans*-6-Chloro-3-methylcyclohexanone conformations and octant projection diagrams. (b) CD spectra in methanol (———) and isooctane (- - - - -). [Reproduced from D. A. Lightner, Chap. 5 in Reference 14 by permission of Elsevier Science Publishers, Amsterdam]

TABLE 5. Chair conformers of 2-oxo-*p*-menthanol, octant projection diagrams, predicted and observed n → π^* Cotton effects

Conformation	Octant diagram	Cotton effect	
		predicted	observed
		(+)	$\Delta\varepsilon + 1.76^a$
		(−)	$\Delta\varepsilon = -1.36^b$

[a] In methanol.

[b] In isopentane-methylcyclohexane 5:1.

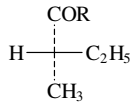
Methanol interferes with intramolecular hydrogen bonding, and the equatorial isopropyl isomer is the major species present.

III. COMPILATION OF KETONE AND ALDEHYDE CD

A. Acyclic Ketones and Aldehydes

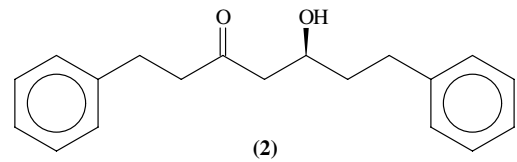
The acyclic aldehydes and ketones are expected to give substantially weaker CD than that of their cyclic counterparts because of the conformational mobility of the former, as was borne out by Djerassi and Geller[75] in an early study of a series of optically active methyl-substituted aldehydes and ketones. Since then only a few studies on acyclic aldehydes and ketones have appeared[76,77].

Potapov and coworkers[78] applied the octant rule to (+)-2-*s*-butyl alkyl ketones (**1**), which exhibit very strong temperature- and solvent-dependent CD Cotton effects. The shift in $\Delta\varepsilon$ from positive to negative by changing the steric demand of R group was rationalized on the basis of changing the conformational preference of the *s*-Bu group in **1**.



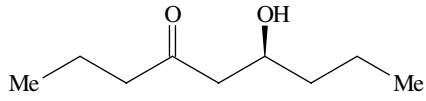
(**1**)

in EtOH:
R = Me, +0.076 (278); Et, (+) CD;
i-Pr, (−) CD; *i*-Bu, +0.088 (280);
cyclo-C_6H_{11}, +0.010 (310), −0.008 (275)



(**2**)

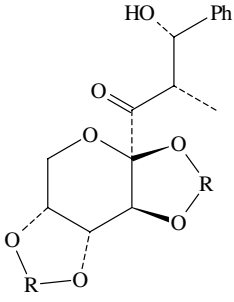
CCl_4 −0.03 (310), +0.05 (277)
CH_3CN −0.20 (283)



(3)

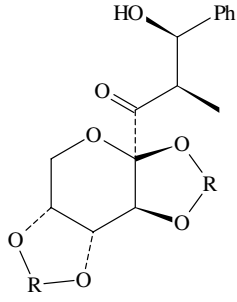
CCl_4	−0.02 (312), +0.17 (280)
CH_3CN	−0.18 (287)

The strong solvent dependence of the molecular rotation and CD of **2** and **3** on solvent polarity was attributed to formation/breaking of an intramolecular hydrogen bond between the carbonyl and hydroxy group[79].

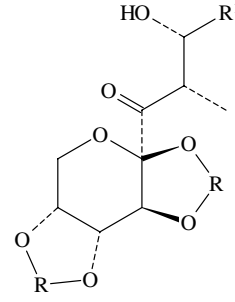


R = $CHMe_2$

−0.76 (315)[80]



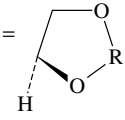
+2.70 (300)[80]

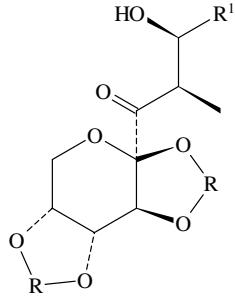


+0.14 (320)[80]

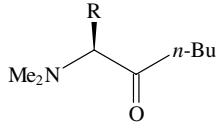
R = $CHMe_2$

R^1 =

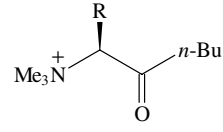




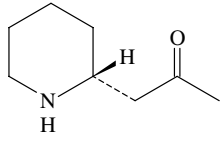
+1.21 (297)[80]



−0.05(315), +0.06(281)
−2.53(318), +2.76(240)
−1.09(304), +0.96(238)[81]

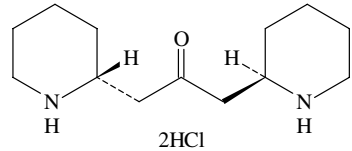


R = Me	+1.15(292)
R = $CHMe_2$	+1.67(295)
R = CH_2CHMe_2	+1.36(295)[81]



−0.038(285)

Sulfate −0.111(281)[82]



2HCl

+0.084(287)[82]

Biologically active cyclic tetrapeptides (**4–7**) showed: (1) a conformational preference in the epoxyketone moiety; (2) no n $\rightarrow \pi^*$ peptide bond contribution to $\Delta\varepsilon$ near 288 nm; and (3) anti-octant perturbation of oxirane ring.

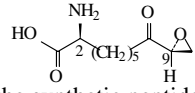
(**4**) cyclo (Aib-L-Phe-D-Pro-2*S*,9*S*-Aoe) − 0.26 (288)

(**5**) cyclo (Aib-L-Phe-D-Pro-2*S*,9*R*-Aoe) + 0.25 (288)

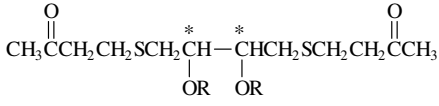
(**6**) cyclo (D-Pro-L-Ala-D-Ala-L-Aoe) − 0.24 (288)

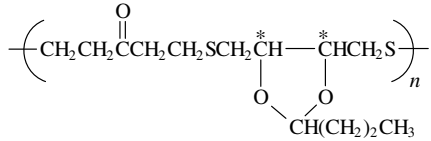
(**7**) cyclo (D-Phe-L-Leu-L-Pip-L-Aoe) − 0.23 (288)[83]

where Aib = α-aminoisobutyric acid, Pip = pipecolic acid and Aoe =



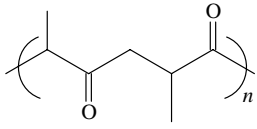
The identity of the Cotton effects of natural peptides **6** and **7** with the synthetic peptide **4** having a known oxirane configuration allowed for assignment (9*S*) of the absolute configuration of the L-Aoe residue[83].

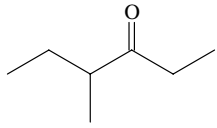




R = H +0.026 (285), −0.051 (245)[84]
R = $CH_3(CH_2)_2CH$ +0.004 (290)[85]

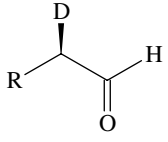
−0.014 (285)[85]

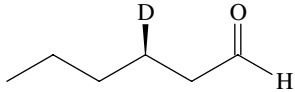


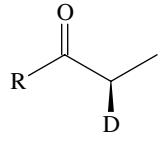


−1.56 (275)[86] +0.12 (284)

The CD data for a series α- or β-deuterated aliphatic aldehydes (**8**, **9**) and ketones **(10)** were reported[87].



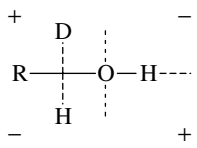




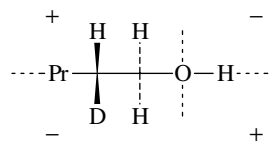
(8a) R = *n*-Pr −0.034 (298) **(9)** +0.006 (298) **(10a)** R = *n*-Pr −0.079 (298)
(8b) R = *i*-Pr −0.028 (298) **(10b)** R = *i*-Pr −0.098 (298)

The n $\rightarrow \pi^*$ Cotton effects for **8–10** were consistent with the preferred (*ca* 1 kcal mol^{-1}) eclipsed conformation of the carbonyl/α-alkyl moiety as shown in the octant projections below.

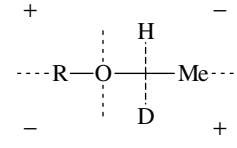
The 'anti-octant' or dissignate behavior of deuterium was discussed earlier (Section II.F), and it operates as expected in compounds **8–10**. The octant representations



(8)



(9)

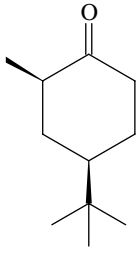


(10)

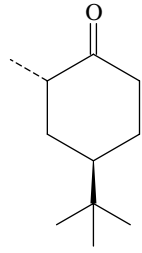
show also that when the carbonyl perturber is displaced one carbon farther away, as in the aldehyde **9** compared to **8**, the $\Delta\varepsilon$ magnitude is decreased five-fold, thus demonstrating the 'proximity rule' in these cases. Changes of solvent polarity did not appear to affect the conformational preference in **8–10**, though variable-temperature effects were observed.

B. Cyclic Ketones and Aldehydes

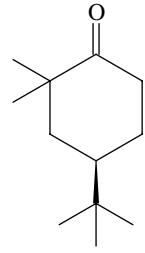
Djerassi and coworkers[88] showed the extraordinary sensitivity and utility of the chiroptical methods in detecting subtle conformational changes by CD measurements on chiral 4-*tert*-butylcyclohexanones.



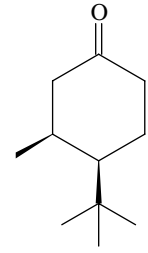
(11)
−0.46(298)[88]



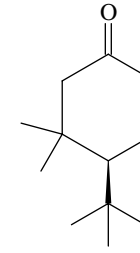
(12)
+1.33(296)[88]



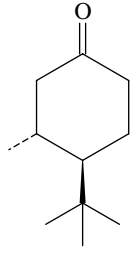
(13)
+1.36(295)[88]



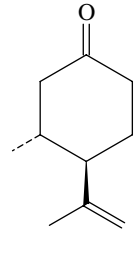
(14)
−0.17(297)[88]



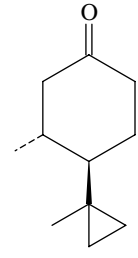
(15)
−0.39(303)[88]



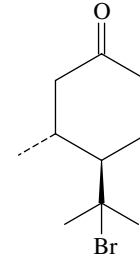
(16)
+3.39(299)[88]



(17)
−0.45(297)[88]



(18)
−0.70(295)[88]

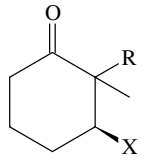


(19)
+2.71(297)[88]

While the ketones **11–15** are anchored by an equatorial *tert*-Bu group in the preferred chair conformation, and the octant contributions of α- or β-methyl substituents follow according to expectation, the CD of ketone **16** was unanticipated. The predicted CD of **16** in a chair conformation (with β-equatorial methyl group) was weak and negative as was

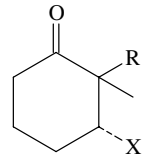
found for **17** and **18** ($\Delta\varepsilon$ *ca* −0.5). The $\Delta\varepsilon$ of compounds **11–19** were calculated approximately from the reported rotational strength using the relationship: $[R] = 3.32 \cdot \Delta\varepsilon$[88]. The observed strong positive Cotton effect for **16** and for the similar bulky substituted **19** led to a reasonable assumption that the twist-boat form is of lower energy, confirmed by an empirical force-field calculation. The unusually large positive n → π^* CD of **16** indicates that the presence of equatorial substituent adjacent to the 4-*tert*-butyl blocking group causes the twist-boat conformation to become energetically preferred due to release of an unfavorable nonbonded steric repulsion between the 4-equatorial *tert*-Bu and 3-equatorial Me interaction.

^{1}H-NMR and CD spectroscopy have been used to determine the equatorial ⇄ axial equilibrium in β-heteroatom-substituted cyclohexanones[89].

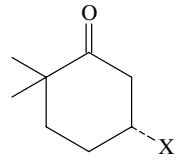


R = CH_3 or CD_3

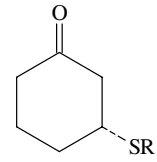
X	Δε
OH	+0.07
OAc	−0.67
OMe	−0.80[89]



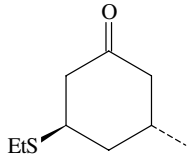
X	Δε
F	+0.33
Cl	+1.69
SEt	+2.97
Me	−0.51[89]



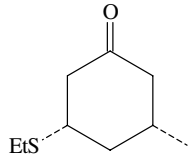
X	Δε
OAc	+0.06
Me	+1.38[89]



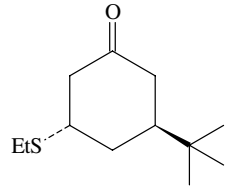
R	Δε
Et	+0.41
4-*t*-BuC_6H_4	+2.85[90]



+1.41[89]



−2.85[89]



−1.27[89]

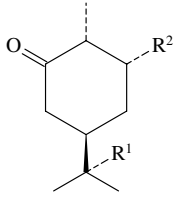
[All data are for $n \rightarrow \pi^*$ (296–301 nm) Cotton effect measured in EPA at RT.]

Comparison with monosubstituted cyclohexanones showed that in the case of F, OH, OMe, OAc and Me substitution, the 3-keto group enhanced the axial preference of the substituent, the effect being greater for more electronegative substituents. Less electronegative substituents (Cl, Br and SR) showed a decreased axial preference[89].

The octant rule holds for 2-methylpiperidin-4-one **(20)** and *trans*-decahydroquinolin-4-ones (**21–23**).

The CD of bicyclic ketone **24**[95] as hydrochloride as well as **25**[96] was compared to that of their carbocyclic analog (+)-norcamphor **(26)**[49], and the absolute configuration was established as (1*R*,4*S*) and (1*R*,4*R*) for **24** and **25**, respectively. Comparison between (−)-**24**·**HCl** and (+)-**26** was based on an earlier finding that the relative geometry of the lone pair on the N atom and the C_α−CO bond greatly influences the CD of α-aminoketones, whereas the coupling between n → π^* and $\pi \rightarrow \pi^*$ transitions is removed by protonation in (−)-**24**·**HCl**.

The CD of all *trans*-fused ketones belonging to the perhydro-naphthalene, -anthracene, -naphthacene and -phenanthrene has been reported. These studies provided the pure ring

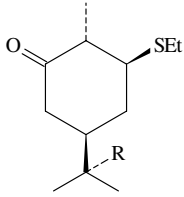


$R^1 = H$[91]

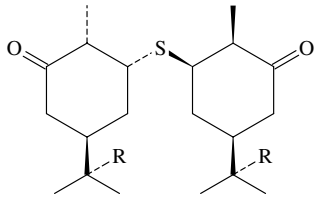
$R^2 = H$ +0.94 (290)
$R^2 = SEt$ +1.39 (291), +0.85 (248)
$R^2 = SBu\text{-}t$ +1.44 (290), +1.03 (248)
$R^2 = SPh$ +1.15 (295), +1.36 (260)

$R^1 = OMe$[91]

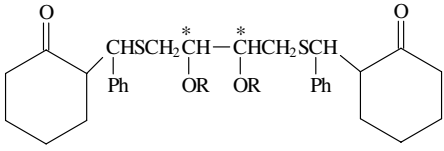
$R^2 = H$ +0.83 (292)
$R^2 = SEt$ +1.34 (290), +0.83 (248)
$R^2 = SBu\text{-}t$ +1.40 (291), +1.11 (249)
$R^2 = SPh$ +1.12 (294)



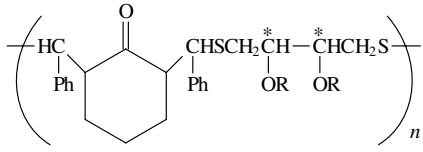
R = H −1.82 (288), +0.39 (249)
R = OMe −1.58 (289), +0.45 (247)[91]



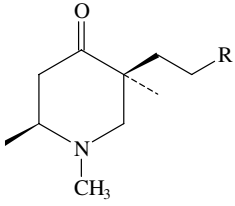
R = H +3.26 (289), +2.55 (247)
R = OMe +3.19 (288), +2.97 (243)[91]



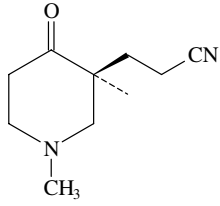
+0.37 (293), −1.25 (244)
+0.08 (290)



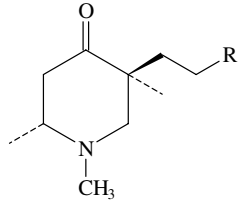
R = H +0.30 (294), −0.30 (247)[84]
R = $CH_3(CH_2)_2CH$< +0.15 (300)[85]



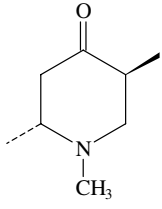
R = CN +1.17 (300)
R = COOMe +1.44 (298)[92]



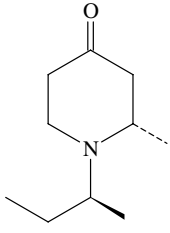
+1.04 (300)[92]



R = CN −0.88 (299)
R = COOMe −0.91 (300)[92]

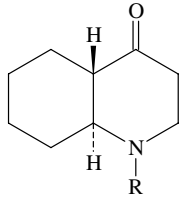


−0.15 (300)[92]

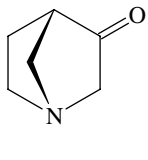


(20)

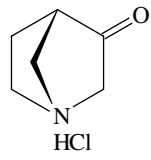
+0.16 (296)[93]



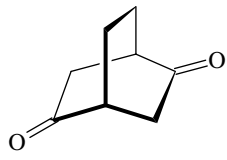
(21) R = H +0.76 (296)
(22) R = (*S*)-$CH_3CH_2(CH_3)CH$ +0.73 (293)
(23) R = (*S*)-$PhCH_2(CH_3)CH$ +0.68 (304)[94]



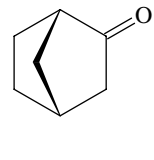
(−)-(**24**)
−2.1 (309)



(−)-(**24·HCl**)
−0.012 (313),
+0.123 (282)

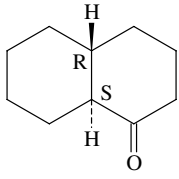


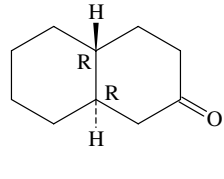
(−)-(**25**)
−0.78 (298)

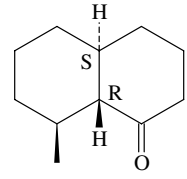


(+)-(**26**)
−0.25 (305),
+0.15 (280)

additive contributions (including from the front octants) of third and fourth annelated unsubstituted rings to the previously proposed empirical rules[43,49,97,98] for extended decalones.

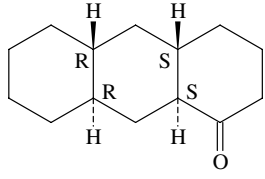


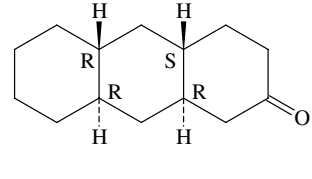




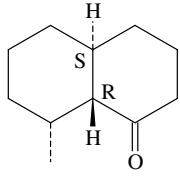
(**27**)

Hexane	+0.81 (296), +3.6 (188)[43]	−1.12 (297), −0.5 (190)[43]	−1.43 (297), −2.72 (192)[99]
MeOH	+0.95 (292)[43]	−1.37 (290)[43]	−1.85 (293)[99]
CF_3CH_2OH	−1.9 (189)[100]	+1.0 (190)[100]	



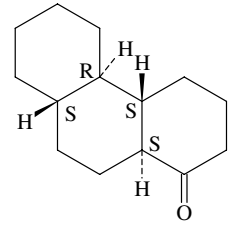


Hexane	+0.76 (295), +3.9 (187)[101,102]	−1.37 (297), +1.5 (185)[43]
MeOH	+1.01 (290), <0 (<196)[101,102]	−1.86 (290)[43]
CF_3CH_2OH	−1.9 (188)[100]	+2.8 (194)[100]

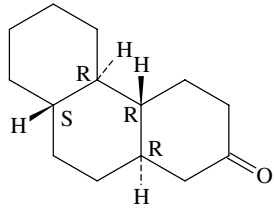


(**28**)

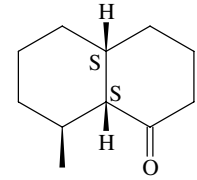
−0.53 (299), −3.02 (189)[99]
−0.54 (295)[99]



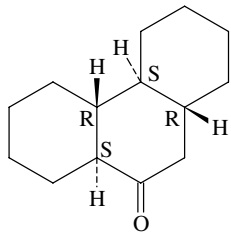
Hexane +1.20 (296), +1.40 (189)
MeOH +1.67 (291), −2.10 (192)[102]



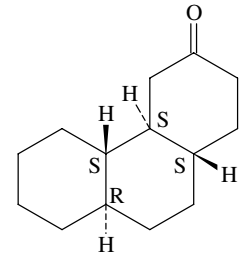
−0.56 (297), +0.2 (193)
−0.72 (288)[102]



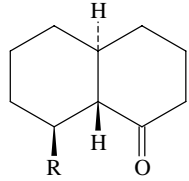
+1.26 (300), +3.55 (190)
+1.37 (296)[99]



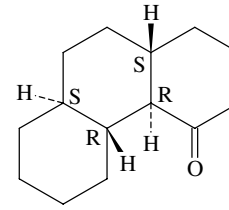
Hexane −0.47 (296), −0.7 (190)
MeOH −0.75 (293)[103]



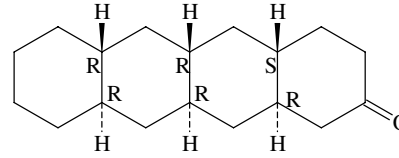
+1.40 (298), −1.0 (195)
+1.70 (290)[103]



R = CO_2H −1.09 (289)
R = CH_2OH −1.50 (293)
R = CO_2Me −1.23 (292), −1.89 (208)
−1.38 (290), −0.38 (208)[99]

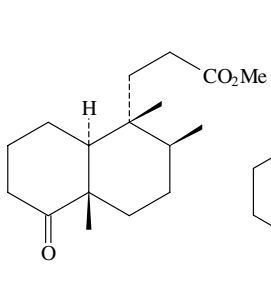


Hexane +1.46 (295), <0 (195)
MeOH +2.14 (293), −2.2 (196)[104]

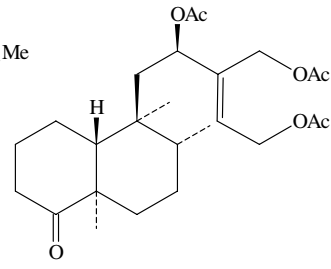


−1.55 (298), +2.0 (187)
−2.05 (291)[102,105]

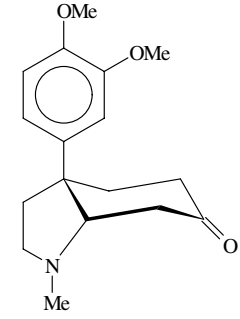
The contribution of the methyl substituent in 8-methyl-1-decalones **27** and **28** is octant consignate but different in magnitude for the axial and equatorial methyl group, though they are nearly symmetrically located with respect to the horizontal carbonyl plane[99].



+0.14 (298)[106]

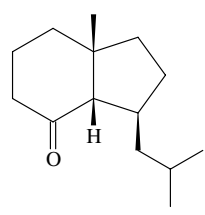


−0.19 (297)[107]

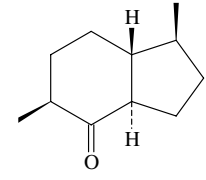


−0.42 (303), +0.32 (269)
Methiodide −0.31 (330), +0.39 (273)[108]

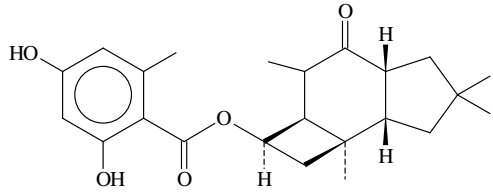
X-ray analysis of hydrindanone **29** showed a *cis* ring fusion. The absolute configuration of **29** was proposed by applying the octant rule[109]. The absolute configuration of the *trans*-fused hydrindanone **30** was correlated by chemical transformations of (−)-carvone. The ketone **30** CD is in accord with the octant rule[110].



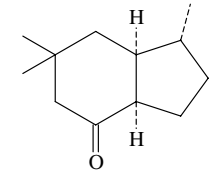
(29)
+0.37 (304)



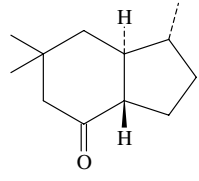
(30)
+1.33 (294)



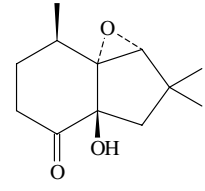
+0.94 (318)[111]



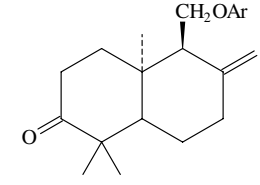
−1.82 (293)[112]



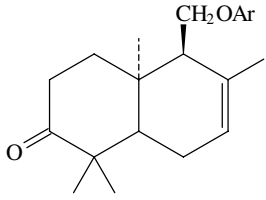
+1.07 (286)[112]



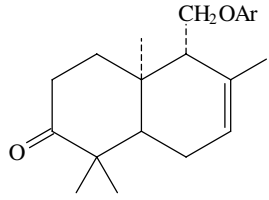
+0.19 (318)[113]



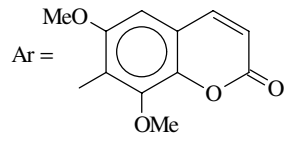
−0.10 (338), +0.87 (298),
sh −1.55 (230)[114]

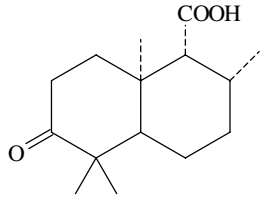


+0.80 (340), +2.40 (295)[114]

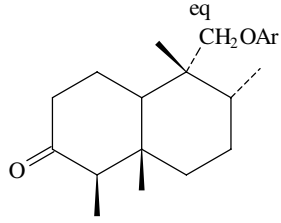


−0.44 (345), +1.12 (299), −4.40 (210)[114]

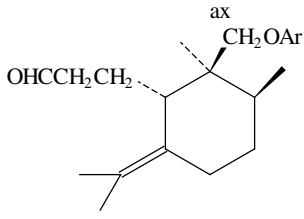




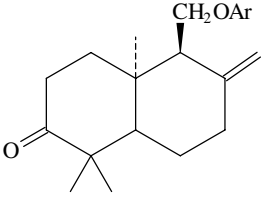
+0.04 (318), −0.23 (289)[114]



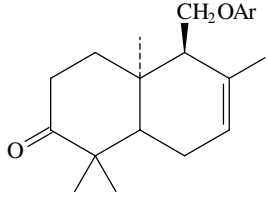
+0.05 (335), −2.53 (290)[114]



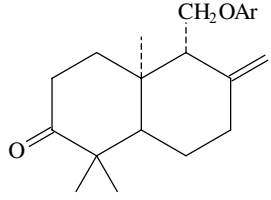
−0.24 (350), −0.85 (293)[114]



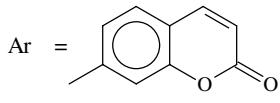
−0.42 (330), +0.05 (295), −0.50 (245), −19.5 (203)[115]

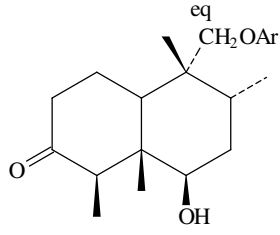


−0.58 (328), +0.04 (295), −10.3 (203)[115]

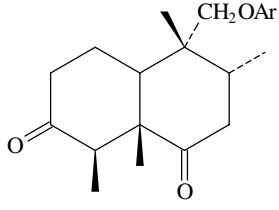


−0.50 (330), −4.5 (204)[115]

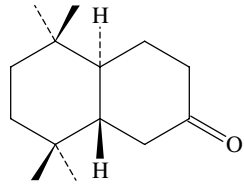




−0.42 (330), +1.60 (294)[115]

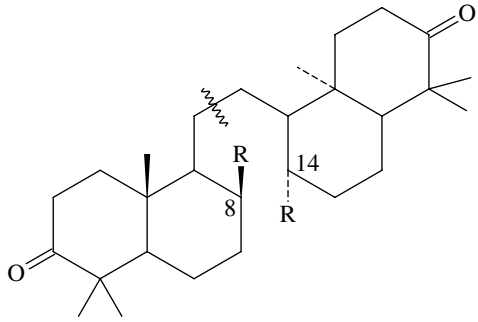


−1.20 (326), +3.10 (290)[115]



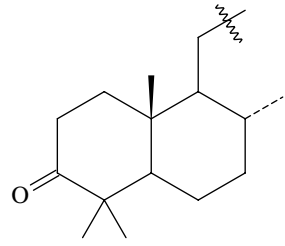
+1.07 (295)[116]

An interest in anomalous CD properties of 4,4-dimethyl-3-keto steroids and 4,4,8β-trimethyl-3-keto steroids[117,118] continued in the studies of Tsuda and coworkers on onoceranediones[119,120]. Analysis of the CD spectra of **31–35** in methanol and dioxane led to the conclusion that the A-ring conformation in solution is in equilibrium between chair



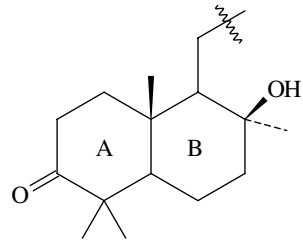
(31)

R = H	−0.28 (317), +0.36 (283)
R = CH_3	−0.12 (319), +1.50 (289)
R = OH	−0.22 (319), +1.04 (288)
R = OAc	−0.11 (320), +0.96 (280)
R = CH_2OH	−0.10 (323), +1.13 (292)
R = CH_2OAc	−0.10 (323), +1.22 (289)



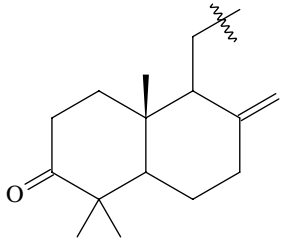
(32)

−0.90 (302)



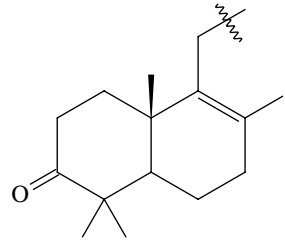
(33)

−0.31 (315), +0.36 (283)



(34)

−0.34 (305), +0.12 (272)

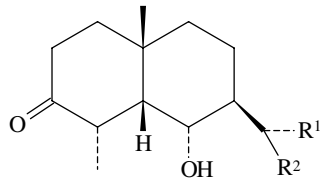


(35)

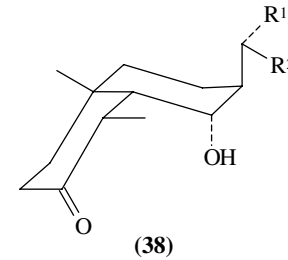
−0.12 (320), +1.59 (290)

and twist forms with variable ratios. This equilibrium was affected by minor changes at remote positions and by the polarity of the solvent. An increase of the steric bulkiness of the 8β-substituent increased the A-ring twist population. Introduction of an 8α-substituent in **33** decreased the flexibility of the B-ring, thus increasing the A-ring chair population[120].

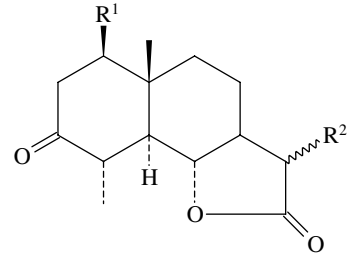
X-ray crystallographic analysis revealed that methyl *cis*-tetrahydro-α- **(36)** and -β-santoninate **(37)** have a nonsteroid decalone conformation in the solid state. Furthermore, positive Cotton effects shown by both *cis*-fused decalone analogues indicated the presence of such nonsteroid conformation **(38)** in solution, in accord with the octant rule[121].



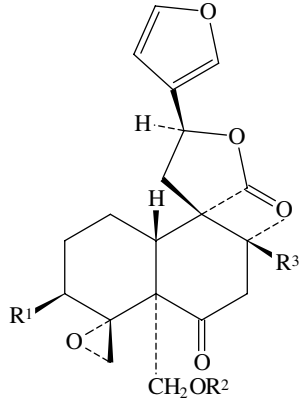
(36) $R^1 = CH_3$, $R^2 = CO_2CH_3$ +0.67 (284), +0.78 (213)
(37) $R^1 = CO_2CH_3$, $R^2 = CH_3$ +0.58 (284)[121]



(38)

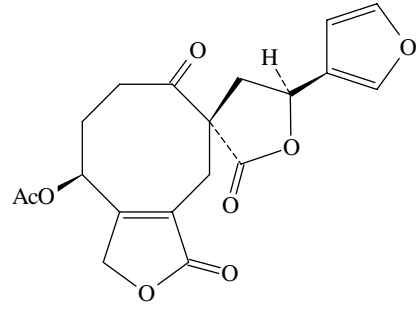


$R^1 = H$, $R^2 = \alpha\text{-}CH_3$ +0.83 (285), +1.03 (215)
$R^1 = H$, $R^2 = \beta\text{-}CH_3$ +0.91 (285), −0.72 (215)
$R^1 = OH$, $R^2 = \alpha\text{-}CH_3$ +0.64 (282), +1.33 (215)
$R^1 = OH$, $R^2 = \beta\text{-}CH_3$ +0.66 (283), −0.59 (220)[122]



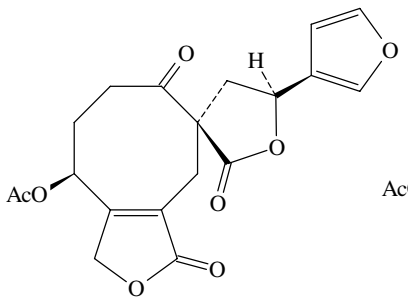
(39)

R^1	R^2	R^3	
H	H	H	−0.89 (299)[123]
H	Ac	H	−0.51 (300), −0.40 (225)[123,124]
OH	H	H	−0.87 (302)[125]
OH	Ac	H	−0.52 (301)[125]
10β-OH	OAc	Ac	OH	−0.71 (298), −0.62 (225)[126]



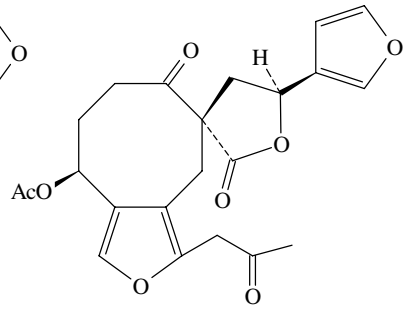
(40)

−3.14 (299), +4.26 (242)[126]



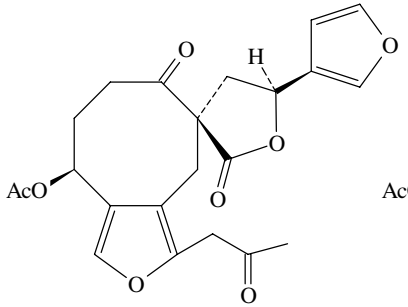
(41)

+1.74 (296), −0.65 (252)[126]



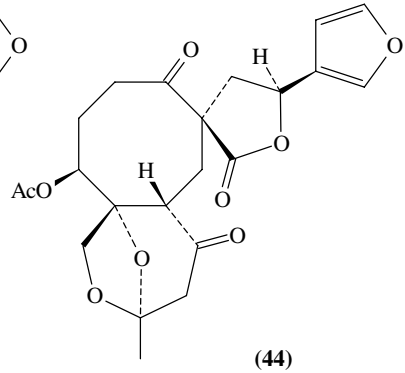
(42)

−2.20 (289), +2.30 (225)[126]



(43)

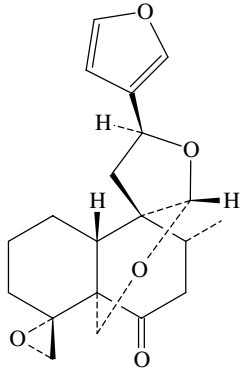
+2.29 (288), −3.77 (232)[126]



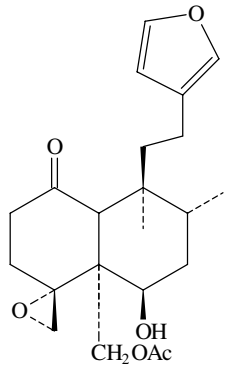
(44)

+0.18 (320), +0.22 (308),
+0.10 (300), −0.26 (276)[126]

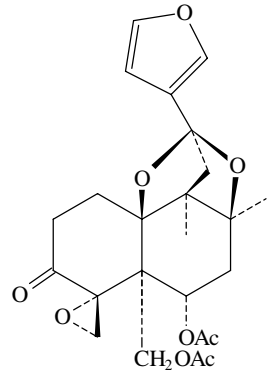
New diterpenoids belonging to *neo*-clerodane type **(39)**, some having an unusual *neo*-clerodane rearranged skeleton with eight-membered ketone ring (**40–44**), were recently described[126].



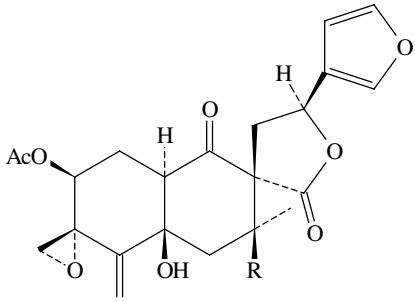
+0.93 (303)[127]

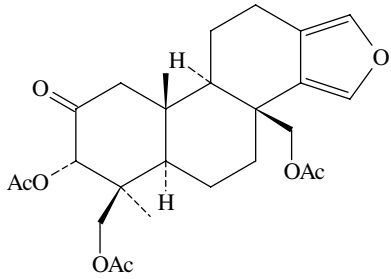


−2.00 (295)[127]

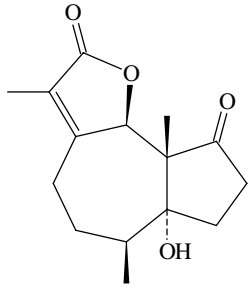


+1.98 (298)[128]

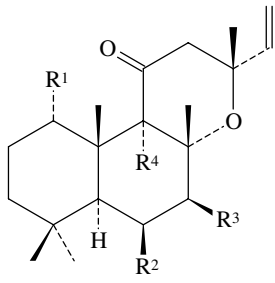


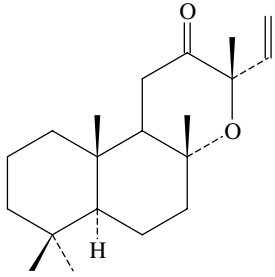


R = H sh−0.20 (312), −0.51 (293), −0.06(250) +1.95 (290)[130]
R = OH sh−0.23 (315), −0.57 (295), −0.08 (252)[129]



+0.58 (310), −0.10 (269)[131]





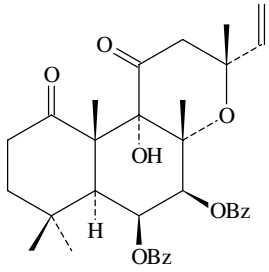
−0.15 (305)[132]

	R^1	R^2	R^3	R^4	
(45)	OH	OH	OAc	OH	−0.73(314)[132]
					−0.75(312)[133]
	H	OH	OAc	OH	−0.97(300)[132]
	H	OH	OAc	H	−1.94(303)[132]
					−2.71(312)[133]
	H	OAc	OH	OH	−1.67(305)[132]
	H	OAc	H	OH	−0.18(305)[132]
	H	H	H	OH	−0.27(305)[132]

The absolute stereochemistry of forskolin **(45)** and of the $C_{(6)}$ and $C_{(7)}$ dibenzoyl derivative **(46)** was unequivocally assigned by applying the exciton chirality method, thus placing R^3 (OAc in **45**) substituent at β-position[134].

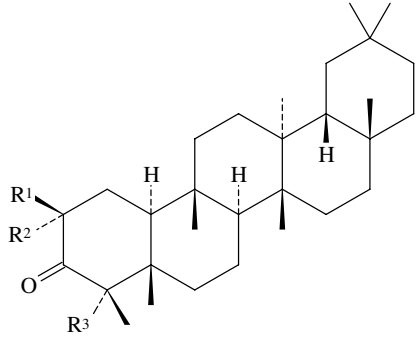
CD data for n → π^* Cotton effect of D:A-friedo-oleanones (**47–51**) have been interpreted on the basis of the octant rule, with the prediction that the D and E rings adopt a boat-boat conformation for **48** and **50**[138].

Intermediate-intensity positive n → π^* Cotton effects (all in dioxane) of the 3-oxotriterpenoids **54**, **57–59** were attributed to an A-ring chair-boat conformational equilibrium. The contribution of the boat form (like in 2β-methyl model derivatives **53** and **56**) was estimated to be *ca* 30%[140].

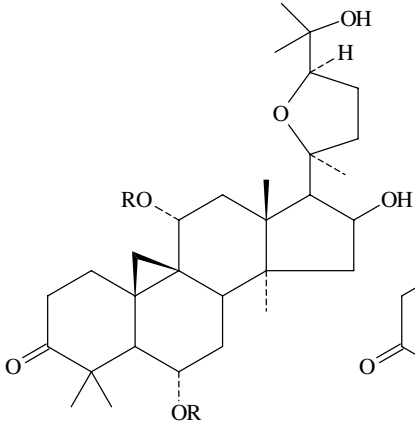


(46)

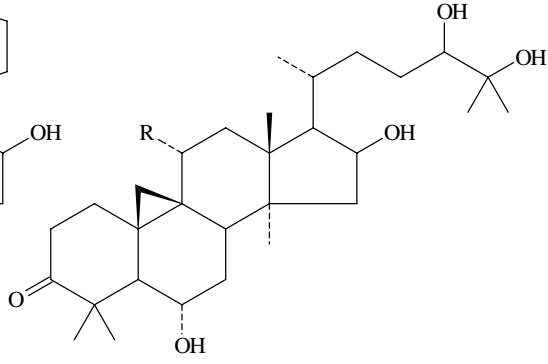
+15.18 (239), −2.42 (221)[134]



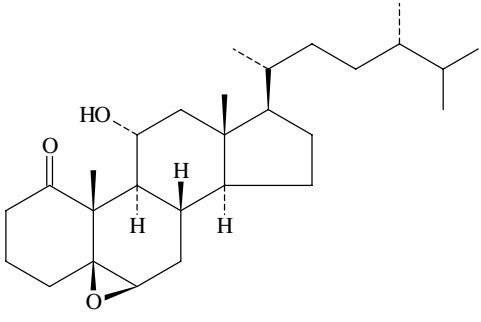
R^1	R^2	R^3	
H	H	H	−2.68(290)[135]
H	OAc	H	−1.47(300)[135]
OAc	H	H	−2.36(298)[135]
H	H	OAc	−3.17(300)[135]



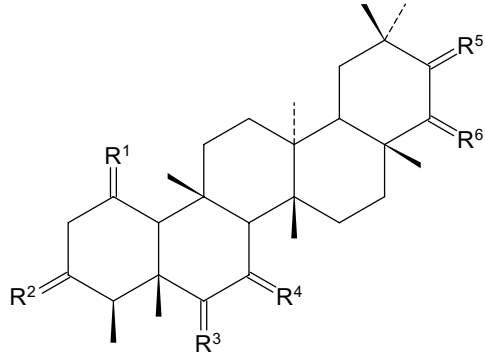
R = H +1.44 (287)
R = Ac +0.30 (280)[136]



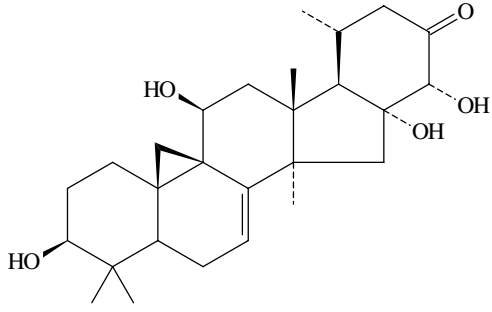
R = H +1.60 (287)
R = OH +1.03 (290)[136]



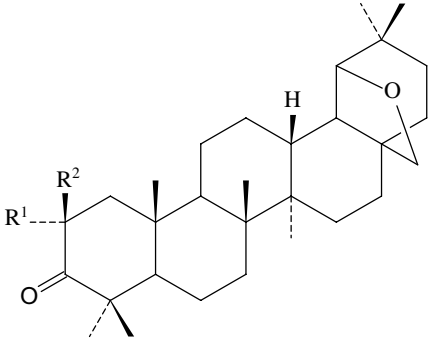
−2.18 (285)[137]



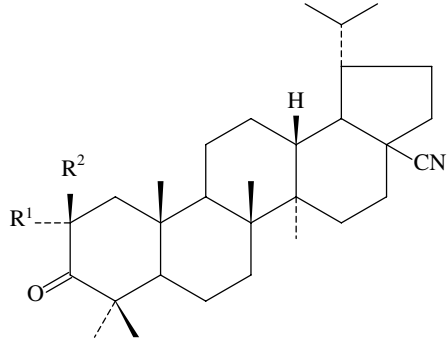
	R^1	R^2	R^3	R^4	R^5	R^6	$\Delta\varepsilon(CHCl_3)$	λ_{max}
(47)	O	H_2	H_2	H_2	H_2	H_2	−1.17	293
(48)	H_2	O	H_2	H_2	H_2	H_2	−3.46	294
(49)	H_2	H_2	O	H_2	H_2	H_2	+2.49	293
(50)	H_2	H_2	H_2	H_2	O	H_2	+8.98	295
(51)	H_2	H_2	H_2	H_2	H_2	O	+2.38	294



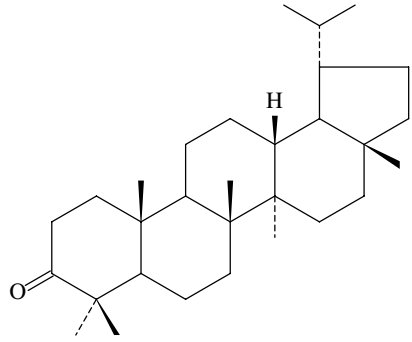
−5.36 (284), −14.51 (213)[139]



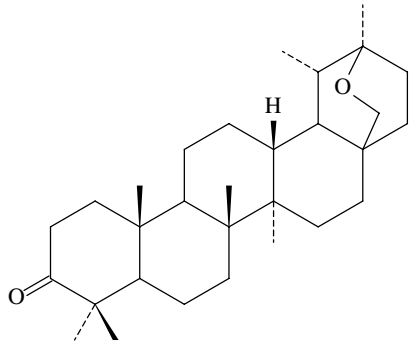
(52) $R^1 = CH_3$, $R^2 = H$ −0.60(293)
(53) $R^1 = H$, $R^2 = CH_3$ +3.65(294)
(54) $R^1 = R^2 = H$ +0.76(293)



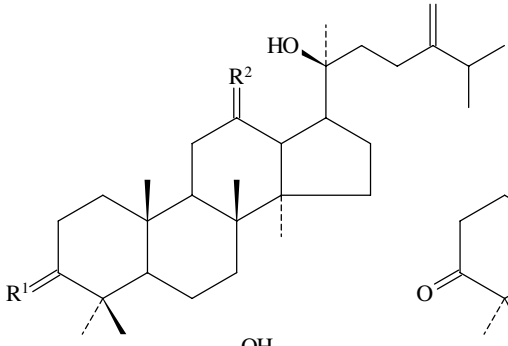
(55) $R^1 = CH_3$, $R^2 = H$ −0.71(292)
(56) $R^1 = H$, $R^2 = CH_3$ +3.85(291)
(57) $R^1 = R^2 = H$ +0.55(292)



(58) +0.63 (293)

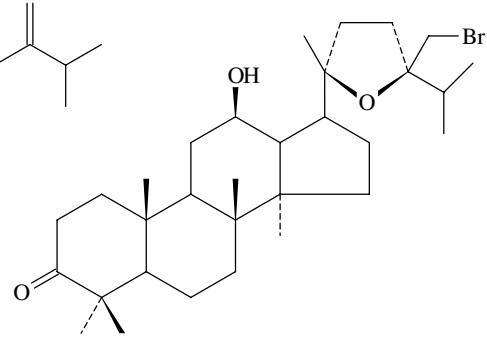


(59) +0.73 (293)

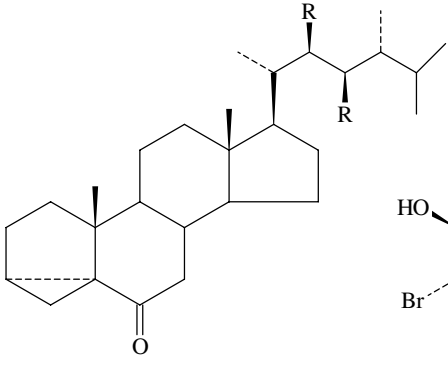


R^1 = O, R^2 =  +0.35 (293)[141]

R^1 = H,H, R^2 = O −0.60 (287)[141]



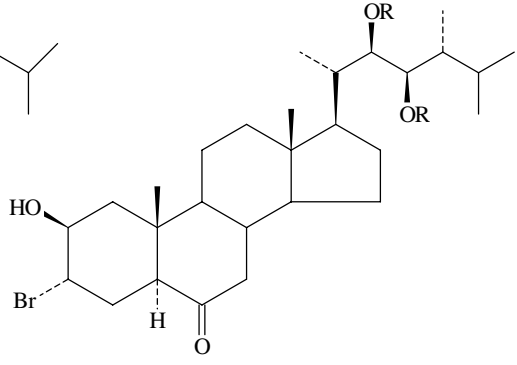
+0.37 (292)[141]



R = bond −2.70 (292)

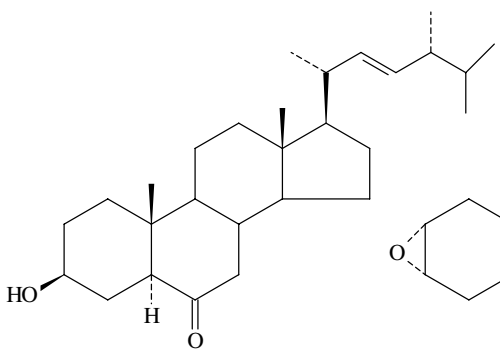
R = HO− −1.43 (300)

R = Me_2C(O−)(O−) −2.88 (292)[142]

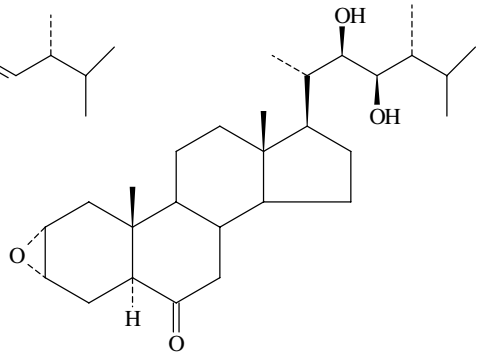


R = H −2.11 (292)

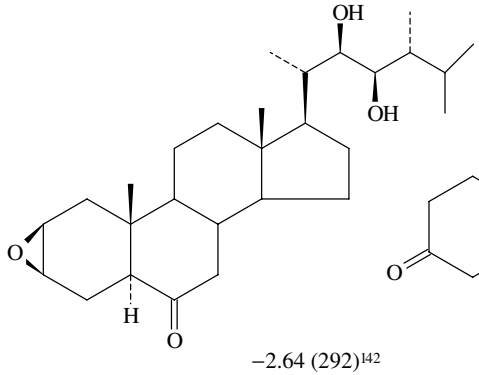
R = Me_2C  −1.95 (291)[142]



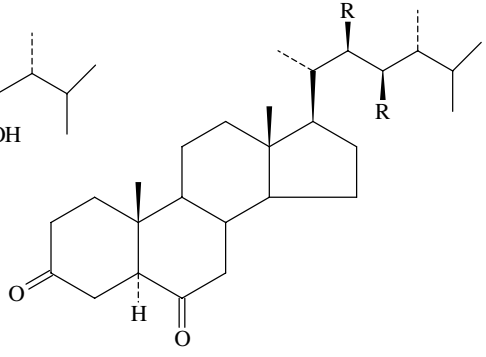
−2.04 (293)[142]



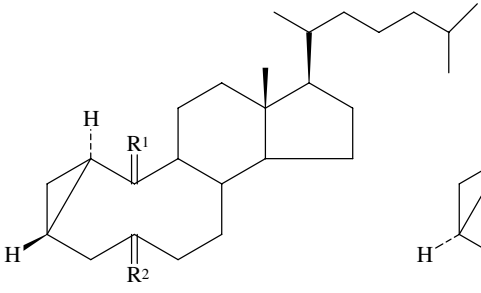
−1.79 (292)[142]

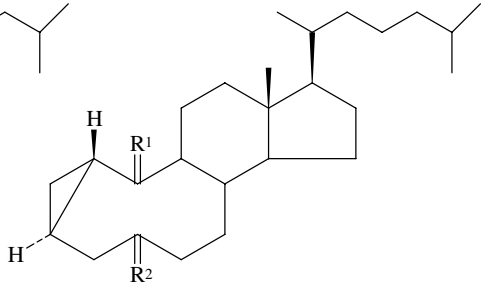


−2.64 (292)[142]



R = bond −2.95 (291)
R = HO− −3.51 (294)[142]

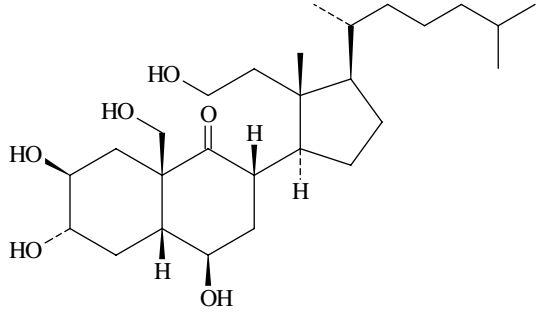




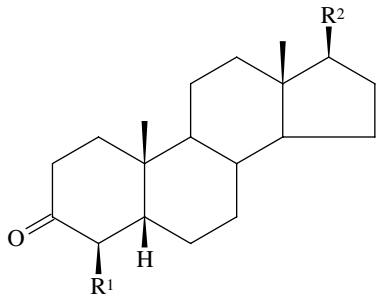
$R^1 = CH_2$, R^2 = O
+0.75 (317), +1.22 (307),
+1.22 (298), −6.10 (212)[143]
R^1 = O, R^2 = α-OAc,β-H
sh +0.07(315), sh +0.17 (302),
+0.28 (287), −1.30 (199)[143]
R^1 = O, R^2 = α-H,β-OAc
+0.06 (319), +0.01 (306),
+0.13 (278), −1.60 (201)[143]

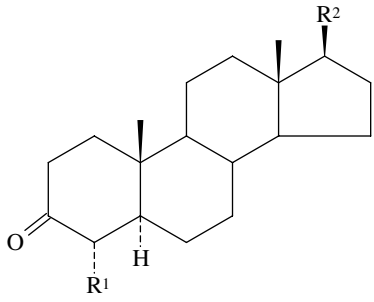
$R^1 = CH_2$, R^2 = O
+0.67 (319), +1.23 (309),
+1.11 (294), +11.0 (198)[143]
R^1 = O, R^2 = α-OAc,β-H
+2.72 (292), +0.80 (205)[143]

R^1 = O, R^2 = α-H,β-OAc
+2.23 (288)[143]



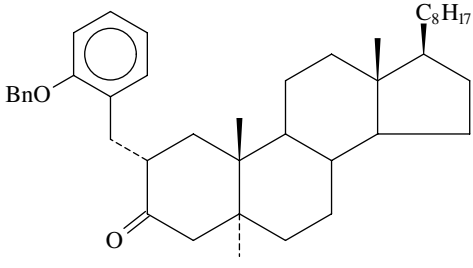
−2.48 (295)[144]



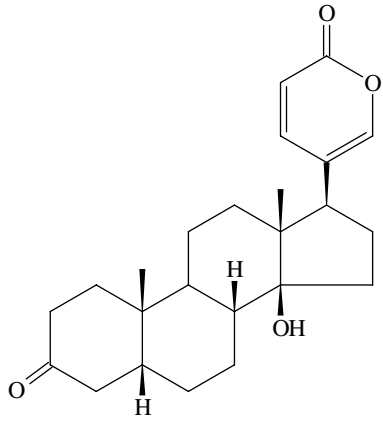


$R^2 = CH(CH_3)CH_2CH_2CO_2CH_3$

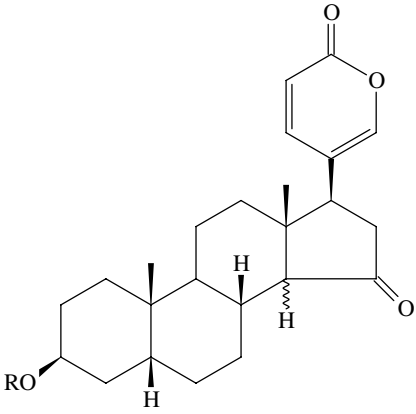
$R^1 = H$	−0.82 (292)	$R^1 = CH_3$	+1.27 (289)
$R^1 = CH_3$	−0.39 (285)	$R^1 = (CH_3)_2$	−0.27 (309)[145]
$R^1 = (CH_3)_2$	−0.94 (299)[145]		



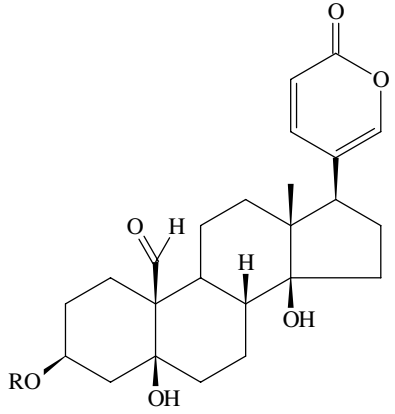
+1.01 (296)[146]



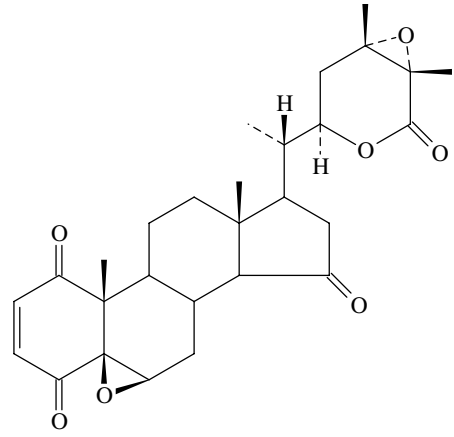
sh −1.3 (305), −1.55 (293),
−1.06 (247), +4.7 (212)[147]



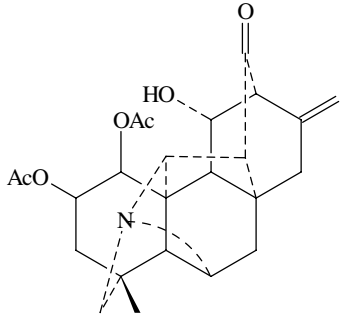
14β-H, R = H
−2.97 (313), −3.10 (304),
−0.39 (248), +2.2 (220)
R = Ac
−4.11 (308), +2.3 (223)
14α-H R = H sh +1.12(315),
+2.48(292), +4.2 (211)
R = Ac
sh +1.16 (316),
+2.80 (296), +3.7 (211)[147]



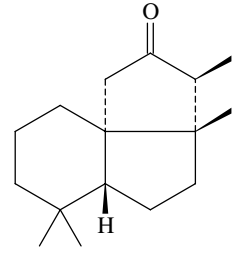
R = H −1.61 (294), sh −0.98 (257),
+5.9 (212)
R = Ac −1.67 (293), sh −1.16 (257),
+4.9 (212)[147]



+2.76 (294)[148]

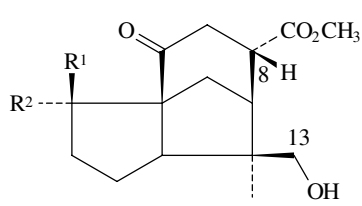


−3.91 (309), −1.29 (252)[149]

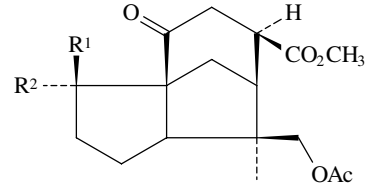


+4.57 (310)[150]

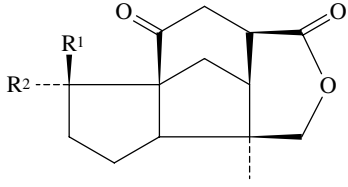
The CD spectra of six derivatives (**60–65**) of cedran-10-one devoid of a $C_{(8)}$–$C_{(13)}$ oxide bridge exhibit negative Cotton effects near 290 nm in accordance with the octant rule and a chair conformation of the six-membered ring[151]. The corresponding ketones with oxide bridge show a preference for a boat-like conformation and exhibit positive $n \rightarrow \pi^*$ Cotton effects[152].



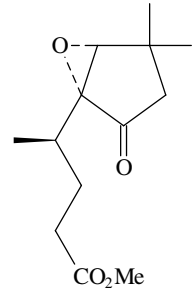
(60) $R^1 = CO_2CH_3$, $R^2 = H$
−1.97 (285)
(61) $R^1 = H$, $R^2 = CO_2CH_3$
−1.97 (287)



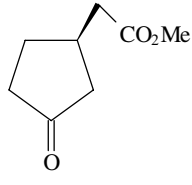
(62) $R^1 = CO_2CH_3$, $R^2 = H$
−2.33 (287)
(63) $R^1 = H$, $R^2 = CO_2CH_3$
−2.82 (288)



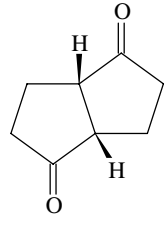
(64) $R^1 = CO_2CH_3$, $R^2 = H$
−2.06 (285)
(65) $R^1 = H$, $R^2 = CO_2CH_3$
−1.97 (287)



+2.29 (310)[113]

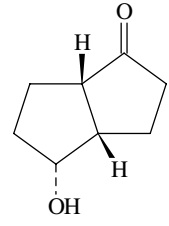


−1.82 (291)[153]



(66)

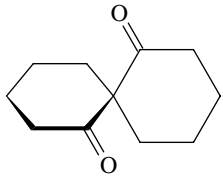
+4.67 (300)



(67)

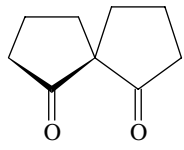
+1.40 (296)

The $n \rightarrow \pi^*$ CD of diketone **66** is 60% larger than twice the CD of the corresponding monoketone **67**, indicating interaction between the nonconjugated chromophores[154]. A similar enhancement was found in spiro[5.5]undecane-1,7-dione **(68)**[155].

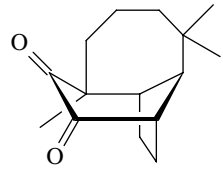


(−)-(*S*)-**(68)**

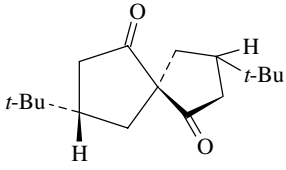
−5.35 (316)



+2.4 (315), −0.56 (287)
+6.8 (222)[156]

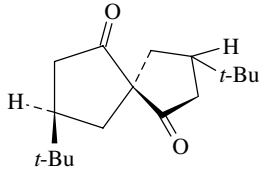


+0.82 (425), −0.77 (298)[156]



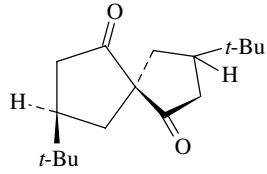
(−)-(3*S*,5*R*,8*S*)

+0.40 (329), −3.60 (292)[157,158]



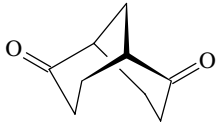
(+)-(3*R*,5*R*,8*S*)

+1.87 (311), −1.07 (285)[157,158]



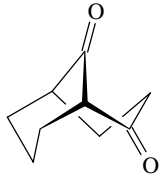
(+)-(3*R*,5*R*,8*R*)

+6.40 (298)[157,158]



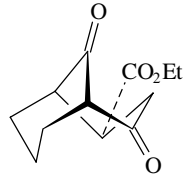
(−)-(1*R*,5*R*)-**(69)**

−1.19 (297)



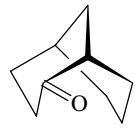
(−)-(1*S*,5*R*)-**(70)**

−0.42 (283), −1.25 (210)



(−)-(1*R*,2*S*,5*S*)-**(71)**

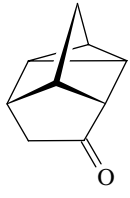
+0.83 (315), +0.78 (304)
−0.67 (278), −4.47 (209)



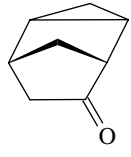
(+)-(1*S*,5*S*)-**(72)**

+0.15 (292)

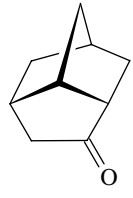
Chromatographic separation (50–60%ee) on triacetylcellulose and CD spectra of bicyclo[3.3.1]nonadiones **69–71** were described[159]. The enantiomer, (+)-(1*S*,5*S*)-**69** ($\Delta\varepsilon_{302}$ +3.20), and monoketone **72** were reported earlier[160].



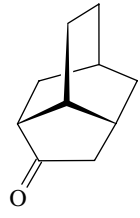
+4.24 (287)[161]



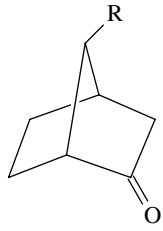
+6.36 (293)[162]



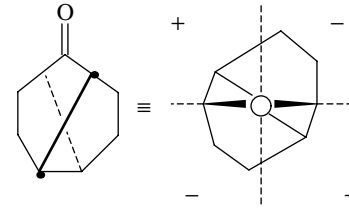
−1.85 (299)[161]



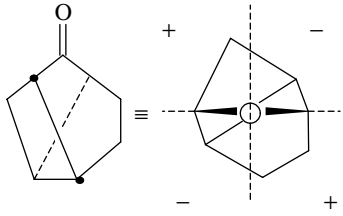
+2.70 (300)[163]



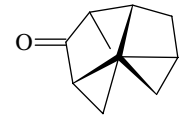
R = CO_2CH_3 +0.14(302)[164]
R = CO_2H +0.18(302)[164]
R = $CH_2CO_2CH_3$ +0.21(308)[164]



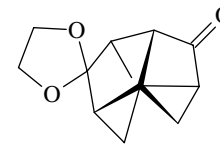
(−)-brexan-2-one
−2.23 (300)[164]



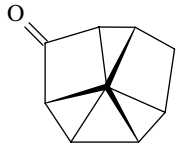
norbrexan-2-one
+1.21 (296)[164]



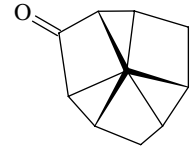
(−)-ditwist-brendan-5-one
+2.13 (293)[165]



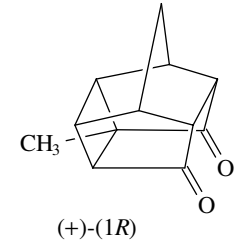
(−)-
+3.36 (292)[165]



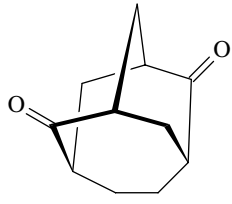
(+)-C_2-bishomo-cuban-6-one
+0.39 (302)[165]



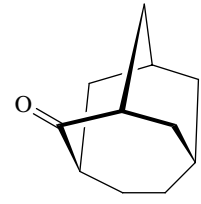
(+)-D_3-trishomo-cuban-4-one
−1.70 (293)[165]
(−)-enantiomer
+1.99 (293)[166]



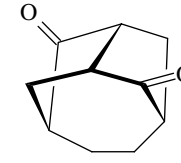
(+)-(1*R*)
−0.13 (298)[167]



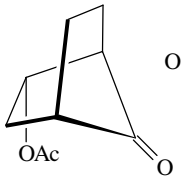
(+)-(1*S*,3*R*,6*R*,8*S*)
+0.40 (302)[168]



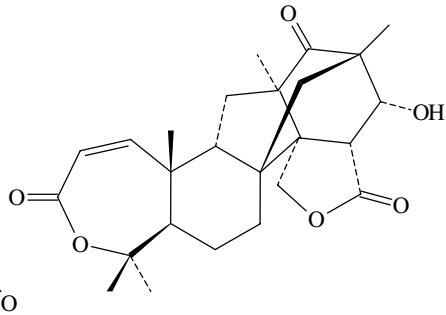
(+)
+0.05 (301)[168]



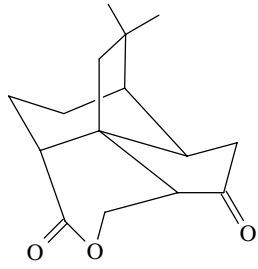
(−)-(1*S*,3*R*,5*S*,7*R*)
−2.19 (301)[169]



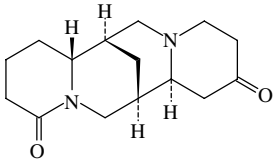
(−)-(1*R*,2*S*,4*S*)-
−0.17 (296)[170]



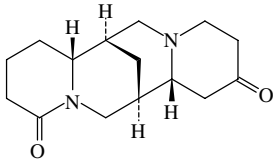
−1.76 (296)[171]



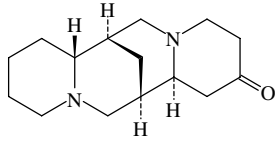
(−)-(**73**)
+2.68 (298), −3.33 (216)[172]



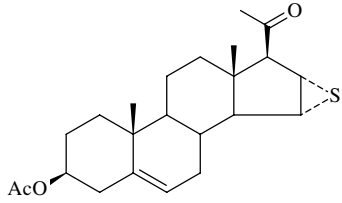
−2.19 (296), +3.4 (245),
−5.3 (214);
$HClO_4$ salt: −0.87(293),
+10.5(232),
−29.4 (204)[173]



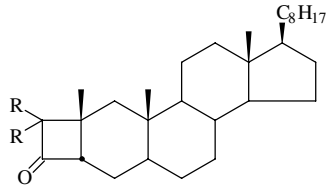
+0.94 (284), +9.5 (224),
−15.3 (202);
HCl salt +0.2 1(284),
+11.5 (225),
−22.9 (203)[173]



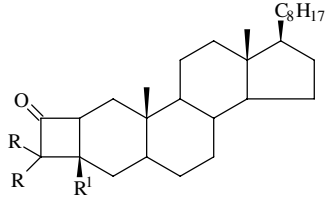
−1.93 (294), +0.55 (256),
$HClO_4$ salt −0.86 (292),
+1.0 (230)[173]



+5.70 (312), −3.87 (275),
+14.25 (220)[174]



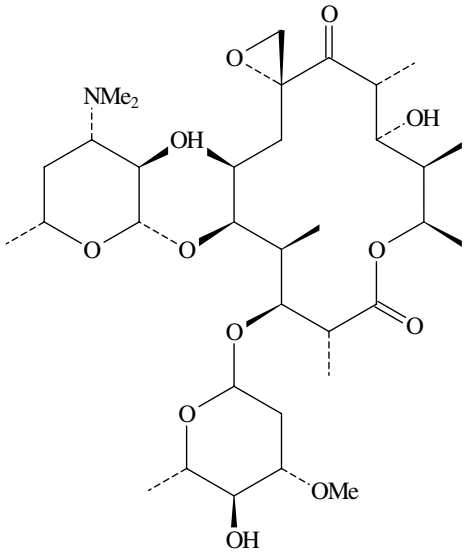
(74) R=H +0.67 (297)
(75) R=Cl +2.65 (313)[175]



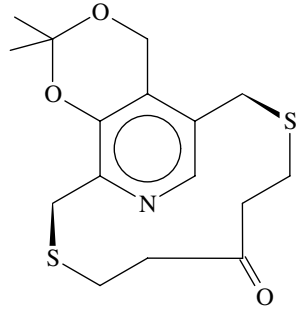
R^1=H, R=H −3.64 (299)
R^1=CH_3, R=H −4.58 (297)
(76) R^1=CH_3, R=Cl −2.10 (325)[175]

An empirical estimation of the sign and magnitude of $\Delta\varepsilon$ of (−)-quadrone **(73)** indicated that strain effects and octant-dissignate contributions of the pseudoaxial α-hydrogens dominate the CD spectrum of **73**[172].

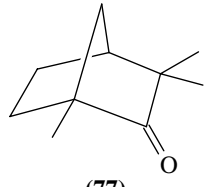
A half-boat conformation of the cyclobutanone ring (in an octant projection) of **74** correctly explains the observed positive CD near 300 nm. A pseudo-axial chlorine substituent in **75** substantially enhances the positive Cotton effect. The cyclobutanone ring in **76** is nearly planar, thus the effect of *exo* and *endo* chloro substituents is effectively cancelled while the remainder of cholestane skeleton resides in a negative octant[175].



−1.52 (298)[176]



+10.69 (297), −1.13 (257), +9.88 (236)[177]

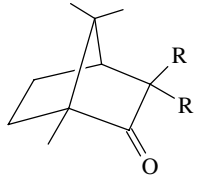


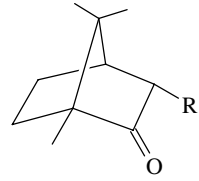
(77)

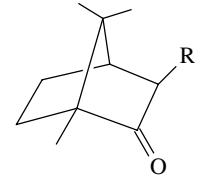
−0.68 (292) (C_6H_{12})
−0.96 (289) (EtOH)[178]

The CD of fenchone **(77)**, where the applicability of the octant rule is not obvious, and its sulfur and selenium analogues have been compared[178].

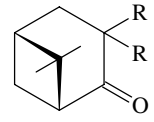
The CD of (+)-camphor and (−)-carvone was measured in gas phase in the temperature interval 100–200 °C[179]. Gas-phase and vacuum UV CD measurements of the same ketones using synchrotron radiation were reported[180]. (+)-3-Methylcyclohexanone was the first example in synchrotron radiation CD measurement in the range of 130–205 nm[181].



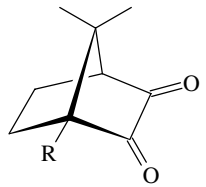


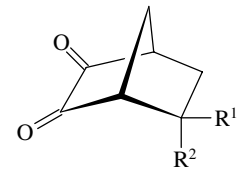


R = H	+1.68 (303)		
R = $PhCH_2$	+6.48 (306)	+4.20 (303)	+0.08 (300)[182]
R = 2-$ClC_6H_4CH_2$	+5.10 (302)	+1.63 (305)	
R = 4-$ClC_6H_4CH_2$	+4.17 (306)	+2.80 (302)	
R = 2, 6-$Cl_2C_6H_3CH_2$		+1.11 (303)[182]	
R = Me	+2.96 (298)		
R = Et	+3.19 (300)		
R = $-(CH_2)_4-$	+2.95 (298)[182]		



R = H	+1.91 (300)
R = CH_3	+2.26 (291)
R = $-(CH_2)_4-$	+1.82 (287)
R = $PhCH_2$	+1.00 (288)
R = 4-$ClC_6H_4CH_2$	+0.55 (285)[183]





(78) R = CH3 −0.45 (484), +0.29 (293)[156]
R = D +0.020 (487), +0.017 (465), +0.017 (303), +0.018 (286)[184, 185]

(79) R = CH_2OH −0.69 (483), +0.10 (294)[186] +0.21 (473)(solid state)[187]
R = F +0.05 (509), −0.42 (489), +0.24 (292)[186]
R = Cl −1.80 (488), +1.02 (280)[186]

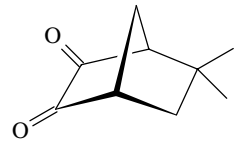
(80) R = Br −2.82 (477), +1.17 (280)[186]
R = CO_2Me −1.01 (477), +0.14 (268)[186]
R = NH_3^+ −0.61 (465), +0.62 (288)[186]

(81) R^1 = Me, R^2 = H −0.69 (506), +1.43 (283)[186]

(82) R^1 = H, R^2 = Me +0.30 (488), −0.12 (294)[186]

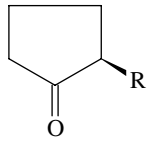
(83) $R^1 = R^2$ = Me, −0.41 (491), −0.56 (296)[186]

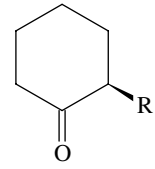
(84) $R^1 = CO_2Me$, R^2 = H −0.59 (484), +0.41 (293)[186]

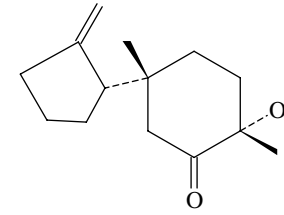


−0.39 (508), +0.09 (455), +0.82 (295)[186]

Crystallographic analysis of camphorquinone derivatives **79** and **80** showed that the α-diketone chromophore is planar[186]. The CD magnitude of model compounds similar to **79** varies with the polarizability of the vicinal substituent. An 'octant rule' with signs opposite to those for monoketones correctly predicts the long-wavelength CD sign in bicyclo[2.2.1]heptane-2,3-ones **81–84**[186]. The CD of camphorquinone **(78)** radical-anion has been also reported[188].

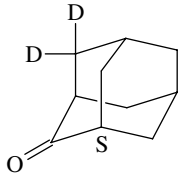






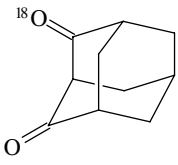
R = CH_3	−2.02 (310)[189]	R = CH_3	−0.30 (288)[191]	+0.25 (308)[192]
R = D	−0.042 (312), +0.013 (285)[189]	R = D	+0.029 (288)[190]	
R = D	−0.017 (299)[190]			

Schippers and Dekkers reported on the CD and circularly polarized fluorescence of 4,4-dideuterio-adamantan-2-one **(85)**[193]. The CD of **85** originates in transitions to a totally symmetric n $\rightarrow \pi^*$ excited state with double minimum potential in the C=O out-of-plane bending mode.

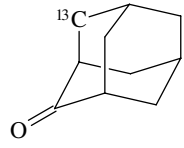


(85)

−0.08 (299)[193]

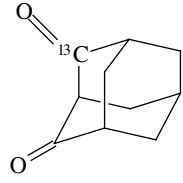


(86)



(87)

$-4.8.10^{-3}$ (296)[195]



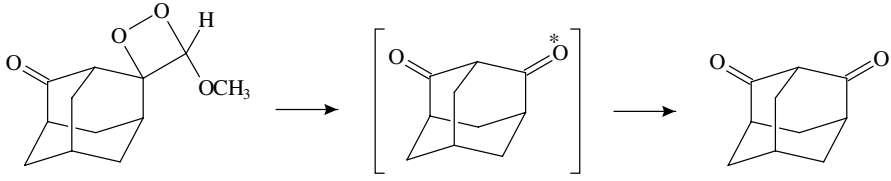
(88)

+0.087(321), −0.070(298), +0.033 (260)[195]

The synthesis and CD of (1*S*)-2,4-adamantanedione-4-^{18}O **(86)**, whose chirality is solely due to isotopic substitution, have been described. The CD of a sample with 69%ee and 65% isotopic purity consists of three major positive bands at 320, 307 and 297 nm with $\Delta\varepsilon \approx 0.08$[194].

The chirality of (1*S*)-2-adamantanone-4-^{13}C **(87)** and (1*S*)-2,4-adamantanedione-4-^{13}C **(88)** is solely due to ^{13}C substitution. Since the ^{13}C ring carbon of **87** is located in a positive octant, from the negative Cotton effect of **87**, it follows that ^{13}C makes a smaller contribution than ^{12}C. Diketone **88** exhibits three CD bonds with remarkably large amplitudes, which were attributed to different n $\rightarrow \pi^*$ transitions[195].

Meijer and Wynberg have reported preliminary results on the studies of compounds that are chiral solely in excited state[196]. This property can be found in *meso* compounds with two identical chromophores, one of them being selectively excited.



(89) **(90)**

The optically active 1,2-dioxetane of 2,4-adamantanedione **(89)** was synthesized. Thermal activation of **89** yielded chemiluminescence ($\lambda_{max} = 420$ nm characteristic of ketone fluorescence), pointing to intermediate **90** which is chiral only in its excited state due to the out-of-plane geometry of one of the two carbonyl groups. However, circular polarization of chemiluminescence measurement of **90** has not detected optical activity at the moment of emission. The authors have concluded that fast, relative to the lifetime of ketone singlet excited state, intramolecular n, π^* energy transfer caused racemization of **90**[196].

Using a qualitative approach and implementation of empirical rules, a computer package program which combines computer graphics and molecular mechanics with rule-based correlations was developed to assist the prediction of CD properties from the three-dimensional structure of a molecule[197].

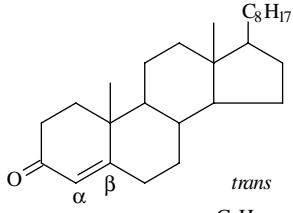
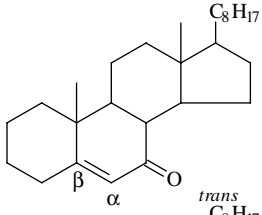
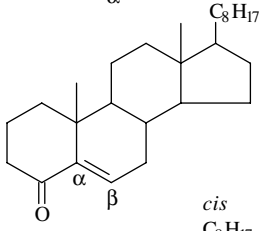
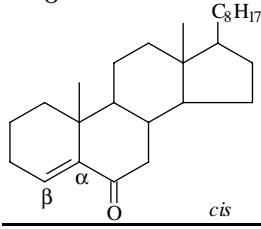
IV. UNSATURATED KETONES

When two carbonyl chromophores or a carbonyl and a carbon–carbon double-bond chromophore are brought into close proximity, as in α,β- and β,γ-unsaturated ketones, an inherently dissymmetric extended chromophore is created if the two chromophores are dissymmetrically disposed[19]. The coupling is expressed through coulombic mixing of the local states of the separated chromophores and through interchromophoric charge transfer states. The relative importance of charge transfer diminishes with increasing distance between the chromophores. Consequently, whereas coulombic and charge transfer interactions are both important for coupling between C=O and C=C chromophores in α,β-unsaturated ketones, charge transfer is generally of small importance in β, γ, δ, etc. unsaturated ketones. For both theoretical and practical reasons, the octant rule does not apply to dissymmetric α,β- and β,γ-unsaturated ketones. Their n $\rightarrow \pi^*$ Cotton effects have been explained on the basis of different chirality rules.

A. α,β-Unsaturation

Gawroński has published a comprehensive review of α,β-unsaturated ketones[198]. α,β-Unsaturated ketones are often non-coplanar and thus dissymmetric. For such cases, a helicity rule was proposed to correlate the sign of the $C_\beta{=}C_\alpha{-}C{=}O$ C–C torsion angle with the n $\rightarrow \pi^*$ Cotton effect. For *cis*-enones a negative torsion angle correlates with a negative Cotton effect; for *trans*-enones it correlates with a positive Cotton effect[198]. A few examples of applications of this helicity rule to the n $\rightarrow \pi^*$ Cotton effects of *trans* and *cis* steroid ketones may be found in Table 6. In principle, a better correlation between CD and stereochemistry might be found for the $\pi \rightarrow \pi^*$ type transitions of α,β-unsaturated ketones[19]; however, Gawroński analyzed three bands in the 185–260 nm ($\pi \rightarrow \pi^*$) region and found that the Cotton effects are variously influenced by the presence of axial allylic substituents, α' or β' axial alkyl groups as well as the enone dissymmetry[198]. For the special cases of *planar* α,β-unsaturated ketones, Snatzke[199] proposed a sector rule for the n $\rightarrow \pi^*$ transition with a sign pattern opposite to that of the octant rule.

TABLE 6. The correlation of predicted and observed n → π* Cotton effects with the sign of the α,β-unsaturated ketone torsion angle[a]

α,β-Unsaturated steroid ketone	$C_\beta{=}C_\alpha{-}C{=}O$ torsion angle sign	Predicted n → π* Cotton effect	Observed n → π* Cotton effect
 *trans*	positive	negative	$\Delta\varepsilon = -1.31$
 *trans*	negative	positive	$\Delta\varepsilon = +1.35$
 *cis*	positive	positive	$\Delta\varepsilon = +1.43$
 *cis*	negative	negative	$\Delta\varepsilon = -1.2$

[a]Data from Reference 198.

B. β,γ-Unsaturation and the Extended Octant Rule

A chirality rule, called the extended octant rule, was proposed long ago to correlate the sign of the n → π* Cotton effect with absolute stereochemistry of β,γ-enones[19,200]. Although not really an octant rule, this chirality rule states that when the intersection of the two planes containing the C=O and C=C chromophores has a dihedral angle (ϕ, Figure 13) whose absolute value is greater than 90°, a negative Cotton effect is predicted for negative ϕ and a positive Cotton effect is predicted for positive ϕ[19,199]. Here, the dihedral angle ϕ is defined as the C−C−C−C torsion angle of $O{=}C{-}C_\alpha{-}C_\beta{=}C_\gamma$. The rule was extended to other geometries of β,γ-unsaturated ketones, including smaller and

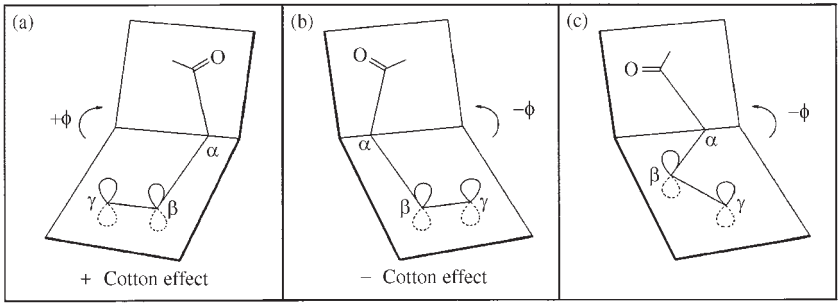


FIGURE 13. Extended octant rule applied to enantiomeric dissymmetric orientations of β,γ-unsaturated ketone chromophores. When the absolute of the dihedral angle ϕ is $>90^\circ$, a positive Cotton effect is predicted for the geometry of (a) and a negative for (b). In a transoid arrangement of β,γ-unsaturated ketone (c) the $\Delta\varepsilon$ values are often quite small (References 200 and 201)

larger angles about the α-carbon that encompass a range of cisoid (Figure 13a and b) and transoid (Figure 13c) dissymmetric orientations, all with dihedral angles, $|\phi| > 90^\circ$. This chirality rule may fail when $\Delta\varepsilon$ values are not large, when ordinary octant perturbations are of the same magnitude as those from the coupling of locally excited C=O n $\rightarrow \pi^*$ and C=C $\pi \rightarrow \pi^*$ transitions[201].

More recently, Schippers and Dekkers[202] correlated the cosine of the angle between the O=C and C_β=C_γ bonds ($\cos\xi$), defined in Table 7, and sign of the n $\rightarrow \pi^*$ Cotton effect. When ξ is less than 90° but greater than -90° (or when $\cos\xi$ is positive), a positive Cotton effect is predicted. When ξ is less than 270° but greater than 90° (or when $\cos\xi$ is negative), a negative Cotton effect is predicted. These workers formulated the new chirality rule for β,γ-unsaturated ketones: $\cos\theta = -(\text{sign } x \cdot y) \cdot (\cos\xi)$. Here, θ is the angle between the electric and magnetic transition moments of the erstwhile n $\rightarrow \pi^*$

TABLE 7. Relationship between $\cos\theta$, $\cos\xi$ and the n $\rightarrow \pi^*$ CD Cotton effects of β,γ-unsaturated ketones. ξ is the angle of intersection of the Z and Z' axes of the C=O and C=C bonds, respectively. Angle θ is the angle between the C=O axis and $\vec{r}$, the electric dipole moment associated with the n $\rightarrow \pi^*$ transition

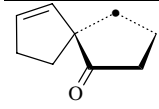
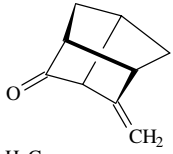
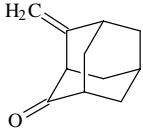
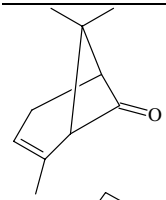
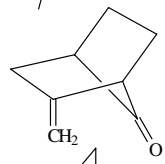
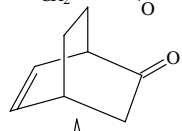
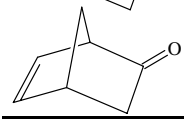
Ketone	ξ^a	$\cos\xi$	Obs. $\Delta\varepsilon$	θ^a	$\cos\theta$
	105°	−0.26	−3.14	101°	−0.19
	90°	0	+5.4	82°	+0.14
	90°	0	+2.55	83°	+0.13

TABLE 7. (*continued*)

Ketone	ξ^a	$\cos\xi$	Obs. $\Delta\varepsilon$	θ^a	$\cos\theta$
	75°	+0.26	+4.71	76°	+0.24
	70°	+0.34	+5.69	74°	+0.28
	60°	+0.50	+12.0	55°	+0.57
	55°	+0.57	+18.8	48°	+0.67

[a]See Figure 14.

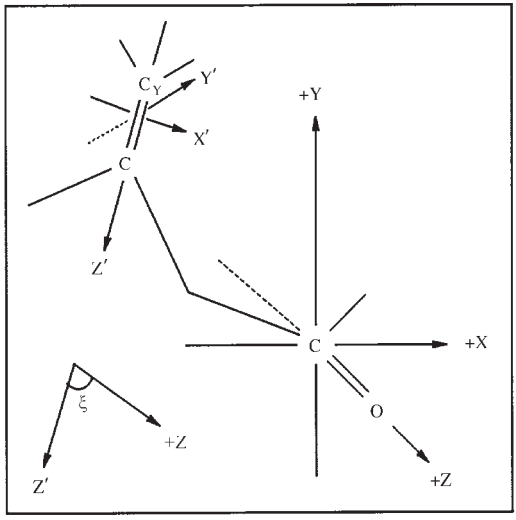
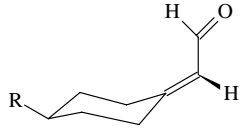


FIGURE 14. Chirality rule reference frame for C=O (X, Y, Z) and C=C (X', Y', Z') chromophores of β,γ-unsaturated ketones. The C_α atom connecting the chromophores lies in the XZ plane; the Y' axis is perpendicular to the plane of the C=C group. ξ denotes the angle between Z and Z' axes. The chirality rule is given by: $\cos\theta = -(\text{sign } XY)\cdot(\cos\xi)$, where X and Y are the Cartesian coordinates of C_β and θ is the angle between the C=O axis and $\vec{r}$ (the electric dipole moment associated with the transition). Applications are shown in Table 7

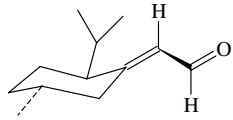
transition, x and y are the Cartesian coordinates of C_β, and ξ is the angle of intersection of axes drawn along and through the C=O and C=C bonds (Figure 14). The correlation for the limited number of examples of Table 7 is quite good, but only one example has been reported with a negative value of $\cos\xi$. Additional experimental support of the chirality rule has been published recently[203], and a detailed theoretical treatment of 2-norbornenone supported the concept but not all of the assumptions, while clearly showing the importance of extrachromophoric perturbers[204]. Recently, a theoretical analysis was presented for β,γ-unsaturated ketones based on coupling between $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions[205].

V. COMPILATION OF UNSATURATED KETONE AND ALDEHYDE CD

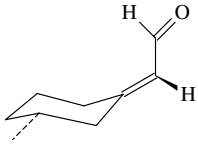
Walborsky and coworkers[206] have reported the CD of series conjugated cyclohexylidene aldehydes and ketones. These compounds served as additional examples supporting the planar diene rule for CD $\pi \rightarrow \pi^*$ transition[208].



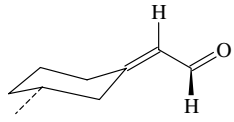
R = CH_3 −0.61 (347), +2.08 (230)
R = $C(CH_3)_3$ −0.72 (347), +2.65 (231)[206]



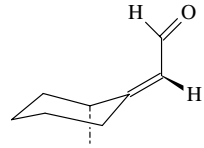
+0.44 (348), −2.70 (236)[206]



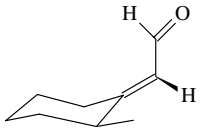
−0.70 (347), +0.82 (230)[206]



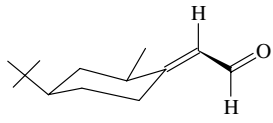
+0.62 (348), −4.55 (232)[206]



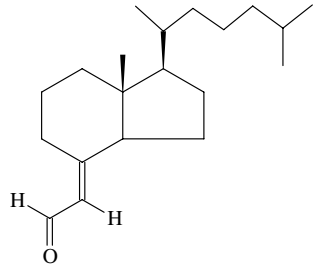
−0.87 (348), +4.93 (323)[206]



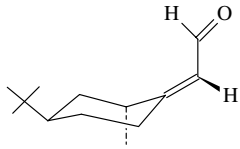
−0.65 (346), +3.58 (231)[206]



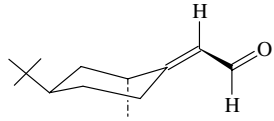
+0.58 (347), −3.36 (232)[206]



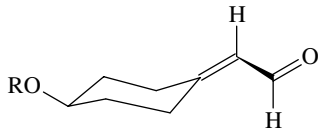
+1.74 (347), −5.76 (236)[207]



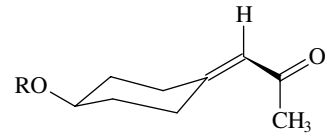
−0.80 (347), +3.48 (233)[206]



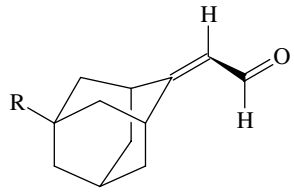
+0.47 (347), −2.16 (233)[206]



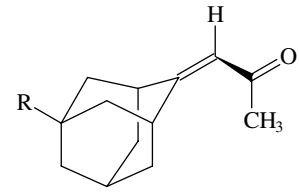
R = H +0.29 (346), −1.00 (230)
R = TBDMS +0.57 (347), −3.30 (235)[209]



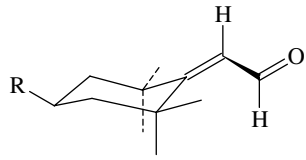
R = H −0.05 (337), +2.30 (238)
R = TBDMS −0.07 (345), +0.90 (240)[209]



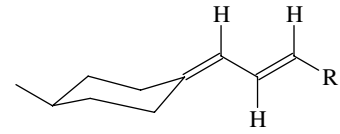
R = OH +0.78 (345), −4.2 (231)
R = CH_3 +0.13 (345), −1.9 (235)[209]



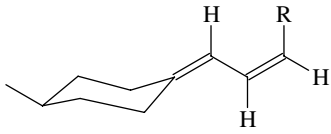
R = OH −0.12 (337), +4.30 (239)
R = CH_3 −0.03 (332), −0.80 (240)[209]



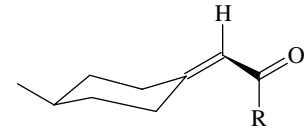
R = OH −1.09 (357), +16.39 (242)
R = CH_3 −0.94 (358), +12.45 (244)[210]



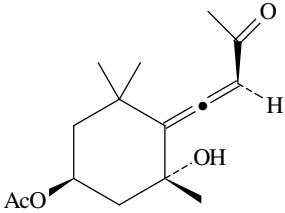
R = CHO −0.22 (350), +0.30 (277)
R = $COCH_3$ −0.04 (347), +1.20 (287)
R = COtBu −0.03 (350), +1.60 (287)[211]



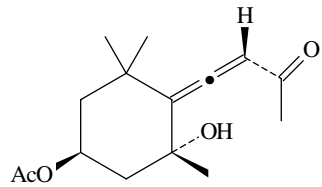
R = CHO −0.40 (289)
R = $COCH_3$ −1.40 (290)[211]



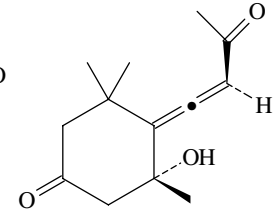
R = CH_3 −0.05(363), +2.9 (235)
R = $C(CH_3)_3$ −0.03 (367), +2.7(237)[211]



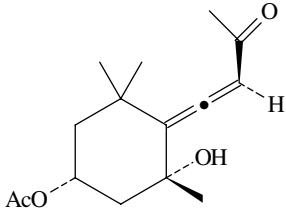
+0.06 (325), −5.4 (250),
+6.6 (225) [212]



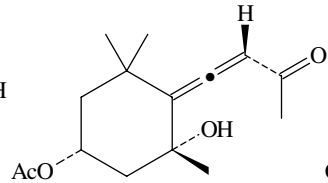
+0.3 (330), −4.1 (253),
+7.1 (227)[212,213]



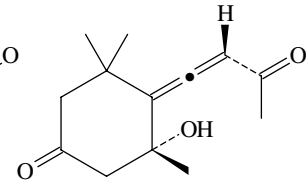
+2.3 (296), −6.6 (253),
+7.8 (229)[212]



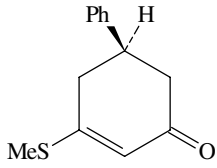
−0.3 (330), −1.5 (251), +1.2 (231)[2 12]



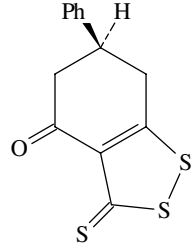
−0.3 (321), +0.2 (297), +2.9 (235)[2 12]



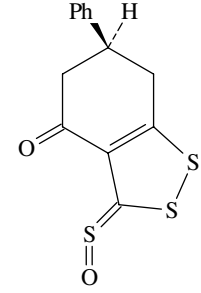
+2.2 (296), −3.0 (253), +5.0 (230)[2 12]



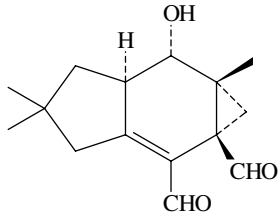
−1.73 (329), +2.55 (285), +5.00 (211)[2 14]



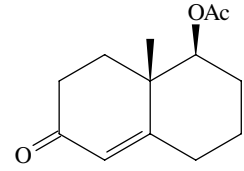
+0.26 (502), −0.76 (400), +2.83 (317), +5.48 (272), −3.75 (235)[2 15]



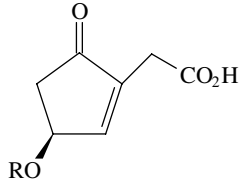
+0.96 (464), −0.71 (390), −1.04 (360), −1.40 (275), +1.48 (247)[2 15]



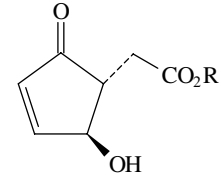
+0.47 (367), +1.42 (338), −10.17 (285), +5.45 (239)[2 16]



−0.8 (322), +7.4(236)[2 17]

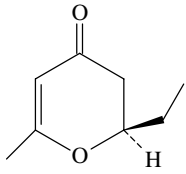


R = H +2.44 (318), −16.46 (224)
R = PhCO +1.89 (320), −28.86 (230)[2 18]



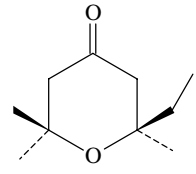
R = H −2.35 (320), +18.54 (221)
R = Me −1.41 (312), +9.30 (222)[2 18]

The absolute configuration of a new sex pheromone (hepialone, **91**) was determined[219] on the basis of a rule for (nearly) planar α,β-enones[198]. The (*R*) configuration of **91** is supported also by the negative n $\rightarrow \pi^*$ CD Cotton effect of the saturated ketone **92** (obtained by β-methylation of **91**) where the equatorial β'-ethyl group has larger contribution than equatorial β-methyl group and β-axial methyl group has small or dissignate contribution.



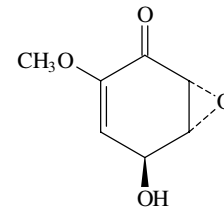
(91)

+0.89 (312), +2.15 (261)[219]

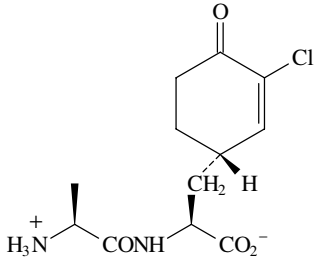


(92)

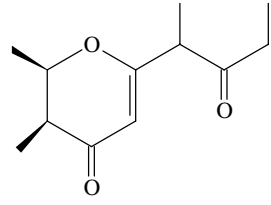
(–) (300)[219]



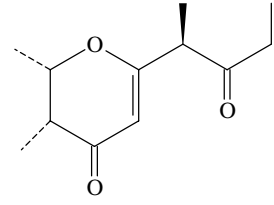
+2.88 (330), +1.52 (300),
+7.52 (270), −2.88 (220)[220]



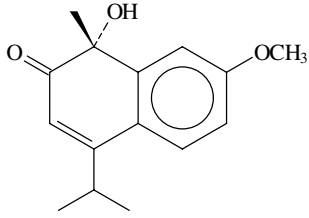
−0.45 (312),
+7.03 (245)[221,222]



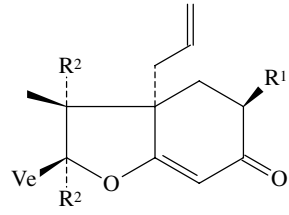
+0.49 (359), +1.03 (344),
−0.23 (285), +0.69 (260)[223]



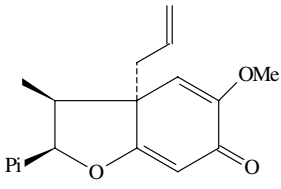
−0.42 (360), −0.87 (344),
−13.0 (287), +9.1 (260)[223]



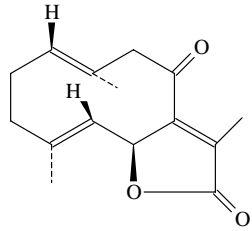
+3.09 (371), −3.70 (329),
+1.58 (247), −1.06 (226)[224]



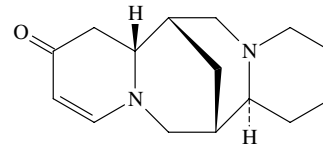
R^1	R^2	Ve = veratryl
OMe	H	+1.68 (301), −3.47 (267), −4.21 (258)
H	H	+2.23 (301), −3.53 (267), −4.18 (258)
OMe	bond	+2.71 (301)[225]



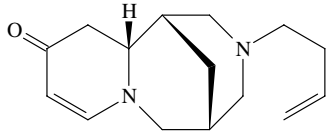
Pi = piperonyl
+4.12 (334), +18.03 (298),
−3.61 (277), −6.18 (258)[225]



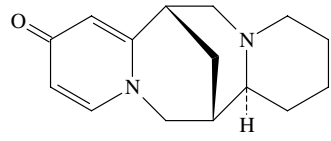
+0.69 (308), −0.46 (257),
−0.58 (238)[226]



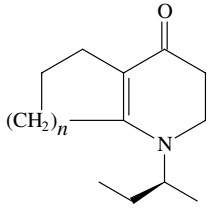
−4.5 (337), +1.1 (298)
Perchlorate
−4.6 (327), +2.5 (294)[227]



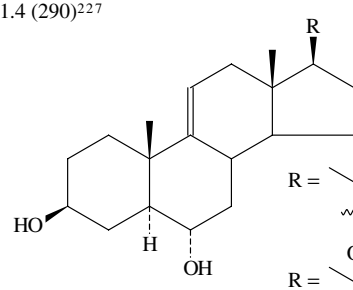
−6.3 (335), +1.0 (290)
Perchlorate
−7.8 (328), +1.4 (290)[227]

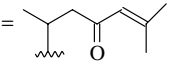


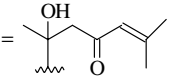
−2.6 (261)[227]

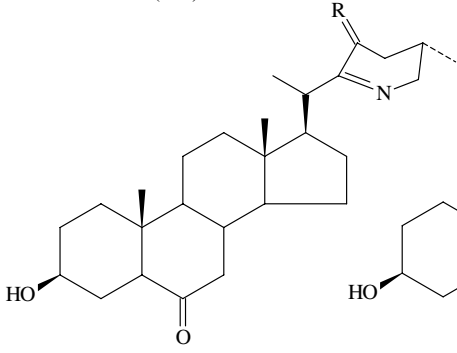


n = 1 +3.33 (335)
n = 2 +3.19 (336)
n = 3 +2.71 (337)[228]

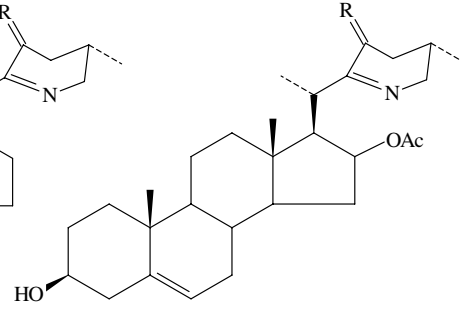


R =  −0.49 (325)[229]

R =  −0.32 (326)[229]

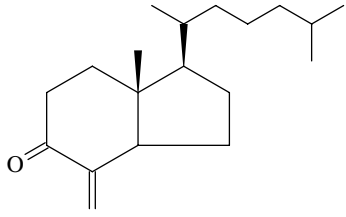


R = H,H −1.74 (292), +3.55 (236)
R = O −0.11 (385), sh −1.83 (291), −2.32 (285), −1.97 (220)[230]



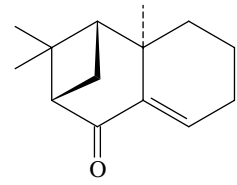
R = H,H +1.96 (239), −0.56 (212)
R = O −0.21 (408), −0.61 (280), sh +3.09 (215), +4.01 (200)[230]

A series of steroidal and related cisoid α,β-enones was synthesized, and their CD was investigated[231,232], adding new examples of enones containing γ-transoid or γ-cisoid allylic substituents. The relation between structure and observed Cotton effects was discussed in terms of previously published rules.



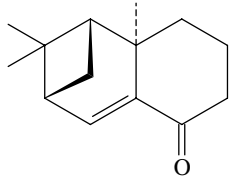
(93)

−0.10 (352), +0.23 (301),
−3.25 (235), +5.30 (204)



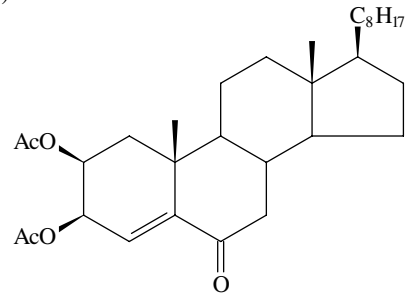
(94)

−0.55 (321), −4.01 (234)



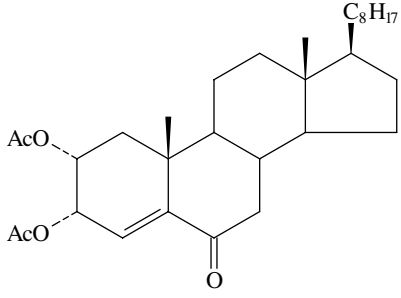
(95)

+0.73 (323), −2.23 (226)



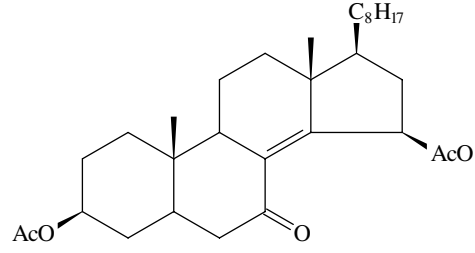
(96)

−1.67 (320), −6.19 (232),
+11.0 (198)



(97)

−2.07 (325), +11.30 (225),
+11.1 (200)

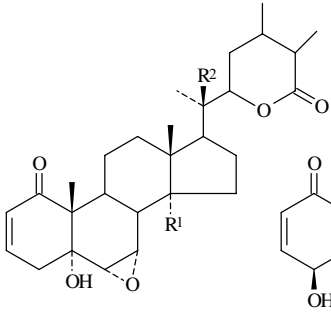


(98)

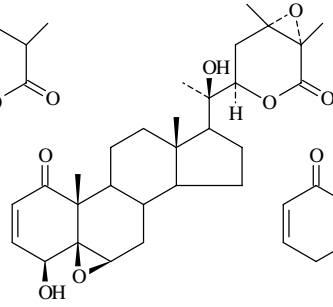
−1.05 (332), −3.24 (248),
+1.50 (218), +11.30 (193)

All cisoid α,β-enones studied, including compounds **93–98**, obey the helicity rule for $n \rightarrow \pi^*$ transition Cotton effects[49,233,234]. The sign of the 222–272 nm $\pi \rightarrow \pi^*$ band is also in accord with the helicity rule for unsubstituted enones, while the polar C−O

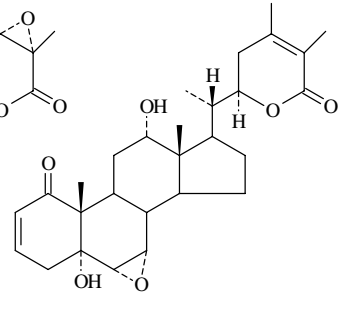
allylic bond strongly influences the $\pi \rightarrow \pi^*$ band[235]. However, compounds **93** and **94** have opposite signs to those predicted by the helicity rules. Substituents at the γ-cisoid position (as in **98**) also show a remarkable contribution to the first $\pi \rightarrow \pi^*$ transition. The shorter-wavelength $\pi \rightarrow \pi^*$ transition (200–220 nm) exhibited a sign opposite to that of the $n \rightarrow \pi^*$ transition[231].



R1 = OH, R2 = OH
–1.96 (337), –1.70 (216)
R1 = OH, R2 = H
–2.04 (338), +0.30 (240),
–1.53 (215)
R1 = H, R2 = OH
–2.39 (338), +0.29 (241),
–1.56 (209)[236]

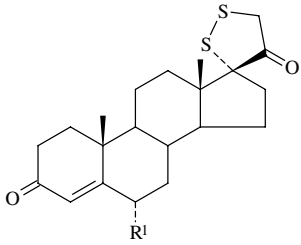


–1.76 (345), –0.23 (290)
–1.95 (239)[236]

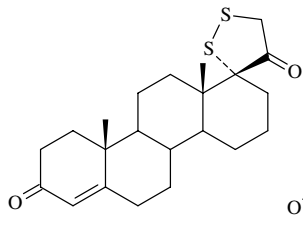


–1.90 (337), +4.00 (253)[236]

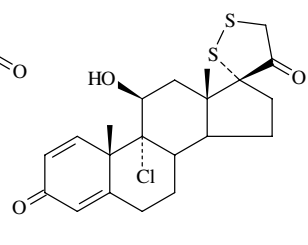
Beecham and Collins[237] analyzed the CD of 22 steroidal 4-en-3-ones. Based on similarities of Cotton effect amplitudes, ratios of heights of 0-0/0-2 lines and X-ray structural data, they concluded that the chromophore conformation is identical within the series possessing 17α-, 17β- and 6α-substituents. A low-intensity, spin-forbidden singlet–triplet $n \rightarrow \pi^*$ transition might be the origin of a weak positive Cotton effect at 384 nm ($\Delta\varepsilon$ +0.001 to +0.020) observed in addition to the main vibronically-structured negative Cotton effect ($\Delta\varepsilon$ −1.20 to −1.50) for 0-2 line at 339 nm. In three of the 6β-substituted compounds, this pattern was modified by a positive CD with the same vibrational progression, thus giving an overall bisignate shape: e.g. $\Delta\varepsilon_{339}$ +0.51, $\Delta\varepsilon_{297}$ −0.13 for 6β-methylcholest-4-en-3-one[237].



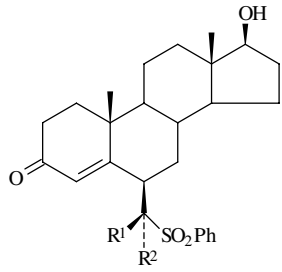
R1 = H +0.20 (375), –4.83 (317),
–3.64 (307), +2.74 (282)[238,239]
R1 = CH_3 +0.22 (376), –4.45 (318),
–3.33 (307), +2.46 (282)[238]



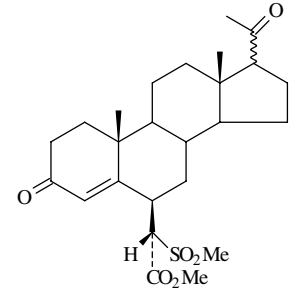
–1.73 (347), +2.13 (317),
+2.13 (308), +11.0 (219)[238,239]



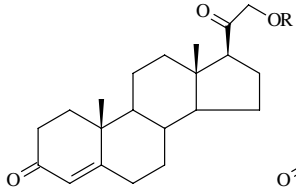
+1.03 (349), –3.95 (316),
–3.54 (306), +7.12 (257)[240]



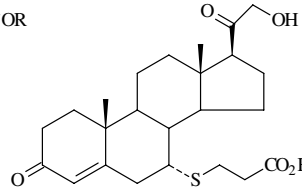
$R^1 = CO_2Me$, $R^2 = H$
+0.15 (378), −0.45 (326), −3.81(240), +18.2 (219)
$R^1 = H$, $R^2 = CO_2Me$
+0.59 (360), −0.74 (265), −2.08 (238), +13.4 (220)[241]



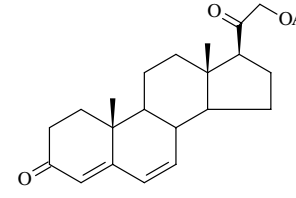
17β–
+0.52 (360), +2.86 (294), +12.5 (220)
17α–
+0.53 (359), −1.99 (292), +4.5 (223)[241]



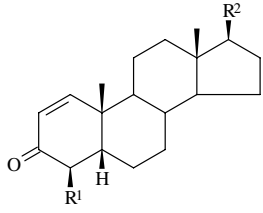
R=H −1.27 (324), +4.4 (286), +8.8 (232)
R=Ac −1.16 (324), +4.1(286), +11.1(233)[242]

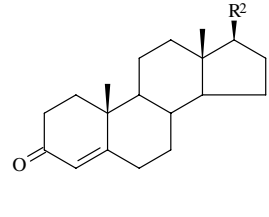


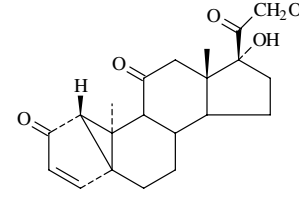
−0.49 (324), +3.7 (286), +2.3 (234)[242]



+6.0 (342)[242]







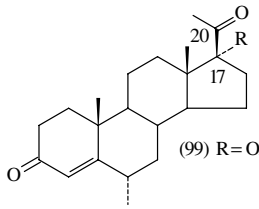
$R^2 = CH(CH_3)CH_2CH_2CO_2CH_3$

$R^1 = H$ +18.5 (231)
$R^1 = CH_3$ +17.4 (236)
$R^1 = (CH_3)_2$ +13.1 (232)[145]

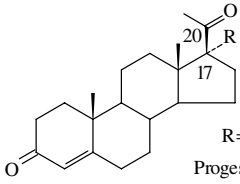
+8.7 (224)[145]

R=H −4.71(343), +11.41(278), −11.11(226)
R=Ac −5.21(343), +12.22 (277), −11.71(225)[243]

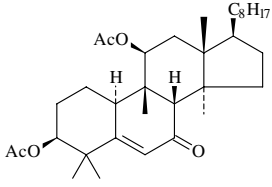
Caution in using a solid state conformation to explain CD data in solution was indicated in the work of Kirk and colleagues[224]. They found that the CD of 17α-acetoxy-6α-methyl progesterone (**99**) in solution did not deviate from that of analogous compounds, while the CD of crystalline samples of **99** in SE30 (silicone polymer) or KBr showed an inverted sign of the n $\rightarrow$ π^* band. Exhaustive NOE experiments supported the CD data, concluding that the A ring of **99** in solution is in a normal (1α,2β) half-chair conformation — while X-ray studies had shown that **99** crystallizes with an A-ring inverted (1β,2α) conformation.



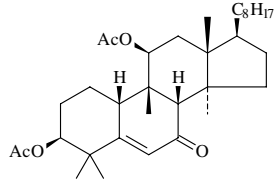
		Enone	20-Oxo		
		n → π*	n → π*	π → π*	π → π*
(99) R = OAc	MeOH	−1.2 (326)	+3.4 (284)	+6.4 (235sh)	+8.6 (213)
	SE30	(+) (330)	(++) (300)	(+++) (255)	(+) (205)
R = H	MeOH	−1.4 (330)	+2.6 (292)	+6.8 (240sh)	+9.9 (220)
	KBr	(−) (332)	(+) (296)	(++) (249)	



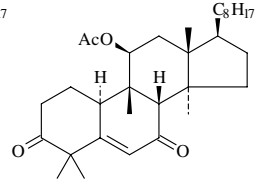
R = H	MeOH	−1.2 (325)	+4.0 (284)	+8.0 (233sh)	+10.3 (214)
Progesterone	SE30	(−) (328)	(++) (298)	(+++) (230)	(++) (210)
R = OH	MeOH	−1.0 (331)	+2.6 (293)	+6.7 (235sh)	+10.3 (218)
	SE30	(+) (328)	(+) (282sh)	(++) (268)	
R = OAc	MeOH	−1.7 (321)	+3.3 (287)	+4.6 (245sh)	+9.4 (215)
	SE30	(+) (320)	(+) (300sh)	(++) (250)	(−) (210)



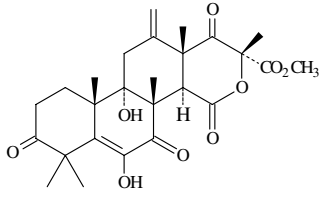
−0.79 (340), +16.4 (239)[245]



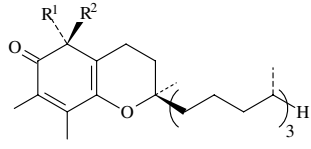
−0.89 (341), +18.8 (238)[245]



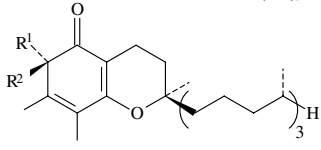
sh −0.98 (337), −3.58 (293), +12.2 (248)[245]



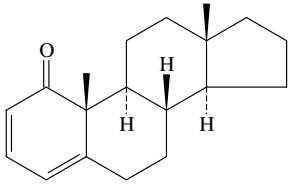
−1.12 (317), −6.33 (275), −2.79 (221)[246]



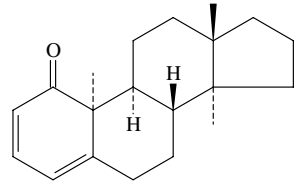
$R^1 = CH_3$, R^2 = OH
+3.3 (376), −3.4 (320)
R^1 = OH, $R^2 = CH_3$
−3.9 (376), +4.7 (320)[247]



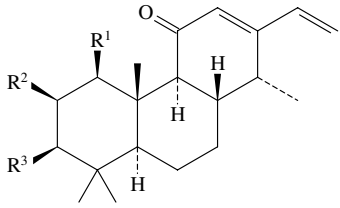
$R^1 = CH_3$, R^2 = OH
−10.7 (349), +15.6 (304)
R^1 = OH, $R^2 = CH_3$
+9.1 (349), −12.2 (304)[247]



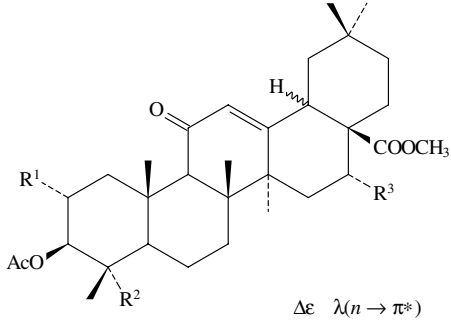
+0.30 (402), −17.90 (317)[248]



−2.70 (382), +16.79 (315)[248]



R^1	R^2	R^3	
H	OH	O=	−2.78(369), −8.74(289), +2.28(263)
OH	OH	OH	−5.36(345), +4.41(277), −4.17(228)
OH	H	OH	−5.17(347), +4.84(278), −3.25(230)
H	O=	OH	−3.27(368), +3.97(271)[249]



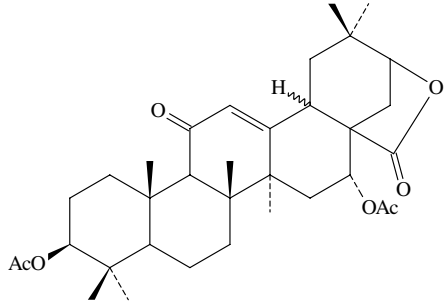
$R^1 = R^3 = H$, $R^2 = CH_3$

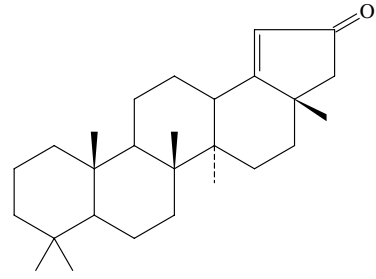
$R^1 = H$, $R^2 = CH_3$, $R^3 = OAc$

$R^1 = R^3 = H$, $R^2 = CH_2OAc$

$R^1 = OAc$, $R^2 = CH_2OAc$, $R^3 = H$

	$\Delta\varepsilon$	$\lambda(n \rightarrow \pi^*)$	$\Delta\varepsilon$	$\lambda(\pi \rightarrow \pi^*)$
18α-H	−0.15	353	+3.45	242
18β-H	+0.17	362	−1.15	246
18α-H	−1.27	339	+1.50	255
18β-H	+0.56	336	−1.47	253
18α-H	−1.84	337	+2.80	247
18β-H	+0.18	362	−2.90	248
18α-H	−1.45	337	+3.23	245
18β-H	+0.20	361	−2.05	246[250]

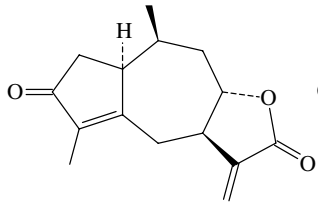




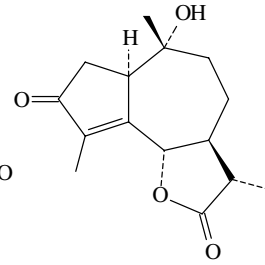
18α-H +0.05 (393), −0.98 (342), +0.95 (265), −3.90 (237)

18β-H −0.08 (347) −3.48 (246)[250]

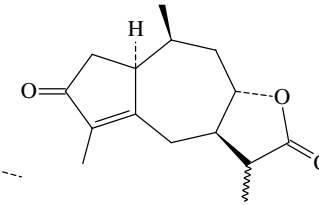
−1.3 (346), −2.9 (331), −3.1 (319), −10.2 (235)[251]



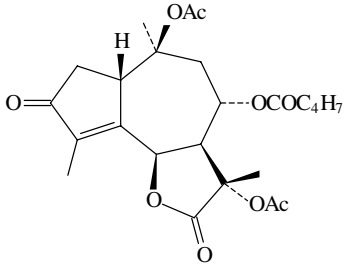
−0.68 (317), +9.70 (238)[252]



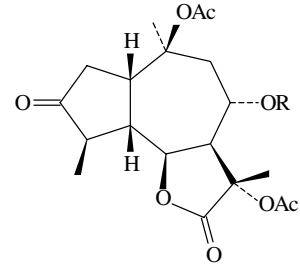
−1.41 (320), +8.22 (238)[252]



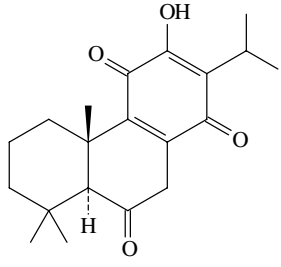
−0.67 (306), +7.03 (240)[252]



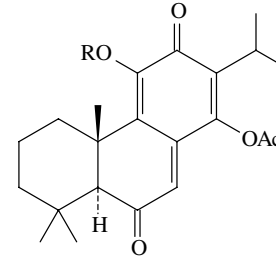
+1.38 (330), −9.87 (234)[252]



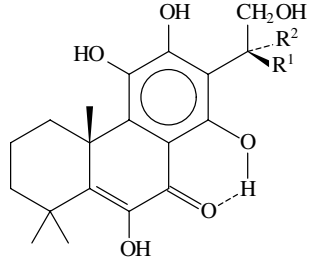
R = $COC(CH_3)=CHCH_3$ + 2.54 (299), −3.64 (213)[253]
R = H +1.48 (301), −1.03 (212)[253]
R = COPh +2.40 (300), −2.68 (227)[253]



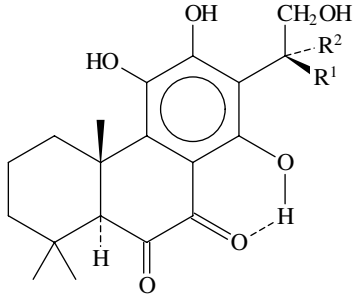
+1.42 (430), −6.15 (342),
−6.39 (329), +2.13 (270)[254]



R = H +2.58 (450), −2.21 (380),
−4.79 (333), −4.42 (318)
R = Ac −1.15 (450), −0.62 (330),
+13.62 (273), −3.08 (242)[254]

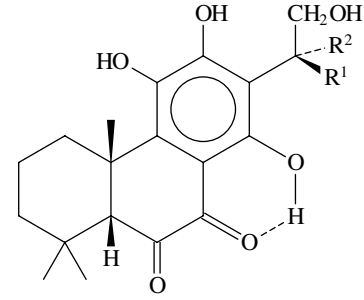


R^1 = H, R^2 = CH_3
−0.30 (390), −2.77 (304),
+5.84 (283), −1.68 (232)
R^1 = CH_3, R^2 = H
−1.80 (390), −4.51 (305),
+6.41 (284), +6.51 (270)[255]



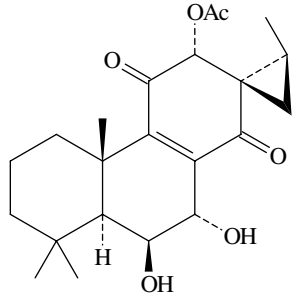
$R^1 = H, R^2 = CH_3$
+3.76 (443), −1.22 (398), +1.31 (350), +3.43 (301), +4.49 (280)

$R^1 = CH_3, R^2 = H$
+2.94 (446), −0.82 (398), +0.65 (360), −1.71 (328), +3.84 (298), +3.02 (281)[255]

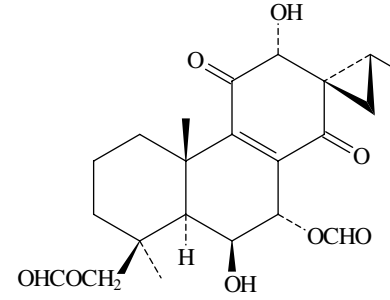


$R^1 = H, R^2 = CH_3$
+1.09 (460), −3.11 (420), +4.20 (347), +2.10 (279)

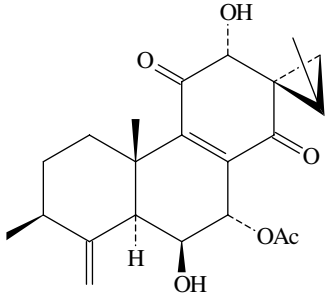
$R^1 = CH_3, R^2 = H$
+0.42 (460), −2.35 (420), +2.02 (352), +1.01 (298)[255]



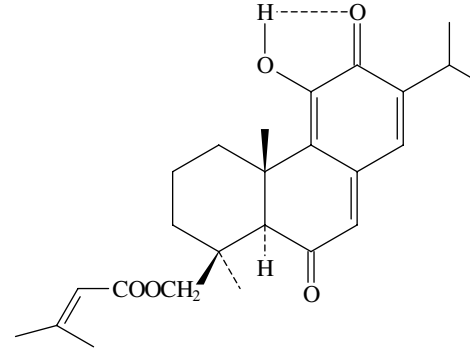
+0.43 (380), −0.55 (325), +8.79 (259), −0.42 (242), +1.29 (234)[256]



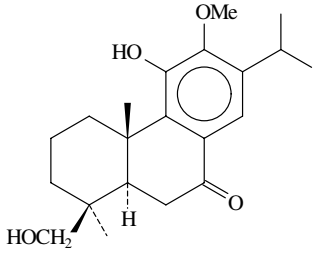
−1.08 (340), +20.0 (242)[256]



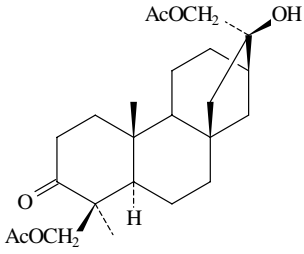
−0.20 (420), +7.20 (252), +7.20 (232)[256]



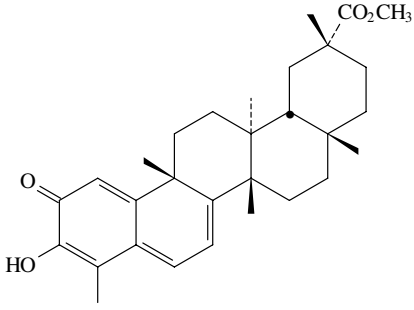
+2.11 (445), −2.21 (370), −7.34 (336), −6.73 (320), −3.12 (257)[257]



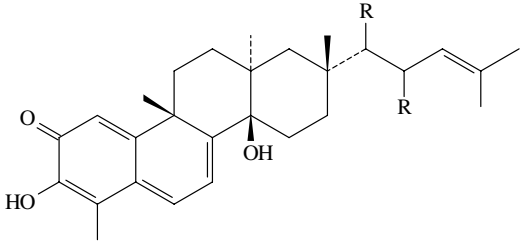
+0.82 (320), −1.44 (272)[257]



−0.46 (324), +1.54 (292)[257]

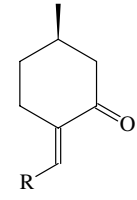


−0.5 (434), +1.0 (375), −1.1 (261)[258]



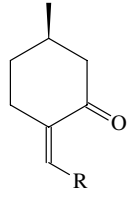
R = H −0.6 (434), +1.0 (373), −1.0 (263), +0.2 (240)

R = bond −2.1 (434), +1.8 (368), −2.2 (263), +1.9 (241)[258]



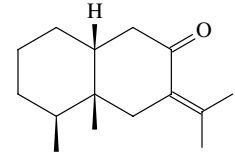
R = CH_3 +0.62 (326)

R = Ph +1.24 (345), −9.88 (280)[259]

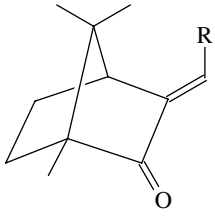


R = CH_3 +0.23 (325)

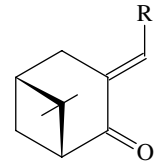
R = Ph +0.55 (335), −2.45 (275)[259]



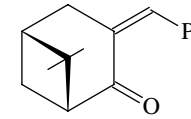
−0.38 (325), +3.42 (243)[260,261]



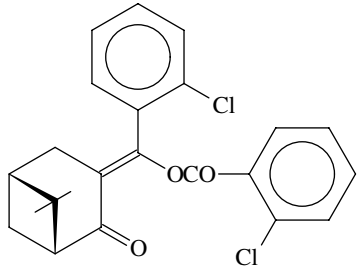
R = H	+0.83 (344)
R = Cl	+0.41 (338)
R = Ph	−1.46 (364)
R = 4-$CH_3C_6H_4$	−1.80 (364)
R = 4-$CH_3OC_6H_4$	−2.60 (362)
R = 4-FC_6H_4	−1.53 (365)
R = 4-ClC_6H_4	−1.78 (366)
R = 4-BrC_6H_4	−2.08 (355)
R = 4-pyridyl	−0.87 (372)[262]



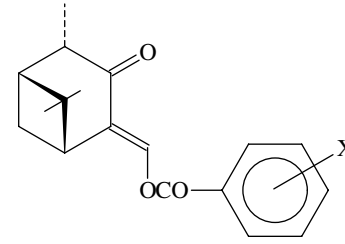
R = H	+0.22 (334)[263]
R = Ph	+1.57 (340)[265]
R = 2-ClC_6H_4	+1.50 (342)[263]
R = 2-BrC_6H_4	+1.00 (344)[263]
R = 4-ClC_6H_4	+1.68 (343)[263]
R = 4-BrC_6H_4	+1.69 (345)[263]
	−25 (275)[264]
R = 2-$CH_3C_6H_4$	+0.97 (352)[265]
R = 2-$CH_3OC_6H_4$	+0.73 (362)[265]
R = 4-$CH_3C_6H_4$	+1.76 (349)[265]



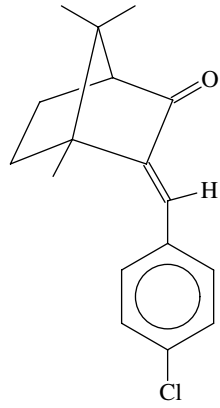
−0.57 (334)[265]



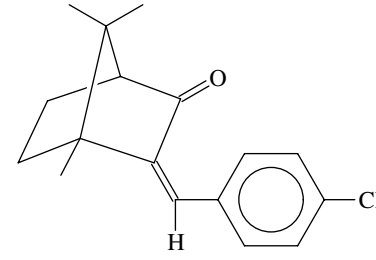
+0.69 (345)[263]



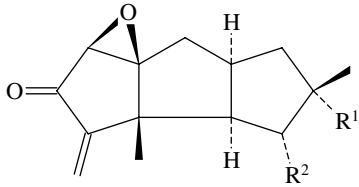
X = H	+0.85 (333), +6.10 (270)
X = 4-Cl	+0.52 (343), +5.30 (266)
X = 2,6-Cl_2	+0.42 (345), +3.90 (258)[266]



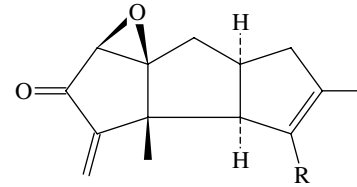
+1.60 (348), −41.2 (278)[267]



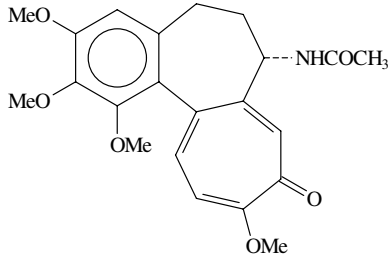
−1.50 (389), −11.2 (297)[267]



$R^1 = CO_2H$, $R^2 = H$
−0.86 (369), −1.04 (352),
+0.68 (267), +1.85 (232)
$R^1 = CH_3$, $R^2 = OH$
−0.95 (372), −2.14 (338)
-1.07 (257), +1.39 (226)[268]

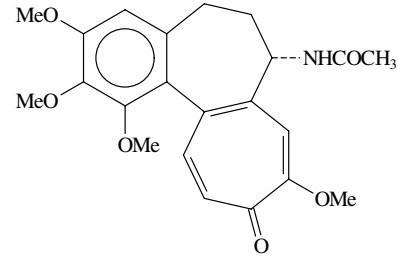


R = CO_2H
−2.31 (356), −0.08 (271)
+8.80 (238), −4.02 (215)
R = CH_2OH
−2.98 (360), −0.97 (261)
+5.73 (228)[268]



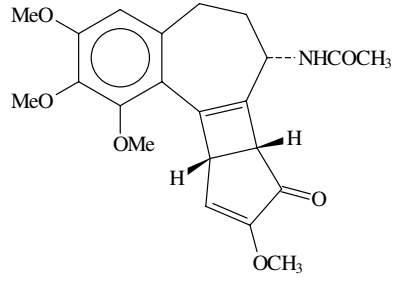
(100)

−9.26 (351), −8.21 (274), +11.0 (232)



(101)

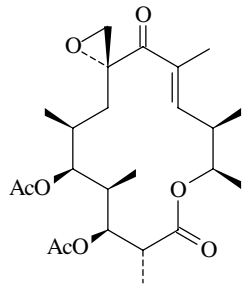
−13.1 (345), +2.31 (257), +13.5 (238)



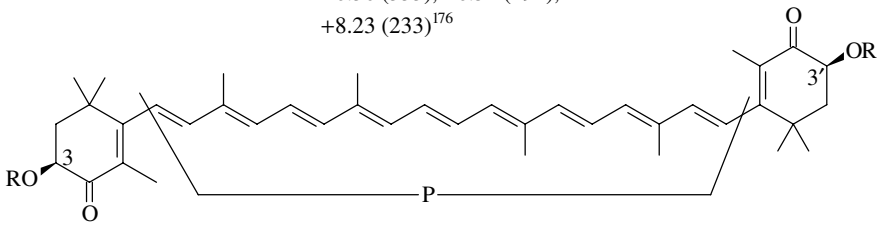
(102)

+13.5 (350), −49.6 (293), −15.9 (212)

The CD spectra of approximately fifty alkaloids of colchicine **(100)** and isocolchicine **(101)** types and alkaloids with altered tropolone rings (e.g. **102**) have been reported[269]. Six to seven CD bands of these alkaloids were identified in the 400–190 nm region. The 350 nm Cotton effect appears to result from a $\pi \rightarrow \pi^*$ transition of methoxytropone system. The pH-dependent changes in the CD spectra were studied following ionization of a free phenolic group on ring A, a hydroxy group on the tropolone ring or substituted amino group in colchicine **(100)** analogues[270].



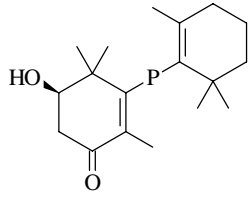
−0.36 (333), +0.51 (294),
+8.23 (233)[176]



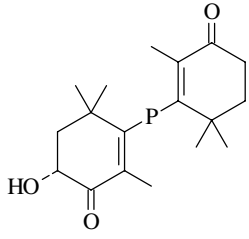
(3*S*, 3′*S*)-Astaxanthin R = H −3.2 (521), +6.7 (384), −23.1 (323), +12.5 (280), −14.4 (249), +12.8 (224)[271,272]

R = Ac +4.5 (387), −19.6 (321), +12.1 (278), −14.7 (248)[271]

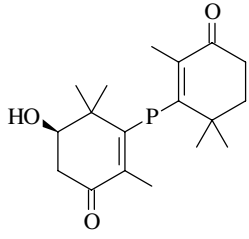
R = $CH_3(CH_2)_{14}CO$ +3.7 (385), −16.4 (320), +11.5 (279), −13.0 (248)[271]



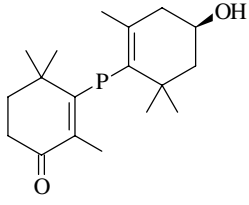
+2.0 (285), +5.0 (225)[273]



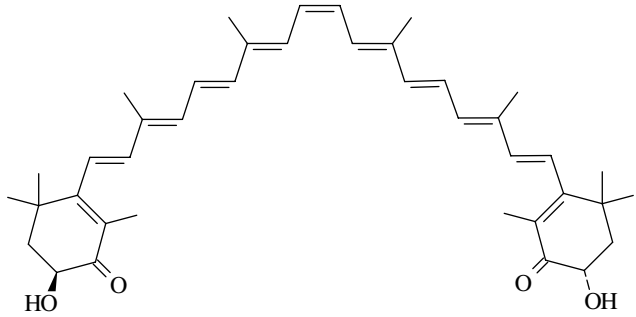
−2.1 (380), +10.9 (316), −7.0 (278), +6.9 (246)[272]



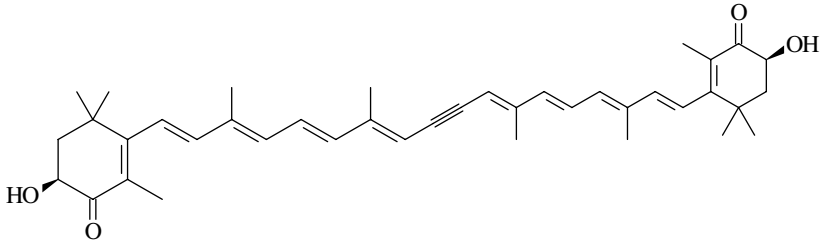
+1.5 (300), −1.0 (270), +3.5 (250), −0.5 (240), +7.0 (225)[273]



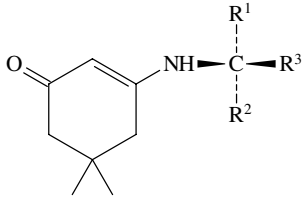
+2.5 (345), −7.5 (295), +4.5 (258)[273]



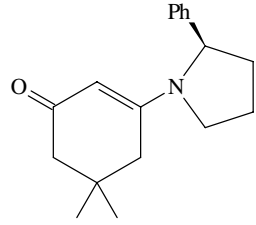
+6.3 (477), −24.0 (380), +9.0 (305), −8.0 (266)[271]



−5.9 (466), +7.5 (365), −25.5 (282)[271]

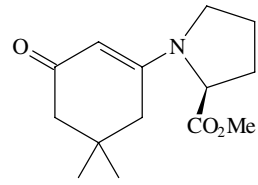


(103)



(104)

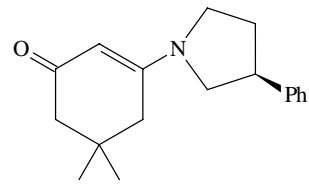
+28.0 (289)[274]



(105)

−16.1 (286)[274]

R^1	R^2	R^3	Reference 274
C≡CH	Me	H	−32.5 (274)
Et	C≡CH	H	+27.9 (274)
C≡CH	*n*-Pr	H	−25.2 (274)
C≡CH	Et	Me	+1.4 (276)
CH=CH_2	Et	H	−16.8 (278)
n-Pr	COOMe	H	+17.7 (274)



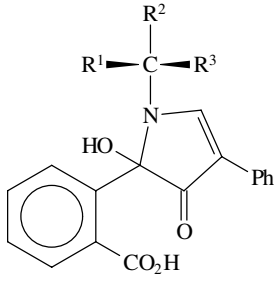
(106)

+15.0 (292)[274]

Chromophoric derivatives for the optically transparent amino group, such as dimedone derivatives **103–106**, were prepared for assigning the absolute configuration of primary and secondary amines. The vinylogous planar amide chromophore (280–290 nm $\pi \rightarrow \pi^*$

absorption) shows positive Cotton effects for derivatives possessing the (*R*) configuration in primary and secondary amines[274].

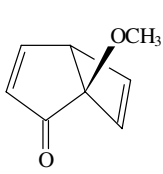
Fluorescamine has been used as a Cottonogenic reagent for secondary amines (forming aminoendione chromophore)[275] and for primary amines (forming pyrrolinone chromophore, **107**)[276] whose *in situ* CD was directly correlated with the amine absolute configuration.



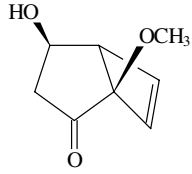
(107)

Amine	
(*R*)-α-methylbenzylamine	+5.01 (387), −7.29 (275)
(*R*)-α-(1-naphthyl)ethylamine	+4.73 (388), −8.02 (287)
(*R*)-α-phenyl-l-propylamine	+5.34 (386), −8.95 (270)
(*R*)-norepinephrine	+1.55 (385), −3.48 (285)
(*R*)-2-aminobutane	+0.38 (385), −0.95 (288)

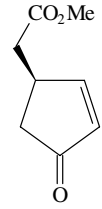
Circularly polarized (laser) light is widely used not only to study the absorption properties of enantiomers, but also to generate optically active compounds via enantioselective photochemical process.



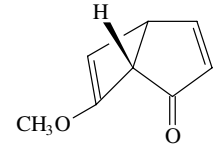
(+)-(1*R*,5*S*)-**(108)**
+2.5 (350)
(calcd from 3.7% ee)



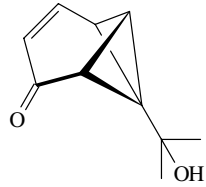
(+)-(1*R*, 4*R*,5*S*)-**(109)**
+7.8 (305)
(calcd from 2% ee)



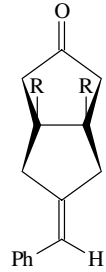
(+)-(4*S*)-**(110)**
−0.32 (320)
(calcd from 1.6% ee)



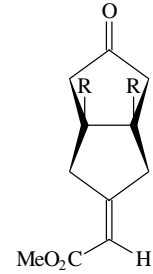
(−)-(1*S*,5*R*)-**(111)**
−2.0 (350)
(calcd from 1.6% ee)



(+)-(*R*)-**(112)** + 1.02 (353)



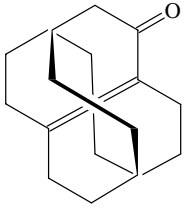
R = H (44%ee) +0.17 (319), +0.32 (308)
R = CH_3 (8%ee) +0.17 (319), +0.34 (305)[280]



R = H (34%ee) +0.13 (318), +0.22 (307)
R = CH_3 (27%ee) −0.04 (318), +0.02 (312), −0.03 (307), +0.04 (300)[280]

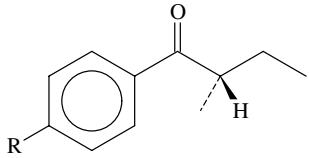
Some difficult-to-resolve enones were obtained by enantioselective hydration of **108** and **109**[277], or laser phototransformation using circularly polarized light on **108**, **110**, **111**[278] and **112**[279].

UV irradiation of a *cis* bicyclic α,β-unsaturated ketone in diethyl (+)-tartrate afforded *trans* ketone **113** enriched in the (−)-enantiomer, with an estimated optical purity of 0.5–1%[281].

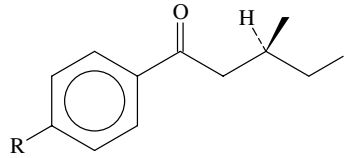


(113)

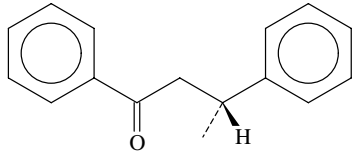
−0.67 (307)[281]



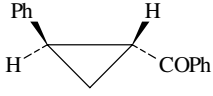
R = H −0.030 (350), +0.027 (327)
R = CH_3 −0.052 (347), +0.015 (313)
R = CH_3O −0.102 (343), −0.041 (317)[282]



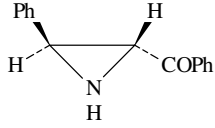
R = H −0.030 (357)
R = CH_3 −0.016 (354), +0.009 (310)
R = Cl −0.043 (353)[282]



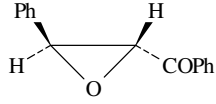
−0.34 (328), −0.12 (287), −0.49 (252), +2.24 (219)[283]



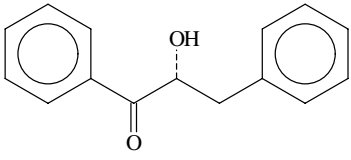
−4.76 (312), −7.76 (260)[284]



−4.21 (315), −9.00 (263), +6.97 (232)[284]

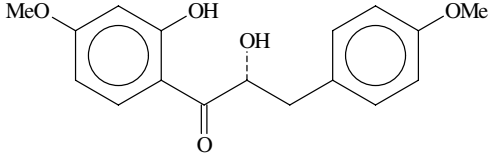


−2.86 (322), −6.30 (257), +8.31 (235)[285]



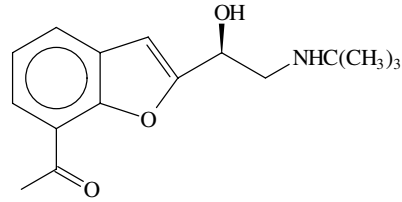
(114)

+0.65 (305), −1.39 (278)[285]



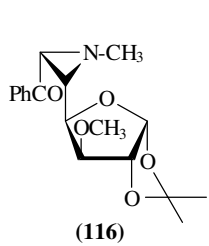
(115)

−3.30 (310), +1.05 (246), −1.15 (230)[286]

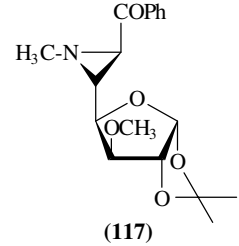


+0.27 (286), +0.79 (267),
−6.77 (231)[287]

Chiral chalcone epoxides with oxygenation patterns of naturally occurring flavonoids and isoflavonoids were transformed into the corresponding α-hydroxydihydrochalcones similar to **115**, and their CD was reported[288]. (+)-(αR)-Enantiomers showed a weak negative 310–330 nm n $\rightarrow \pi^*$ transition, followed by positive (260–290 nm) and negative (230–250 nm) $\pi \rightarrow \pi^*$ Cotton effects. Due to the profound influence of intramolecular hydrogen bonding (involving α- and 2′-OH functions) on the conformation and hence the sign of the Cotton effect, conclusions based on CD regarding the absolute configuration of **115** analogues are reliable for similarly derivatized α- and 2′-OH functionalities (compare **114** and **115**).



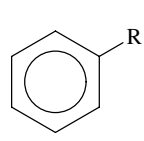
(116)



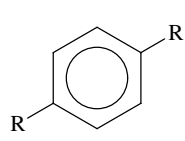
(117)

−0.48 (330), +1.21 (277), +5.45 (253) −0.73 (344), −0.72 (263), +2.85 (240)

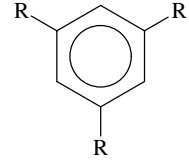
The absolute configuration assignment of both chiral centers in 2-glycosyl-3-benzoylaziridines was achieved by comparing the CD properties of series *cis*- **(116)** and *trans*- **(117)** isomers[289].



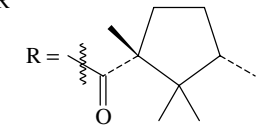
−2.53 (325)

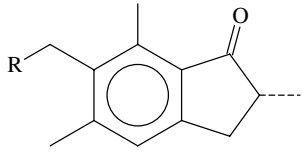


−4.90 (334)

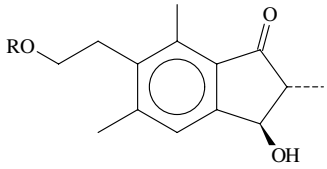


−5.22 (327)[290]

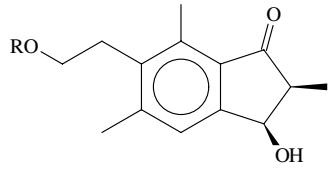




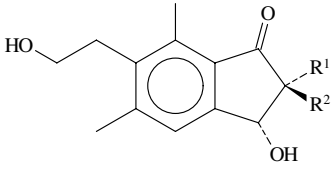
R = CH_2OH (MeOH) +0.54 (326)
(C_6H_{12}) −0.30 (366), −0.35 (348), −0.21 (334), +0.10 (326), +0.07 (315)
R = CH_2OAc +0.55 (323)
R = CH_2OGlu +0.57 (324)[291]



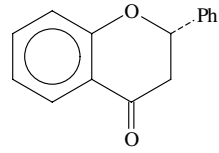
R = H −5.21 (325)
R = Glu −5.01 (325)[291]



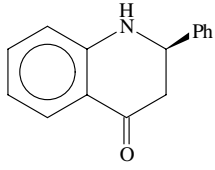
R = H −6.19 (330)
R = Glu −5.56 (330)[291]



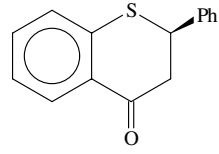
$R^1 = CH_2OH$, R^2 = Me +5.54 (330)
R^1 = Me, $R^2 = CH_2OH$ +5.60 (330)[291]



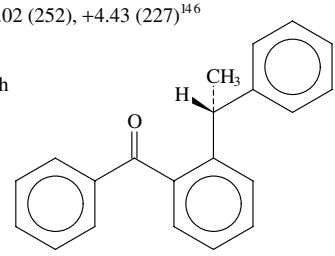
(−)-(*S*)-**(118)**
+2.24 (342), −4.77 (311),
−3.02 (252), +4.43 (227)[146]



(−)-(*R*)-**(119)**
−2.25 (368), +2.81 (326),
+0.99 (267), −5.93 (235)[146]

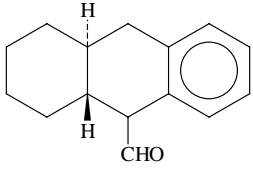


(−)-(*R*)-**(120)**
−2.56 (364), +2.01 (322),
+2.57 (271), −11.32 (229)[146]

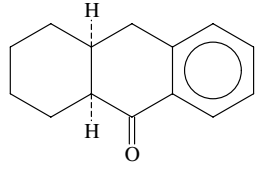


+2.33 (346),
+0.61 (303),
−0.61 (286), +6.06 (255)[292]

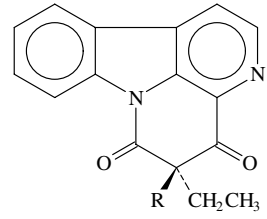
The n → π^* and $\pi \rightarrow \pi^*$ CD transitions of aza- **(119)** and thiaflavonone **(120)** were identified. Opposite signs were found for the Cotton effects of (−)-**119** and (−)-**120** as compared to those of known (−)-(*S*)-**118**. According to the helicity rule, the heterocyclic ring must also adopt the opposite conformation because the phenyl substituent is equatorially oriented in all three flavonones. Thus, the (2*R*) absolute configuration was assigned to (−)-**119** and (−)-**120**[146].



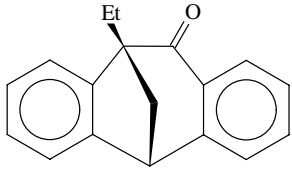
−1.43 (305), −1.02 (271)
−1.02 (225), +9.30 (201)[293]



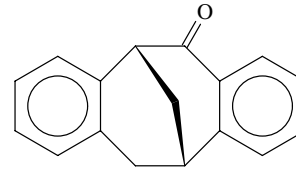
+0.49 (343), −0.11 (286),
+1.42 (243), −4.30 (210)[293]



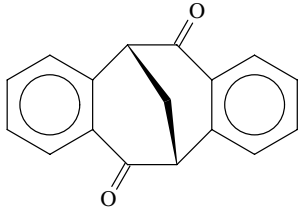
R = Me −2.40 (366), +1.75 (332),
+0.60 (303), −1.95 (274)
R = nPr +1.10 (362), −1.35 (332),
−0.50 (304), +1.35 (273)[294]



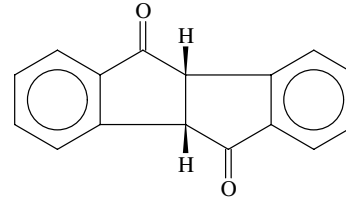
−6.18 (358), +4.97 (293),
−13.5 (258), +38.2 (232)[295]



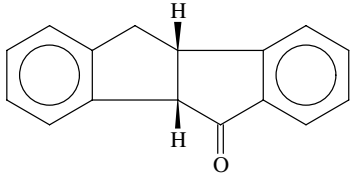
+6.29 (355), −1.17 (275),
−0.63 (258), −2.61 (225)[283]



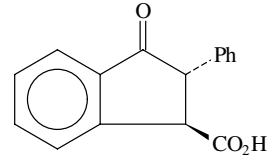
+20.2 (357), −11.5 (293),
+58.6 (265), −48.2 (241)[283]



−7.12 (348), +7.29 (299),
−16.8 (259), +18.9 (244),
+56.8 (209), −54.8 (198)[296]

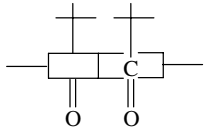


+0.50 (331), +1.2 (291),
−3.9 (268), −7.2 (251),
+38.1 (206)[296]

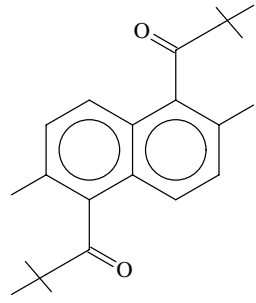


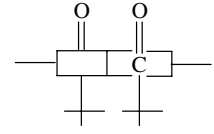
−1.06 (331), −0.86 (293),
−0.35 (269), −6.12 (244),
+6.66 (210)[296]

Octant diagram projections for the n → π^* 335 nm transition of axially chiral conformational enantiomers ($\Delta G^{\ddagger}$ = 19.8 kcal mol^{-1}) of 2,6-dimethyl-1,5-bis(2,2-dimethylpropanoyl)naphthalene (**121a** and **121b**)[297] led to the assignment of absolute configuration.



(121a)

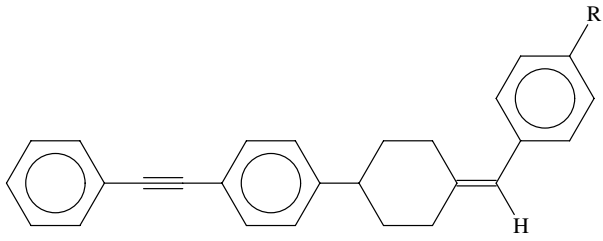




(121b)

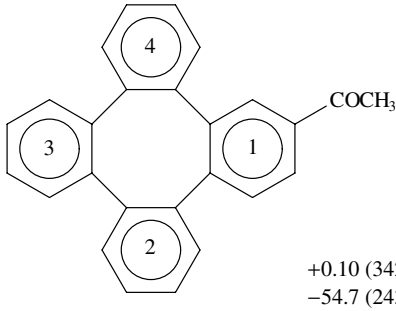
The enantiomeric conformers **121a** and **121b** were resolved using low-temperature HPLC on a chiral stationary phase, and their differential absorption ($A_l - A_r$) was reported as a signal from an on-line CD detector.

Two other ketones **(122)** containing axially chiral aromatic compounds were recently reported[298].



(122)

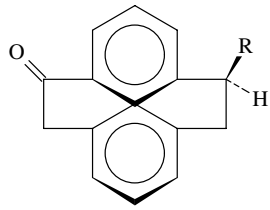
R = COCH3 +0.14 (355), −26.3 (287)
R = COPh +0.03 (376), −33.6 (304)



(+)-**(123)**

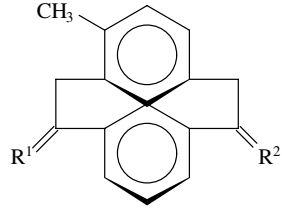
+0.10 (342), −0.19 (317), +28.3 (267),
−54.7 (243), +26.2 (223), −22.0 (209)

2-Acetyl[a,c,e,g]cyclooctatetraene **(123)** has been resolved by repeated HPLC on swollen microcrystalline triacetylcellulose, and its CD has been reported[299]. Both longer-wavelength Cotton effects were assigned to n → π^* transitions from the acetyl group, possibly in two different conformations. The absolute configuration of (+)-**123** was assigned as (*R*) for the 1-2 and 3-4 biphenyl units on the basis of calculations by the coupled oscillator technique of the rotational strengths of the dominant transitions (267 and 243 nm).

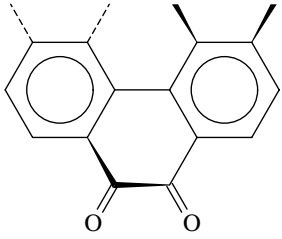


(−)-(*S*)

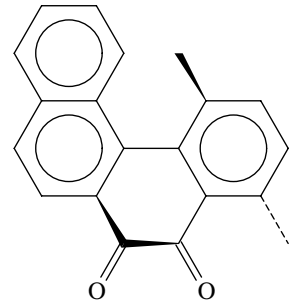
R = H −11.12 (318)
R = OH −10.00 (321)[300]



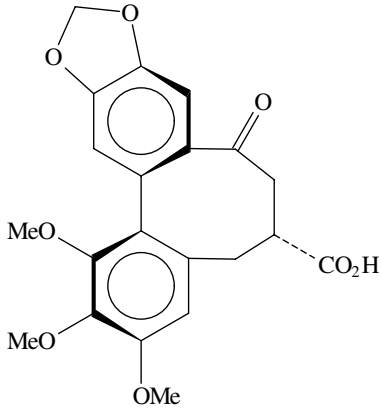
$R^1 = H_2$, R^2 = O +10.09 (321)
R^1 = O, $R^2 = H_2$ −9.19 (321)[301]



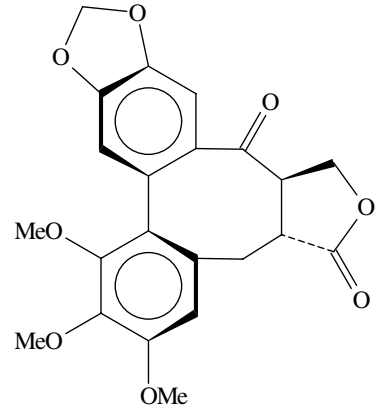
−1.5 (475), −1.8 (405), +0.8 (358), −4.8 (316), +0.8 (290)[302]



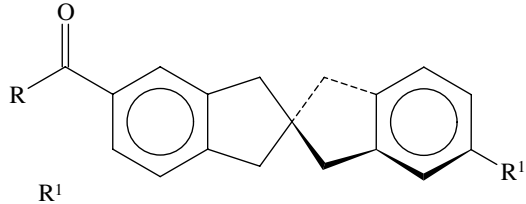
−1.0 (475), −0.6 (400), −0.4 (370) +1.6 (320), −3.9 (270)[302]



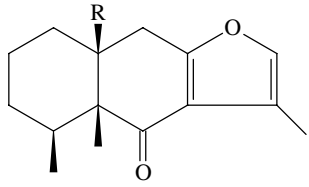
+1.32 (339), + 6.64 (297) −0.42 (275), +29.1 (243), −29.1 (221)[303]



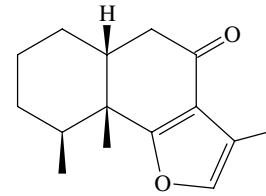
−1.01 (338), −6.85 (304), +5.29 (276), −41.0 (244), +39.6 (218)[303]



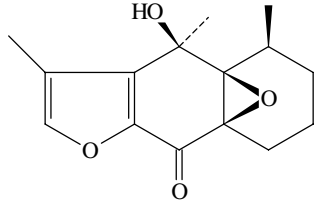
R	R^1	
CH_3	$COCH_3$	+2.45 (280), +10.79 (264), −11.83 (247)
CH_3	C_2H_5	+0.22 (284), +1.54 (260), +1.72 (254)
H	CHO	+2.45 (293), +11.63 (267), −12.85 (252)
OCH_3	$COCH_3$	+1.80 (287), +9.43 (257), −10.96 (240)[304]



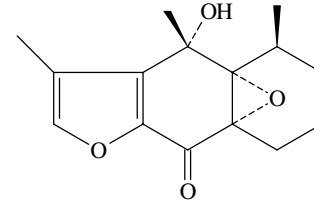
R = H +0.18 (327), −0.19 (287)
R = OH −0.28 (326), +1.55 (264)[260,261]



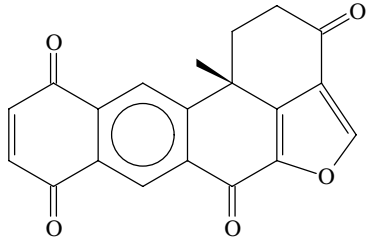
+2.37 (311), −0.74 (267)[260,261]



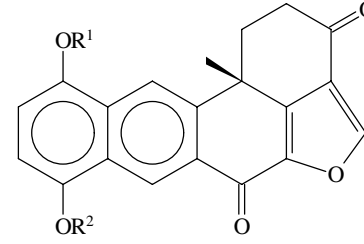
−0.66 (330)[305]



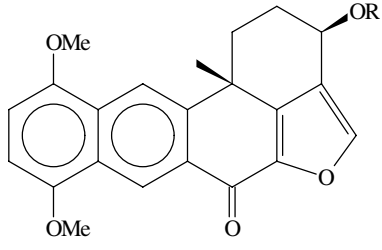
+0.92 (336)[305]



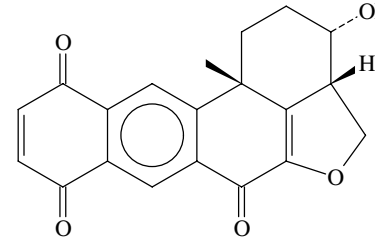
+2.8 (216)[306]



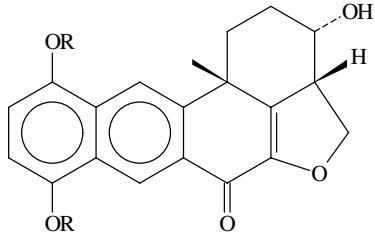
$R^1 = R^2 = H$ +2.8 (345), +6.4 (244), −4.5 (229)[306]
$R^1 = SO_3Na$, $R^2 = H$ −4.8 (301), +3.3 (244), −11.5 (230)[306]
$R^1 = R^2 = CH_3$ +1.8 (413), +1.4 (383), +1.7 (363), +2.8 (347), −5.5 (303), +4.6 (244), −8.9 (232)[306,307]



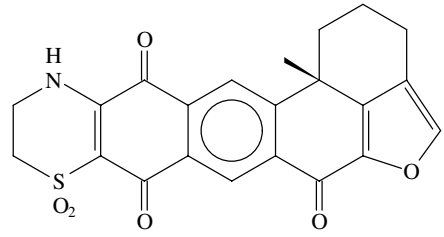
R = H +1.8 (406), +4.6 (344), −5.8 (307), +1.8 (283), −11.8 (239), +13.6 (217)[306]
R = TBDMS +5.6 (344), −6.2(307), +2.6 (283), −11.7 (240), +16.5 (218)[306]



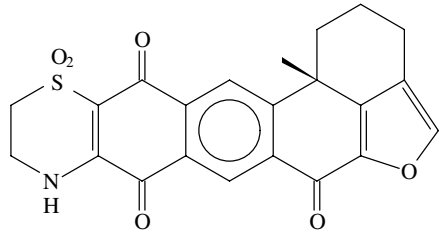
−1.8 (335), +3.9 (250)[308]



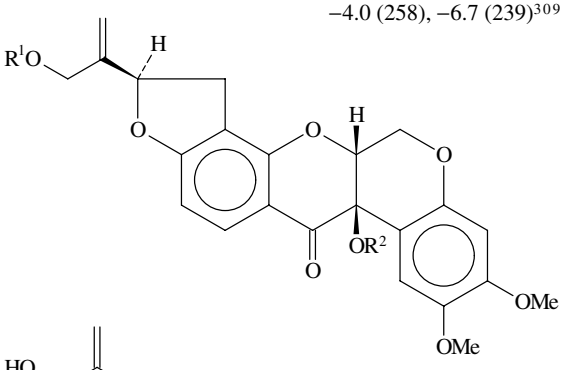
R = Me +0.7 (397), −3.8 (326),
+2.0 (281), +3.4 (235)
R = H +0.5 (420), −4.5 (325),
+2.1 (282)[308]



+1.8 (399), −3.5 (337)
+4.0 (304), −1.2 (277),
−6.6 (243)[309]

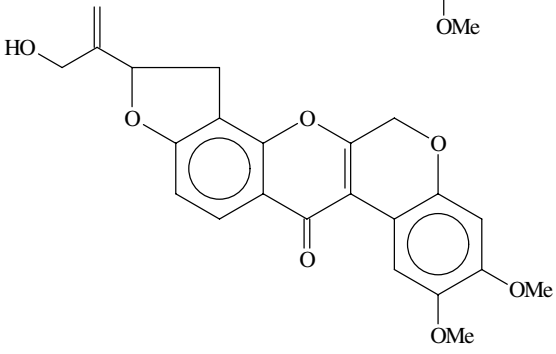


+2.0 (414), −4.0 (346),
+2.8 (303), +6.3 (282),
−4.0 (258), −6.7 (239)[309]

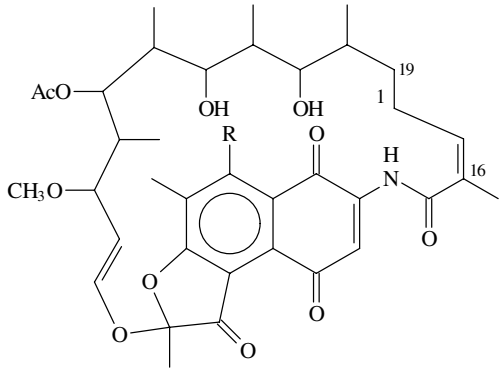


R^1 = β-D-Glu, R^2 = H
−4.01 (320), −1.27 (295),
−4.03 (275), +5.45 (239)

$R^1 = R^2$ = H
−4.79 (320), −1.30 (295),
−5.09 (275), +7.88 (237)[310]



−0.39 (320), −0.82 (295),
−1.39 (275)[310]



Rifamycin S (R = OH)

MeOH/H^+
+7.06 (437), −4.89 (353), +12.4 (300),
−24.6 (278), +41.4 (225)[3 11]

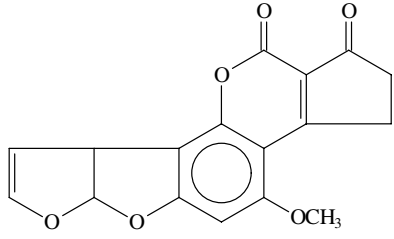
MeOH/OH^-
+2.81 (515), +6.38 (426), +22.9 (338),
−22.7 (314), −9.83 (270), +25.7 (227)[3 11]

R = OCH_3
−2 (470), +5 (342), +28 (310), −10 (285),
−15 (254), +81 (233), −74 (209)[3 12]

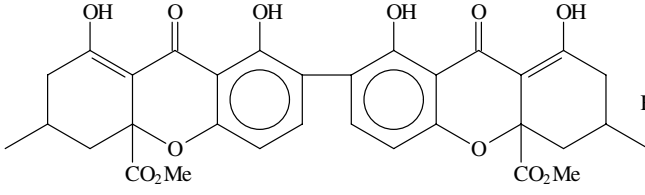
16,17,18,19 - Tetrahydrorifamycin
+4.81 (420), −2.29 (346), +12.0 (301),
−5.13 (274), +7.38 (239)[3 11]

Hexahydrorifamycin
+3.93 (433), +3.99 (333), +8.62 (300),
−3.55 (274), +3.02 (252), +2.37 (235)[3 11]

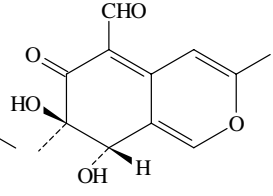
The observed complex CD of the antibiotic rifamycin chromophore was simulated (250−190 nm) by means of coupled oscillator theory, from coupling of the long-axis polarized aromatic transition with dienone transition[312].



−5.48 (354), −2.0 (264),
−19.38 (219)[3 13]

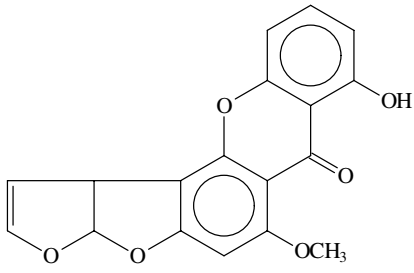


+3.50 (370), +2.20 (340), +3.06 (330),
−2.63 (269), −2.85 (263), −12.7 (224)[3 13]

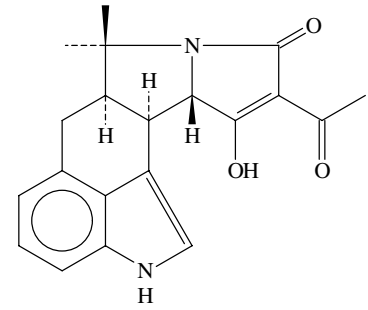


−1.71 (405), +4.29 (360),
+2.15 (312), −6.15 (276),
+8.01 (237)[3 13]

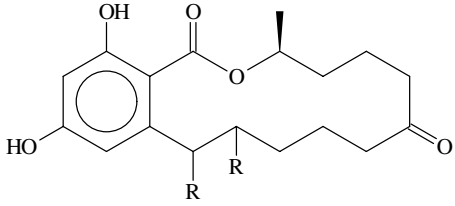
An octant projection diagram predicts a dissignate halogen contribution in the $C_{(5)}$ halogen-substituted bicyclo[2.2.1]hept-5-en-2-ones (**125** and **126**), and a consignate



−2.58 (325), +1.42 (290), +1.42 (270)[3 13]

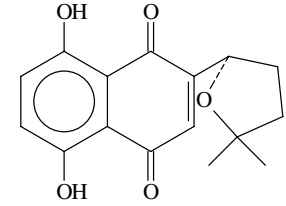


+1.8 (301), −4.56 (269)[3 13]

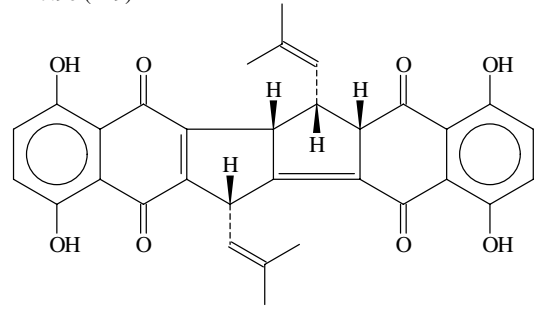


R = H −4.60 (299), −7.60 (260), +1.40 (231), +6.16 (195)[3 14]

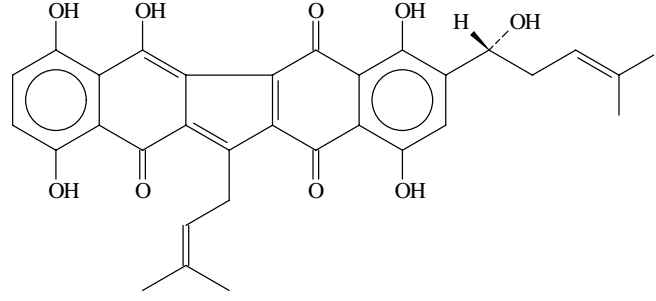
R = bond sh −2.63 (307), −17.93 (273), +17.90 (229) [3 13-3 15]



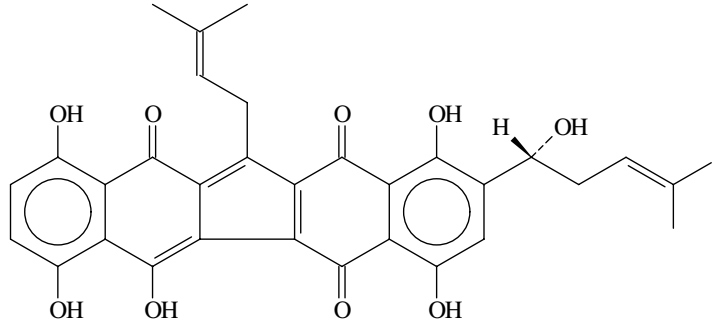
+0.06 (330)[3 16]



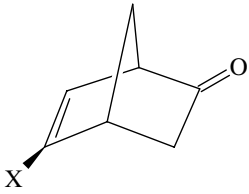
−0.08 (500), −0.08 (280)[3 16]

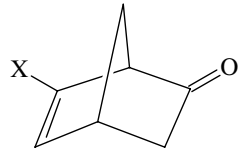


−0.55 (304), +0.55 (276), −1.27 (234)[3 16]



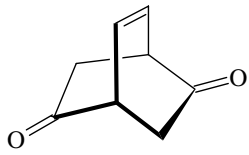
−0.91 (302), −0.91 (270), +3.45 (234), +4.73 (218)[316]



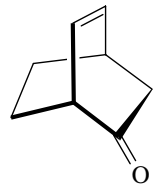


(124) X = H +18.8 (306)[202]
(125) X = Cl +20.4 (318), +30.8 (306), +25.8 (295), −5.6 (220)[203]
(126) X = Br +23.3 (320), +34.4 (308), +28.3 (297), −7.2 (220)[203]

(127) X = Cl +18.6 (320), +28.8 (308), +23.2 (297), −6.6 (232)[203]
(128) X = Br +23.4 (320), +34.0 (308), +28.4 (297), −6.6 (232)[203]



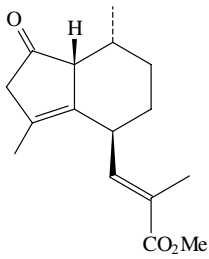
(−)-(**129**)
−16.9 (304)



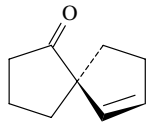
(+)-(**130**)

contribution in $C_{(6)}$ substituted enones **127** and **128**. The experimental data showed no significant difference (n $\rightarrow$ π^*) between unsubstituted and β- or γ-halogenated derivatives[203]. The results confirmed the interpretation that the n $\rightarrow$ π^* transition in β,γ-enones is to a large extent determined by an admixture of $\pi \rightarrow \pi^*$ olefinic transitions polarized along the $C_{(\beta)}$–$C_{(\gamma)}$ direction[202,317].

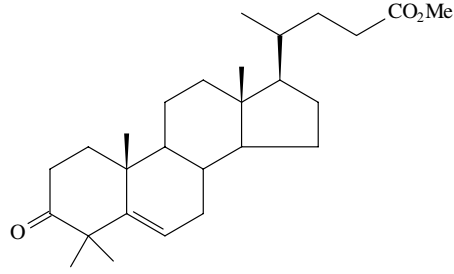
The C_2 symmetrical 5,7-dioxobicyclo[2.2.2]oct-2-ene **(129)** CD has been reported[96]. Its absolute configuration was assigned utilizing the extended octant rule[200] and correlated with that of (+)-**130**. Optically active **129** was reported earlier as formed in 3.5%ee by preferential photodestruction of (1*S*,4*S*)-enantiomer using right circularly polarized light[318].



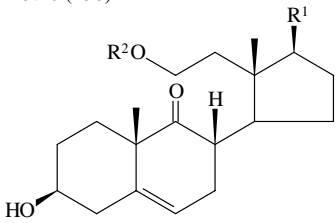
−0.49 (325), +3.20 (238)[319]

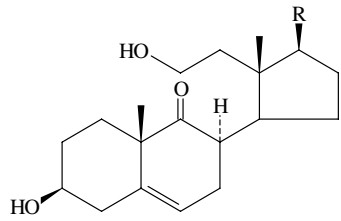


−3.14 (306)[320,321]

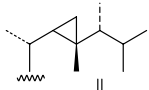


+1.0 (299)[145]

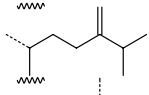




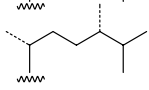
R^2 = H, R^1 =



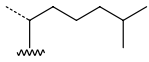
−1.45 (295), −1.02 (220)



−1.70 (285), −1.03 (220)

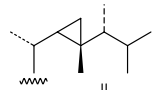


−2.30 (290), −1.67 (220)

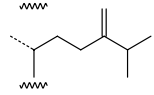


−1.97 (293), −1.33 (220)

R =

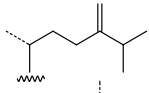


+9.85 (300)

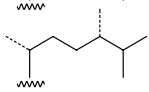


+3.64 (290)[322]

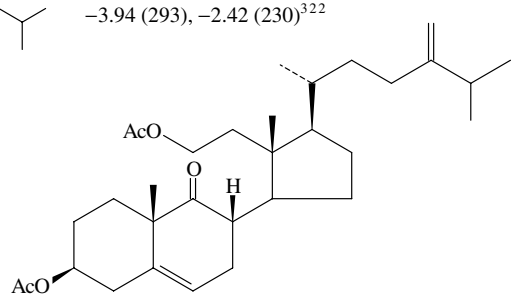
R^2 = Ac, R^1 =



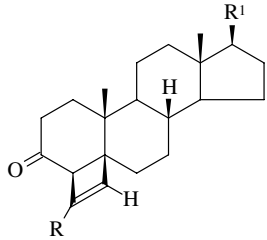
−3.97 (295), −2.58 (220)

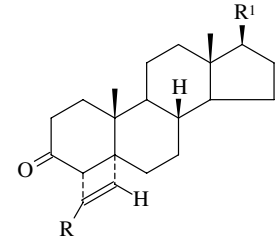


−3.94 (293), −2.42 (230)[322]

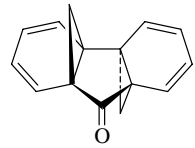


−3.64 (290), +2.12 (225)[322]



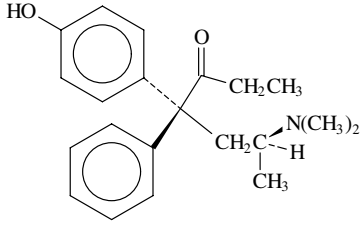


(131) −8.05(308), −7.43(299) R = *n*-C_3H_7, R^1 = $COCH_3$ **(136)** +13.45 (292)
(132) −7.67(296), R = *n*-C_3H_7, R^1 = OH **(137)** +9.41 (296)
(133) −2.35(307), −2.18(299) R = H, R^1 = $COCH_3$ **(138)** +12.47 (293)
(134) −5.23 (296) R = H, R^1 = OH **(139)** +6.40 (295)
(135) −6.22(297) R = H, R^1 = C_8H_{17} **(140)** +8.29 (295)[323]

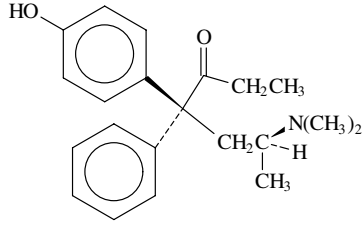


−8.0(282), +11.3 (243),
−40.0 (200)[324]

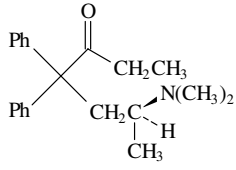
The structure of 4′-propyl-4β,5β-ethenopregnane-3,20-dione **(131)** as the main product of photochemical [2 + 2] cycloaddition of 1-pentyne to progesterone and 4α,5α-analogue **138** was confirmed by X-ray analysis. The CD data of **131–140** were in agreement with A/B-*cis* and A/B-*trans* fusion in **131** and **138**, respectively, and with the cyclobutene ring (main perturber of the C=O n → π^* transition) lying in a (−)-octant of **131** and a (+)-octant of **138**[323].



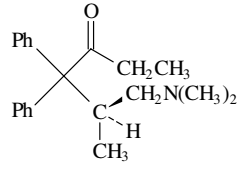
(+)-(4*S*,6*S*) · HCl salt +10.2 (296)[325]



(+)-(4*R*,6*S*) · HCl salt +21.3 (298)[325]



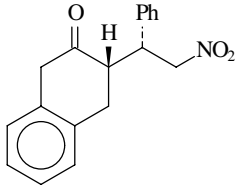
(+)-(6*S*)-methadone +1.48 (307)
(+)-(6*S*)-methadone · HCl +12.8 (295)[326]



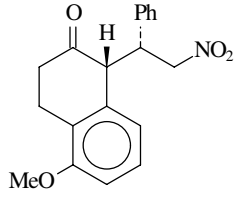
(−)-(5*S*)-isomethadone −2.42 (310)
(−)-(5*S*)-isomethadone · HCl −9.73 (300)[326]

An unusually strong CD for open-chain ketones **141** was recently reported[327]. Ketones **141** were formed by hydrogenation of β,γ-unsaturated precursors ($\Delta\varepsilon$ not reported) which were obtained by enantioselective protonation of samarium enolates (Table 8).

The CD of a series of eight differently-substituted analogues of 9,10-ethano-9,10-dihydroanthracen-11-one (**142** and **143**) was studied experimentally and theoretically[329]. Alteration of the substituent(s) on the benzene ring(s) affects the transition dipole magnitude and the transition energy of the aromatic chromophore without much change in the polarization direction.



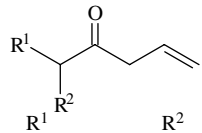
−3.19(299), −1.30(268)[328]



+1.38(303), +1.86(275)[328]

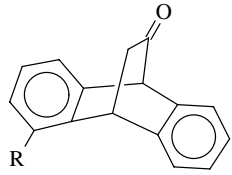
P. Vogel's group studied exhaustively the 5,6,7,8-tetramethylidenebicyclo[2.2.2]octane system and its metal carbonyl complexes. The preparation and CD spectra of tricarbonyliron complexes (**144–147**) were reported[333]. The chirality of complexes **144** and **146** is due uniquely to the coordination of $Fe(CO)_3$ moieties. The signs of the Cotton effects for (+)-**144** and (+)-**146** obey the octant rule, as the *endo*-$Fe(CO)_3$ of **144** and **146** fall in a positive octant, while the second *exo*-$Fe(CO)_3$ (*syn* to the carbonyl) lies almost on the *XY* nodal plane, and thus its contribution is expected to be small. The deuterium-substituted free tetraenone **148**, however, showed an anti-octant behavior. The CD spectra of **144** and **146** are strongly temperature and solvent dependent.

TABLE 8. CD of ketones **141** in Et_2O (corrected for 100% ee)



→ saturated sample **(141)**

R^1	R^2	Configuration	$\Delta\varepsilon^{max}$	λ_{max}
Ph	Me	*R*	−6.0	292
Ph	Et	*R*	−8.1	292
	Me	*R*	−2.5	295
	Me	*R*	−1.3	295
t-Bu	Me	*R*	−1.8	300
	Me	*R*	−0.8	295
p-ClC_6H_4	*i*-Pr	*S*	+6.8	293
$PhCH_2$	Et	*S*	+9.3	293
$PhCH_2$	*i*-Pr	*S*	−0.7	293
o,*o*-$Cl_2C_6H_3$	Me	*R*	−6.1	290

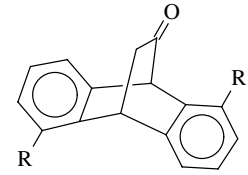


(142)

R = CH_2OH −0.29 (307), + 1.50(276), +11.0(221)

R = CO_2H −1.33 (303), +6.07(282), +19.6(228)

R = NH_2 −0.34 (308), +2.50(275), +21.7(228)[329]

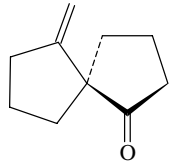


(143)

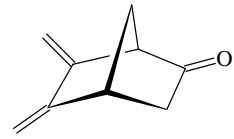
R = CH_2OH −0.08 (319), + 1.13(269), −1.98(232)

R = CO_2H −0.08 (329), +4.02(294), +6.73(237)

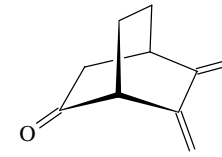
R = NH_2 +7.12 (304), −5.01(263), +13.3(237)[329]



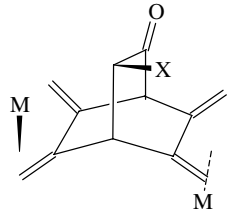
+1.50 (309)[320,321]



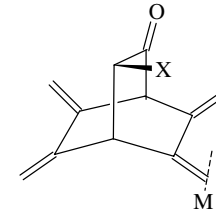
−0.36 (324), +0.59 (318), −0.97 (298), −1.20 (288), +10.3 (248)[330,331]



+1.2 (320), −2.5 (280), +14.5 (253)[332]



M = $Fe(CO)_3$

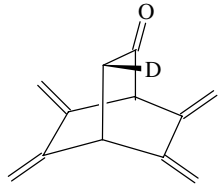


X = H (+)-(**144**)
sh + 2.0 (355), +19.6 (310), −1.4 (269), +8.4 (241)

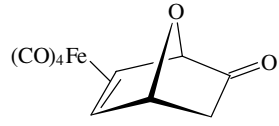
X = H (+)-(**146**)
+ 15.3 (317), +4.4 (270), sh −6.0 (240)

X = D (+)-(**145**)
sh + 2.0 (355), +19.5 (310), −1.3 (269), +8.5 (242)[333]

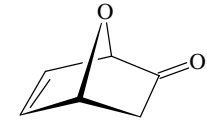
X = D (+)-(**147**)
+ 15.2 (317), +4.4 (270), −6.0 (240)[333]



(−)-(**148**)
+0.13 (330), +0.12 (316), +0.07 (304)[333]

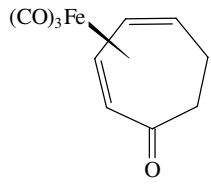


+33.4 (312)[334]



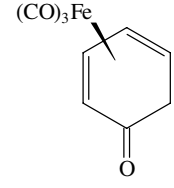
+13.2 (312), +20.8 (205)[335]

The CD properties of a number (η^4-polyene) $Fe(CO)_3$ complexes containing carbonyl group have been described[336,337]. Tricarbonyliron complex of 2,3-dihydrotropone **(149)** was resolved by HPLC and its absolute configuration determined by X-ray and CD[338].



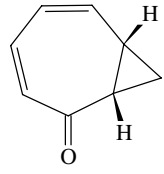
(+)-(**149**)

+7.5 (385), −10.5 (305), +13.0 (250)[338]



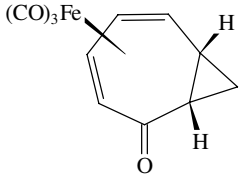
(+)-

+9.0 (370), −6.5 (305), +4.0 (260)[338]



(−)-(**150**)

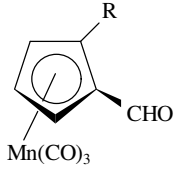
−6.6 (353), +32.2 (280), −37.8 (215)[339]



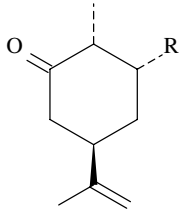
(+)-

+5.9 (380), −2.4 (305), +11.8 (250)[339]

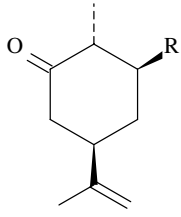
The absolute configuration of homotropone **(150)** and its $Fe(CO)_3$ complexes was deduced from comparison between experimental and theoretically calculated (CNDO/S) CD of preferred *trans* conformation[339].



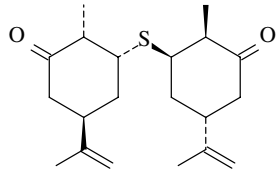
R = $CH_2N(Me)_2$	−1.93 (341), +1.11 (285)
R = $CH_2N(Me)_2$·HCl	+5.54 (363), −3.85 (287)
R = (R)-$CH(CH_3)N(Me)_2$	−2.78 (339), +2.20 (273)
R = (R)-$CH(CH_3)N(Me)_2$ ·HCl	+7.75 (364), −5.47 (288)[340]



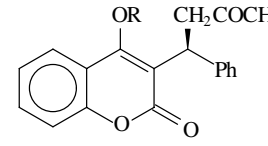
R = H	+1.55 (290)
R = SEt	+2.12 (290), +0.91 (259)
R = St-Bu	+2.18 (290), +1.30 (253)
R = SPh	+1.79 (294), +1.36 (265)[91]



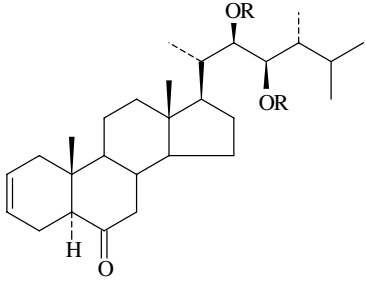
R = SEt	−0.79 (290), +0.44 (250)
R = SPh	−4.67 (291), +1.67 (260)[91]



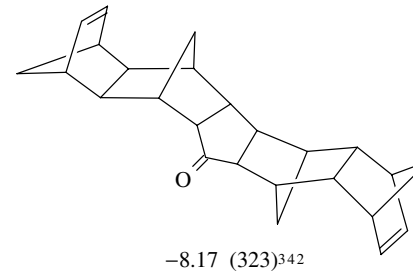
+4.70 (288), +2.55 (247)[91]



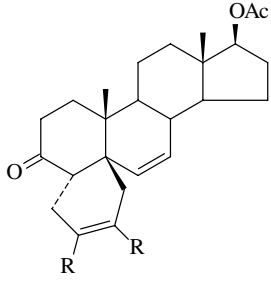
R = H −1.33 (300), +6.48 (268), +2.67 (236), −34.2 (219)
R = CH_3 +3.36 (315), −2.85 (277), −0.64 (258), −1.30 (243), +4.15 (221)[341]



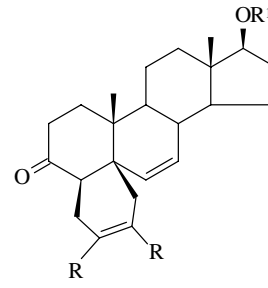
R = H −2.77 (293)
R = Me_2C −1.94 (293)[142]



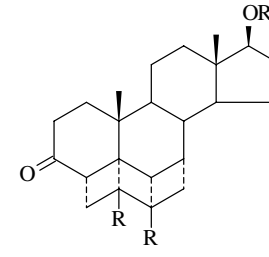
−8.17 (323)[342]



R = H +2.29 (290)
R = CH_3 +1.40 (290)[343]



R = H, R^1 = H −4.92 (294)
R = H, R^1 = Ac −5.55 (294)
R = CH_3, R^1 = H −1.30 (293)
R = CH_3, R^1 = Ac −5.67 (293)[343]



R = H, R^1 = Ac +0.70 (297)
R = CH_3, R^1 = H +0.66 (295)[343]

VI. EXCITON CHIRALITY

Movement of an electron from the ground electronic state of a molecule to an excited state creates a momentary dipole, called an electric transition dipole. Thus, associated with each electric transition is a polarization (electric transition dipole moment) that has both direction and intensity which vary according to the nature of the chromophore and the particular excitation. When two or more chromophores lie sufficiently close together, their electric transition dipoles may interact through dipole–dipole (or exciton) coupling. Exciton coupling arises from the interaction of two (or more) chromophores through

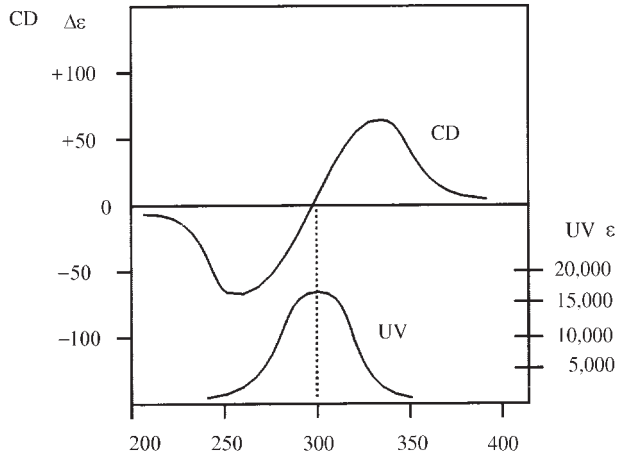


FIGURE 15. Typical bisignate exciton coupling CD spectra (upper) and bell-shaped UV (lower) spectra for chromophores with electronic transitions near 300 nm. The shape of the observed CD curve is due to overlapping, oppositely-signed positive and negative CD transitions from electronic excitation into (two) exciton states

their (locally) excited states. These excited-state dipole–dipole interactions, which lie at the heart of exciton coupling, are most effective when the electric dipole transitions are strongly allowed — as in $\pi \rightarrow \pi^*$ UV-visible transitions. Exciton coupling leads to shifted and broadened, if not split, UV-visible spectra of the composite molecule[344]. When the chromophores are held in a chiral orientation, exciton coupling is typically seen as two oppositely-signed CD Cotton effects flanking the relevant UV-visible absorption band(s) (Figure 15). The signed order of the CD transitions may be correlated with the relative orientation of the relevant electric dipole transition moment from each chromophore, thereby leading to an assignment of absolute configuration of the composite molecule[345].

The correlations comprise the exciton chirality rule, which was derived from nonempirical calculations. It states that when the relevant transition moments are oriented in a positive chirality, the long-wavelength component of the associated exciton couplet can be expected to exhibit a positive Cotton effect (Figure 16). When they are oriented in a negative chirality, the long-wavelength Cotton effect is negative. Thus, from the CD spectrum, one can determine the helical orientation of the transition moments and therefore the absolute configuration of the molecule, if the preferred conformation is known.

Applications of the exciton chirality rule have become numerous during the past fifteen years and claim an extraordinarily high degree of success in predicting absolute configuration[15,345]. In most applications of exciton chirality to the determination of absolute configuration, the molecule under study is derivatized with a suitable chromophore and its circular dichroism spectra are measured and analyzed. Successful application of the rule depends on knowing which chromophores are interacting and the orientation of the component chromophores' electric dipole transition moments.

In most of these studies, hydroxyl has been the typical resident functional group, which is derivatized with appropriate acids containing chromophores suitable for exciton coupling. The ideal chromophore would have a very intense UV-visible transition, located in a convenient spectral window, and with the orientation of its electric transition moment being well-defined relative to alcohol R−OH bond. One of the most successful has been *p*-dimethylaminobenzoate, which has an intense (ε *ca* 30, 000) transition in an

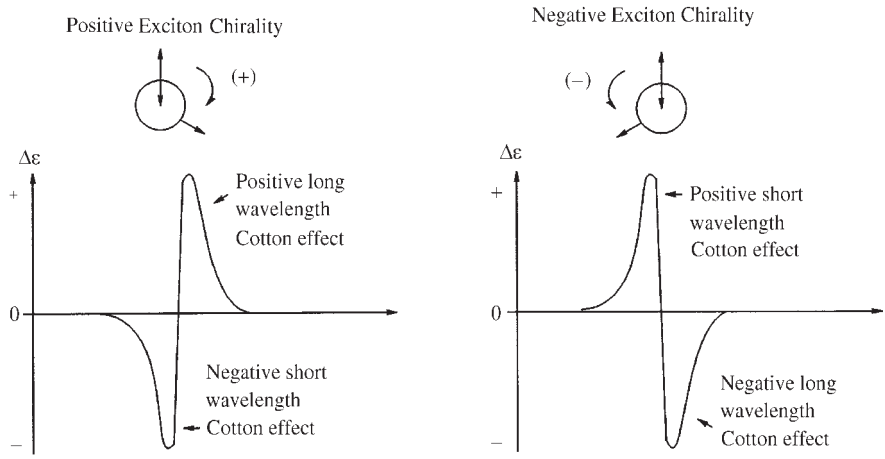


FIGURE 16. The exciton chirality rule relates the torsion angle or helicity of two electric dipole transition moments (⟷) to the signed order of the CD Cotton effects

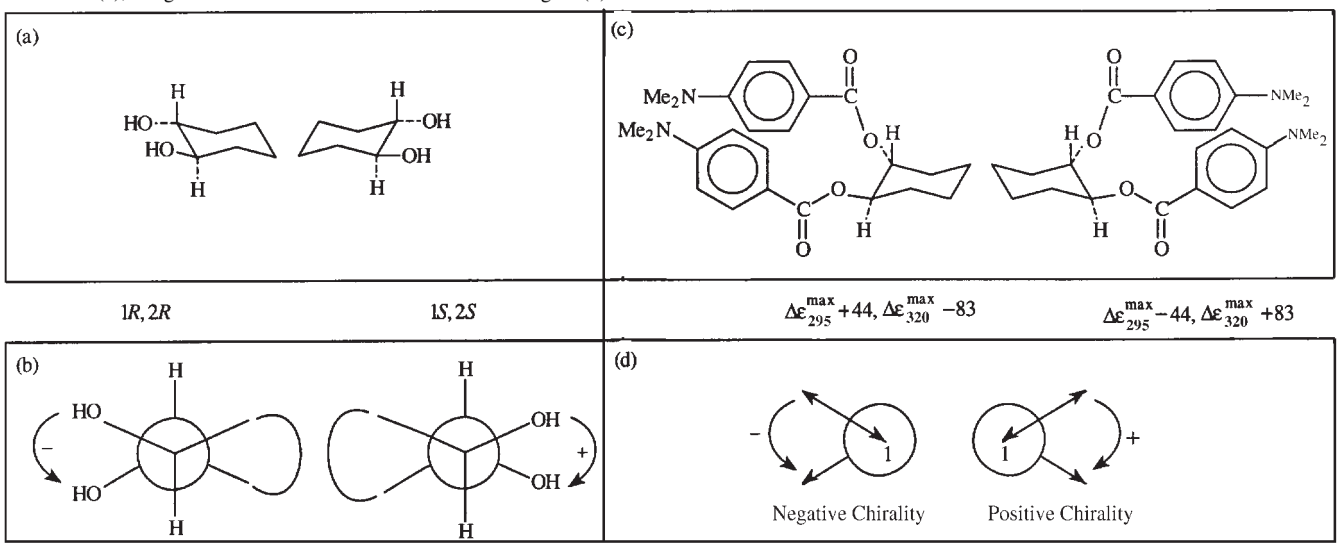
easily accessible, generally noninterfering, region (near 310 nm). The associated electric dipole transition moment of charge transfer transition is oriented along the long axis of the molecule, from nitrogen to carboxyl. Although the chromophore might adopt a large number of different conformations (relative to its point of attachment on the chiral molecule) by rotating about the ester bonds, one conformation (*s-cis*) apparently predominates, and the relevant transition dipoles are thus aligned parallel to the ester R−O bond. One can determine the relative helicity (+ or −) of the transition dipoles by inspection and assign absolute configuration from the CD spectrum[14,15,345].

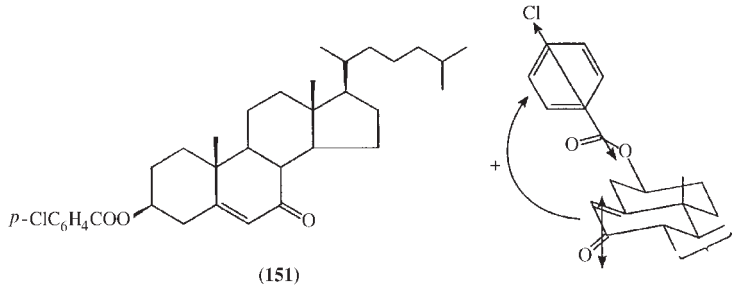
The cyclohexane ring of *trans*-1,2-cyclohexanediol (Table 9) adopts a chair conformation, with diequatorial preferred. The two enantiomers exhibit oppositely signed O−C−C−O torsion angles. In the bis-*p*-dimethylaminobenzoate derivatives, the electric transition moments lie parallel to the alcohol C−O bonds. Thus, the relative orientation (helicity) of the two transition dipoles correlates with the signs of the torsion angles. According to the exciton chirality rule, a positive exciton chirality is predicted for the (1*S*,2*S*) enantiomer, and a negative exciton chirality is predicted for the (1*R*,2*R*) enantiomer — in complete agreement with the observed bisignate Cotton effects.

Orientation, proximity and chromophore are paramount considerations in applying the exciton chirality rule. Extrachromophoric considerations are relatively unimportant. Thus the CD spectra of bis-*p*-dimethylaminobenzoates of 5α-cholestan-2α,3β-diol and (1*R*,2*R*)-cyclohexanediol (both diequatorial diols with the same absolute configurations) are essentially identical. Other steroid diols, whether with vicinal hydroxyls or very distant hydroxyls, give bisignate CD Cotton effects originating from exciton coupling — with a signed order consistent with the exciton chirality rule[15,345].

Soon after the original development of exciton chirality method[346,347] for steroidal diols, Koreeda, Harada and Nakanishi[348] extended its application to exciton interaction between benzoate transition at 230 nm (ε 14,000) and enone $\pi \rightarrow \pi^*$ transition at 230–260 nm (ε 7,000–15,000). The *p*-chlorobenzoate of 3β-hydroxycholest-5-en-7-one (**151**, Figure 17) exemplifies the application of this method[348]. The 3β-hydroxy-enone has a $\Delta\varepsilon$ typical of the *s-trans* enone chromophore, and the relative orientation (helicity) of the two interacting dipoles in *p*-chlorobenzoate **151** is shown in Figure 17. Such positive exciton chirality

TABLE 9. Conformational structures (a) and Newman projection diagrams (b) of (1*S*,2*S*)- and (1*R*,2*R*)-cyclohexane diol. Bis-*p*-dimethylaminobenzoate derivatives (c), bisignate CD Cotton effect data and torsion angles (d)[14]

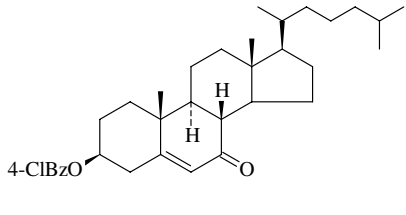




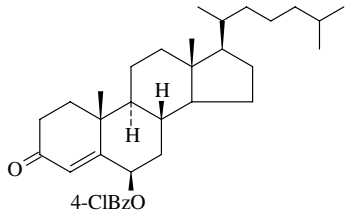
(**151**)

FIGURE 17. 3β-Hydroxycholest-5-en-7-one *p*-chlorobenzoate and its conformation (right) showing the orientation of the *p*-chlorobenzoate and enone transition dipoles giving a positive exciton chirality

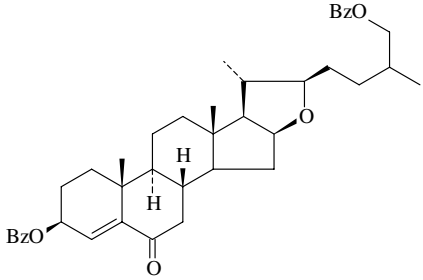
is predicted to give rise to splitting of the CD band into a positive lower-energy Cotton effect and a negative higher-energy Cotton effect, which were experimentally observed: *p*-chlorobenzoate **151** exhibits $\Delta\varepsilon_{246}$ +16.7 and $\Delta\varepsilon_{221}$ −21.6. In contrast, the corresponding acetate ester is noninteracting and has $\Delta\varepsilon_{max}$ around 210 nm. Large exciton interactions have also been found between two α,β-unsaturated ketone chromophores[348].



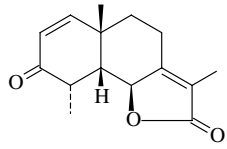
+16.7 (246), −21.6 (221)[348]



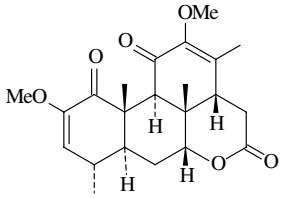
−24.4 (247), +23.0 (224)[348]



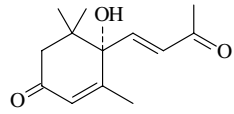
−25.1 (242), +3.2 (221)[348]



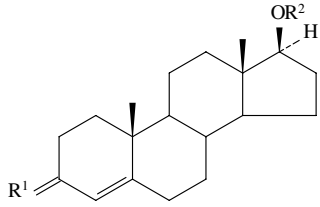
−23.0 (228), +11.3 (208)[348]



−2.5 (330), +10.4 (266), −9.5 (242)[348]

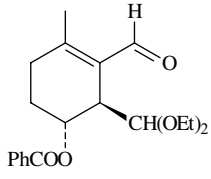


+38.4 (242), −30.2 (208)[348]

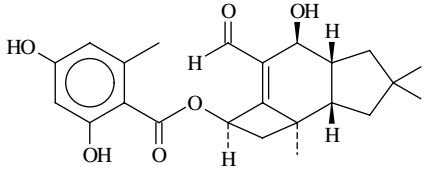


(152) R^1 = O, R^2 = 4-ClC_6H_4CO +25.6 (247), −1.8 (230), +8.4 (212)
(153) R^1 = O, R^2 = H sh +7.6 (236), +11.0 (215)
(154) R^1 = OH, H, R^2 = 4-ClC_6H_4CO +5.0 (241)

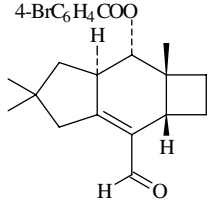
The pure contribution from exciton coupling in testosterone 17β-(*p*-chlorobenzoate) **(152)** was estimated by subtracting the CD spectra of exciton interaction-free 17β-hydroxy-4-en-3-one **(153)** and 4-en-3β-ol-17β-(*p*-chlorobenzoate) **(154)** from the experimental CD spectrum of **152**. The exciton CD curve (+16.2 (247), −12.8 (230)) obtained is much more symmetrical, as required by the theory[349]. Several more examples of benzoates and sorbates of steroidal 4-en-3-ones were treated in similar way, thus smoothing the imbalance of the exciton Cotton effects due to contributions of component chromophores.



−1.65 (335), −3.00 (242), +4.00 (217)[350]

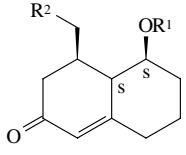


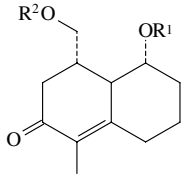
+0.3 (384), −0.8 (336), +2.0 (300), −24.1 (270), +21.0 (250)[351]



+3.4(256), −8.4(238)[353]

The absolute configuration of Wieland–Miescher ketone analogues bearing an angular protected hydroxymethyl group was unambiguously determined after regio- and stereoselective reduction of the saturated ketone function to *cis*-alcohols and application of the exciton chirality method to bicyclic enone-benzoate chromophoric systems **155–158**[352].



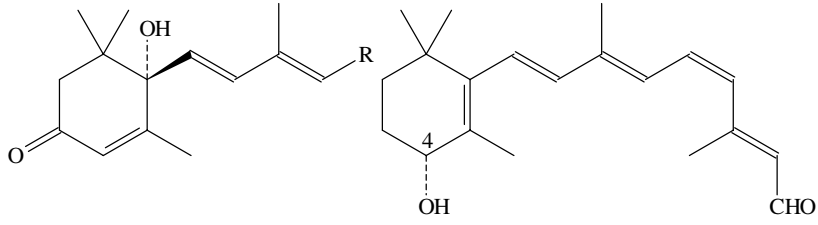


(155) R^1 = 4-ClC_6H_4CO, R^2 = H +40.6 (247), −16.0 (228)

(156) R^1 = 4-ClC_6H_4CO, R^2 = OMEM +38.1 (248), −15.5 (230)[352]

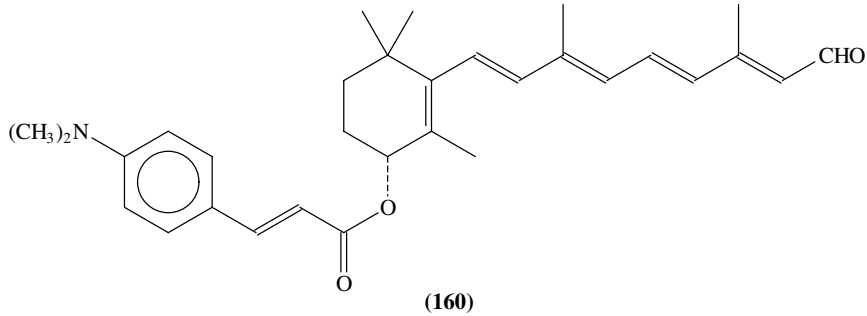
(157) R^1 = 4-$MeOC_6H_4CO$, R^2 = Ac −30.4 (261), +14.7 (241)

(158) R^1 = 4-$MeOC_6H_4CO$, R^2 = Me −25.0 (260), +12.1 (242)[352]



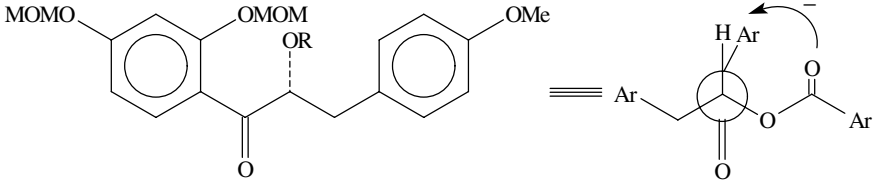
(159)

R = CN +49.4 (261), −37.0 (227)
R = CO_2CH_3 +50.5 (261), −38.9 (228)[354]



(160)

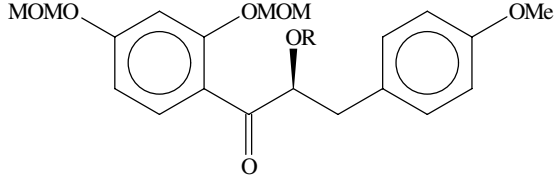
The (4*R*)-absolute configuration of a new chromophore of native visual pigment **(159)** (negative Cotton effect at 375 nm, negative Cotton effect at 254 nm) was established by the CD exciton chirality method applied to the 4-(dimethylamino)cinnamate **(160)**. The split negative (381 nm) and positive (338 nm) exciton effects of **160** show a counterclockwise helicity between pentaenal and α-4-(dimethylamino)cinnamate chromophores[355].



(161)

−4.57 (283), +5.81 (245)

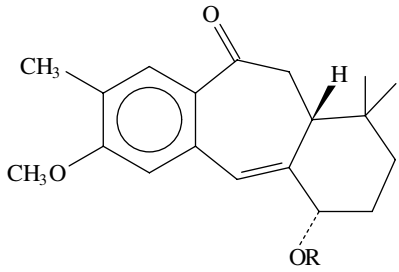
R = 4-$MeOC_6H_4CO$



(162)

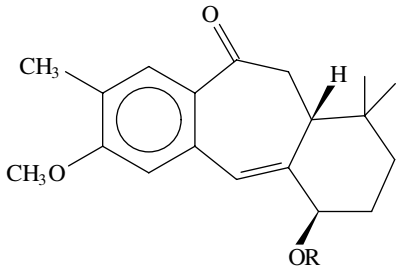
+5.10 (282), −7.97 (245)

Exciton interaction between *p*-methoxybenzoate and benzoyl chromophores in the preferred conformation of **161** allowed for assignment of the (αR) absolute configuration on the basis of an observed negative exciton chirality[356]. This also correlates with the absolute configuration of a novel natural 4-methoxy-αR,2′,4′-trihydroxydihydrochalcone. A series of 12 differently-substituted **161** or **162** analogues with an oxygenation pattern similar to that in natural flavonoids was reported by the same group. As with **161** or **162**, exciton-type Cotton effects were observed[288].



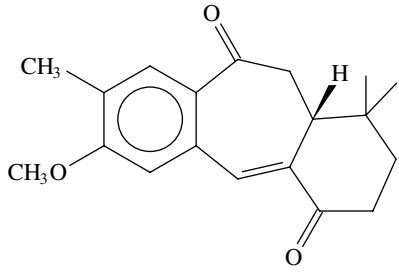
R = H −14.5 (333), +5.0 (295), +11.7 (260)

R = 4-$CH_3OC_6H_4CO$ −10.9 (335), +5.1 (293), +4.9 (285), +22.9 (263), −10.9 (245)[357]



(163) R = H −13.2 (340), +7.2 (296), +1.5 (270), +2.1 (263)

(164) R = 4-$CH_3OC_6H_4CO$ −5.8 (345), +8.0 (299), −72.1 (262), +16.0 (245)[357]

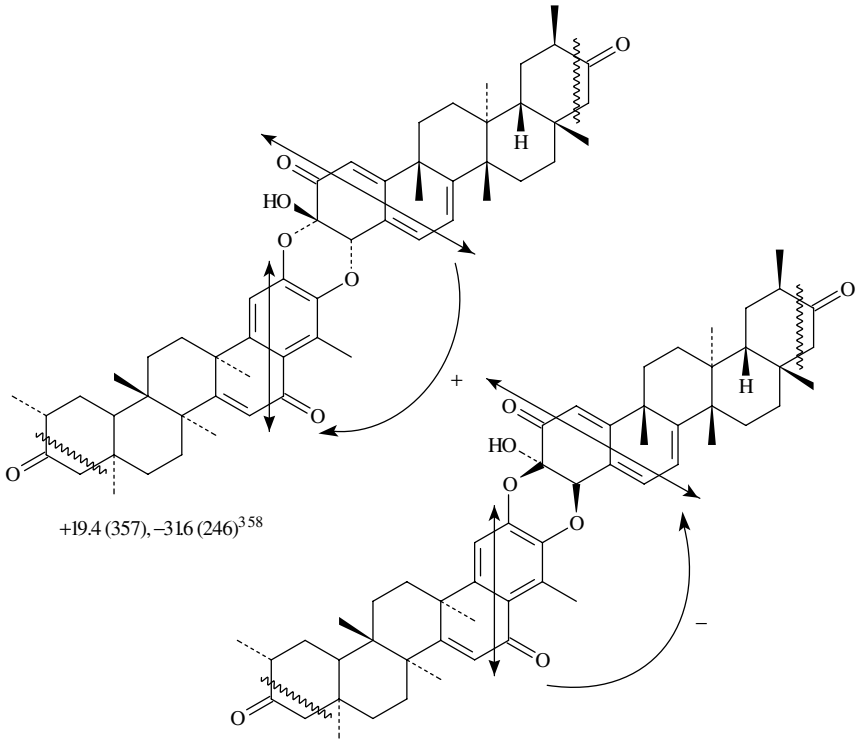


−9.9 (347), +8.2 (303), −15.8 (267)[357]

The absolute configuration of the benzocycloheptenone, (−)-isofavelol **(163)**, was confirmed as (9*R*,12*R*) by X-ray crystallographic analysis of its 4-bromobenzoyl derivative, and by exciton chirality between the *o*-ketostyrene and 4-methoxybenzoate chromophores in **164**[357].

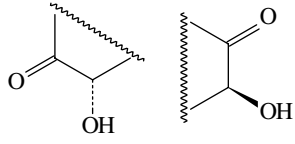
No exciton coupling was observed for the dialdehyde **165**. The CD of (+)-**166** also shows a simple pattern. The small amplitude of those Cotton effects can be attributed to the complicated polarization spectra of benzophenone chromophore and to the conformational flexibility of the 2-tolyl group. In contrast to (+)-**165** and (+)-**166**, the quinone (+)-**167** exhibits relatively strong Cotton effects ascribed to exciton interaction between favorably oriented transition moments in the 9,10-anthraquinone chromophore[359].

The CD spectrum of ketone **168** also exhibits split Cotton effects: $\Delta\varepsilon_{275}$ −17.4 and $\Delta\varepsilon_{252}$ +24.7, corresponding to an intramolecular charge transfer transition at 261 nm (ε 28 300). Since this transition is polarized along the direction from the benzene ring to

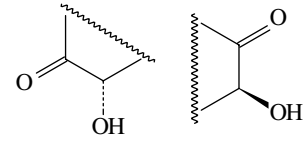


+19.4 (357), −31.6 (246)[358]

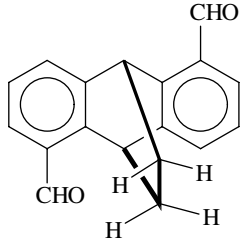
−12.2 (397), +12.3 (331), −60.0 (261)[358]



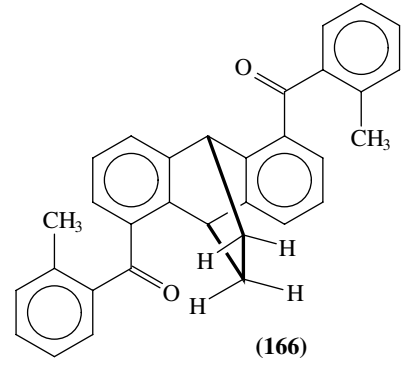
+21.2 (359), −34.9 (246)[358]



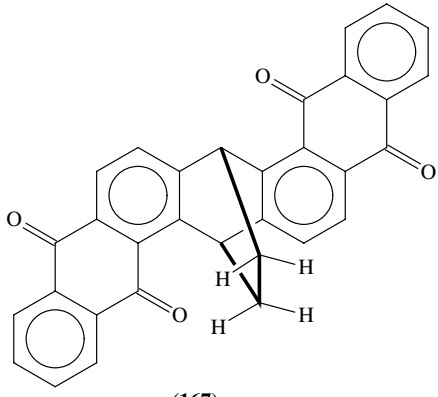
−10.0 (397), +9.7 (331), − 48.2 (262)[358]



(165)
−1.1 (335), +16.0 (297),
+29.4 (240), +31.2 (219)[359]

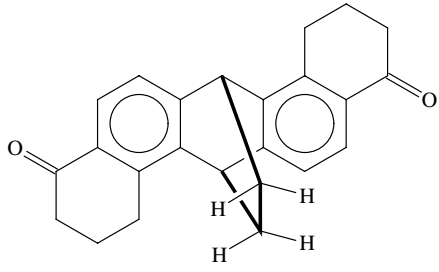


(166)
+6.6 (289), +10.6 (254),
−4.1 (228)[359]



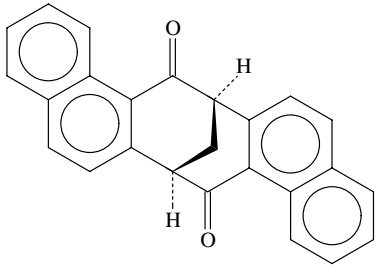
(167)

+33.6 (360), −2.1 (324), −44.1 (279),
+133.4 (260), −26.3 (247), +12.3 (232)
+34.2 (221)[359]



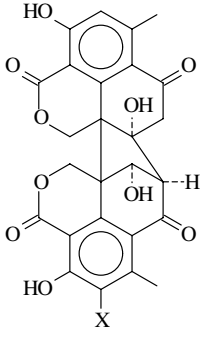
(168)

+0.4 (330), +2.3 (302),
−17.4 (275), +24.7 (252), +51.9 (214)[360]

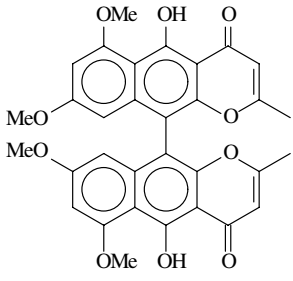


(169)

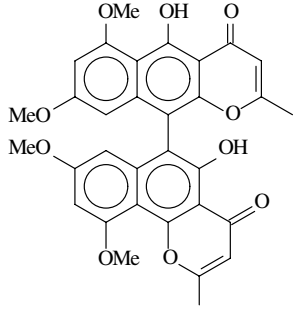
−37.6 (351), +22.9 (315), −12.6 (279),
−89.0 (254), +222.0 (217)[361]



(170) X = Cl
(171) X = H + 3.80 (342), −18.40 (294)
+ 13.60 (275), −24.10 (247),
+ 39.70 (231)[362]



−5.05 (432), +4.00 (373),
+5.70 (343), −1.04 (320),
+2.61 (303), −73.1 (282),
+70.9 (267), −17.4 (250),
−6.53 (240)[363]



−1.87 (403), +1.32 (361),
+1.20 (350), +1.49 (343),
−33.0 (288), +70.24 (273),
−51.24 (251), −31.66 (245)[363]

the carbonyl group, a positive exciton chirality is predicted — similar to other dibenz[a, h]anthracene derivatives where it was actually observed. It was suggested that homoconjugation between the two tetralone chromophores changes the relative sequence of relevant energy levels[360].

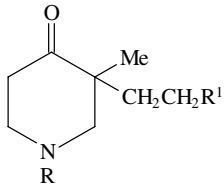
The absolute configuration of diketone **169** was confirmed by comparison of the experimental CD with that calculated by the SCF-CI-Dipole Velocity MO method[361].

By simplifying the chromophoric system of gilmaniellin **170** to *m*-divinylbenzene and applying the exciton chirality method to the CD couplet at 247 and 231 nm of **171**, its absolute configuration was determined as shown[362]. The sign of n $\rightarrow \pi^*$ CE (342 nm) is in agreement with the rule[234], which correlates the CD of transoid enone (acetophenone moiety) with its helicity.

VII. ADDENDUM

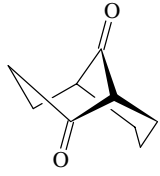
The following references/data were found during a search of *Chem. Abstr.*, Gen. Subject Index, 'Circular dichroism', Vol. 122 (Jan.–June), 1995.

Conformational analysis of 3,3-disubstituted piperidin-4-ones **(172)** using NMR and CD spectroscopy was presented recently[364].



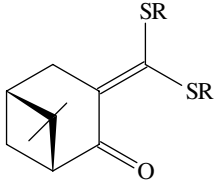
R = Me, CH_2Ph, (*S*)-CHMePh
R^1 = CN, CO_2Me

(172)

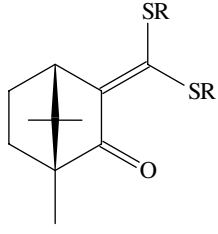


(−)-(1*R*, 5*S*)-**(173)**[365]

−0.42 (283), −1.25 (210)[159]



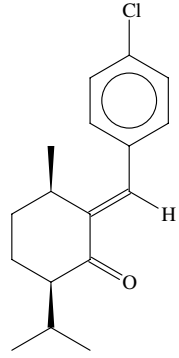
Reference 368



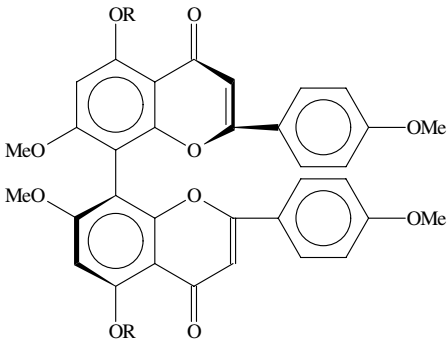
Reference 368

R	$\Delta\varepsilon_{max}$ $\lambda(n \rightarrow \pi^*)$ Dioxane		$\Delta\varepsilon_{max}$ $\lambda(\pi \rightarrow \pi^*)$ EtOH		$\Delta\varepsilon_{max}$ $\lambda(n \rightarrow \pi^*)$ Dioxane		$\Delta\varepsilon_{max}$ $\lambda(\pi \rightarrow \pi^*)$ EtOH	
CH_3	+0.025	408	+1.00	340	−0.56	380	+12.5	300
CH_3CH_2	+0.058	417	+0.67	330	−0.82	375	+11.2	300
$PhCH_2$	+0.179	413	+4.31	337	−0.99	375	+9.9	325
$-(CH_2)_2-$	+0.052	380	+1.62	342	−0.37	355	+13.1	315
$-(CH_2)_3-$	+0.068	397	+3.76	345	−0.60	375	+16.9	325

Berg and Butkus[365] reinvestigated the CD spectra of bicyclo[3.3.1]nonane-2,6-dione (**69**) and bicyclo[3.3.1]nonane-2,9-dione (**70**). They analyzed earlier reported CD spectral data[159] and compared them with calculated CD using Schellman's computational method. The comparison showed that the absolute configuration of α,ε-diketone (−)-**69** is in agreement with the earlier assignment. The absolute configuration of the (−)-enantiomer of α,γ-diketone **70**, however, has to be reversed to (1*R*,5*S*) as shown for **173**. The incorrect earlier empirical assignment[159] was explained by the spatial relationship of the two carbonyl chromophores in **173**. In the major chair-boat conformer they are placed close to the nodal planes where Cotton effects change their sign. In addition, the cyclohexanedione ring in **173** adopts a boat conformation[365]. The calculations also confirmed strong transannular orbital interactions in **173**, as was observed in **69**[366].

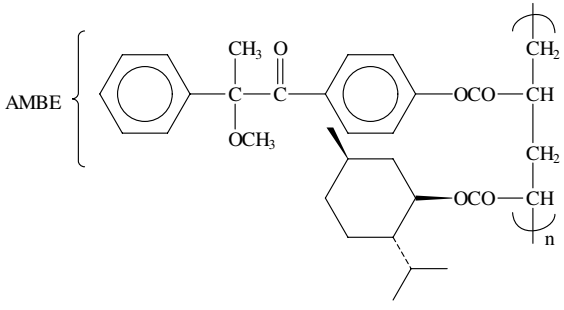


+2.02 (332), −26.35 (272)[367]



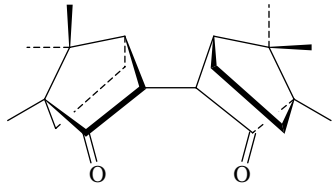
(+)-(aR)

R = H +28.1 (360), −66.4 (324), +24.8 (267)
R = Me +38.9 (344), −69.1 (310), +29.5 (258)
R = (+)-camphor-sulfonyl +71.7 (348), −79.4 (314), +33.9 (249)[369]

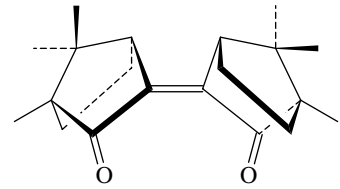


AMBE co-units (mol%)	$n \rightarrow \pi^*$ $\Delta\varepsilon \cdot 10^2$ (λ)	$\pi \rightarrow \pi^*$ $\Delta\varepsilon \cdot 10^2$ (λ)	$\Delta\varepsilon \cdot 10^2$ (λ)
79	−2.7 (339)	−9.5 (270)	−22.9 (253)
15	−11.2 (338)	−26.5 (269)	−70.7 (255)

$\Delta\varepsilon$ referred to one AMBE repeating unit [370].



(174)



EtOH	+2.14 (309), −2.59 (282)	−0.31 (441), +0.94 (351),
Hexane	+2.16 (315)	+19.63 (272)[371, 372]
	+1.63 (305), −1.96 (282)	

Sotiropoulos and colleagues[371] reported recently the crystal structure and CD spectrum of (1*R*,3*R*,4*R*)-3-((1*R*,3*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-2-oxohept-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**174**, 3,3′-dicamphor). This compound appears to be the first example of exciton coupling between two n → π^* transitions from isolated carbonyl chromophores, as incorporated in α,δ-diketone **174**.

VIII. ACKNOWLEDGMENTS

We wish to thank Professors Carl Djerassi, Albert Moscowitz and Günther Snatzke, without whose pioneering work much of what is written in this chapter would not have been possible. Special thanks go to those authors, Professors Djerassi and J. F. King, and journals or books for allowing use of illustrations from their articles.

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CHAPTER **6**

Dipole moments of compounds containing double bonds

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I. INTRODUCTION

Compounds with double bonds are important for the theory of dipole moments and dipole moments are of importance for determining structure of compounds with double bonds. There are two reasons for this. All double bonds give some degree of rigidity to the molecule which enables the partial dipole moments to be treated as vectors of known

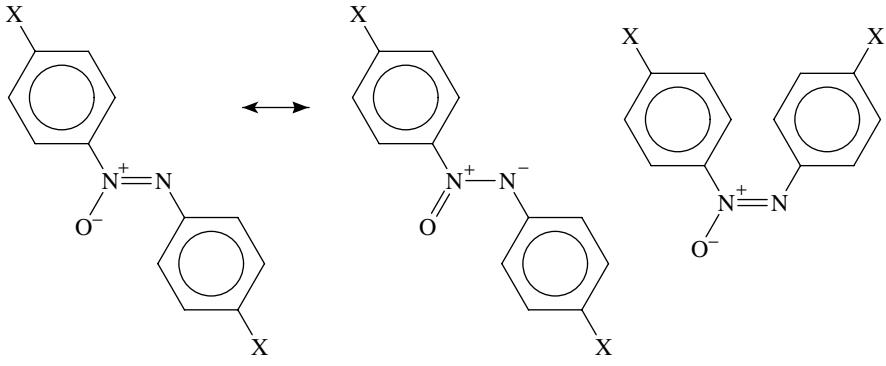
direction. Second, some double bonds, particularly C=O and C=N, themselves possess a considerable dipole moment of known direction and of a reasonably constant magnitude. Therefore, dipole moments were one of the first physical methods applied for determining configuration on the double bond or conformation on the adjacent single bonds (or partial double bonds). The example of (*E*)- and (*Z*)-1,2-dichloroethenes[1] may be considered as the first in history when configuration was determined directly and nonempirically, from a pure principle. Numerous further examples were reviewed in a previous article[2] in this series. Particularly important was the extension to partial double bonds whose double-bond character is sufficiently strong to keep the molecule in a relatively stable conformation. In this case dipole moments are often an efficient experimental approach (esters, amides).

Nevertheless, when this article is continued after two decades, it should not remain restricted to stereochemical problems. During that time, other very powerful methods will have been developed which are mostly easier and often also more reliable. Particularly, the recent development in X-ray analysis gives a completely reliable proof of configuration valid even for the isolated molecule: in the case of conformation it may appear necessary to prove that it is unchanged in solution (see for instance Reference 3). While X-ray is the most reliable method, NMR spectroscopy is the fastest. It still uses some empirical rules and comparison with model compounds, but in a modern version (2-D NMR, NOE) it is also completely trustworthy. Therefore, many recent dipole-moment studies investigated compounds whose steric arrangement was already known, and attention was focused on the electron distribution on the individual bonds, or in conjugated systems. The difference in the point of view may be explained as follows.

The dipole moment of a molecule can be generally interpreted in one of two ways. If we know — with a certain approximation — the electron distribution on the individual parts of the molecule, expressed say in terms of partial dipole moments or bond moments, then we can determine the mutual position of these parts to each other. The other possibility is that if we know the steric arrangement, i.e. configuration and conformation, then we can determine the electron distribution in some of the parts and express it, for instance, in terms of resonance formulas, of special moments valid only in this molecule, etc. Thus, in 1933 the dipole moments of substituted azoxybenzenes (**1**, **2**) were first used for determining their configuration. Although the reasoning was not exact with respect to modern views, the result was right[4]. The simplest proof today would be a reference to the 4,4′-dichloro derivative. Since **1a** and **2a** possess similar dipole moments, quite different from **1c**, the configuration *Z* is assigned to **1a**.

Fifty years later, when the configuration was known beyond any doubt, the dipole moments were reinterpreted in terms of electron distribution[5]. The direction of μ was determined for **1a** by means of substituted derivatives; the same was done for (*E*)-azobenzene as reference. The vector difference between $\boldsymbol{\mu}$ of these two compounds should represent the bond moment N−O. The standard N^+-O^- bond moment† was derived from trimethylamine oxide and the dipole moment anticipated for the ideal structure **1a** was calculated; the vector difference against $\boldsymbol{\mu}_{exp}$ was called the mesomeric dipole moment $\boldsymbol{\mu}_m$ according to the vector equation 1. This finding was explained by mesomerism of the two formulas **1a** and **1b**. Since the derived $\boldsymbol{\mu}_m$ was not oriented† from O toward N(2) but merely from O toward N(1), it was concluded that these mesomeric formulas do not describe the electron distribution completely and a hypothesis was advanced that the nitrogen atom N(1) could allocate more than its equivalent of eight electrons[5]. This

† Direction of the dipole moment is shown always from the positive toward the negative end; in the bond moments the first atom is positive. Units D (debye) are used throughout for better comparison with the previous review[2]; 1 D = 3.334 10^{-30} C m.



(1a) X = H μ_{exp} 1.70[†] **(1b)** **(1c)** μ_{exp} 4.71

(2a) X = Cl μ_{exp} 0.96

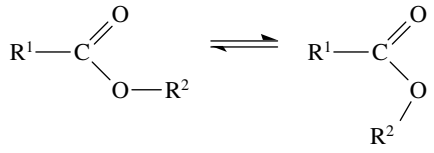
hypothesis need not be accepted: the example should only show how the dipole moments can be exploited in two different ways.

$$\boldsymbol{\mu}_m = \boldsymbol{\mu}_{exp} - \boldsymbol{\mu}_{calc} \tag{1}$$

In the examples which will follow, usually only one of the two problems is dealt with, although we do not exclude solving both problems only from the dipole moment values. Due to the competition of other methods, the stereochemical applications are suitable mainly for compounds with many heteroatoms and unstable conformations (unsuitable for NMR). Estimation of conjugation remains specific for dipole moments but is only a formal approach and may become, in some cases, too abstract. Actually, the two interpretations appear together rather often, and for this reason they will not be separated in this article either. Instead, the material will be divided according to individual bonds: n–π conjugated systems will be arranged according to the main, formally double bond (for instance amides under the C=O bond), π–π conjugated systems according to the bond which is dealt with later. The whole material covered exceeds a little that delimited for this Volume but corresponds to that in the previous article[2].

Let us mention that there are still other relations between conformation and dipole moments. Relative stability of conformational isomers was often brought in connection with their dipole moments. For instance, the preferred *sp* conformation of esters **(3a)**, or of carboxylic acids, was often explained by the lower dipole moment[6] compared to the conformation **3b**, or in other words by the electrostatic repulsion[7–9] of partial dipoles in **3b**. Reasoning of this kind is usually based on anticipated rather than measured moments: that of **3b** cannot be directly measured. Interaction of more distant dipoles is commonly neglected, viz both its effect on the conformation and on the total μ (see, for example, Klinot and coworkers[10]). This is in fact the fundamental assumption underlying all analyses of dipole moments.

Dipole moments of solutes are also involved in the so-called reaction-field theory[11,12] which predicts generally the Gibbs energy of solvation, and from it the stability of conformers as dependent on solvents. Besides the dipole the quadrupole moment is also taken into the calculations. For instance, conformational equilibria of cyclic halo ketones were predicted from the dipole moments of the two conformers with fair success[13]. However, the whole theory was criticised[14,15] that there is too much arbitrariness in the



μ_{calc} 1.6 μ_{calc} 3.4

(3a) **(3b)**

parametrization, so that almost any experimental result can be fitted. In any case, it is true in a qualitative sense that the form with a larger dipole moment is preferred in a polar solvent (see, for instance, Malecki and Nowak[16]).

II. PROGRESS IN THE DIPOLE MOMENT METHOD

A. Experimental Procedures

Concerning the dipole moments in general theory, experimental determination and applications in chemistry, see References 17 and 18. Since our last review[2] there has been little progress in this respect. The common experimental methods were compared and almost no difference was found between the two mostly used (Halverstadt–Kumler and Guggenheim–Smith)[19]. New methods of calculating μ from standard permittivity measurements were advanced[20], which particularly allow extending the measurements to polar solvents[21–23]. They have not been used more broadly: all data cited in this review were obtained in nonpolar solvents or in the gas phase. On the other hand, in nonpolar solvents problems may arise with dimerization of certain compounds: the calculations used until now were corrected from the statistical point of view[24]. These problems may be avoided by working at sufficiently low concentrations, although for some compounds (such as carboxylic acids) reliable values for the monomer cannot be obtained. The correction term for atomic polarization was also reinvestigated. Although it is still at issue[25], particularly in the case of certain symmetrical compounds and their apparent small dipole moments[26,27], the standard correction of 5% is recommended as a mean value for compounds of various structures[19].

A simplified experimental method which avoids measuring both density and refractive index (the Higasi method) has attracted new attention and was recommended[28], modified[29] and a new similar procedure advanced[30]. More trustworthy in our opinion is a statistical test[31] which concluded that the Higasi method is both inaccurate and biased and can be of acceptable accuracy only for compounds with rather high dipole moments.

Dipole moments determined in the gas phase by microwave spectroscopy are always accepted as reliable standards. However, even in this method errors may arise[32]. Moreover, this approach has remained restricted to rather small molecules. For the simplest molecules the method of molecular beam electric resonance can yield actual standards[33], by three orders more accurate than common methods. A program was started for measuring standard values of μ in solution at conditions similar to the gas phase[34]. A high-frequency technique allowed working in a nonpolar solvent (cyclohexane) at high dilution (weight fraction 10^{-4}). However, only few data are available at present and their accuracy is not particularly high.

We may conclude that the dipole moments determined 20–30 years ago by standard methods either in solution or in the gas phase are directly comparable to those measured

today in the same state. Older data in solution must usually be recalculated; see, for instance, Reference 5.

B. Calculations

Dipole moment for a given structure can be predicted by at least four methods: *ab initio*, semiempirical calculations, molecular mechanics and the bond moment scheme. At the present state of development, one cannot say generally which is preferable. The *ab initio* methods require a rather large basis and/or special sophisticated methods[35–37], so that they are of limited importance for molecules of that size which are dealt with in this review. Even so, the results are of different reliability in individual cases[38–40]. As an exception, even a simpler variant with a small basis may work[41]. One of the most difficult problems for calculations seems to be the too large moment of the nitro group[41] which is so popular in experimental work. Recently, the 6-31G(+sd+sp) basis was recommended[42] specially for dipole moments but the examples given represent molecules that are still small for our purposes. The *ab initio* methods can be combined with the reaction-field theory to calculate μ in different solvents[43,44]; experimental verification is difficult.

It is thus not surprising that semiempirical methods are still in use, either as standard methods[45–49] or in numerous special modifications[50–57] advanced for dipole moments, sometimes still for a particular class of compounds such as the second-row elements[55], nitrogen[56] or phosphorus[57] compounds. All these variants may possibly work, each in a certain range of derivatives. Sometimes, the results are quite satisfactory[47], in other cases quite bad[48,49,51], for instance particularly for benzene derivatives with polar substituents[49] which are so important in the common analysis. Various semiempirical methods were compared many times[45,46,50–53] but it is not possible to say which is generally preferable.

Molecular mechanics has often been found satisfactory within a limited set of compounds. One possible approach, called the IDME method[13], can be viewed as addition of bond moments improved by an additional inductive term. By incorporating the concept of reaction-field theory, effective μ in various solvents can be obtained. The examples given concern mainly halogen and oxo derivatives, particularly of cyclic structures[13]. The second approach, elaborated more extensively, is the proper molecular mechanics in the MM3 force field[58]. Within its framework μ can also be obtained as a merely marginal result: calculation is also based on bond moments but uses more differentiated values (compared to the simple vector addition mentioned below). Some parameters must be determined for every class of compounds separately. Of the compounds dealt with in this review, particularly aldehydes and ketones[58], diketones[59], carboxylic acids and esters[60], amides[61] and oximes[62] were elaborated. Each extension needs a couple of new empirical parameters and, with a small number of compounds, it is difficult to assess the success of this method. In a somewhat strange approach[63] the geometry is obtained from MM, then μ calculated *ab initio*.

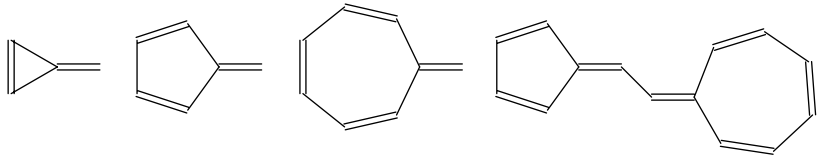
Last but not least, simple vector addition of bond moments still remains a method of choice in most structural applications. In detailed studies on rigid model molecules it was found that its principle is not quite exact[64] but the deviations from additivity were of a size which can be neglected in routine work. Particularly, a constant C−H bond moment was criticised as an oversimplification[65,66] since μ of hydrocarbons is not zero[67]. Nevertheless, the system works reasonably in practice and may still be improved when the bond or group moments are determined and applied in a certain range of similar compounds. A refinement taking into account the mutual polarization of all bonds was already mentioned[13]. This works for halogen and oxo derivatives, but it is not applicable for most compounds dealt

with here. Its simplified version, in the form of a computer program, should serve merely for demonstrative purposes[68]. Nevertheless, a deviation from the additive behavior may be appreciable even in monofunctional derivatives when a strongly polar group is bonded to a larger hydrocarbon residue[69]. Therefore, in detailed studies it is better to compare only molecules of similar size. In our opinion, the addition of bond moments is the method of choice, particularly when the effect of a remote substituent is to be accounted for. It works particularly well for substituents on the benzene ring which are used as references for determining the direction of other moments in the same molecule. This approach has been proved in numerous examples[2]. Sometimes, the concept of bond moments need not be used explicitly and the anticipated values of μ can be taken directly from model compounds[10].

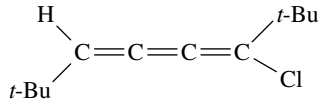
For determining conformation from the experimental dipole moments, two methods in common use may be considered as standard[17]. In the first, dipole moments of several *para*-substituted aromatic derivatives are measured[70]. In the second, the dipole moment is combined[71] with the Kerr constant, ${}_{\mathrm{m}}K$; one can make do with a single compound, but evaluation of the Kerr constant may be too complex and sometimes not completely reliable. In either case, a graphical representation is useful: either μ^2 values are plotted of substituted vs unsubstituted derivatives[70], or μ^2 vs ${}_{\mathrm{m}}K$[71]. In the first method, it has been commonly assumed that a distant substituent contributes an additional component to the overall dipole moment but does not itself influence the conformation. Many examples were given in the previous review[2] and further ones are given here. This principle is mostly an acceptable approximation, but it has also its limitations as revealed in one example by comparison with more accurate NMR results[72].

III. C=C BONDS

Unsymmetrical olefinic hydrocarbons possess very small dipole moments which nevertheless can be measured in the gas phase by microwave spectroscopy[67]. Within the framework of bond moments[17], these values are usually accounted for by attributing different values to the C−H bonds according to the hybridization on carbon: $\mathrm{H-C_{sp^2}}$ may be taken conventionally as zero, then $\mathrm{H-C_{sp^3}}$ equals 0.3 D. However, the dipole moment of styrene[73] (0.12 D) cannot be included in this scheme and should be interpreted either by a nonzero value for the $\mathrm{C_{ar}-C_{sp^2}}$ bond, or by different values for $\mathrm{H-C_{sp^2}}$ and $\mathrm{H-C_{ar}}$. In common calculations from bond moments, such details are neglected. With the conjugated systems **4–6**, μ was compared to similar nonconjugated hydrocarbons[74]. The result was that **4** has an aromatic character, **5** and **6** do not. Compound **7** has a very high μ[75]; the aromatic character of the two rings is obvious.

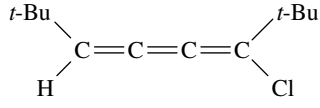


μ_{exp} 1.90	μ_{exp} 0.42	μ_{exp} 0.48	μ_{exp} 3.71
μ_{calc} 2.34	μ_{calc} 0.43	μ_{calc} 0.49	
(4)	**(5)**	**(6)**	**(7)**



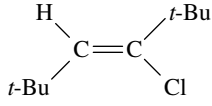
μ_{exp} 1.7

(8a)



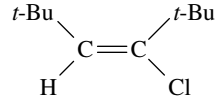
μ_{exp} 2.3

(8b)



μ_{exp} 2.0

(9a)

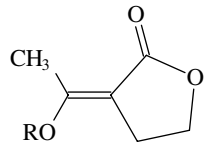


μ_{exp} 2.3

(9b)

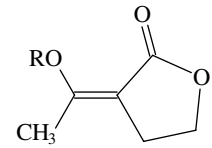
For determining configuration on a C=C bond, the dipole moment approach is not of much use. An exceptional case was reported[76] concerning the configuration on the cumulated double bonds in the 1,2,3-butatriene derivatives **8a**,**b**. The long-range coupling constants, $^5J_{HH}$, have not brought any decision and other methods were prevented by the properties of these compounds (rather unstable liquids). Resolution made on the basis of dipole moments exceeds the framework of bond moments: within it the dipole moments of **8a** and **8b** should be equal. In the second approximation, one can consider also the polarization of the hydrocarbon chain by the C−Cl dipole: then greater μ is anticipated for **8b**. This assumption was checked on simple ethene derivatives **9** used as model compounds, then the configuration of **8a** and **8b** was deduced from experimental dipole moments.

When a C=C bond is involved in an n–π conjugation, the electron distribution must be taken into consideration together with the conformation. In the compound **10** the C=C bond is conjugated with an ester group but the problem was configuration on C=C. It was assigned on the basis of dipole moments[77]; their anticipated values were obtained from bond moments with variable conformation on C−O. The only possible solution was finally *ap* conformation on C−O and zero μ_m. Agreement with experiment is not good: assignment was made merely in a qualitative sense by comparing the two isomers. In this case, there were evidently possibilities of assignment also by other methods.



μ_{calc} 3.0
μ_{exp} 1.71

(10a)

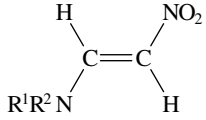


μ_{calc} 5.4
μ_{exp} 4.86

(10b)

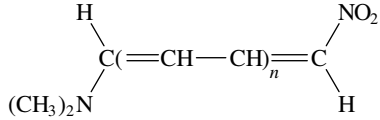
Dipole moments of nitrovinylamines **11** were larger than the sum of bond moments and the simple algebraic difference was taken as a measure of through-conjugation[78]. Conformation was assumed as planar. In this way, the exact direction of the mesomeric moment μ_m remained unknown: evidently the structure of the compound would not allow one

to introduce the necessary substituents. When the conjugated chain is extended (**12**), the calculated dipole moment increases[79] with the number of vinyl groups up to $n = 24$: the calculated values are overestimated but the trend could be reproduced well. As expected, the high dipole moments are strongly reduced, when the chain is rotated by 90° around one single bond[80]. Further push–pull systems were studied theoretically[81], some of them containing also benzene rings instead of ethene units[79,82,83]. In the case of vinyl ethers and vinyl sulfides, neither the conformation nor n–π conjugation can be neglected. According to IR spectra and from the temperature dependence of μ, an equilibrium of the *sp* and *sc* (<C=C–O–C 90°) forms (**13a**,**b**) was assumed for methyl vinyl ether[84], *sc* is populated at higher temperatures and prevails in *t*-butyl vinyl ether. The mesomeric moment of 0.72 D expressing the n–π conjugation was obtained previously from model compounds (for methyl vinyl sulfide 0.24 D). However, this result is at variance with calculations[85] claiming equilibrium of the *sp* and nearly planar *ap* conformations (**13a**,**c**). A more reliable analysis was carried out in the case of the dichloro derivatives **14** and **15**. It started from the assumption that the *t*-butyl ether **15** must be in the *ap* conformation[86]: no minor form was detected by IR spectroscopy. The dipole moment of **15** was measured and its direction estimated by means of the experimental Kerr constant. From it a group moment of the $Cl_2C{=}CH$ residue was evaluated and from it the dipole moments anticipated for the methyl ether **14** in various conformations; the same was done for the Kerr constant. The result was that even the methyl ether **14** (and ethyl and *i*-propyl ethers as well) is in the *ap* conformation. This example shows a very ingenious combination of various methods.



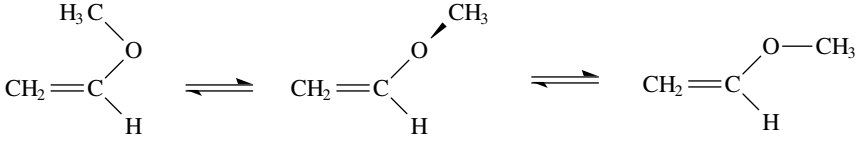
μ_{calc} 2.3

(11)



μ_{calc} 11.94–25.52

(12)



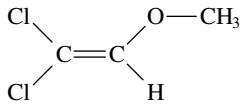
μ_{calc} 1.11
μ_{exp} 1.11

(13a)

μ_{calc} 1.88

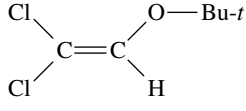
(13b)

(13c)



μ_{calc} 2.77
μ_{exp} 2.74

(14)

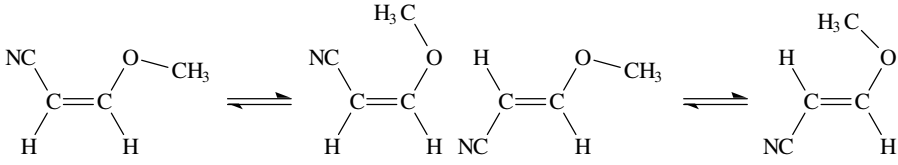


μ_{exp} 3.18

(15)

The $Cl_2C{=}CH$ group moment was not further resolved and no mesomeric moment was calculated. Ethenethiol has *sp* conformation in the gas phase as determined by MW and IR spectroscopies; at this opportunity the dipole moment was also measured[87].

With 3-methoxypropenenitriles (**16**, **17**) the problem was still more difficult since the conformation and conjugation were both estimated from dipole moments only[88]. Similarly, as in the preceding example, the *Z* isomer was taken as a fixed model which can have only *ap* conformation. Then the difference between the calculated and experimental moments was attributed to $n{-}\pi$ conjugation. In the case of the *E* isomer, the conformation *sp* seems possibly somewhat preferred but, irrespective of the conformation, the conjugation is strong, stronger than in the isomer *Z*. Again the analysis is incomplete since the directions of the mesomeric moments are not known exactly.



μ_{calc} 4.50
μ_{exp} 4.98

(16a)

μ_{calc} 3.06

(16b)

μ_{calc} 3.12

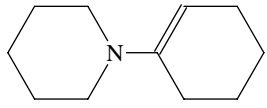
(17a)

μ_{calc} 4.38

μ_{calc} 3.24

(17b)

In the conjugated system $C{=}C{-}N$ the configuration on N can be assumed as planar. Then the conformation can be unambiguous and attention is focused on the electron redistribution due to conjugation. For instance, in **18** the conformation was not exactly known; conjugation was expressed[89] by the mesomeric moment of 0.9–1.5 D, calculated in a rather complex way.



(18)

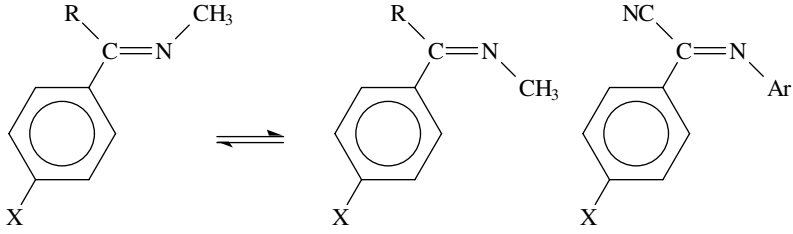
An interesting example of exploiting the dipole moment of simple olefins is the equilibrium between (*E*)- and (*Z*)-1,2-dichloroethenes in various solvents[90]. Equilibrium constants were determined indirectly (without achieving equilibrium conditions) and correlated with the solute dipoles and quadrupoles within the framework of reaction-field theory[11] with relative success.

IV. C=N BONDS

A. Isolated C=N Bonds

The C=N bond appears as most interesting from the point of view of dipole moments: it has itself a considerable moment, gives rise to variable configurations and can be involved in many conjugated systems. Nevertheless, an isolated C=N has been dealt with relatively rarely. Configurational equilibrium of some azomethines was investigated[91] mainly with the idea to compare the possibilities of dipole moments and of NMR spectroscopy. In the 4-chloro derivatives **19**, the substituent enabled the equilibrium to be determined

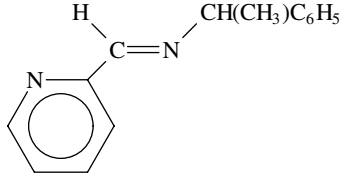
independently and nonempirically. However, NMR spectroscopy gives this equilibrium more precisely. With some other azomethines, the dipole moment of the equilibrium mixture was calculated using the NMR results and was in agreement with experiment[91]. In the azomethines **20** the dipole moments are more telling for the configuration, due to the presence of the polar CN group[92]: only the *E* configuration is present.



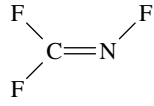
X = H, Cl
R = CH_3, C_2H_5, *i*-C_3H_7, *t*-C_4H_9

(19a) **(19b)** **(20)**

In the more complex azomethines **21** the configuration on C=N was in fact known from NMR; dipole moments served mainly to determine the *ap* conformation on the $C_{ar}-C(N)$ bond[93]. With the simple fluorinated azomethine **22** there are no stereochemical problems. The detailed geometry was determined[94] by both electron diffraction (ED) and by microwave (MW), and the dipole moment was also measured but not interpreted; even its direction is not known with certainty.



(21)

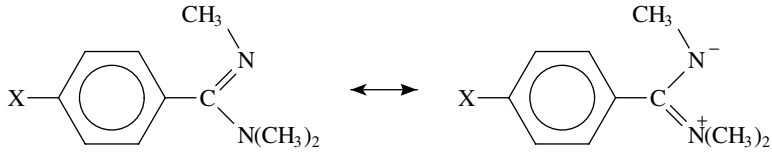


μ_{exp} 1.41

(22)

B. Conjugated Systems X−C=N

Structural chemistry of amidines is complex, including problems of tautomerism, configuration on the C=N bond, conformation on the C−N bond and electron distribution in the conjugated system. These problems were often mixed together in the literature but may be solved separately on suitable model compounds. In the case of *N*,*N*,*N*′-trimethylbenzamidines **(23)** it is in principle possible to deduce both the configuration and extent of resonance (**23a** ↔ **23b**) solely from dipole moments[95]. These possibilities are shown in Figure 1, which may serve also generally as an example of this kind of dipole moment analysis. The direction of the experimental dipole moment was determined by triangulation from the moments of the unsubstituted amidine (HX), its 4-nitro derivative (NX) and the nitro group itself (NH). Of the vectors calculated for the configurations (*E* and *Z*), none matches the experimental vector exactly: the difference would represent the mesomeric dipole moment $\boldsymbol{\mu}_m$ according to equation 1. Now, the



R = H μ_{exp} 2.48

(23a) **(23b)**

configuration *E* is unacceptable since the direction of $\boldsymbol{\mu}_m$ would have no physical meaning, while for the configuration *Z*, $\boldsymbol{\mu}_m$ has approximately the expected direction from N toward N′. Nevertheless, the configuration was confirmed independently from the NOE in ^{1}H NMR spectra[95]. The value of $\boldsymbol{\mu}_m$ 0.88 D means weaker conjugation than say in amides or thioamides and is also rather dependent on the substitution on the two N atoms, i.e. on their basicity. The problem of evaluating the extent of conjugation is generally complex. One has to keep in mind that one always compares an experimental dipole moment of a real molecule with an anticipated moment of an idealized nonrealistic structure (Figure 1). Further details of the analysis will be explained later (Section V.D) on the example of amides concerning which several approaches[89,96–99] can be compared.

Configuration of *N*,*N*-disubstituted amidines is thus regularly *E*, reversed rather than in amidines with a free NH_2 group which are *Z*[95]. Derivatives with only one substituent at the amino group are in the middle and their conformation may be sensitive to small steric effects. In **24** a tautomeric equilibrium would be degenerate, hence the problem is simplified. In the case of *N*,*N*′-diaryl derivatives, three forms are possible (**24a–c**); the fourth would be very improbable for steric reasons. From dipole moments an equilibrium

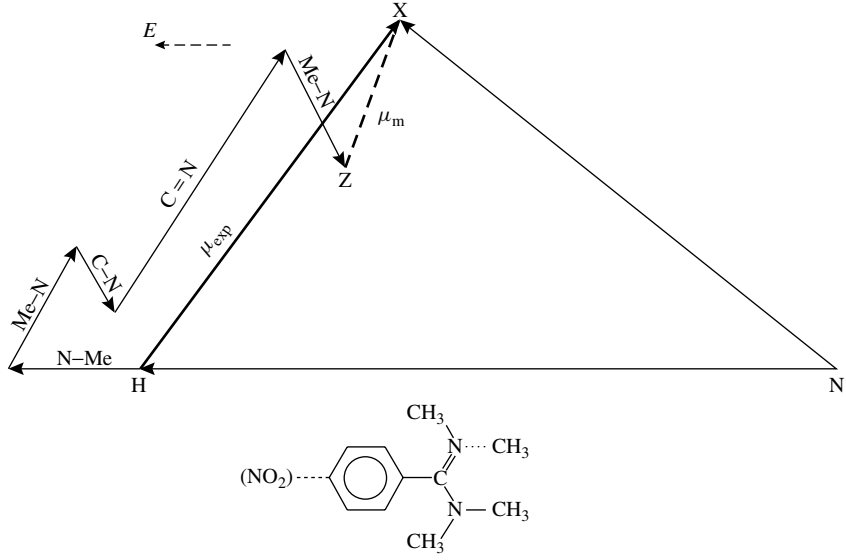
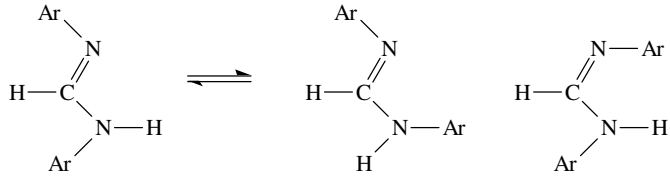


FIGURE 1. Determination of the configuration (*E* or *Z*) and of the electron distribution (the mesomeric dipole moment μ_m) of the amidine **23** on the basis of the experimental dipole moment (μ_{exp})

of **24a** and **24b** was deduced[100] while the mesomeric moment was found to be near to zero. The configuration and conformation of *N*,*N*′-dimethyl-4-nitrobenzamidine observed in the crystalline form[101] corresponds to **24b** (in contrast to the very similar amidoxime derivative; see later, Section IV.C). Dipole moments have not yet been published[102] but are also in agreement with an equilibrium of two forms, corresponding to **24a** and **24b**.



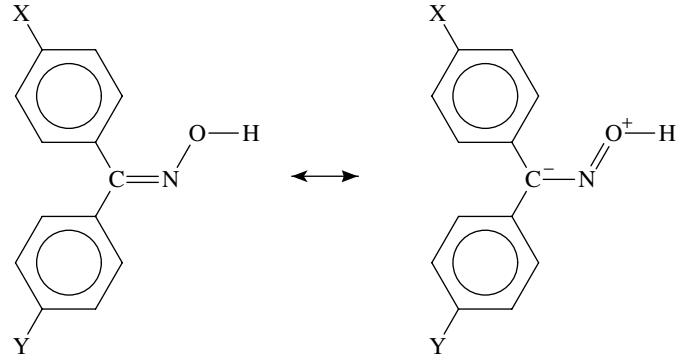
(24a) **(24b)** **(24c)**

$Ar = C_6H_5$ μ_{exp} 1.83

C. Conjugated Systems C=N−X

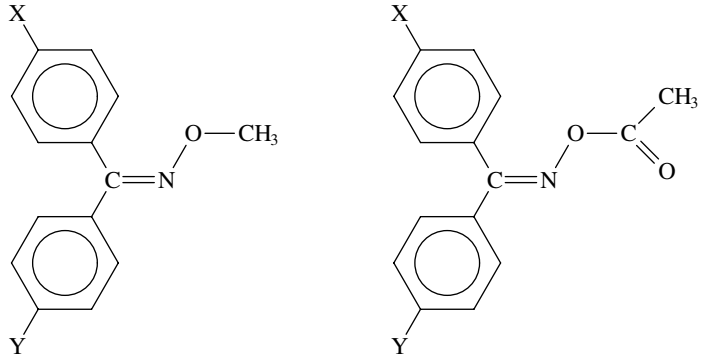
To this class belong first the derivatives of hydroxylamine, i.e. oximes and related compounds; much less attention has been given to the derivatives of hydrazine. The stereochemistry of oximes is connected with dipole moments by a long tradition since the configuration of nitrones was the first historical success of this approach[103], in fact the first solution of a stereochemical problem by a purely physical method. The history was described in the previous report[2]. However, the tradition is misleading and oximes are not just a suitable object for determining configurations by dipole moments. The problem is not so much in the *a priori* unknown conformation on the N−O bond, since this is almost uniformely *ap* as in **25**. More important is the n−π conjugation within the system C=N−O. Although it is evidently not strong, it may depreciate the results since the difference between stereoisomers is also small: it is dependent only on the small bond moment N−O, whose value was redetermined and essentially confirmed[104]. Determination of configuration of oximes[105,106] and of similar derivatives[107−109] was thus in the past depreciated by the unknown extent of conjugation, which was usually included in any way into the values of the bond moments, with a better or worse approximation. Today, when the configuration of oximes is known without any doubt, the problem may be reversed and the conjugation evaluated on some derivatives with known stereochemistry.

As a model system, benzophenone oxime and its two stereoisomeric 4-bromo derivatives **(25)** were chosen[110]. The direction of the experimental group moment was determined by triangulation, and the mesomeric moment estimated to be 1.62 D in the expected direction, approximately from O toward C. In the O-methyl derivatives **(26)** the mesomeric moment is reduced to 0.75 D. These results were confirmed by a statistical analysis of bond lengths in the C=N−O system[110]. They prove an evident conjugation and thus explain certain shortcomings in the previous stereochemical studies[105−109] where this conjugation was neglected. New problems arose with O-acetyl oximes[110]. Their configuration and conformation **(27)** is known from dipole moments and from X-ray but μ_m has a strange direction from C toward O in the C=NO group. Evidently the interpretation by mesomeric formulas is not sufficient for all kinds of electron distribution. It is true that results of such analysis may be affected by the conjugation with the benzene ring which can be only approximately corrected for. Nevertheless, MW spectroscopy of the simple (*E*)-acetaldoxime[111] yielded a similar value and direction of the dipole moment (in the gas phase); analysis into components was not attempted.



X,Y = H μ_{exp} 1.08

(25a) **(25b)**

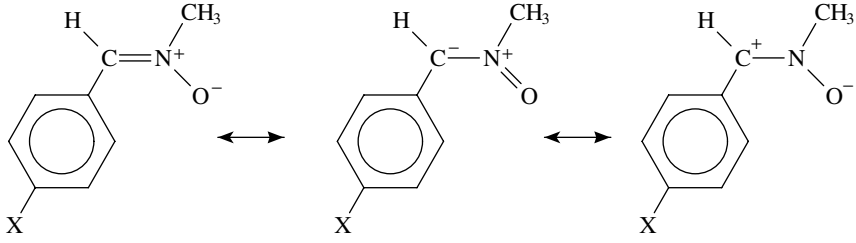


μ_{exp} 0.66 μ_{exp} 3.75

(26) **(27)**

A unique system with strong conjugation is represented by nitrones (imine oxides) **(28)** since already the basic mesomeric formula **28a** is polar. Configuration on the C=N bond is well known; in the past it has been determined first by dipole moments[103]. A recent dipole study[98] was thus concentrated on the electron distribution as expressed by the mesomeric formulas **28a–c**. When **28a** is taken as basic reference structure, a participation of **28b** should by manifested by a mesomeric moment oriented from O toward C, in the case of **28c** from C to N. The $\boldsymbol{\mu}_m$ found was almost exactly from O toward N and was interpreted tentatively by a structure in which the nitrogen atom allocates somewhat more than its equivalent of eight electrons. This somewhat strange hypothesis is confirmed by the bond lengths: while N–O is markedly shortened, C=N is not stretched. The same effect was observed with azoxy compounds[5] (weaker) and was considered also with nitro compounds[112] (stronger).

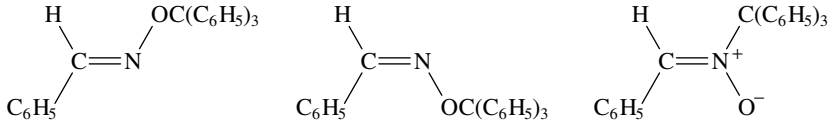
In the past, an important problem was distinguishing nitrones from the isomeric oxime O-ethers[113]. Among other possibilities the difference in dipole moments[2] is also quite



(28a) **(28b)** **(28c)**

X = H μ_{exp} 3.49

convincing; compare for instance **26** and **28**. In the case of stereoisomeric benzaldoxime-O-trityl ethers **(29)** the experimental dipole moments were used only for a proof[114] that **29b** does not possess the nitrone structure **30** as believed previously. Configuration of **29** was determined mostly by chemical reasoning, although it would follow also from the dipole moment rather safely: within the framework of conventional bond moments **29b** should have somewhat greater μ than **29a**.

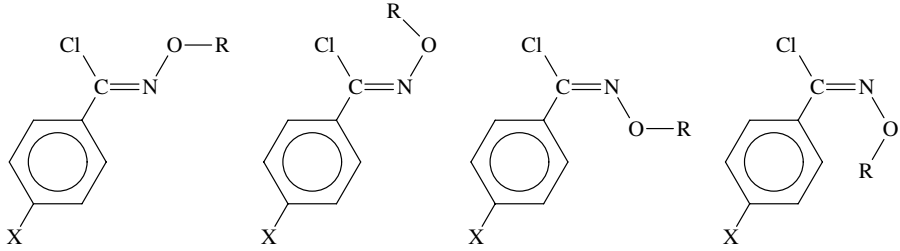


μ_{exp} 0.84 μ_{exp} 1.23 μ_{calc} 3.4

(29a) **(29b)** **(30)**

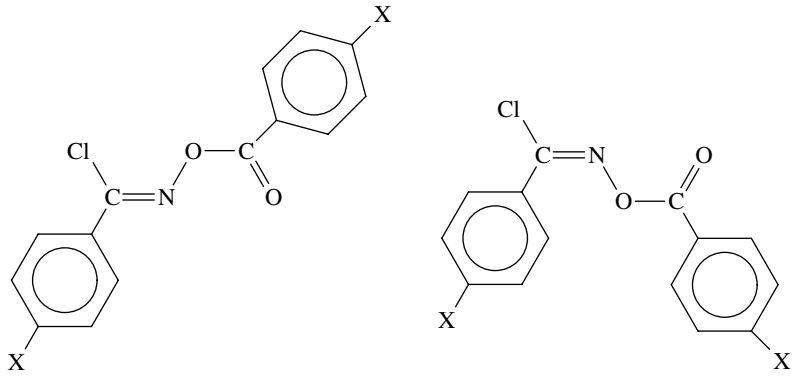
D. Conjugated Systems X−C=N−Y

Mesomeric moments within the group C=N−O can also explain the long controversy concerning the configuration of hydroximoyl chlorides. Both *E* and *Z* configurations **(31)** were claimed on the basis of dipole moment values[108,109]; the analyses were only slightly different but the final results were controversial. The problem is that the configuration on C=N itself has only small impact on the dipole moment: more consequential are the conformation on the N−O bond and the mesomeric moments. The latter was not taken into account at that time, so that a misassignment could easily arise. Shortly after these publications, the configuration (**31a**) was solved by X-ray analysis[115], after overcoming purely technical problems. With a knowledge of configuration in the crystal state, it was easy to prove that it is unchanged in solution[116] (opposite cases are very rare in the field of C=N configurations[117]); then the dipole moments were analyzed again[116]. Compared to standard bond moments, there is a change of electron density which, however, cannot be expressed by any simple mesomeric structure. Formally, it can be visualized as if the polarity of the C−Cl bond would be reduced. The misassignment was also made possible by the choice of improper model compounds. Note that even a cyclic reference model compound was investigated[109] whose dipole moment did not agree with standard bond moments[116]: nevertheless the assignment[109] made on its basis was right. This shows that the correct and incorrect assignments in this case were essentially fortuitous.



(31a) **(31b)** **(31c)** **(31d)**

The importance of a suitable model is clearly seen from the example of *O*-benzoylbezhydroximoyl chlorides **(32)** which were investigated independently at the same time[118]. Although the molecule of **32** is evidently more complex than **31**, its configuration and conformation **(32a)** can be determined more easily and more reliably. Very important is the possibility of introducing substituents from two sides. It enables a solution to be achieved even without resorting to the bond moments within the C=N−O grouping, by simple triangulation based only on the C_{ar}−Cl bond moments. In the first approximation one can say that μ of the parent compound is not much changed by substitution with chlorine on either end **(32a)**. Further proofs, also quite convincing, were obtained by comparison of UV, NMR and IR spectra with substituted (*E*)-*O*-benzoylbenzaldoximes[118], whose steric arrangement is well known.

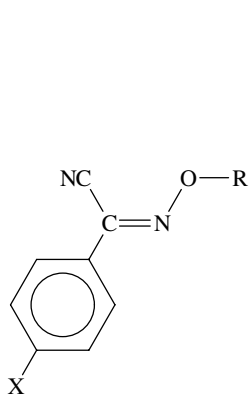


X = H μ_{exp} 2.09
X = Cl μ_{exp} 1.79

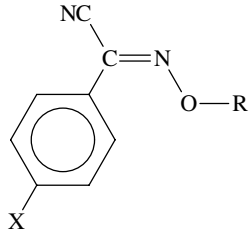
(32a) **(32b)**

O-Methylbenzhydroximoyl chlorides (**31**, R = CH_3) were prepared later. A great advantage was that both stereoisomers were isolated. The first assignment of configuration on the basis of dipole moment[119] was wrong for the same reason as in the case of parent hydroximoyl chlorides. A definite solution was again achieved by X-ray analysis[120]. With the knowledge of configuration and conformation and with the experience acquired above, an analysis of dipole moments was undertaken[121] focused only on the conjugation or electron distribution. A relatively small mesomeric moment $\boldsymbol{\mu}_m$ was revealed, oriented approximately from O toward C in both stereoisomers. In terms of mesomeric structures,

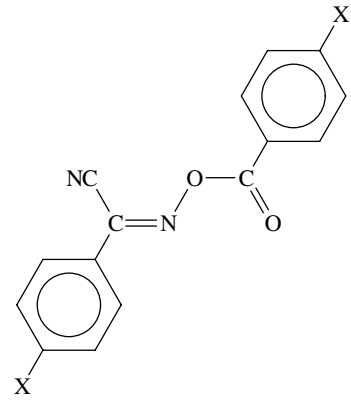
it should be represented by an electron transfer from O up to the benzene ring in **31a**. In the isomer **31c** the vector μ_m suggests an electron transfer toward chlorine which cannot be easily represented by a mesomeric structure. Very similar results were obtained with hydroximoyl cyanides **33**, which were also isolated in both stereoisomers[122]. The main result is that conjugation is evidently dependent on configuration: it is stronger when the conjugated groups are in *trans* position. With a knowledge of mesomeric corrections it was possible to determine configuration of (*Z*)-*O*-benzoylbenzhydroximoyl cyanide **(34)** which was obtained only as one stereoisomer[122], while a 4,4′-bis-derivative was not available.



(33a)

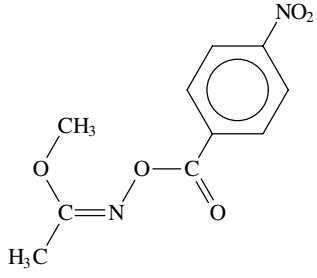


(33b)

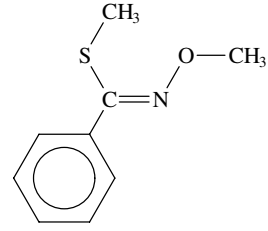


(34)

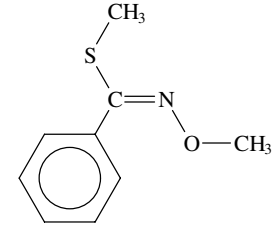
The derivatives of *O*-methylacethydroximic acid **(35)** and *S*-methylthiobenzhydroximic acid **(36)** contain still one additional axis of rotation, the C−OMe or C−SMe bond, respectively. Their steric arrangement could be determined from dipole moments[123,124] when previous experience on similar compounds was exploited. In **35** the conformation on N−O was assumed *ap* as it is uniformly in all derivatives of this type; also the conformation *sp* on C−O in the ester group is beyond discussion. Conformation of the methoxy group was in similar derivatives rather flexible[107]; it can be approximated by a free rotation or by equal representation of the two planar conformations. With these assumptions it was not difficult to decide[123] between *E* and *Z* configurations on the C=N bond: the observed configuration *Z* is common for benzoyl derivatives of oximes and of hydroximic acids. In the second case **(36)** there was an advantage of having both stereoisomers[124]. With similar assumptions as above (free rotation around the C−S bond etc.), the calculated dipole



(35)



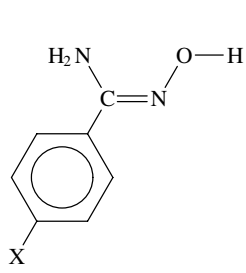
(36a)



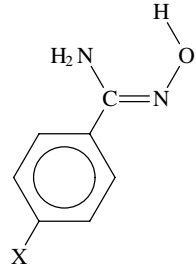
(36b)

moments were sufficiently different for the two stereoisomers. The result was supported by systematic comparison of several derivatives, some of which could be assigned by special methods, for instance exploiting intramolecular hydrogen bonds[124].

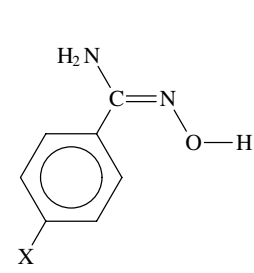
Various substituted amidoximes have been investigated from both the point of view of steric arrangement and conjugation. The problem is that both stereoisomers were isolated only rarely[125]; moreover, the configuration is not uniform and depends on the substitution on nitrogen. Amidoximes with an unsubstituted NH_2 group are known only in one isomer. Isolation of the second, less stable stereoisomers was assumed as impossible since a prototropic equilibration would be possible[126]. Steric arrangement in solution was investigated by means of dipole moments in the standard approach[126]. Of the four *a priori* possible forms **37a–d**, the *Z* configuration was revealed unambiguously, together with the conformation *ap* on the N–O bond **(37a)** which is common for all oximino derivatives. The same steric arrangement follows from the dipole moments of O-benzoyl derivatives **(38)**, where it is determined with yet more certainty due to the possibility of introducing substituents from either side. (In the first approximation the configuration is evident from the dichloro derivative **38**.) Configuration and conformation of these simple amidoximes is thus uniform, both in solution and in the crystalline state. In the subsequent dipole moment study of additional substituted amidoximes attention was focused on the conformation in the rest of the molecule[127].



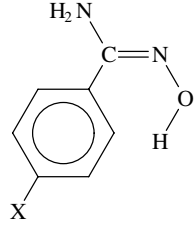
(37a)



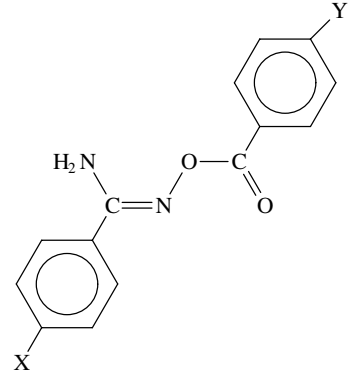
(37b)



(37c)



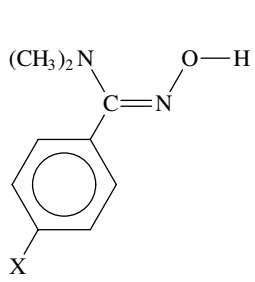
(37d)



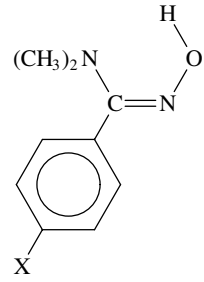
X = Y = H μ_{exp} 4.71
X = Y = Cl μ_{exp} 4.58

(38)

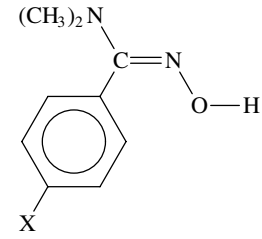
In *N*,*N*-dialkylamidoximes a reversal of configuration takes place. The stable form is *E*,*ap* **(39c)**, which was found several times in crystal and is also compatible with the dipole moments in solution[128]. It seems thus common for all amidoximes with two substituents in the amino group. When two stereoisomers are isolated[125], then the form corresponding to **39c** is thermodynamically stable. Also, *O*-benzoyl derivatives **40** keep the same arrangement[128]: in this case μ_{exp} of the dichloro derivative is distinctly different.



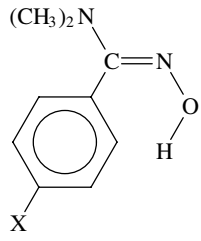
(39a)



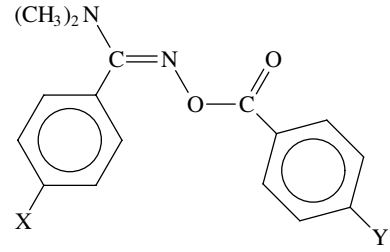
(39b)



(39c)



(39d)



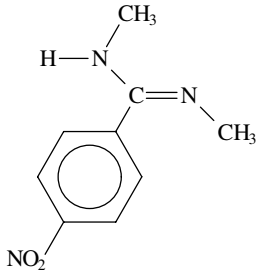
X = Y = H μ_{exp} 4.38
X = Y = Cl μ_{exp} 3.57

(40)

It remains to mention derivatives with just one substituent on the NH_2 group. Concerning the configuration, they should take an intermediate position: in addition, one has to deal with the conformation on C−N. These compounds have been less studied. Compared to structurally very similar amidines, a remarkable difference was found[101]. While *N*,*N*′-dimethyl-4-nitrobenzamidine in the crystal is in the form *E*,*sp* **(41)**, *N*′-methyl-4-nitrobenzamidoxime is *Z*,*ap* **(42)**. Dipole moments in solution are compatible with a conformational equilibrium, but analysis is made imprecise by the mesomeric moments which are not known exactly[102]. In a previous analysis[129] of μ of derivatives similar to **42** (H and Cl in place of NO_2) the form *Z*,*ap* was also preferred, although the presence of a minor conformer could not be completely excluded.

Nitrone derivatives of a unique structure were prepared recently[130]. The two stereoisomers **43a** and **43b** are in equilibrium in solution; configuration was determined by means of NMR spectroscopy. Dipole moments were calculated by MNDO for both stereoisomers, but were not measured. In our opinion one suitable approach has thus been omitted.

In the chemistry of hydrazones, some specific problems may arise. Dipole moments of α-chlorohydrazones **44** suggested the configuration *Z* and conformation *ac* on the N−N



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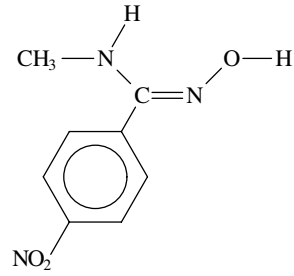

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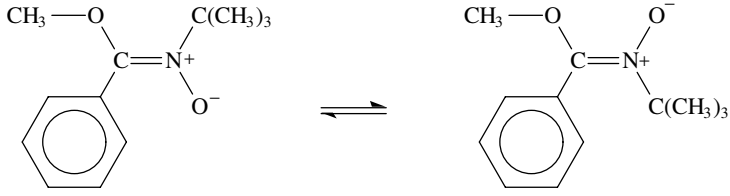
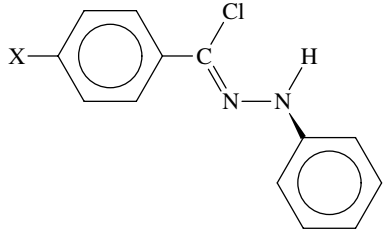


μ_{calc} 3.31

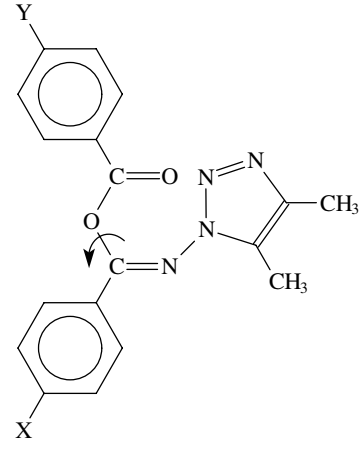
(43a)

μ_{calc} 4.71

(43b)



(44)



(45)

bond[131], in agreement with the crystal structure, but the fit with experiment was rather bad. A formal explanation was suggested that the N−N bond, connecting two quite different atoms, should be attributed a small bond moment directed from N_{sp^3} toward N_{sp^2}. This is evidently an *ad hoc* explanation and should be verified on further examples.

Another example from the chemistry of hydrazones **(45)** represents a complex problem[132]. The group moment of the heterocycle was taken from theoretical calculations; conformation on (O)C−O is evident. One has to determine conformations on N−N and (N)C−O bonds, but the most important problem is the configuration. The final result was a form near to **45** with a torsional angle <C−O−C−C near to 90°. In previous examples, we preferred to express the conformations at this position as an equilibrium of two planar forms or a formally 'free rotation': all these interpretations are indistinguishable within the framework of dipole moment theory. In any case, this example is at the limits of possibilities of this approach.

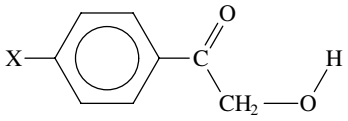
V. C=O BONDS

A. Isolated C=O Bonds

An isolated C=O cannot give rise to any configuration. Within the framework of the bond moment scheme, all aliphatic oxo compounds should possess equal dipole moments. The C=O bond moment could be derived from μ of formaldehyde, measured with extreme accuracy[33] (2.33168 D). Within the second approximation, individual carbonyl compounds can be distinguished[133] since the C=O dipole is large and produces perceptible induced moments in the hydrocarbon rest. For the same reason the mutual position of several carbonyl groups has a great impact on the molecular moment, and the conformation can be investigated relatively easily[134]. Usually this conformation is not very interesting: when the functional groups are separated by a longer chain, it is then approaching the statistical model of a free rotation of all parts (random coil)[2]. Also, in halogen ketones, the mutual position of C=O and C−Hal dipoles has a great impact on the overall dipole moments and their electrostatic interaction is considered an important factor controlling the conformational equilibrium[8,13]. In steroidal ketones with an additional substituent, the values of μ were used to determine conformation of the six-membered ring[10].

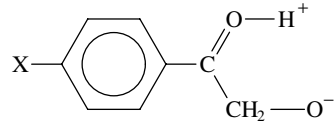
The dipole moment of a carbonyl compound can also be strongly influenced by an intramolecular hydrogen bond. In hydroxyketones **46** the dipole moments anticipated from bond moments (μ_{BM}) were compared with experiment[135] and the difference expressed as a vector μ_H expressing the electron transfer due to hydrogen bonding (equation 2). Surprisingly, the direction of μ_H was not from carbonyl oxygen toward hydrogen but merely in the direction of the O−H bond.

$$\mu_H = \mu_{exp} - \mu_{BM} \tag{2}$$



μ_H 1.36

(46)



(46a)

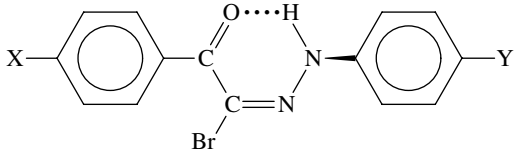
This result was explained by simple AM1 calculations[136] which suggested that the most important electron transfer takes place in the carbonyl group, from carbon toward oxygen. In the whole conception one must imagine a pseudomolecule which has the exact geometry of the real, hydrogen-bonded molecule but does not contain any hydrogen bond. Such a pseudomolecule must also be modeled in the quantum chemical calculations.

Alternatively, the intramolecular hydrogen bond can be represented as a very fast or even somewhat slower equilibrium between two positions of hydrogen (**46** ⇌ **46a**). The observed $\boldsymbol{\mu}_{exp}$ would then depend on the dipole moments of the two forms according to vector equation 3 for a fast equilibrium, or (nonvector) equation 4 for a slow equilibrium. Slow or fast here means with respect to the rate of orientation of a molecule in solution. This explanation could be correct for other molecules with stronger hydrogen acceptors[137] but in the case of compounds **46** it was not in agreement with dipole moment values[138].

$$\boldsymbol{\mu}_{exp} = (1 - p)\boldsymbol{\mu}_{BM} + p\boldsymbol{\mu}_{HB} \tag{3}$$

$$\mu^2_{exp} = (1 - p)\mu^2_{BM} + p\mu^2_{HB} \tag{4}$$

In the hydrazones of 2-bromo-1-phenylglyoxal **(47)** the dipole moment produced by the hydrogen bond was still much larger[131] since the geometry in the six-membered ring is more favorable. In all these studies it was necessary to have *a priori* good spectroscopic evidence of the intramolecular hydrogen bond.

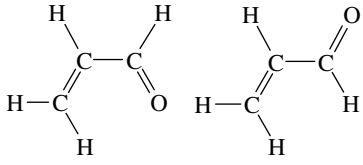


μ_H 3.4

(47)

B. Conjugated and Cumulated Systems C−C=O

When a C=O bond is conjugated with C=C, the dipole moment increases. The classical explanation by participation of the polar mesomeric formula agrees with all known facts. The conjugation is stronger and the dipole moment greater in the conformation *ap* than in *sp* (stereoelectronic effect). Good examples are the stereoisomers of propenal **(48)** investigated by microwave spectroscopy[139]. The greater μ in the *ap* conformation is accompanied by the shorter C−C bond showing more double-bond character. In **49** the

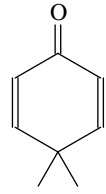


μ_{exp} 2.552

(48a)

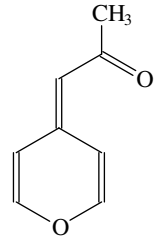
μ_{exp} 3.117

(48b)



μ_{exp} 4.452

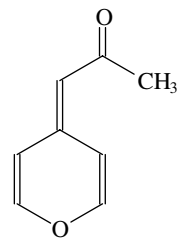
(49)



μ_{calc} 3.54

μ_{exp} 3.17

(50a)

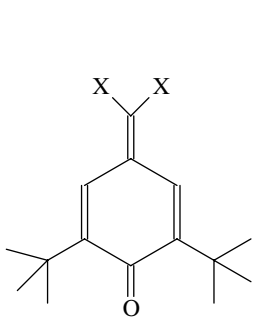


μ_{calc} 6.35

(50b)

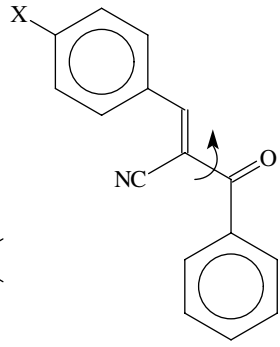
conjugation is crossed, though μ is very high: this relatively large molecule was still investigated by MW[140].

In an interesting example, the stereoelectronic effect was exploited for determining conformation on the central, partially double bond[141]. Dipole moments of **50a**,**b** were calculated at the semiempirical level and compared with the experiment: the conformation *sp* was revealed, the same as in the crystalline phase. Of course, conjugation is strengthened by the donor atom at the other end of the conjugated system. This effect is still more expressed[142] in the quinone methide derivatives **51**, which are conformationally rigid. In addition, the strengthened conjugation was observed also in the dipole moments in the excited state and in the UV spectra[142]. In cyanochalcones **52** and **53** dipole moments were used, in combination with ^{1}H NMR, for determining *E* configuration on the C=C[143], and further, for estimating conformation on C–C. The latter was near to planar *ap* as shown in the formulas, but agreement with the calculations was not good[143]. In the long conjugated chain of retinal, configurations on C=C are well known: as expected μ of the all-*E* isomer was higher than of the all-*Z* isomer[144] but the difference was small (4.02 against 3.89 D).



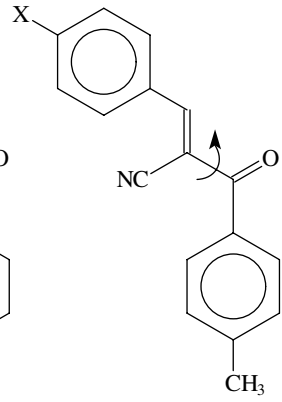
$X = CH_3$ μ_{exp} 4.60
$X = NC_5H_{11}$ μ_{exp} 10.8

(51)



$X = H$ μ_{exp} 3.94

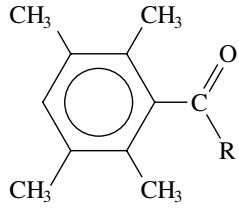
(52)



μ_{exp} 4.29

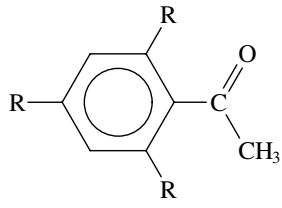
(53)

Conjugation of a carbonyl bond with an aromatic ring may be already at the border of our subject, but has been studied rather extensively from the points of view of both mesomerism and conformation. Generally, conjugation is strong enough to keep coplanarity of the C=O bond with the ring but can be distorted by steric hindrance. In tetraalkyl derivatives **54** a decrease of dipole moments was observed[145] from methyl to *t*-butyl, and interpreted by a nonplanar conformation with increasing torsional angle from 49° to 90°. These values should not be considered as quite realistic, rather as some effective mean, although they were confirmed also by ^{1}H NMR spectroscopy. The same trend was observed[146] in trialkyl derivatives **55** and compared to similar effects in ^{13}C NMR spectra. In another dipole moment study these acetophenone derivatives were taken as standard in which the conjugation and also its steric hindrance are evident; they were also compared to other derivatives, particularly nitro compounds which are probably not conjugated or only very weakly[147]. Some kind of steric hindrance was also anticipated in acetophenone



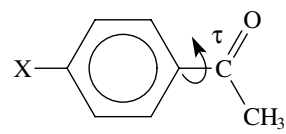
R = CH_3 μ 2.83
R = *t*-C_4H_9 μ 2.65

(54)



R = CH_3 μ 2.81
R = *t*-C_4H_9 μ 2.52

(55)



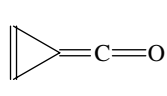
X = *t*-C_4H_9 $\tau = 10°$
X = NO_2 $\tau = 20°$

(56)

para derivatives without methyl substituents **(56)**. In the case of certain substituents X, their conformation was claimed to be nonplanar[148] but the result was dependent not only on dipole moment measurements but mainly on the Kerr constant and should be certainly confirmed by other means. In the simple molecule of benzaldehyde, any distortion of planarity cannot be forced experimentally, but can be studied theoretically[149]. In the nonplanar form, μ would be reduced by 0.38 D. In substituted benzophenones μ depends on the position of benzene rings which are rotated out in the same sense by unequal angles[150]. In substituted diacetylnaphthalenes, the coplanarity is evidently prevented by strong steric hindrance: μ was calculated and discussed but not measured[151].

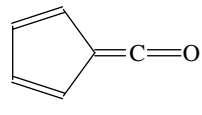
In other aromatic or heterocyclic compounds, the conjugation was not evaluated and dipole moments exploited only for determining conformation. Examples are fural and diformylfuran[152]: the preferred conformation was very near to free rotation.

The conjugated cyclic ketenes **57–59** are analogous to cyclic ketones **4–6** and their aromatic character was deduced from the calculated dipole moments in a similar way[74]. The result was that **57** is aromatic but less than **4**, while **58** and **59** are not aromatic.



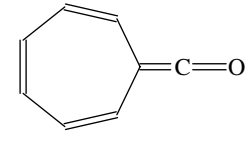
μ_{calc} 4.39

(57)



μ_{calc} 0.39

(58)

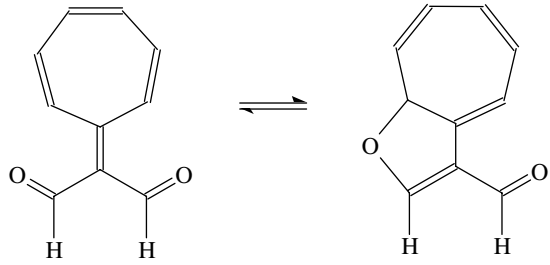


μ_{calc} 1.30

(59)

Structure and conformation of the conjugated dialdehyde **60** is known from X-ray; in solution it is in equilibrium with **61**. Experimental μ was first decomposed into the contributions of **60** and **61** (as in equation 4, μ of **61** was estimated from bond moments), then the strong electron displacement in **60** was revealed[153]. As expected, the seven-membered ring bears some negative charge. In some *ortho* and *para* quinones, μ was calculated[154] but not analyzed in terms of conjugation.

In 1,2-diketones or their functional derivatives no conjugation is apparent in the dipole moment values, but these can serve for determining conformation on the central, formally single bond. In (*E*)- and (*Z*)-benzil monoximes **(62)** the configuration on C=N was known, and the *ap* conformation on N−O was assumed (and finally confirmed): from dipole



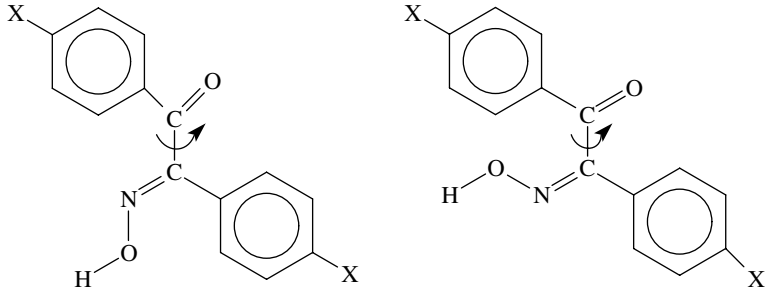
μ_{calc} 1.25
μ_{exp} 5.25

(60)

μ_{calc} 1.71

(61)

moments mainly the *ap* conformation on C−C was deduced[155] for either isomer, the same as in the crystal. Deciding in this case was the possibility of *para* chloro substitution.



X = H: μ_{calc} 2.56
μ_{exp} 3.16

(62a)

μ_{calc} 2.56
μ_{exp} 3.13

(62b)

Several curious molecules with cumulated C=C bonds and a carbonyl group at the end have received attention. Problems were the separation of unstable compounds and the measuring technique, and also the direction of the dipole moments and sometimes even the geometry: the exact linearity can be doubted in some cases. In the series of compounds **63** with an increasing number of cumulated double bonds, the dipole moments (in the gas phase) change in an irregular way[156]; the compound with $n = 2$ is not linear.

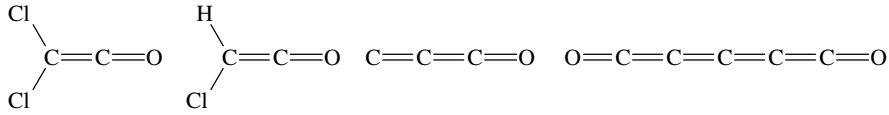
$$H_2C(=C)_n=O$$

μ_{exp} 2.332, 1.422, 2.297, 1.977

(63)

While dichloroketene **(64)** is practically nonpolar[157], monochloroketene **(65)** has an appreciable moment[158], noncollinear with the C=O bond but oriented with the negative end probably nearer to the oxygen. The parent ketene was investigated theoretically:

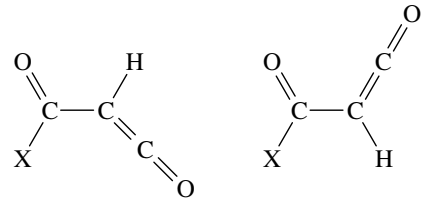
particularly interesting was its protonation (on carbon) and the dipole moment of the protonated form[159]. The dipole moment of an ion is an unusual concept: in principle it is possible to express an arbitrary system of charges in space as a sum of a pole, a dipole, a quadrupole etc., but in common chemical applications one such term is given a physical meaning only when the preceding terms are zero.



$\mu_{exp} < 0.1$ μ_{exp} 1.2 μ_{exp} 2.39

(64) **(65)** **(66)** **(67)**

The molecule C_3O with an electron sextet **(66)** is strongly polar[160]: according to *ab initio* calculations the negative end of the dipole is on oxygen[161]. However, agreement with experiment was not good, even at the 6-31G* basis. The symmetrical molecule of **67** should be nonpolar if it is exactly linear[162]. Dipole moments of various derivatives **68** were only calculated[163] and not measured.

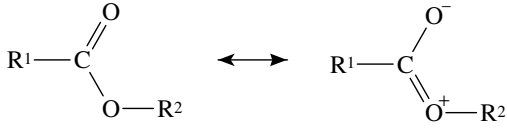


$X = CH_3$ μ_{calc} 2.18 μ_{calc} 3.84

(68a) **(68b)**

C. Conjugated Systems O−C=O and S−C=O

The extremely stable and general *sp* conformation of esters and carboxylic acids **(3a)** is one of the remarkable features of stereochemistry. It was observed uniformly[2] in all other molecules with the group O−C=O and also with their heteroatom analogues with S, Se or Te. In contrast with the rigid conformation, the conjugation in the ester molecule, expressed by the formulas **69**, is relatively weak and can be just detected in the dipole moment values[164].

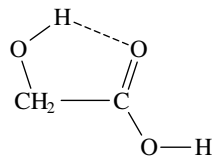


(69a) **(69b)**

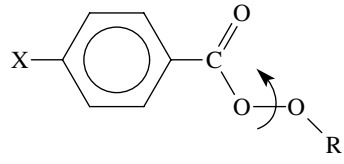
Stereochemical studies were oriented toward finding esters of special structure with reversed conformation and/or with the presence of the second conformer in smaller amounts. As reviewed previously[2], these attempts were mostly unsuccessful and claims of the conformation *ap* were again rebutted. The only exception are certain formates, particularly *t*-butyl formate, in which more *ap* form is present in polar solvents[6,165]. A more recent dipole moment study[166] assumed the *ap* form even in nonpolar solvents in para-substituted phenyl formates in an amount of 10%, but the uncertainty was of the same magnitude.

A further problem was the exact direction of the group moment COO. The agreement of two independent studies is not bad: 100° from the C−C(O) bond (on the basis of substituted benzoates[164]) or 116° (from aliphatic esters referring also to the Kerr constant[167]). In further esters, conformation of neighboring groups was dealt with: in substituted phenyl esters and in phenyl acetates the position of the phenyl ring (from dipole moments and from the Kerr constant[168,169]), in chloroalkyl esters the position of the C−Cl bond[170]. As in ketones, the dipole moment of the COO group can also be influenced by an intramolecular hydrogen bond. The hydrogen-bonded structure of glycolic acid in the gas phase **(70)** was determined twice[171,172] but the direction of the dipole moment is not quite certain and the differences between the two studies exceed the given experimental errors.

The conformation and the dipole moments of peroxy compounds were reviewed[173] in 1983. In peresters **(71)** it could be difficult to deal both with the conformation on the O−O bond and with the conjugation inside the COO group. The problem was solved so that the conjugation was estimated to be equal as in structurally similar esters; then the conformation was determined from experimental dipole moments[164]. As expected, the conformation is nonplanar as the conformation of hydrogen peroxide: the dihedral angle is rather sensitive to structure **(71)**. Steric arrangements of diacyl peroxides **(72)** have been reported previously[2]. Later the problem was reinvestigated, since the substitution from two sides allowed the geometry to be determined more exactly[174]. Certain quite small

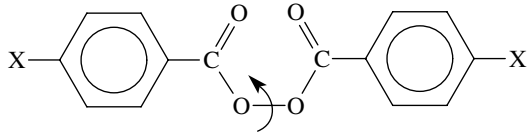


(70)



R = CH_3 τ ~ 130°
R = *t*-C_4H_9 τ ~ 170°

(71)

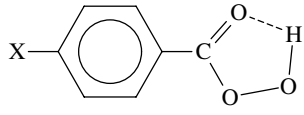


τ 115°

(72)

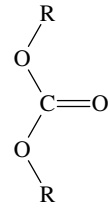
differences in angle were required compared to the solid state geometry; only the dihedral angle τ is enlarged more, to 115° (the crystallographic value being 91°). Remarkably enough, the conformation is only slightly changed when the central atoms O−O are replaced by O−CH_2 or by other groups[175].

In peroxy acids[176] **(73)** the hydrogen bond is manifested by a contribution to the dipole moment, μ_H: this is larger than in the case of ketones **46**, which also have a five-membered ring. The conformation of **73** was known previously, and the conjugation was only estimated while attention was focused on the hydrogen bond[176].



μ_H 2.46

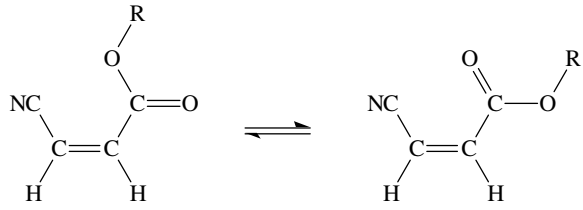
(73)



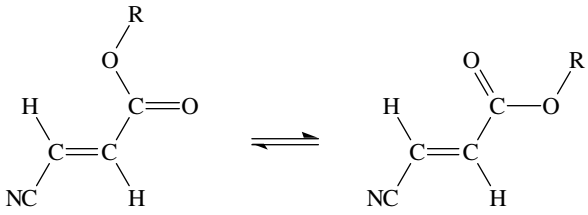
(74)

In alkyl or aryl carbonates, the problem of conformation is repeated twice on the two C−O bonds linked to the same central atom. It was stated generally[177] that in such cases the common conformation of the monofunctional compound is repeated in either moiety. This holds with a few exceptions and/or modifications when the molecule is strongly crowded. This is also the case of carbonates. According to this rule, the *sp*,*sp* conformation **(74)** was found in carbonates in two independent investigations. In the first[178] *para*-substituted phenyls were used in place of R; the second started from the fixed conformation of trimethylene carbonate and besides the dipole moment exploited also the Kerr constant[179].

Conjugation of the carboxyl group with C=C bonds affects its group moment only marginally, but conformation on the partially double bond can be sometimes determined from the overall dipole moment. In alkyl acrylates and methacrylates dipole moments were little influenced by conjugation[180] and were insufficient for a decision whether or not the conjugation is hindered. In (*Z*)-cyanoacrylates[181] the conformation **75a** prevails in a ratio 2:1, in agreement with the IR spectra. In the *E*-isomers, the two conformers (**76a**,**b**) are indistinguishable either by dipole or by IR spectroscopy[181]. Electron distribution in this system was not dealt with, but it was tacitly assumed as unchanged by conjugation. Dipole moments of aromatic esters are influenced by the conjugation with the aromatic ring and by its steric hindrance[182] similarly as mentioned with the aromatic ketones[145] **(54)**.

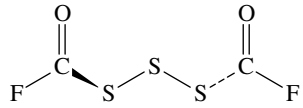


(75a) **(75b)**



(76a) **(76b)**

Conjugated systems S−C=O were sometimes investigated[183] together with similar compounds containing the groups O−C=S and S−C=S (the latter are mentioned in Section VI). The *sp* conformation of *S*-methyl thiobenzoate was determined by simple comparison with the bond-moment values[184]. The same result was obtained already previously with more precision, exploiting also several substituted derivatives[185]. The dipole moment of the trisulfide **77** was measured[186] but the conformation was not speculated about, although it could be estimated from other trisulfides to be approximately as shown in **77**.

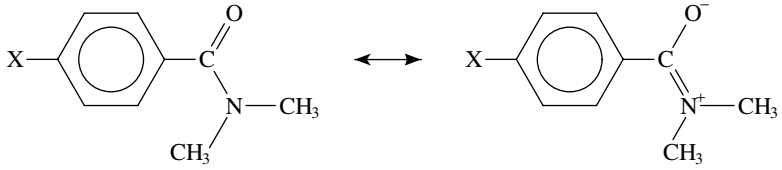


(77)

D. Conjugated Systems N−C=O

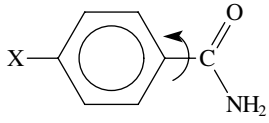
Amides represent a class of compounds which, although very important, are not quite suitable for dipole moment measurement due to the low solubility and association in nonpolar solvents. These problems are avoided[187,188] in substituted *N*,*N*-dimethylbenzamides **(78)**: the dipole moments were interpreted in terms of resonance by the approach described in Section IV.B. The mesomeric dipole moment μ_m is appreciable[187] (1.4 D) but its orientation is not from N toward O but merely toward C. If we avoid speculations, a modest conclusion would be that mesomeric formulas do not describe the structure completely. In substituted benzamides **(79)**, μ_m is smaller (*ca* 0.6) and the conclusion less safe[187]. On the contrary, dipole moments of the same compounds **(79)** were interpreted by a nonplanar conformation; an important piece of evidence was from the Kerr constant[189]. This result should be accepted cautiously since some similar previous conclusions from the Kerr constant[190] were in error. The dipole moment of the parent formamide was calculated at a high level[191] (in connection with an investigation of its tautomeric equilibrium) but was not analyzed.

The example of amides offers us an opportunity to present the problem of mesomeric dipole moments more generally. Let us suppose that the real structure of a molecule is represented as mesomeric between the two limiting structures: the dipole moments of these structures can be anticipated as vectors **A** and **B**. The effective experimental dipole moment of the compound is then given by the vector equation 5, where p is a measure of relative importance of the two structures. Equation 5 is formally identical with equation 3 and is always valid for mesomeric structures, since these are assumed to equilibrate by



X = H μ_{exp} 3.81
μ_m 1.4

(78a) **(78b)**



X = H $\tau = 39°$
X = NO_2 $\tau = 0°$

(79)

an infinite velocity.

$$\boldsymbol{\mu}_{exp} = (1 - p)\mathbf{A} + p\mathbf{B} \tag{5}$$

Since **A** and **B** have been obtained by calculation, their directions are known. This need not apply to $\boldsymbol{\mu}_{exp}$ whose direction has to be determined by more sophisticated procedures, for instance from comparison with substituted derivatives[187]. Furthermore, calculation of **A** and **B** need not be equally feasible: the polar form has a much larger dipole moment whose calculation is more difficult. The problem was solved in the literature on several levels, according to the data which were available and using more or less sophisticated concepts.

Let us follow the example of *N*,*N*-dimethylformamide in Figure 2.

(1) When only **A** and the absolute value of $\boldsymbol{\mu}_{exp}$ are known, the latter can be represented by a circle arc. When the absolute values of the vectors **A** and $\boldsymbol{\mu}_{exp}$ differ, one can state that there is some conjugation or mesomerism (in a qualitative sense).

(2) In order to evaluate the extent of resonance quantitatively, one can use the definition of $\boldsymbol{\mu}_m$ according to equation 1, which corresponds geometrically to constructing a triangle. A solution is possible if the direction of $\boldsymbol{\mu}_m$ can be anticipated[96,97]. In the case of amides, if one assumes the direction of $\boldsymbol{\mu}_m$ from N toward O, one obtains $\boldsymbol{\mu}_m$ as A_1E' in Figure 2.

(3) A better estimate is possible when the direction of $\boldsymbol{\mu}_{exp}$ is known. Then the above assumption is not necessary and $\boldsymbol{\mu}_m$ is obtained as A_1E. In the example in Figure 2 the direction of $\boldsymbol{\mu}_{exp}$ was transferred from *N*,*N*-dimethylbenzamide[187] where it should be essentially identical: μ_m 1.4 was obtained. The direction of $\boldsymbol{\mu}_m$ obtained in this way need not be always identical[5,98,187] as anticipated in point (2) above: in such a case one has a new result to explain.

(4) When **B** is also known, equation 5 can be solved for p. In geometrical terms this equation requires that the end point of $\boldsymbol{\mu}_{exp}$ must lie on the line connecting the end points of **A** and **B**. When this is not fulfilled, the deviations show the inaccuracy of calculations or of the whole approach. In simple calculations, **B** is controlled by the two charges in

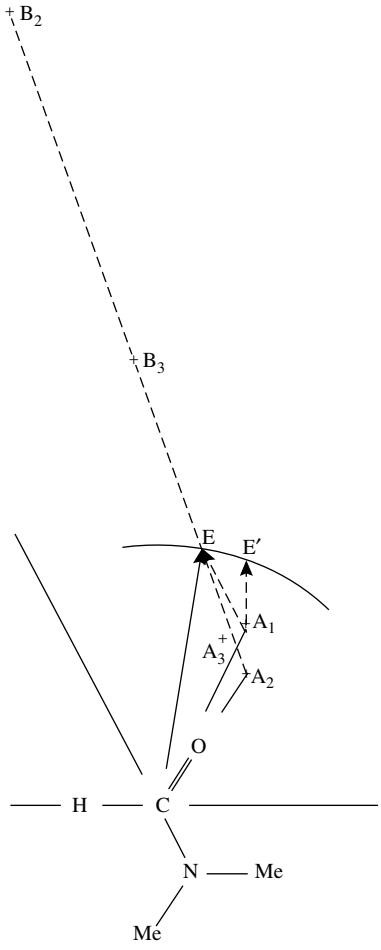
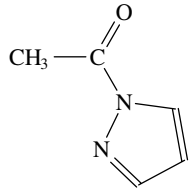


FIGURE 2. Analysis of the experimental dipole moment (E) of *N*,*N*-dimethylformamide and/or *N*,*N*-dimethylbenzamide in terms of the resonance structures **78a** and **78b** (A and B) and of the mesomeric dipole moment (μ_m) according to various approximations

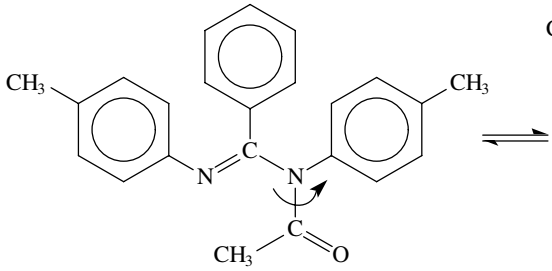
78b. Using the values shown by A_2 (little different from A_1) and B_2 one obtained[89] $p = 0.19$, $\mu_m = 1.9$; the full calculation was rather complex.

(5) The previous procedure may be improved by a more sophisticated calculation[99] of **B**, taking into account induction caused by the charges in the remaining parts of the molecule. Using the values denoted A_3 and B_3 in Figure 2, one obtains[99] $p = 0.34$, $\mu_m = 1.3$. When the above methods are compared, the most sophisticated one need not always be the best. In a concrete example, the differences are usually not dramatic (see Figure 2). In the writer's opinion, the results possess some reliability only as far as they are near the nonpolar classical structure: then $\boldsymbol{\mu}_m$ or p appear as small corrections. Commonly, their values are used only to compare similar systems. Then it is sufficient when all these values have been determined by the same method.

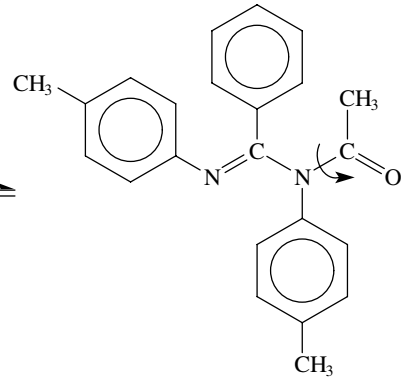
With monosubstituted amides, attention was focused on the conformation on the N−C bond. This can usually be determined from dipole moments[192], sometimes even the conformation on the next bond can be estimated with some probability[193]. The same applies to disubstituted amides with unequal substituents: in the case of compound **80** the substituents were connected to a heterocycle[194]; the conformation *ap* **(80)** was practically the only one present. Acylated amidines **81** represent one of the most complex problems solved by means of dipole moments combined with the Kerr constant[195]. In addition to the configuration on C=N, one has to determine conformations on five single bonds. Of these, three (on the N−C_{ar} and C−C_{ar} bonds) do not affect μ but affect ${}_mK$. When certain angles were estimated on the basis of model compounds, the final solution was that conformation on N−C(O) is nonplanar while on N−C(N) it is planar and gives rise to an equilibrium of two conformers. The problem certainly would be worth elaborating by means of further experimental methods.



(80)



(81a)



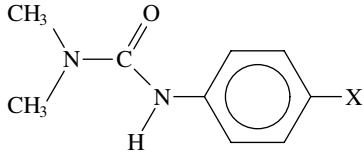
(81b)

There is some confusion concerning the conformation of substituted ureas[196,197], when one difficulty is again in the small solubility. For a dipole moment study combined with IR spectroscopy, derivatives of **82** were selected[196] which have only one axis of rotation. The mesomeric moment is of less importance and could be estimated in advance. Then conformation was solved in favor of the *sp* form **82**. In hydroxyureas **83** there is one rotational axis more and the conformation found[198] should be considered as approximate.

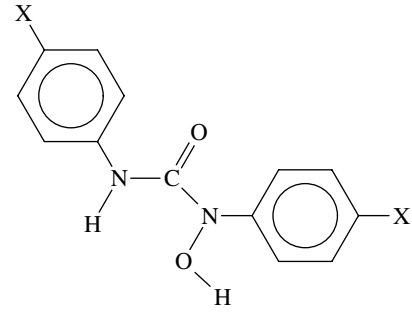
Dipole moments of hydroxamic acids were originally interpreted[199] in terms of the conformational equilibrium of **84a** and **84b**. When some proof of the hydrogen bond were received from IR spectroscopy, the interpretation was preferred[138,200] that the only form present is **84a** and the enhanced dipole moment is due to the component μ_H like in the structurally similar ketones **(46)** or peroxy acids **(73)**. The effect of conjugation, μ_m, is much smaller and can be estimated from model compounds without depreciating the value of μ_m. Compared to the named molecules, the hydrogen bond in hydroxamic acids is of intermediate strength between **46** and **73**; see the values of μ_H. A very near value of μ was

calculated for formohydroxamic acid[201]: within the framework of bond moments, μ of formohydroxamic and benzohydroxamic acid should be equal. However, the molecule of the former should be not quite planar according to MP2(full)/6-31+G** calculations[201]. In *N*,*O*-diacylhydroxylamines (**85**) the main problem was the steric arrangement. Although there are *a priori* three axes of possible rotation, the conformation was obtained unambiguously and relatively precisely[200] in agreement with some X-ray structures and with the previous estimate[199]. A great advantage for the dipole moment analysis is the possibility of exploiting substitution from two sides.

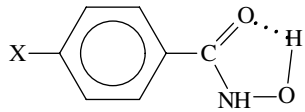
A cumulated system N=C=O occurs in isocyanates. Measurements of dipole moments of *para*-substituted phenyl isocyanates[202] served to determine the magnitude and direction of the bond moment. Since it lies at a small angle (*ca* 21°) to the C_{ar}–N bond, its direction is not obtained with great accuracy and μ is not sensitive to the conformation on this bond. No attempt was made to analyze the group moment into components, as it would be probably of little value. The same problems are encountered with other heterocumulenes; see Section VI. Vinyl isocyanate exists in the gas phase in two conformers, **86a**,**b**. Their dipole moments are equal within experimental error[32]: conjugation is evidently negligible and hence independent of conformation.



(82)

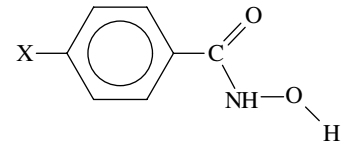


(83)

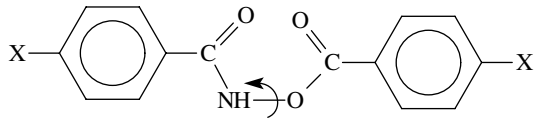


μ_H 2.16

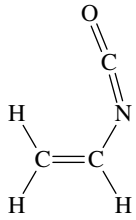
(84a)



(84b)

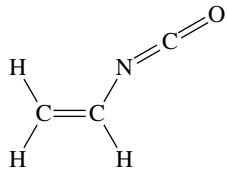


(85)



μ_{exp} 2.14

(86a)

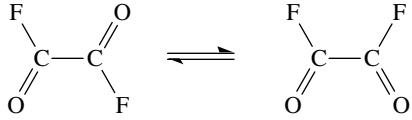


μ_{exp} 2.12

(86b)

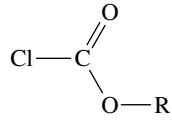
E. Conjugated Systems X−C=O

In acyl halides, any n–π conjugation can be only very weak, nevertheless an attempt was made to evaluate it from dipole moments of *para*-substituted benzoyl chlorides and bromides[203]. Only in the latter was an electron transfer from bromine toward carbon found (1.8 D), which cannot be interpreted as a sign of n–π conjugation but rather as diminished polarity of the C−Br bond. On the other hand, the conjugation of the COX groups with the benzene ring is stronger in the case of chlorides. Oxalyl fluoride exists in the gas phase in the equilibrium[204] of **87a** and **87b**. The dipole moment of the latter was calculated with relative success.

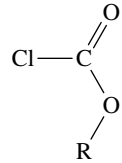


(87a)

(87b)



(88a)



(88b)

The structural unit of acyl chlorides is also contained in the molecule of chloroformates. Their conformation had long been controversial since the agreement of calculated and experimental dipole moments was not sufficient. The literature has been reviewed previously[2]; of particular importance were two dipole-moment papers[205,206] preferring the unnatural *sp* conformation **88b**. (Notation *sp* corresponds to *ap* in common esters.) The difficulty lies in that the resulting μ is relatively small and the bond-moment scheme is not exactly valid due to the proximity of strongly polar bonds. Recently the problem was attacked by two approaches with conforming results[3,207]. In the first, X-ray analysis of 4-nitrophenyl chloroformate gave conformation *ap* **(88a)** and IR spectroscopy furnished proof that the conformation in solution is not different[3]. Then the experimental dipole moments of aryl chloroformates[206] were analyzed in terms of bond moments[3]. The difference from the anticipated value from the formula **88a** does not correspond to an electron transfer from −O− toward =O or from Cl toward =O, but it should be formally represented by reduction of the C=O bond moment and increasing the C−Cl bond moment. A second approach[207] was based on dipole moments and Kerr constants of methyl, trichloromethyl and aryl chloroformates, when the same conformation **(88a)** was established. In this way, the claim[208] based on IR and NMR spectra, that chloroformates exist in an equilibrium of **88a** and **88b** was disproved.

VI. C=S BONDS

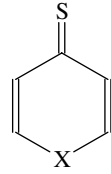
Generally the same problems are encountered as with the C=O bonds. Dipole moments are usually larger mainly because the C=S bond is longer; also the $n-\pi$ conjugation is stronger[209] due to the greater ability of sulfur to accommodate a negative charge[210]. Dipole moments of the simplest compounds, i.e. thioformaldehyde, thiopropionaldehyde and thioacetone, are not always accessible experimentally but were calculated on a rather high level[211–213] (also the seleno analogue $CH_2{=}Se$[212,214]). The compounds with cumulated double bonds **(89)** were both calculated[213] and measured in the gas phase[156,215] (also the seleno analogue $CH_2{=}C{=}Se$[216]). Their dipole moments are in this case lower than those of the corresponding oxygen derivatives **63** but show similar alternation along the series. In contrast to **63** the sulfur derivatives are all linear[156]. The unstable compound **90** with an electron sextet[217] is an analog of **66** and has a considerably higher μ. The calculated dipole moments of pyrothione and thiapyrothione **(90)** are larger than their oxygen analogues[218]: the main reason was seen in the longer C=S bond. Tropothione has also a larger dipole moment[219] than tropone (4.42 compared to 3.72 D).

μ_{exp} 1.647, 1.021, 2.064

(89)

μ_{exp} 3.704

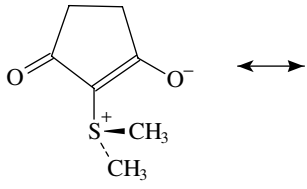
(90)



X = O, S

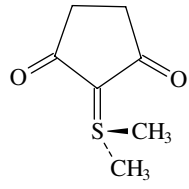
(91)

In the sulfonium ylide **92** and similar compounds[220], the central C–S bond may acquire considerable double-bond character (**92a** ↔ **92b**). The calculated bond lengths correspond merely to a single bond, but μ reveals strong back-donation. The conformation of the derivative **93** was also estimated from the dipole moment[220].

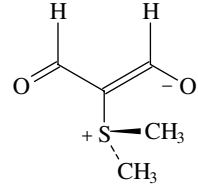


μ_{exp} 5.46

(92a)



(92b)

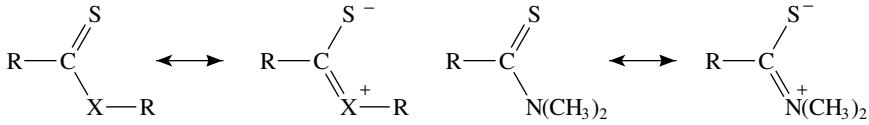


μ_{exp} 4.56

(93)

In the conjugated systems X–C=S attention was focused mainly on the conformation around the C–X bond. Calculations preferred the *sp* form **(94a)** for dithiocarboxylic acids[221], thionesters[7] and dithioesters[221]; this is the same form as preferred in normal esters **(3a)** but the energy difference against the *ap* form is lower. Explanation of this preference is still sought in the interaction of dipoles[7], although this has been shown to

be insufficient[2]. Older dipole-moment studies of thiolbenzoates[185] and thionbenzoates[222] were also directed toward determining conformation. They were later recalculated[209] to evaluate also the n–π conjugation **94a** ↔ **94b**. A particularly strong conjugation was found[209] in thiobenzamides and *N*,*N*-dimethylthiobenzamides **(95)**. Conjugation in several systems X=C−Y with n–π conjugation can be now compared quantitatively; in Table 1 they are expressed in terms of the mesomeric dipole moment $\boldsymbol{\mu}_m$. The agreement of different methods is not so bad considering the approximate character of several assumptions. Some regularities emerge which could be *a priori* expected. Conjugation is stronger when the donor group is more basic ($NMe_2 > NH_2 > SMe > OMe$) and when the acceptor group is a stronger acceptor (=O > =NH). The most efficient acceptor group is =S, but this is due at least partly to the longer C=S bond and only less importantly to the ability of sulfur to accommodate the negative charge. Most interesting, but somewhat puzzling, are the directions of $\boldsymbol{\mu}_m$. The theoretical expectation should be from Y toward X and this direction was taken as reference (angle $\theta = 0^\circ$) in Table 1. Most strange is this angle in *t*-butyl esters and thiolesters, but the absolute values are small and not so dependable. In amidoximes the values of θ evidently differ as a function of the configuration of the chain.



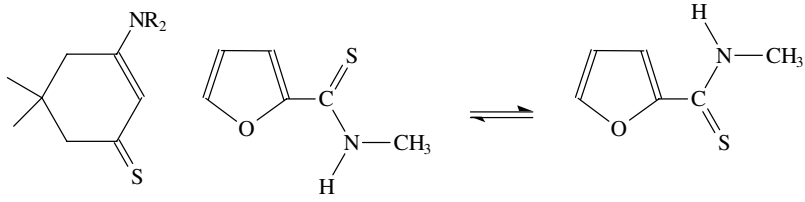
(94a) **(94b)** **(95a)** **(95b)**

In thioamide vinylogues **(96)** the conjugation was proved in a qualitative sense from the enhanced values of dipole moments[223]. The derivatives of furane **(97)** were investigated by several experimental methods[224]: while the conformation on C−N followed mainly from IR spectra, dipole moments served to determine conformation of the furan ring on the C_{ar}−C bond but the result was not convincing (due also to some misprints).

TABLE 1. Mesomeric dipole moments (μ_m) and relative importance of the polar mesomeric structure (p) in n–π conjugated systems −C(=X)−Y

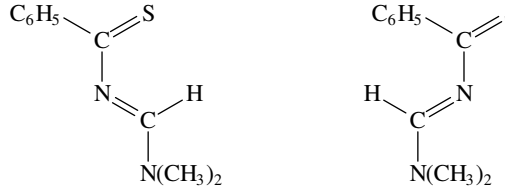
X	Y	$\mu_m{}^a$	μ_m $(\theta)^b$	m^* $(p)^c$	μ_m $(\theta)^d$
O	OCH_3	0.4	0.2 (25°)		
	$OC(CH_3)_3$		0.5 (52°)		
	NH_2		0.9 (19°)		
	$N(CH_3)_2$	1.7	1.4 (26°)	1.9 (0.21)	1.32 (19°)
	SC_2H_5	0.3	0.5 (−44°)		
S	OC_2H_5	1.2	1.0 (−19°)		
	NH_2		1.9 (0°)		
	$N(CH_3)_2$	3.2	2.55 (12°)	3.7 (0.36)	2.49 (−2°)
Se	$N(CH_3)_2$	3.7		4.1 (0.39)	
NCH_3-(*E*)	$N(CH_3)_2$	2.1	0.9 (−25°)	1.9 (0.18)	
NOH-(*Z*)	NH_2		0.8 (−14°)		
NOH-(*E*)	$N(CH_3)_2$		1.2 (−49°)		

[a] Method of calculation (2), Section V.D., References 96,97,256.
[b] In parentheses, angle θ to the Y...X direction, method (3), Section V.D. References 128 and 95.
[c] The moment m^* is proportional to μ_m, method (4), Section V.D. Reference 89.
[d] In parentheses, angle θ to the Y...X direction, method (5), Section V.D. Reference 99.



(96) **(97a)** **(97b)**

In substituted thioureas[196] and hydroxythioureas[198], attention was focused on the conformation while conjugation was accounted for by means of small correction terms. The resulting conformation was the same as in the oxygen analogues, **82** and **83**, respectively. Dipole moments of 3-aza-1-thiabutadienes, of which **98** is an example, were calculated[225] for the two conformations **98a** and **98b**, applying small correction terms for the possible conjugation. The configuration on the C=N bond was known from X-ray crystallography and other proofs. The *sp* conformation **98a** is clearly prevailing in solution. Calculated dipole moments of sulfur derivatives of carbamic acid were compared[226]: μ of NH_2CSOH is greater than of NH_2COOH, and that of NH_2CSSH is greater than that of NH_2COSH.



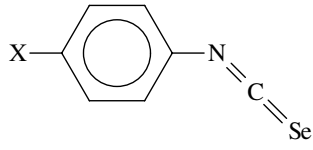
μ_{calc} 4.29 μ_{calc} 6.69

μ_{calc} 4.59

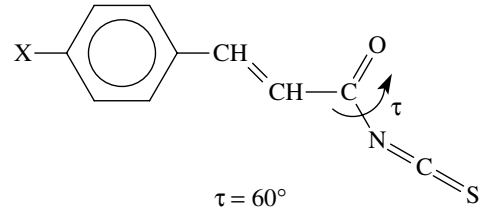
(98a) **(98b)**

Heterocumulenes involving a C=S bond were investigated rather extensively. On simple ethyl isothiocyanate the N=C=S group moment was found at an angle of 29° to the C−N single bond (in the gas phase[227]). When individual heterocumulenes are compared[228], this angle seems to increase slightly from NCO to NCS and NCSe: for isoselenocyanates it was determined[228] from aryl derivatives **99** in the standard way as in the case of isocyanates[202] and isothiocyanates[229]. In the same paper[228] also conjugation of NCSe with the benzene ring was quantitatively estimated: the value of μ_m is between 0.6 and 0.8 D for all heterocumulenes. The nonaxial position of the NCS dipole allows in principle determination of the conformation of this group with respect to certain polar neighbors. However, the deviation from the C−N bond is small and the results must be hardly precise. In the case of cinnamoyl isothiocyanates the conformation on C−C(O) and (O)C−N bonds was at question: the suggested result[230] is given by the formula **100**. In chalcone derivatives **101** we have a similar steric arrangement[231] as far as the NCS group is in the *para* position. When it is in *meta*, an additional axis of rotation

arises and the problem seems to exceed the possibilities of the approach. In arylsulfonyl isothiocyanates[232] **(102)** there is only one axis of rotation and the dipoles are great, but the small angle of the NCS group moment is still a problem and the conformation is merely an approximation.

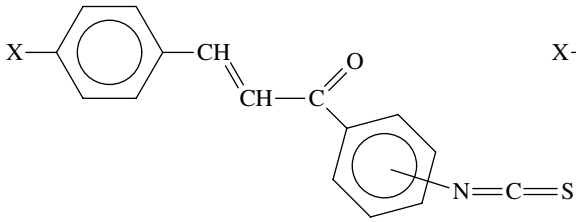


(99)

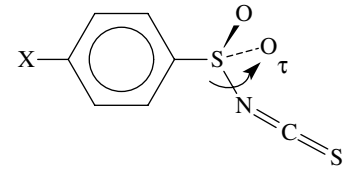


$\tau = 60°$

(100)

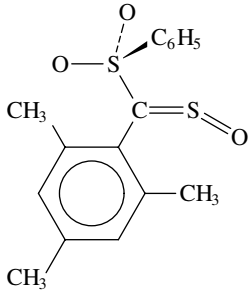


(101)



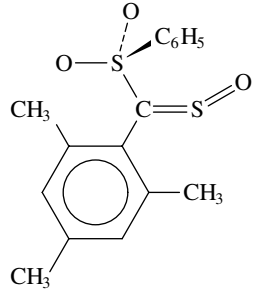
$\tau = 80°$

(102)



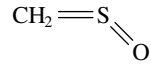
μ_{exp} 4.83

(103a)



μ_{exp} 4.68

(103b)



μ_{exp} 2.994

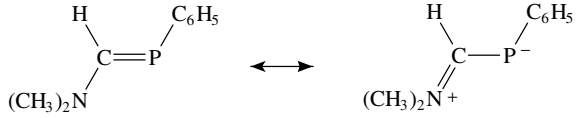
(104)

Interesting structures with a formally tetravalent sulfur in which the C=S bond gives rise to two stable configurations were already mentioned previously[2]. They were augmented by the derivatives **103** and analogous sulfoxides and sulfides. Here dipole moments were used only as a supporting method[233] in combination with ^{1}H NMR spectra: configuration on C=S was based only on the latter; μ helped in determining the conformation on C−S. Since it was evaluated only in a less efficient way (without exploiting substitution),

the conformations **103a** and **103b** are only approximate. In any case it is certain that the nonplanar arrangement S=C−S−C is in contrast with the planarity in **94**. For the simplest compound of this class **(104)** the dipole moment was measured by MW[234].

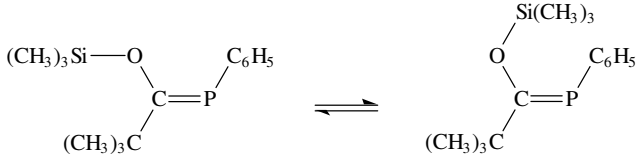
VII. C=P BONDS

The chemistry of phosphorus compounds was reviewed with particular attention to dipole moments[235,236]. Compounds with a C=P bond present the same problems as the C=N bond: of course the number of derivatives is restricted and difficulties may arise with their stability. The simplest compound CH_2=PH was investigated by MW in the gas phase[237]. From its dipole moment, 0.896 D, the P=C bond moment of 0.02 D was deduced[238], which however was based on different bond moments than used here. In any case this bond is only slightly polar.



μ_{calc} 1.34
μ_{calc} 3.43

(105a) **(105b)**



μ_{calc} 2.28
μ_{exp} 2.29

μ_{calc} 2.32

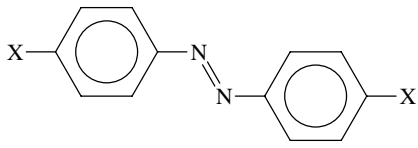
(106a) **(106b)**

Conjugation is possible from either end of the C=P bond. A series of compounds with the N−C=P systems was investigated by dipole moments[239]. From the difference of experimental μ and that calculated from bond moments, n–π conjugation was deduced, for instance in **105a** ↔ **105b**; the mesomeric dipole moment was not explicitly evaluated. The *E* configuration of **105** was known *a priori* from spectroscopy. On the other hand, no perceptible n–π conjugation was found in **106**. Its conformation cannot be deduced from dipole moments and is probably hardly rigid[239].

VIII. OTHER DOUBLE BONDS

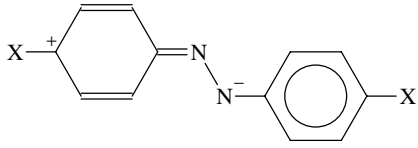
This section exceeds the subject of this Volume, nevertheless it is included in order to cover the same range of compounds as previously[2]. Mentioned in particular are compounds of interest in the theory of dipole moments and those presenting similar problems as with the C=X bonds.

The N=N bond is formally nonpolar in the bond-moment system; in symmetrical molecules it is nonpolar really. The nonzero dipole moments of symmetrical azo compounds **107** were explained[27] by participation of mesomeric formula **107b**. This explanation is unacceptable. The symmetrical formula **107c** must participate to the same extent as **107b** and the resulting dipole moment is zero according to equation 3 — extended to three or more structures. The effective dipole moment would be zero only if calculated similarly as in equation 4, but this is not possible since a mesomeric transition must always be faster than any physical process. Apparent dipole moments of some symmetrical molecules are not yet completely understood[26]; evidently all cases cannot be explained in the same way. For compounds **107** an abnormally high atom polarization is probable, but formation of CT complexes is also possible. When $X = OCH_3$ or $COOC_2H_5$ the evident explanation is in unsymmetrical conformations like **108**: exchange of conformation is no more infinitely fast and the effective dipole moment is given by equation 4.

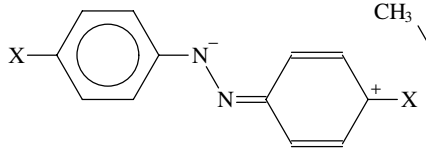


$X = CH_3$ μ_{exp} 1.23
$X = Br$ μ_{exp} 2.47

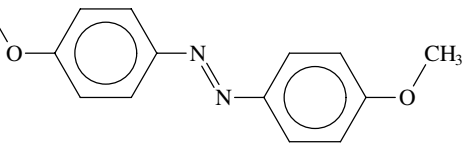
(107a)



(107b)



(107c)

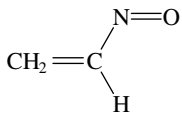


μ_{exp} 5.97

(108)

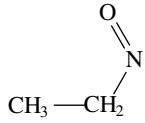
In azoxy compounds (**1**, **2**) both the configuration on N=N and electron distribution within the conjugated system can be dealt with[5]. The compounds were chosen as an example of the two possible approaches in Section I.

The N=O bond can cause conformational problems in conjugated systems. According to MW, the stable conformation of nitrosoethene[240] is *ap* **(109)** while nitrosoethane represents a mixture of eclipsed conformations *sp* **(110a)** and *ac* **(110b)** with the former prevailing[241]. Of course, conformation has here a minute effect on μ since it concerns only the hydrocarbon residue. (Within the framework of the bond-moment scheme, μ would be not affected.) In nitrosomethane[242] itself $\mu = 2.320$, but its direction seems doubtful. According to μ in solution[243], the conformations *ap* and *sc* of 2-nitro-2-nitrosopropane **(111)** are populated almost equally. Nitrous acid exists in a mixture of *sp* and *ap* conformers[244]; in alkyl nitrites only *ap* was revealed[245]. Similarly as with the compounds **109** and **110**, measurement of μ represented only a small supplement of the whole analysis and the results were not discussed. This is common in MW work.



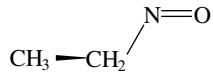
μ_{exp} 2.77

(109)



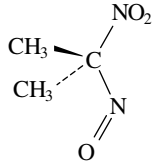
μ_{exp} 2.398

(110a)



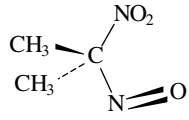
μ_{exp} 2.288

(110b)



μ_{calc} 1.65

(111a)

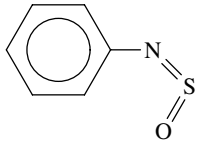


μ_{calc} 4.47

μ_{exp} 3.48

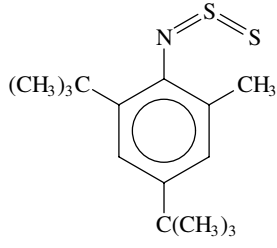
(111b)

Of the compounds with a N=S bond, thionylamines are known only in the *Z* configuration **(112)**. Previous reasoning based essentially on dipole moments[2] was reinvestigated and the configuration confirmed also by other methods[246]. The same configuration was found for thiothionylamines **113** and the dipole moments were analyzed in terms of bond moments[247]. Compared to thionylamines, the negative charge is more dissipated here, also to nitrogen; the S=S bond is highly polar. Further derivatives with a N=S bond **(114)** are symmetrical and cannot exist in different configurations. The dipole moments were analyzed[248] in terms of a variable S=N bond moment, but a more natural interpretation would probably be a through-conjugation of electron-attracting substituents (NO_2) with the lone electron pair on nitrogen, expressed by μ_m.



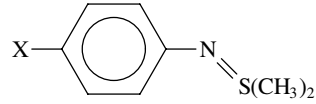
μ_{exp} 1.95

(112)



μ_{exp} 1.51

(113)

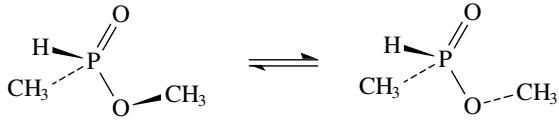


X = F μ_{exp} 5.53

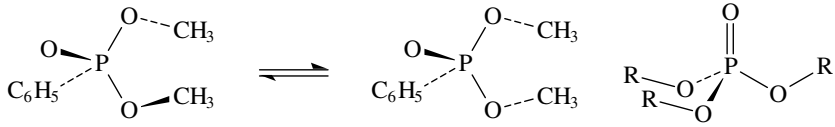
X = NO_2 μ_{exp} 10.1

(114)

The P=O and P=S bonds were investigated[235,236] within a broad program dealing with dipole moments of phosphorus compounds, almost always combined also with the Kerr constant. Only a few examples of the problems may be mentioned here. On compounds with isolated P=S, P=O or P=N bonds, these bond moments were evaluated[235]; they are not quite constant but in any case decrease in the order given. In further studies attention is focused on conformations of the neighboring radicals, particularly of the phenyl groups[249,250]. In compounds with conjugated systems O−P=O, S−P=O and S−P=S, the main problem was their conformation but conjugation with an adjacent aromatic ring was also dealt with[236]. Regularly, the results with oxygen and sulfur compounds are very similar. Nonplanar conformation of methyl phoshinates (**115a**,**b**) was deduced from their dipole moments[251]; it thus differs sharply from carboxylic esters **(3)**. In phenyl phosphonates **116** a mixture of conformations **116a** and **116b** was found[252], while in phosphates **117** with bulky groups such as R = $Si(CH_3)_3$ the surprising *sp* conformation was claimed as important[253]. The last example with a great number of possible conformations belongs to the most complex problems attacked by this approach: the results may have merely approximate validity.



(115a) **(115b)**



(116a) **(116b)** **(117)**

Bond moments of the P=N, As=P and Sb=P bonds were also evaluated[254]. In the compounds $ArN{=}P(C_6H_5)_3$ the conformation of the phenyl group was dealt with[255].

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CHAPTER **7**

Acidity, basicity and H-bonding of double-bonded functional groups: Nitrones, nitriles and thiocarbonyls

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I. ABBREVIATIONS

ρ	reaction constant	K_d	dissociation constant of ion pairs
σ^+	electronic substituents constant	LFER	linear free-energy relationship
ACRYL	acrylonitrile	MP	Møller–Plesset
AM	Austin model	PA(B)	Proton affinity for base B
Bph	*p*-biphenylyl	PES	photoelectron spectroscopy
Fl	9-fluorenyl	PTC	phase transfer catalyst
FUM	fumaronitrile	SCF	self-consistent field
GB	gas-phase proton transfer basicity	TCNE	tetracyanoethylene
IP	ionization potential	ZPE	zero-point energy

II. INTRODUCTION

The aim of this review is to focus on the acidity and basicity as well as some aspects of hydrogen bonding of organic compounds containing double-bonded functional groups.

Whereas the subject of basicity of C=O groups has already been covered by Palm and coworkers[1], in this chapter we summarize more recent results and significant developments in the field of nitrones, nitriles and thiocarbonyls. This chapter is not exhaustive in scope, but rather consists of surveys of the most recent two decades of work in this still developing area. As indicated by the title of this contribution, we emphasize the more physical aspects such as acidity, basicity and proton affinity; less attention is paid to synthesis, structure and bond theory which can be found in other specialized chapters of this book.

To many organic chemists working in the field of synthesis, it is not obvious that questions about the basicity of double-bonded functional groups are of great importance. However, the basicity of double-bonded groups in general and of nitrones, nitriles and thiocarbonyls in particular is by no means a simple problem. Especially the deeper knowledge of the interaction of these functionalized organic compounds with protic and aprotic acids is extremely important for the development of the general concepts of basicity.

In Section IV–VI we systematically discuss the acidity, basicity and, where appropriate, the hydrogen-bonding of nitrones, nitriles and thiocarbonyls. Since this review very much relies on physical measurements and the discussion of acid–base reactions, Section III provides a brief introduction to proton affinity and a short summary of the acid–base concept and the quantitative measure of basicity.

III. ACID–BASE REACTIONS

A. Gas-phase Proton Affinities[2]

The energy required to dissociate a proton from gas-phase cationic species, BH^+, is called the *proton affinity* of the base B, PA(B), and is measure of both the acidity of BH^+ and the basicity of B.

$$BH^+(g) \longrightarrow H^+(g) + B(g), \quad \Delta E = PA(B)$$

Most of the bases discussed in this context in text-books contain non-bonding lone-pair electrons which become bonding electrons in the protonated species. Examples are: B = NH_3, H_2O, C_2H_5SH, C_5N_5N, CO,.... In general, the proton affinity of the double-bonded groups discussed in this chapter clearly falls into this category. There are also some bases that contain no lone-pair electrons; these are usually π bond-pair bases which react with protons to form species containing three-centre bonds. For example, there are two possibilities to protonate a nitrone group (cf Section IV): (i) protonation at the lone-pair electrons of the oxygen atom or (ii) protonation at the double bond (Scheme 1). However, in the case of compounds containing double-bonded functional groups for energetic reasons protonation usually takes place at the lone-pair electrons.

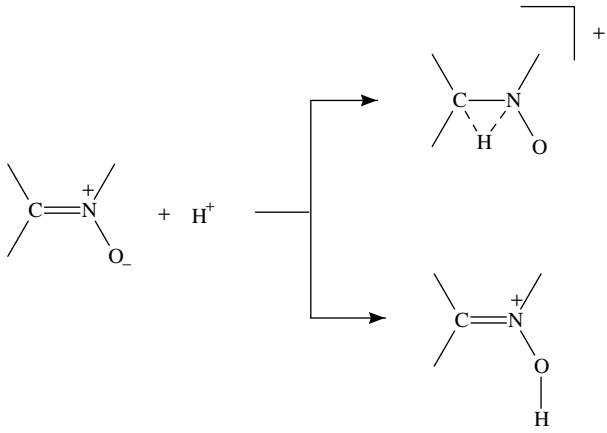
(N.B. There are also σ bond-pair bases which react with protons to form species containing three-centre bonds, e.g. $CH_4 + H^+ \rightarrow CH_5^+$; however, by their very nature these compounds do not belong in this chapter on double-bonded groups.)

It is well established that the energy of ionization, ΔH°_{ion}, of a neutral acid HAR_n can be expressed as follows:

$$\Delta H^\circ_{ion} = D(H{-}AR_n) + IP(H) - EA(AR_n)$$

where IP is the ionization potential and EA the electron affinity.

On going from one acid to another, IP(H) of course is constant and $D(H{-}AR_n)$ might be expected to be fairly closely correlated with ΔH°_{ion}, particularly when the molecules HAR_n have similar electronic structures. Hence for any isoelectronic set of AH_n molecules the heat of ionization would be expected to be linearly related to the electron affinity of the



SCHEME 1. Two possibilities to protonate a nitrone group

radical. This expection has been confirmed, for example in the series $R_2C{=}O$, $R_2{=}NH$, $R_2{=}CH_2$.

Similarly, the proton affinity of a base B can be expressed as follows:

$$PA(B) = D(H{-}B^+) + IP(H) - IP(B)$$

where $D(H{-}B^+)$ is the energy required to dissociate a hydrogen atom from the protonated base and IP(B) is the ionization potential of B.

B. Aqueous Acidities of Protonic Acids

The protonic character, or acidity, is one of the most important features of many hydrogen compounds discussed in this chapter. There are many different acid–base theories[3] and we will find that the one introduced by Hammett is most suitable for the discussion of the compounds included in this chapter. The classical definitions are those of Brønsted[4] and Lowry[5,6] on the one hand and the one given by Lewis[7–9] on the other hand. Brønsted and Lowry suggested that acids can be defined as proton donors and bases as proton acceptors. The acid–base interaction is considered to follow the general equation 1, where x and y denote the charges on the acid and base, respectively.

$$\underset{\text{acid I}}{HA^x} + \underset{\text{base II}}{B^y} \rightleftharpoons \underset{\text{base I}}{A^{x-1}} + \underset{\text{acid II}}{HB^{y+1}} \qquad (1)$$

Chemical species that differ from each other only to the extent of the transferred proton are termed *conjugates*. As long as one is dealing with a protonic solvent system, the Brønsted–Lowry definition is as useful as any.

The pH of an aqueous solution, where the concentration of the solute is not very high, is a good measure of the proton-donating/accepting ability of the solvent. But unfortunately this is no longer true in concentrated solutions because activity coefficients are no longer at unity. A measurement of solvent acidity is needed which works in concentrated solutions and applies to mixed solvents as well. This is established in the Hammett acidity function (H_0)[10,11]. This function is used for acidic solvents of high dielectric constants; H_0 is

defined (equation 2) for any solvent including mixtures of solvents.

$$H_0 = \mathrm{p}K_{\mathrm{BH}_w^+} - \lg \frac{[\mathrm{BH}^+]}{[\mathrm{B}]} \tag{2}$$

Using weak bases (B) as indicators, which are partly converted in acidic solvents to the conjugated acids BH^+, the H_0 value is measured. Two typical indicators are the *o*-nitroanilinium ion (pK in water -0.29) and the 2,4-dinitroanilinium ion (pK in water -4.53)[12]. By means of spectrophotometric methods it is possible to determine the ratio of $[BH^+]/[B]$ for each indicator, therefore H_0 can be calculated for any solvent system, provided that the pK value of this indicator in water ($\mathrm{p}K_{\mathrm{BH}_w^+}$) is known. If H_0 is known for a particular solvent system, the pK_a values can be calculated for any acid–base pair.

Equation 3 defines the h_0 value; a_{H^+} is the activity of the proton and f_I and f_{HI^+} are the activity coefficients of the indicator and its conjugated acid, respectively.

$$h_0 = \frac{a_{H^+} f_I}{f_{HI^+}} \tag{3}$$

H_0 is related to h_0 by equation 4. So H_0 is analogous to pH and h_0 to $[H^+]$. Indeed, in diluted aqueous solutions H_0 is equal to pH: $H_0 = \mathrm{pH}$. H_0 reflects the ability of a solvent system to donate protons, but it can be applied only to acidic solutions of high dielectric constants, mostly mixtures of water with acids like nitric acid, sulphuric acid, perchloric acid etc.[13].

$$H_0 = -\lg h_0 \tag{4}$$

It is important to realise that the H_0 treatment is valid only when the f_I/f_{HI^+} ratio is independent of the nature of the base (the indicator). However, although the bases are structurally similar, the treatment is limited. Many deviations are found, even if similar bases are compared[14–18]. Besides H_0, other acidity scales have been introduced. For example, H_- for bases with charge of -1, H_R for aryl carbinols[19,20], $H_{R'}$ for aryl olefins and other molecules, whose conjugated acids are stable carbocations that do not form hydrogen bonds with the solvent[21,22], H_c for bases that protonate on carbon[23], H_E for aliphatic esters[24] and H_A for unsubstituted amides[25–28].

Another acidity function was proposed by Bunnett and Olsen (equation 5)[29–32]:

$$\lg \frac{[\mathrm{SH}^+]}{[\mathrm{S}]} + H_0 = \phi(H_0 + \lg[\mathrm{H}^+]) + \mathrm{p}K_{\mathrm{SH}^+} \tag{5}$$

where S is a base that is protonated by an acidic solvent. The parameter ϕ is the slope of a plot $\lg([SH^+]/[S]) + H_0$ against $H_0 + \lg[H^+]$, while the intercept is the pK_a of the acid SH^+ (referred to infinite dilution in water). The value of ϕ expresses the response of the equilibrium $S + H^+ \rightarrow SH^+$ to changing acid concentration. A negative ϕ indicates that the lg of the ionization ratio $[SH^+]/[S]$ increases, as the acid concentration increases, more rapidly than $-H_0$. A positive ϕ value indicates the reverse.

A corresponding equation which applies to kinetic data is given in equation 6.

$$\lg k_\psi + H_0 = \phi(H_0 + \lg[\mathrm{H}^+]) + \lg k_2^\circ \tag{6}$$

In this equation k_ψ is the pseudo-first-order rate constant for the reaction of a weakly basic substrate taking place in an acidic solution and k_2° is the second-order rate constant at infinite dilution in water. In this case ϕ characterizes the response of the reaction rate to changing acid concentration of the solvent.

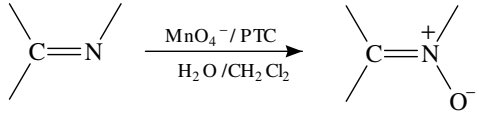
Another type of classification system was devised by Bunnett[33–36] for reactions occurring in moderately concentrated acid solutions. $\lg k_\psi + H_0$ is plotted against $\lg a_{H_2O}$, where k_ψ is the pseudo-first-order rate constant for the protonated species and a_{H_2O} is the activity of water. Most of these plots are linear or nearly so. According to Bunnett, the slope (w) of such a plot tells us something about the mechanism. Thus, when w is between -2.5 and 0, water is not involved in the rate-determining step; when w is between 1.2 and 3.3, water is a nucleophile in the rate-determining step; and when w is between 3.3 and 7, water is a proton-transfer agent. These rules hold for acids in which the proton is attached to oxygen or nitrogen.

IV. NITRONES

A. Synthesis of Nitrones Under Phase Transfer Catalyst Conditions

Nitrones are very interesting moieties in organic chemistry. They are highly versatile synthetic intermediates and spin trapping reagents[37–40]. They are usually prepared by either condensation of aldehydes with hydroxylamines or oxidation of the corresponding hydroxylamines[37–40]. These methods are associated with some problems concerning the preparation of the starting hydroxylamines.

An elegant method to prepare nitrones is the oxidation of imines with permanganate ions under PTC conditions (equation 7)[41].



(7)

Other oxidation reactions of imines, for example with peracid, lead to oxaziridines as the main product[42]. With *t*-amyl hydroperoxide as oxygen donor, $MoCl_5$ or $Mo(CO)_6$ catalyse the oxidation of imines to give oxaziridines, but no nitrones were found[43]. However, nitrones can be prepared from secondary amines with selenium dioxide[44] or sodium tungstate[45] as catalysts and hydrogen peroxide as oxygen donor.

The results of the oxidation of different imines according to equation 7 are listed in Table 1. The yields of the nitrones are reasonable except for those species where a phenyl group is attached to the imine nitrogen.

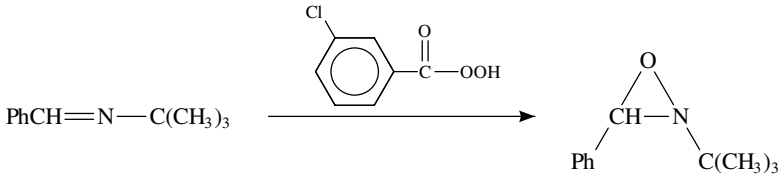
TABLE 1. Oxidation of imines **1** to nitrones **2** with potassium permanganate under phase transfer conditions[a]

Imine	Nitrone **2**, yield, %	Other products (yield, %)
1a, PhCH=NCMe$_3$	89	**4a**, PhC(O)NHCMe$_3$ (11)
1b, PhCH=NPh	36	**4b**, PhC(O)NHPh (15)
1c, *p*-NO$_2$C$_6$H$_4$CH=NCMe$_3$	81	**4c**, *p*-NO$_2$C$_6$H$_4$C(O)NHCMe$_3$ (19)
1d, *p*-MeOC$_6$H$_4$CH=NCMe$_3$	66	**4d**, *p*-MeOC$_6$H$_4$C(O)NHCMe$_3$ (15)
		3d, *p*-MeOC$_6$H$_4$CH-O-NCMe$_3$ (3)
1e, Me$_2$CHCH=NCMe$_3$	76	*p*-MeOC$_6$H$_4$CHO (16)
		4e, Me$_2$CHC(O)NHCMe$_3$ (24)
1f, Me$_3$CCH=NPh	13	Me$_3$CCHO (4)

[a]Reaction conditions: imine (2.5 mmol), $KMnO_4$ (5 mmol), $(Me(CH_2)_3)_4N^+Cl^-$ (PTC) (0.5 mmol), H_2O (pH 4.1) (5 mL) and CH_2Cl_2 (5 mL) for 24 h at room temperature.

1. Influence of different PTCs and pH values on the formation of nitrones

The permanganate ion oxidation of imines to nitrones is very much dependent on the reaction conditions. For the investigation of this dependency, reactions with benzylidene-*t*-butylamine, **1a**, were carried out (equation 8). **1a** was oxidized with *m*-chloroperbenzoic acid to give the corresponding oxaziridine **3a**. As byproduct traces (<3%) of the nitrone **2a**, amine **4a** and benzaldehyde were formed. The permanganate ion and *m*-chloroperbenzoic acid may then oxidize the imine in two different ways.



(8)

(1a) **(3a)**

In the oxidation with permanganate the best imine:permanganate ratio is 1:2. Ratios of 1:3 or 1:4 lead to a slight decrease in the yield of the nitrone **2a** (80%) and a slight increase in the amount of the formed amide **4a** (20%). A reduced ratio to 1:1 leads to a drastic decrease of the nitrone and also of the amide.

Another important feature is the solvent. For example, in dry organic solvents like acetone, methanol, acetonitrile or methylene chloride **1a** was not oxidized by potassium permanganate within 24 h. If a small amount of water (pH 4.1) was added to the reaction mixture, the oxidation took place. Figure 1 shows the variation of the yield of **2a** and **4a** as

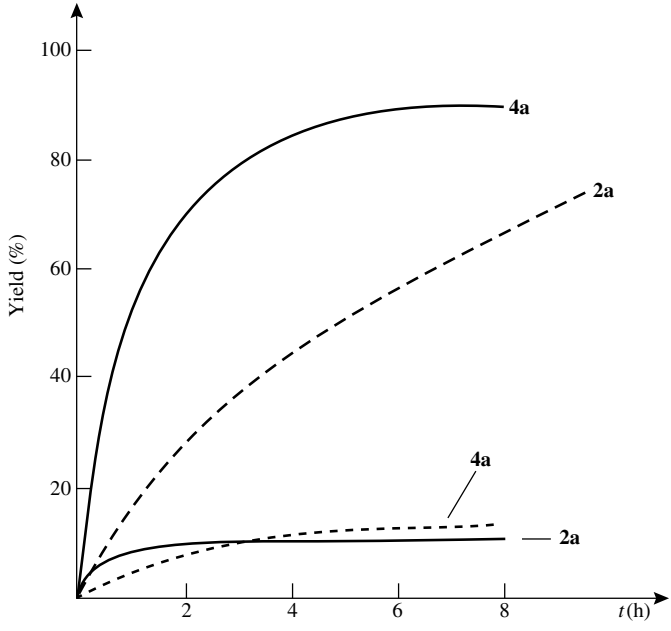


FIGURE 1. The variation of the yield of **2a** and **4a** as a function of time for the reaction of **1a** with potassium permanganate in acetonitrile/water (solid line) and under standard conditions (dotted line)

a function of time for the reaction of **1a** with potassium permanganate in acetonitrile/water (solid line) as well as under the standard conditions (dotted line).

Phase transfer catalysts (PTCs) are known to play an important role in the permanganate ion oxidation of alkenes[46–53] and it was found that they are also important for the imine oxidation[41]. In the absence of PTCs only a slow reaction was observed. The influence of different PTCs on the reaction course of the permanganate ion oxidation of **1a** has been studied and the results are listed in Table 2[41]. It has been found that long-chain tetraalkylammonium salts are the best PTCs for that oxidation reaction[41].

As mentioned before, the acidity and basicity of the aqueous phase is important. Table 3 shows the results of some experiments of the oxidation reaction from PhCH=NCMe$_3$, **1a**, with potassium permanganate[41]. The nitrone **2a** is formed under acidic, neutral and basic conditions in the aqueous phase in relative good yields. The best results were obtained at pH 4.1.

2. Discussion of a possible formation mechanism

The reaction mechanism of the oxidation reaction can be discussed in different ways[41]. One is the frontier orbital approach. It was suggested that the oxidation proceeds via a [3 + 2] cycloaddition of two oxygen ligands of the permanganate ion to the imine bond. The frontier orbitals of the permanganate ion have the right symmetry to interact with the π and π^* orbitals of the imine[41]. A possible reaction mechanism is shown in Scheme 2. Figure 2 shows the frontier orbitals of an imine and Figure 3 presents the interaction diagram for the formation of the permanganate ion-imine complex.

TABLE 2. Oxidation of PhCH=NCMe$_3$, **1a**, with potassium permanganate using different phase transfer catalysts[a]

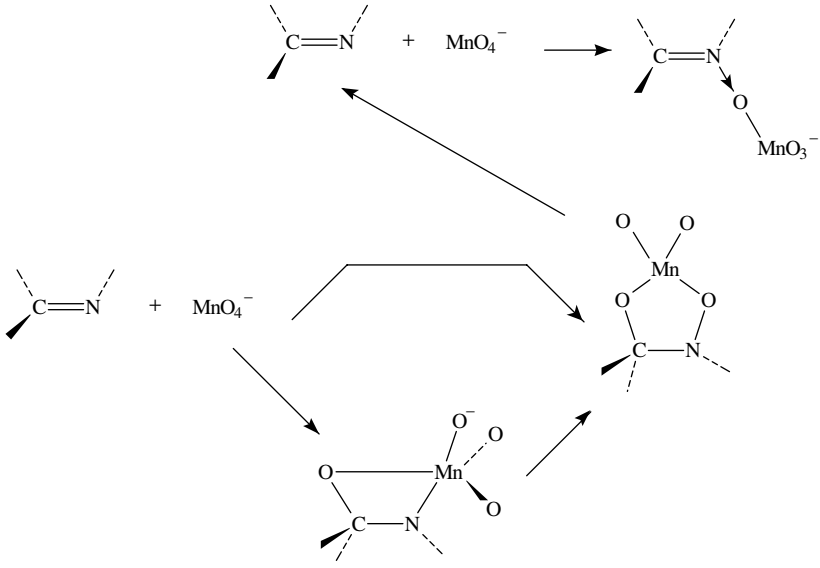
Phase transfer catalyst	Products (yield, %)
$[CH_3(CH_2)_3]_4N^+Cl^-$	**2a** (89), **4a** (11)
$[CH_3(CH_2)_7]_4N^+Br^-$	**2a** (80), **4a** (20)
$(CH_3)_4N^+Cl^-$	**2a** (69), **4a** (19), C_6H_5CHO (11)
$C_6H_5CH_2(CH_3CH_2)_3N^+Cl^-$	**2a** (76), **4a** (23)
$C_6H_5CH_2(CH_3)_3N^+BF_4^-$	**2a** (66), **4a** (16), C_6H_5CHO (17)
$(C_6H_5CH_2)_2(CH_3)_2N^+Cl^-$	**2a** (68), **4a** (30)
$C_6H_5(CH_3)_3N^+IO_3^-$	**2a** (26), **4a** (33), C_6H_5CHO (34)
$(C_6H_5)_3CH_3P^+I^-$	**2a** (50), **4a** (18), C_6H_5CHO (32)

[a]Same reaction conditions as given in Table 1.

TABLE 3. Oxidation of PhCH=NCMe$_3$, **1a**, with potassium permanganate at different acidities[a]

pH	Products (yield, %)
2.0	**2a** (64), **4a** (24)
4.1	**2a** (89), **4a** (11)
6.2	**2a** (76), **4a** (18)
8.0	**2a** (74), **4a** (10)
10.4	**2a** (73), **4a** (25)
12.0	**2a** (74), **4a** (20)

[a]Same reaction conditions as given in Table 1.



SCHEME 2. Possible reaction mechanism (see text)

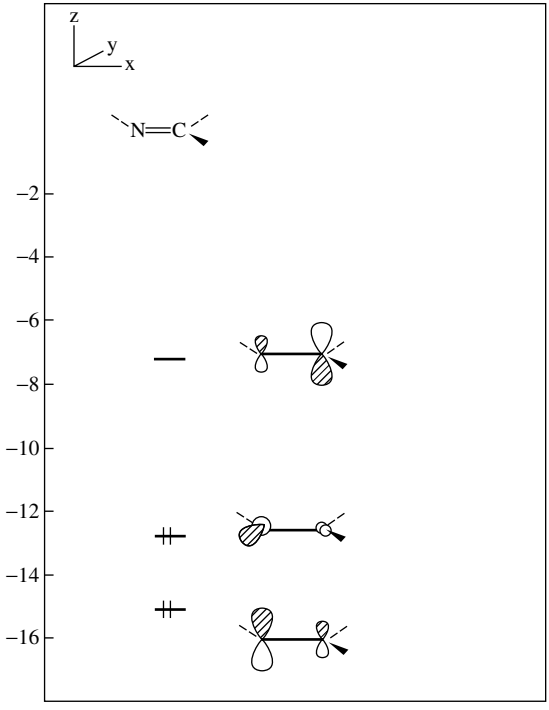


FIGURE 2. The frontier orbitals of an imine

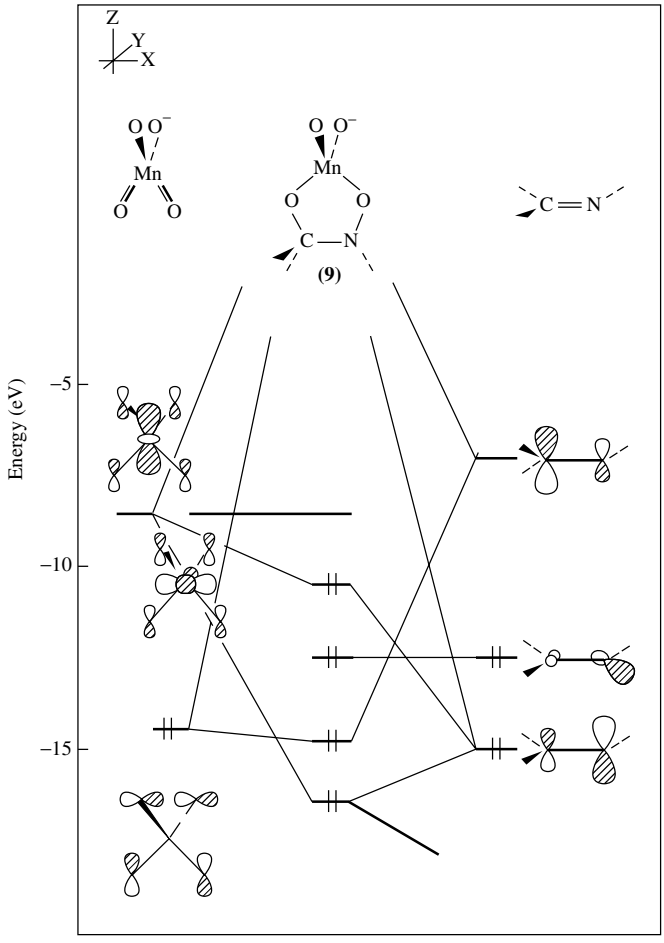


FIGURE 3. Interaction diagram for the formation of the permanganate ion–imine complex, **9**, from the permanganate ion (left) and the imine (right)

TABLE 4. pK_a values of nitrones of type $RC_6H_4CH{=}N(O)CH_3$

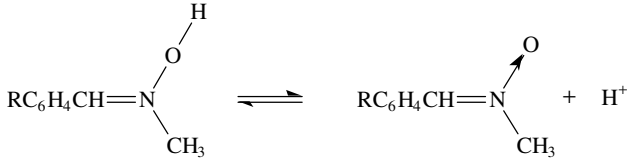
R	pK_a	R	pK_a
H	8.26	*m*-Br	6.98
p-$N(CH_3)_2$	11.49	*p*-SCN	7.23
p-OH	9.79	*m*-NO_2	6.32
p-OCH_3	9.43	*p*-NO_2	6.10
m-OH	8.13	*o*-OH	6.41
p-CH_3	8.72	*o*-OCH_3	8.83
p-SCH_3	8.83	*o*-Cl	7.14
p-Cl	7.67	*o*-NO_2	6.82
p-Br	7.55	2,4,6-CH_3	8.77

TABLE 5. pK_a values of nitrones of type RCH=N(O)CH_3

R	pK_a	R	pK_a
2-Naphthyl	8.05	2-Thienyl	8.05
2-Hydroxy-1-naphthyl	5.25	2-Furyl	8.26
2-Methoxy-1-naphthyl	8.95	5-Bromo-2-furyl	7.64
9-Anthryl	7.95	5-Iodo-2-furyl	7.74
Pyrrol-2-yl	10.19	5-Nitro-2-furyl	5.02
1-Methylpyrrol-2-yl	11.29	1-Methylindol-3-yl	11.27
Indol-2-yl	11.18	Quinolin-2-yl	12.47

B. Influence of the Substituents on the pK_a Values

Very interesting studies are those concerning the equilibria according to equation 9 and equation 10[54]. These show the influence of the substituents which are attached to the carbon atom of the nitrone group on the pK_a values. The pK_a values are listed in Tables 4 and 5 and were analysed with the aid of various correlation equations such as equation 11.



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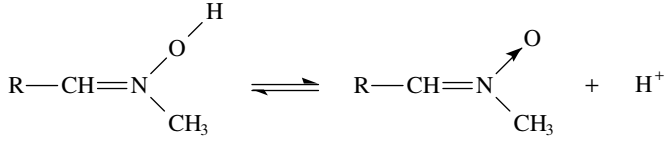


(10)

$$\lg K = \lg K_0 + \rho^{\sigma} \tag{11}$$

The parameters of the correlation equation (equation 11) are given in Table 6. They describe the basicity of the nitrones $RC_6H_4CH{=}N(O)CH_3$ using various sets of parameters of substituents, including the $\sigma N \rightarrow O$ constants used for the correlation of the properties of N-oxides[55]. It can be seen from Table 6 that the best correlation is achieved by means of the electronic substituent constants σ^+ and the constants $\sigma N \rightarrow O$, the sensitivity of the reaction in equation 9 to the influence of the substituents corresponding to the value of the reaction constant (ρ 2.10) in the analogous series of *N*-benzylideneaniline N-oxides[56]. Multiparameter correlation of pK_a values for nitrones of type $RC_6H_4CH{=}N(O)CH_3$ are shown in equations 12 and 13. The results of these equations are listed in Table 7.

$$\lg K = \lg K^0 + \rho_i\sigma_i + \rho_c{\sigma_c}^+ \tag{12}$$

TABLE 6. Parameters of equation 11

Type of σ	ρ	r	s	δpK	$\delta\rho\sigma$
σ	3.26	0.987	0.83	0.07	0.16
σ^+	2.11	0.994	0.57	0.06	0.08
$\sigma N \rightarrow O$	2.02	0.996	0.38	0.06	0.07

TABLE 7. Parameters of equations 12 and 13

Type of σ	Equation	ρ_i	ρ_c	$\rho_{i,c}$	r	δpK	$\delta\rho_i$	$\delta\rho_c$	$\delta\rho^{i,c}$	s
σ^+	12	2.69	1.96	—	0.997	0.09	0.20	0.08	—	0.28
σ^+	13	2.69	1.96	−0.01	0.997	0.10	0.21	0.13	0.59	0.23
$\sigma N \rightarrow O$	12	1.90	2.05	—	0.996	0.11	0.29	0.10	—	0.26

$$\lg K = \lg K^0 + \rho_i\sigma_i + \rho_c\sigma_c{}^+ + \rho_{i,c}\rho\sigma_i\sigma_c{}^+ \quad (13)$$

The best correlation by means of equations 12 and 13 is achieved by using the $\rho_c{}^+$ constants, and the parameters ρ_i and ρ_c for the methylamine N-oxides coincide almost quantitatively with the values of these correlation constants for the benzylideneaniline N-oxide series[56]. This confirms the complete monotypicity of the electronic influences of the substituents R in the nitrone series containing different radicals on the nitrogen atom, although the replacement of the N-methyl group by N-phenyl in the nitrones $RC_6H_4CH{=}N(O)CH_3$ lowers their basicities by more than an order of magnitude[54]. The low absolute value of the $\rho_{i,c}$ constant with a considerable mean square error in $\delta\rho_{i,c}$ shows the additivity of the transmission of the electronic effects of the substituents R in the nitrones (Table 4) by induction and conjugative mechanisms. The contributions of the two effects mentioned to the differences in the free energies of ionization due to the substituents are approximately the same[54].

Intramolecular hydrogen bonds in o-$HOC_6H_4CH{=}N(O)CH_3$ stabilize the non-protonated molecule and considerably lower the basicity as compared with the corresponding methyl esters (by 2.5–3 pK_a units).

A consideration of pK_a values of the compounds listed in Table 5 enables the comparison of the nucleophilicities of some hetaryl and polynuclear aryl substituents in the reaction of equation 10 with those of phenyl substituents. Contrary to expectations based, for example, on the values of Streitwieser's constants, in the reaction series the naphthyl and anthryl units behave as acceptors with respect to the phenyl group. This behaviour is obviously connected with the high polarizability of the N-oxide group. The basicities of *N*-thienylidenemethylamine N-oxide [2-thienyl-$C_6H_4CH{=}N(O)CH_3$] and *N*-furfurylidenemethylamine N-oxide [2-furyl-$C_6H_4CH{=}N(O)CH_3$] are similar to that of N-benzylidenemethylamine N-oxide, while the derivates of pyrrole-1-carbaldehyde and indole-3-carbaldehyde (see Table 5) have pK_a values which are higher by 2–3 pK_a units.

C. Oxaziridine as a Building Block for Nitrones

1. Introduction

The structure of nitrones is hidden in that of the oxaziridines (Figure 4)[57]. For both compounds the preparations and properties have been reviewed[58–63]. The main reactions

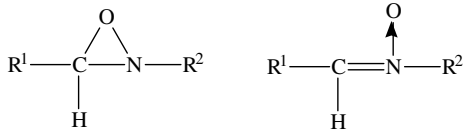


FIGURE 4. Oxaziridine (I) and nitrone (II)

of simple oxaziridines are ring-opening reactions, presumably to relieve steric strain, followed by rearrangements or cleavage.

2. Hydrolysis and rate constants of oxaziridine compounds and nitrones under variation of the pH value and reaction medium

In aqueous acids, oxaziridines were shown to undergo ring opening and cleavage to form carbonyl compounds and N-substituted hydroxylamines[61,62]. For example, 2-*t*-butyl-3-phenyloxaziridine is hydrolysed in aqueous acid to yield benzaldehyde and *N*-*t*-butylhydroxylamine. An interesting question is that of the mechanism of this reaction[64]. One way to answer this question is to look at the rate constants of hydrolysis, k_ψ of *N*-*t*-butylbenzaldoxime in HCl, $HClO_4$ and H_2SO_4, in sodium acetate–acetic acid buffer at pH 4.05 and NaOH at 24.2 °C (Table 8)[57]. The rate constants for the hydrolysis of 2-*t*-butyl-3-phenyloxaziridine are listed in Table 9. Figure 5 shows a plot of $\lg k_\psi$ vs pH (for $C_{H^+} < 1$ M) and against -H_0 (for $C_{H^+} > 1$ M) for (a) the oxaziridine and (b) the nitrone.

All the profiles exhibit a rate maximum similar to those exhibited for the hydrolysis of moderately basic substrates, for example amides[65–67], esters[68], ureas[69] and dipeptides[70]. It was found[66–73] that both the magnitude and the position of the rate maximum depend on the nature of the mineral acid used as the catalysing medium. For the nitrone the position of the maximum shifts to lower acidity in the order $HCl \cong H_2SO_4 < HClO_4$, and for the oxaziridine the order is $HCl < H_2SO_4 < HClO_4$. For both substrates the magnitude of $k_{\psi_{max}}$ decreases in the order $HCl > H_2SO_4 > HClO_4$. In the pH region the profiles for HCl and $HClO_4$ are superimposable and slightly greater than that for H_2SO_4. At higher acidities the profiles for HCl and $HClO_4$ are nearly parallel, but that for H_2SO_4 decreases more rapidly with increasing values of $-H_0$. Data measured in two concentrations of sodium acetate–acetic acid buffer at pH 4.05[57] are identical, corroborating the conclusion

TABLE 8. Rate constants for hydrolysis of *N*-*t*-butylbenzaldoxime[a] at 24.2 °C

[medium] (M)	$10^5\ k_\psi$ (s^{-1})	[medium] (M)	$10^5\ k_\psi$ (s^{-1})	[medium] (M)	$10^5\ k_\psi$ (s^{-1})	[medium] (M)	$10^5\ k_\psi$ (s^{-1})
HCl		$HClO_4$		pH (HCl)		H_2SO_4	
10.0	3.61	7.55	1.13	2.00	34.20	7.08	0.729
8.56	10.2	6.75	2.29	2.10	30.60	6.35	1.970
7.55	20.3	5.90	6.10	2.25	21.60	5.55	5.760
6.52	44.7	4.56	28.00	2.52	11.80	4.75	20.500
5.58	89.0	3.30	65.80	3.05	3.92	4.20	45.200
4.58	142.0	2.30	135.00			3.25	124.000
3.58	280.0	1.55	330.00	NaOH		2.90[b]	119.000
2.60	473.0	0.900	597.00			2.38	294.000
1.67	767.0	0.405	632.00	1.00	1.29	1.65	514.000
1.15	978.0	0.160	451.00	0.10	*ca* 0.15	0.805	830.000
0.575	857.0	0.080	271.00			0.375	840.000
0.200	482.0	0.008	31.00	sodium acetate–		0.168	506.000
0.150	371.0			acetic acid buffer		0.0800	349.000
0.095	302.0			at pH 4.05		0.0695	412.000
0.078	256.0					0.0600	276.000
0.059	192.0			0.100	0.545	0.006	38.300
0.030	101.0			0.020	0.545		

[a] [substrate] = $2–5 \times 10^{-5}$ M.
[b] D_2SO_4.

TABLE 9. Rate constants for hydrolysis of 2-*t*-butyl-3-phenyloxaziridine[a] at 24.2 °C

[medium] (M)	$10^5\ k_\psi$ (s^{-1})	[medium] (M)	$10^5\ k_\psi$ (s^{-1})	[medium] (M)	$10^5\ k_\psi$ (s^{-1})	[medium] (M)	$10^5\ k_\psi$ (s^{-1})
HCl		$HClO_4$		pH		H_2SO_4	
9.73	5.26	7.55	1.03	2.00	36.80	7.08	0.447
8.52	12.9	6.75	2.24	2.10	32.3	6.35	1.45
7.60	25.1	5.90	5.52	2.52	11.9	5.55	4.81
6.55	45.7	4.56	23.6	3.05	2.99	4.75	18.1
5.57	89.0	3.30	68.3			4.20	46.3
4.50	169.0	2.30	163.0	NaOH		3.25	116.0
3.68	238.0	1.55	345.0			2.90[b]	118.0
2.82	403.0	0.900	684.0	1.00	1.34	2.38	257.0
1.80	917.0	0.405	706.0	0.1	*ca* 0.10	1.65	496.0
1.67	1060.0	0.160	461.0			0.805	942.0
1.15	987.0	0.080	283.0	sodium acetate–		0.375	883.0
0.920	896.0	0.008	31.7	acetic acid buffer		0.168	568.0
0.550	748.0			at pH 4.05		0.080	358.0
0.200	552.0					0.0695[b]	417.0
0.150	428.0			0.100	0.528	0.060	275.0
0.078	309.0			0.020	0.512	0.006	37.7
0.059	203.0						
0.030	112.0						

[a][substrate] = $1–8 \times 10^{-4}$ M.
[b]D_2SO_4.

of other groups[64] that the reaction is catalysed specifically by hydrogen ions, and not by general acids. Base catalysed hydrolysis exists but is much slower than the acid catalysed reaction.

The immediate changes in UV spectra[57] exhibited by the substrates on addition of mineral acids are consistent with a rapid protonation equilibrium, $S + H^+ \rightleftarrows SH^+$, to form the conjugated acid. In order to interpret the rate data, one must first correct the observed values of k_ψ for the amount of protonated substrate. Spectrophotometric methods are widely applicable for determination of the ionization ratio, $I = C_{SH^+}/C_S$, of moderately basic substrates[74]. For *N*-*t*-butylbenzaldoxime and 2-*t*-butyl-3-phenyloxaziridine, however, the rate of the hydrolysis reaction ($t_{1/2} \cong 1$ min) at the maximum in the profile at 24.2 °C made it impossible to measure the zero-time absorption of the substrates. However, allowing for medium effects in the absorption spectra, the substrates appeared to be essentially fully protonated in solutions of $C_{H^+} > 2$ M in all three acids.

The data at high acidities using existing rate correlation expressions applicable to hydrolysis of a fully protonated substrate have also been analysed[57]. Plots of the Zucker–Hammett A-2 relationship[74], $\lg k_\psi$ against $\lg C_{H^+}$, were curved; plots of the Bunnett ω criterion[33–36], $\lg k_\psi$ against $\lg a_w$, were nearly linear, while those of the Bunnett–Olsen linear free-energy relationship[30], $\lg k_\psi$ against $(H_0 + \lg C_{H^+})$, were good straight lines. Values of ω and ϕ parameters obtained are summarized in Table 10.

The values of ω lie outside the range 1.2–3.3, said to be characteristic of water acting as a nucleophile in the rate-determining step[33–36]. Moreover, values of ϕ are all >0.58, and thus also fall in the region indicative of water acting as a proton transfer agent[30]. Bearing in mind the magnitude of Arrhenius parameters (*vide infra*) and in view of the fact that the reactions are not generally acid catalysed, such a mechanism seems to be very unlikely. Values of ϕ for hydrolysis of amides[66,67,74] were found to lie outside Bunnett

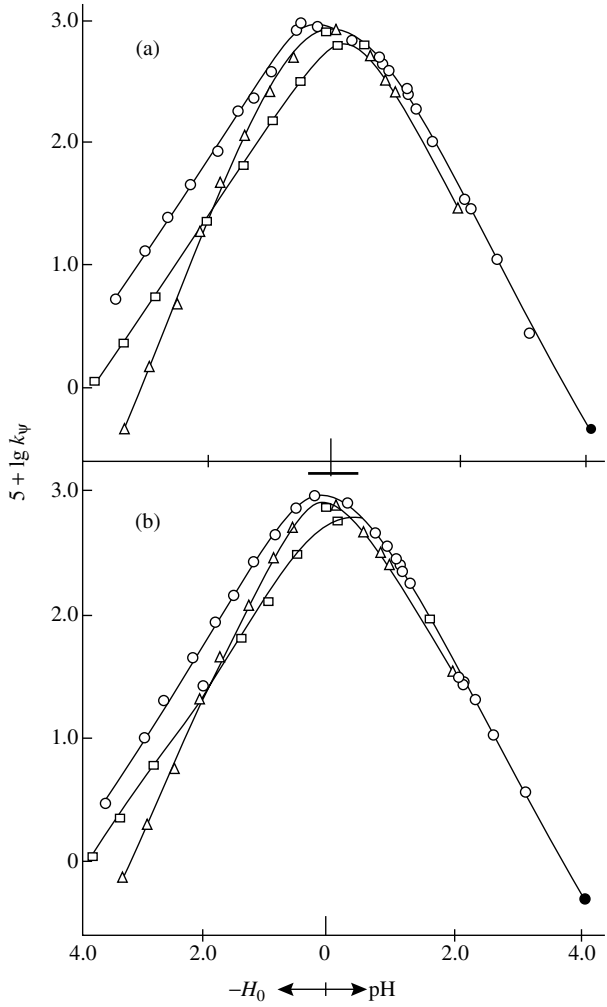


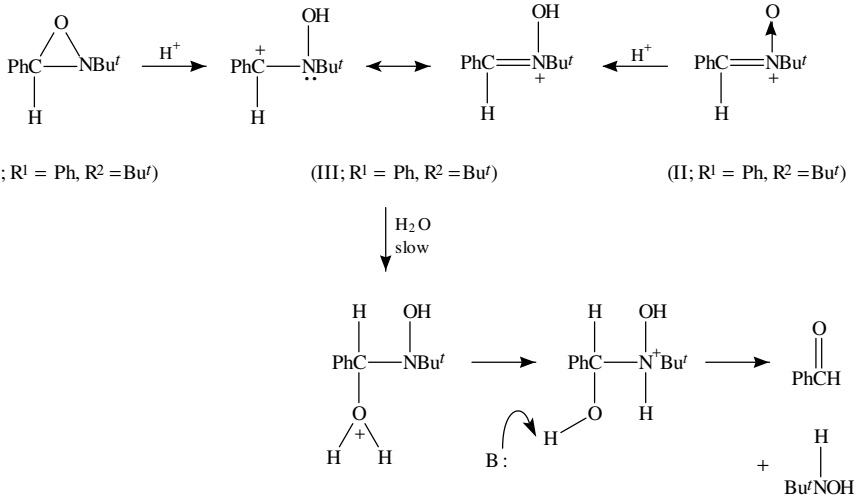
FIGURE 5. Rate constants (a) for hydrolysis of 2-*t*-butyl-3-phenyloxaziridine and (b) for *N*-*t*-butylbenzaldoxime at 24.2 °C as a function of acidity in HCl (○), $HClO_4$ (□), H_2SO_4 (△) and NaOAc–HOAc buffer (●)

TABLE 10. Analysis of rate data for hydrolysis of *N*-*t*-butylbenzaldoxime and 2-*t*-butyl-3-phenyloxaziridine at 24.2 °C by use of Bunnett ω and Bunnett–Olsen linear free-energy relationships

Acid	2-*t*-Butyl-3-phenyloxaziridine		*N*-*t*-Butylbenzaldoxime	
	ω	ϕ	ω	ϕ
HCl	3.80	0.80	3.80	0.96
$HClO_4$	3.78	0.84	3.40	0.88
H_2SO_4	6.21	1.49	5.70	1.44

and Olsen's original classification and it has been suggested that limits on values of ω and ϕ may have to be revised for application to each particular class of substrates.

The investigations of the UV spectra, the rate constants of hydrolysis and additional investigations of deuterium isotope and temperature effects of *N*-*t*-butylbenzaldoxime and 2-*t*-butyl-3-phenyloxaziridine[57] suggest a mechanism which is shown in Scheme 3. If the protonated nitrone is the intermediate in both reactions, the formation from either nitrone or oxaziridine should have no effect on the subsequent behaviour under identical conditions.



SCHEME 3. Reaction scheme (see text)

Tables 8 and 9 and Figure 5 show that the rate data for hydrolysis of nitrone are almost identical to that for the hydrolysis of oxaziridine under all conditions of acidity at 24.2 °C. This evidence confirms that the 'salt' of both oxaziridine and nitrone has the same kinetics on addition to water and forms products at a rate greater than that of unprotonated oxaziridine or nitrone. The decreasing rate at higher acidities is due to decreasing water activity in the acid media and is well explained by the Bunnett and Bunnett–Olsen criteria of the mechanism. The presented evidence[57] is consistent with the mechanism outlined in Scheme 3, for example, a rapid protonation pre-equilibrium of nitrone (**II**) and oxaziridine (**I**) to form a common intermediate (**III**) followed by slow nucleophilic attack by water and rapid decomposition to benzaldehyde and *t*-butylhydroxylamine.

V. NITRILES

A. Influence of the Substitution of the Cyano Group on the Basicity of Nitriles

A very interesting observation was the decrease in basicity of the cyano group in α-sulphur-substituted nitriles in comparison with the corresponding sulphur-free compounds[75]. The basicity constants for the nitriles (Table 11) were corrected to give $\lg K_{as} + \delta E_s$ values. These values consider the steric effects of the substituents.

A comparison of the corrected basicity constants indicates the order of basicities of the studied nitriles. This order is unsubstituted > α-sulphur > β-chloro > α-oxygen and it seems to follow the inductive effects of the substituents. Figure 6 shows the correlation

TABLE 11. Basicity constants ($\lg K_{as}$ and $\lg K_{as} + \delta E_s$), σ^* and E_s values of the substituents for nitriles[76]

Nitrile	$\lg K_{as}$	σ^*	E_s	$\lg K_{as} + \delta E_s$[a]
RC≡N				
5 H = Me	0.785	0.000	0.00	0.785
6 R = Et	0.895	−0.100	−0.07	0.898
7 R = *n*-Pr	0.890	−0.115	−0.36	0.903
8 R = *i*-Pr	0.946	−0.190	−0.47	0.963
9 R = *n*-Bu	0.899	−0.130	−0.39	0.913
10 R = *t*-Bu	0.974	−0.300	−1.59	1.032
11 R = CH_2SMe	0.612	+0.420	−0.34	0.624
12 R = CH_2SEt	0.674	+0.560	−0.47	0.691
13 R = CHMeSEt	0.740	+0.490	−1.53	0.796
14 R = CH_2OMe	0.342	+0.520	−0.19	0.349
15 R = $[CH_2]_2]Cl$	0.477	+0.385	−0.90	0.510

[a] δ 0.0367.

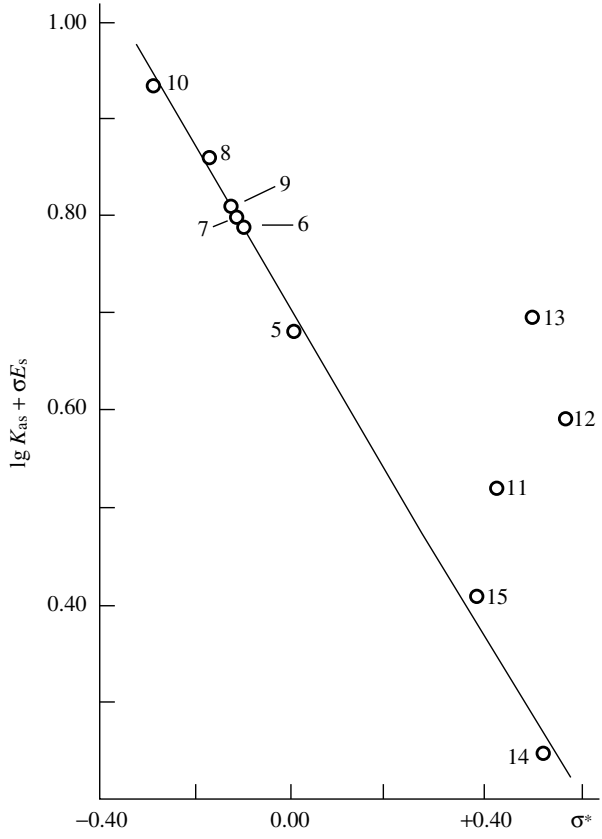


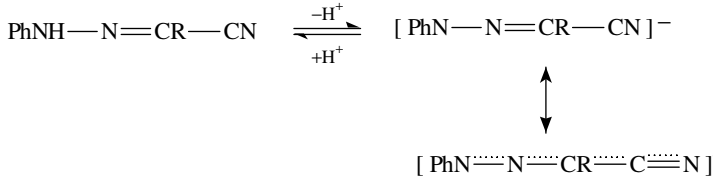
FIGURE 6. Correlation between $\lg K_{as} + \delta E_s$ and σ^* (ν 0.997)

between the corrected basicity constants $\lg K_{as}+\delta E_s$ and the Taft's values σ^*. The sulphur-substituted nitriles **11–13** deviate from the linear correlation. A possible cause of this is an interaction between sulphur and the cyano group.

B. α-Arylhydrazononitriles

1. Introduction

α-Arylhydrazononitriles are more acidic than other arylhydrazono derivatives[77]. This was shown in an investigation concerning the synthesis, structure and chemical reactivity of certain α-arylhydrazononitriles[78–83]. The acidity of these compounds was attributed to the stabilization of their anions by delocalization of the negative charge, as shown in equation 14.



(14)

2. Influence of the anion stabilization on the activity and pK_a values of α-arylhydrazononitriles and substituent effects

The effects of substituents of aryl moieties on the pK_a values of the compounds listed in Table 12 are an interesting subject and supply more information about their structures in alkaline media. Such information might be of interest for biochemists because of the mechanism of the inhibitory action of these compounds for oxidative phosphorylation which is known to be dramatically increased by the introduction of certain substituents on the aryl moiety of these compounds.

The specific reaction constants for the ionization reaction of the ArNH−N=C(CN)$_2$ series were found to be 1.34 and 1.40, respectively. For the ArNH−N=C(CN)−COPh series the specific reaction constants were 2.00 or 2.40, respectively. These specific constants for ionization reactions were calculated from correlation of the obtained pK_a values with Hammett's σ and σ° constants.

TABLE 12. Apparent pK_a values of mono-substituted derivatives of some α-arylhydrazononitriles

ArNH−N=C(CN)$_2$		ArNH−N=C(CN)−COPh	
Ar	pK_a	Ar	pK_a
Phenyl	6.23	Phenyl	7.20
m-Tolyl	6.35	*m*-Tolyl	7.30
p-Tolyl	6.15	*p*-Tolyl	7.25
p-Anisyl	6.22	*p*-Chlorophenyl	6.50
p-Aminophenyl	6.25	*p*-Bromophenyl	6.55
p-Chlorophenyl	5.73	*m*-Nitrophenyl	5.50
p-Bromophenyl	5.50		
m-Nitrophenyl	4.92		
p-Nitrophenyl	5.10		

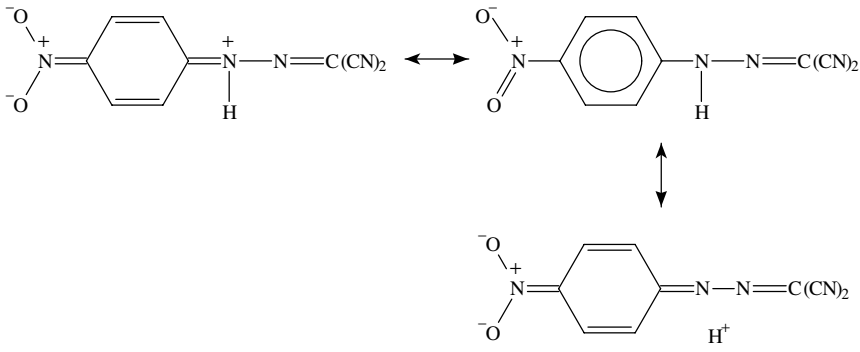


FIGURE 7. Resonance structure of α-*p*-nitrophenylhydrazononitrile

A closer look at the pK_a values indicates that electron-attracting substituents on the aromatic moiety enhance the ionization reaction of these compounds. In general, substituents affect the reaction in a way similar to their effect on ionization of carboxylic acids rather than that for phenolate anions[84,85] which may indicate that the negative charge in the anions of the ArNH−N=C(CN)$_2$ series and the ArNH−N=C(CN)−COPh series is not centred on the nitrogen atom directly linked to the aromatic moiety and is delocalized on the −N−N=C(CN)(X) moiety (X = CN or COPh). The small difference between the pK_a values of the *m*-NO_2 and the *p*-NO_2 substituted derivatives may be explained by the fact that in the α-*p*-nitrophenylhydrazononitrile the strong $-I$ effect of the NO_2 group is counter-balanced by the resonance effect of this substituent (Figure 7) which, by delocalization of the lone pair of electrons on the nitrogen atom, would stabilize the molecule; thus the proton inhibits the release from the nitrogen atom.

In conclusion, the data indicate that hydrazones with electron-withdrawing substituents on the aryl moiety are more acidic than arylhydrazones without such functional groups.

C. Compounds Forming Ambident Carbanions

1. Introduction

The equilibrium CH acidity (pK value) of compounds forming ambident carbanions gives information about the stabilization of those anions[86]. It was shown[87,88] that the relative CH acidity of compounds containing electron-withdrawing groups (for example PO, COOAlkyl, CN) at the α position to the CH bond increases if the polar solvent DMSO and the K^+ cation are replaced by the weakly polar DME and by the Li^+ cation (transmetallation method) during measurements of the pK values. In a solvent with low dielectric constant the pK values decrease. This observation can be explained by additional stabilization of the carbanions in the ion pairs as a result of coordination of the cation with the heteroatoms of the α-substituents, to which the negative charge is partly transferred. This is an important effect in the chemistry of ambident carbanions[89,90] and it must be taken into account for a correct assessment of the equilibrium acidity.

2. Correlation between the equilibrium C−H acidity (pK value) and stabilization of the corresponding carbanions

In most cases the equilibrium CH acidity of the investigated compounds in DMSO is practically independent of the nature of the cation. This indicates full dissociation of the

lithium and potassium derivates of the corresponding CH acids in DMSO and confirms the view[91,92] that carbanions with strongly delocalized charge do not form ion pairs with alkali metal cations in DMSO. Smaller pK values were obtained in DME for the investigated compounds with Li^+ than with Cs^+ (Table 13). The difference ΔpK was not constant for different substances. The variations of pK values in DME are due to ionic association. The degree of association can be estimated from the data by spectral and conductometric measurements. The hypsochromic shift of λ_{max} (position of the maxima in the absorption spectra) due to replacement of Cs^+ by Li^+ signifies[93] that the lithium derivates of the nitriles are present in DME in the state of intimate ion pairs. On the contrary, the carbanion of the standard CH acid 9-phenylfluorene (bathochromic shift, Table 14) forms solvent-separated ion pairs with Li^+ in DME. This is in agreement with the fact that the K_d value of phenylfluorenyllithium (Table 14) is one to three orders of magnitude greater than the K_d values of the lithium derivates of the investigated nitriles. The caesium derivates also form intimate ion pairs in DME, but they are less stable than those with Li^+. The K_d values of the caesium derivates are one to two orders of magnitude greater than the K_d values of the corresponding lithium derivates, while phenylfluorenyl caesium is more weakly dissociated than the caesium derivates of nitriles. The heteroatom of the functional group plays a great part in the formation of intimate ion pairs by ambident carbanions,

TABLE 13. Equilibrium CH acidity of some nitriles in DMSO and in DME (relative pK values) at 25 °C

Compound No.	Compound	pK_{DMSO}[a]		pK_{DME}[a]		ΔpK[b]
		Li^+	K^+	Li^+	K^+	
16	$PhCH_2CN$	22.3	22.2	19.6	22.4	2.8
17	Ph_2CHCN	18.2	18.3	16.1	18.3	2.2
18	Ph(Bph)CHCN	—	17.3	15.5	17.5	2.0
19	p-$NO_2C_6H_4CH_2CN$	13.1	13.1	10.9	13.0	2.1
20	FlCN[a]	—	9.6[c]	7.9	9.4	1.5
21	$CH_2(CN)COOEt$	13.8	13.8	10.4	13.0	2.6
22	$CH_2(CN)_2$	—	12.2	9.7	11.9	2.2

[a] The pK values of compounds **16–18**, **20** and **21**, determined in DMSO (K^+) and in DME (Li^+), were also published in other publications[88,94].
[b] $\Delta pK = pK_{DME}(Cs^+) - pK_{DME}(Li^+)$.
[c] The converted published value[94,95].

TABLE 14. Absorption maxima in the spectra of carbanions (λ_{max}, nm), dissociation constants of ion pairs (K_d, mol L^{-1}) and pK_1 values ('free-ion' scale) in DME at 25 °C

Compound No.[a]	λ_{max}		$K_d \cdot 10^7$		pK'	ΔpK_1[b]	ΔpK_2[b]
	Li^+	Cs^+	Li^+	Cs^+			
16	330	340	0.1	7.5	22.3 (0.2)	2.7	−0.1
17	385	400	0.6	13.0	18.0 (0.2)	1.9	−0.3
18	435	460	1.2	20.0	17.1 (0.3)	1.6	−0.4
19	520	540	1.4	30.0	12.4 (0.3)	1.5	−0.6
20	405	420	4.0	30.0	8.9 (0.4)	1.0	−0.5
c	410	395	79.0	4.0	(18.5)	—	—

[a] For designation see Table 13.
[b] $\Delta pK_1 = pK' - pK_{DME}(Li^+)$; $\Delta pK_2 = pK' - pK_{DME}(Cs^+)$.
[c] 9-Phenylfluorene.

the cause of coordination between the cation and the heteroatom. The comparison of the pK values of DMSO and DME is difficult, because the transition of the solvent affects the solvation energy of the anions, so the differentiation in the acidity in DMSO is not directly due to ionic association. It makes sense in comparing the pK values measured in DME with pK' values characterizing the acidity of the compounds on the 'free-ion' scale in the same solvent[88], i.e. on the pK scale reflecting the ionization of CH acids to form free carbanions and not their ion pairs.

The pK' values in DME were calculated by means of equation 15 where pK is the value measured with Li^+ or with Cs^+, and K_d° and K_d are the dissociation constants of the lithium and caesium derivates of 9-phenylfluorene and the given CH acid, respectively.

$$pK' = pK + \lg\left(\frac{K_d^\circ}{K_d}\right) \tag{15}$$

The averages of the two pK' values are given in Table 14. The deviations of the latter from the average (given in parentheses) are not more than 0.4 pK units, and this corresponds to the error in the determination of pK'. The differences of pK' and pK determined in DME (Li^+) (ΔpK_1) give an idea of the relative ability of the various substituents to coordinate the Li^+ cation. The coordinating ability decreases with an increase in the number of phenyl groups attached to the carbanionic centre. This is clearly due to the decrease in the negative charge at the heteroatom as a result of an increase in the degree of pπ conjugation of the carbanionic centre with the aromatic fragment of the molecule. The differences in the pK' and pK values determined in DME (Cs^+)(ΔpK_2) are comparatively small. The minus sign at ΔpK_2 signifies that the corresponding ambident carbanions are less stabilized by Cs^+ cations than the carbanion of the standard CH acid. Specific interactions at the heteroatoms of the anions with such large cations are probably insignificant. Certainly a correct assessment of the role of structural factors in equilibrium CH acidity will require a detailed account of the effect of the cation (as well as the solvation of the anion) on the pK values.

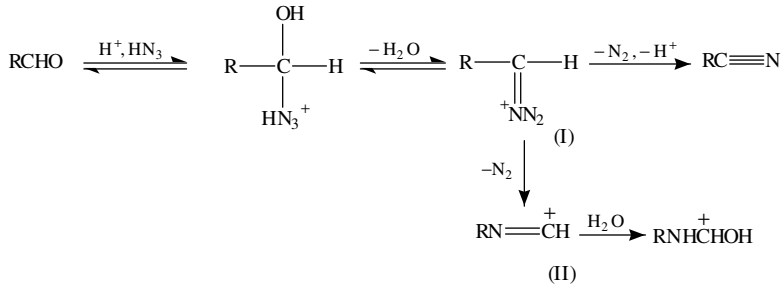
D. The Schmidt Reaction: The Transformation of Carbonyl Groups into Nitriles

1. Introduction

A well known possibility to transform carbonyl groups (−COOH, −CHO, −COR) into nitriles is the Schmidt reaction[96]. In the reaction of aldehydes with hydrazoic acid (HN_3) in the presence of acidic catalysts a mixture of two products is formed[97,98]. Unlike ketones, aldehydes react in both the protonated and unprotonated form[99]. Where the protonated form is reactive, the controlling stage of the reaction is the addition of unprotonated hydrazoic acid to the protonated aldehyde[100]. An interesting question is on which factors the ratio of nitrile and formamide in the reaction depends. On the basis of the available experimental data a reaction mechanism (Scheme 4) was proposed[98,101].

2. Discussion of possible reaction mechanisms

According to Scheme 4 elimination of a proton from the iminodiazonium ion (I) forms the nitrile. Rearrangement of the ion (I) leads to formanilide. But there are no data available supporting these ideas. Another possible way for the formation of nitrile is a rearrangement of the iminocarbonium ion (II) of the type which occurs in the isomerization of isonitriles to nitriles[99]. It was found that in 71.2–90.4% sulphuric acid, phenyl isocyanate is converted quantitatively into formanilide. For a better understanding of the



SCHEME 4. Proposed reaction mechanism of the Schmidt reaction

Schmidt reaction some experiments starting with benzaldehydes and hydrazoic and sulphuric acid, used as a catalyst, were carried out. If the reaction is carried out in 71.2% sulphuric acid, the protonated form of the aldehyde is practically absent and the only product is benzonitrile. If the acidity of the medium is increased, the proportion of benzonitrile gradually decreases, and in 87.4% sulphuric acid only formanilide is obtained. The effective rate constants for the formation of nitrile and formanilide at 20 °C are 64.0 and 67.0 L mol^{-1} min^{-1}, respectively. A very interesting aspect is that the change in the ratio of the reaction products takes place in the same range of sulphuric acid concentrations where acid–base equilibrium of benzaldehyde is observed. Based on these results the formation of nitrile and formanilide can be described as shown in Scheme 5.

$$B + HN_3 \longrightarrow \text{nitrile}$$

$$BH^+ + HN_3 \longrightarrow \text{formanililde}$$

SCHEME 5. Formation of nitrile and formanilide

Thus in the reaction of aldehydes with hydrazoic acid, nitriles are generated from the unprotonated form (B) and the formanilides from the protonated form (BH^+) of the aldehyde. A relationship between the ratio of the concentrations of the nitrile [N] and formanilide [F] and the pK_a value is given in equation 16.

$$\lg F = \lg \frac{[F]}{[N]} = \lg \frac{[BH^+]}{[B]} = pK_a - mH_0 \tag{16}$$

TABLE 15. Products from reaction of benzaldehyde with hydrazoic acid in aqueous solution of sulphuric acid ε_N 11250; ε_F 3750; λ_{anal} 225 nm

H_2SO_4 (wt%)	$-H_0$	lg F
76.3	6.90	−0.6466
76.9	7.02	−0.4364
77.8	7.16	−0.3837
78.3	7.24	−0.2668
79.4	7.43	−0.0452
80.8	7.65	−0.0012
81.8	7.73	0.2844
82.5	7.91	0.3458
84.1	8.15	0.7189
84.6	8.23	0.8988

This equation takes into account that benzaldehyde is a Hammett base and $F = [F]/[N]$. Equation 16 can be used to obtain pK_a for benzaldehye, because a linear relation should be observed between $\lg F$ and H_0 with a slope equal to unity.

The UV spectroscopy is a good experimental method for the determination of the concentration of nitrile and formanilide in the reaction. The absorption maxima of the nitrile and the formanilide in Figure 8 do not shift with the increase in the concentration of sulphuric acid and the characters of the spectra are virtually unchanged. The $\lg F$ values calculated from the experimental data are given in Table 15. The dependence of the extinction coefficients of the products from the reaction of benzaldehyde with hydrazoic acid on the acidity of the medium is shown in Figure 9.

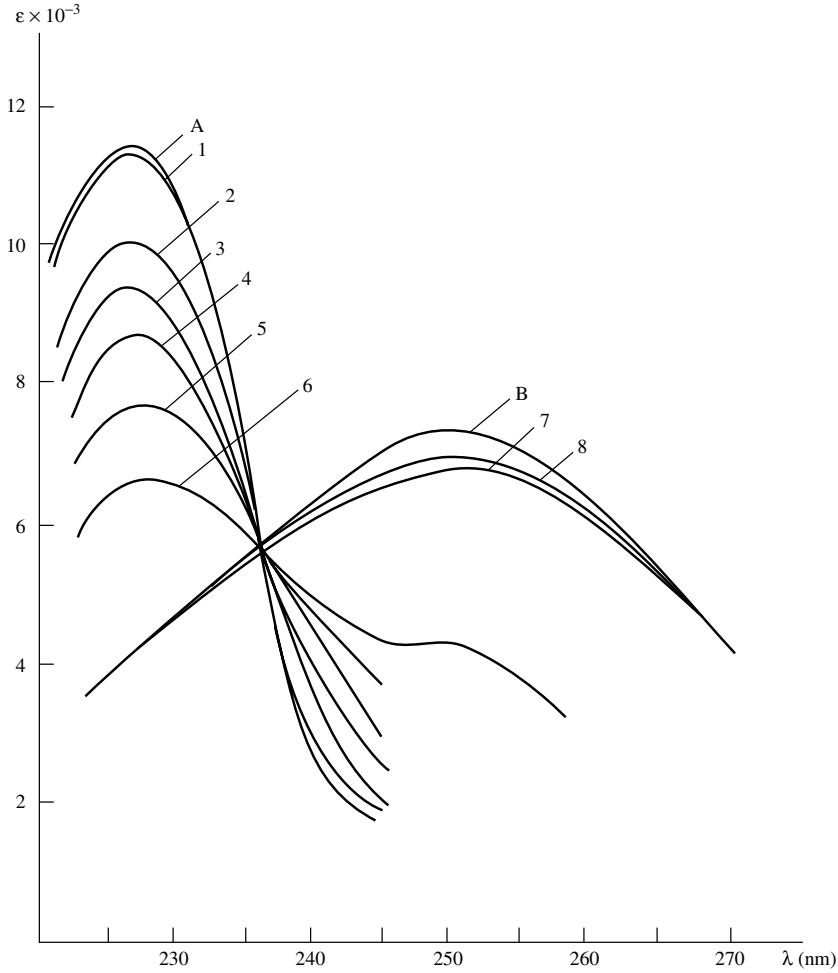


FIGURE 8. UV spectra of benzonitrile, formanilide and the reaction products in sulphuric acid: (A) benzonitrile, 71.2% sulphuric acid; (B) formanilide, 87.4% sulphuric acid. Reaction products in sulphuric acid at concentrations, %: (1) 71.2; (2) 76.3; (3) 76.9; (4) 78.3 (5) 80.8; (6) 81.8; (7) 85.8; (8) 87.4 (reproduced from Reference 96)

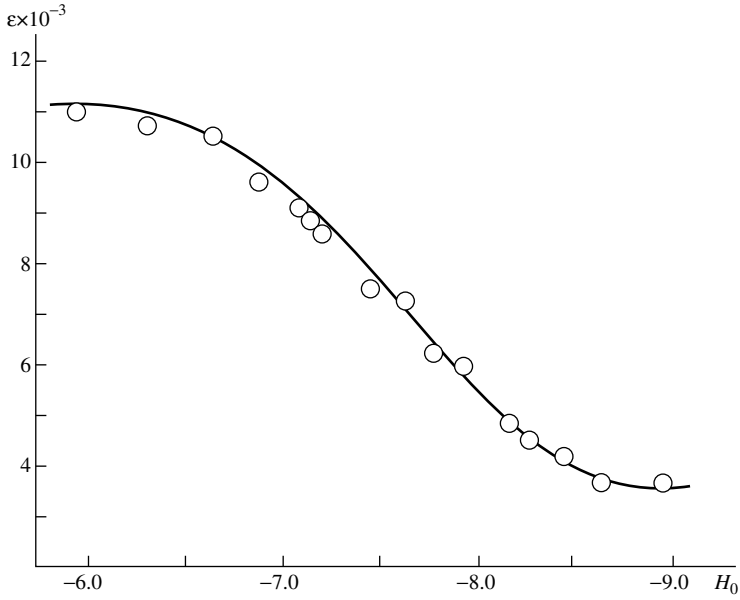


FIGURE 9. The dependence of the extinction coefficients of the products from the reaction of benzaldehyde with hydrazoic acid on the acidity of the medium (reproduced from Reference 96)

E. Super-basic Nitriles

1. Iminologue, cyanamide benzologue and vinylogue compounds and their hydrogen-bond basicity

Quite fascinating compounds are the super-basic nitriles[102]. The cyanamides are the most basic nitriles presently known[103,104]. The high basicity of such compounds is explained by a so-called 'push–pull' mechanism, described schematically by the resonance structures.

$$R_2N{-}C{\equiv}N \longleftrightarrow R_2N^{+}{=}C{=}N^{-}$$

This is the 'parent compound'. Offsprings are called 'iminologue' for an interposition of a CH=N imino transmitter group between the 'pushing' NMe_2 and the 'pulling' C≡N groups. In the same way interposition of a phenylene or of a vinyl group, respectively, gives a cyanamide benzologue or a vinylogue compound. The pK_{HB} scale[105,106] is that one which is used for the comparison of the strength of the hydrogen-bond basicity of nitriles. The pK_{HB} value is the logarithm of the forming constant of the complex between the nitrile and 4-fluorophenol (equation 17–19).

$$R{-}C{\equiv}N + p\text{-}FC_6H_4OH \rightleftharpoons p\text{-}FC_6H_4OH\cdots N{\equiv}C{-}R \tag{17}$$

$$K_{HB} = [\text{complex}]/[\text{nitrile}][4\text{-fluorophenol}] \tag{18}$$

$$pK_{HB} = \lg K_{HB} \tag{19}$$

The pK_{HB} values of some nitriles are mentioned in Table 16. The infrared spectra show only one symmetrical $\nu(OH\cdots)$ absorption and high-frequency shifts of the $\nu(C{\equiv}N)$

TABLE 16. Hydrogen-bond basicity of cyanamides and related compounds

Compound	pK_{HB}[a]	ΔpK_{HB}[b]	Reference	Type
4-(Dimethylamino)benzonitrile	1.23	−0.33	105	cyanamide benzologue
Dimethylcyanamide	1.56	0	102	cyanamide
Piperidine-1-carbonitrile	1.58	+0.02	102	cyanamide
Diethylcyanamide	1.63	+0.07	102	cyanamide
trans-Dimethylaminoacrylonitrile	1.70	+0.14	107	cyanamide vinylogue
N^2-Cyano-N^1,N^1-dimethylformamidine	2.09	+0.53	107	cyanamide iminologue
N^2-Cyano-N^1,N^1-dimethylacetamidine	2.24	+0.68	102	cyanamide iminologue
Tri-*n*-butylamine	1.57		105	
Pyridine	1.88		105	
Triethylamine	1.93		105	
4-Picoline	2.03		105	

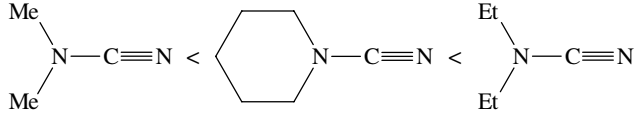
[a]The precision is estimated to lie within ±0.03 pK units. The pK values were measured of dilute solutions of 4-fluorophenol (*ca* 0.004 mol dm^{-3}) and of nitriles (0.02–0.1 mol dm^{-3}) to ensure that only complexes of 1:1 stoichiometry are formed.

[b]$\Delta pK_{HB} = pK_{HB}(\text{compound}) - pK_{HB}(Me_2NC{\equiv}N)$.

band[102]. These observations suggest a unique site hydrogen bonding on the sp nitrogen of the nitrile group[103]. Indeed, there is no known example where hydrogen bonding occurs at the pushing group of 'push–pull' molecules in dilute solutions[106].

A comparison of the relative basicities of the reported nitriles (Table 16) gives some idea of the order of basicity of the nitriles.

(a) Further alkyl substitutions of dimethylcyanamide lead to more basic species.



1.56 1.58 1.63 pK_{HB}

(b) Benzologues exhibit decreased hydrogen-bonding ability whereas vinylogues and iminologues give more basic compounds.

$$Me_2N{-}C_6H_4{-}C{\equiv}N < Me_2N{-}C{\equiv}N < Me_2N{-}CH{=}CH{-}C{\equiv}N < Me_2N{-}CH{=}N{-}C{\equiv}N$$

1.23 1.56 1.70 2.09 pK_{HB}

(c) Methyl substitution of the imino group gives the most basic nitriles presently known.

$$Me_2N{-}CH{=}N{-}C{\equiv}N < Me_2N{-}C(Me){=}N{-}C{\equiv}N$$

2.09 2.24 pK_{HB}

Table 16 shows that the cyanamide iminologues are actually more basic on the hydrogen-bonding basicity scale than many pyridines or tertiary amines are. This knowledge and the aforementioned basicity orders will make it possible to create still more basic nitriles by an appropriate selection of alkyl substituents R, R′, R″ in the amidine skeleton of cyanoamidines.

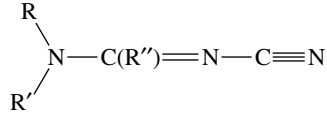


TABLE 17. Gas-phase basicity (kcal mol^{-1}) of cyanamides and related compounds

Compound	GB	Reference
Dimethylcyanamide	197.5	104
Piperidine-1-carbonitrile	201.4	102
trans-Dimethylaminocrylonitrile	205.6	102
N^2-Cyano-N^1,N^1-dimethylformamidine	204.0	102
Pyridine	212.6	131
4-Picoline	215.9	131
Triethylamine	223.4	131
Tri-*n*-butylamine	227.0	131

2. Gas-phase proton transfer basicity

There are differences between hydrogen-bond basicity and Brønsted basicities[108,109]. The question is whether the structural features are peculiar to the pK_{HB} scale. In the gas phase there is the possibility of the investigation of individual molecules. The measured gas-phase proton transfer basicities (GB) of some nitriles are reported in Table 17.

It was also shown for dimetylcyanamide by molecular-orbital calculation using *ab initio* methods with geometry optimization that the proton adds preferentially to the cyano nitrogen[110]. There are different sequences in the GB and the pK_{HB} scales observed within the investigated nitriles. Iminologues are less efficient than vinylogues at increasing gas-phase basicity. Moreover, in contrast to the hydrogen-bond basicity, the cyanamide iminologue turns out to be less basic than ternary amines: even the most basic sp-nitrogen bases do not overcome the basicity of sp^2 or sp^3 nitrogen on the GB scale.

F. Gas-phase Ion Chemistry

1. Investigation of HCN and MeCN using ion cyclotron resonance (ICR) techniques

The gas-phase ion chemistry of HCN, MeCN and various alkyl nitriles has previously been investigated[111] using ion cyclotron resonance techniques (ICR)[112–115]. The developments in such techniques have made it possible to quantify base strengths relative to a variety of cationic reference acids in the gas phase[116–130].

The most widely studied reference acid is the proton. Proton affinity, PA(B), is defined for a base B as the heterolytic bond dissociation energy for removing a proton from the conjugated acid BH^+ (equation 20). The homolytic bond dissociation energy $D(B^+{-}H)$ defined by equation 21 is related to PA(B) and the adiabatic ionization potentials IP(H) and IP(B) (equation 22) are derived from the thermochemical cycle shown in Scheme 6.

$$BH^+ \longrightarrow B + H^+ \quad \Delta H = D(B{-}H^+) \equiv PA(B) \tag{20}$$

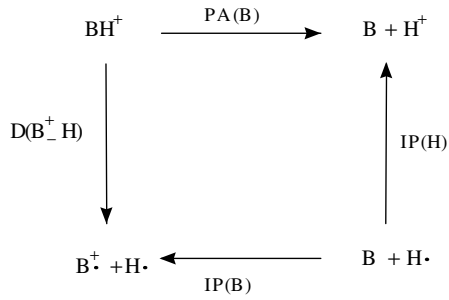
$$BH^+ \longrightarrow B^{\cdot +} + H\cdot \quad \Delta H = D(B^+{-}H) \tag{21}$$

$$PA(B) - D(B^+{-}H) = IP(H) - IP(B) \tag{22}$$

ICR techniques or high-pressure mass spectrometry have been used to determine the equilibrium constants for proton transfer between two bases (equation 23). The determined relative free energies of protonation are accurate ($\pm$0.2 kcal mol^{-1} in most instances).

$$B_1H^+ + B_2 \rightleftharpoons B_1 + B_2H^+ \tag{23}$$

$$\Delta H = PA(B_1) - PA(B_2)$$



SCHEME 6. Thermochemical cycle

A relative scale of PA(B) has been established by examining the reaction shown in equation 23 for a large number of organic and inorganic bases. These data can be calibrated by reference to a variety of species for which absolute values of PA(B) may be derived from appearance potential measurements. The molecular ionization potentials IP(B) and the homolytic bond dissociation energies $D(B^+-H)$ are linear functions of the proton affinity PA(B) for a homologous series of amines[117–121].

Electron impact at energies just above the first ionization potential in the systems of HCN and MeCN leads to reactions which are shown in equation 24.

$$CH_3CN^+ \cdot + CH_3CN \longrightarrow CH_3CNH^+ + CH_2CN \tag{24}$$

CH_3CNH^+ ('protonated parent') was shown to form dimers (equation 25) at pressures of about 3×10^{-6} torr, but the formation is slower than at higher pressures ($> 3 \times 10^{-5}$ torr).

$$MH^+ + M \longrightarrow MHM^+ \tag{25}$$

Proton transfer in mixtures of nitriles with various bases was found to be fast, so the equilibrium constants for the reaction in equation 23 could be readily measured. Rate constants for exothermic proton transfers were typically 10^{-9} cm^3 molecule^{-1} s^{-1}. The results of the experiments with these mixtures are reported in Tables 18 and 19.

The proton affinity results reflect changes in polarizability and inductive effects with the substituent group R. Comparison of proton affinities in the nitrile and primary amine series (Figure 10) reveals that the magnitude of these effects is linearly related in the two series but larger for the nitriles. A least-squares fit to the data is given by equation 26 with all quantities in kcal mol^{-1}[111].

$$PA(RCN) = 1.3153\ PA(RNH_2) - 90.68 \tag{26}$$

2. Photoelectron spectroscopy (PES) of nitrile compounds

A very useful method for the physical investigation concerning the orbital energies is the photoelectron spectroscopy (PES). Spectra of some nitriles are shown in Figure 11. Assignment of the low-lying bands in the photoelectron spectra of nitriles has been the subject of several experimental and theoretical papers[132–144]. In MeCN (Figure 11a) the CN π band is clearly separated from the N lone-pair σ band allowing a reliable assignment (Table 19)[132–134]. The photoelectron spectra of EtCN (Figure 11b) and CH_2=CHCN (not shown) have been similarly assigned except CH_2=CHCN has an additional band at 10.91 eV which is associated with ionization of the C=C π bonding electrons[133,134].

TABLE 18. Reaction mixtures studies and derived PA(RCN) values[a]

RCN	Reference base	PA(B)[b]	$\delta_R \Delta G^{\circ}$ [c]	PA(RCN)[d]
c-C_3H_5CN	HCO_2-*n*-Bu	193.4	0.67 ± 0.2	194.1
i-PrCN	HCO_2Et	192.1	0.95 ± 0.2	193.1
n-BuCN	HCO_2Et	192.1	0.71 ± 0.2	192.8
n-PrCN	HCO_2Et	192.1	0.71 ± 0.2	192.3
n-PrCN	Me_2O	191.4	0.84 ± 0.2	192.2
n-PrCN	EtCN	191.0	1.18 ± 0.2	192.2
EtCN	*n*-PrCN	192.3	-1.18 ± 0.2	191.1
EtCN	HCO_2Et	192.1	-1.08 ± 0.2	191.0
EtCN	*i*-PrCHO	191.6	-0.22 ± 0.2	191.4
EtCN	Me_2O	191.4	-0.27 ± 0.2	191.1
EtCN		189.8	0.88 ± 0.2	190.9
EtCN	EtCHO	189.0	1.88 ± 0.2	190.9
CH_2=CHCN		189.8	-1.20 ± 0.2	188.8
CH_2=CHCN	EtCHO	189.0	-0.20 ± 0.2	188.8
CH_2=CHCN	MeCN	188.0	0.76 ± 0.2	188.8
$ClCH_2CH_2CN$	MeCN	188.0	-0.87 ± 0.2	187.1
BrCN	AsH_3	182.0	0.3 ± 0.5	181.5
BrCN	HCO_2H	181.5	-0.3 ± 0.7	180.8
BrCN	F_2CHCH_2OH	179.0	$>1.5 \pm 0.5$	>180.5
ClCN	F_2CHCH_2OH	179.0	-0.5 ± 0.5	178.5
ClCN	HCHO	176.0	$>1.5 \pm 0.5$	177.9

[a] All data in kcal mol^{-1}.
[b] All data relative to PA(NH_3) = 202.3±2.0 kcal mol^{-1}. Relative to NH_3, reported values are estimated to be accurate to ±1 kcal mol^{-1}, with higher accuracy for smaller differences.
[c] Free-energy differences for equation 23 derived from ICR determination of the equilibrium constant for proton transfer from the reference base to RCN.
[d] Derived from the data of columns 3 and 4 and corrected for changes in ΔS calculated from symmetry number changes for equation 23.

For HCN the CN π and N lone-pair σ bands are closer in energy but several detailed analyses resulted in a convincing assignment[132,134–139]. While the N lone-pair ionization has been unambiguously assigned in ClCN and BrCN, interaction of the CN π orbitals with the halogen π lone-pair orbitals is substantial, resulting in two bands which may be associated with ionization of the CN π electrons[133,140]. The lower of these are given in Table 19; the upper bands are at 15.13 and 14.19 eV in ClCN and BrCN, respectively[133]. Data for the nitrile CN π and N lone-pair σ adiabatic ionization potential and PA(RCN) results are summarized in Table 19 along with $\sigma D(B^+ - H)$ values calculated using the N lone-pair σ ionization potentials†

In accordance with equation 22, it is of interest to consider the variation of the quantity IP(H)−IP(RCN) with PA(RCN) (Figure 12). It is apparent that CN π ionization potentials are poorly correlated with PA(RCN) values; for N lone-pair σ ionization potentials, however, the data fall closely about a straight line. A least-squares fit to these data, excluding

† The notation πIP(RCN) and σIP(RCN) is adopted here to designate the CN π and N lone-pair σ adiabatic ionization potential. Similarly $\pi D(B^+ - H)$ and $\sigma D(B^+ - H)$ refer to $D(B^+ - H)$ values defined by equation 21 for CN π and N lone-pair σ states of the radical cation.

TABLE 19. Nitrile proton affinities, adiabatic ionization potential and homolytic bond dissociation energies[a]

RCN	PA[b]	πIP	σIP	$\sigma D(B^+ - H)$[c]
HCN	175.9	313.9[d]	322.8[d]	185.2
$CH_2(CN)_2$	178.0	292.4[e]	309.2[e]	173.7[e]
			313.4[e]	177.8[e]
ClCN	178.5	285.0[f]	318.2[f]	183.2
Cl_3CCN	178.7		320.1[g]	185.2
BrCN	181.2	273.7[f]	312.7[f]	180.3
$ClCH_2CN$	181.9	297.5[g,h]	313.4[g,h]	181.7
$ClCH_2CH_2CH$	187.1	282.5[h]	305.3[h]	178.8
MeCN	188.0	281.3[i]	303.0[i]	177.4
CH_2=CHCN	188.8	285.0[g]	300.7	175.9
EtCN	191.0	273.3[g,h]	296.3[g,h]	173.8

[a] All data in kcal mol^{-1}.
[b] Data from Table 18.
[c] Calculated using equation 22 and the N lone-pair σ ionization potential.
[d] References 132 and 136.
[e] Reference 141, both n^+ and n^- values are given.
[f] References 133 and 140.
[g] Reference 133.
[h] Reference 111.
[i] References 111, 132 and 133.

the points for $CH_2(CN)_2$ which are discussed below, is given in equation 27 with all quantities in kcal mol^{-1}.

$$\text{IP(H)} - \sigma\text{IP(RCN)} = 1.7270\ \text{PA(RCN)} - 313.54 \tag{27}$$

It is reasonable to assume that the N lone-pair σ ionization potential but not the CN π ionization potential is related to PA(RCN). Stabilization of the protonated species is effected by charge redistribution in the R−C−N−H σ system. Similarly in the σ state of the radical cation, charge stabilization results from electron redistribution in the R−C−N· σ system. The presence of the radical site in the latter case allows for greater redistribution by electron donation into the partially filled orbital and accounts for the larger effect of changes in R on the ionization potential as compared to the proton affinity (equation 27 and Figure 12). It has been suggested that decreasing $D(B^+ - H)$ in the amine series Me_nNH_{3-n} ($n = 0, \ldots, 3$) can be attributed to the effects of π hyperconjugation[121]; the present series evidence the effects of σ hyperconjugation which are reflected in the dependence of $\sigma D(B^+ - H)$ on PA(RCN) (Table 19).

$$R{-}C{\equiv}N^{+}\bullet \longleftrightarrow R^{+}\bullet C{\equiv}N: \longleftrightarrow R\bullet\ {}^{+}C{\equiv}N:$$

In the π state of the radical cation, charge stabilization is affected by different factors. Most important is the interaction of the CN π orbitals with orbitals of π symmetry in R.

Exceptions to the relationship between σIP(RCN) and PA(RCN) (equation 27) are the two data points (Figure 12) for the ionization potentials of n^+ and n^- combinations of nitrogen lone-pairs of $CH_2(CN)_2$. This might be the result due to resonance stabilization of the radical cation arising from the lone-pair interactions. Other studies of molecules containing equivalent lone-pairs support this explanation[124]. The two nitrogen atoms are separated by about 4 Å, so the space interactions should be slight. But the n^+ and n^- orbitals should be destabilized by 'thru bond' interaction[141]. This is consistent with other

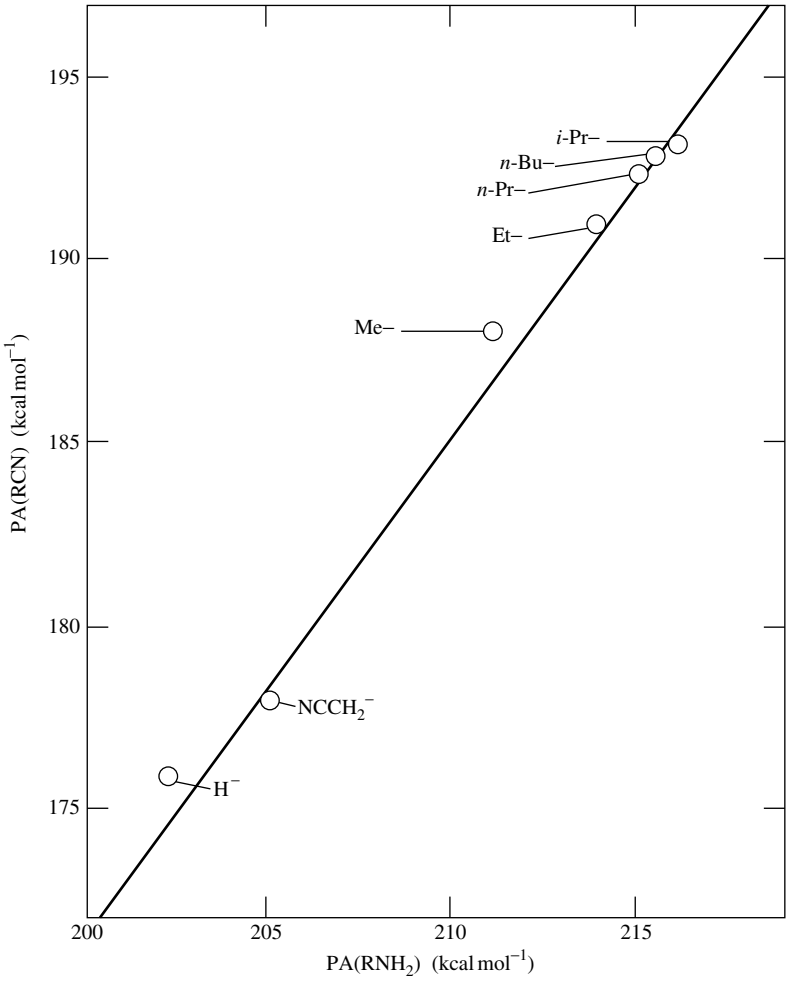


FIGURE 10. Proton affinities of nitriles, RCN, vs proton affinities of primary amines, RNH_2

results[111] in which both of the observed ionization potentials are lower than the ionization potentials predicted by equation 27. It describes the relationship between N lone-pair σ ionization potentials and nitrile proton affinities and is a useful tool for assigning photoelectron spectra. A good example is the spectrum of $ClCH_2CN$ (the first three bands are shown in Figure 13a and a complete spectrum appears in Reference 132); $PA(ClCH_2CN) = 181.9$ kcal mol^{-1} and equation 27 predict $\sigma IP(ClCH_2CN) = 13.57$ eV, identifying the strong sharp peak at this energy as the N lone-pair ionization. The first band at 11.95 eV may be assigned to the Cl lone-pair ionization by noting reduced intensity in the He(II) spectrum of $ClCH_2CN$ (Figure 13b); second-row lone-pairs are relatively weaker as compared to first-row π and σ bands in He(II) spectra[142]. The middle band at 12.90 eV in the $ClCH_2CN$ spectrum can then be assigned to the CN π ionization. The peak at 13.17 eV in this band, a spacing of 2200 cm^{-1}, results from excitation of

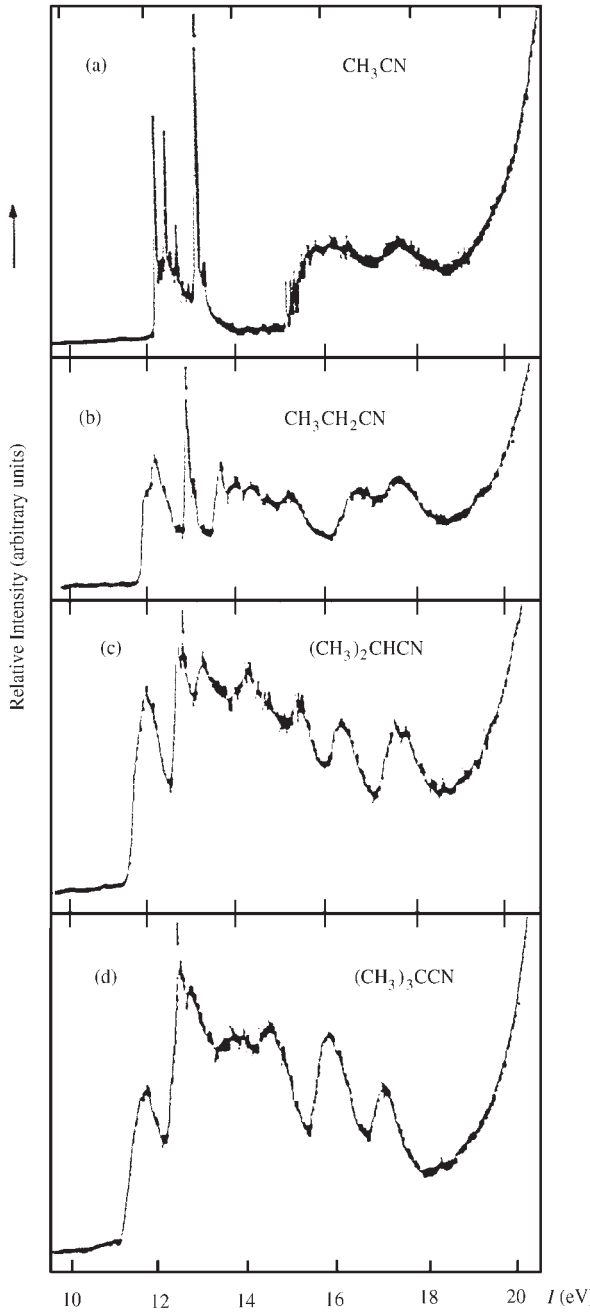


FIGURE 11. He(I) photoelectron spectra of some nitriles. Adiabatic N lone-pair σ ionization potentials predicted by equation 27 are indicated by the vertical line above each spectrum

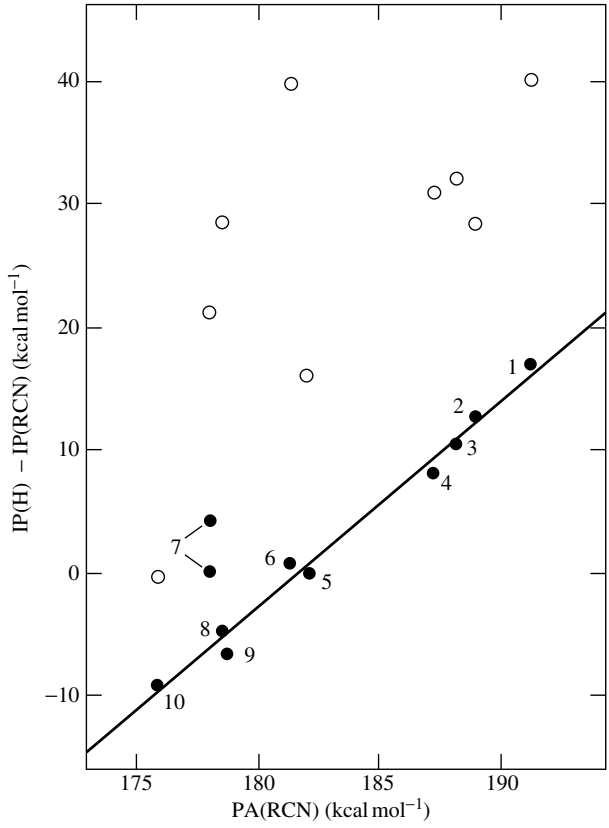


FIGURE 12. The quantity of IP(H) − IP(RCN) vs PA(RCN) for adiabatic (○) CN π and (●) N lone-pair σ ionization potentials for nitriles; (1) EtCN, (2) CH_2CHCN, (3) MeCN, (4) $ClCH_2CH_2CN$, (5) $ClCH_2CN$, (6) BrCN, (7) $NCCH_2CN$, (8) ClCN, (9) Cl_3CCN, (10) HCN

the C≡N stretching vibration. Assignment of the $ClCH_2CH_2CN$ spectrum (Figure 13c) is similar to that of $ClCH_2CN$, all peaks being shifted to lower ionization potentials by about 0.4 eV[†]. An increasing size of R in the alkyl nitriles RCN has as a result that in the photoelectron spectra the ionization potentials of C−C and C−H σ bands decrease and obscure the region of the N lone-pair.

Equation 27 is a useful tool in chemistry for assigning spectra. The slope and intercept of such relationships depend on the nature of the basic site, whether charge is localized in orbitals of π or σ symmetry and whether the system is closed or open shell. But also caution must be exercised in developing relationships between ionization potentials and molecular properties such as base strength: the correct ionization potential must be chosen and molecules in which the presence of equivalent lone-pairs leads to resonance stabilization of the radical cation should be regarded as potential exceptions.

[†] This spectrum may be complicated by the presence of significant populations of both *trans* and *gauche* conformers of $ClCH_2CH_2CN$.

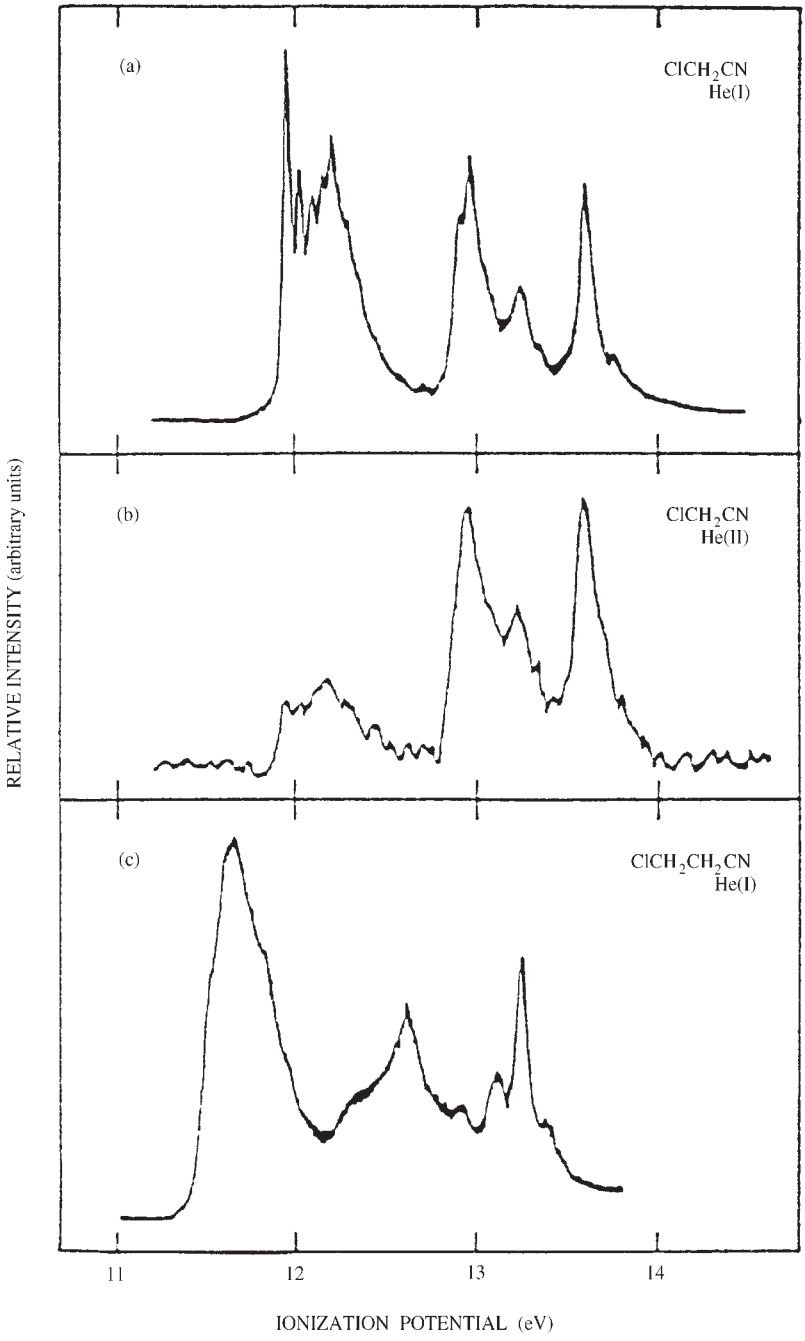


FIGURE 13. (a) He(I) photoelectron spectrum of $ClCH_2CN$, (b) He(II) photoelectron spectrum of $ClCH_2CN$, (c) He(I) photoelectron spectrum of $ClCH_2CH_2CN$

VI. THIOCARBONYLS

A. Iridium Thiocarbonyl Complexes

1. Synthesis

In the chemistry of the carbonyl group the parent complex *trans*-$IrCl(CO)(PPh_3)_2$ is well known[143]. It has been shown that this complex undergoes many interesting reactions including oxidative addition[144], homogeneous catalysis[145], adduct formation with Lewis acids[146], stabilization of molecules that do not exist at room temperature[147] and activation of coordinated ligands[148]. The ligands play an important role in regulating the acidity and basicity of complexes of the type *trans*-$IrCl(CO)(PPh_3)_2$ toward Lewis acids. This has been indicated by recent kinetic and thermodynamic results on the rate of reversible oxygenation of metal complexes[149,150] and activation of molecular hydrogen by metal complexes[151]. It is very interesting to investigate the analogous thiocarbonyl compound *trans*-$IrCl(CS)(PPh_3)_2$. This complex can be prepared according to equation 28[143,152].

$$IrCl(N_2)(PPh_3)_2 \xrightarrow{CS_2} IrCl(C_2S_5)(PPh_3)_2 \xrightarrow{\text{excess } PPh_3} IrCl(CS)(PPh_3)_2 \qquad (28)$$

2. Adduct formation with Lewis acids

$IrCl(CS)(PPh_3)_2$ is an orange-yellow crystalline solid. This complex reacts with a number of Lewis acids to give adducts listed in Table 20.

Unlike the parent carbonyl compound $IrCl(CO)(PPh_3)_2$ the thiocarbonyl complex forms 1:1 adducts with the aid of the acidic cyano olefins only. The stoichiometry of the adducts of $IrCl(CO)(PPh_3)_2$ and $IrCl(CS)(PPh_3)_2$ with BX_3 (X = Cl, Br) has not been satisfactorily established[143].

These adducts are extremely unstable with respect to hydrolysis and form products listed in Table 21. These results are in agreement with other reports for HCl oxidative additions[153]. Here $\Delta\bar{\nu}_{CS}$ (Table 20) is the change in the thiocarbonyl stretching frequency

TABLE 20. Adducts of $IrCl(CS)(PPh_3)_2$ with Lewis acids

Lewis acid	Adduct, Colour	$\bar{\nu}_{CS}$ (cm^{-1})	$\Delta\bar{\nu}_{CS}$ (cm^{-1})
C_6N_4 (TCNE)	1:1, off-white	1370	+38
$C_4N_2H_2$ (FUM)	1:1, off-white	1350	+18
C_3NH_3 (ACRYL)	no reaction		
BCl_3	1:n^a, tan	1361	+29
BBr_3	1:n^a, tan	1377	+45
BF_3	no reaction		
C_2H_4	no reaction		

[a] $n = 1,2$.

TABLE 21. Oxidative addition products with iridium (I) complexes

Complex	Addendum	$\bar{\nu}_{IrH}$ (cm^{-1})	$\Delta\bar{\nu}_{CO}$; $\Delta\bar{\nu}_{CS}$ (cm^{-1})
$IrCl(CO)(PPh_3)_2$[a]	HCl	2240	+70
$IrCl(CO)(PPh_3)_2$[b]	HCl	2245	+70
$IrCl(CS)(PPh_3)_2$[a]	HCl	2240	+45

[a] Reference 143.
[b] Reference 152.

upon adduct formation in the reaction between 'isostructural' and 'isoelectronic' four-coordinated iridium(I) complexes and Lewis acids. In order to determine $\Delta\bar{\nu}$, an 'isolated' quadratic potential for the carbonyl stretching motion was proposed. The fundamental vibration frequency is given by equation 29 were k is the force constant and μ is the reduced mass of the atom pair.

$$\bar{\nu} = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}} \tag{29}$$

Upon forming the differential and neglecting the term containing $d\mu$ (since the reduced masses are not affected by adduct formation) equation 30 was obtained[143].

$$\bar{\nu} = \frac{1}{4\pi}\sqrt{\frac{1}{k\mu}}dk \tag{30}$$

Thus, in order to compare differential changes in $\bar{\nu}_{CO}$ and $\bar{\nu}_{CS}$ one has to form the ratio shown in equation 31.

$$\frac{\bar{\nu}_{CO}}{\bar{\nu}_{CS}} = \sqrt{\frac{k_{CS}\mu_{CS}}{k_{CO}\mu_{CO}}}\frac{dk_{CO}}{dk_{CS}} \tag{31}$$

If this equation is written in terms of finite changes, equation 32 is obtained where κ represents the ratio of changes in force constants.

$$\frac{\Delta\nu_{CO}}{\Delta\nu_{CS}} = 0.865\ \kappa \tag{32}$$

If one assumes κ is at unity, i.e. constant change in force constants upon adduct formation, the carbonyl frequency shift upon adduct formation should be 0.865 of the thiocarbonyl shift for the formation of the same adduct. If κ is assumed to be as large as 1.47, that is, equal to the ratio of the frequencies, $\bar{\nu}_{CO}/\bar{\nu}_{CS}$, then the ratio in equation 32 becomes 1.27. A comparison of changes in stretching frequencies upon adduct formation is given in Table 22.

In so far as the decrease in chemical reactivity is an indication of diminished transition metal basicity, it was proposed[143] that the thiocarbonyl complex is less basic than its carbonyl analogue. This conclusion is substantiated by the spectral shifts in Table 22 and is also in agreement with molecular orbital calculations which predict the thiocarbonyl complex to be less basic than the carbonyl complex[155,156].

It was proposed that the tentative order of relative basicity of isostructural and isoelectronic iridium(I) complexes is the following one[143]:

$$IrCl(CO)(AsPh_3)_2 > IrCl(CO)(PPh_3)_2 > IrCl(CS)(PPh_3)_2$$

TABLE 22. Comparison of changes in stretching frequencies for carbonyl and thiocarbonyl iridium(I) adducts[a]

Lewis acid	$\Delta\bar{\nu}_{CO}$ (cm^{-1})	$\Delta\bar{\nu}_{CS}$ (cm^{-1})
C_6N_4 (TCNE)	100[b]	38
$C_4N_2H_2$ (FUM)	69[b]	18
BCl_3	110	18
BBr_3	110	28

[a]Reference 143.
[b]Reference 154.

B. Compounds Containing Carbonyl and Thiocarbonyl Groups

1. Introduction

It is very interesting to observe the protonation behaviour of a compound containing both a carbonyl and a thiocarbonyl group (Figure 14)[157]. R is an acyl group.

2. Protonation behaviour

The protonation of amides (A) to yield the conjugated acids (AH^+) in aqueous sulphuric acid takes place on the carbonyl oxygen[158–161] and the ionization ratio ($I = [AH^+]/[A]$) has been found to depend on the acidity of the solution as measured by the H_A acidity function[25,162,163] where K_{AH^+} is the thermodynamic dissociation constant of the conjugated acid (equations 33 and 34).

$$\lg\left(\frac{[AH^+]}{[A]}\right) = pK_{AH^+} - H_A \tag{33}$$

$$K_{AH^+} = -\operatorname{antilg} pK_{AH} = \frac{a_{H^+}a_H}{a_{AH^+}} \tag{34}$$

The protonation of N-substituted thioureas (B) occurs on the thiocarbonyl sulphur atom[158–160] and it has been found[157,164] to follow the H_0''' acidity function; see equation 35[16].

$$\lg\left(\frac{[BH^+]}{[B]}\right) = pK_{BH^+} - H_0''' \tag{35}$$

The conjugated acid of benzamide has a pK_{AH^+} value of -1.74, so that the amide is half-protonated in 35.2% sulphuric acid[25,162,163]. On the other hand *N*-methylthiourea has a pK_{BH^+} value of -1.75 and is half-ionized in 22.6% sulphuric acid[157]. The two compounds are almost identical in their basicity, although the *N*-methylthiourea is half-protonated in less concentrated acid because its protonation is governed by a different acidity function.

In Scheme 7 the protonation of *N*-benzoylthiourea (I) is shown. Amide as well as thiourea functions may be expected to have reduced basicities. The interesting question is on which atom the protonation may take place: on the oxygen or on the sulphur atom? In fact, both the sulphur and the oxygen atom are protonated. The cause for this is the different acidity functions.

Three experimental findings indicate that the first protonation takes place on the thiourea thiocarbonyl, occurring in 35–60% sulphuric acid: First, there are changes in the ultraviolet absorption (Table 23) which are qualitatively very similar to those observed when *N*-methylthiourea is protonated in sulphuric acid, and different from those observed for protonated benzamide. This comparison is shown in Figure 15.

For both compounds the strong absorption band at longer wavelength is most probably due to a $\pi \rightarrow \pi^*$ transition and undergoes a blue shift as the acid strength is increased[165,166]. A simple equilibrium involving B and BH^+ has been supported for

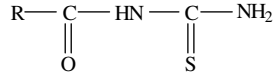
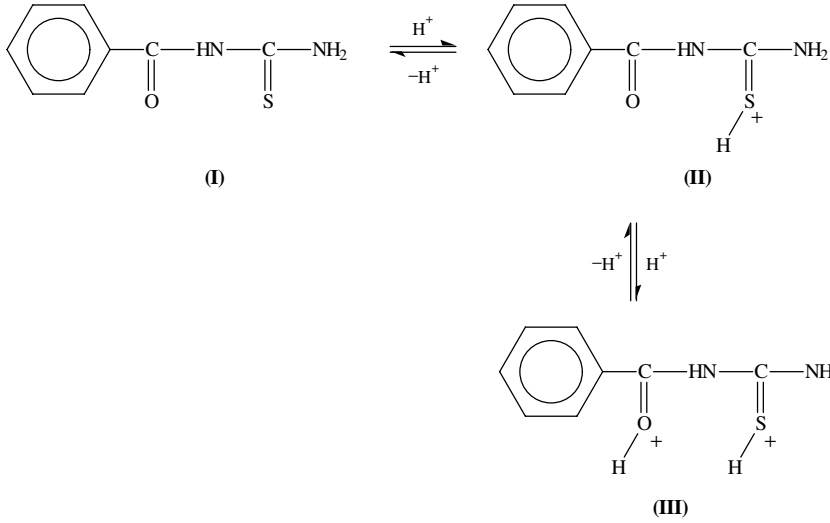


FIGURE 14. Compound containing a carbonyl and a thiocarbonyl group



SCHEME 7. Protonation of *N*-benzoylthiourea

TABLE 23. Absorption spectra of *N*-acylthioureas

Acyl group	λ_B (nm)	10^{-3} ε_B	λ_{BH^+} (nm)	10^{-3} ε_{BH^+}	$\lambda_{BH_2^{2+}}$ (nm)	10^{-3} $\varepsilon_{BH_2^{2+}}$
Acetyl	265	12.7	225	10.4	232	9.2
					218	9.7
Benzoyl	275	13.0	252	16.2	267	13.2
	239	13.3				
p-Methoxybenzoyl	285	23.6	300	17.2	298	14.1
	216	17.2	225	16.5	225	14.2
m-Chlorobenzoyl	278	11.5	252	18.0	258	16.8
	239	12.0				
p-Chlorobenzoyl	275	15.6	266	17.6	284	16.1
	248	16.6				
m-Fluorobenzoyl	278	12.4	248	18.0	254	15.1
	237	13.4				
p-Methylbenzoyl	275	16.9	271	15.0	291	15.5
	260	15.5				
m-Methylbenzoyl	274	14.8	258	14.9	277	13.5
	243	14.3				
o-Methylbenzoyl	274	14.4	233	13.1	264	8.8
			250[a]	11.6	236	10.8
p-Nitrobenzoyl	266	17.9	264	18.4		

[a] Shoulder.

the *N*-acylthioureas, because good isosbestic points for the spectral curves in different concentrations of acid are observed. Secondly, the ionization ratio, determined by the conventional spectrophotometric method[167], was found to follow H_0''' (equation 35) and not H_A (equation 33). This is shown for *N*-benzoylthiourea in Figure 16 where the slope of the straight line obtained by plotting $\lg([BH^+]/[B])$ vs H_0''' lies close to unity, as required by equation 35; a similar plot against H_A has a slope of 2.2.

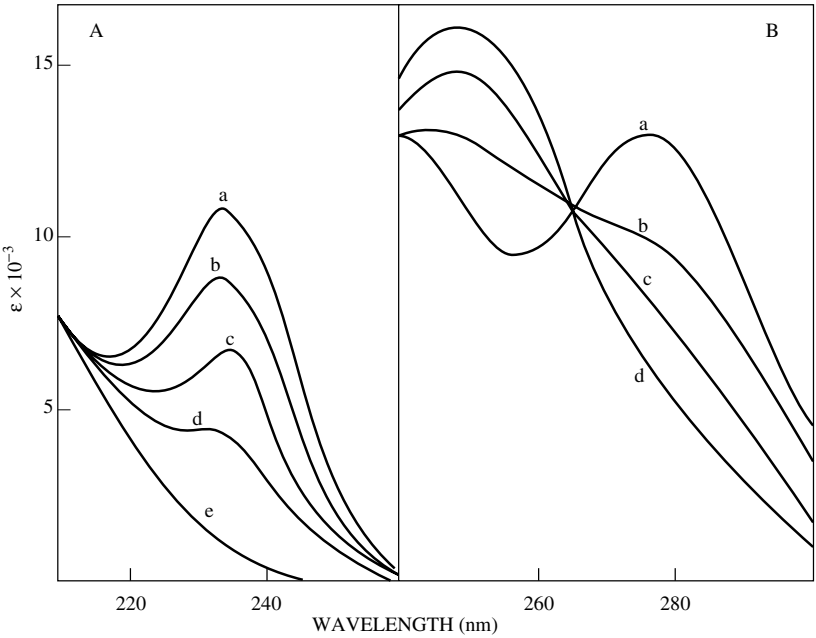


FIGURE 15. (A) Ultraviolet spectra of *N*-methylthiourea in (a) 0.0%, (b) 15.9%, (c) 21.3%, (d) 27.1%, (e) 66.4% sulphuric acid. (B) Ultraviolet spectra of *N*-benzoylthiourea in (a) 0.0%, (b) 47.0%, (c) 52.7%, (d) 62.4% sulphuric acid

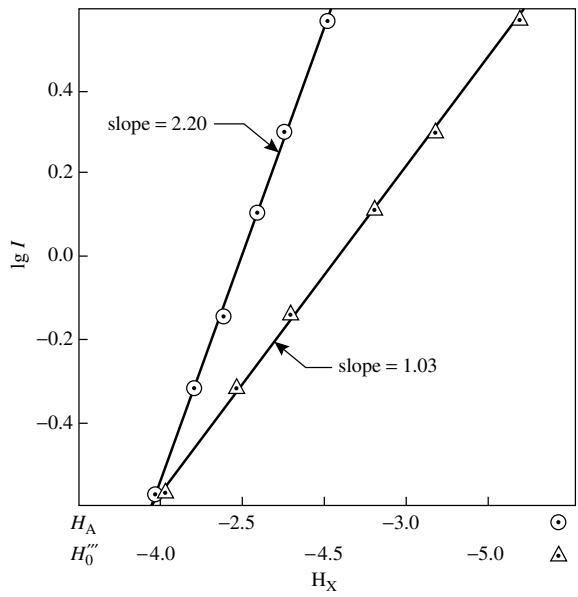


FIGURE 16. Variation of ionization ratio of *N*-benzoylthiourea in 35–60% sulphuric acid with acidity function: (⊙, H_A; △, H_0''')

The slope and the pK_{BH^+} values obtained by application of equation 35 to spectral data for *N*-benzoylthiourea and six *meta*- and *para*-substituted *N*-benzoylthioureas are given in Table 24. A plot of these pK_{BH^+} values vs σ yields the straight line shown in Figure 17, the slope (Hammett ρ value) of which equals -0.42 (correlation coefficient 0.961).

This ρ value is the third finding which indicates thiocarbonyl protonation. The Hammett ρ value for protonation of *meta*- and *para*-substituted benzamindes is -0.92[157] and the value for protonation on the oxygen of *N*-benzoylthiourea is expected to lie close to this value. However, the ρ value for the protonation of thiocarbonyl would be expected to be considerably smaller. The ρ value of -0.42 for the S-protonation of *N*-benzoylthioureas is rather high in comparison with *trans*-cinnamate ions in water (25 °C: $\rho = -0.466$) and substituted 3-phenylpropionate ions ($\rho = -0.212$)[168]. The found ρ value may indicate that the hydrogen-bonded form shown in Figure 18 plays an important role in the reaction.

An increase in the sulphuric acid concentration from 60 to 68% has only a minor effect on the ultraviolet spectra of *N*-benzoylthioureas. At concentrations higher than

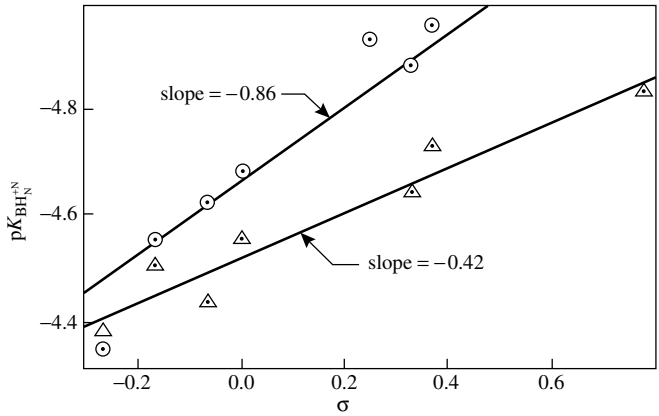


FIGURE 17. Dependence of p*K* values of *meta*- and *para*-substituted *N*-benzoylthioureas on σ(Δ, pK_{BH^+}; $\odot$, $pK_{BH_2^{2+}}$)

TABLE 24. Mono- and diprotonation constants of *N*-acylthioureas

Acyl group	$-pK_{BH^+}$	Slope[a]	$-pK_{BH_2^{2+}}$	Slope[b]
Acetyl	4.64 ± 0.12[c]	1.09	4.61 ± 0.12[d]	1.02
Benzoyl	4.55 ± 0.02	1.03	4.68 ± 0.06	1.07
m-Chlorobenzoyl	4.73 ± 0.06	1.09	4.96 ± 0.06	1.04
p-Chlorobenzoyl			4.93 ± 0.05	1.00
m-Fluorobenzoyl	4.64 ± 0.04	1.10	4.88 ± 0.07	1.00
p-Methoxybenzoyl	4.37 ± 0.06	1.03	4.34 ± 0.05[d]	1.13
o-Methylbenzoyl	4.65 ± 0.05	1.12	4.67 ± 0.04	1.08
m-Methylbenzoyl	4.43 ± 0.20	1.05	4.62 ± 0.08	1.05
p-Methylbenzoyl	4.50 ± 0.18	0.97	4.55 ± 0.05	1.00
p-Nitrobenzoyl	4.83 ± 0.06	1.17		

[a] Slope of ($[BH^+]/[B]$) vs H_0'''.

[b] Slope of $\lg([BH_2^{2+}]/[BH^+])$ vs H_A.

[c] Absorbance measurements extrapolated to zero time.

[d] Change in absorbance on protonation was small.

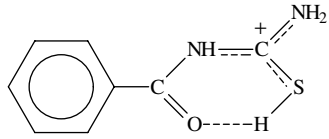


FIGURE 18. Hydrogen-bonded form of protonated *N*-benzoylthioureas

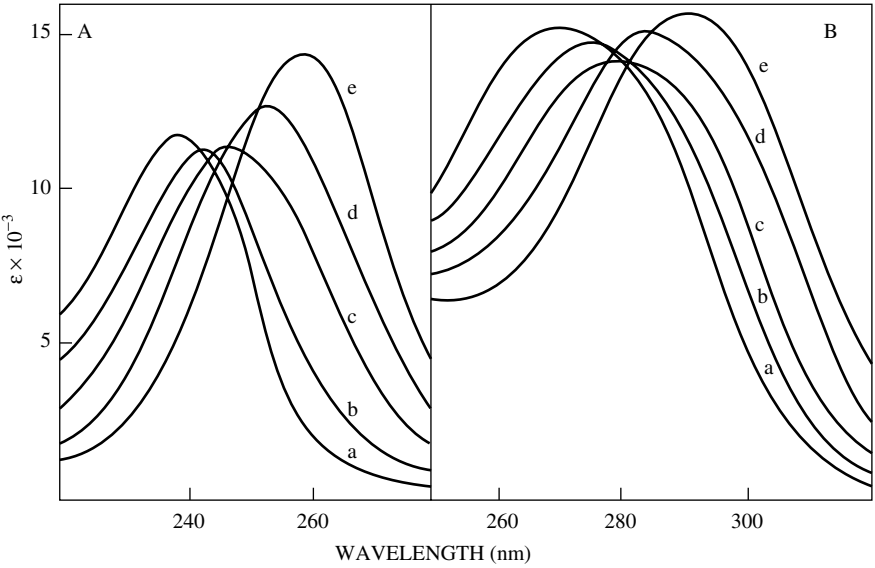


FIGURE 19. (A) Ultraviolet spectra of *N*-*p*-toluamide in (a) 0.0%, (b) 20.5%, (c) 32.8%, (d) 42.3%, (e) 57.2% sulphuric acid. (B) Ultraviolet spectra of *N*-*p*-toluoylthiourea in (a) 60.0%, (b) 73.4%, (c) 80.0%, (d) 85.7%, (e) 96.1% sulphuric acid

68% systematic changes in the spectra indicate a second protonation. This is shown in Figure 19 in which the spectral changes of *N*-*p*-toluamide and *N*-*p*-toluoylthiourea are compared. The similarity in the character of the spectral changes indicates that in both cases protonation takes place on the amide oxygen. For the other thioureas reported in Table 23 the spectral changes are similar in 70–100% sulphuric acid, so they are also protonated twice. Another reason indicating that the protonation in higher concentrated sulphuric acid is taking place on the amide oxygen comes from the change in $\lg([BH_2^{2+}]/[BH^+])$ (obtained by analysis of spectral changes in usual way)[167], following H_A and not H_0'''. An example is given in Figure 20. Finally, the $pK_{BH_2^{2+}}$ values of *meta*- and *para*-substituted *N*-benzoylthioureas (obtained by application of equation 33 to spectral data, Table 24) indicates a ρ value of -0.86, which is in reasonable agreement with a ρ value of -0.92 for the protonation of benzamides (see above).

The diprotonation of the *N*-benzoylthioureas is complete in 100% sulphuric acid. A comparison of the mono- and diprotonation constants (Table 24) shows that the oxygen and sulphur atoms of *N*-benzoylthiourea and other *N*-acylthioureas have about equal basicities, but in spite of this fact protonation on oxygen requires much stronger acids than does protonation on sulphur. These results are caused by the fact that $-H_A$ (which

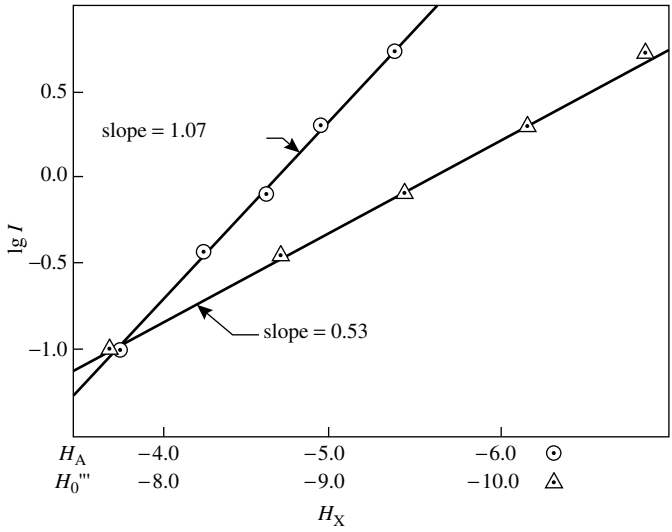


FIGURE 20. Variation of ionization ratio of *N*-benzoylthiourea in 65–96% sulphuric acid with acidity function (⊙, H_A; △, H_0''')

governs protonation on oxygen) increases with acid concentration more slowly than $-H_0'''$ does (which governs protonation on sulphur).

C. Thioformaldehyde, Thioacetaldehyde and Thioacetone

1. Introduction

The three prototypical thiocarbonyl compounds thioformaldehyde, thioacetaldehyde and thioacetone are extremely reactive species. Under typical experimental conditions[169,170] these compounds readily undergo polymerization reactions. Because of their rapid self-reaction and the difficulty in their generation it is very hard to investigate these compounds. At temperatures below −50 °C thioacetone can be kept for a short time, but at higher temperatures it polymerizes quite rapidly[171]. Even in the vapour phase at *ca* 30 mtorr of pressure, the lifetime of thioacetaldehyde is of the order of 10 seconds while that of thioacetone is several minutes[172,173]. Possibilities for studying the energetics and dynamics of such reactive compounds are gas-phase ion–molecule techniques[174–179]. These techniques applied on the above-mentioned thiocompounds produce some interesting results[180].

2. Gas-phase ion–molecule studies

The enolate anions of thioacetaldehyde and thioacetone were generated in a flow tube by rapid (presumable) E2 elimination reactions of F^- with the appropriate sulphide (equations 36 and 37, respectively)[181].

$$F^- + H_2C{=}CH{-}S{-}CH_2CH_3 \longrightarrow H_2C{=}CH{-}S^- + H_2C{=}CH_2 + HF \quad (36)$$

$$F^- + H_2C{=}C(CH_3){-}S{-}CH_2CH_3 \longrightarrow H_2C{=}C(CH_3){-}S^- + H_2C{=}CH_2 + HF \quad (37)$$

For both reactions the yields of the enethiolate ions are better than 95%; small amounts of HF*N* thioenolate cluster ions were also observed[182,183]. The results of some acid–base and exchange chemical studies of enethiolate anions are summarized in Table 25.

$$H_2C{=}C(R){-}S^- + HA \longrightarrow ? \quad A + C_2H_3RS \tag{38}$$

$$H_2C{=}C(R){-}S^- + DA \longrightarrow ? \quad \text{H/D exchange} \tag{39}$$

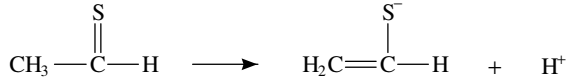
The hydrogen/deuterium exchange has proven to be an extremely valuable tool for the analysis of gas-phase anion structures and reactivity[184–187]. The data which are reported in Table 25 suggest an absolute gas-phase basicity (ΔG°) of $H_2C{=}CH{-}S^-$ is 341 ± 3 kcal mol^{-1}[180]. Using the same data and making the additional assumption that entropy changes in these acid–base reactions are negligible allows one to assign the proton affinities (PA) as follows: PA[$H_2C{=}CH{-}S^-$] = 348 kcal mol^{-1} and PA[$H_2C{=}C(CH_3){-}S^-$] = 351 kcal mol^{-1} with PA[A^-] = ΔH°_{acid}[AH]. The data for the enethiolate of acetone (see Table 25) clearly show that it is a stronger base than the enethiolate of acetaldehyde: $H_2C{=}C(CH_3)S^-$ will slowly abstract a proton from hydrogen sulphide and rapidly from acetic acid; it will undergo exchange with 2-methylpropane-2-[^{2}H]thiol (⩾3 exchanges, slow reaction) and 2-methylbutane-1-[^{2}H]thiol (5 exchanges, moderately slow reaction); all four processes are substantially different when $H_2C{=}CHS^-$ is the reaction ion[188]. The absolute gas-phase basicity (ΔG°)[189] of $H_2C{=}C(CH_3){-}S^-$ is 344 ± 3 kcal mol^{-1}. It must be noted that the basicities found for the enthiolates, as compared to the corresponding thiols, would be expected for carbon protonation based on the known acidities[190]

TABLE 25. Summary of bracketing (equation 38) and hydrogen/deuterium exchange (equation 39) experiments for thiocarbonyl enolate anions (R = H, Me)

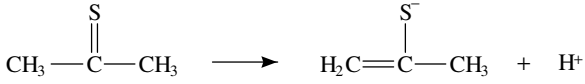
HA[a]	ΔG°_{acid}[b] (kcal mol^{-1})	ΔH°_{acid}[b] (kcal mol^{-1})	Proton transfer observed to $H_2C{=}C(R){-}S^-$[c]	
			R = H	R = Me
CF_3CH_2OH	354.2	361.8	—	no[d] (0)
CH_3SH	350.6	356.9	no	no
$(CH_3)_3CSH$	346.3	352.5	no (0)	no (⩾3[e])
$CH_3CH_2CH(CH_3)CH_2SH$	*ca* 346[f]	*ca* 352[f]	no (⩾1[e])	no (5)
H_2S	344.9	351.2	no	trace
PhOH	342.3	349.2	no	yes
CD_3CO_2H	—	—	trace (2)	—
CH_3CO_2H	341.5	348.6	indeterminate[g] (2)	yes[d]
$CH_3CH_2CO_2H$	340.3	347.4	yes (2)	indeterminate[g]
HCO_2H	338.2	345.2	yes	yes
$CH_3COCH_2COCH_3$	336.5	343.7	yes	—
ΔG°_{acid}[$CH_3C(R){=}S$]			341	344
{ΔH°_{acid}[$CH_3C(R){=}S$]}			(348)	(351)

[a] DA is the same acid as listed except for replacement of most protons by deuterium. A dash in any column indicates that data are not available.
[b] All acidities, unless noted, are from the standard compilation, Reference 190.
[c] The number of H/D exchange with DA, via equation 39, is shown in parentheses.
[d] DA used instead of HA for proton transfer studies.
[e] Exchange is extremely slow, no that kinetic limitation on observing all equivalent exchange prevails.
[f] Approximate acidity based on analogy to known compounds and some brief experimental work[180].
[g] Because $CH_3CO_2^-$ and $H_2C{=}CHS^-$ [or $CH_3CH_2CO_2^-$ and $CH_2{=}C(CH_3)S^-$] have the same nominal *m/z*, proton transfer is indeterminable[180].

of alcohols and carbonyl compounds: acetaldehyde enolate is 11.8 kcal mol^{-1} less basic than ethoxide (that is, $\delta\Delta G_{acid}^{\circ} = 11.8$ kcal mol^{-1}) while $H_2C{=}CHS^-$ is 8 kcal mol^{-1} less basic than ethanethiolate and acetone enolate is 6.9 kcal mol^{-1} less basic than isopropyloxide, while $H_2C{=}C(CH_3)S^-$ is 3 kcal mol^{-1} less basic than propane-2-thiolate. Furthermore, acetone enolate is 2.9 kcal mol^{-1} more basic than acetaldehyde enolate and $H_2C{=}C(CH_3)S^-$ is 3 kcal mol^{-1} more basic than $H_2C{=}CHS^-$ while propane-2-thiolate is 1.9 kcal mol^{-1} less basic than ethanethiolate. These comparisons suggest that either the basicity data reported correspond to carbon protonation or that enethiolates, which protonate on sulphur, show a different sensitivity to substituent effects than simple aliphatic thiols do[191,192†]. Therefore, it is proposed[180] that the anionic basicities (Table 25) are indicative of gas-phase acidities of the carbonyl compounds (equations 40 and 41).



$$\Delta G^{\circ}_{reaction} = \Delta G^{\circ}_{acid}\ [CH_3CH{=}S] = 341 \pm 3 \text{ kcal mol}^{-1} \quad (40)$$



$$\Delta G^{\circ}_{reaction} = \Delta G^{\circ}_{acid}\ [(CH_3)_2C{=}S] = 344 \pm 3 \text{ kcal mol}^{-1} \quad (41)$$

D. Compounds with Carbonyl Groups versus Thiocarbonyl Compounds

1. Introduction

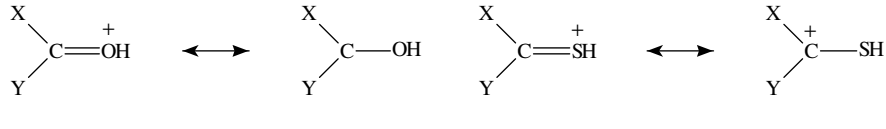
Reflecting on compounds with carbonyl groups in comparison with thiocarbonyl groups, we see that oxygen and sulphur atoms differ in their size (covalent radii[193] O: 0.66 Å, S: 1.04 Å) and electronegativity (Pauling scale[194] O: 3.5, S: 2.4), but both of them show the same behaviour concerning the positive charge of the incoming proton, which is relayed to the sp^2 carbon through both the oxygen and the sulphur (Scheme 8). A useful physical condition is the gas phase. Results measured in this phase can be compared with theoretically calculated data. A simple process in the gas phase is the protonation of a base B (equation 42).

$$B(g) + H^+(g) \longrightarrow BH^+(g) \quad (42)$$

2. Gas-phase basicity and proton affinity

Currently available techniques[195–199] allow the determination of the intrinsic proton basicity, GB (gas-phase basicity, equation 43), and the proton affinity, PA (equation 44), of B, respectively.

† For simple aliphatic thioketone–enethiol tautomerism it has been assumed that the tautomers are similar in energy, and therefore one can anticipate only small differences, if any, in basicities of the sulphur and carbon sites[191,192].



(Ia) **(Ib)** **(IIa)** **(IIb)**

SCHEME 8. Protonated carbonyl and thiocarbonyl groups

$$\mathrm{GB} = -\Delta G_{\mathrm{H}^+}(\mathrm{g}) \tag{43}$$

$$\mathrm{PA} = -\Delta H_{\mathrm{H}^+}(\mathrm{g}) \tag{44}$$

The systematic study of gas-phase proton exchange reactions between bases has led to the development of a new formalism describing the quantitative effects of substitution on the GBs of organic compounds[200]. Because of their formal simplicity and general importance, proton transfer reactions are excellent models for the study of other acid–base reactions, both in the gas phase and in solution[201].

Most of the experimental information on structural effects on GBs available nowadays originates in a substantial body of data for N (sp, sp^2 and sp^3) and O (sp^2 and sp^3) N-donor bases and small data sets for S (sp^3) and P (sp^3) compounds[202–208]. In the next passage thiocarbonyl compounds of the form X(CS)Y and some results of studies are presented[209]. These compounds were chosen for various special reasons: (i) Their structure and reactivity can be varied within very wide limits by appropriate choices of X and Y. (ii) Extremely little is known about their intrinsic (gas-phase) reactivity[210] and the stabilizing or destabilizing role of the different substituents. (iii) Carbonyl compounds (a natural yardstick for comparison) have received a great deal of attention recently[211–213].

The standard free-energy change, $\delta\Delta G_{\mathrm{H}^+}(\mathrm{g})$ (the values are given in Table 26), was investigated by proton transfer reactions (equation 45) in the gas phase between a given base B and a reference compound B_{ref} (equation 46).

$$\mathrm{BH}^+(\mathrm{g}) + \mathrm{B}_{\mathrm{ref}}(\mathrm{g}) \longleftrightarrow \mathrm{B}(\mathrm{g}) + \mathrm{B}_{\mathrm{ref}}\mathrm{H}^+(\mathrm{g}) \tag{45}$$

$$\delta\Delta G_{\mathrm{H}^+}(\mathrm{g}) = -RT \ln K_{\mathrm{p}} \tag{46}$$

The gas-phase basicity GB of B is the negative of $\Delta G_{\mathrm{H}^+}(\mathrm{g})$, the standard free-energy change for the reaction described in equation 42. All GBs are referred to ammonia.

$$\mathrm{B}(\mathrm{g}) + \mathrm{NH_4}^+(\mathrm{g}) \longrightarrow \mathrm{BH}^+(\mathrm{g}) + \mathrm{NH_3}(\mathrm{g}) \tag{47}$$

$$\Delta\Delta G = \delta\Delta G_{\mathrm{H}^+}(\mathrm{g}) + \Delta\Delta G_{\mathrm{H}^+}(\mathrm{std}) \tag{48}$$

$$\mathrm{GB(B)} = -\Delta\Delta G_{\mathrm{H}^+}(\mathrm{g}) \tag{49}$$

$\Delta\Delta G_{\mathrm{H}^+}(\mathrm{g})$ is the average of the $\Delta\Delta G$ values obtained by equation 48, where $\Delta\Delta G_{\mathrm{H}^+}$ (std) pertains to equation 50.

$$\mathrm{B}_{\mathrm{ref}}(\mathrm{g}) + \mathrm{NH_4}^+(\mathrm{g}) \rightleftharpoons \mathrm{B}_{\mathrm{ref}}\mathrm{H}^+(\mathrm{g}) + \mathrm{NH_3}(\mathrm{g}) \tag{50}$$

The proton affinities, PA (equation 44), are not determined directly from ICR (ion cyclotron resonance) spectrometry, but entropy terms were instead evaluated in SCF *ab initio* calculations[209]. These absolute PA values and those relative to ammonia, ΔPA, are summarized in Table 27[209], which also contains the theoretical proton affinities obtained at different levels of theory.

TABLE 26. Experimental determination of gas-phase basicities of selected thiocarbonyl and carbonyl compounds[a]

Compound	Standard	$\Delta\Delta G_{H^+}$ (std)[b]	$\delta\Delta G_{H^+}$(g)	$\Delta\Delta G_{H^+}$(g)	$\Delta\Delta G_{H^+}$(g) (av)	$T\Delta\Delta S_{H^+}$(g)	ΔPA[f]
$SC[N(CH_3)_2]$	4-Me pyridine	−22.5	−0.26	−22.76	−22.8 ± 0.1	0.63[c]	−22.2
	4-Et pyridine	−23.3	0.50	−22.80			
$SC(NHCH_3)_2$	n-$C_5H_{11}NH_2$	−17.4	−1.05	−18.45	−18.4 ± 0.1	0.52[c]	−17.9
	t-$C_4H_9NH_2$	−19.0	0.72	−18.28			
$CH_3C(S)N(CH_3)_2$	n-$C_5H_{11}NH_2$	−17.4	−0.60	−18.0	−18 ± 0.2	0.78[c]	−17.3
	$(HC{\equiv}C\text{-}CH_2)_3N$	−17.8	−0.21	−18.01			
	C_5H_5N	−18.8	0.47	−18.27			
2-Imidazolinethione	$C_3H_7NH_2$	−15.1	−2.09	−17.19	−17.3 ± 0.2	2.96[c]	−14.3
	n-$C_5H_{11}NH_2$	−17.4	0.03	−17.43			
	t-$C_4H_9NH_2$	−19.0	1.71	−17.29			
$(1\text{-}C_{10}H_{15})_2CS$	$H_2C{=}CHCH_2NH_2$	−13.3	−1.76	−15.06	−15.0 ± 0.1	0.90[c]	−14.1
	n-$C_3H_7NH_2$	−15.1	0.26	−14.84			
$C_2H_5OC(S)N(CH_3)$	pyridazine	−13.6	−0.70	−14.30	−14.3 ± 0.1	1.02[d]	−13.3
	n-$C_3H_7NH_2$	−15.1	0.82	−14.28			
$HC(S)N(CH_3)_2$	$H_2C{=}CHCH_2NH_2$	−13.3	−0.02	−13.32	−13.3 ± 0.1	0.58[c]	−12.7
	pyridazine	−13.6	0.39	−13.21			
$(c\text{-}C_3H_5)_2CS$	4-Me pyrazole	−12.7	−0.38	−13.08	−13.0 ± 0.2	1.2[c]	−11.8
	3-Me pyrazole	−12.9	−0.01	−12.91			
	$H_2C{=}CHCH_2NH_2$	−13.3	0.15	−13.15			
$CH_3OC(S)N(CH_3)_2$	$(t\text{-}C_4H_9)_2S$	−10.7	−1.30	−12.00	−11.9 ± 0.2	1.47[c]	−10.4
	c-$C_3H_5NH_2$	−12.0	0.25	−11.75			
$SC(NH_2)_2$	$(t\text{-}C_4H_9)_2S$	−10.7	−0.26	−10.96	−10.9 ± 0.1	1.08[c]	−9.8
	c-$C_3H_5NH_2$	−12.0	1.15	−10.85			
$CH_3C(S)NH_2$	2-fluoropyridine	−7.9	−0.41	−8.31	−8.2 ± 0.1	1.94[c]	−6.2
	CH_3NH_2	−10.5	2.48	−8.02			
$(t\text{-}C_4H_9)_2CS$	pyrazine	−6.1	−1.54	−7.64	−7.8 ± 0.2	0.90[e]	−6.9
	2-fluoropyridine	−7.9	0.10	−7.80			
	$HC{\equiv}C\text{-}CH_2NH_2$	−8.5	0.57	−7.93			

(*continued overleaf*)

TABLE 26. (*continued*)

Compound	Standard	$\Delta\Delta G_{H^+}$ (std)[b]	$\delta\Delta G_{H^+}$(g)	$\Delta\Delta G_{H^+}$(g)	$\Delta\Delta G_{H^+}$(g) (av)	$T\Delta\Delta S_{H^+}$(g)	ΔPA[f]
Thiocamphor	pyrazine	−6.1	−1.03	−7.13	−7.3 ± 0.3	0.90[e]	−6.4
	$(c\text{-}C_3H_5)_2CO$	−6.1	−1.43	−7.53			
	$(CH_3)_2NCOOCH_3$	−6.8	−0.60	−7.40			
	2-fluoropyridine	−7.9	0.83	−7.07			
$CH_3C(S)OC_2H_5$	$(C_2H_5)_2S$	−1.7	−1.25	−2.95	−2.9 ± 0.3	1.21[c]	−1.7
	$(i\text{-}C_3H_7)_2O$	−2.2	−0.96	−3.16			
	$H_2C(CH_3CO)_2$	−4.0	1.33	−2.67			
$CH_3OC(S)SCH_3$	$(i\text{-}C_3H_7)_2O$	−2.2	−0.53	−2.73	−2.7 ± 0.1	1.02[c]	−1.7
	$H_2C(CH_3CO)_2$	−4.0	1.35	−2.65			
Cl_2CS	$c\text{-}C_3H_6$	21.8	0.14	21.94	22.2 ± 0.2	1.20[c]	23.4
	C_6H_5Cl	21.6	0.77	22.37			
$(c\text{-}C_3H_5)_2CO$	3-cyanopyridine	−6.1	−0.03	−6.13	−6.1 ± 0.1		
	$(i\text{-}C_3H_7)_2S$	−6.7	0.68	−6.02			
$(1\text{-}C_{10}H_{15})_2CO$	2-fluoropyridine	−7.9	−2.38	−10.28	−10.2 ± 0.1		
	$(t\text{-}C_4H_9)_2S$	−10.7	0.50	−10.20			
$OC(HNCH_3)_2$	$c\text{-}C_3H_5NH_2$	−12.0	−0.94	−12.94	−13.0 ± 0.1		
	$H_2C{=}CHCH_2NH_2$	−13.3	0.31	−12.99			

[a] All values in kcal mol^{-1}. The nominal temperature is 333 K.
[b] Values from Reference 210.
[c] Theoretical (*ab initio*) values; see Reference 209.
[d] Taking the same value as for $CH_3OC(S)N(CH_3)_2$.
[e] Estimated using symmetry numbers; see Reference 210.
[f] $PA(NH_3) = 204.0$ kcal mol^{-1} taken from Reference 214.

TABLE 27. Structural effects on the gas-phase basicities of carbonyl and thiocarbonyl compounds X(CO)Y and X(CS)Y[a]

Groups		-GB (relative to NH_3)	
X	Y	X(CO)Y	X(CS)Y
$N(CH_3)_2$	$N(CH_3)_2$	−18.9[b]	−22.8[c]
CH_3	$N(CH_3)_2$	−13.7[b]	−18.4[c]
$NHCH_3$	$NHCH_3$	−13.0[b]	−17.9[c]
1-$C_{10}H_{15}$ (1-Adamantyl)	1-$C_{10}H_{15}$ (1-adamantyl)	−10.2[b]	−14.1[c]
H	$N(CH_3)_2$	−8.5[b]	−12.7[c]
CH_3O	$N(CH_3)_2$	−6.6[b]	−10.4[c]
c-C_3H_5	*c*-C_3H_5	−6.1[c]	−11.8[c]
t-C_4H_9	*t*-C_4H_9	−3.1[b]	−6.9[c]
Camphor	thiocamphor	−2.0[b]	−6.4[c]
CH_3	OC_2H_5	3.9[b]	−1.7[c]
H	H	33.0[b]	18.3[d]
F	F	53.2[b]	36.3[e]

[a] All values in kcal mol^{-1}.
[b] From Reference 210.
[c] From Reference 209.
[d] Determined by combining the difference between GBs of H_2CO and H_2CS according to Reference 210 (14.7 kcal mol^{-1}) with the value of GB (H_2CO) from Taft's laboratory corrected as indicated in Reference 209.
[e] Obtained by using the *ab initio* PA of F_2CS and correlation equation linking calculated and experimental PAs (see Figure 22). The $T\Delta\Delta S$ term is from the *ab initio* calculation.

There is a linear relationship between the experimental values and the theoretical ones obtained at the MP2/6-31+G(d,p)//6-31G* level after including the corresponding ZPE corrections (see Figure 21). Also significant is the fact that this correlation presents a slope very close to unity and that it covers a wide range (about 50 kcal mol^{-1}) of the basicity scale. Figure 22 illustrates the reasonably good linear relationship between the aforementioned *ab initio* MP2 values and those obtained at the AM1 semiempirical level.

It must be noted that in this case the slope of correlation is greater than unity (1.39). Nevertheless, the goodness of the correlation clearly indicates that relative gas-phase basicities are quite well reproduced.

A direct comparison of structural effects on the GBs of carbonyl and thiocarbonyl compounds (summarized in Table 28) sets the stage for further discussions.

$$\Delta\text{GB (CS)} = (0.797 \pm 0.055)\Delta\text{GB (CO)} + (6.24 \pm 0.86) \tag{51}$$

in kcal mol^{-1}, $n = 12$ data points, $r = 0.9971$ and sd = 1.3 kcal mol^{-1}

Equation 51 embodies the linear correlation existing between both sets of intrinsic basicities (see also Figure 23). The breath of structural effects involved (72.1 and 59.1 kcal mol^{-1} for carbonyl and thiocarbonyl compounds, respectively) is possibly the largest ever reported for any linear free-energy relationship[216–218] (LFER). The slope in equation 51 reflects the fact that differential substituent effects are 29% smaller in the thiocarbonyl series than in the carbonyl series. This notwithstanding, thiocarbonyl compounds are consistently more basic than their carbonyl homologues within the entire range of reactivity examined here[209].

Experimental evidence indicates that most ketones, esters, amides and ureas are protonated on the carbonyl oxygen when they are in acid solution[219,220] and the same

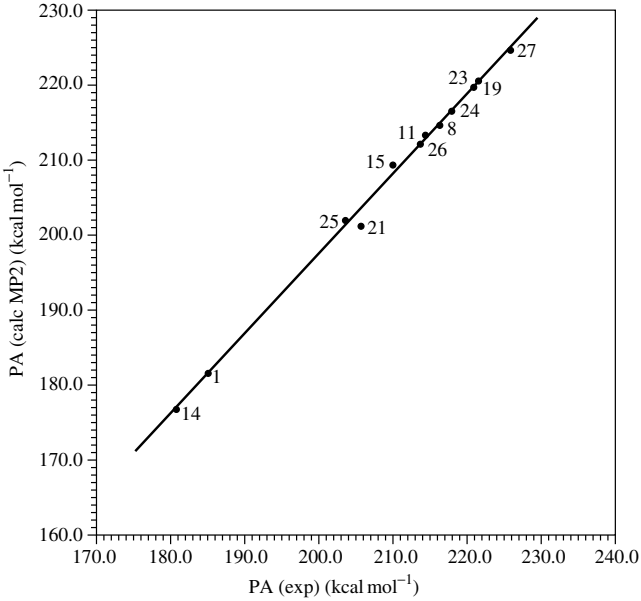


FIGURE 21. Linear correlation between calculated and experimental proton affinities. The computed data were obtained at the MP2/6-31+G(d,p)//6-31G* level. The correlation equation is PA (exp) = (0.932 ± 0.037)PA(calc) + (16.1 ± 16.1) kcal mol^{-1}, $r = 0.996$, sd = 0.85 kcal mol^{-1}. (The numbers in this Figure refer to the compound numbers in Table 28)

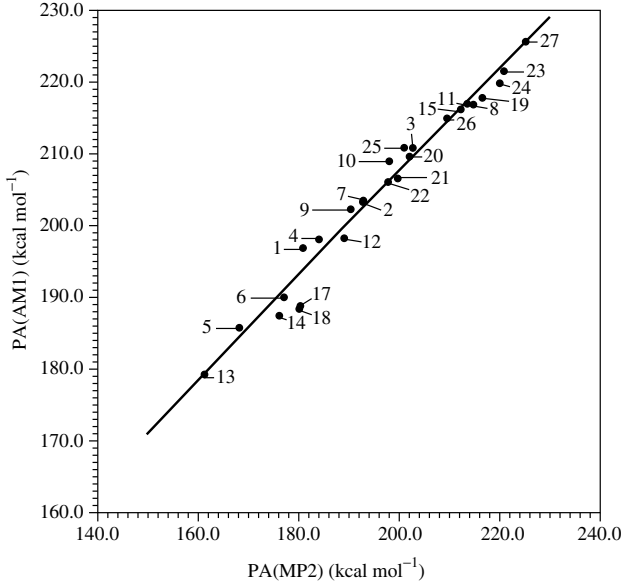


FIGURE 22. Linear correlation between proton affinities calculated at the AM1 semiempirical level and at the MP2/6-31+G(d,p)//6-31G* level. (The numbers in this Figure refer to the compound numbers in Table 28)

TABLE 28. Proton affinities (kcal mol^{-1}) of thiocarbonyl compounds X(CS)Y

	X	Y	PA (*ab initio*)[a]	PA (AM1)	PA (exp)[b]
23	H	H	181.5	196.9	185.0
24	CH_3	H	190.6	202.3	
25	NH_2	H	202.9	211.0	
26	OH	H	184.6	198.0	
27	F	H	168.9	185.8	
28	Cl	H	177.8	190.1	
29	C_2H_5	H	193.1	203.3	
30	$N(CH_3)_2$	H	214.9	217.3	216.7
31	OCH_3	H	192.6	203.6	
32	CH_3	CH_3	197.8	206.3	
33	NH_2	NH_2	212.6	216.6	213.8
34	OH	OH	189.4	198.3	
35	F	F	162.0	179.3	
36	Cl	Cl	176.7	187.5	180.7
37	CH_3	NH_2	209.6	215.1	210.2
38	CH_3	OH	192.5		
39	CH_3	F	180.8	188.3	
40	CH_3	Cl	180.7	188.7	
41	CH_3	$N(CH_3)_2$	220.0	220.8	221.3
42	CH_3	OCH_3	198.0	209.3	
43	CH_3	OC_2H_5	201.3	211.1	205.7
44	C_2H_5	OCH_3	200.1	206.8	
45	$NHCH_3$	$NHCH_3$	220.9	221.9	221.9
46	$NH(CH_2)$	$NH(CH_2)$	216.8	218.2	218.3
47	OCH_3	SCH_3	202.1	209.9	203.7[c]
48	$N(CH_3)_2$	OCH_3	213.7	217.3	214.4
49	$N(CH_3)_2$	$N(CH_3)_2$	225.2	226.1	226.2
50	$C(CH_3)_3$	$C(CH_3)_3$		214.7	211.1
51	Thiocamphor	thiocamphor		213.1	210.4
52	Ad	Ad		218.2	218.1

[a] Obtained at the MP2/6-31+G(d,p)//6-31G* level and including ZPE corrections.
[b] PA (NH_3) = 204.0 kcal mol^{-1} taken from Reference 215.
[c] Taken from Reference 211.

holds for the homologous thionocompounds[221,222]. In a direct comparison of the pK_a values of the corresponding conjugated acids of the couples CH_3CONH_2/CH_3CSNH_2, $PhCONH_2/PhCSNH_2$ and ε-caprolactam/ε-thiocaprolactam one finds that the carbonyl compounds are more basic by 1.5–2.0 pK units. This is a consequence of two facts: (i) the strong attenuation of polarizability effects in aqueous solution[223] (pK_a values are referred to the standard state of pure water) and (ii) the poorer solvation of protonated thiocarbonyl compounds in aqueous solution.

Substituents have strong effects on the gas-phase basicity of thiocarbonyl compounds. A model which deals with such effects is that of Taft–Tompson[224,225]. It considers substituent effects classified according to their origin in field (σ_F), resonance (σ_{R+}) and polarizability (σ_α) effects. For all the monosubstituted derivates which are listed in the last three tables it was found[209] that both experimental and calculated proton affinities follow this model quite well. For the particular case of MP2 PAs, equation 53 is fulfilled by differential substituent effects, δ_XPA, which is defined in equation 52. Figure 24 illustrates the remarkable good agreement which exists between the values predicted by equation 53 and those obtained in the MP2 calculations[209]. Equation 53 indicates that for thiocarbonyl compounds the field and the resonance term are dominant: the first because thiocarbonyl

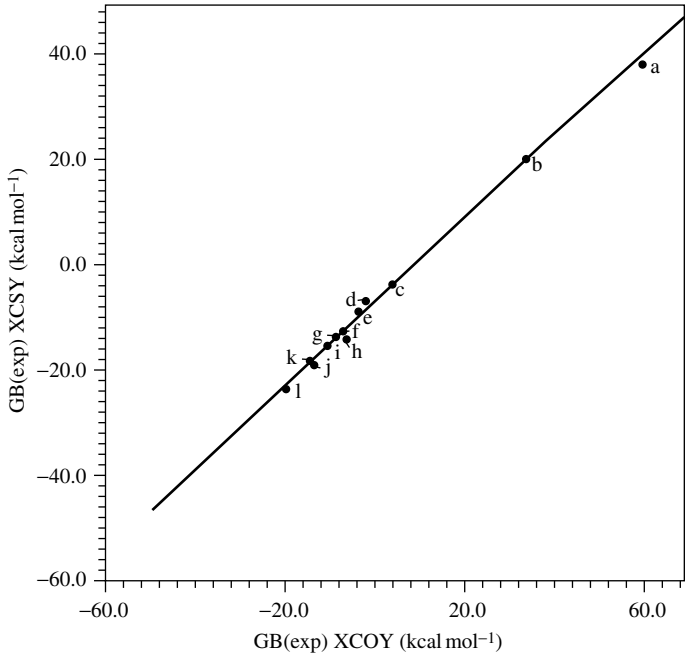


FIGURE 23. Linear correlation between the experimental gas-phase basicities of carbonyl and thiocarbonyl compounds: (a) X = F, Y = F; (b) X = H, Y = H; (c) X = Me, Y = OEt; (d) camphor, thiocamphor; (e) X = *t*-Bu, Y = *t*-Bu; (f) X = *c*-C_3H_5, Y = *c*-C_3H_5; (g) X = H, Y = NMe_2; (h) X = MeO, Y = NMe_2; (i) X = $C_{10}H_{15}$, Y = $C_{10}H_{15}$; (j) X = Me, Y = NMe_2; (k) X = NHMe, Y = NHMe; (l) X = NMe_2, Y = NMe_2

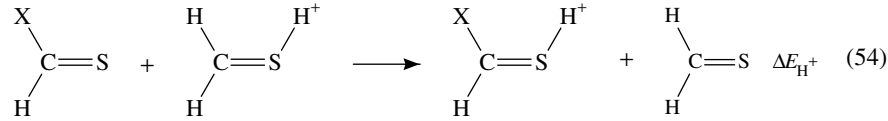
derivates present sizeable dipole moments[209]. Therefore the ion–dipole interactions which take place in the protonation process are significant. On the other hand, electronegative substituents enhance the C^+-S^- polarity of the C=S bond and hence the aforementioned interactions. The large weight of the resonance contribution can be explained in terms of dominant MO interactions between π-type orbitals.

$$\delta_X PA = PA(HCSX) - PA(H_2CS) \tag{52}$$

$$\delta_X PA = -(19.0 \pm 1.6)\sigma_\alpha - (46.8 \pm 2.0)\sigma_F - (46.4 \pm 1.6)\sigma_{R^+} \tag{53}$$

with $n = 9$, $r = 0.9978$ and sd = 1.1 kcal mol^{-1}

Another important question related to substituent effects on gas-phase basicities of thiocarbonyl compounds is whether these substituent effects arise from interactions within the neutral or within the protonated species, or both. It is useful to define the relative proton affinities along the monosubstituted series of compounds by means of the process shown in equation 54.



(54)

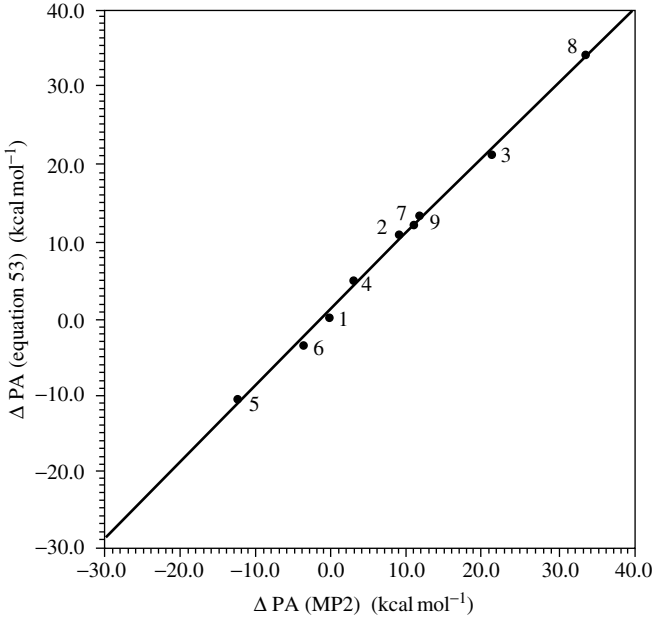
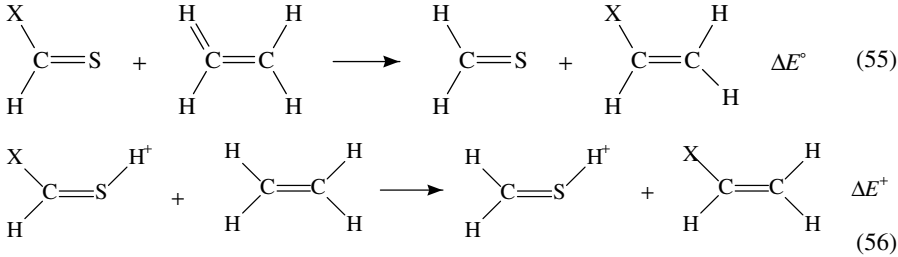


FIGURE 24. Linear correlation between proton affinities, relative to H_2CS, evaluated using equation 53 and those obtained at the MP2/6-31+G(d,p)//6-31G* level. (The number in this Figure refer to the compound numbers in Table 28)

This process may be subdivided into two reactions, accounting for substituent effects on the neutral (equation 55) and on the protonated species (equation 56), respectively.



It is obvious that the process in equation 54 is obtained by adding the reverse of equation 56 to the reaction in equation 55. This analysis has been carried out for $-CH_3$, $-NH_2$, $-OH$, $-F$ and $-Cl$ monosubstituted derivates. The values of ΔE_{H^+} and those of ΔE° and ΔE^+ have been summarized in Table 29. The first conspicuous fact is that the reaction in equation 55 is always endothermic.

This indicates that all substituents lead to a stabilization of the thiocarbonyl group, which prefers to be substituted by electronegative groups, although this stabilization is not significantly different for amino or hydroxy groups. Quite importantly, a similar finding has been reported for a wide set of carbonyl compounds[226]. This may be interpreted as a significant analogy between thiocarbonyl and carbonyl derivates considering the stabilizing effects of the different substituents, which is well reflected in the linear correlation

TABLE 29. SCF-6-31G* energies (kcal mol^{-1}) corresponding to the isodemic reactions in equations 54–56[209a]

X	Y	ΔE°		ΔE^{+}		ΔE_{H^+}	
		C=S	C=O	C=S	C=O	C=S	C=O
CH_3	H	+3.5	+6.2	+13.5	+18.8	−10.0	−12.6
NH_2	H	+18.9	+21.5	+42.0	+50.3	−23.1	−28.8
OH	H	+16.4	+26.5	+20.6	+32.3	−4.2	−5.8
F	H	+4.1	+19.6	−5.5	+6.4	+9.6	+13.1
Cl	H	+0.2	+8.3	−5.1	−0.7	+5.3	+9.0
CH_3	CH_3	+1.6	+10.2	+9.7	+19.3	−8.1	−9.1
NH_2	CH_3	+17.2		+37.0		−19.8	
OH	CH_3	+17.0		+19.9		−2.9	
F	CH_3	+6.2		−1.4		+7.6	
Cl	CH_3	−0.4		−6.1		+5.7	
NH_2	NH_2	+12.6		+21.3		−8.7	
OH	OH	+17.0		+21.3		−4.3	
F	F	+6.4		+0.3		+6.1	
Cl	Cl	−7.1		−9.4		+2.3	

[a]The total energies of the 6-31G* optimized structures of ethylene and its CH_3, NH_2, OH, F and Cl derivatives are (in Hartrees, H) −78.03172, −117.07147, −133.06170, −152.88539, −176.88195, −536.93369.

(equation 51) and in Figure 23 and which indicates that similar effects must be responsible for the variations observed in their intrinsic basicities upon substitutions.

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Granted copyright permissions from the publishers below are highly appreciated: American Chemical Society, Publication Office: Fig. 1,2,3 (J. Org. Chem., **54**, 126 (1989)); Fig. 10,11,12,13 (J. Am. Chem. Soc., **98**, 2081 (1976)); Fig. 15,16,17,19,20 (J. Am. Chem. Soc., **94**, 6096 (1972)); Fig. 21,22,23,25 (J. Am. Chem. Soc., **115**, 12468 (1993))

Royal Society of Chemistry: Scheme 3, Fig. 5 (J. Chem. Soc., Perkin Trans. 2, 1744 (1973)); Fig. 6 (Chem. Soc., Perkin Trans. 2, 2025 (1977))

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CHAPTER **8**

Complex formation involving compounds with double-bonded functional groups

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I. INTRODUCTION

Weak interactions in non-covalent complexes are not only an interesting field for speculative investigations, and a useful tool for explaining many properties or phenomena, but

are also important for projecting new practical synthetic routes, in the fields of scientific and technical research.

Interactions between molecules and between parts of the same molecule are of fundamental importance for investigating and explaining many different behaviours in different fields.

There are very important factors that affect the interactions between molecules of solutes and solvents and explain solvent effects[1]. Simple solubilization of a compound in a solvent is possible if certain solute/solvent interactions take place. The usual general solvent[2] parameters may be used to explain the physical and chemical behaviours of solutes, but often better explanations are obtained when specific interactions depending on the peculiarities of interacting molecules are considered[3–5].

When two or more reactants first approach one another, non-covalent recognition and attraction of the molecules or of parts of the molecules takes place and permits system aggregation, which may be of importance in obtaining the reaction products. For instance, the approach of a carbocation to a π system of olefins starts by forming a charge-transfer (CT) complex which precedes the formation of the C–C bond[6].

Usually, simple chemical reactivities (regarding covalent bond forming and breaking) can be estimated by changes in energy (or enthalpy). In more complicated processes, such as biological processes, the entropy changes may be more important than energy changes and some modifications are considered to be entropy-controlled processes. The formation of weak interactions may be related to a small enthalpy variation, but to a significant entropy change.

Generally speaking the interest in the formation of weak interactions, generally non-covalent interactions, such as electron donor–acceptor interactions[7] or hydrogen bonding interactions[8], may be summarized by the following main points:

(i) Physical properties, with particular emphasis on spectroscopic properties, regarding not only solute/solvent interactions, but also self-association of solutes, population of conformers and positions of tautomeric equilibria.

(ii) Chemical properties: the immediate neighbourhood of a solute (a reagent in a solvent) may be very important for defining its reactivity.

(iii) Investigation of reaction pathways: many reactions, both organic and inorganic, may be unified in a common general mechanism if the electrophilic reagent and nucleophilic reagents are considered electron acceptors and electron donors, respectively forming a molecular complex by means of weak interactions, involving or competing with the solvents[7].

The free energy relationship for electron transfer (FERET) starts with the presence of weak interactions (similar to donor–acceptor complexes) yielding the ion pair radical[7].

(iv) Molecular recognition is an important step in self-aggregation of molecules, including Diels–Alder reactions and some types of olefin polimerizations[9].

(v) In biological processes[10] the non-covalent interactions are of fundamental importance: the catalysis of chemical reactions, enzyme catalysis in particular, neutralization of toxins, hormone action in stimulating cellular activities and understanding the action of pharmaceutical chemicals are examples[11] of processes starting with non-covalent interactions between receptors and ligands, with solvent intervention.

While a complete classification of the complexes (and of some intermediates)[12] is beyond the scope of this chapter, the term ‘complexes’ is often applied to several different kinds of interactions (involving also hydrogen bonding interactions). A formal distinction is made between non-covalent and covalent complexes.

The main interactions may be divided into three main groups:

(i) Intermolecular and intramolecular hydrogen bonding interactions, which are both well known[13,14].

(ii) Donor–acceptor interaction[15] is an attractive electrostatic interaction[16]. Charge-transfer complexes start with this kind of interaction.

(iii) Van der Waals interactions are important when interactions (i) and (ii) are absent or very weak[17,18]. Basically, van der Waals systems involve attractive forces other than chemical bonds, including both points (i) and (ii). With true van der Waals molecules the main attraction comes from dispersion energy[19].

II. OLEFINS. NON-COVALENT INTERACTIONS

A. Olefins: Electron Donor–Acceptor Complexes

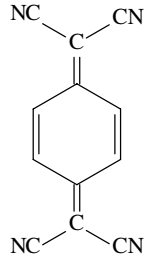
The C=C olefin double bond is usually considered to be an electron-rich centre which is prone to reactions with electrophiles. When strong electron-releasing groups such as amino, alkoxy or phenyl groups are bonded to the carbon atoms forming the double bond, the π bond's capacity to release electrons is enhanced and the olefin is defined as an electron-donor olefin. On the other hand, when the C=C double bond bears substituents that attract electrons, the olefin is an electron-acceptor olefin.

The ability of molecules to form donor–acceptor complexes depends not only on their ionization potential, electron affinity and polarizability, but also on the requirements and properties of partners.

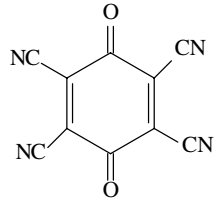
In principle, the same olefin can act as a donor molecule or an acceptor molecule depending on the properties of the partner[20]. In the same way, the C=C double bond is a π donor or a π acceptor[21], depending on the nature of the groups bonded to it.

Donor–acceptor interactions are the first step in some Diels-Alder reactions[7,22] between electron-poor olefins and electron-rich olefins, and also in spontaneous polymerization which can occur during cycloaddition reactions of olefins[23].

True CT complexes are formed between unsaturated electron acceptors, among which the derivatives with cyano and nitro groups predominate. The most common strong electron acceptors are 1,2,4,5-tetracyanobenzene, 7,7,8,8-tetracyanoquinodimethane **(1)**, tetracyano-*p*-benzoquinone **(2)**, tetracyanoethylene (TCNE) **(3)** and many electron-donor



(1)



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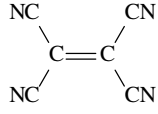

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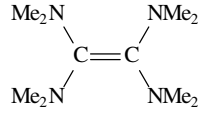


(4)

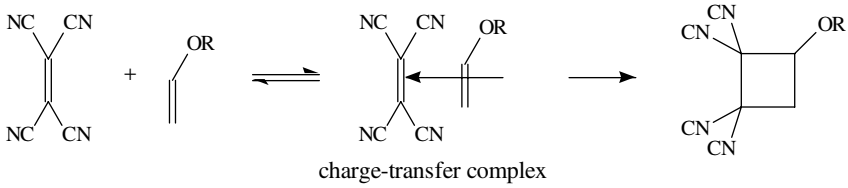
hydrocarbons including alkenes, cycloalkanes, alkynes and aromatic hydrocarbons. In the field of the unsaturated electron donors, tetrakis(dimetylamino)ethylene **(4)**[15] is a strong electron donor.

Generally, equilibrium 1 is quickly established, and it is a standard common model in donor–acceptor interaction investigations.

$$\text{DONOR} + \text{ACCEPTOR} \overset{K}{\rightleftharpoons} \text{CHARGE-TRANSFER COMPLEX} \qquad (1)$$

CT complexes exhibit spectral properties different from those of the separate compounds, and spectroscopic methods are widely used in their investigations and in quantitative evaluations of K (equation 1) values[15].

Scheme 1 illustrates the Diels–Alder reaction through a complex.



charge-transfer complex

SCHEME 1

Tetrakis(phenylethynyl)ethene **(5)** forms π complexes with 2,4,7-trinitrofluoren-9-one **(6)** and (2,4,7-trinitrofluoren-9-ylidene)malonitrile **(7)**[24]. In the solid state the CT complexes show a 1:2 stoichiometry; in solution ($CHCl_3$) the purple-coloured complex between **5** and tetracyanoethylene shows a 1:1 stoichiometry. Such complexes may be of interest as potential new materials *e.g.* in the field of non-linear optics.

The most common donor/acceptor ratio for a CT complex is 1:1, but there are examples of different ratios, such as 2:1. In theory a 1:2 ratio donor/acceptor is possible, depending on the experimental conditions and on the relative amounts of partners used.

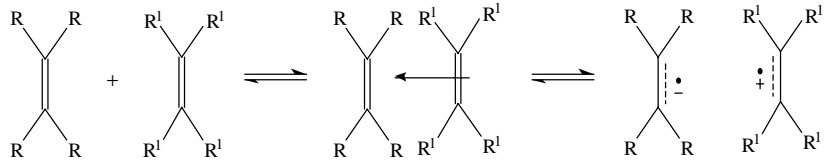
7,7,8,8-Tetracyanoquinodimethane **(1)** and tetracyanoethylene **(3)** are able to form CT complexes with crown ethers which are electron-donor molecules[25]. A recent study has recorded the spectral properties and stability constants of 89 tetracyanoethylene CT complexes with donors[26]. The main interaction in these complexes is an electron transfer ($\pi \rightarrow \pi^*$) between the HOMO of the donor and the LUMO of the acceptor.

The formation of CT complexes between alkenes is considered to be the first step of the cycloaddition reactions, and it may also be the first step of some types of olefin polymerization[23]. The CT complex obtained from strong electron donors and strong electron acceptors may produce a complete charge separation with formation of an ion-radical pair (cation radical and anion radical pair), as illustrated by Scheme 2.

9-Cyanoantracene (and indene) form CT complexes with TCNE; these complexes were studied[27] using time-resolved picosecond spectroscopy. Irradiation of the CT complex produced an ion radical pair as shown in Scheme 2.

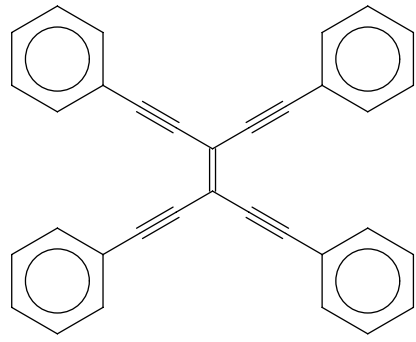
The electron transfer (if there is an ion radical pair) intermediate is generally thought to participate in the polar mechanism for cycloaddition reactions[28]. Recently, the electron transfer mechanism for the zwitterionic cycloaddition of tetracyanoethylene and bis(4-methoxycinnamyl) ether has been discounted and there is now strong support for the theory that a polar mechanism is also operative for other systems[29].

The ground states of electron donor–acceptor complexes between *trans*-stilbene and electron-deficient alkenes (fumaronitrile, dimethyl fumarate and maleic anhydride) are formed and the isomerization of *trans*-stilbene (and of fumaronitrile to maleic nitrile) has

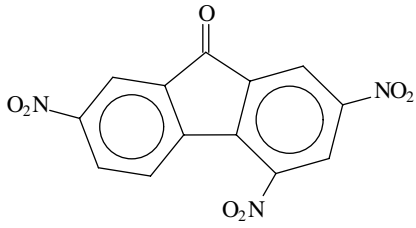


R = electron-withdrawing group
R^1 = electron-releasing group

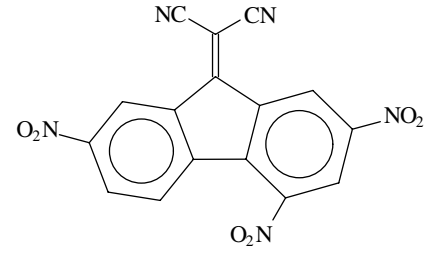
SCHEME 2



(5)



(6)



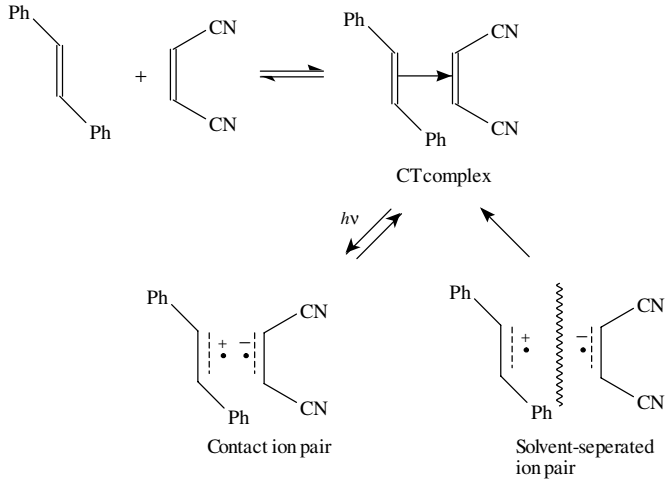
(7)

been investigated to check the importance of the presence of oxygen, which favours the isomerization of *trans*-stilbene.

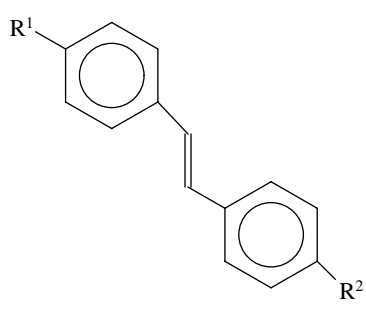
'Exciplexes' are defined as molecular complexes which are stable under electronic excitation[30]. The picosecond (or femtosecond) laser photolysis methods are suitable for investigating the very rapid photo-induced processes related to CT complexes.

trans-Stilbenes **(8)**/fumaronitrile complexes are used to investigate some aspects of the microdynamics of these complexes (by picosecond absorption spectroscopy)[31,32], e.g. for the formation of contact ion pairs and solvent-separated ion pairs, as shown in Scheme 3[33].

The excited *trans*-stilbene/fumaronitrile complex produces a locally excited triplet state, which is considered to be responsible for isomerization of substituted stilbenes. Similarly, the CT complexes between aromatic hydrocarbons and fumaronitrile produce the isomerization of fumaronitrile to malonitrile[34].



SCHEME 3



$R^1 = H; R^2 = OCH_3$
$R^1 = R^2 = CH_3$
$R^1 = H; R^2 = CH_3$
$R^1 = Cl; R^2 = CH_3$
$R^1 = R^2 = H$
$R^1 = H; R^2 = Cl$
$R^1 = H; R^2 = F$
$R^1 = R^2 = Cl.$

(8)

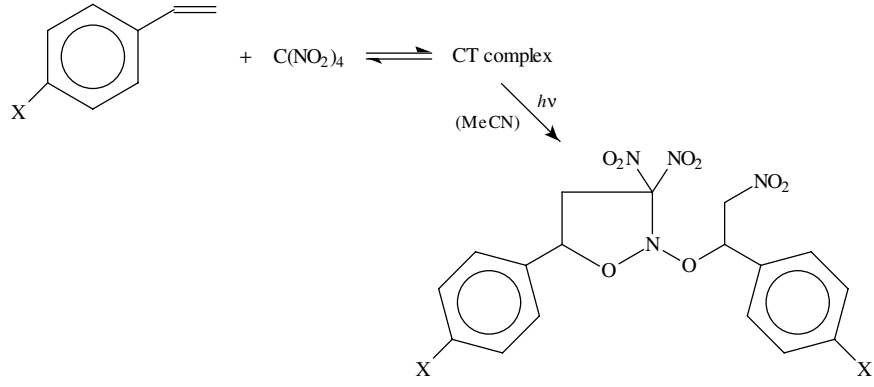
trans-Stilbene/amine exciplexes have been investigated by using trialkylamines and the bicyclic diamine, 1,4-diazabicyclo[2,2,2]octane, in benzene[35] and in acetonitrile[36]: in the more polar solvent, a solvent-separated radical ion pair is formed either directly from the complex or from the exciplex.

Recently[37], the importance of CT complexes in the chemistry of heteroaromatic N-oxides has been investigated in nucleophilic aromatic substitutions. Electron acceptors (tetracyanoethylene and *p*-benzoquinones) enhance the electrophilic ability of pyridine-N-oxide (and of quinoline-N-oxide) derivatives by forming donor–acceptor complexes which facilitate the reactions of nucleophiles on heteroaromatic substrates.

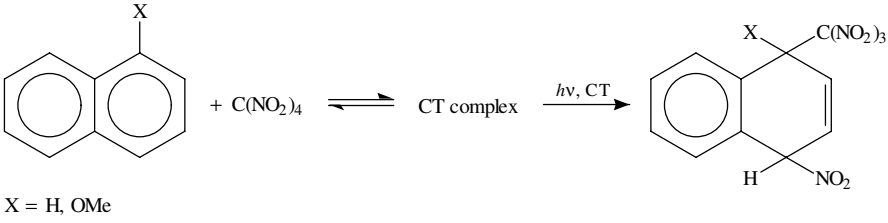
Complexes between tetranitromethane (which is a powerful electron acceptor) and different electron donors (aromatic substrates, alkenes, amines, sulphides, ethers) may be observed and isolated as moderately stable coloured complexes (if stored in the dark). These complexes are usually classified as CT complexes. Irradiation of complexes between alkenes and trinitromethane forms interesting products, which are derived from the nucleophilic attack of the trinitromethide.

Scheme 4 shows the reaction between styrenes and tetranitromethane[38] to produce the isoxazolidine derivatives **9** with 85% yields, by irradiation of the styrene/tetranitromethane

complex. The structure of **9** was investigated by X-ray diffraction. Scheme 4 suggests that in this case the trinitromethide anion (which is an ambident nucleophile) acts as an oxygen nucleophile[39]. In other cases, such as photonitration of the CT complex between naphthalene[40] (and 1-methoxy-naphthalene[41]) and tetranitromethane, the trinitromethide anion is a carbon nucleophile, as shown in Scheme 5.



SCHEME 4



SCHEME 5

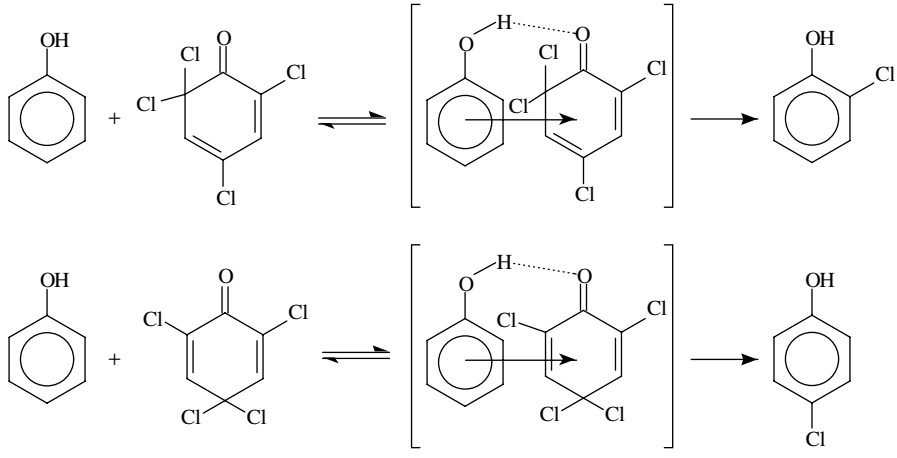
The main products of the photolysis[42] of the complex between 1-methoxynaphthalene and tetranitromethane are 1-methoxy-4-nitronaphthalene and 1-methoxy-4-trinitromethyl-naphthalene.

The ability of compounds with a quinonic structure to form donor–acceptor interactions and CT complexes is useful in regioselective halogenation of phenol (or naphthols and their derivatives).

Chlorination of phenol[43] is obtained mainly in positions 2 or 4, depending on the hexachlorocyclohexadienone used, as shown in Scheme 6. A hydrogen bond between the OH and C=O groups favours the formation of CT complexes (**10**, Scheme 6). In the same way, 2-chloro-1-naphthol and 4-chloro-1-naphthol[44] are obtained from α-naphthol.

B. Complexes Between Olefins and Ozone

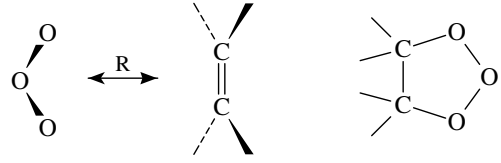
A weakly bonded complex between ozone and ethylene was observed by using a pulsed beam Fourier transform microwave spectrometer[45]. The $C_2H_4-O_3$ complex shows the two partners on two parallel planes at a distance of 3.30 Å (R in **11**). This complex (which is probably a van der Waals complex) enables the primary ozonide **12** to be



(10)

SCHEME 6

formed. Theoretical results confirm microwave results suggesting the internal rotation (in a van der Waals complex, **11**) of ethylene: this rotation exchanges the equivalent pair of hydrogen (or deuterium) atoms for ethylene[46].



(11) **(12)**

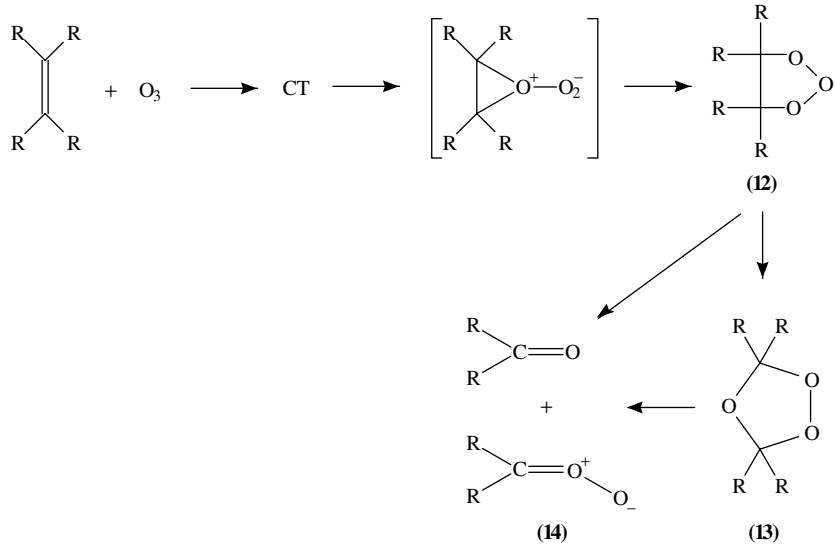
The weakly bonded complex **(11)** is close to the transition state (TS) of the cycloaddition reaction to obtain the ozonide **(12)** and it must occur prior to this TS, which shows a C−O distance of 2.3–2.0 Å, shorter than that calculated for the complex **(11)**.

Despite the complexities of alkene ozonolysis[47], the reaction between alkenes and ozone may be summarized by Scheme 7. The reaction involves several steps[48] with the formation of a variety of intermediates, such as a primary ozonide (1,2,3-trioxolane) **(12)**, its isomer of rearrangement **13** and a carbonyl oxide **(14)**.

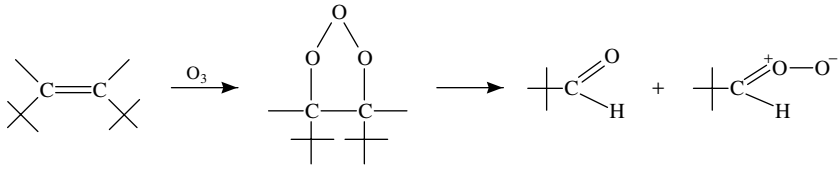
Kinetic data for ozonization reactions of a given number of alkenes in carbon tetrachloride at different temperatures are consistent with the presence of a pre-association equilibrium between the alkene and the ozone when electron-rich alkenes are used[49].

The reaction of *trans*-di-*tert*-butylethylene **(15)** with ozone is shown in Scheme 8. The ozonide **(16)** is an unusually stable (at 60 °C) trioxolane[50]. The decomposition of **(16)** forms the aldehyde **(17)** and the carbonyl oxide **(18)** (as illustrated in Scheme 8, for non-radical ozonization reactions). The carbonyl oxide is an oxygen carrier.

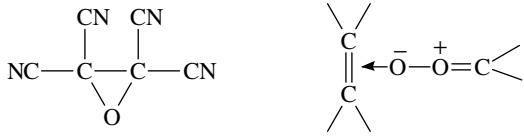
The decomposition of **(18)** in the presence of electron-deficient oxygen acceptors such as tetracyanoethylene forms the tetracyanoethylene oxide **(19)**[51], with 60% yield. The oxygen atom transfer may be considered a general reaction of carbonyl oxides in ozonolysis of C=C double bonds when oxygen-accepting substrates are present.



SCHEME 7



SCHEME 8



A reasonable explanation for the epoxide **19** formation is the presence of a complex such as **20**. The mechanism involving **20** parallels the reaction of ozonolysis of fluoro olefins[52].

In the ozonization reactions of olefins, the radical production may be a significant side reaction[53]. In this case, again, the reaction may be deemed to proceed through a CT complex between ozone and olefins[54].

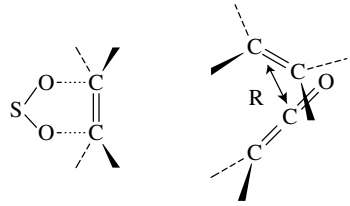
C. Complexes Between Olefins and SO_2 or Ketenes

The microwave spectrum of mixtures of ethylene and sulphur dioxide indicates the presence of an interaction involving the π electrons of ethylene[55]. The SO_2 molecule

may be arranged in two main structures, depending on the fact that sulphur may be closer to the carbon atoms (with structures similar to that illustrated by **11**, for the ozone/olefin complex) than the oxygen atom, as illustrated in **21**. In complex **21**, the distance between the centre of the S−O bond and a carbon atom of ethylene is 3.51 Å.

The properties of weakly bonded van der Waals complexes in reactive systems are studied by pulsed Fourier Transform microwave spectroscopy, which is a powerful tool for investigating many complexes.

The microwave spectrum of the complex between ethylene and ketene (and of deuterated derivatives) reveals[56] a crossed structure **(22)**, while the ketene/acetylene complex shows a planar geometry[57]. This difference in geometry is explained by the different quadrupole moments of two unsaturated hydrocarbons.

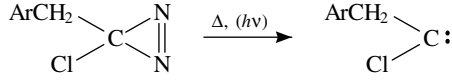


(21) **(22)**

From the qualitative point of view, the structure of the ethylene/ketene complex is similar to the geometry of the TS of the same system in cycloaddition reaction[58]. In **22**, R (= 3.46 Å) is the distance between the centre of mass of the ethylene and the carbon of the carbonyl group of ketene; this carbon is the most electrophilic centre of the ketene. In the case of the complex between acetylene and ketene, the same distance between the centre of mass of acetylene and the carbon of ketene was evaluated (by the same method) at 3.60 Å.

D. Complexes Between Olefins and Carbenes

In thermolysis and photolysis of 3-chloro-3-benzyldiazirines **23**, carbenes **24** are formed as indicated by reaction 2. In both electron-rich (tetramethylethylene) and electron-poor (diethyl fumarate) alkenes (as solvents), cyclopropanes (and chlorostyrenes) are obtained[59]. The probable reaction pathway is the multi-step model shown in Scheme 9.

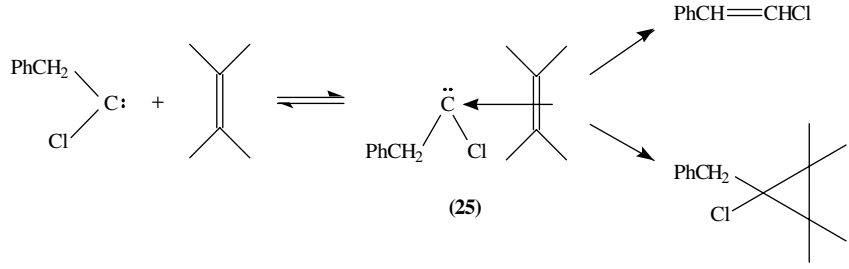


(2)

(23) **(24)**

Negative activation energies for cycloaddition reactions of some carbenes are reported[60] and they confirm the presence of a pre-association equilibrium on the reaction pathway. In addition, the entropy control of the cycloaddition of halocarbenes to the C=C double bond was extensively reported[61] and explained by the presence of a weakly bound intermediate complex **(25)**, which is reversibly formed and is probably a CT complex[62]. Its presence is also supported by direct kinetic data[59,63].

The nature of the complex[63] probably involves the π electrons of the alkene and the vacant p orbital of carbene by CT interaction. The possibility that the intermediate **25** is

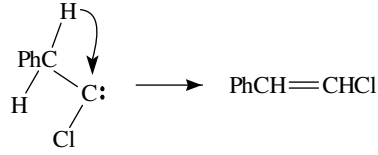


(25)

SCHEME 9

a complex (in a potential energy minimum), or a contact pair in a solvent cage[64,65], also depends on the structure of the partners.

Styrene derivatives may be obtained directly from the carbene, by internal hydrogen migration (reaction 3), or from the complex[59] **(25)**.



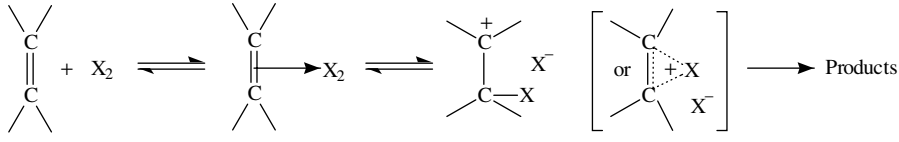
(3)

Theoretical studies[65] on cycloaddition of halocarbenes (mainly CF_2, CCl_2) with ethylene suggest an alternative reaction pathway. This explains the high (negative) entropy value[66] without the intervention of the intermediate complex reported by the multi-step mechanism of Scheme 9[67].

E. Complexes Between Olefins and Halogens: Introduction

Interactions between the C=C double bond and halogens deserve particular attention. The importance of these interactions arises from the fact they are the first step of the reactions of addition of halogens to alkenes (and, in general, of the electrophilic addition to the carbon–carbon double bond[68]), which is a very useful functionalization reaction of the alkene double bond.

When mechanisms involving radicals can be discounted, the main and general reaction pathway of addition of halogens to alkenes is shown in Scheme 10, where X is mainly Cl and Br[69,70].



(26) (27) (28)

SCHEME 10

The nature of the interaction between alkenes and halogens (complex **26** of Scheme 10) preceding the reactions of addition of the halogens to the C=C double bond is labelled according to Mulliken's classification[71] as a CT complex. The nature of the carbonium

ions **27** and **28** has been discussed, and has been the subject of several investigations. When X = Br, there are indications that bromination of alkenes includes the cyclic bromonium ion in the reaction pathway.

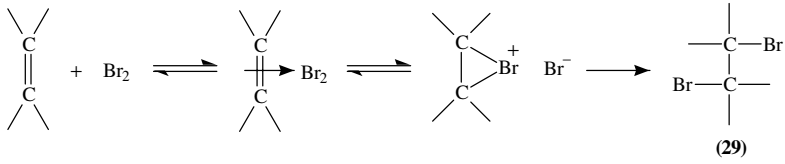
The first step of the reaction is the formation of a π complex between the double bond and the halogen[68,72] (**26** in Scheme 10). This complex may be considered as a 'charge transfer' complex, but there are some doubts about the amount of charge which is transferred. When the amount of the transferred charge is small, the definition 'van der Waals complex' is more appropriate[73].

The decrease of overall reaction rate as the temperature increases[74] confirms the presence of aggregating processes forming complexes (mainly CT complexes) on the reaction pathway of bromination of olefins: the association of solutes is usually favoured by lowering the temperature.

When the olefin used is sterically hindered in relation to the nucleophilic part of the halogenating reagent or toward the solvent (if it is a nucleophilic solvent), the complex **26** of Scheme 10 is in rapid equilibrium with the free reagents and the halonium ion **28** (or the cation **27**)[75].

F. Complexes Between Olefins and Cl_2, Br_2, I_2

The usual reaction between olefins and bromine or chlorine is illustrated in Scheme 11. Final products are di-brominated compounds **29**. Theoretical studies[76] agree with Scheme 11. Both Schemes 10 and 11 involve a quickly established equilibrium of formation of a CT complex between olefin and bromine.



SCHEME 11

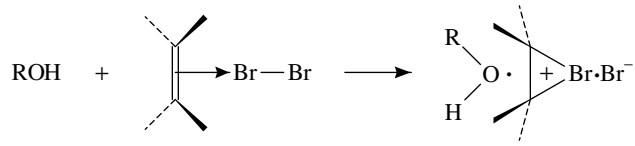
The formation of the complex **(26)** is followed by the formation of a σ complex (**28**, the 'bromonium ion'), in a rate-limiting step. From **28** the products are obtained in a fast step (which is similar to a neutralization) with nucleophiles. The presence of the CT complex is indicated by unambiguous spectroscopic evidence[68,77,78] and also by fast monitoring of reaction mixtures immediately after mixing[79,80].

Basically, the formation of the bromonium ion may be considered either a reversible or irreversible process. In spite of some evidence of reversibility of the formation of bromonium ion, in 1990, Ruasse affirmed that, in protic solvents, 'the ionic intermediate is formed irreversibly'[81]. Now, there is a body of evidence supporting the reversibility of the bromonium ion formation in bromination of olefins.

In a recent article, Bellucci and coworkers extensively discuss this problem[82] and conclude that the kinetic results and the distribution of the obtained products provide strong evidence of a return to a CT complex from ion **28**. See Scheme 10.

The reversibility of the ionization of the CT complex occurs not only with very congested alkenes, but may also be considered a general feature of bromine addition to C=C double bonds in both protic and aprotic solvents[82].

Bromonium ion formation (reversible or irreversible) may be assisted by the presence of a nucleophilic solvent, as shown in **30** of reaction 4 involving alcohols as solvent.

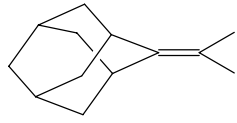


(4)

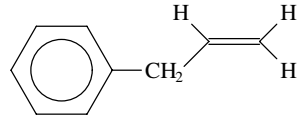
(30)

Kinetic investigations[83] into the bromination of methylidene adamantane **(31)** and allylbenzene **(32)** reveals the importance of the assistance of the solvent to the rate-limiting ionization to form bromonium ion from the CT complex.

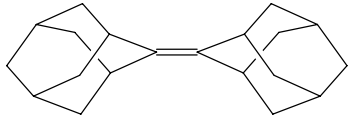
The rate of the return from bromonium ion to CT complex depends on the nature of the solvent and of the substituents bonded to olefin[81,84]. By using adamantylideneadamantane **33**, halonium ions **34** are formed as stable (and isolatable) salts[85], because of steric hindrance of the nucleophilic counter ion. Consequently, the products of addition, such as the dibromides **29**, cannot be obtained.



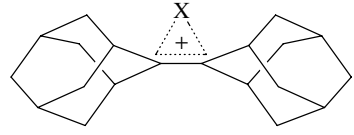
(31)



(32)

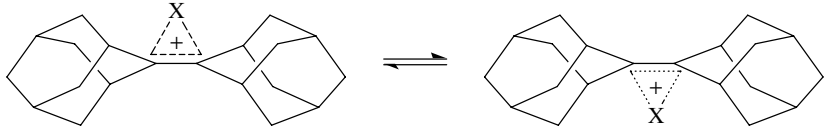


(33)



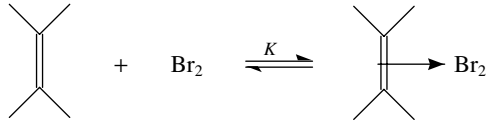
(34) X = Cl, Br, I

In the same way, the thiiranium ion (**34**, X = S−R) has been isolated from a mixture of adamantylideneadamantane and methane sulphenyl chloride[86]. The stability of **34**, X = Br, which is the only known stable bromonium ion, and the fact that **34** cannot form the saturated products of the bromination reactions of olefins enable the investigation[87] (by a dynamic ^{1}H-NMR technique) of equilibrium 5, which proceeds via the dissociation of the 1:1 CT complex between **33** and bromine.



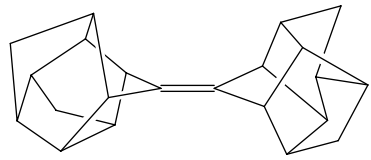
(5)

The stability constants of some CT complexes between olefins and bromine (equation 6) in 1,2-dichloroethane at 25 °C clearly indicates the influence of the alkyl substituents bonded to the double bonds on the K values: K (mol^{-1} dm^3) = 0.47, 9.7, 290 and 700 for cyclohexene[78], tetraisobutylethylene[72], adamantylideneadamantane[79] **33** and *dl*-D$_3$-trishomocubylidene-D$_3$-trishomocubane[88] **35**.



(6)

CT complex



(35)

X-ray diffraction of bromonium (X = Br)[89] and iodonium (X = I)[75] salts confirms the **34** structure.

The bromonium ion tribromide salt of **33**[90,91] (as well as the triflate salt[92]) transfers Br_2 to other olefins by irreversible reactions forming dibromo derivatives.

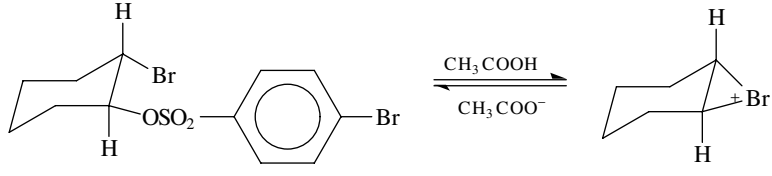
Using the UV/VIS spectrophotometric method, the equilibria of Scheme 12 have been investigated[93] as a model of the bromonium tri- and pentabromides, the intermediates of the reactions of olefin bromination.

$$Bu_4N^+\ Br^- \overset{+Br_2}{\rightleftharpoons} Bu_4N^+\ Br_3^- \overset{+Br_2}{\rightleftharpoons} Bu_4N^+\ Br_5^-$$

SCHEME 12

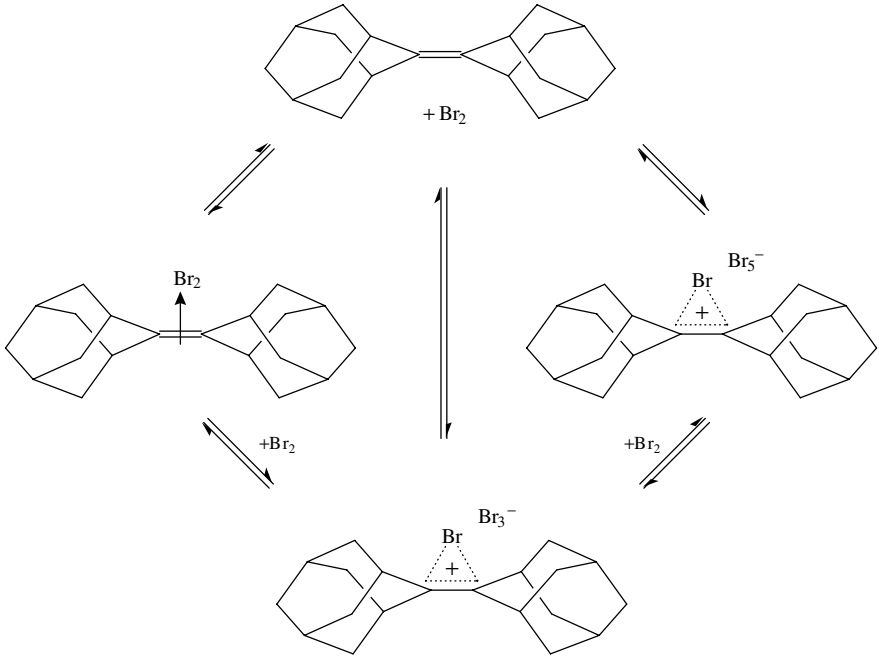
In 1,2-dichloroethane, UV/VIS spectroscopic data indicate that in the mixtures of **33** and bromine there are 2:1, 1:1, 1:2 and 1:3 (**33**:Br_2) complexes. Conductivity measurements of the same mixtures indicate that the complex 1:1 is a CT complex whilst the other complexes are ionic in character. The complexes with stoichiometry 1:2 and 1:3 (**33**:Br_2) are bromonium tribromide and pentabromide, respectively, as indicated in Scheme 13. CT complexes with moderate stability were also reported[90] between **33** and different charged electrophiles (nitrosonium and nitronium salts)

The bromonium ion may be generated by other methods than direct bromination: solvolytic reaction of *trans*-2-bromo-[(4-bromophenyl)sulphonyl]cyclohexane **(36)** (and cyclopentane) forms (reaction 7) the bromonium ion[94] **(37)**. If Br^- is present in the reaction mixture, the generation of Br_2 (and olefin) is observed (Scheme 14). This confirms the reversibility of the bromonium ion formation in the usual bromination pathway. When other olefin scavengers are present, a formal Br^+ transfer is observed[94]. This may occur without the formation of Br_2.

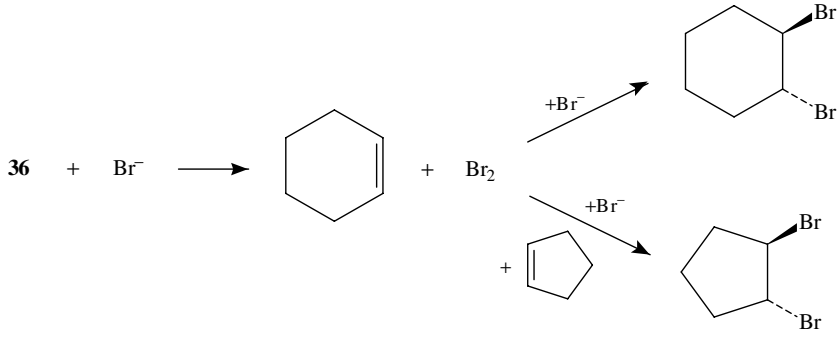


(7)

(36) **(37)**



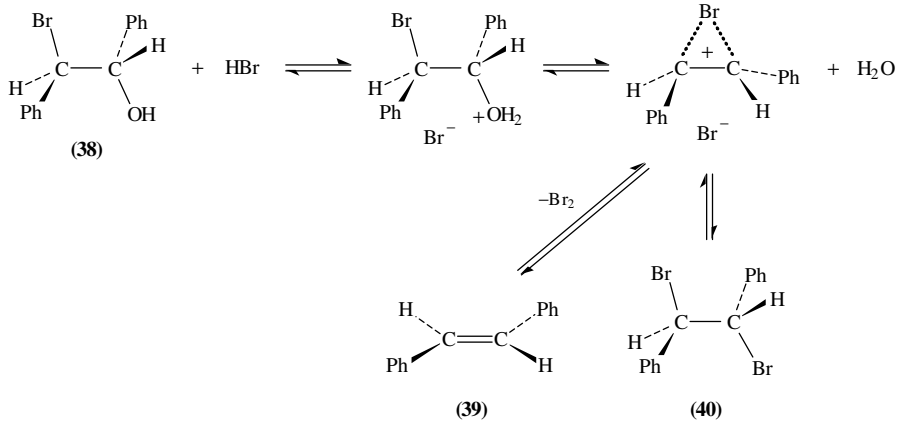
SCHEME 13



SCHEME 14

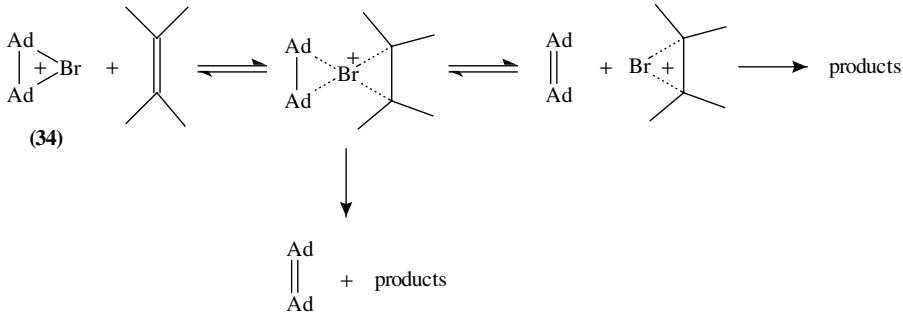
Bromonium ion is generated by reactions of both *erythro* **(38)** and *threo* 2-bromo-1,2-diphenylethane with hydrogen bromide[95] (in 1,2-dichloroethane and in chloroform) as illustrated by Scheme 15. Stilbene **(39)** and the 1,2-dibromo derivative are the main reaction products. Product distribution and kinetic investigations on the bromination of stilbenes clearly confirm the reversibility of the bromonium/bromide formation in bromination of olefins, through an olefin/bromine CT complex.

Kinetic studies[92] of the bromination of cyclohexene, alken-1-ols **41** and 4-pentenoic acid, by the bromonium ion of adamantylideneadamantane bear out the findings shown in Scheme 16.



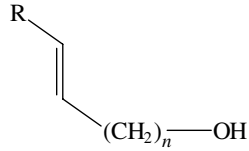
(38) **(39)** **(40)**

SCHEME 15



Ad═Ad = adamantylideneadamantane

SCHEME 16

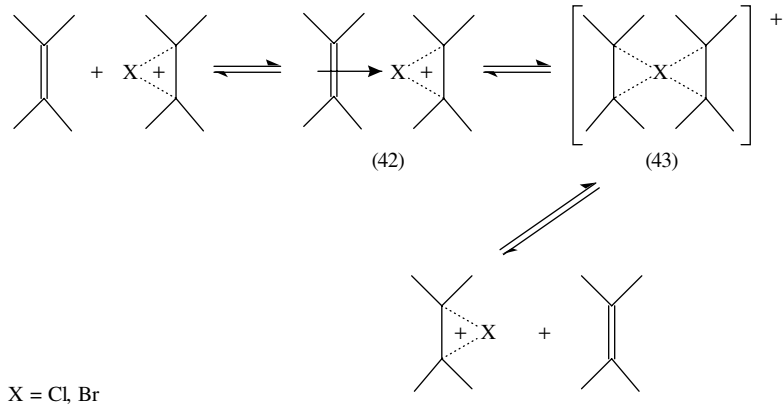


R = H, $n = 3$
R = H, $n = 4$
R = CH_3, $n = 3$

(41)

The addition of an initial amount of adamantylideneadamantane **33** to the reaction mixtures depresses the rate of the Br^+ transfer from **34** to the olefins, because of the competition of **33** with the other olefins (there is an equilibrium **33** ⇌ **34**). In the case of the complex **34**, ^{13}C-NMR spectral data provide indications of the presence of a rapid transfer of Br^+ to olefins, as shown in Scheme 17, probably via a spiro transition state

(43)[75,91]. The bromonium ion may exchange with free olefins through a π complex[73] (**42** of Scheme 17).

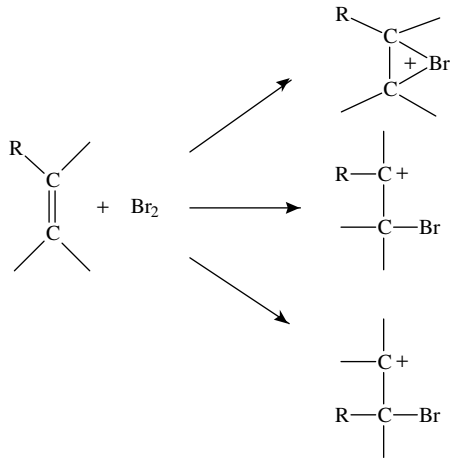


(42) (43)

SCHEME 17

Rotational spectroscopy and *ab initio* calculations give an evaluation of the distance between donor and acceptor for ethene/halogen or interhalogen (BrCl) π complexes[73,96]. *Ab initio* calculations indicate that a 'spiro' transition state[73] **(43)** is involved in the transfer of positive halogens to olefins; an asymmetrical 1:1 halogen-ion/olefin CT complex **(42)** precedes the TS **43**.

In the bromination mechanism different reaction pathways may compete[68], as shown in Scheme 18.



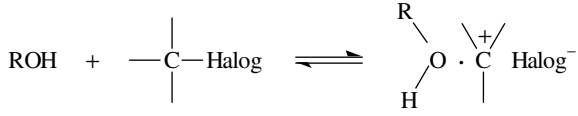
SCHEME 18

The 'multistep pathway'[81] explains some observed features, including the evaluation of the electronic effect of substituents[81,97] using the Hammett (ρ/σ) equation which is a non-linear correlation, but it may also be explained by a single reaction with two or

more steps involving different electronic requirements[98]. A halogen/olefin CT complex precedes the reactions of Scheme 18. The different pathways depend on the nucleophilic power of the solvent and on the nature of the olefin[81,83]. Steric hindrance is relevant to state the nature of the bromonium ion and the importance of the solvent for stabilization.

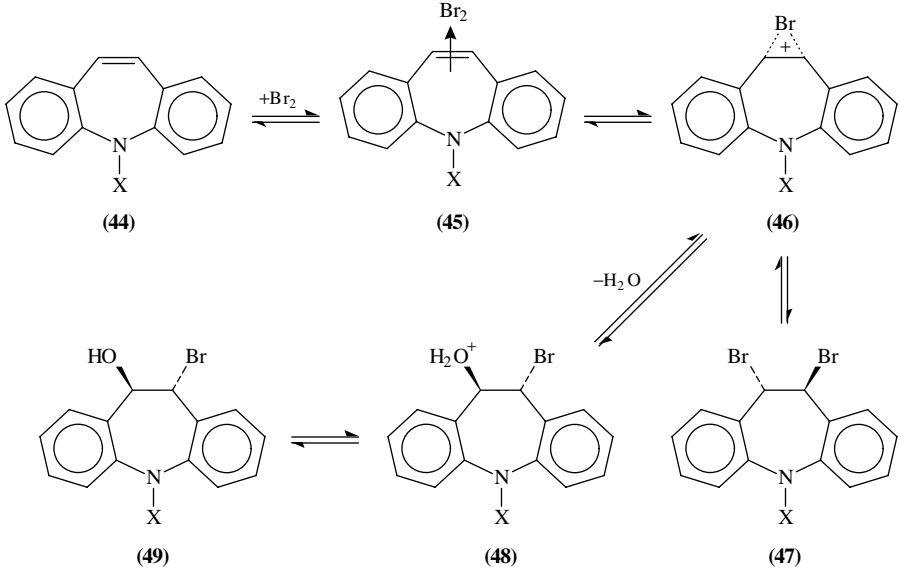
The chemoselectivity of olefin bromination is reported[84] to occur after the attack of the bromine on the double bond, but the formation of the bromonium ion is the slow step of the reaction. As a consequence, the distribution of products and the selectivity of addition of nucleophiles can hardly be explained by substituent effects (both steric and electronic) bonded to the C=C double bond in a fast step of the reaction.

The reversibility of the formation of bromonium ion is a process comparable to the formation of β-bromo carbocations. In fact, the carbocation formation may be solvent-assisted[81] as reported in reaction 8, which parallels reaction 4.



(8)

Furthermore, in the addition of bromine to **44** (in 1,2-dichloroethane, chloroform or carbon tetrachloride, see Scheme 19) to obtain the *trans* dibromo derivative[99] **(47)**, which is found to be in two main conformers[100], the formation of the bromonium ion **(46)** from 5*H*-dibenz[*b*,*f*]azepine-5-carbonyl chloride **(44)** is a reversible step. The formation of the bromonium ion **(46)** follows the association of reagents in the CT complex **(45)**. **49** reacts with hydrogen bromide through the protonated **48**, forming[99] both the dibromo derivative **47** and the olefin **44**. The bromonium ion **(46)** is the probable intermediate



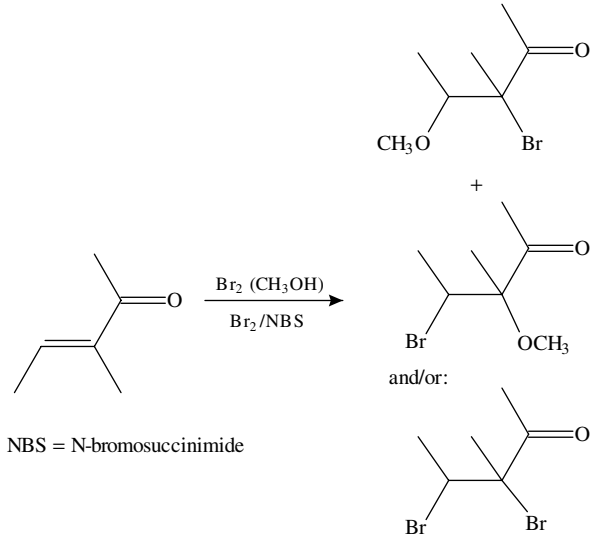
X = COCl

SCHEME 19

of these reactions. Clearly, **45** is formed in a reversible pathway from olefin **(44)** and bromine.

Usually, the attack of the nucleophile on the bromonium ion is a fast process. On the other hand, kinetic investigations[100] on the bromination shown in Scheme 19 indicate that bromonium ion formation (i.e. the ionization of the CT complex **45**) cannot be the RDS. The apparent activation energy for the overall bromination (and the experimental reaction order in bromine, which changes by changing the temperature) confirms the neutralization of the bromonium ion to form the product **(47)** in a step limiting the observed rate of the overall process.

The regiochemistry of the bromination (Scheme 20) of α,β-unsaturated ketones[101] (in methanol) by bromine is affected by the presence of *N*-bromosuccinimide, which also depresses the overall rate of bromination. A possible explanation of the observed behaviour is the presence of a complex **(50)** involving the C=C double bond of olefin, *N*-bromosuccinimide and bromine, as shown in Scheme 21. Probably, NBS acts as a hydrogen bromide scavenger, thereby causing a change in the bromination mechanism from an acid-catalysed pathway to a bromonium ion mechanism.

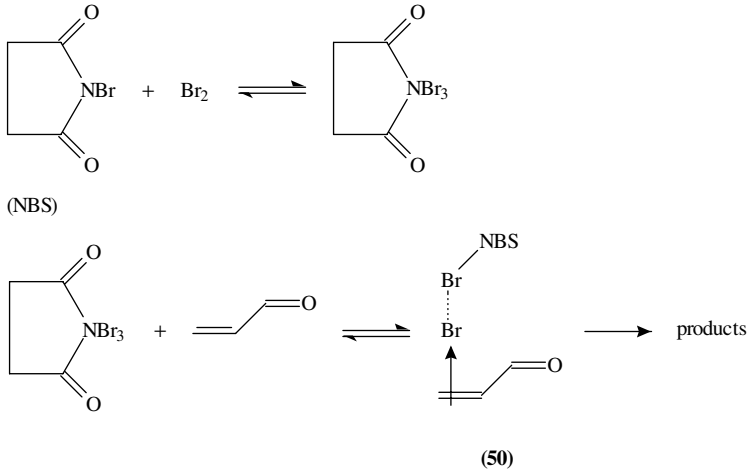


SCHEME 20

The rate of cyclohexene bromination, too (in carbon tetrachloride), is lowered by the presence of NBS (or of other hydrogen bromide scavengers)[74,102]; probably, the reaction is complicated by the presence of further complexes, such as the tribromide of the cyclohexene bromonium ion.

A mixture of ethene and molecular chlorine (in the gas phase), and of the isotopomers $C_2H_5 \rightarrow {}^{37}Cl_2$, $C_2H_5 \rightarrow {}^{35}Cl{}^{37}Cl$ and $C_2H_5 \rightarrow {}^{37}Cl{}^{35}Cl$, was investigated by rotational spectra obtained by a pulsed FT microwave spectrometer[103] (together with other complexes of molecular chlorine and HCN, PH_3)[104].

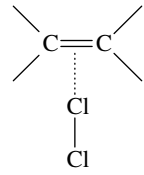
The observations strongly support the hypothesis that the addition of molecular chlorine to the C=C double bond follows the reactions shown in Scheme 10 (X = Cl). The formation of cation **27** (and/or **28**) is the RDS and the reaction, in dark and in fairly polar solvents, is of the second-order law, first order in both reagents.



(50)

SCHEME 21

The formation of **27** is preceded by a rapid equilibrium that forms complex **26** (of Scheme 10, X = Cl): there is evidence of the existence of a molecular complex between the halogen and the C=C double bond **(51)** by means of a weak interaction. The Cl_2 molecule lies along the C2 axis of ethene that is perpendicular to the molecular plane, as shown in **51**. The distance between the C=C bond and the inner chlorine atom is 3.128 Å.



(51)

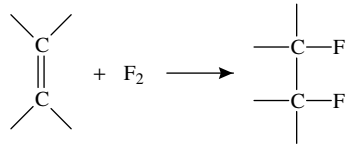
The geometry of the complex between ethene and molecular chlorine, and the strength of these complexes are subjects of discussion[105].

G. Interactions of Fluorine with C=C Double Bond

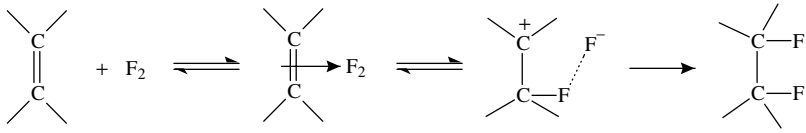
The number of reactions of addition of fluorine to the C=C double bond is not as large as that of addition of chlorine or bromine, and few examples of practical application of reactions of elemental fluorine are available. However, there is wide scope for development[106] of these reactions for preparative purposes.

The behaviour of elemental fluorine differs from that observed for chlorine or bromine, mainly because fluorine addition proceeds in a stereoselective *syn* manner (Scheme 22). The *syn* addition is explained by the formation of tight ion pairs forming the addition products or carbocation rearrangement products[107].

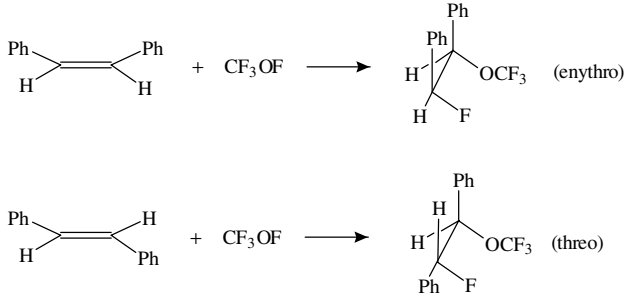
The ion-pair formation is preceded by an initial equilibrium, which quickly leads to a perpendicular π complex (Scheme 23). A similar reaction pathway is reported for the reactions of iodine (and bromine) monofluorides[107,108]. Also, the addition of fluoroxytrifluoromethane CF_3OF to both *cis*- and *trans*-stilbenes[109] enables a *syn* addition



SCHEME 22



SCHEME 23

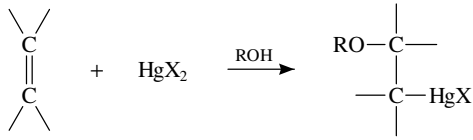


SCHEME 24

(see Scheme 24). This tendency to *cis* addition may be explained by the presence of a short-lived carbocation (because of the unfavourable electron-withdrawing effect of the fluorine atom). The carbocation prefers the addition of a nucleophilic counter part (in a tight ion pair) to rotation around the C−C bond.

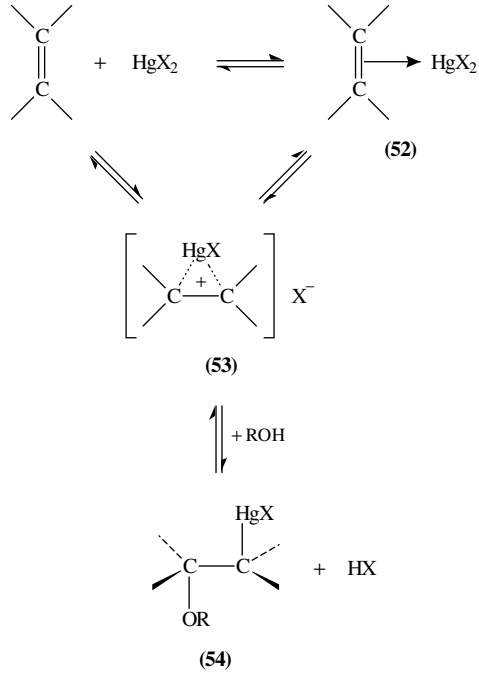
H. Oxymercuration of Alkenes

Oxymercuration of alkenes is an electrophilic reaction involving the addition of mercuric salt and of a protic solvent (alcohols) according to reaction 9. UV/VIS spectrophotometric investigation of the olefin/mercuric salt reaction mixtures in methylene chloride provides evidence of the presence of an electron donor–acceptor complex between olefin and mercuric salt[110] which is considered to be on the reaction pathway of the oxymercuration.



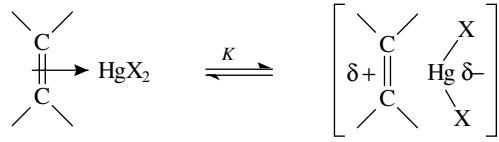
(9)

The usual mechanism of oxymercuration[111] is illustrated in Scheme 25. The presence of the mercuronium ion **(53)** was proposed by Winstein in 1939[112].



SCHEME 25

52 is the molecular complex which is in equilibrium with the starting reagents and with a CT complex **55** which is like that shown in equilibrium 10. The formation of **55** was studied by ^{199}Hg-NMR spectroscopy[111].



(10)

(52) **(55)**

It is clear that the mechanism in Scheme 25 parallels (at least from the qualitative point of view) the mechanism of the addition of bromine to olefins shown in Scheme 11. Kinetic investigations indicate that the oxymercuration reaction involves a series of fast equilibria until the mercuronium ion **(53)** is formed. The subsequent nucleophilic attack of the solvent is probably the rate-limiting step, as indicated by steric requirements in bulky alkenes[111]. In the bromine addition, the formation of the bromonium ion is the rate-limiting step (or the rate-limiting equilibrium). However, the olefin reactivities in both reactions (bromination and oxymercuration) are identical when steric effects in the TS of the two addition reactions are taken into account[110].

I. Electrophilic Addition to Olefins: A Tentative Parallel with Other Reactions

In chemistry there is a tendency to label reactions in well ordered 'pigeon holes' with occasional interconnections. This is not surprising because often researchers in

various fields are anxious to obtain 'taxonomical' classifications. Consequently, attention is focused more on a single reaction or on some peculiarities of a reaction than on general principles. In addition, often the differences between reacting systems are emphasized, while the analogies are by-passed.

Probably, the electrophilic addition to olefins and the electrophilic aromatic substitution are more similar than is generally thought. Nevertheless, the two reactions are described in textbooks in separate chapters with the implicit idea that they are completely different reactions. Mechanistic investigations reveal that some steps show parallel behaviour in both reactions. In particular, the initial steps are similar for both reactions.

Many quantitative results regarding bromination of olefins and of aromatic substrates allow interesting comparisons to be made between the two reactions.

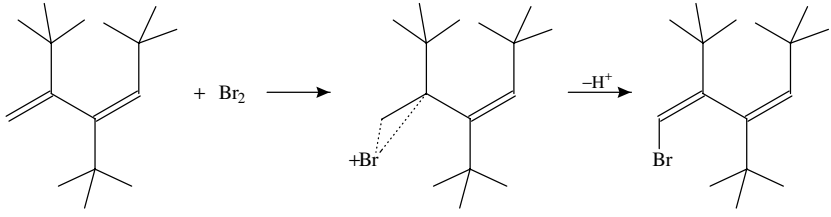
Strong differences in the reactivity of the aromatic C=C double bond compared to the reactivity of the C=C double bond of olefins are observed: olefinic electrophilic additions are faster than aromatic electrophilic substitutions. For instance, the addition of molecular bromine to cyclohexene (in acetic acid) is about 10^{14} times faster than the formation of bromobenzene from benzene and bromine in acetic acid[113,114]. Nevertheless, the addition of halogens to olefins parallels the Wheland intermediate formation in the halogenation of aromatic substrates.

The differentiation of the two kinds of reaction takes place in the step eliminating the positive charge from **27** and **28** in Scheme 10. This may occur by two main pathways:

(i) by neutralization of the positive charge by a nucleophile (which may be the counter ion of the electrophilic reagent or the solvent);

(ii) by elimination of positive charge with the removal of a proton, as usually observed in electrophilic aromatic substitution and in monomolecular elimination reactions of alkyl halides.

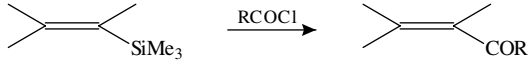
In the case of particular olefins[115], such as 1,2,3-tri-*t*-butylbutadiene **(56)**, which is strongly sterically hindered, the usual dihalogenated products cannot be obtained. Instead of the addition process, the elimination of the positive charge by a proton removal takes place[73], as Scheme 26 illustrates. This reaction can be classified as an electrophilic substitution of the olefins.



(56)

SCHEME 26

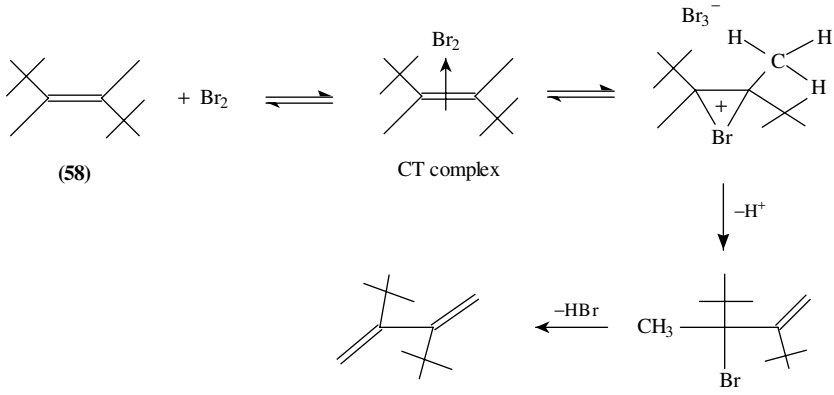
Electrophilic substitution reactions to olefins have been recorded on vinyl silanes[116] **(57)**. Scheme 27 reports the electrophilic substitution of the $SiMe_3$ group by acyl halides. Probably, this reaction too occurs via a complex between the electrophilic part of the reagent and the π system of the olefin, but other mechanisms are possible.



(57)

SCHEME 27

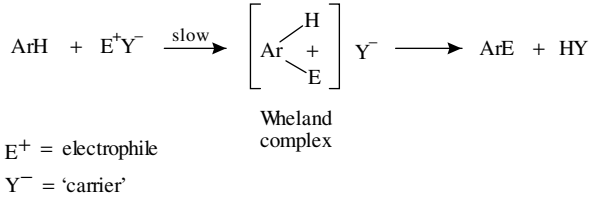
Elimination of the positive charge after the electrophilic attack on the olefin by proton removal is observed also in Scheme 28 between (*E*)-2,2,3,4,5,5-hexamethylhex-3-ene **(58)** and bromine. The CT complex shown in Scheme 28 probably turns into a second complex (with the ratio 1:2 of **58** and bromine) which ionizes to a bromonium/tribromide ion pair.



SCHEME 28

The theory that electrophilic aromatic substitution proceeds via a CT complex has been proposed for a long time in the literature[117,118]. In a recent paper, Kochi examines the relevance of the presence of a CT complex in electrophilic aromatic nitration[119].

The generally accepted mechanism of the electrophilic aromatic substitutions[120,121] involves the direct formation of the σ-complex (the Wheland intermediate) in the RDS (Scheme 29). The reversibility of the formation of the Wheland intermediate is under investigation. Many cases of reversibility of the steps shown in Scheme 29 have long been noted.

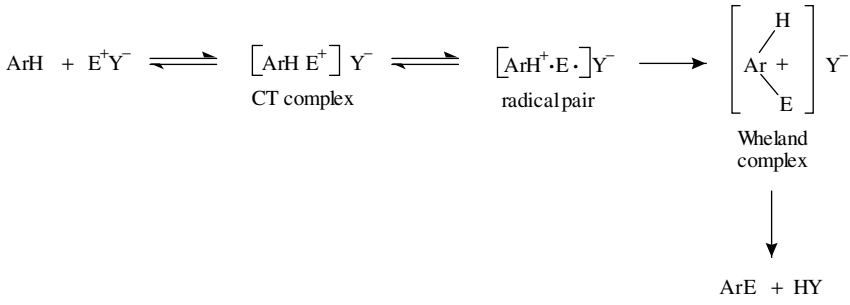


SCHEME 29

As an alternative to the classical mechanism shown in Scheme 29, a multi-step mechanism involving an electron donor–acceptor complex and a radical pair is shown in Scheme 30[122]. The distinction between the two mechanisms is difficult to make[122–125]. They can compete in forming the reaction products: the idea that only one reaction pathway is operating, is an oversimplification. However, two relevant points cannot be disregarded:

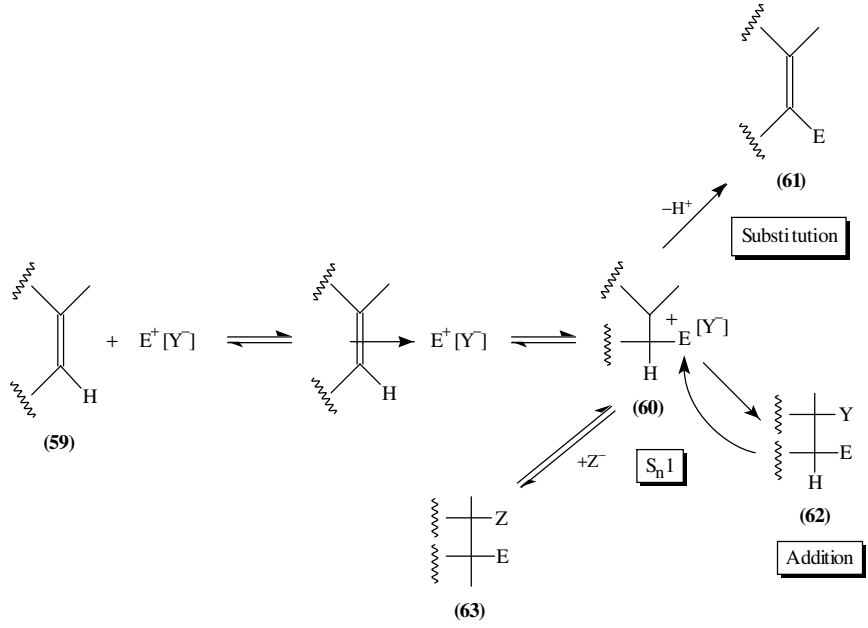
(i) In both reaction pathways, the formation of the substitution products arises from the σ-complex.

(ii) In the reaction mixtures, the presence of donor–acceptor complexes is strongly borne out by spectroscopic evidence. Probably, these complexes are on the reaction pathways of the reactions under consideration.



SCHEME 30

Scheme 31 is a tentative collection of some reactions into a single picture with the purpose of emphasizing the common 'segments' of the reactions. Obviously, Scheme 31 includes some simplifications and assumptions (for instance, the nature of **60** may be questioned), and it may concern cyclic and non-cyclic as well as aromatic substrates.



SCHEME 31

The main reaction pathways indicated in Scheme 31 may be labelled as follows:
59 → **62** (or **63**): electrophilic addition to olefins.
59 → **61**: aromatic electrophilic substitution.
63 (or **62**) → **59** (or **61**): monomolecular elimination.
63 → **62** (and *vice-versa*): monomolecular nucleophilic substitution.
Y^- is the counter ion of the electrophilic reagent or of other nucleophiles present in the reaction mixtures, including neutral solvents.

E is the electrophilic part of the halogen molecule. In the case of the simple addition of halogens, E = Y = F, Cl, Br, I.

Y^- may also be the leaving group in the monomolecular formation of substituted carbocations **(60)**, to yield the saturated derivative **63** (and **63** may equal **62**, if Z = Y), as usually indicated in S_N1 reactions. If Z = E = Br, in the dibromo derivative **63**, the cation **60** has the same form as that obtained by the bromination of olefins.

When Y = halogen (and E = H), **62** (and **63**) are changed into olefin (**61** or **59**) by a monomolecular elimination reaction.

In aromatic electrophilic substitutions, **60** corresponds to the Wheland complex.

Scheme 32 is a simplification of the Scheme 31.

$$\text{NUCLEOPHILE} + \text{ELECTROPHILE} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{INTERMEDIATE}] \xrightarrow{k_x} \text{PRODUCTS}$$

SCHEME 32

The INTERMEDIATE may be obtained by a single equilibrium or by several subsequent equilibria, preceding the formation of the σ bond, such as that reported in equilibrium 11:

$$\text{ELECTROPHILE} + \text{NUCLEOPHILE} \overset{K}{\rightleftharpoons} \text{MOLECULAR COMPLEX} \qquad (11)$$

The MOLECULAR COMPLEX may include all non-covalent interactions (donor–acceptor, hydrogen bonding, ...).

Scheme 32 is the one usually accepted for aromatic nucleophilic substitutions, as expected by considering the obvious idea that an electrophilic attack implies a simultaneous nucleophilic attack (and *vice-versa*). The conventional distinction between the reagent and the substrate is often related to the concentration ratio: the reagent is the one used in excess, while the substrate is the molecule which becomes modified.

In the reactions reported here the olefin is the nucleophile[126]. One obstacle to changing the conventional classification of reactions to a more appropriate and general expression arises also from the fact that usually the electrophilic reagent is a labile particle, often generated *in situ* and rarely in a known concentration.

By following an apparently correct assumption, as shown in Scheme 31, if the carbocation is formed in a RDS, all factors stabilizing **60** (solvent assistance, desolvating phenomena, delocalization of positive charge etc.) are factors enhancing the reaction rates of all pathways affording **60**. On the other hand, the formation of **60** cannot be considered a simple RDS.

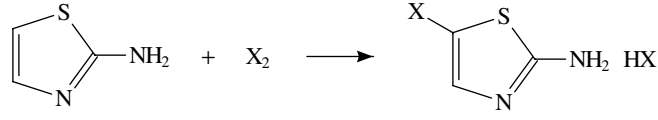
The generalization of Scheme 32 is valid when the products are obtained in a fast step (k_x) from an intermediate obtained in a rate-limiting equilibrium (k_1/k_{-1}) (or in a series of equilibria). The fact that the intermediate cannot be obtained by irreversible reaction implies that the simple idea of the rate-limiting step[127,128] cannot be used[129]: k_1/k_{-1} is an equilibrium limiting the overall rate and the relative rates must be considered; k_1 may be faster than k_x, but if $k_{-1} \gg k_1$ the ratio k_1/k_{-1} is the factor which affects the overall reaction. The idea of the rate-limiting step becomes relatively insignificant when k_{-1} and k_1 are of the same order of magnitude, and that is a frequent situation.

However, the formation of molecular complexes between nucleophile and electrophile (with a possible participation of solvents) in both electrophilic aromatic substitutions and nucleophilic aromatic substitutions is clearly expected, as shown by the conventional use of the terms 'electrophile' and 'nucleophile': these reactions belong to apparently different fields of organic chemistry, but the unification of the two kinds of reaction is mainly a matter of terminology and of details.

Actually, the collision between a discharged centre and a charged centre is the crucial event, whether in S_NAr reactions or in electrophilic aromatic substitution reactions.

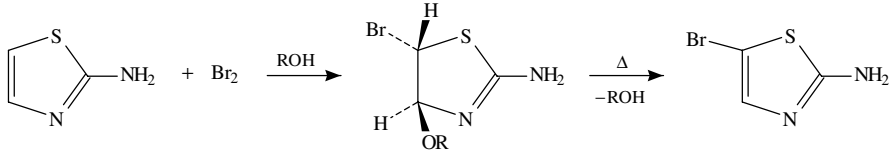
It is of interest to observe that the kinetic behaviour (and the effect of changes of temperature on the rate of reactions) of brominations of olefins and of electrophilic aromatic brominations confirms the presence of pre-associative processes[77,130,131] on the reaction pathway, as well as that observed for some nucleophilic aromatic substitutions[132].

An instance of an apparent electrophilic aromatic substitution (in this case **61** is an aromatic substrate, of Scheme 31), which actually is an electrophilic addition, is the halogenation of 2-aminothiazole derivatives which was usually considered a simple attack of the electrophilic reagent on the heterocyclic 'aromatic' substrate activated by the amino group; see reaction 12. When the bromination of 2-aminothiazole derivatives is carried out in nucleophilic solvents (ROH) and at low temperatures, the partially saturated derivatives **(64)** of Scheme 33 were isolated in 80–95% yields[133]. By heating **64**, the usual halogenated 2-aminothiazoles are obtained, as indicated by Scheme 33. An apparent electrophilic aromatic substitution is actually an addition reaction to the C=C double bond; the elimination reaction is the following, separate step.



(12)

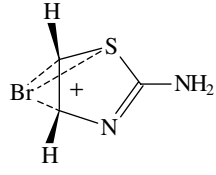
X = Cl, Br



(64)

SCHEME 33

The fact that the partially saturated derivative **(64)** is obtained only in the *trans* form (these reactions are regio- and sterespecific) indicates that the bromonium ion, **65**, which is similar to that usually reported for halogenations of olefins, precedes the saturation of the C=C double bond.



(65)

In the 1,3-thiazole system, the presence of sulphur is a factor stabilizing the bromonium ion, which may be obtained from a donor–acceptor complex.

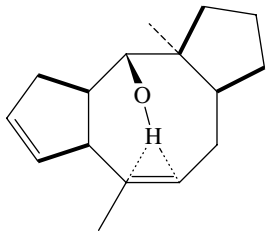
J. Hydrogen Bonding Involving the π System of C=C Double Bond

It is known that π bonds C=C of unsaturated compounds may act not only as electron donors toward metals, but also as proton acceptors for hydrogen bonding[134].

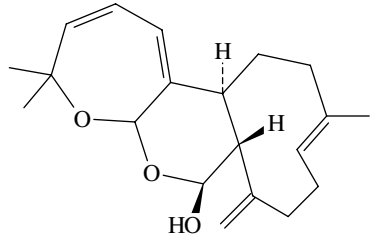
Intramolecular and intermolecular interactions between C−H groups and the π system[135] of carbon double bonds of olefins and of aromatic rings are of interest in the fields of molecular recognition and inclusion complexes in both organic chemistry and biochemistry.

IR and ^{1}H-NMR investigations (as well as non-empirical and empirical calculations of interaction energies[136]) of π facial interactions between hydroxy groups and C=C double bonds of olefins[137,138] emphasize the importance of these interactions in explaining physical and chemical properties of molecules bearing double bonds and acid protons, mainly of O−H and N−H groups.

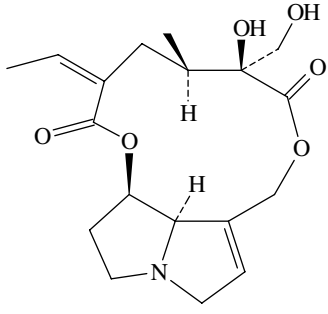
Recent research on the Cambridge structural data base shows[139] 11 alkenes (and 2 alkynes) which are involved in interactions with the −OH group, with distance H···C of olefin <2.4 Å. **66** is an instance of intramolecular hydrogen bonding interactions[140]. Intermolecular hydrogen bonds can be observed in **67**[141] and **68**[142].



(66)



(67)

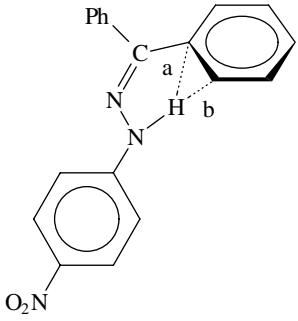


(68)

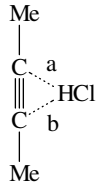
Even if hydrogen bonding with C=C double bonds can be hardly ascribed to a single carbon atom (or to π electrons of the double bond), re-investigation of the structural data would be worthwhile because these hydrogen bonds were unrecognized in the original reports on the investigated structures.

The presence of H···π bonding can relate to apparently anomalous reactivities. These interactions are of importance in chiral recognition and in other intermolecular and intramolecular interactions[143].

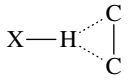
Weak hydrogen-bonding interactions (the bond energy is in the range 1–2.2 kcal mol^{-1}) between terminal alkynes and other alkynes or phenyl rings in the solid state were reported[144]. Hydrogen bonding with the π system of a phenyl ring is revealed also by X-ray diffraction of benzophenone (4-nitro-phenyl)hydrazone: an N—H···π interaction with the C=C bond of a phenyl ring[145] is illustrated in **69**, where **a** is 2.43 Å and **b** is 2.26 Å.



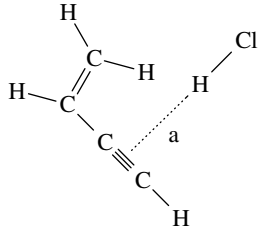
(69)



(70)



(71)



(72)

An on-face hydrogen bonding interaction between a hydroxy group of threonine and the π-cloud of the aromatic ring of the tyrosine of isoenzyme 3-3 of glutathione *S*-transpherase was observed[146]. This interaction appears to act as a substituent bonded to a phenyl ring. In the solid state the H···π distance between HCl proton and the two sp carbon atoms of 2-butyne (co-crystallized, **70**) is 2.41 and 2.37 Å[147].

For intermolecular X—H···C (in **71**) hydrogen amine bonds (X = N) and of hydroxy groups (X = O), the mean obtained from data base analysis is 2.82 and 2.77 Å, respectively, for the C≡C bonds of olefins, and 2.61 and 2.69 Å, respectively, for the C=C triple bonds of alkynes. For the phenyl ring 2.47 and 2.43 Å (X = N and X = O, respectively) are calculated[148].

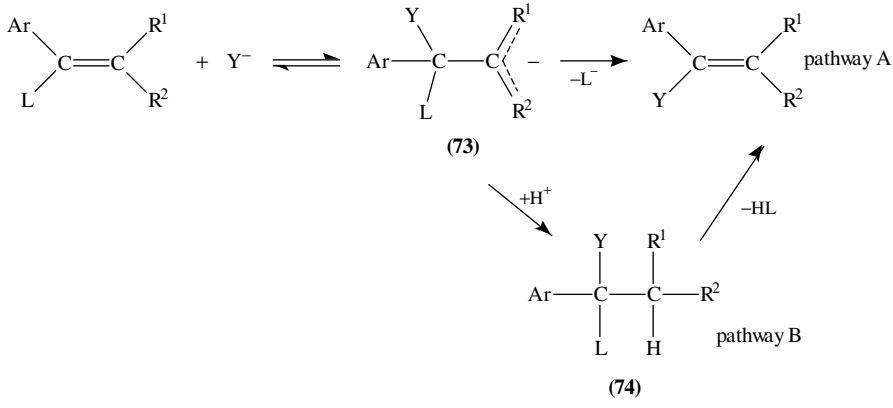
The rotational spectrum of a hydrogen-bonded dimer formed by vinylacetylene and HCl has been recorded by the pulsed-nozzle FT microwave technique[149]. The structure of the complex **72** confirms the geometry of the van der Waals complexes predicted on the basis of simple electrostatic models[150]. The distance between the HCl proton and the centre of the triple bond (**a** in **72**) is 3.629 Å; the same distance with an isolated triple bond is 3.699 Å and with the double bond is 3.724 Å[150].

III. OLEFINS. COVALENT COMPLEXES WITH NUCLEOPHILES

Olefins are usually recorded as being unreactive toward nucleophilic reagents, unless electron-withdrawing groups are bonded to the carbon atoms adjacent to the carbon bearing the activating groups of C=C double bonds[151]. In fact, vinyl halides parallel the behaviour of aryl halides toward nucleophiles.

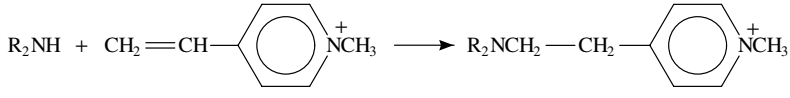
The attack of nucleophiles on activated C=C double bonds is an exciting field of research because the usual reactions of the C=C double bonds are reactions with electrophilic reagents[152,153]. Nitroalkenes react with nucleophiles by addition or substitution reactions that form interesting compounds for synthetic purposes: the nitro group is a versatile precursor for several groups[154].

The usual substitution pathway for activated olefins is illustrated by Scheme 34 regarding anionic nucleophiles. In **73**, R^1 and R^2 are electron-attracting groups; L is the leaving group (usually a halogen atom) and Y^- is the charged nucleophile (in particular, alkoxides and thioalkoxides).



SCHEME 34

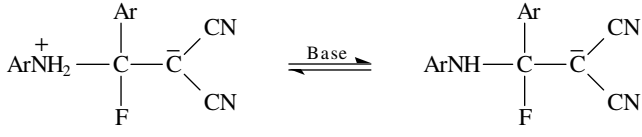
Scheme 34 shows a two-step mechanism (pathway A), similar to the general addition/elimination mechanism of nucleophilic aromatic substitution reactions[155]. Pathway B of Scheme 34 shows the addition–elimination mechanism. When nucleofuge expulsion is difficult (or the leaving group is absent) the saturated derivative **74** of Scheme 34 is the final product. Addition of amines to 1-methyl-4-vinylpyridinium cation **(75)** of reaction 13 is an instance of saturation of a C=C double bond by a nucleophilic attack[156]. R_2NH of reaction 13 may be a primary or a secondary amine.



(13)

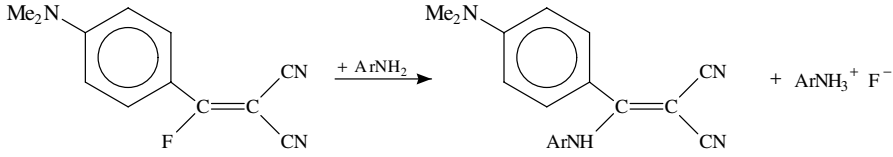
(75)

The reactions between 1,1-dicyano-2-*p*-dimethylaminophenyl-2-fluoroethylene **(76)** and *p*-toluidine or phenylenediamines in acetonitrile[157] form the substitution products **(77)** as shown in Scheme 35. The reaction is of the second order in amine when $ArNH_2$ is *p*-toluidine and it is catalysed by substituted pyridines (and quinolines) in accordance with the presence on the reaction pathway of the zwitterionic complex **78**, which is in equilibrium (see equation 14) with the anionic form **79**.



(14)

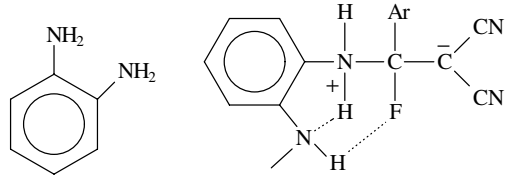
(78) **(79)**



(76) **(77)**

SCHEME 35

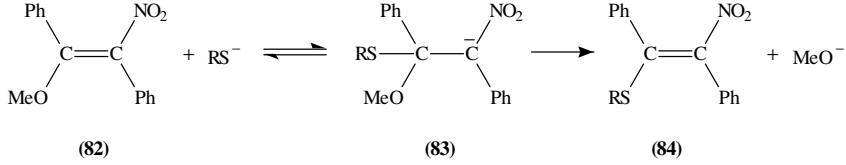
When $ArNH_2$ is *o*-phenylenediamine **(80)**, the reaction is poorly catalysed by the second amino group, but it is mainly catalysed by an external molecule of amine. As a consequence, internal catalysis by an intramolecular complex such as **81** is unlikely. In competition with the substitution (Scheme 34), when the nucleophile (or a base) attacks a hydrogen atom in a β position with respect to the leaving group, an elimination reaction takes place.



(80) **(81)**

Investigations[158] of the stereochemistry of vinylic substitutions on nitroolefins revealed that the lifetime of the carbanion **(73)** of Scheme 34 is sufficiently long to enable rotation around the C=C bond faster than the leaving-group departure[156].

The reactions of β-methoxy-α-nitrostilbene **(82)** with anionic sulphurated nucleophiles[159] showed UV/VIS spectroscopic evidence for the presence of the intermediate **83** in the formation of the substitution product **(84)** illustrated in Scheme 36.



(82) **(83)** **(84)**

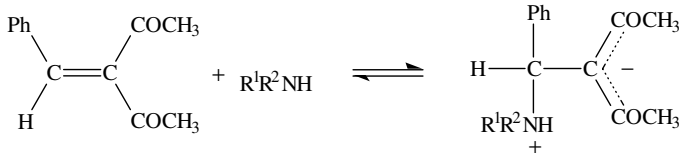
R = C_2H_5; $HOCH_2CH_2$; $MeO_2CCH_2CH_2$; MeO_2CCH_2

SCHEME 36

Piperidine and morpholine react[160] with benzylideneacetylacetone **85** to form a mixture of zwitterionic and anionic adducts (**86** and **87**, respectively) which forms benzaldehyde, acetylacetone and starting amine, as shown in Scheme 37. This has been confirmed by kinetic investigations in DMSO/water (50%).

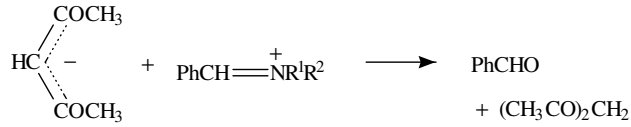
The formations of **86** and **87** parallel the formation of zwitterionic complexes in reactions of amines with nitro-activated aromatic substrates[161].

The substituted benzylidenemalonodialdehydes **(89)** are organic Lewis acids and they react with feeble nucleophiles (ethanol, water) affording[162] the equilibrium mixture of



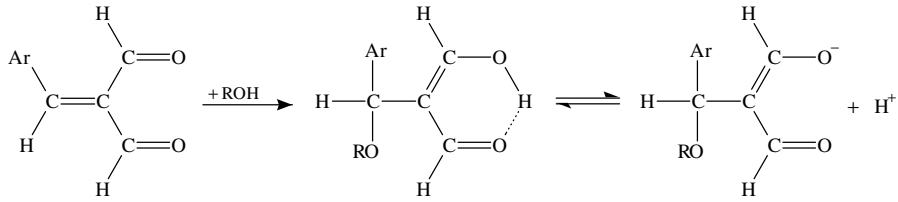
(85) **(86)**

(88) **(87)**



R^1R^2 NH = piperidine, morpholine

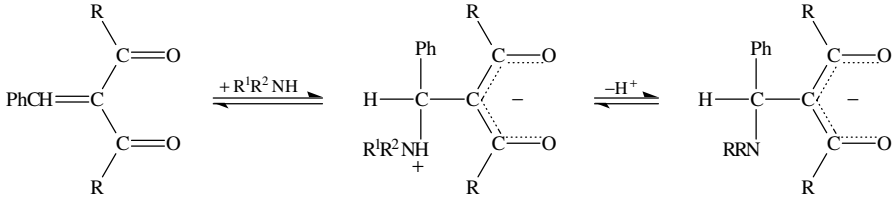
SCHEME 37



(89) **(90)** **(91)**

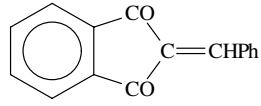
R = H, Et.

SCHEME 38



(93) **(94)**

SCHEME 39



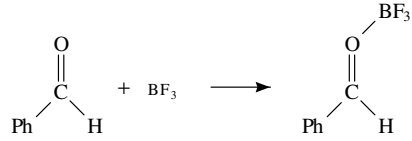
(92)

90 and **91** (Scheme 38). **90** and related dialdehydes[163], as well as vinylic β-diketones[164], such as benzylidene-1,3-indandione **(92)**, react with amines (piperidine, morpholine, *n*-butylamine, 2-methoxyethylamine, glycinamide, cyanomethylamine), forming a mixture of adducts (**93** and **94**) of Scheme 39. Kinetic investigations reveal that the rate of the amine attack on **92** is higher than rate of amine reaction in Scheme 39, when R = Et, *i*-propyl, Ph, and quite comparable to the same reaction of benzylidenemalonodialdehyde **89**. For these substrates the rate is similar to that reported for **85**. High reactivity of **92** is attributed to stabilization through resonance of the adduct of the cyclic structure. The poor reactivity of other substrates is attributed to steric strain in the adducts.

IV. CARBONYL GROUP. ELECTRON DONOR–ACCEPTOR COMPLEXES

Formation of complexes on carbonyl compounds is of fundamental importance in many catalytic processes in organic chemistry. In particular, Lewis acids strongly activate the carbonyl group towards several condensations[165] (including Diels-Alder reactions[166]) and photochemical reactions[167]. Photodimerizations (in solid state and in solution) and cross-cycloadditions of cinnamic esters have been investigated[168] to study the effect of complexation with Lewis acids.

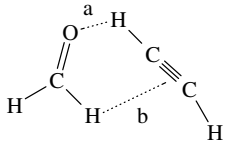
The structure of the complex **(96)** between benzaldehyde **(95)** and boron trifluoride (equation 15) was investigated by X-ray crystallography[169]. In **96**, BF_3 is in the *anti* position to the phenyl ring and this geometry remains also in solutions, as tested by the ^{19}F-NMR spectrum in CD_2Cl_2. An *ab-initio* study[170] on interactions between formaldehyde and boron trihalides showed that these complexes (mainly donor–acceptor complexes) affect spectroscopic properties and the reactivity of the carbonyl group: the polarization of the C=O bond favours the attack of nucleophiles.



(15)

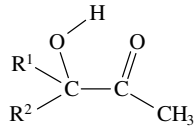
(95) **(96)**

The acid catalysis (by protons) of carbonyl reactivity has been well known for a long time[171] and the hydrogen bonding interactions, both intermolecular and intramolecular, are of interest also in explaining the chemical behaviour of carbonyl compounds. Investigation (by pulsed-nozzle FT microwave spectroscopy) of interactions between formaldehyde and acetylene[172] (and five isotopomers) shows two main interactions, as illustrated in **97** involving a hydrogen bond between the oxygen of the carbonyl group and an acetylene proton, and another hydrogen bond between the π acetylene system and a formaldehyde proton.



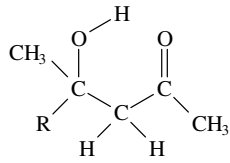
a = 2.39 Å
b = 3.66 Å

(97)



$R^1 = R^2 = CH_3$
R^1 = H, $R^2 = CH_3$

(98)



R = CH_3, H.

(99)

Intramolecular hydrogen bonding is important for determining the conformation of flexible molecules. A great variety of molecules, including simple models and complicated biological systems, were considered when investigating their geometrical properties in the solid state[8], and also in solutions: the feeble internal interactions may be easily modified by weak interaction with solvents.

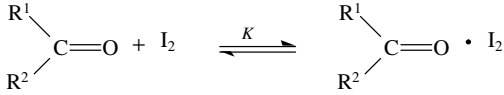
The effects of temperature and pressure[173] (investigated by FT-IR spectroscopy), show that α-hydroxy ketones exhibit stronger internal hydrogen-bonding interactions than β-hydroxy ketones because of their configuration[174]. Five-membered chelate rings **98** are more planar than six-membered chelated rings **99**.

Photoreduction of ketones can occur by direct proton transfer or after the formation of a CT complex. Tertiary amines (triethylamine[175] and 1,4-diazabicyclo[2,2,2]octane[176]) were used as donors; see Scheme 40.

The CT complexes are considered to evolve to excited CT complexes. In Scheme 40, an electron is transferred from the amine to the benzophenone (in the triplet state) forming the CT complex. A proton transfer produces an amine radical **100** and a benzhydrol radical **101**.

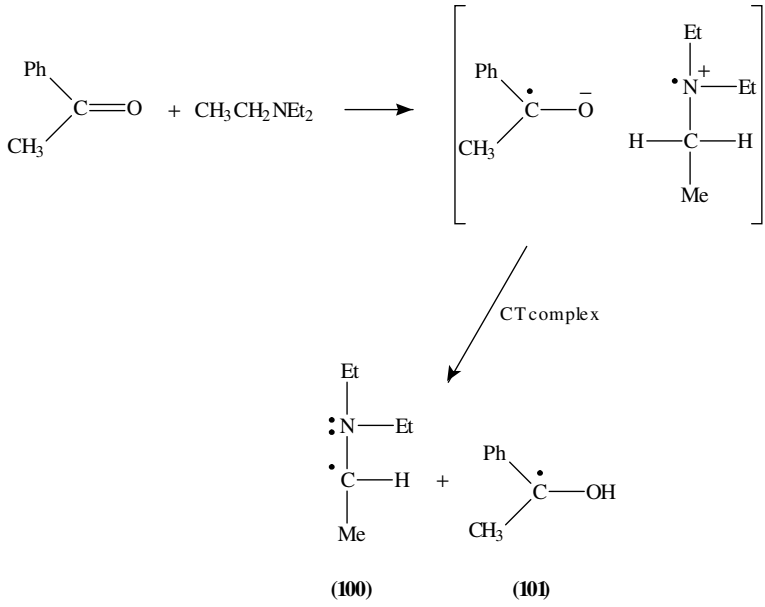
An instance of photoreduction of ketones by complexation with alkylbenzenes[177,178] (as electron donors) is shown in Scheme 41. Products shown in Scheme 41 have been formed by radical coupling reactions. The investigations (using a combination of flash kinetics, steady-state quenching and quantum yield measurements) of the substituents and isotope (H/D) effect indicate that ketones react predominantly through CT complexes.

CT complexes between carbonyl groups and iodine (equilibrium 16) have been well known for a long time[179], as well as complexes with bromine[180].

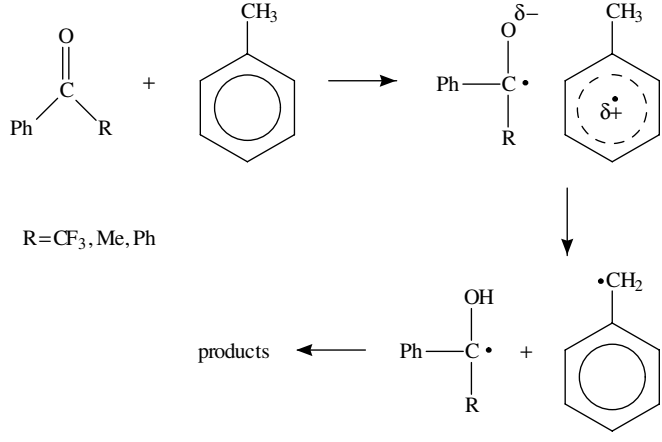


(16)

Comparison of K values[181,182] (obtained by the spectrophotometric method) allows evaluation of the electronic and steric effect of substituents R^1 and R^2 of equilibrium 16, for various carbonyl derivatives (ketones, aldehydes and derivatives of carboxylic acids).



SCHEME 40

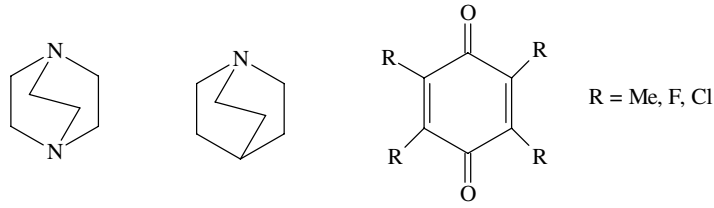


SCHEME 41

Molecular complexes of substituted quinones are electron-acceptor molecules and their reactions with donor molecules have been extensively studied[15].

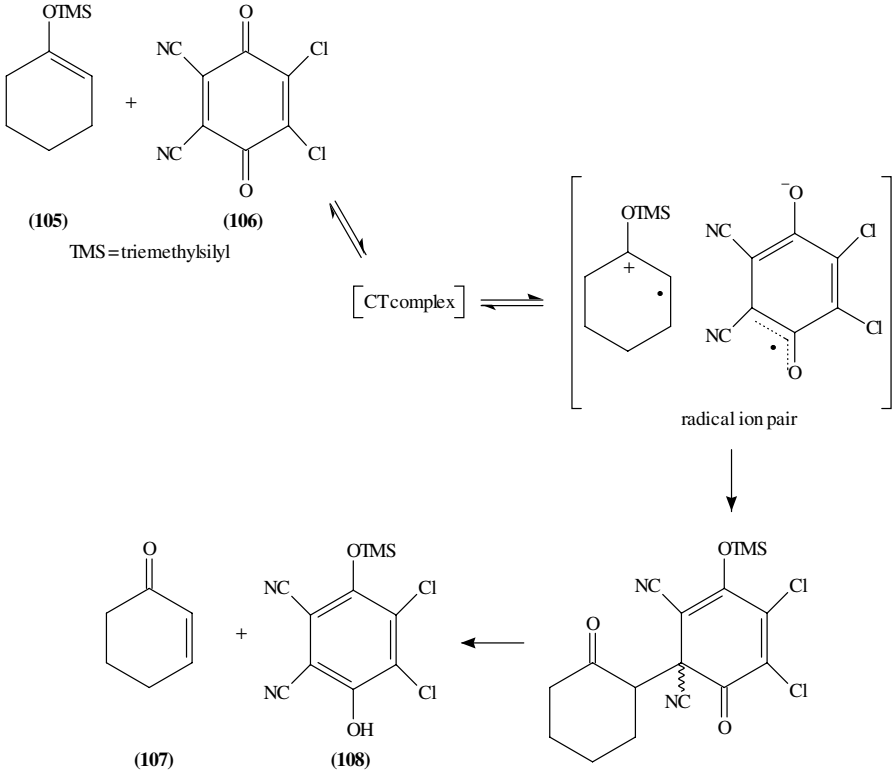
Some bridgehead amines [1,4-diazabicyclo-[2,2,2]octane **(102)**, quinuclidine **(103)** and quinuclidine-3-ol] form 1:1 molecular complexes with quinones **104**. Formation of 2:1 (amine/quinone) complexes was observed in solutions of DABCO **(102)** and chloranil (**104**, R = Cl). These tertiary amines are able to form complexes, while non-bridgehead amines (triethylamine, piperidine) cannot because of steric hindrance or nitrogen inversion[183]. Stable complexes may be predicted (by CNDO/2 calculations) for

the approach of the amine lone pair perpendicular to the quinone plane at four middle points of the bond between the C=O group and C in α position to the carbonyl group.



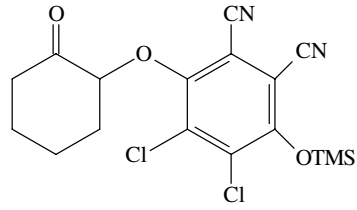
(102) **(103)** **(104)**

The oxidation of silyl enol ethers[184] **(105)** to enone **(107)** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone **(106)** is illustrated in Scheme 42. The electron donor–acceptor complex (red, $\lambda_{max} = 520$ nm) precedes the formation of the adduct **109**, which is unreactive, and **108**, which is the intermediate of the reaction. At 22 °C, the reaction mixture affords a mixture of **108** and of **109**. At 100 °C, **108** is transformed into the final enone **107**.



SCHEME 42

The mechanism of Scheme 42 is an alternative pathway to the hydride abstraction pathway of oxidation of trialkylsilyl enol ethers[185]. The silyl derivatives of 4-aza-3-ketosteroids



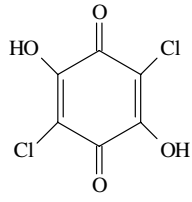
(109)

are oxidized by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone **(106)** via a CT complex and a substrate adduct[186].

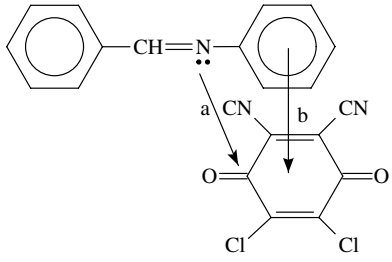
V. IMINO GROUP. ELECTRON DONOR–ACCEPTOR COMPLEXES

While the role of many donor molecules in forming molecular complexes, in particular CT complexes[15], has been often investigated, less attention has been paid to donor molecules bearing the imino group (Schiff bases).

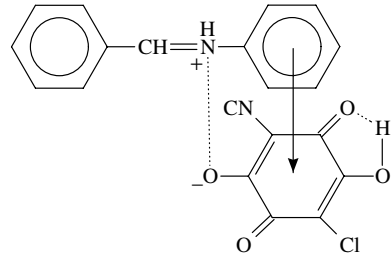
Substituted benzylideneanilines form molecular complexes[187] with **106** and with 2,5-dichloro-3,6-dihydroxy-*p*-benzoquinone **(110)** (chloranilic acid). These complexes were investigated by IR and ^{1}H NMR. The complexes between benzylideneanilines and **106** are CT complexes **(111)**, while complexes with **110** are formed through electron and proton transfer[187], as illustrated in **112**. In **111**, 'a' refers to n $\rightarrow \pi^*$ interaction and 'b' is a $\pi \rightarrow \pi^*$ interaction. sp^2 N-atoms of some heterocyclic imines (such as 2,2′-bipyridyl, 1,10-phenantroline) are also n-donors towards acceptors (tetracyanoethylene, *p*-benzoquinone, chloranil)[188].



(110)



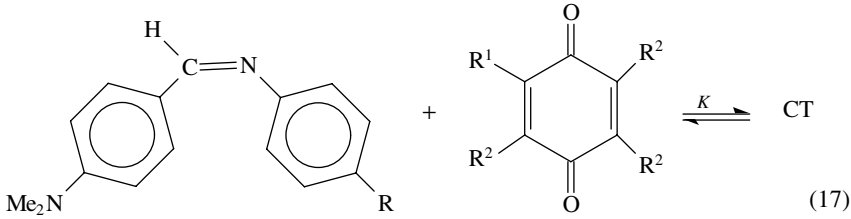
(111)



(112)

Substituted imines **113** form CT complexes with substituted *p*-benzoquinones **114**[189] that show appreciable stability in the absence of oxygen (equilibrium 17). In some cases

K values are obtained by the Benesi–Hildebrand method[15], and they are in the range from 0.8 to 2.5 $dm^3\,mol^{-1}$. Electron-donating groups (R) in **113** enhance the K value according to the electron-donor character of **113**.



(17)

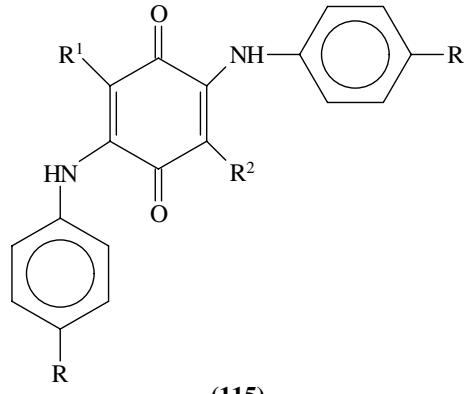
(113)

R = H, Me, Br, Cl, OMe, NO.

(114)

$R^1 = R^2 = Br$,
$R^1 = R^2 = Cl$,
$R^1 = Cl$, $R^2 = CN$.

The complexation of imines **113** favours their hydrolysis, with the formation of substituted anilines which form the products[189] **115** of the substitution of *p*-benzoquinone **114**.



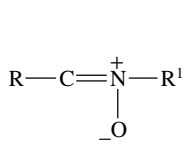
(115)

Donor–acceptor complexes are formed (by π–π interaction) between arylhydrazones and trinitrofluorenes[190], chloranil and tetracyanoethylene[191]. ESR investigation of donor–acceptor mixtures in DMSO and in acetonitrile reveals the presence of a small degree of charge transfer.

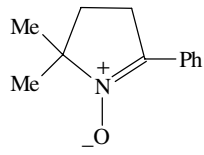
Nitrones (**116** and **117**) form CT complexes[192] with π acceptors (tetracyanoethylene, *p*-benzoquinones). In these 1:1 complexes the stability is moderate; the stability constants were obtained using UV/VIS and they are in the range 0.03–0.15 $dm^3\,mol^{-1}$. The presence of two phenyl groups in **116** enhances the stability of the complexes.

The C=N group of imines may react with nucleophiles at the carbon atom, or they may react at the nitrogen atom with electrophiles, including protons, as illustrated in **118**.

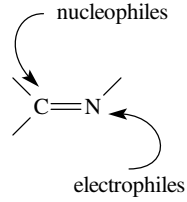
In principle, the sp^2 nitrogen atom of the C=N double bond of N-substituted imines (or of imidines) is a better nucleophile (and a better base[193]) than the sp^3 nitrogen atom



(116)



(117)



(118)

R = R^1 = Me

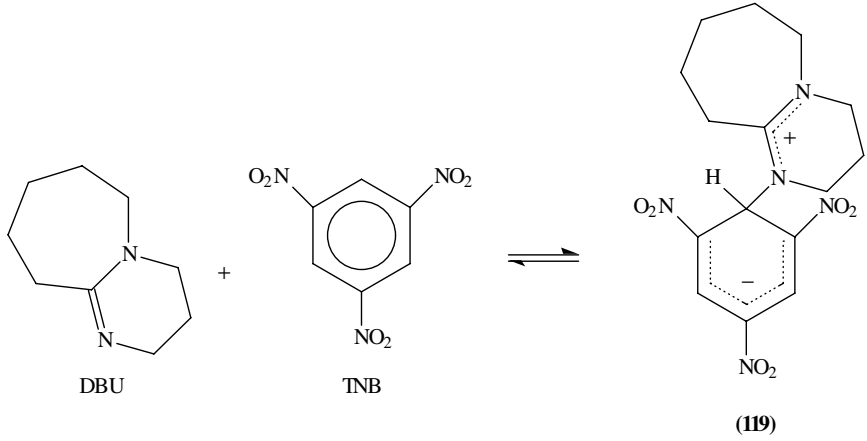
R = Ph, R^1 = Me

R = Ph, R^1 = CMe_3

R = R^1 = Ph

of tertiary amines. A possible explanation is that the steric hindrance in tertiary amines depresses the nucleophilic power of the nitrogen[194].

If the $H_2N-C=NH$ system is considered as a bident nucleophile, internal conjugation strongly increases the nucleophilic ability of the C=NH nitrogen and depresses the nucleophilic ability of the NH_2 group[195].



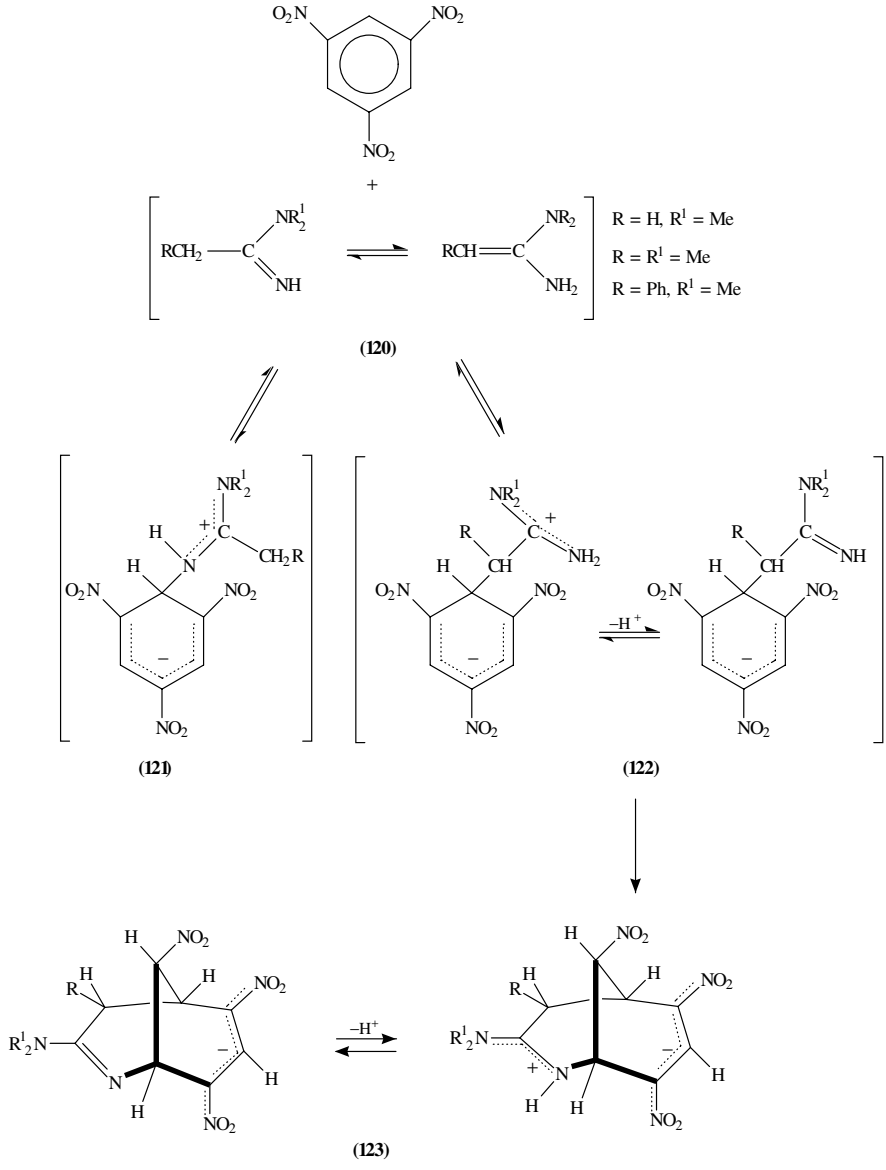
(119)

SCHEME 43

1,8-Diazabicyclo[5,4,0]undec-7-ene (DBU) reacts with 1,3,5-trinitrobenzene (TNB) to yield a zwitterionic complex **(119)**[196] as shown by Scheme 43. The delocalization of the positive charge, as well as the delocalization of the negative charge, are factors stabilizing the zwitterionic complex **(119)**. The presence of another sp^3 nitrogen atom conjugated with the C=N double bond of amidines favours (by an electronic effect) the nucleophilic power of the sp^2 nitrogen. In strongly associating solvents (toluene) the formation of the σ-complex **(119)** is preceded by a quickly established equilibrium that forms a molecular complex between DBU and TNB, as shown in equilibrium 18, where the interaction is mainly a donor–acceptor interaction[197]. The K value decreases as the temperature increases [K = 7.3, 4.9 and 3.1 (mol^{-1} dm^3) at 25, 35 and 45 °C, respectively] as required by an associative process[197]. The presence of the molecular complex on the reaction

pathway of the formation of the complex **119** (and of nucleophilic aromatic substitution reactions in poorly polar solvents when amines are used as nucleophiles) explains the negative dependence of observed rates of substitution reactions on the temperature[197].

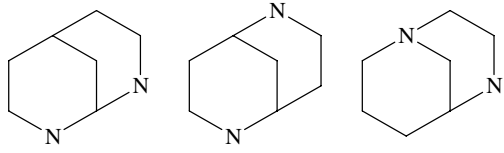
$$\text{TNB} + \text{DBU} \underset{}{\overset{K}{\rightleftharpoons}} \text{MOLECULAR COMPLEX} \qquad (18)$$



SCHEME 44

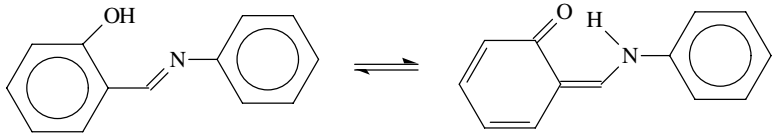
Non-cyclic amidines (**120** of Scheme 44) react as ambident nucleophiles in the reactions with TNB in DMSO forming[198] the two zwitterionic intermediates **121** and **122** of Scheme 44, when the nucleophilic centre is the nitrogen or the carbon atom, respectively. **121** and **122** are in equilibrium with unprotonated forms. Some **122** σ-complexes were isolated as crystalline solids. In **122**, a further nucleophilic attack is carried out by the C=NH group and this forms a *meta* bridged compound **(123)** in protonated or unprotonated forms[198].

The reaction of Scheme 44 is an interesting synthetic route for preparing heterobicyclic ring systems[199] such as **124**, **125**, **126**.



(124) **(125)** **(126)**

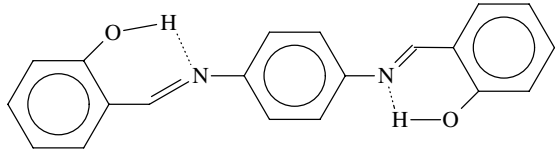
N-Salicylideneaniline (**127** and **128**) derivatives present some interesting aspects[200] of the tautomeric process of equilibrium 19. The position of equilibrium 19 depends on the presence of an internal hydrogen bond[201,202].



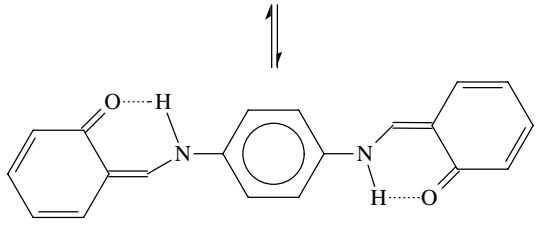
(19)

(127) **(128)**

N,*N*′-Bis(salicylidene)-*p*-phenylenediamine (**129** and **130**; see equation 20) in the crystalline state shows[203] a short intramolecular hydrogen bond. The molecules are planar and form a one-dimensional column. The interplanar space is shorter than in other salicylideneanilines; this fact is an indication that there is an intermolecular CT complex.



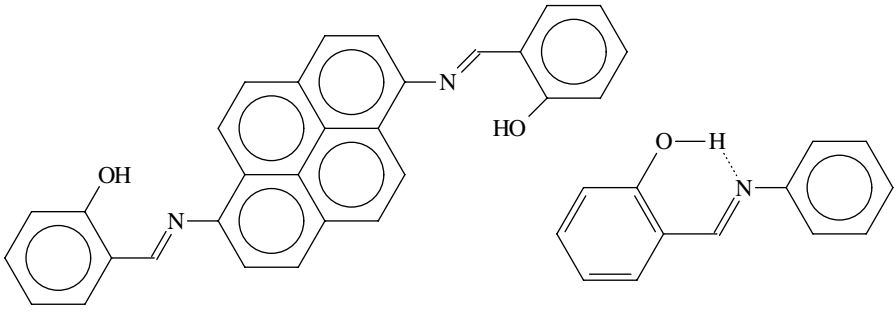
(129)



(20)

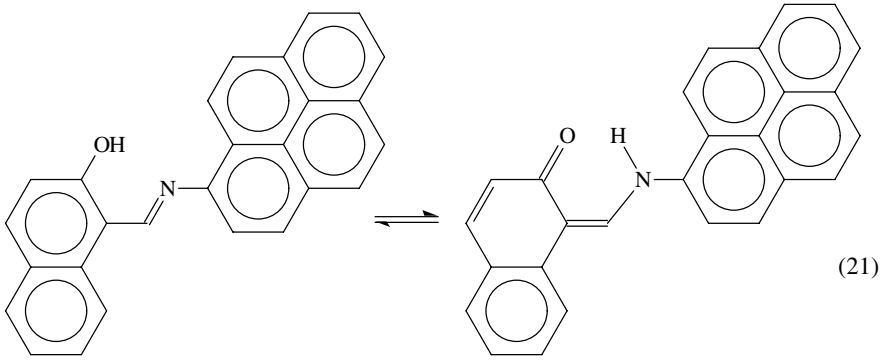
(130)

Optical measurements of *N*,*N*′-disalicylidene-1,6-pyrenediamine **(131)** indicate[204] the absence of a thermal proton transfer, but the crystals of **129** and **130** are thermochromic; spectroscopic changes with changes of temperature are caused by the transfer of proton from the OH group to the imine nitrogen (equilibrium 20). The keto-form **(130)** includes electron-donor and electron-acceptor parts: they interact in an intermolecular CT complex[203], in the crystalline state. Similar behaviour is reported for the *N*-tetrachlorosalicylideneaniline and tetrachlorosalicylidene-1-pyrenylamine pair[205].

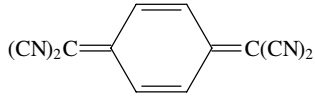


(131) **(132)**

The hydrogen bond (the N···H—O hydrogen bond is short) is responsible for the formation of a pseudoaromatic ring (see **132**) which is planar[206]. Geometrical properties of the moieties used and the presence of substituents can modify the pseudoaromatic hydrogen bond. Thus, the position of the hydrogen is sensitive to the presence of CT complexes, as observed in the case of some complexes[207] between *N*-(2-hydroxy-1-naphthylmethylene)-1-pyreneamine (equilibrium 21) and 7,7,8,8-tetracyanoquinodimethane **(133)** derivatives. Probably, the modification of charge distribution (caused by the formation of CT complexes or by changes of substituents on aromatic rings[208]) in **132** and in other similar compounds is an important parameter in stabilizing the pseudoaromatic hydrogen bond.



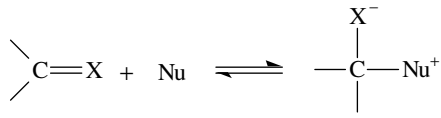
(21)



(133)

VI. COVALENT COMPLEXES INVOLVING C=O AND C=N GROUPS AND NUCLEOPHILES

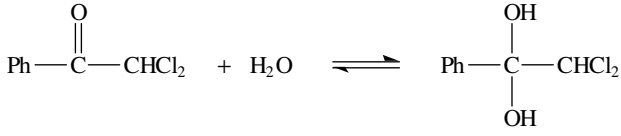
In principle, when carbonyl, thiocarbonyl or iminoyl groups react with a nucleophile, a covalent bond is formed and the carbon hybridization changes from sp^2 to sp^3 (equilibrium 22).



(22)

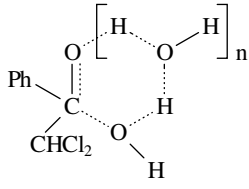
(X = O, S, NR)

Water addition to the carbonyl group of aldehydes and ketones has been known for a long time. α-Halogenoketones react with water to form tetrahedral adducts (reaction 23).

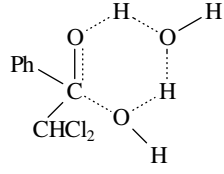


(23)

Kinetic data on equilibrium 23 indicate[209] that in mixed solvents a large number of protons participate in the TS of hydration **(134)** until it reaches the minimum value of 2 **(135)**.



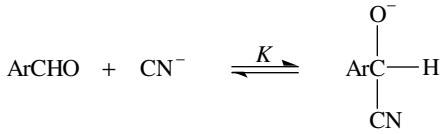
(134)



(135)

The attack of the nucleophile that forms anionic adducts (or zwitterionic adducts, with neutral nucleophiles) parallels the other attacks of nucleophiles on derivatives bearing unsaturated (sp^2) carbon atoms, such as alkenes or aromatic substrates, which are both activated by electron-withdrawing groups. The formation of σ anionic (or zwitterionic) complexes between nitroaromatic derivatives and nucleophiles is a well-known step in nucleophilic aromatic substitution reactions[155,210].

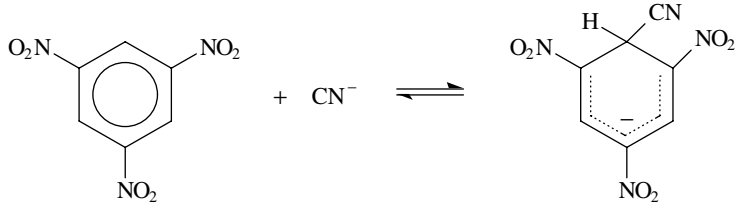
The constant of equilibrium 22 may be calculated by several methods. A competitive method was used[211] to evalute the equilibrium constant in the formation of cyanohydrin anions of substituted benzaldehydes in DMSO (equilibrium 24).



(24)

(136)

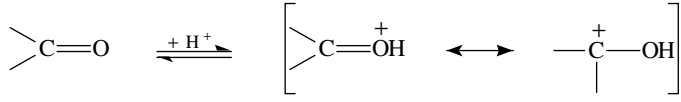
The source of cyanide ions is the Meisenheimer adduct formation between trinitrobenzene and cyanide ions in equilibrium 25. The constant of this equilibrium 25 is well known; if the equilibrium concentration of free cyanide ions is negligible, the concentration of the strong red **137** provides a proof of equilibrium 24. Also, in the case of equilibrium 24, DMSO enhances the reactivity of the anionic nucleophile compared with protic solvents.



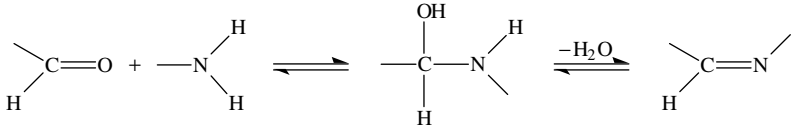
(25)

(137)

The addition of nucleophiles to the carbonyl group may be catalysed by acids obtained by the protonation of the carbonyl oxygen (equilibrium 26). Acid catalysis can also occur during the elimination step which follows the addition step. For example, the reactions of aldehydes with amines (and of all the ammonia derivatives) to form imines are generally assumed to occur in two steps: the first is the addition of nucleophile to yield a *gem* amino alcohol, the second includes the elimination of water from the tetrahedral adduct **138** (see Scheme 45). This elimination is usually thought to be catalysed by electrophiles[171,212].



(26)

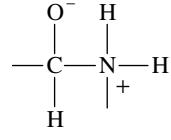


(138)

SCHEME 45

Depending on the experimental conditions either the addition or the elimination step may be rate determining.

The formation of the tetrahedral intermediate **138** may be preceded by the zwitterionic complex **139**, as the first step of the nucleophilic attack on the partially positive carbon of the carbonyl group.

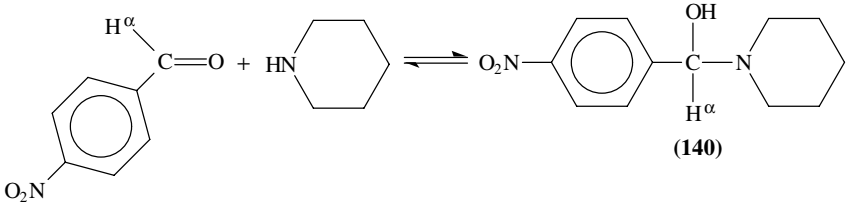


(139)

While Scheme 45 is generally accepted, only very few direct observations of 1,1-amino alcohols **(138)** or of the zwitterionic intermediate **139** were reported[213].

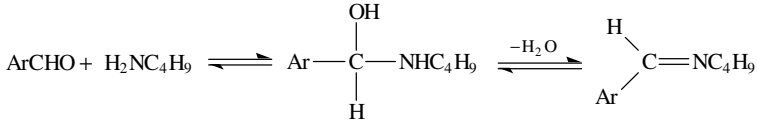
Direct inspection (by ^{1}H NMR) of mixtures of 4-nitrobenzaldehyde, or pyridine-4-carbaldehyde, in hexadeutero DMSO and piperidine reveals the presence of **140** in the reaction mixtures[214].

The starting aldehyde H^{α} signal ($\delta = 10.36$) was shifted to $\delta = 5.33$ as required for a change of sp^2 to sp^3 hybridization by passing from 4-nitrobenzaldehyde to derivative **140** (equation 27). Similar behaviour was observed for mixtures of aromatic aldehydes and of some primary amines (butylamine, *t*-butylamine): the presence of the 1,1-aminoalcohol **(141)** was observed for short times, after the imine **(142)**[215] had been formed (equation 28).



(27)

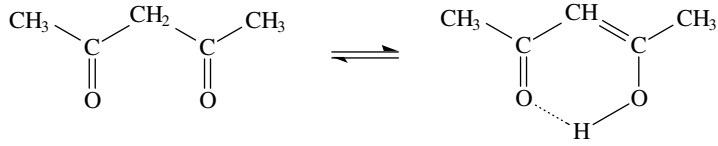
(140)



(28)

(141) **(142)**

Equilibrium 29 regarding the tautomerism of pentane-2,4-dione **(143)** was found to have been completely shifted towards the enol form by a tertiary amine. The predominance of the enol form can be attributed to strong hydrogen-bonding interactions with the amine as shown in **145** and **146**. Low polarity of solvents also favours the enol form **144**.



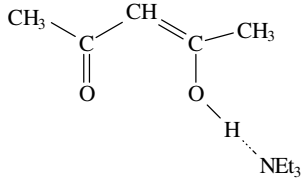
(29)

(143) **(144)**

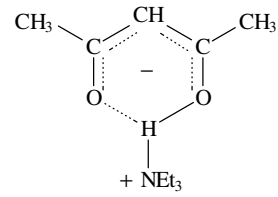
The interaction shown in **146** was investigated by X-ray diffraction[216] of the adduct between diethylamine and **143**. This dimeric complex **(147)** arises mainly from hydrogen-bonding interactions and shows a three-centred hydrogen bond.

The interactions between the carbonyl carbon of **143** and triethylamine shown in **148**, **149** and **150** appear[217] to be a better explanation than the reported (and usually accepted) hydrogen-bonding interactions of **143** in triethylamine. IR and ^{1}H-NMR investigations[217] show the presence of a labile adduct between **143** and triethylamine which reduces the $-CH_2-$ ^{1}H-NMR signal of the keto form. By using an excess of **143** or reducing the temperature or diluting the **143**/triethylamine mixtures with $CDCl_3$, there is an enhancement of the $-CH_2-$ signal of the keto form.

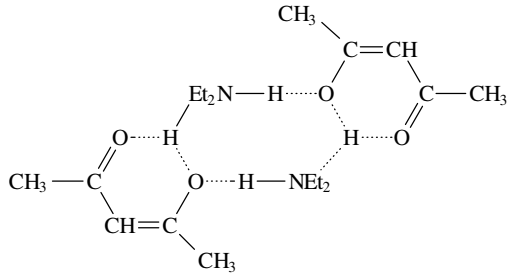
The use of tributylamine or of diisopropylethylamine favours the keto form, as expected if a nucleophilic interaction of the amine on a C=O carbon atom is the driving force for enolization[217]. This conclusion is supported also by *ab initio* calculations[217] on the



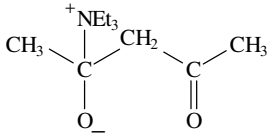
(145)



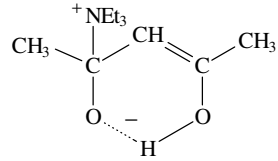
(146)



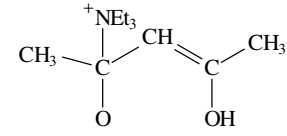
(147)



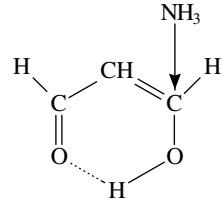
(148)



(149)



(150)

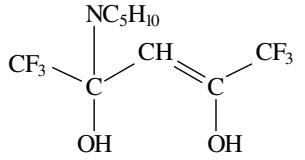


(151)

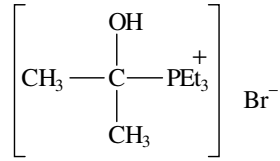
malonodialdehyde/NH_3 system: the carbon/nitrogen interaction **(151)** presents an energy state that is lower than those for the more usual hydrogen-bonding interactions.

1,1,1-Trifluoroacetylacetone **(152)** reacts by a condensation reaction 30 with aromatic aldehydes[218] in the presence of piperidine and acetic acid, in benzene. Triethylamine does not catalyse this reaction. Probably, the product **153** is obtained via the carbinolamine **(154)**, which in turn yields the carbonyl group of the aldehyde. Obviously, the tertiary amine cannot displace a proton and the interaction forms a zwitterionic adduct (see **148**).

$$\underset{\textbf{(152)}}{CH_3COCH_2COCF_3} + ArCHO \longrightarrow \underset{\textbf{(153)}}{ArCH{=}CHCOCH_2COCF_3} \qquad (30)$$



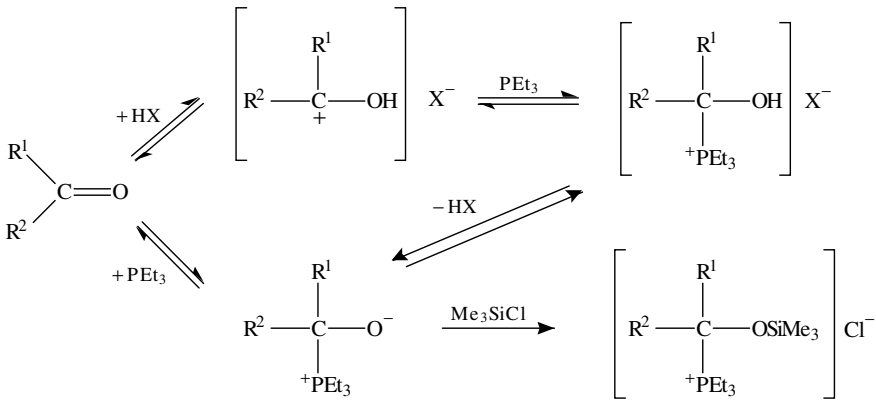
(154)



(155)

1-Hydroxyphosphonium salts and 1-(trimethylsiloxy)phosphonium salts are obtained[219] from the addition of small-sized phosphines (PMe_3 and PEt_3) to a carbonyl group of ketones and aldehydes, in the presence of chlorotrimethylsilane or of the mixture acetone/bromine, which is a source of anhydrous HBr.

X-ray diffraction provides a structural analysis of the adduct obtained between acetone and triethylphosphine **(155)** in the presence of bromine. The process of obtaining **155** is an acid-catalysed process, while the adducts obtained in the presence of chlorotrimethylsilane may be ascribed to neutral attack of the nucleophile leading to the zwitterionic complex, as shown in Scheme 46. In Scheme 46 triethylphosphine may be substituted by trimethylphosphine. When triphenylphosphine or tributylphosphine were used, no reactions were observed, owing to the reduced nucleophilic power of the bulky phosphines and to the insolubility of the obtained adducts.



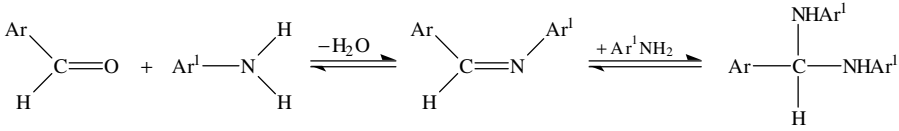
R^1=H, Me; R^2=Me

R^1=H,; R^2=Ph

SCHEME 46

Usually, the reactions of carbonyl compounds and derivatives of ammonia are considered to be concluded with the formation of the imino derivative **(156)**, but there is evidence that the C=N double bond may react faster than the C=O group with nitrogen nucleophiles to form 1,1-diamino derivatives (Scheme 47).

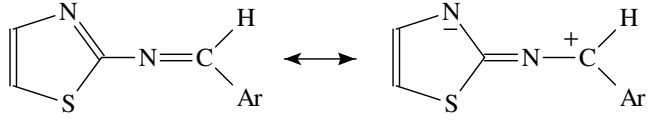
When Ar^1 (Scheme 47) is an electron-withdrawing system, such as 4-nitrophenyl, 2-pyridyl, 2-thiazolyl and 2-benzothiazolyl, aminals **(157)** are obtained in high yields from the reaction mixture of aldehydes and heteroaryl amines in methanol or in DMSO (without



(156) (157)

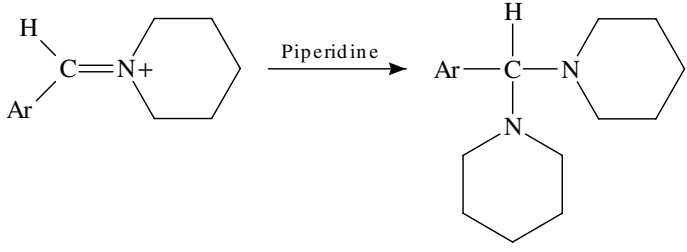
SCHEME 47

catalysts)[220]. Probably the electron-withdrawing moiety of imines **(156)** exerts an activating effect on the C=N bond, as shown in **158**. This appears more prone to nucleophilic attack than the C=O bond, even when electrophilic catalysis is not operating.



(158)

This explanation confirms the usual findings that primary amines give Schiff bases without further complications, while secondary amines (piperidine) and some aromatic aldehydes easily form the *gem*-diamino derivatives[214] **(160)**, probably through the immonium cation **(159)** that is usually accepted in enamine formation (equation 31).



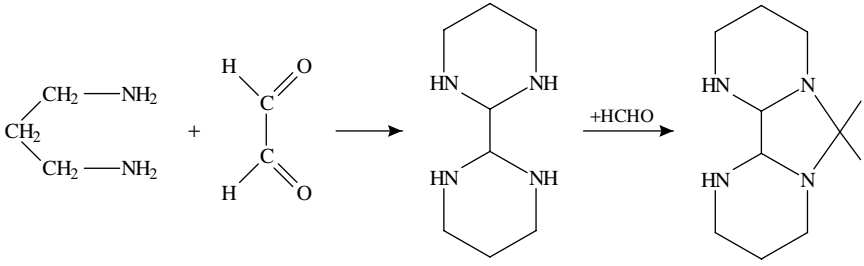
(31)

(159) **(160)**

When the reaction products of the reaction involve the nitrogen atoms of nucleophiles in the formation of heterocyclic derivatives, the formation of 1,1-diamino derivatives is usually used to prepare polyazacyclic derivatives[221]. Scheme 48 shows[222] the formation of fused polyazapolycyclic compounds through a condensation between 1,3-diaminopropane and glyoxal to prepare the 1,1-diamino derivative **161**. The subsequent reaction of **161** with formaldehyde forms fused addition products **(162)**.

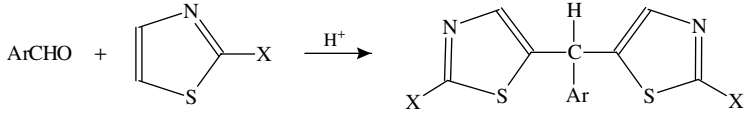
Some authors suggest that the addition of alcohols with amines[223] to some imines containing heterocycles occurs without catalysis.

Another instance of a stable bis-adduct of the carbonyl group of aldehydes is the condensation between aromatic aldehydes and electron-rich thiazole derivatives[224] (Scheme 49) where the nucleophilic centre is carbon 5 of the thiazole ring. When carbon 5 of the thiazole ring is activated by an electron-donating amino or hydroxy group (as in **163**) and in the presence of small amounts of HCl, to activate the carbonyl group, compounds **(164)** are obtained by non-reversible condensation. The reaction of the amino group (bonded in



(161) **(162)**

SCHEME 48



(163) **(164)**

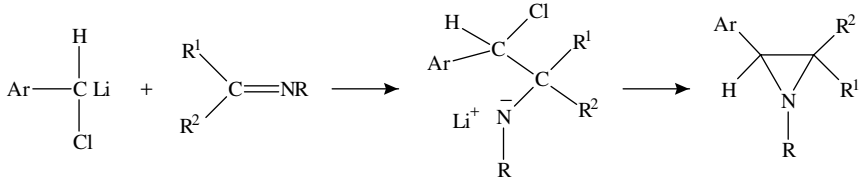
ArCHO = benzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde

X = —NH_2 , —NMe_2 , —OH

SCHEME 49

position 2 of the thiazole ring) on the carbonyl group is illustrated by Scheme 47 and is clearly reversible.

A recent instance[225] of reaction 22 (X = NH) involves the reactions of some (heteroarylchloromethyl)lithium **(165)** reagents with imines **(166)** to form **167** and to produce the heteroaryl aziridines **(168)** as depicted in Scheme 50. Aziridines **(167)** are obtained in the preferential (or exclusive) conformation *E*. A tentative explanation of this behaviour is the different steric compression in the transition states affording isomeric *E* or *Z* aziridines.



(165) **(166)** **(167)** **(168)**

Ar = 2-pyridyl, 2-quinolyl, 2-benzothiazolyl
R = Ph
R^1, R^2 = cyclopentylidene, cyclohexylidene, fluorenylidene
R^1 = H, R^2 = Ph
R^1 = R^2 = Me
R^1 = Ph, R^2 = Me

SCHEME 50

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CHAPTER **9**

Liquid crystals with X=Y groups

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I. INTRODUCTION

Since the last review *Liquid crystals containing X=Y groups* written by J. P. van Meter[1], liquid crystal (lc or LC) chemistry and physics have experienced a tremendous expansion.

TABLE 1. CAS online investigation on liquid crystals with different functional groups

Liquid crystal containing	Total	⩾1991
Imine or Schiff base or azomethine	518	84
Nitrone or *N*-oxide	40	6
Imidoyl cyanide	1	1
Stilbene	146	50
Azo or azoxy or thioester or amide	908	252
Ester	2582	n.a.
Ester and ferroelectric	304	87

During the last 20 years a large number of new fields related to liquid crystalline properties and mesomorphism have been discovered or invented and, as a result, very new research topics have been initiated. Far beyond investigations on simple nematics with the purpose of using them in twisted nematic displays, very actual research areas like lyotropic LCs as model systems for cell membranes, discotics, ferro-, ferri- or antiferroelectric LC's as recent material for the next generation of flat panel displays, or LC's with non-linear properties or guest–host systems for optical data storage have been studied all over the world. Therefore our impression is that the synthesis of new liquid crystalline compounds has not followed only the researchers' curiosity as may have been true in the early years, but more than ever the demand of the commercial market, the need for mesomorphic materials with additional physical qualities and the challenge of the realization of new devices for displays, electro-optic modulators or storage devices have governed the researchers' efforts. The strong anisotropy in most of the physical properties like molecular orientation, birefringence, polarizability and dielectricity have been used as a support for the aspired functionality, e.g. in thin films for second harmonic generation in non-linear optics.

J. P. van Meter[1] decided to classify following the different chemical functional groups containing an X=Y moiety. A Chemical Abstracts Service online research resulted in an immense number of references as of January 1995 (Table 1); even concentrating on the data published since 1991 did not yield a complete representation in this work. Generally speaking, various X=Y groups have been present in most liquid crystals with the exception of the cyanobiphenyls (nCB), cyanoterphenyls (nCT), phenylcyclohexyls (nPCH), cyclohexylcyclohexyls (CCH) and others, which have been used mostly in commercial mixtures for display applications. Due to the large number of references we aimed at a different division of the contents considering modern applicational aspects. We also included sections dealing with liquid crystalline polymers and carbohydrates with mesomorphic properties knowing that they overlap with the more chemical classification of Section IV.

We hope that we can give scientists who are not this familiar with liquid crystals an introduction to this breathtaking and interdisciplinary field of chemistry, physics and material research as well as point out new and challenging research topics at the eve of a new millennium.

II. GENERAL CLASSIFICATION

Basically, mesomorphism has its origin in the intermediate state between the three-dimensional lattice of an ordered crystal and the zero order in an isotropic liquid. Two different kinds of ordering occur in any material's phase: short-range order in the direct surrounding of the atom, ion or molecule under interest, like the solvate cloud around a solved species, and the long-range order in crystals with an identical repeating unit along the crystal axes. The latter can be subdivided again in two parts: on the one hand there

is the so-called position ordering which describes the more or less fixed location of the involved species. On the other hand one has to consider the orientation ordering which describes the preferred direction of, e.g., the crystal axes within the lattice. The presence of structural ordering results in anisotropic physical properties and the combination with fluid behaviour allows for the realization of interesting applications. Within the class of mesomorphic compounds, different possibilities of classification have been established, focussing on the mesomorphic behaviour as an individual material property. Thus the following subdivisions have been suggested in the literature (Figure 1).
Mesomorphic Materials:

- *Plastic crystals*: The long-range orientational order is lost, the long-range positional order is preserved, i.e. a plastic quasi-crystalline lattice is still present.
- *Lyotropic liquid crystals*: Due to the influence of a penetrating solvent which intercalates into the lattice, a long-range orientational order depending on the individual lyotropic phase is given, but no positional ordering can be observed. Common examples are soaps or the double layers of lipid structures.
- *Thermotropic liquid crystals*: Mesomorphism has its origin in the energetic preference of the formation of one- or two-dimensional ordered phases due to molecular interactions like attractive or repulsive forces with increasing temperature. The transition of the three-dimensional ordered crystal lattice to a lower ordered state is called the melting point; the transition of the lowest ordered mesophase to the isotropic melt is defined as the clearing point. In between, several phase transitions of several related lc phases are possible. The so-called monotropic LC's only show mesomorphism during cooling, i.e. the clearing point has to be at lower temperatures than the melting in LC's opposite to enantiotropic LC's, which show the mesophases during the heating as well as the cooling process. The thermotropic liquid crystals may be split again into several subdivisions (Figures 1 and 2).
- *Discotic liquid crystals*: The molecules possess a disc shape; in many cases they are polysubstituted benzene or triphenyl derivatives with lateral extended aliphatic chains. These molecules arrange, e.g., in large columns; a discotic nematic phase is known too.

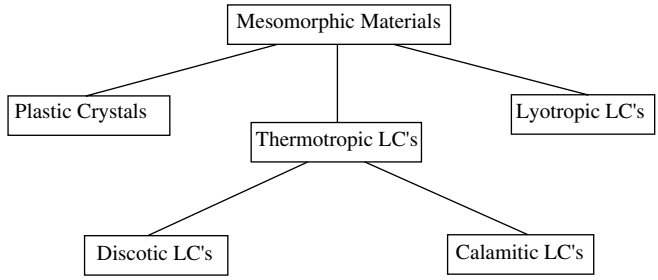


FIGURE 1. General classification of mesomorphic compounds

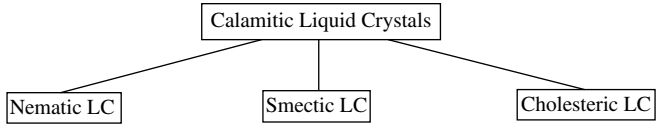


FIGURE 2. Subdivision of calamitic liquid crystals

- *Calamitic liquid crystals* consist of rod-like molecules, i.e. a pronounced shape anisotropy with one extended principal axis and two short perpendicular ones. Three main classes can be described as in Figure 2.
- *Nematic phase*: Due to the rod-like shape and the resulting repulsive and attractive forces between neighbouring molecules (a quantitative description is formulated, e.g., in the so-called nematic potential) the preferred direction of all molecule's principal axes is called the director of the phase. The centres of the molecule's inertias are distributed statistically; without external forces, the orientation of the director from one domain to the next as well as within a domain changes permanently, observable at the scattering of the nematic phase. Oriented nematics are uniaxial, though biaxiality is sometimes discussed. The nematic phase can be treated as a one-dimensional ordered fluid[2]. The phase-transition enthalpy at the clearing transition is negligible small ($<2.5\ kJ\,mol^{-1}$) and often hard to detect with standard differential scanning calorimetric (DSC) methods[3]. Up to now the nematics have been the most used systems in commercial display applications or electro-optic devices.
- *Smectic phases*: Generally speaking, in the various kinds of smectic phases the molecules are arranged either in layers, parallel or tilted (S_A or S_C), with or without any interaction with the next layer, in case of the ordered smectic phases hardly distinguishable from real crystalline phases. The phase-transition enthalpies between highly ordered smectic phases are small ($2-4\ kJ\,mol^{-1}$). Actually, around 15 different smectic phases are known; the most important are shown in Figure 3. Some of the highly ordered phases are strongly related to each other, for example the orthogonal S_B phase undergoes a structure distortion during cooling to the orthorhombic S_E phase (Figure 4).
- *Cholesteric liquid crystals*: Historically, the name is derived from cholesterol; chiral molecules like the steroids show a certain form of the nematic phase, the cholesteric one. The rigid rods are oriented parallel within virtual layers in one preferred direction (director); the director changes from one single virtual layer to the next continuously, with a certain value creating a helix. The distance between two parallel oriented directors is called the pitch (*ca* 0.2 μm).

Due to the large number of known liquid crystal compounds, some common structure principles can be claimed; to a certain degree potential LC behaviour can be predicted[4–7]. Typical structure elements of rod-like molecules are described in the following and shown in Figure 5:

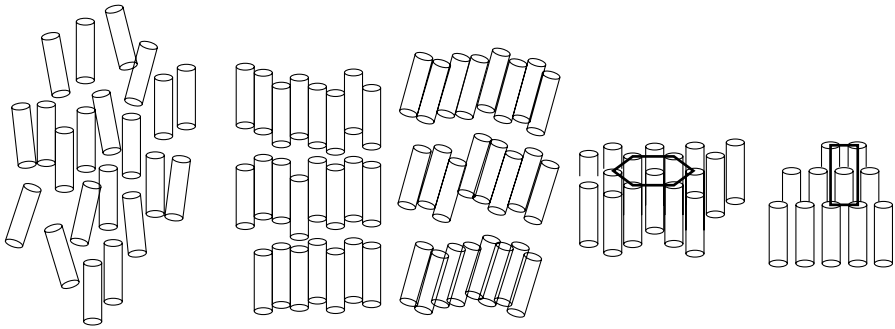


FIGURE 3. Schematical drawing of the main liquid crystal phases

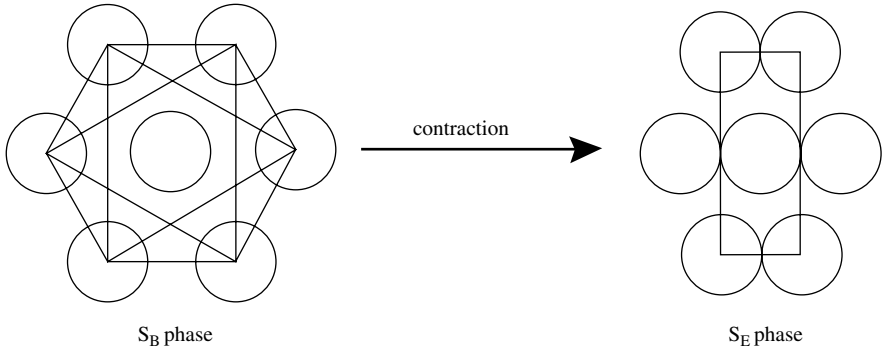


FIGURE 4. Change in the molecular arrangement between the S_B and S_E phase

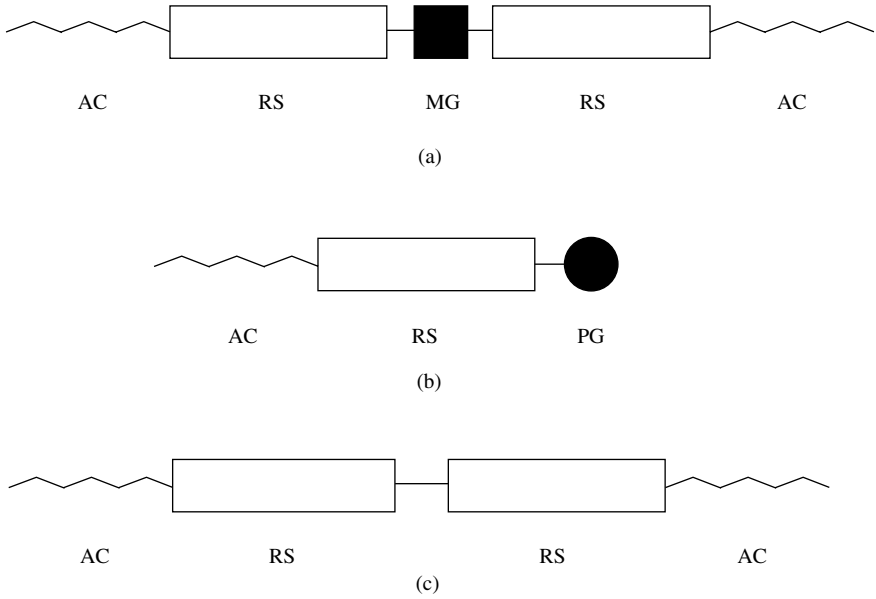


FIGURE 5. Common structure elements of liquid crystal molecules

(a) A central middle group (MG) is supported on both sides with rigid ring systems (RS) carrying lateral aliphatic chains (AC).

(b) A central rigid ring system contains an aliphatic chain and polar groups (PG) like cyano or nitro facing each other.

(c) Two or more ring systems with one aliphatic chain are attached directly.

In general, the following molecular moieties are helpful for the formation of mesomorphic properties:

- enhanced shape anisotropy (rod- or disc-like), structural aspect ratio at least more than 3,
- rigid core with flexible lateral aliphatic chains,

- no branched units,
- permanent dipole moment
- large polarizability via extended conjugation length,
- anisotropy in the polarizability,
- polar lateral groups attached to the rigid core.

In many cases the middle group consists of an unsaturated X=X or X=Y group like azo, azomethine or C=C and the conformation at the double bond is (*E*) or *trans*, while a (*Z*) or *cis* conformation would destroy the lc phase due to the smaller shape anisotropy. A twist like in the azomethine, or the step in the azo moiety, has no significant influence on the formation of lc phases. In many cases the extensions of the aliphatic chains support mesophases with lower ordering like S_C, S_A or N, due to the large number of *gauche* conformations in the chain, and the packing is more similar to that in liquids[8].

The unequivocal characterization of the mesophases is quite often very tricky and problematic. Each phase shows typical textures under a polarizing microscope; a lot of them are documented in precise photos and pictures, but the formation of a texture depends strongly on the sample preparation, surface treatment, temperature control and other parameters. DSC curves and the phase-transition enthalpies yield important information, but the only unequivocal and suitable tool for the determination of the mesophases is given in the different x-ray methods, and nowadays modern resonance and atomic probe techniques attract more and more notice and acceptance[9–11]. A general description is given in the next section.

III. STRUCTURE IDENTIFICATION AND CLASSIFICATION

There are some methods available for the classification of the mesogenic phases as well as the description of their structure and molecular arrangement. They must all be used together for a complete and reliable characterization. The most important are:

- thermal polarizing microscopy,
- differential scanning calorimetry,
- scattering methods using X-ray, synchrotron or neutrons beams.

Thermal polarizing microscopy: Usually, the first step in an investigation of newly synthesized liquid crystalline compounds is to characterize the observed textures and texture changes in the liquid crystalline phase range. Since it is not a static process, the combination of a polarizing microscope with a temperature-controlled hot stage allows the phase transitions to be observed. Today, it is common to improve the equipment by using a video system to record the observed textures. For a correct determination of the mesophases it is sometimes necessary to align the LC material on the surface to obtain a good homogeneous or homoetropic orientation which quite often simplifies the interpretation. There are some typical textures which can be correlated with a certain lc phase. In fact it is possible to distinguish between nematic, fluid smectic phases and crystalline smectic phases due to the differences in the viscosities. For some highly ordered phases or crystalline smectics it is possible to find characteristic textures[12,13]. Usually, the proper identification of the phase just by observation of textures is difficult and needs much experience. For a more precise identification of the mesophases a combination of different techniques have to be used which are more sensitive to individual structural features.

Differential scanning calorimetry (DSC): Since lc's form phases in a thermodynamic sense, a transition from one phase to another is accompanied by a phase-transition enthalpy. Nevertheless, there are phase transitions of second-order character which can hardly be detected by DSC since there is no phase-transition enthalpy but just a change in heat capacity. A typical example is the transition from orthogonal phases to tilted phases.

The tilt of the phase by cooling can change slowly from 0° to a certain value in the tilted phase. In this case the phase transition will be of second order or weak first order, i.e. the sharp separation of the first- and second-order phase transitions is blurred. Moreover, for pre- or post-transformational effects close to the phase-transition temperature, phase-transition enthalpies cannot be registered. Enantiotropic phases *per se* are observable during heating and cooling, monotropic phases only by cooling. In the last case, the lc phase is not in thermodynamical equilibrium. Because of the kinetics of phase formation, the transition temperatures measured during either heating or cooling of enantiotropic liquid are sometimes different, in particular the crystallization process can be regulated by time. Quite important are glass-forming processes, when a certain 'freezing' temperature is hardly reproducible. Despite the outstanding advantages of DSC, static calorimetric methods are still in use. As a rule the melting process from the crystalline state to an ordered smectic phase (e.g. S_E) is comparable with the other transition enthalpies present in the sample. All transition enthalpies summed up, including the transition from crystalline smectic phases to fluid smectic phases, (e.g. S_A), take about 85%, and to the nematic phase about 95%, of all the measured enthalpy values. Hence a precise measurement of the phase-transition enthalpies is essential for a correct phase determination.

Scattering methods using X-ray, synchrotron or neutrons beams: According to Figure 2, calamitic liquid crystals can be subdivided into nematic and smectic phase-forming compounds depending on the order between the individual molecules. In case of the nematic phases, the molecules are spontaneously oriented with their long axes parallel to each other, as described. In the case of the smectic phases, the molecules are arranged parallel in layers with the centre of gravities more or less equidistant from each other. The principal structural behaviour of nematic and smectic phases is shown in Figure 3. Whereas in nematic phases the arrangement is unidirectional (director), in some smectic phases biaxiality exists.

In general, the calamitic phases can be subdivided into fluid and crystalline phases. In fluid phases the molecules are organized in layers, but the correlation between the layers is weak and within the layers the behaviour is more liquid-like. By scattering methods using X-ray (or synchrotron) beams, the layer thickness d can be calculated from the scattering angle Θ in the small-angle region following Bragg's equation. The fluid smectic phases are the S_A and the S_C phases. The first is an orthogonal phase, where the molecules are arranged in layers with their long molecular axes parallel to the normal of the layer. In case of the S_C phase the molecules are tilted (up to *ca* 40°) within the layer. The average distance between the molecules perpendicular to the principal molecular axis, usually between 4–5 Å for calamitic liquid crystals, can be calculated from the diffuse wide-angle reflections. For proper identification and assignments of the reflexes a well-defined position of the layers with respect to the incident beam is required. In principle, it is possible to obtain samples by surface orientation techniques where the molecules are arranged parallel to the X-ray beam. External magnetic or electric fields can be employed to orient the lc phase with the long axis of the molecules oriented perpendicular to the X-ray in monodomains[14]. Sometimes, the field strength is not enough to produce a

TABLE 2. Common structure elements of liquid crystals

Wing (endgroup):	alkyl, O-alkyl R′-OOC-R CN, SCN, NCS, F, NO_2
Ring systems:	phenyl, pyridine, pyrane, thiophene, pyrimidine, dioxolan, naphthalene, cyclohexane, ... and derivatives
Bridging units:	azomethine, azo, N-oxide, stilbene, tolane, aliphatic chains, alkyl ethers, ... and derivatives

macrodomain in the sample. Some metallomesogenes contain paramagnetic centres, when as a consequence of the total magnetic anisotropy the long axes of the molecules orient perpendicular to the magnetic field[15]. Some special kinds of LC's form various subphases. Molecules containing strong polar end groups, like cyano or nitro, as well as side chain polymers, sometimes possess not only S_{A1} but also other smectic phases like A2, Ad and so on. This is related to the interaction of the polar groups between molecules[16,17].

In crystalline smectic phases the arrangement of the molecules within the layer is ordered in a hexagonal, orthorhombic or monoclinic fashion and the layers are correlated to each other. The in-plane order of the mesophase is indicated by the existence of sharp wide-angle reflection. The in-plane correlation is recorded by a small value of Full Width of Half Maximum (FWHM) and, in principle, by more than one wide-angle reflex.

In discotic phases the orientation of the molecules is perpendicular to the molecular plane. Here, the columns can be arranged in a nematic or columnar manner. In the nematic phase the molecules possess a centre of gravity randomly ordered, but with the short molecular axis of each molecule more or less parallel. In the columnar phase, beside the preferable orientation of the short molecular axes, the disc-like molecules are ordered forming columns. Depending on the correlation strength between he columns these phases can be subdivided into ordered or disordered. A third possibility is to have a thermodynamically preferable position of the columns in the mesophase, like in a hexagonal cell. Additionally, a tilt of the columns is also possible.

Following the thermodynamical laws, the order within the individual mesophases increase normally during cooling. In some very special cases (e.g. for polar molecules) sometimes an inverse phase sequence occurs, where cooling gives rise to a less ordered phase like a nematic phase at low temperature. This phenomenon, so-called re-entrance, has been well investigated and different models have been proposed to explain the behaviour[18,19].

IV. CHEMICAL CLASSIFICATION

Almost any common functional group can be used in lc molecules. According to Figure 5 in Section II, Table 2 lists the favoured molecular moieties separated into polar or non-polar end groups, ring systems and bridging or linkage groups. Especially in the latter the X=Y moiety is widely distributed. In the following we present interesting examples carrying the various carbonyl-type groups like ester, aldehydes, amides, imides and azomethines. Due to their increasing importance in electro-optic devices like LC displays or in non-linear optics, azo, stilbene and tolane containing molecules are also treated in more detail. Ferroelectric and carbohydrate liquid crystals as well as lc polymers and metallomesogenes will be presented separately in Section V.

A. Liquid Crystals Containing an Ester Moiety

A reasonable number of liquid crystals consist of at least one or more ester groups, therefore it is common to introduce mesomorphism via condensation of non-mesomorphic compounds with benzoates, hydroxybenzoates or related building blocks. A very large number of different molecules with ester groups exists, in most cases in combination with other X=Y functionalities like azomethine or related ones[5]. In the following we concentrate on liquid crystals with more unconventional molecular structures. Matsuzaki and Matsunaga reported different series of complex benzoates[20]. Two complex benzoates are shown in Figure 6, where the large 1,2,3-tris[4-(4-alkoxybenzylideneamino)benzoyloxy]benzene contains additional azomethine units as bridging groups. The mesomorphic properties of both compounds are listed in Table 3. In case of the naphthalene-derived benzoates only monotropic phases occur, while with increasing chain length the S_A phase

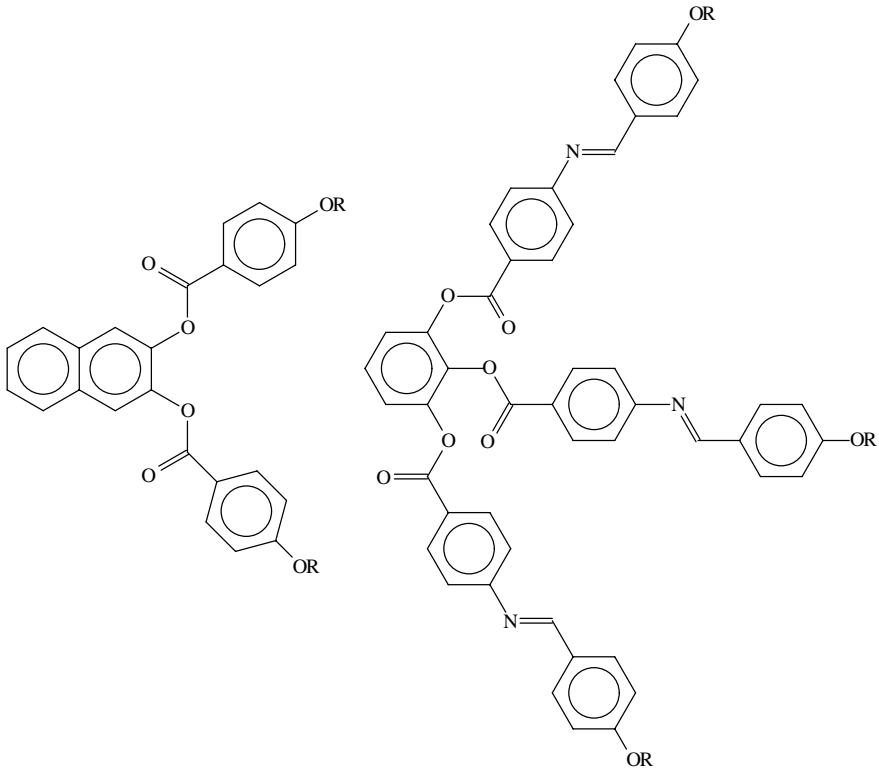


FIGURE 6. Complex benzoate-type liquid crystals ($R = C_nH_{2n+1}$)

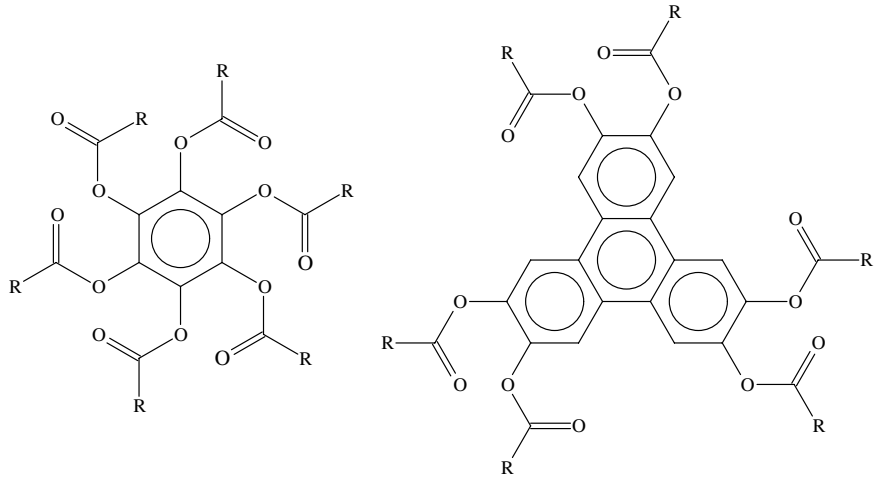
TABLE 3. Polymorphism of (a) 2,3-naphthylene-bis-(4-alkoxybenzoates) and (b) 1,2,3-tris[4-(4-alkoxybenzylideneamino)benzoyloxy]benzoates

(a) 2,3-Naphthylene-bis-(4-alkoxybenzoates)

n	C		S_A		N		I
4	•	127			(•	19)	•
6	•	93			(•	35)	•
8	•	90			(•	55)	•
10	•	85			(•	65)	•
12	•	84	(•	66)	(•	70)	•
14	•	84	(•	73)			•
16	•	87	(•	76)			•
18	•	91	(•	79)			•

(b) 1,2,3-Tris[4-(4-alkoxybenzylideneamino)benzoyloxy]benzoates

n	C		S_B		S_A		I
6	•	89	(•	87)	•	119	•
8	•	96	(•	88)	•	122	•
10	•	100	(•	83)	•	122	•
12	•	104			•	119	•
14	•	106			•	118	•



(a) (b)

FIGURE 7. (a) Hexa-alkanoates of benzene and (b) of triphenylene

TABLE 4. Mesomorphic data of the hexa-alkanoates of (a) benzene and (b) triphenylene[45] and (c) related benzoates of triphenylene[21]

(a) Hexa-alkanoates of benzene

n	C_1		C_2		D		I
5	•	75.7	•	94.5			•
6			•	81.2	•	87.0	•
7			•	79.8	•	83.4	•
8			•	80.4	(•	76.6)	•
9	•	50.5	•	85.5			•

(b) Hexa-alkanoates of triphenylene

n	C		D_1		D_2		D_3		I
6	•	108			•			120	•
7	•	64			•			130	•
8	•	62			•			125	•
9	•	75			•			125.5	•
10	•	67	(•	56)	•	108		121.5	•
11	•	80	•	93	•	111		122.3	•
12	•	83	(•	81)	•	99.2		118	•
13	•	86.5			•	96		111	•

(c) Hexa-benzoates of triphenylene (Ph = phenyl group)

R	C		D		N_D		I
$C_5H_{11}O$-Ph	•	224			•	298	•
$C_6H_{13}O$-Ph	•	186	•	193	•	274	•
$C_9H_{19}O$-Ph	•	154	•	183	•	227	•
$C_{10}H_{21}O$-Ph	•	142	•	191	•	212	•
$C_{11}H_{23}O$-Ph	•	145	•	179	•	185	•
C_7H_{15}-Ph	•	130	•	210			•
C_8H_{17}-Ph	•	179				192	•

is preferred like in other series. The more complex and space-filling tris-benzoate shows a monotropic S_B and an enantiotropic S_A phase. The large molecular mass of one single molecule causes the phase transition temperatures to an occasional slight change with increasing chain length. Similar molecules like the above-mentioned ones often possess discotic phases, i.e. the molecular shape is disc-like or closely related; different phase types like discotic nematic, or columns with hexatic arrangement, can be found. The molecule on the left-hand side in Figure 7 is close to that presented in the previous figure, but the resulting mesomorphic behaviour taken from Table 4 is totally different. A similar disc, but derived from a more complex aromatic system, is drawn on the right-hand side of Figure 7, the hexa-alkanoates of triphenylene. Solid state polymorphism as well as one discotic mesophase occur in the first molecule; with increasing chain length the phase width decreases till the mesophase finally disappears. In the triphenylene-derived hexa-alkanoates three different columnar discotic phases can be observed, while longer chains result in the depression of all transition temperatures. Introduction of an alkylated benzoate unit in the triphenylene series leads to an exotic group of materials with mesomorphic properties, the carbonaceous liquid crystals. Thermal treatment of organic, especially polyaromatic, molecules results in a graphitization and large, planar compounds were formed[21]. Besides the columnar discotic phase a new fluid phase with low ordering was observed; due to the similarity of the great fluidity and the same schlieren texture the phase was labelled discotic nematic N_D (Table 4c). Short aliphatic wings allow for high-temperature mesophases; elongation again decreases all transition temperatures[21].

B. Liquid Crystals Containing Azo-, Azomethine, Stilbene or Tolane Units

At the beginning of the seventies and early eighties aspired material properties with regard to display applications were the only driving force for the search and synthesis of new lc compounds. However, later on new and promising research topics appeared, so we concentrate here on additional molecular quantities essential for applications in the wide area of non-linear optics[22–25]. In addition to the common building blocks for lc molecules, polar groups with opposite electron affinity, like dialkylamino and nitro, must be attached at an elongated conjugated π-system (push–pull system) containing aromatic rings as well as bridging groups like azo, stilbene, tolane or azomethine (Figure 8a). The latter interrupts the conjugated system due to the dihedral angle upto 60° between the substituents attached at the azomethine bond. Simple lc's containing a stilbene unit were described by Fouquey and coworkers[26] (see Figure 8b and Table 5). The mesomorphism

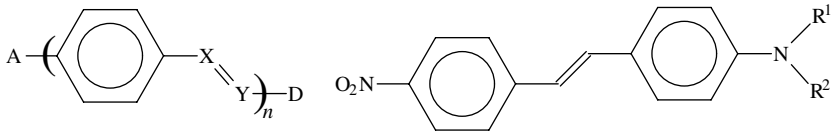


FIGURE 8. (a) Basic structure of an organic molecule with non-linear optical properties (A: acceptor, D: donor unit) and (b) liquid crystalline stilbenes

TABLE 5. Mesomorphic properties of simple stilbene liquid crystals

Compound	Phase sequence (°C)
$R^1 = C_{12}H_{25}$; $R^2 = H$	C 109.0 S_E 141.0 I
$R^1 = C_7H_{15}O-p-C_6H_4CH_3$; $R^2 = H$	C (94.0) S_E 100.0 I
$R^1 = C_{12}H_{25}O-p-C_6H_4CH_3$; $R^2 = H$	C_1 99.0 C_2 108.0 S_A 178.0 I

has been introduced using elongated chains as wing end groups, when due to the extended total molecular length ordered smectic phases are favourable. The presence of aromatic moieties in the side chain suppresses these ordered structures and leads to monotropic phases or to solid state polymorphism combined with a simple S_A phase. The given push–pull system should result in improved non-linear optical properties. With increasing molecular length and enhanced structural complexity a more and more complicated phase behaviour is expected. The addition of a second bridging group to the azobenzene, stilbene or azomethine core results in the appearance of a large number of different phases. Figure 9 shows ten substituted azomethines with either a stilbene or a tolane core;

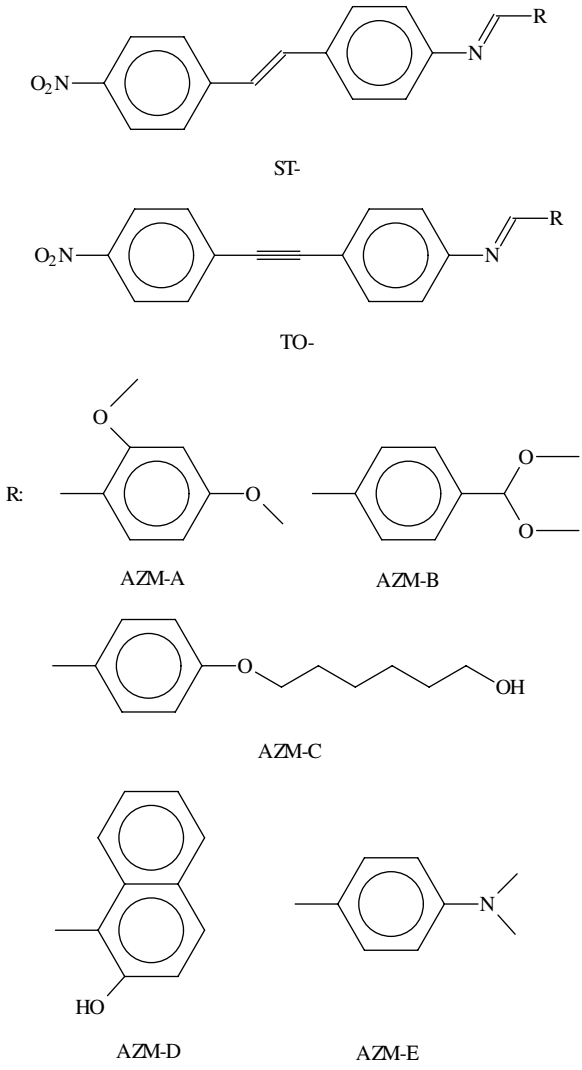


FIGURE 9. Structures of stilbene and tolane derived azomethine liquid crystals

TABLE 6. Mesomorphic properties of azomethine/stilbene/tolane liquid crystals

Compound	Phase sequence (°C)	Trans. enthalpy (kJ mol^{-1})
ST-AZM-A	C 177.3 N 259.3 I	26.3/0.2
ST-AZM-B	1. cycle: C_1 99.3 S_E 128.3 S_B 132.6 S_A 164.2 N 181.9 I Change in the 2. cycle: C_1 96.6 S_E; C_2 116.1 S_E	22.3/2.2/7.9/n.a./0.2
ST-AZM-C	C 154.9 S_E 165.5 S_B 174.6 N 300.0 decomp.	22.3/1.3/5.9
ST-AZM-D	C 300.0 decomp.	n.a
ST-AZM-E	C 307.0 decomp.	n.a
TO-AZM-A	C 194.4 N 212.6 I	39.9/0.2
TO-AZM-B	C 221.6 N 300<I	15.8/n.a
TO-AZM-C	C 139.1 S_X 152.4 275.5 I	22.3/5.1/0.3
TO-AZM-D	C 233.5 I	n.a
TO-AZM-E	C 263.9 N 298.4 I	30.0/0.2

TABLE 7. Structural anisotropy of stilbene and tolane based azomethines

	ST/TO-AZM-A	ST/TO-AZM-B	ST/TO-AZM-C	ST/TO-AZM-D	ST/TO-AZM-E
Length/width	2.2/2.6	2.2/2.9	2.9/4.5	1.7/2.1	2.3/2.8
λ	0.21/0.16	0.21/0.14	0.05/0.13	0.41/0.26	0.22/0.08

Table 6 compares the mesomorphic properties[27–31]. In case of compound TO-AZM-B the unprotected aldehyde was unfortunately obtained, even when we started with the diethoxy-protected one. The presence of extended aliphatic chains are not an imperative necessity for the introduction of liquid crystallinity; even short polar groups allow for mesomorpic behaviour. With the exception of the naphthyl compound all molecules show a pronounced structural anisotropy numerically expressable either using the length/width ratio or using the more sophisticated structural biaxiality parameter λ[32] with the long molecular axis as the principal axis z, and x and y as the short ones (equation 1). Important for the estimation of λ is the difference between the two short axes relative to the molecular length. An enhanced uniaxial structural anisotropy yields a small λ-value, 4′-pentyl-4-cyanobiphenyl (CB5) as a typical nematic liquid crystal, which has an estimated length-to-width ratio of 2.6 and a biaxiality parameter of 0.01. Hence the values given in Table 7 for stilbene and tolane differ slightly due to the various X=Y linkage groups.

$$\lambda = 0.25 \times \sqrt{6} \times \frac{y - x}{z - 0.5(y + x)} \tag{1}$$

Generally speaking, the tolanes possess an improved structural anisotropy in comparison to the stilbenes, hence mesogenic phases with low ordering are preferred; TO-AZM-E shows liquid crystalline behaviour opposite to that of ST-AZM-E, while both naphthalene compounds exhibit only normal melting. Mixtures of the mentioned stilbene/azomethines with simple nematics like CB5 are interesting for coloured guest–host displays because, due to the pronounced structural anisotropy, they stabilize the nematic phase even at room temperature far beyond their own temperature range of liquid crystallinity. Normally, common solutes like solvent molecules or anthraquinone dyes act as ‘impurities’ and disturb the nematic phase and depress the clearing temperature. High-precision density measurements can be used as a reliable method for the determination of the clearing point due to the density gap $\Delta\rho$ between the nematic and the isotropic phase[30]. Figure 10 shows the change in density of the mixtures at three different concentrations (mole fraction

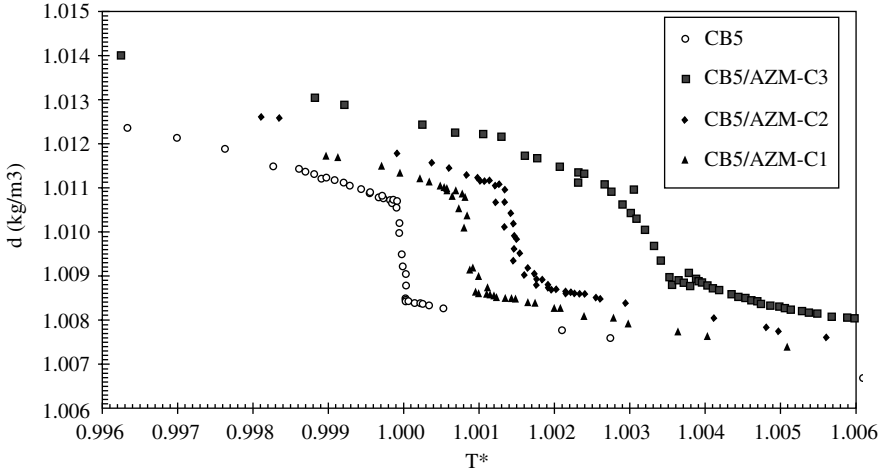


FIGURE 10. Reduced temp. vs density plot at different concentrations of ST-AZM-C in CB5

$x \times 10^3 = 0.6; 1.1; 2.3$) of the solved dye in the nematic host CB5. Increasing dye amount raises the nematic–isotropic transition temperatures $\Delta T = 0.40, 0.69, 1.55\,^{\circ}C$ relative to the value of pure CB5, 34.85 °C, defined as reduced temperature $T^* = 1$. Additionally, the order parameter S_{op} as a measure of the nematic ordering estimated via UV/Vis dichroism experiments is elevated with increasing dye amount. Pure CB5 possesses an order parameter around 0.44 ($T^* = 0.999$)[33]; the investigated mixtures all show an improved value (0.52, 0.55, 0.56) at the same reduced temperature. As a consequence the accessible contrast ratio between on- and off-state in a guest–host display should be improved too. For these elongated molecules with two linkage groups the optical order parameter can be predicted within a certain range using easily accessible thermodynamic data[30].

Another series of molecules containing one or two X=Y moieties are presented in Figure 11[34]. The two simple stilbenes ODAPS and ODANS were forced to be liquid crystalline via the octadecyl group; due to the missing polar endgroup the pyridyl compound shows only a monotropic phase and solid state polymorphism (Table 8). The introduction of the nitro group results in a more complex phase behaviour; again an ordered S_E phase can be observed. The other molecules differ basically in the bridging groups between the aromatic portions. DEANBAZB with the rigid core, the small diethylamino group and the resulting enhanced shape anisotropy has higher transition temperatures comparable to the related azomethine compounds presented earlier. The substitution of one azo link by a stilbene unit and the hexyl groups lowers the phase-transition temperatures drastically; in the related molecule 4′-*N*,*N*-dihexylamino-4-nitrostilbene with only one bridging group, no mesomorphism occurs. Further substitution and a lateral cyano moiety leads to a monotropic phase. Another group of molecules with lc as well as potential non-linear optical properties contains a cinnamoyl moiety which can be photocrosslinked (Figures 12 and 13). In both cases a nematic phase occurs and again the mesophase of the nitro compound ZSNAZB is located at higher temperatures and is stable till decomposition around 300 °C[35,36]. The presence of the flexible butyl group dramatically lowers the phase-transition temperatures (Table 9). The purpose of the synthesis was the affixation of the dyes using UV-light at a modified polymethacrylate containing a cinnamoyl moiety in the side chain too and the formation of an additional network. The application of

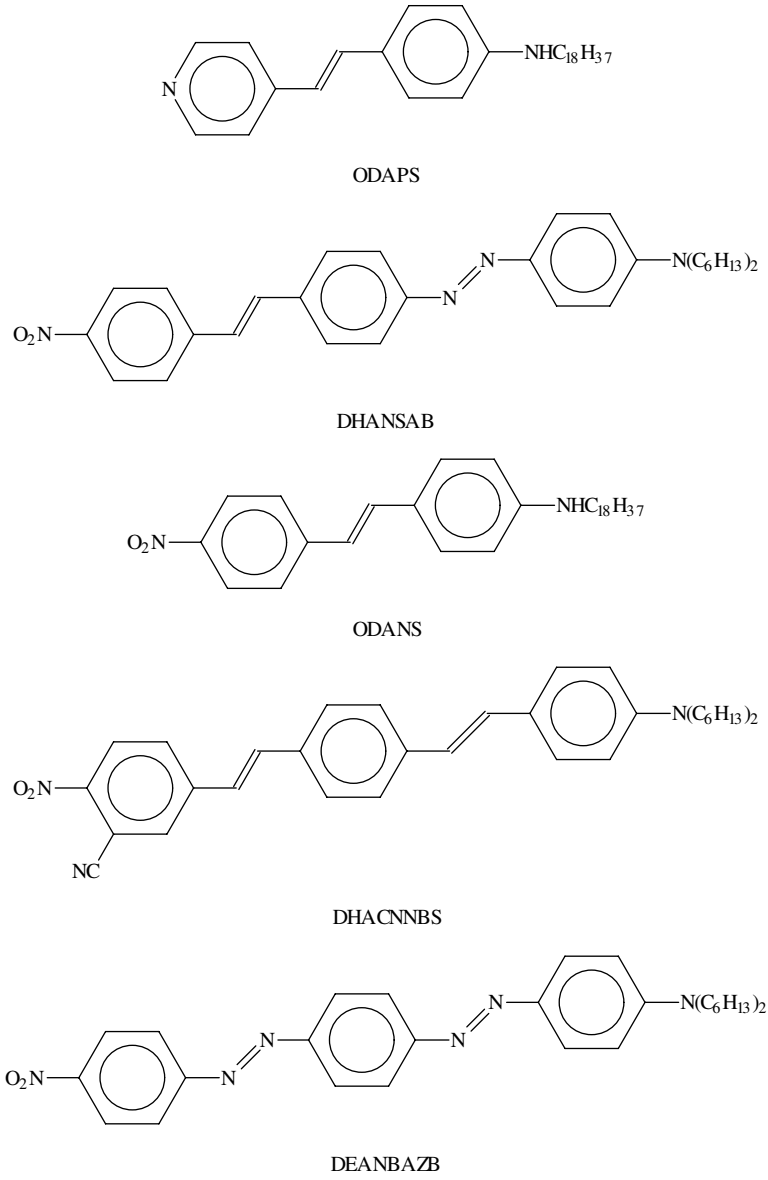


FIGURE 11. Structures of stilbene and azo derived liquid crystals

photocrosslinking of cinnamoyl-substituted compounds and the resulting formation of a discotic mesophase has been described[37].

Liquid crystals with a large molecular mass are able to form a glassy state with mesomorphic behaviour. Yitzchaik and coworkers[38] report about a new class of copolymers with non-linear optical properties, and a monomeric representative with a glassy metastable

TABLE 8. Polymorphic properties of stilbene and azo derived compounds

Compound	Phase sequence (°C)	Trans. enthalpy (kJ mol^{-1})
ODAPS	1. cycle, heating: C_1 70.0 C_2 83.8 C_3 99.6 I	2.6/51.0/16.2
	cooling: C 87.8 S_C 97.0 I	22.9/7.3
	2. cycle, heating: C 95.8 I	38.6
ODANS	C 110.6 S_E 129.1 S_C 135.2 I	52.1/6.6/2.2
DEANBAZB	C 222.8 S_X 260.6 I	25.9/6.7
DHANSAB	C 172.6 S_C 181.1 I	25.7/3.6
DHACNNBS	Heating: C 137.6 I	31.0
	Cooling: C 118.7 S_E 137.6 I	27.0/2.5

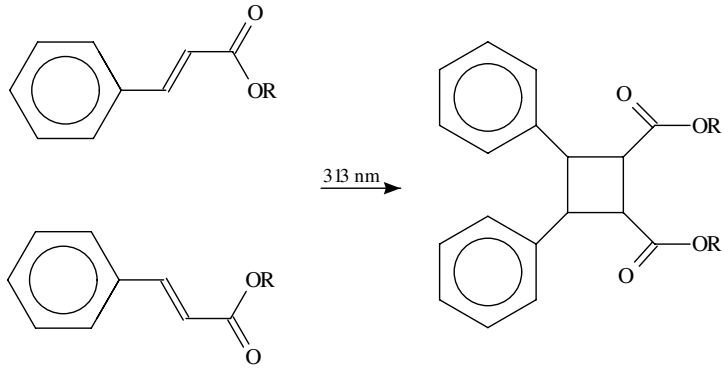
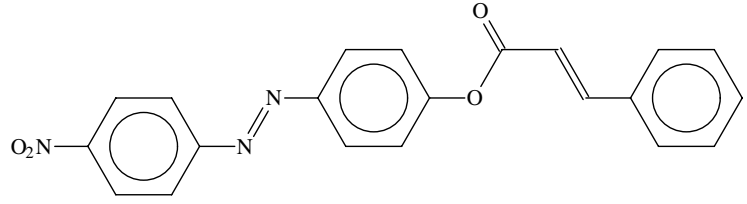
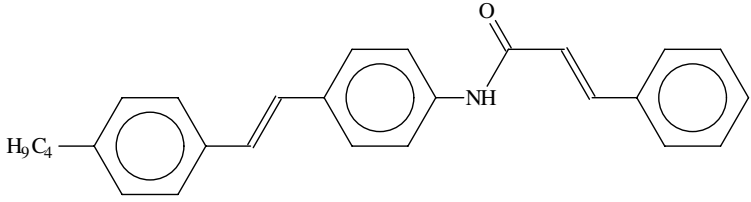


FIGURE 12. UV-induced crosslinking of cinnamic acid derivatives



ZSNAZB



ZSBST

FIGURE 13. Structures of stilbene and azo derived cinnamic acid compounds

TABLE 9. Polymorphic properties of stilbene and azo derived cinnamic acid derivatives

Compound	Phase sequence (°C)
ZSNAZB	C 268.7 N 318.0 (decomp.)
ZSBST	C 115.4 N 184.3 I

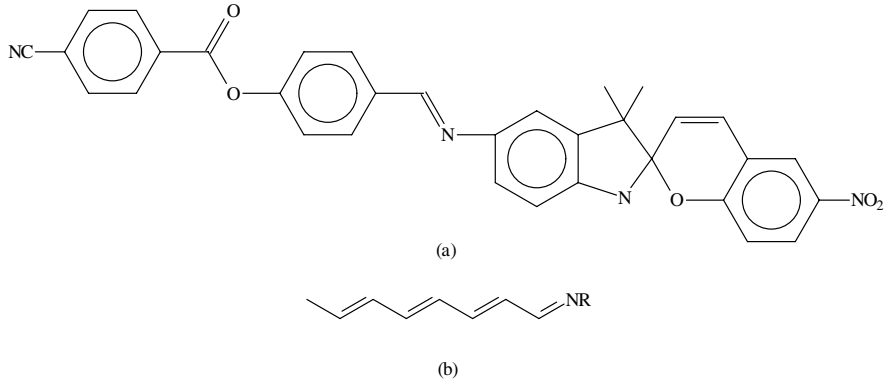


FIGURE 14. (a) Spiropyran with glassy nematic state and (b) polyene azomethine liquid crystal

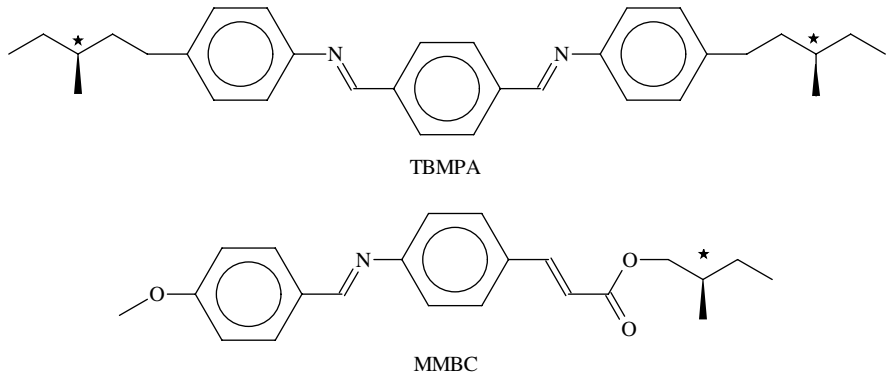


FIGURE 15. Chiral nematics with blue phases[41,46]

nematic-like mesophase can be depicted from Figure 14a[39]. The simplest azomethine lc contains only one polyene group (as the rigid part) and an aliphatic chain on both sides of the azomethine bond (Figure 14b). R varies from methyl to *n*-decyl, and all of them show smectic properties, the latter one only a monotropic mesophase. With increasing alkyl chain lengths the clearing points decrease slightly from 78 to 63 °C; the melting points rise from 35 to 75 °C[40].

A different phenomenon is the appearance of the so-called blue phases in case of chiral LC's, first observed at cholesteric LC's. Sometimes, one or more blue phases occur close below the clearing point with a very small phase width and bright blue or green colours. Figure 15 shows some typical representatives containing one or more X=Y groups in

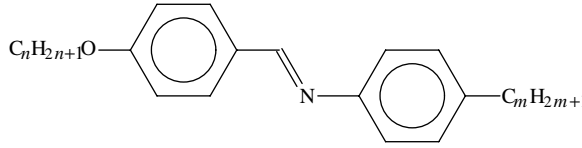
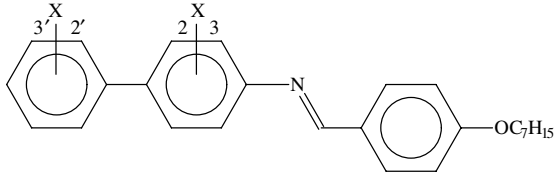


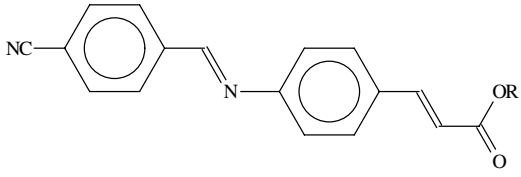
FIGURE 16. Structure of the *N*-(4-*n*-alkoxybenzylidene)-4′-*n*-alkylanilines (*n*O.*m*)

TABLE 10. Transition temperatures (°C) of the 6O.m series[42]

M	m.p.	S_G-S_B or S_A	S_B-S_A- or N	S_G-N	S_A-N	N-I
1	58	(44)	(53)	—	—	76
2	47	—	—	58	—	70
3	34	61	—	—	68	81
4	30	57.5	59	—	69.5	78
5	40	45	62.5	—	75	85
6	15	35	63	—	77	82
74	27	—	66	—	80.5	84
8	29	—	66.5	—	81.5	83



X	T_{N1} (°C)	ΔT_{N1} (H->Cl) (°C)
H	163.5	
3 Cl	96.0	67.5
2′Cl	52.0	111.5
2 Cl	45.0	118.5
3′Cl	smectic	–



alkyl	T_{N1} (°C)
—$CH_2CH_2CH_2CH_2CH_3$	136.5
—$CHCH_2CH_2CH_2CH_3$ (CH_3)	<20
—$CH_2CHCH_2CH_2CH_3$ (CH_3)	112
—$CH_2CH_2CHCH_2CH_3$ (CH_3)	103
—$CH_2CH_2CH_2CHCH_3$ (CH_3)	119.5

FIGURE 17. Top: Lateral substituted biphenyls, bottom: chain branched cinnamoyl liquid crystals

chiral nematics. The first compound (TBMPA) has the following phase sequence[41]:

C 91 S_{X1} 133 S_{X2} 160 N* 169 BP 170 I [°C].

Following the simple azomethines as mentioned before, comprehensive studies on *N*-(4-*n*-alkoxybenzylidene)-4′-*n*-alkylanilines (Figure 16) allow for a general structure-mesomorphic property investigation. Variations in the two chains lengths and the azomethine unit (C=N or N=C) are both possible, but the authors concentrated on the first item. As typical representatives, Table 10 lists the transition temperatures of the 6O.m series. Shorter chains favour the formation of the S_G phase, and in general complex phase sequences appear, while a weak odd–even effect for the clearing point can be observed, and the change of the melting point seems to be occasional. More data with respect to different chain lengths were reported by Goodby and collaborators[42].

Another interesting structure property relationship can be depicted from the influence of lateral substituents (Figure 17,top) or chain branching (Figure 17,bottom)[43]. In the first one a broadening of the molecule influences the phase behaviour; the lateral substituents in the 2 or 2′ positions reinforce the twist between the phenyl groups and decrease the clearing point by about 120 °C. The branching of the terminal aliphatic wing group strongly affects the transition temperatures if the branching is far apart from the free chain end. The last-mentioned example is related to a quite new research topic, the antiferroelectric liquid crystals, which are very interesting for new and fast lc display.

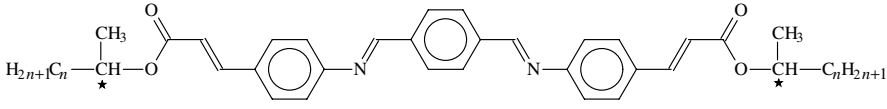


FIGURE 18. Structure of 1-methyl-alkyl-terephthalidene-bis-aminocinnamate (MnTAC)

TABLE 11. Polymorphism of (a) chiral and (b) racemic 1-methyl-alkyl-terephthalidene-bis-aminocinnamate

(a) Chiral 1-methyl-alkyl-terephthalidene-bis-aminocinnamate

n	Compound	C		S_O*		S_Q		S_C*		S_A		I
2	(*S*,*S*)-M3TAC	•	151	—	—	—		•	223	•	236	•
3	(*R*,*R*)-M4TAC	•	131	•	192	—		—		—		•
4	(*R*,*R*)-M5TAC	•	107	•	167	—		—		—		•
5	(*R*,*R*)-M6TAC	•	99	•	144	—		—		—		•
6	(*R*,*R*)-M7TAC	•	93	•	128	•	131	—		—		•

(b) Racemic 1-methyl-alkyl-terephthalidene-bis-aminocinnamate

n	Compound	C		Sc		S_o		S_C		S_A		I
2	rac-M3TAC	•	160	—		—		•	226	•	243	•
3	rac-M4TAC	•	137	•	145	•	201	•	202	—		•
4	rac-M5TAC	•	88	—		•	182	—				•
5	rac-M6TAC	•	85	—		—		•	175			•
6	rac-M7TAC	•	101	—		•	158	—		—		•
7	rac-M8TAC	•	87	—		—			153	—		•
8	rac M9TAC	•	83	—		•	145	—		—		•
9	rac-M10TAC	•	98	—				•	135	—		•
10	rac-M11TAC	•	79			•	126	—		—		•

Like in the closely related ferroelectric liquid crystals, one or more chiral centres in the molecule are essential, and the mesomorphic properties of the pure enantiomer or diastereomer differ from those of the racemic mixture. From Figure 18 one can depict a typical representative with antiferroelectric properties; again an azomethine unit and two cinnamoyl moieties form the central core of the molecule[44]. Table 11 compares the mesomorphic properties of the pure diastereomers with the racemic mixtures, both with different aliphatic chain lengths. In most cases the phase-transition temperatures of the mixtures are slightly lower than those of the pure chiral compounds, and increasing chain length decreases the clearing points dramatically.

V. MODERN TOPICS

A. Liquid Crystal Polymers

Hundreds of liquid crystalline polymers have been synthesized to date[47,48]. As compared with the low molecular mass LC's, they have such advantages as easy processing, the capability to form fibres and films, and the possibility to have a liquid crystalline structure frozen in glass; but also such disadvantages as high viscosity and, therefore, much slower times of electro-optical response, which is important, e.g., for display applications. The four most typical structures of liquid crystal polymers (LCP) are shown in Figure 19. The chemical structure of the mesogenic moieties is in general the same,

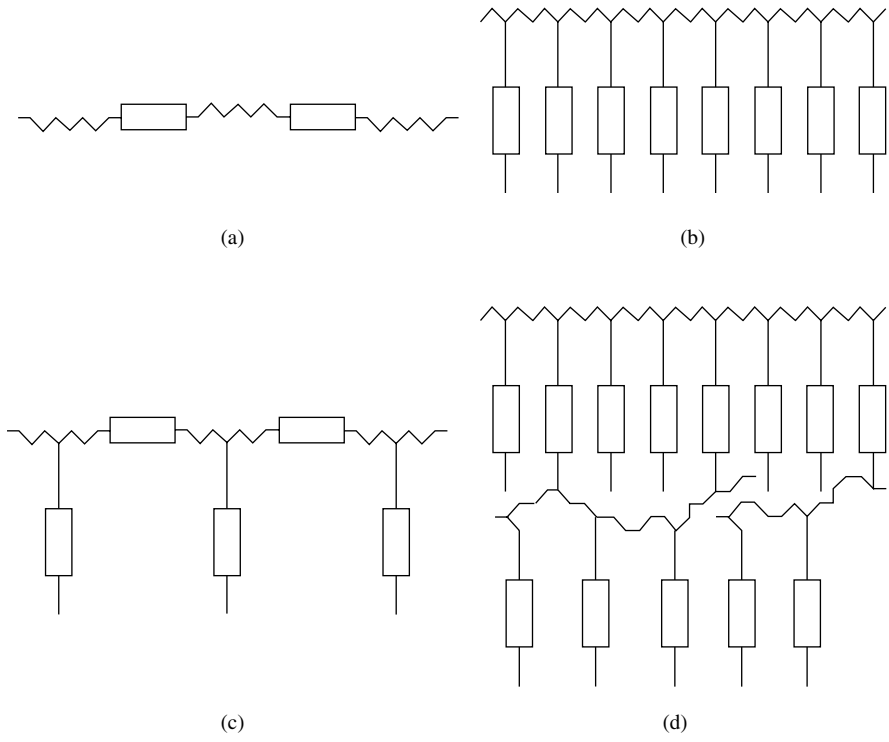
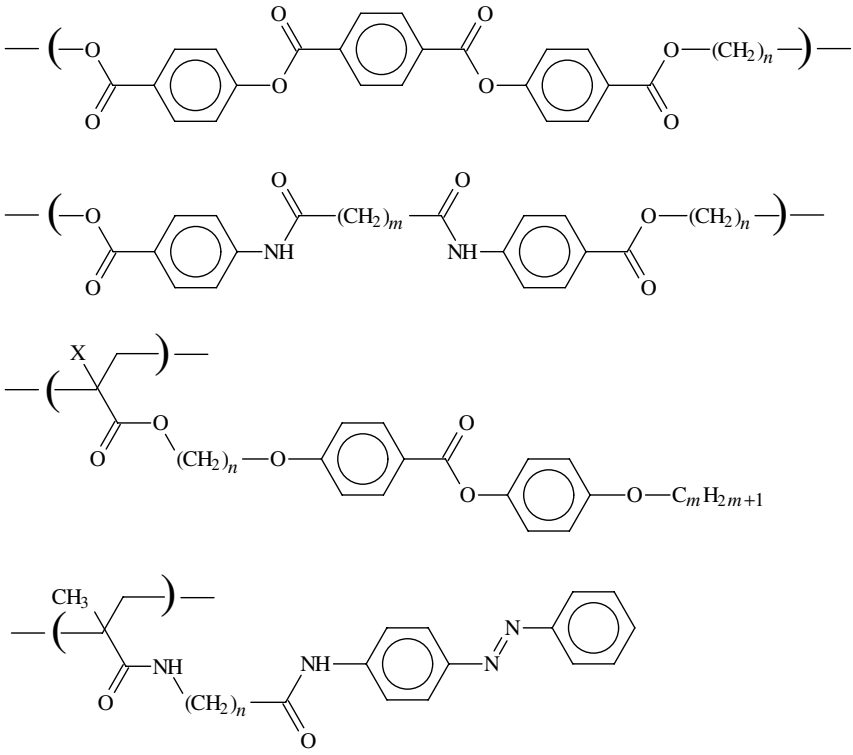


FIGURE 19. Main structural types of the LC polymers: (a) main chain, (b) side chain, (c) combination of (a) and (b), (d) crosslinked polymer networks

as mentioned above for the low molecular mass liquid crystals (Section IV). The only difference would be that the flexible terminal groups at one or both sides of the rigid mesogenic core possess another attachment at the opposite end — either to a polymeric main chain, or to the next moiety, hence forming the chain themselves. A >C=X double bond can be incorporated into different parts of an LC macromolecule. The two most popular are (i) attachment groups between different structural parts of the molecule (main chain, spacers, mesogenic cores, terminal groups), and (ii) the bridging groups between aromatic rings within the mesogenic moiety. Side chain and combined LC polymers containing polymerizable vinyl groups (>CH=CH_2) at the 'free ends' of the mesogenic side chains are also very important for the formation of crosslinked polymer networks.

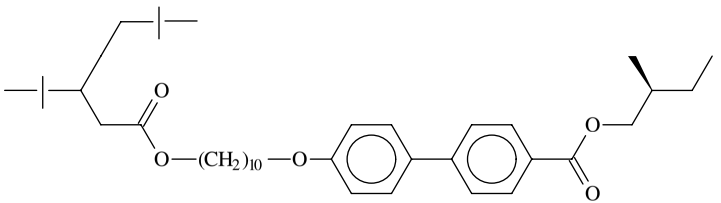
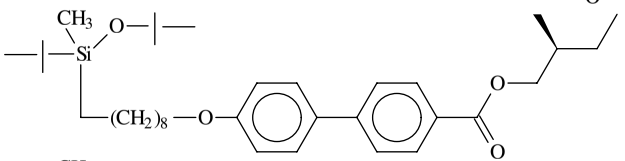
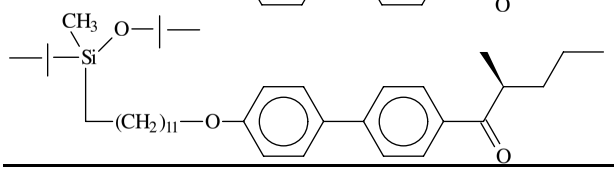
From the very beginning of investigations on the LCP's, the ester group was widely used in the chemical structure of all types of LCP's. Thus, hundreds of the synthesized side chain LC polyacrylates and polymethacrylates contain an ester linkage between the main chain and the side groups[49,50], as do also polychloroacrylates[51] and many others. Side chain and combined polysiloxanes often have mesogenic cores attached to the spacers and/or to terminal hydrocarbon radicals by ester groups. Some LC polyacrylamides have been also synthesized[52]. According to the main chain LC polymers, the amide attachment is also very important, especially for the so-called lyotropic LCP's which form the liquid crystalline phases in non-aqueous solutions. They are widely used in industrial production



X = H, Cl, CH_3; m, n = 5–11

FIGURE 20. Main and side chain LC polymers with ester and amide attachment groups

TABLE 12. LC behaviour and P_S values for polymers with different attachment groups

Polymer	Phase transition temp. (°C)	P_S (nC cm^{-2})
	(gl) 11 S_F* 52 S_C* 57 S_A 116 I	3.0[66]
	(gl) 32 S_C* 115 S_A 123 I	—[67]
	S_H* 58 S_C* 66 S_A 170 I	56[58]

of high-strength construction materials and plastics (Kevlar, Vectra etc.). Figure 20 shows some examples of liquid crystals with ester and amide attachments[53–56]. Just recently some side chain polymers have been reported containing ketone attachment groups, $-C(=O)-$[57,58]. As compared with the ester group, the ketone attachment results in higher clearing temperatures, i.e. in a wider range of LC behaviour. For the compounds forming the ferroelectric SmC* phase, the ketone bonding gives also higher maximum values of the spontaneous polarization P_S. Table 12 presents the phase behaviour and P_S values for some polymers with similar chemical structure of mesogenic side chains, but having different attachment groups between the biphenyl aromatic cores and the chiral terminal radicals.

Many LC polymers contain double bonds in such mesogenic moieties as phenyl benzoates (A)[59], phenyl cinnamoates (B)[60], stilbenes (C)[61] and benzylidenanilines (D)[62] (Figure 21). Chirality is very important in the field of liquid crystals (cholesteric and ferroelectric smectic C* phases). Very interesting is the usage of double bonds to introduce the axial chirality in LC polymers, i.e. the absence of mirror symmetry not due to a single chiral carbon atom, but because of a large mesogenic fragment with lack of symmetry as a whole (Figure 22)[63].

Crosslinked LC elastomers (Figure 19d) are very promising for piezoelectric and ferroelectric applications, and also as non-linear optic materials. The first synthetic step to such materials is the preparation of usual side chain or combined LC copolymers doped with a small part of side chains containing a polymerizable >C=C< double bond at the end (Figure 23 shows a particular example of a crosslinkable LC polymer[64]). The copolymer can be further photocrosslinked, giving an elastic polymer film which reveals

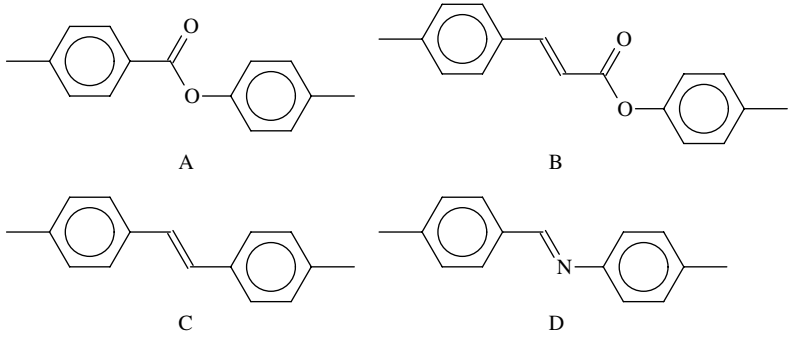


FIGURE 21. Mesogenic aromatic cores used in side chain polymers

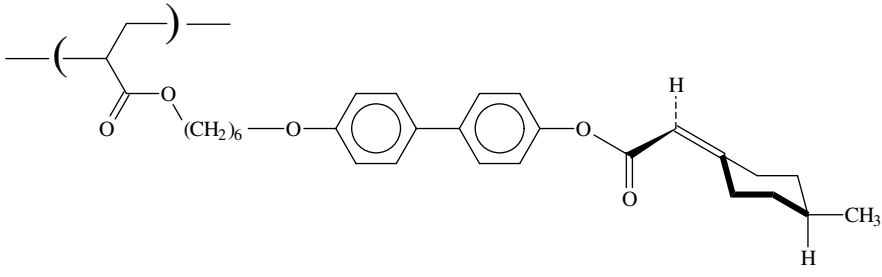


FIGURE 22. Side chain polymer with axial chirality

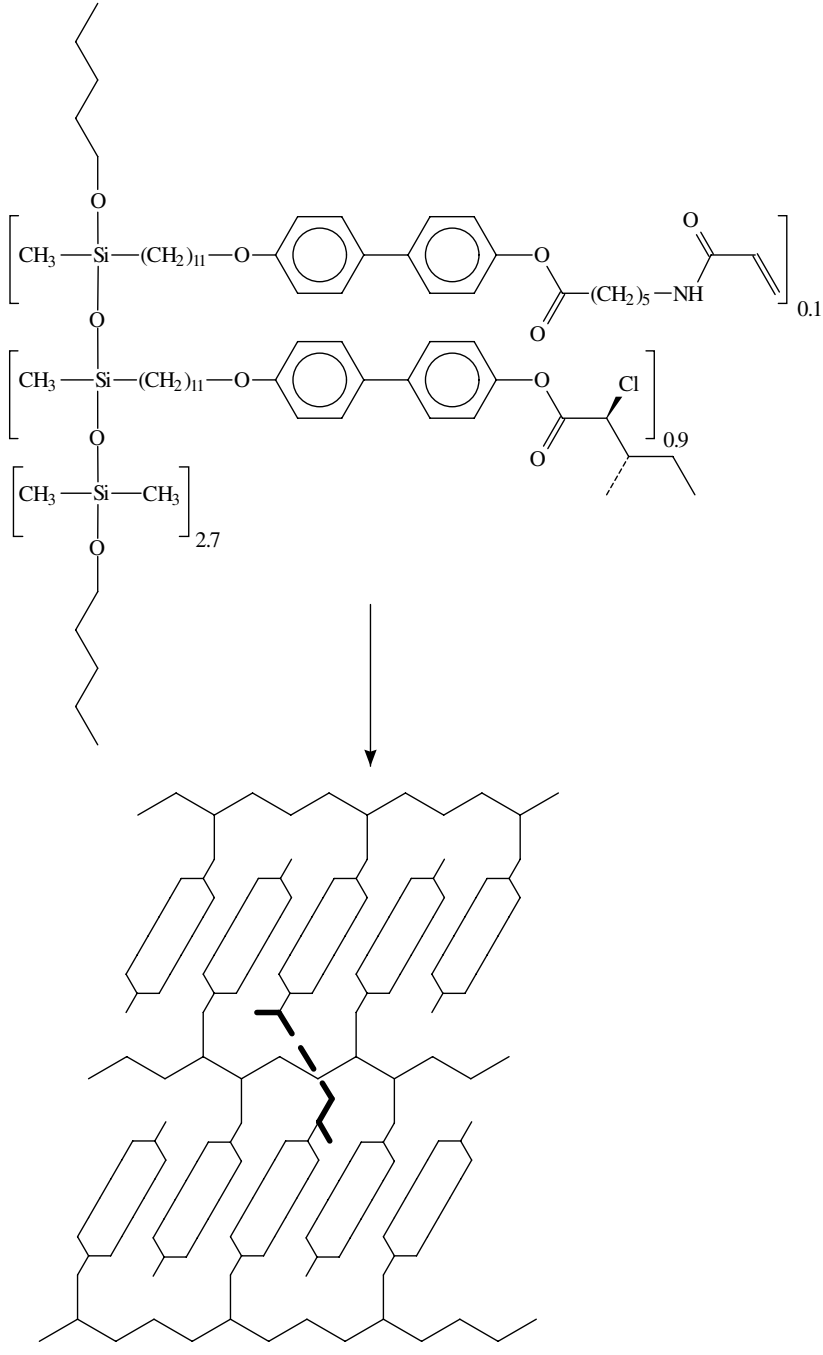


FIGURE 23. Preparation of a crosslinked LC elastomer

TABLE 13. Change in phase transitions after crosslinking the polymer

Polymer	Phase transition temp. (°C)
Not crosslinked	S_X 29 S_C^* 53 S_A 89 I
Crosslinked by 2 wt.% of init. and 365 nm UV radiation	S_C^* 49 S_A

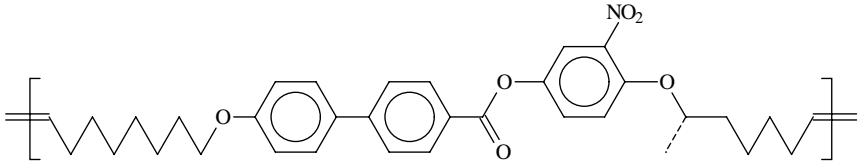


FIGURE 24. Main chain polymer synthesized via olefin metathesis reaction

ferroelectric switching and a piezoelectric coefficient up to 7 $pC\,N^{-1}$. Phase transitions of the crosslinkable polymer and of the resulting LC elastomer are compared in Table 13. Before finishing this short review on liquid crystalline polymers containing >C=X double bonds, we should mention also the recent results of Walba and collaborators[65] on the main chain LC polymers obtained by the olefin metathesis (Figure 24). The approach proposed seems to be very promising for the creation of advanced polymeric LC's with −CH=CH− double bonds in the polymer chain.

B. Metallomesogenes

A rather new class of liquid crystalline materials combines mesomorphic properties with the remarkable magnetic and optical features of inorganic metal complexes, the so-called metallomesogenes. First we will start with a discussion of general aspects of metallomesogenes illustrated with compounds containing different X=Y groups, and then we will proceed to the interesting magnetic properties of LC's containing metal ions. For a more detailed description of this essentially interdisciplinary topic, the reader is strongly referred to the excellent reviews written by Espinet's group[68], Hudson and Maitlis[69] or Giroud-Godquin and Maitlis[70]. The *de novo* design of a metal complex exhibiting mesomorphic behaviour is based on the sophisticated choice of appropriate ligands. The chemical classification proposed in Table 2 (Section IV) presents a wide variety of different functional groups which are common in pure organic liquid crystals. Hence typical metallomesogenic representatives are given in Figure 25. Some of these molecular moieties can in principle be coordinated to metal ions and therefore act as donor groups in ligands suitable for the formation of metal-containing LC's. In contrast, only a limited number of ligand types have tended to dominate the field of rod-like LC's, including the following:

- monodentate ligands: 4-stilbazoles (or azomethines) and 4-substituted pyridines (A,B),
- bidentate chelate moieties: most of them contain carbonyl-type groups such as 1,3-diketones, malondialdehydes (D), carbonic acids, azomethines (G) and sulphur analogues (−C=S) such as thiocarbonic acids (E), 1,3-dithiolenes (F) orthometallated imines (H) and azines,
- miscellaneous ligands like ferrocenes[71] (C), all in Figure 25.

Following the general scheme of the basic structural elements of rod-like liquid crystalline molecules, the donor atom or set of donor atoms can be

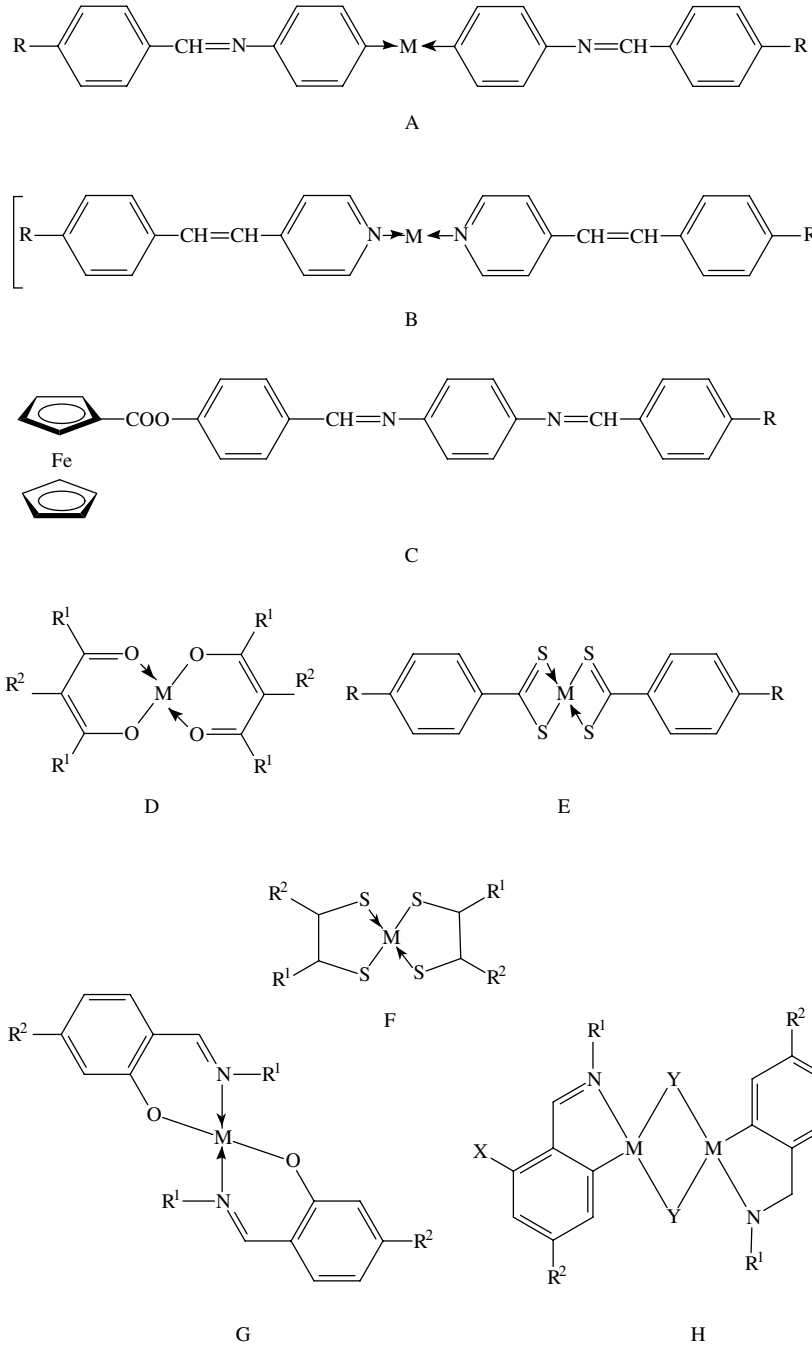


FIGURE 25. Structures of representative examples of metallomesogenes

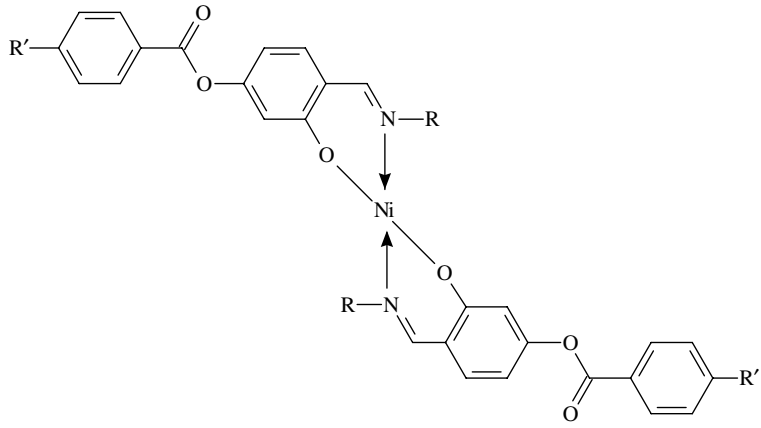
- located in the rigid ring system (A,B,H),
- located in the central middle group (G, H with R^1 being aliphatic and D with R^1 and R^2 being aromatic),
- attached on the aliphatic chains (C),
- attached as a polar group to the central rigid ring system (G, H with R^1 being aromatic, D with R^1 being aromatic and R^2 being aliphatic or vice versa) and, as shown in E and F, all in Figure 25.

The phase formation must be regarded as a consequence of the overall shape of the mesogenic molecule. Consequently, the complexation with long monodentate ligands such as aryls or 4-stilbazoles leads to nematic or smectic phases. It must be pointed out that Hg-aryls (Figure 25A with M = Hg) — presented long ago in the year 1910 — can be regarded as the first example of a metallomesogen[72]. Thirteen years later, Vorländer reported that diarylmercury compounds form smectic phases[73]. Since substituted pyridines are able to form stable complexes with different metal ions, they are often used for the synthesis of metallomesogenes. Bruce and coworkers[74] reported on Ag(II) bis-stilbazole compounds, and showed that the reaction of Ag salts with stilbazoles lead to the first ionic mesogenes with high transition temperatures. The polymorphism of such compounds may be interesting for possible applications in electrochemistry. The first metal-containing liquid crystalline compound based on a β-diketone ligand was obtained by the complexation of Pd(II) with a complex having R^1 = H; R^2 = Ph-OC_8H_{17} (Figure 25D)[75]. The general structure of β-diketones (R^1 = alkyl, R^2 = H) or malondialdehydes (R^1 = H and R^2 = alkyl) used for the synthesis of metallomesogenes is displayed in Figure 25D. β-Diketones are able to form square-planar complexes with a wide varity of metal ions [Ni(II), Pd(II), Pt(II), Cu(II)]. Complexes with R^1 = alkyl and R^2 = H form discotic phases[76,77] whereas compounds having the inverted substitution pattern (R^1 = H and R^2 = alkyl) tend to form nematic or smectic phases[78]. In general, rod-like ligands with alkyl chains extended parallel to each other give rise to calamitic crystals whereas disc-like ligands tend to form discotic phases.

Some examples have promising magnetic properties, but for possible applications it is necessary to increase the chemical and thermal stability of the metal containing LC's. It is known that the complexation of d-metal ions with sulphur-containing ligands leads to extremely stable complexes. Hence a large number of metallomesogenes containing C=S groups were synthesized. The synthesis and phase characterization of dithiolen complexes (Figure 25F) was reported by Giroud-Godquin and coworkers[79,80]. The X-ray structure investigation on single crystals of a compound with R^2 = H and R^1 = Ph-C_8H_{17} with M = Ni(II) showed that in the crystalline phase the phenyl groups in the chains were arranged in *trans*-position[81]. Complexes of Ni(II) and Pd(II) with dithioacids (for general chemical structure, see Figure 25E) and long alkyl chains[82] form smectic phases; the presence of shorter chains results in a nematic phase[70]. Orthometallated imines (Figure 25G) have been synthesized by Barbera and collaborators[83]. The dinuclear M = Pd(II) complexes with Y = Br, Cl, SCN and Y = H, Cl, Br, CN exhibit smectic phases, whereas in the case of Y = OAc^-, the geometry of the bis-acetate bridging unit Pd–$(OAc)_2$–Pd is assumed to cause a drastic deviation from the planar arrangement of all phenyl groups and, as a consequence, no mesogenic behaviour was observed.

One important reason for the current research is the combination of molecular ordering due to the anisotropic physicochemical properties, and the fact that many metal ions possess unpaired electrons and, as a consequence, interesting magnetic properties arise. Selected examples of magnetic investigations on azomethine complexes are given

in the following: The electronic ground state of Ni(II) complexes correlates strongly with their coordination, consequently variations in the coordination which may occur at the crystalline → mesophase or mesophase → isotropic phase transition can result in drastic changes of the magnetic or optical properties. In case of mesogenic Ni(II)–Schiff-bases (for general chemical structure, see Figure 26) it was reported that a conversion of the total spin state of their metal ion as a consequence of a variation in coordination geometry from planar to tetrahedral takes place at the phase transition from crystalline to mesogenic[84]. The reported magnetochromism can be considered as molecular bistability. Therefore, such a kind of liquid crystalline compound may play an important role in the emerging field of molecular electronics, i.e. the use of molecular systems in electronic circuits and devices. The short-range order in a mesogenic phase may provide the existence of magnetically ordered structures in metallomesogenes. EPR investigations on a Cu(II)–β-diketone complex[85] provided evidence for the existence of a one-dimensional magnetic ordered structure in the crystalline phase. Similar results obtained from magnetic susceptibility measurements have been presented for a Cu(II)–malondialdehyde complex[74]. In addition, using polynuclear clusters enables the design of special intramolecular exchange interactions. Such a kind of antiferromagnetic exchange interactions has been reported for a dinuclear oxo-bridged Fe(III)–azomethine complex[86]. The incorporation of a metal ion possessing a large paramagnetic anisotropy enhances the overall magnetic anisotropy and leads to liquid crystalline compounds which can be easily oriented in an external magnetic field. This has been shown in the case of some rare-earth-containing azomethine compounds[87].



R′ = —OC_7H_{15} R = —$CH_2C^*H(CH_3)C_2H_5$

R′ = —$OC_{12}H_{25}$ R = —$CH_2C^*H(CH_3)C_2H_5$

R′ = —OC_7H_{15} R = —$C^*H(CH_3)C_{11}H_{23}$

R′ = —OC_7H_{15} R = —$C^*H(CH_3)C_6H_{13}$

FIGURE 26. Structure of the mesogenic Ni(II) complexes exhibiting magnetochromism

C. Carbohydrate Liquid Crystals

With carbohydrates, these transition temperatures are sensitive to the rates of heating and cooling, to the history of the sample, and due to the impurities by decomposition products, for example. For these reasons, they may not be exactly reproducible between samples and investigators. G. A. Jeffrey[88]

For these the clearing points during heating and cooling show considerable differences (5–7 °C). We have never observed this phenomenon in carbohydrate mesogenes before, and can offer no explanation this time. H. A. van Doren and coworkers[89]

The above statements of two of the most important scientists in this research area characterize a real serious problem, the reproducibility of the experimental results. Nevertheless, outstanding reviews about carbohydrate LC's are available in the literature and strongly recommended for further reading[88,90]. The basic structure element of all cyclic carbohydrates is an X=Y moiety as a terminal or inner carbonyl group and a hydroxy group of an aliphatic polyalcohol forming a cyclic hemiacetal, usually a furan or pyran derivative (Figures 27 and 28). Though liquid crystalline carbohydrates (LC-CH) have been known for several decades, they still have the status of a more exotic class of organic materials. In 1911, E. Fischer observed the double melting behaviour at a series of long-tailed alkyl-pyranosides[91], which were identified in 1938 as thermotropic liquid crystals[92]. Even in 1967 scientists still described mesomorphism of similar compounds only as a double melting behaviour (Figure 29a)[93]. Until the mid-eighties scientific interest was very small, and by 1991 approximately 1000 LC-CH's with mesomorphic properties had been described in the literature. The first thioglycosides were synthesized in 1982 (Figure 29b)[94], the first chiral columnar discotic phase of a peralkylated glucopyranose was observed in 1985, and in the same year the boundary between thermotropics and lyotropics mentioned in Section II blurred (Figure 30a)[95–97], the given S_{Ad} phase in *n*-decyl-*β*-D-glucopyranoside was shown to be identical with the lyotropic one containing up to 32% water (Figure 30b). As a result of the rapid increase new kinds of different

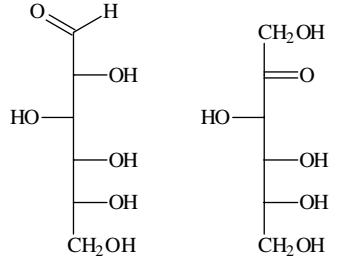


FIGURE 27. D-Glucose and D-fructose as typical carbohydrate representatives

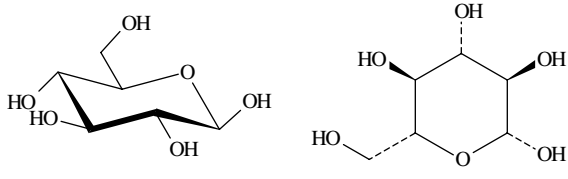
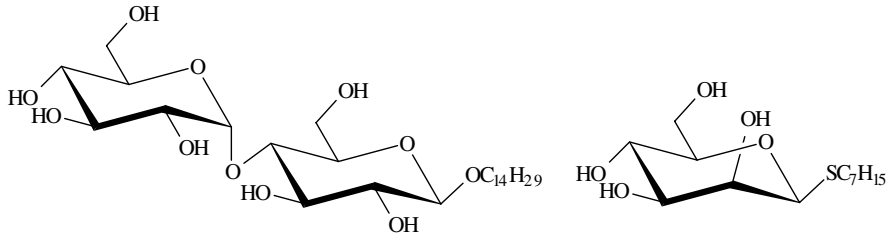


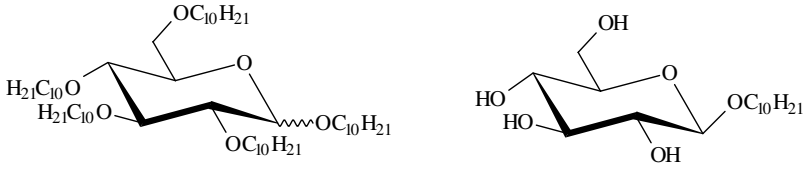
FIGURE 28. Chair conformation and pyrane description of *β*-D-glucopyranose



(a) (b)

C 106 ? 258 I C 64 N 151 I (°C)

FIGURE 29. (a) 1-Tetradecyl-4-*O*-(α-D-glucopyranosyl)-β-D-glucopyranoside and (b) 1-heptyl-thio-α-D-mannopyranoside



(a) (b)

C 27 (D 33) I
C 31 (D 37) I

Cl 65 C2 70 SAd 134 I (°C)

FIGURE 30. (a) Penta-*O*-decanoyl-(α/β)-D-glucopyranoside and (b) 1-decyl-*O*-β-glucopyranoside

LC-CH classes were investigated, N-substituted aldonamides showing a lamellar phase without solvent were synthesized[98,99] (Figure 31a) followed by *n*-alkyl-gluconamides in 1986 (Figure 31b)[100] and different alkylamidoglucitols (Figure 31c)[101] as well as the first dithioacetals (Figure 31d)[102]. The mesophase of the latter was first identified to be smectic, but later revised to be discotic hexagonal[103]. Like in common LC's, carbohydrates with short aliphatic chains ($n < 6$) do not normally possess any mesophase, and in mid-sized chain lengths ($n = 6,7$) only monotropic ones could be observed. Extended chains ($n > 8$) lead to mesomorphism, mostly identified as smectic phases. The very interesting family of discotic liquid crystals were accessible at the end of the eighties and beginning of the early nineties: a columnar hexagonal phase was identified via X-ray diffraction[103], the first di- or oligosaccharides with columnar discotic arrangement in 1991[104] as well as the important group of acylated glycosides in the same year[105] (Figure 32). In the last ten years carbohydrate LC's with nearly every kind of typical sugar moiety were synthesized, but in the following we will concentrate on the various kinds of glycosides. In a large number of systems it is possible to establish a structure-mesomorphism relationship. Additionally, well accepted models for the molecular arrangement in the widely distributed S_A phase will be presented.

An excellent overview dealing with liquid crystalline glycosides containing cyclic carbohydrate portions was written by Vill's group[106]; Goodby and coworkers[101] presented a

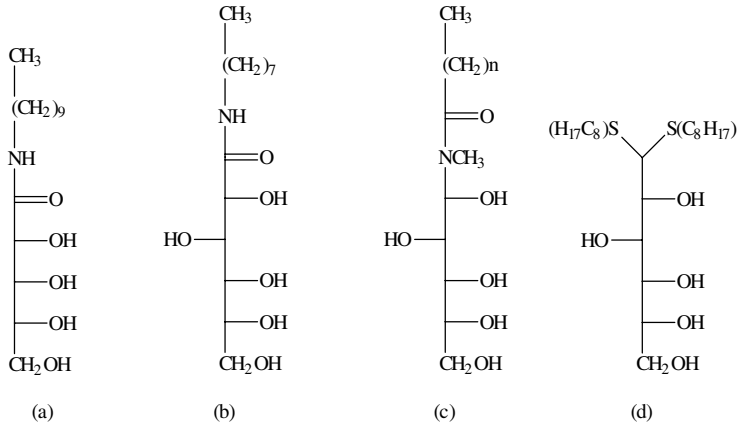
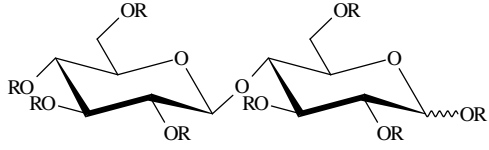


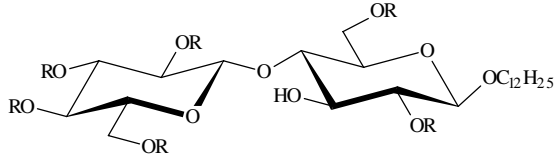
FIGURE 31. (a) *N*-Decylribonamide, (b) *n*-octylgluconamide, (c) 1-deoxy-1-(*N*-methyloctylamido)-D-glucitol and (d) D-glucose-*S*,*S*-dioctyl acetal



R = COC_9H_{19}

C66 Dho 90 I

(a)



R = $C_{11}H_{23}$

C74 D 93 I (°C)

(b)

FIGURE 32. Examples of first discotic LC-CH's

large number of important data related with alicyclic LC-CH's. Following the accessible data, different kinds of glycosides were described in literature:

- (un)-protected cyclic sugar portions with aliphatic glycosides,
- (un)-protected cyclic sugar portions with alicyclic carbohydrate glycosides,
- (un)-protected cyclic di- or tri-saccharides,
- (un)-protected alicyclic di- or trisaccharides.

Simple glycosides represented in the α/β-D-glucopyranose-derivatives are shown in Figure 33a; the related mesomorphic data are given in Table 14. Solid state polymorphism can only be observed in case of the β-glycosides, and all compounds have only a S_A phase. The typical odd−even effect is present, and the α-glycosides possess higher transition temperatures and a larger phase range than their β-anomers. The related mannopyranosides (Figure 33b) and galactopyranosides (Figure 33c) show only the S_A phase, the clearing temperatures of the mannosides in comparison to the glucosides are higher, the melting temperatures are lower (Table 15). The β-galactosides possess higher transition temperatures than the β-glucosides. Again, the latter only show solid state polymorphism. So one can conclude that axially oriented hydroxy moieties stabilize the S_A phase in an unequivocal manner due to a stronger intermolecular hydrogen bridge to the next smectic layer. An increasing number of sugar units like di- or trisaccharides leads in general to an increase in the phase-transition temperatures; in all cases the S_A phase occurs[106]. A different behaviour is expected considering the alicyclic glycosides. Table 16 lists a series of homologues of the mentioned 1-deoxy-1-(*N*-methylalkylamido)-D-glucitol (Figure 31c). An odd−even effect cannot be observed, and without exception the phase transition temperatures rise with increasing chain length. The amphilic character of these compounds is

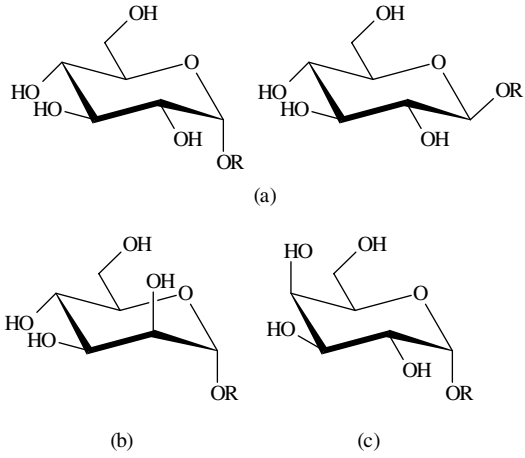


FIGURE 33. (a) α/β-D-Glucopyranoside, (b) α-D-mannopyranoside and (c) β-D-galactopyranoside

TABLE 14. Mesomorphic data of α/β-D-glucopyranosides with different chain lengths (°C)

n-Heptyl	C	53	S_A	99	I	C_1	56	C_2	59	S_A	69	I			
n-Octyl	C	72	S_A	118	I	C	67	S_A	106	I					
n-Nonyl	C	65	S_A	130	I	C_1	51	C_2	68	S_A	113	I			
n-Decyl	C	76	S_A	138	I	C_1	65	C_2	70	S_A	136	I			
n-Dodecyl	C	77	S_A	151	I	C_1	55	C_2	63	C_1	80	S_A	143	I	
n-Hexadecyl	C	108	S_A	175	I	C_1	78	C_2	110	S_A	145	I			

TABLE 15. Mesomorphic data of α-D-mannopyranosides and β-D-galactopyranosides (°C)

n-Octyl	C	55	S_A	134	I	C	98	S_A	133	I				
n-Decyl	C	65	S_A	153	I	C_1	82	C_2	94	S_A	157	I		
n-Dodecyl	C	74	S_A	162	I	C_1	55	C_2	99	S_A	166	I		

TABLE 16. Phase range of various 1-deoxy-1-(*N*-methyl-alkylamido)-D-glucitols (MEGA *n*-2)

n	Name	Phase range
4	MEGA6	C 71 I
5	MEGA7	C 87 I
6	MEGA8	C 78 I
7	MEGA9	C 90 (S_A 61) I
8	MEGA10	C 91 (S_A 88) I
9	MEGA11	C 92 S_A 113 I
10	MEGA10	C 94 S_A 125 I

shown by forming lyotropic phases with water ($n = 8–11, 17$) due to the large number of polar hydroxy groups. The introduction of an ethylendiamine bridge between the glucose moiety and the alkylamido portion destroys the mesomorphism, so that only solid state polymorphism occurs, while methylation of one amino nitrogen restores the liquid crystalline behaviour[101]. Peralkylation of the unprotected hydroxy groups of the pyranoses allows for the synthesis of discotic carbohydrates. Per-*n*-decanoyl-α/β-D-glucopyranose possesses only a monotropic discotic phase within a very small range:

$$\alpha: \quad \text{C 34 (D 27) I}; \quad \beta: \quad \text{C 38 (D 32) I } [^\circ\text{C}]$$

X-ray investigations of the crystal phase of a series of glycosides lead to two different models describing the molecular arrangement in the important S_A phase[107–109]. Comparing the measured value of the layer thickness using X-ray analysis, it is obvious that two molecules arrange in a bilayered way. One model (Figure 34, left side) describes the dimer with a partially overlapping core consisting of the cyclic carbohydrate moiety with the interacting hydroxy groups via hydrogen-bonding. The elongated aliphatic chains form the outside with weak van der Waals interaction between the smectic layers. The second approach suggests the opposite, i.e. the aliphatic chains set up the core and the hydrophilic carbohydrate portions form the outside boundary to the next layer, as in cell membranes (Figure 34, right side). The latter model is in agreement with investigations on the given fluid lamellar lyotropic phase. In general, the hydrogen bridges are responsible for the bilayer formation (the S_{Ad} phase); polar solvents like water or

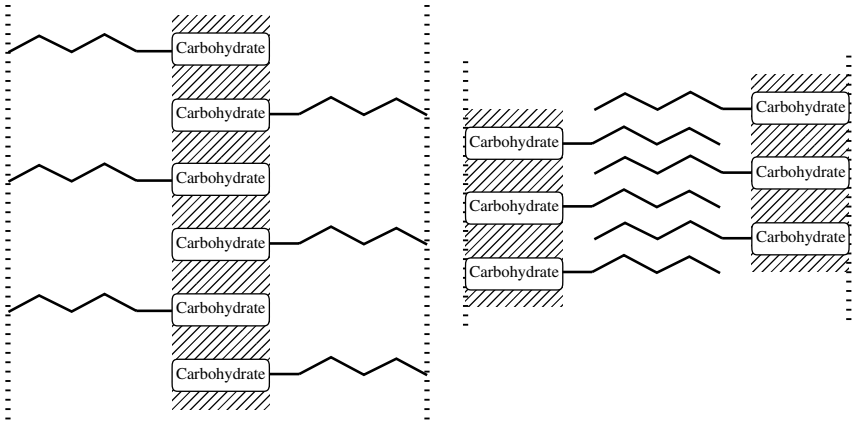


FIGURE 34. Proposed models of bilayer formation in the S_{Ad} phase

alcohols interpenetrate the direct carbohydrate/carbohydrate interaction and increase the distance between neighbouring molecules in one layer[108]. Even more complex systems like *n*-octyl-α-glucosylarabonamid or related molecules[110,111] can be described, and the obtained structural data are in good agreement with X-ray investigations (Figure 35)[112]. The total molecular extension is 22.5 Å, the length of the aglycon is 17.9 Å and that of the octyl-group is 10.9 Å. The measured *d*-value for the layer thickness is 33.7 Å, and Figure 36 gives an impression of the assumed molecular arrangement in the S_{Ad} phase. The most important advantage of carbohydrates is their unlimited presence as natural raw material. A large number of natural products contain sugar moieties, therefore it is a challenge to modify or combine these molecules with other building blocks thus introducing new interesting properties. An actual result is the synthesis of liquid crystalline umbelliferyl-β-D-glucosides[113] (Figure 37, top). As in other lc glucosides as smectic A phase occurs, but a common bilayer formation has not been detected. With increasing chain length the mesomorphic behaviour changes from non-liquid crystalline ($R = C_7H_{15}$) over monotropic to an enantiotropic S_A phase.

The last examples contain the azomethine or Schiff-base unit[114]. Simple pyran derivatives cannot be treated as carbohydrates because the typical amphiphilic character due to the large number of hydroxy moieties is missing. On the other hand, pyran is the central core of all hexose-carbohydrates. The listed compounds contain the classical structural subunits as mentioned in the beginning, so they represent a link between the standard lc's and the carbohydrate family (Figure 37, bottom) . The authors discuss four different types via variation of the bridging units X,Y and the terminal aliphatic chains (Table 17). The combination of the phenol ether with the CH=N group allows only for monotropic behaviour; the turnover of the azomethine results in stable enantiotropic nematic phases. All the amino-bridged derivatives possess an S_A phase, and in the case of short aliphatic chains the nematic phase is present too. The given pyran derivatives demonstrate in a typical manner how the change of substituents influences the liquid crystalline properties. In the following we summarize the basic structure elements of liquid crystalline carbohydrates and try to assume some structure-mesomorphic property relationships on the basis

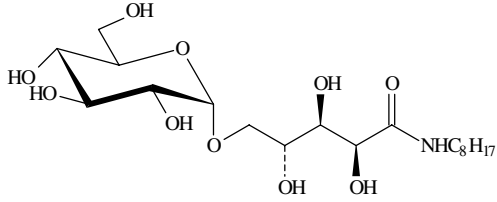


FIGURE 35. Structure of *n*-octyl-α-glucosylarabonamid

TABLE 17. Schematic list of mesomorphic properties

X	Y	Z	Phase behaviour
O	CH=N	OC_nH_{2n+1}, $n = 6$–10	C, (N), I
O	N=CH	OC_nH_{2n+1}, $n = 4$–12	$n = 4$: C, S_A, N, I $n > 4$: C, N, I
NH	N=CH	OC_nH_{2n+1}, $n = 1$–9	$n = 1,2$: C, S_A, N, I $n > 3$: C, S_A, I
NH	CH=N	OC_nH_{2n+1}, $n = 4$–10	$n = 4$–6: C, S_A, N, I $n > 6$: C, S_A, I

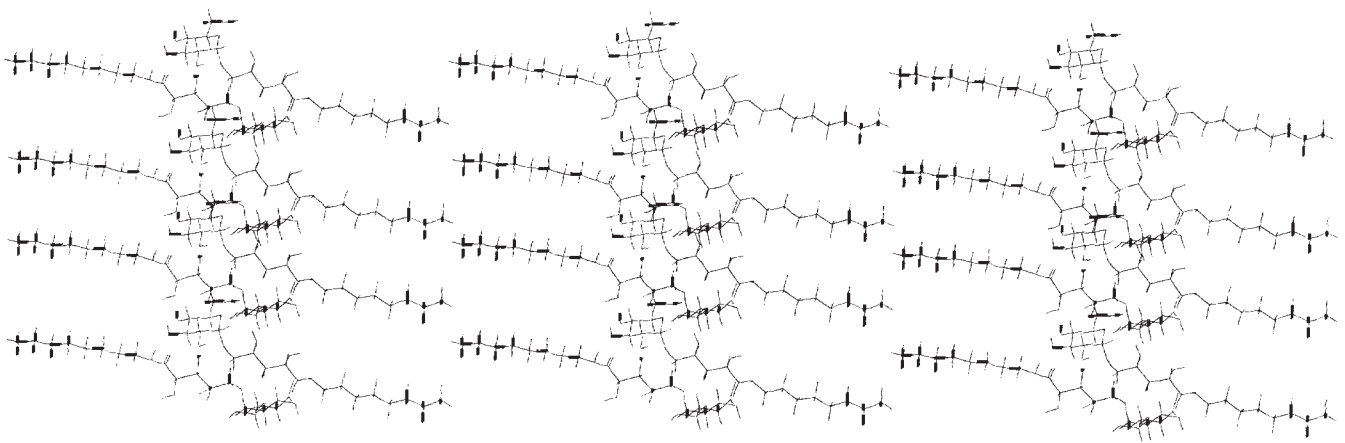


FIGURE 36. Assumed arrangement in the S_{Ad} phase of *n*-octyl-α-D-glucosylarabonamid

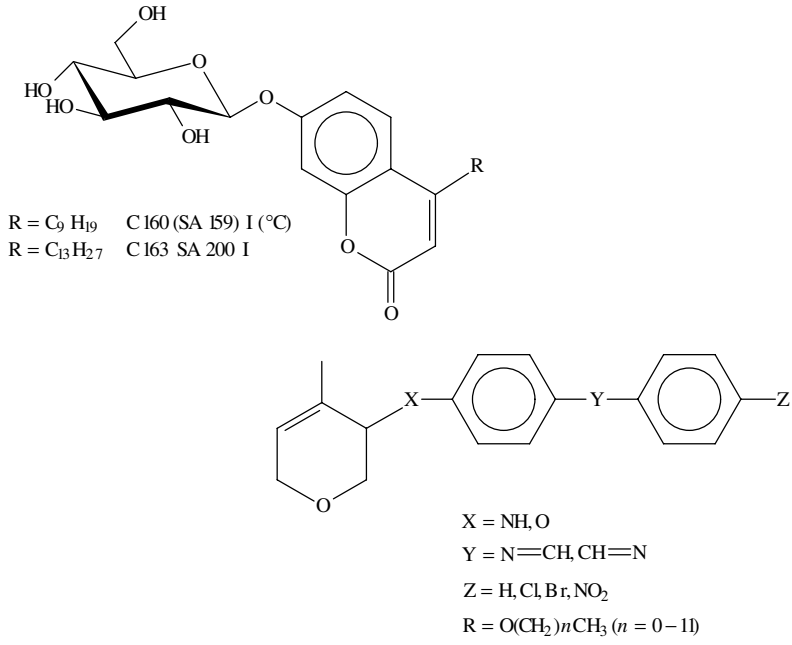


FIGURE 37. Top: First liquid crystalline umbelliferyl glycosides and bottom: simple pyran derivatives

of the investigated systems:

- different carbohydrates (cyclic, alicyclic, mono, di, oligosaccharides) possible,
- long aliphatic chains ($n > 6$) attached as glycosides (O, C, S, N type) favourable,
- α-/β-anomers possible,
- hydroxy groups protected or unprotected,
- acetalization of the carbonyl group destroys lc properties; exception: dithioacetals,
- terminal -OH, -Cl, -CN(!) moieties destroy lc properties.

For the next years a rapid increase in this field of research is expected.

D. Ferroelectric and Antiferroelectric Liquid Crystals

In solid state all the 10 pyroelectric crystal groups allow in principle for bistable switching behaviour. This is the proper ferroelectricity. Under certain conditions ferroelectricity (improper) can be realized in liquid crystals. This was shown by Meyer and coworkers[115] in 1975. Since that time intense activities have been initiated, applying this property for flat-panel devices, switches, light modulators etc. In principle, three effects can be observed and used:

- *S*urface *S*tabilized *F*erroelectric *L*iquid *C*rystals (SSFLC)[116]: Here all three vectors of spontaneous polarization (P_S) are initially aligned by surface effects in thin cells (*ca* 2 µm). The switchability is due to 180° rotation of the P_S vectors on a cone.
- *D*eformed *H*elical *F*erroelectrics (DHF)[117]: In a thicker cell (*ca* 5 µm) the surface stabilization no longer dominates and a helical structure is formed with the helix axis parallel to the glass plate. The external electrical d.c. field can influence and modulate the helix.

- Electroclinic effect[118,119]: Close to the phase transition from the tilted SmC* phase to the orthogonal SmA* phase the tilt angle becomes soft (soft mode). Consequently, one can realize faster switching times than in SSFLC and DHF cells.

Antiferroelectric LC's with tristable switching have been known for the last ten years[120,121]. The chemistry of ferroelectric and antiferroelectric liquid crystals follows the rules valid for calamitic LC's, but with some additional constraints:

- The structure must build up a tilted phase, commonly a smectic C phase. The molecules contain at least one chiral centre and the symmetry cannot be assumed as C_{2h} symmetry, but only as C_{2v} symmetry. This is consistent with a polar twofold axis perpendicular to the long molecular axis.
- The molecule dipole moment is oriented perpendicular to the long axis.

The first investigated ferroelectric LC is DOBAMBC (*p*-decyloxybenzylidene-*p'*-amino-2-methylbutylcinnamate)[122], the structure is presented in Figure 38. DOBAMBC with a small spontaneous polarization at $T_c - T = 10$ K of *ca* 3 nC cm^{-2} shows a typical behaviour for compounds with X = Y (−C=N−, −C=C−, −C=O−) groups.

Azomethine derived ferroelectric liquid crystals: As DOBAMBC, many ferroelectric LC's were prepared utilizing amyl alcohol as the chiral source. The reason for the small spontaneous polarization of DOBAMBC is the separation between the C=O dipole moment and the chiral carbon. This effect can be explained by the intramolecular rotation or vibration of the carbonyl dipole moment relative to the chiral carbon, because they are not adjacent. There are some rules linking the molecular structure and the direction of the spontaneous polarization (minus or plus). In order to reduce the separation between the carbonyl dipole moment and the chiral carbon, ferroelectric LC's were synthesized utilizing a secondary alcohol as the chiral source. Ferroelectric LC's with large spontaneous polarizations have large dipole moments at the chiral centre. Ferroelectric LC's with halogen or nitrile units connected directly to the chiral carbon were synthesized from chiral lactic acids or amino acids.

Azo and azoxy series of ferroelectric liquid crystals: Several of these were prepared; one of them is shown in Figure 39. Unfortunately, these materials are not so stable and therefore useless for practical applications.

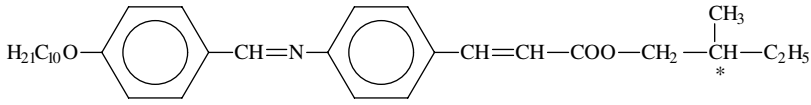


FIGURE 38. Chemical structure of DOBAMBC

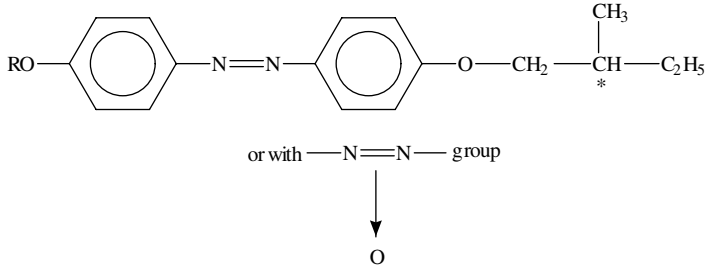


FIGURE 39. Azo and azoxy compounds (R = alkyl)

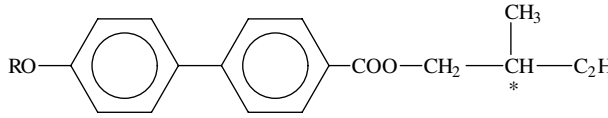


FIGURE 40. Chemical structure of 4-alkoxybiphenyl-4′-carboxylate compounds

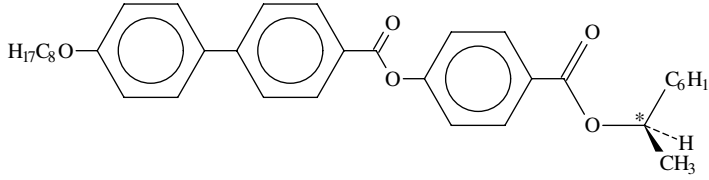


FIGURE 41. Chemical structure of MHPOBC

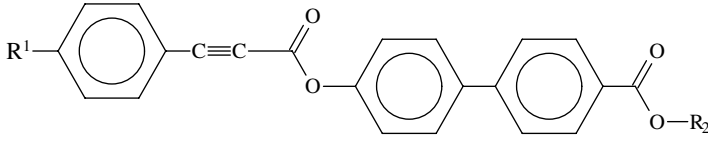


FIGURE 42. Chemical structure of an antiferroelectric liquid crystal (R^1:alkoxy, R^2 = 4-methylheptyloxycarboxyl)

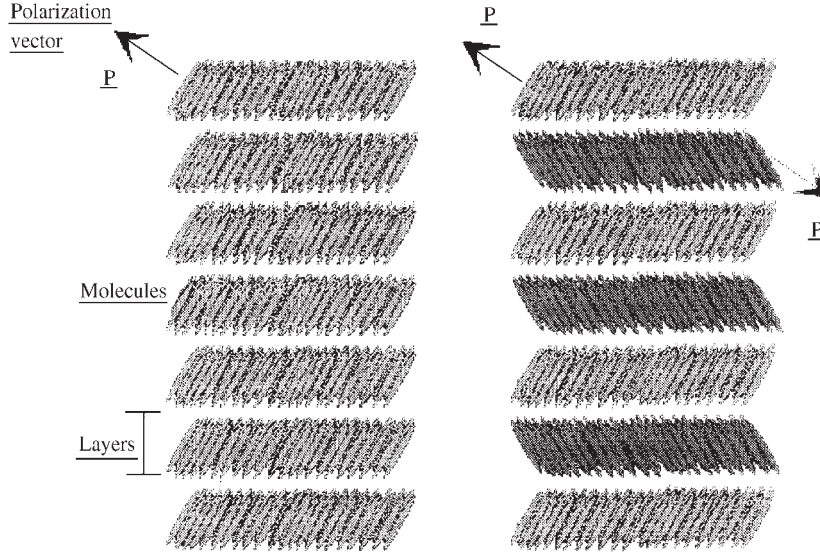


FIGURE 43. Structures of the ferroelectric and antiferroelectric smectic C* phases in their unwound states

Biphenyl and aromatic ester series of ferroelectric liquid crystals: Numerous 4-alkoxy (or 4-alkyl) biphenyl-4′-carboxylate compounds were synthesized. The basic chemical structure of these is presented in Figure 40. These compounds show ferroelectric phases at room temperature, but their spontaneous polarizations are relatively small.

Several polycyclic ferroelectric LC's were prepared by utilizing amyl and secondary alcohols as the chiral source in which biphenyl and phenyl rings were connected via an ester linkage. Also, various heterocyclic ferroelectric LC's were synthesized by the introduction of chiral units into heterocyclic compounds (pyrimidine or pyridazine rings). Many ferroelectric mixtures consisting of achiral LC's with a smectic C phase and chiral dopand were prepared to improve the value of the spontaneous polarization[123]. In principle, all antiferroelectric lc's show similar structures. 4-(1-methylheptyloxycarbonyl)pheyl-4′-octyloxybiphenyl-4-carboxylate (MHPOBC) exhibits an antiferroelectric chiral smectic phase (Figure 41). The antiferroelectric compound with a similar structure was also synthesized and its physical properties investigated (Figure 42). The characteristic molecular and layer arrangement of the ferroelectric and antiferroelectric smectic C* phases in their unwound states are presented in Figure 43.

VI. APPLICATIONS OF LIQUID CRYSTALS

A. Current Display Technology

The most important application of liquid crystals are electro-optic devices, especially the various kinds of displays. After the invention of the simple twisted nematic display by Schadt and Helfrich[124] in the beginning of the seventies, the development and subsequent commercialization in LCD technology increased in an incomparable way. Table 18[125] demonstrates the triumphal procession of the liquid crystal based devices which was not possible without the tremendous research effort of chemists, physicists and electronic engineers. In the following we want to present the most important display devices and of course the materials which can be tailored for any aspired device property, e.g. nematic phase range, switching time, threshold voltage, contrast ratio and many more. Many of the compounds used contain the X=Y unit described in the previous sections; especially, lc's containing the C=O moiety were used in eutectic mixtures with ten or more components. Table 19 lists the requirements which modern displays have to fulfill[126]. Some of them like contrast ratio or display size, have been already realized with LC modules till now, while others like large viewing angle or brightness have not been established satisfactorily with the current technology. Even new competitors like coloured plasma displays in VGA (video graphics array: at least 640 × 480 pixels, 16 colours or grey levels) resolution are available, and represent alternatives to the LCD technology[127]. In the following an overview about the actual display types is given:

TABLE 18. History of LCD development

Year	Passive/Active device	Application
1971	invention twisted nematic (TN) cell	
1973	TN cell	CMOS LCD calculator
1975	TN cell	electronic watches, and games
1979	TN DOT matrix LCD	alphanumeric displays
1983	TN DOT matrix LCD	graphical displays for pocket computers
1986	super twisted nematic (STN) cell	graphical displays for pocket computers
1987	D-STN B/W display; TFT display	laptop; 3″ TV
1988	colour D-STN display	colour LCD camcorder
1992	TFT display	14,2″ colour display
1994	STN display	10,4″ SVGA colour display

TABLE 19. Profile of displays for multimedia application

Item	Characteristics
Display dimension	20–50 cm diagonal
Number of pixels	10^6
DOT configuration	256 grey scale or full colour
Contrast ratio	>100:1
Viewing angle	$\pm 90^\circ$
Brightness	1000 cd/m^2
Switching time	0.1 ms
Panel thickness	0.1 cm
Temperature range	wider than 10–50 °C
Lifetime	10^5 h

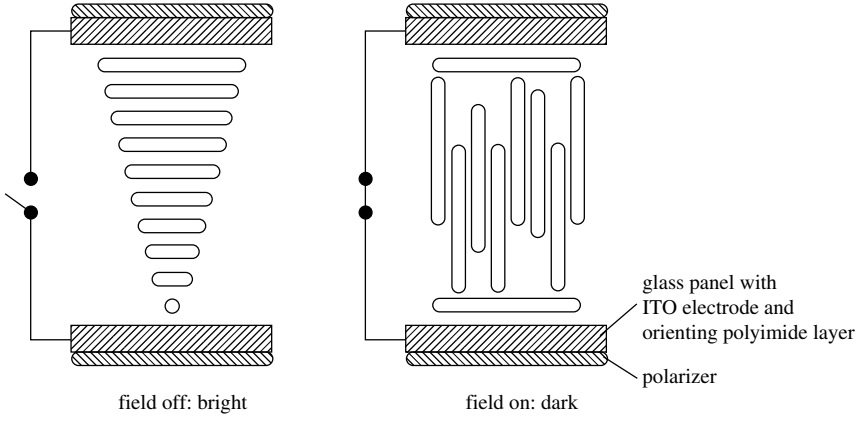


FIGURE 44. Schematic drawing of the TN cell

(1) *Twisted Nematic (TN) Cell*: The classical TN cell consists of two glass panels, which carry on the inside a conductive layer of indium-tin-oxide (ITO) as well as a polyimide layer in a sandwich construction. The polyimide acts as an aligning substrate and orients the director of the first nematic monolayer at the surface; the induced orientation at the top electrode is perpendicular to the one at the bottom but both are homogeneous in the plane of the surface. Typical characteristic properties of a commercial TN element are[128] contrast: 20:1; driving voltage: 3–25 V; temp. range: −55 to +80 °C; switching time, on: 20 ms, off: 50 ms; viewing angle: $\pm 60^\circ$ and a life-time of 10^5 h. Actual TN displays used in laptops allow for a realization of 16 or better 256 grey levels (standard VGA with 640×480 pixel). Without an electric field and due to the nematic potential the alignment propagates through the whole liquid crystal layer (thickness between 2–10 μm) (Figure 44, left side). According to the 90° twist of the orienting layers the director of the nematic phase turns from the top to the bottom electrode by 90° too. With the exception of the first lc monolayers all molecules orient parallel to the applied E field (Figure 44, right side). A thin polarizer foil is attached on top of each glass substrate, and the polarization is parallel to the orientation layer. In case of the field off, the linear polarization of the incoming light follows the twist of the molecules and the display occurs transparent. The polarization of the outcoming light is perpendicular to the incoming one. After switching on the E field, the twist of the nematic orientation is destroyed and the incoming light is blocked at the polarizer[124,129].

(2) *Guest–Host Cell*: A full coloured RGB (red, green, blue colours) display can be realized in two principle ways; in both cases one pixel consists of three subpixels containing the RGB colour. In the first situation a dye (guest) is dissolved in the nematic compound (host); the display appears coloured if the polarization of the incoming light is parallel to the dipole transition moment of the dye, achieved by mounting a polarizer in front of the display. The dye itself has to orient with the solvent — the nematic phase — and must not destroy the nematic ordering, therefore the guest should be of anisotropic shape like the host molecules too (Figure 45). Basic investigations on guest–host systems were presented previously[29,30,130,131]. Figure 46 shows the fundamental guest–host cell suggested by Heilmeier and Zannoni[132]. In the field-off state the polarization of the incoming light and the transition moment are parallel, absorption takes place and the display appears coloured. In the on-state the guest–host mixture orients parallel to the electric field, the transition moment and the light polarization are perpendicular, the display occurs colourless. An outstanding review about the various guest–host displays was written by Uchida and Wada[133]; Ivashenko and Rumyantsev[134] summarized the accessible dye materials. The main disadvantages of the guest-host display are the photobleaching of the dye, the low contrast ratio (*ca* 5–10) and the large fabrication costs. Therefore, with a few exceptions (Table 18) this display has not been commercialized. The second approach follows the classical TV cathode-ray approach: RGB filters in front of the passive or active matrix display allow for the aspired colour mixture. Two different display types are commercially successful: first the simple (passive) matrix (double) super-twisted nematic display (STN-LCD), and the active matrix thin-film transistor display (TFT-LCD).

(3) *STN-LCD*: To overcome the multiplexing limit due to the poor threshold characteristics of the simple TN display, the super-twisted nematic display was established under consideration of the birefringence properties of the nematic phase[135]. The best twist angle of 270° in the cell in combination with a low driving voltage and an optimized multiplexing can be achieved by doping the nematic phase with a small amount of chiral agents, which introduce a right- or left-handed helical arrangement as in the cholesteric phase[136]. The combination of two single STN cells with opposite-handed helices improves the transmission over the whole visible spectral range (Figure 47).

(4) *Passive Matrix LCD*: The realization of high resolution displays, or even the more simple alphanumeric displays, requires the independent addressing of each pixel. Different matrix techniques have been established; common characteristics are the rectangular

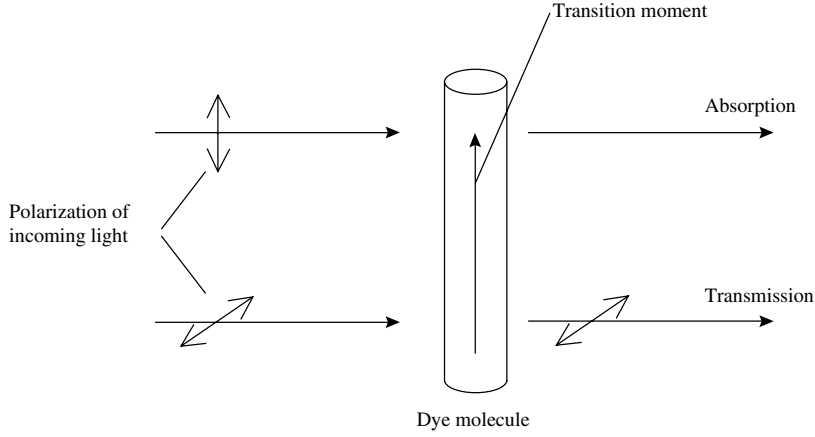


FIGURE 45. Absorption depends on the angle between transition moment and polarization

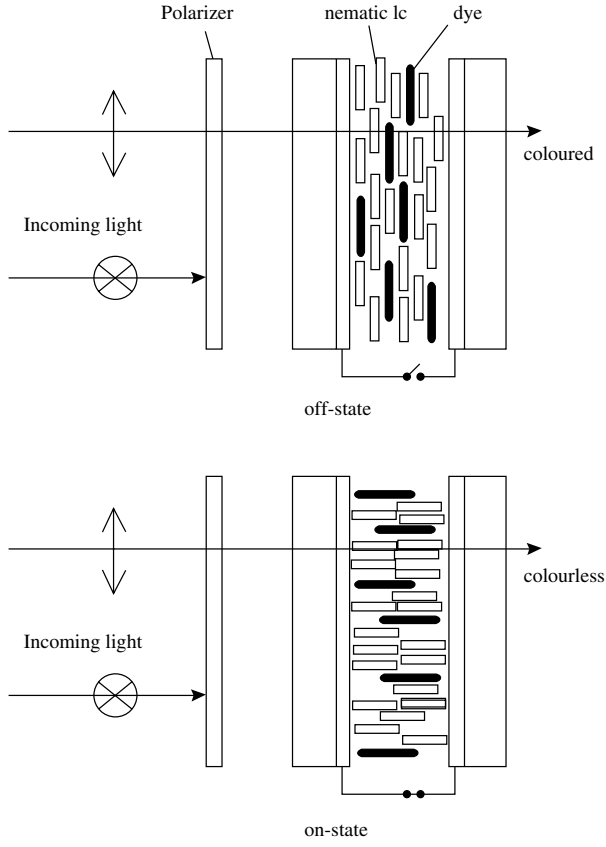


FIGURE 46. Schematic drawing of the guest–host cell[138]

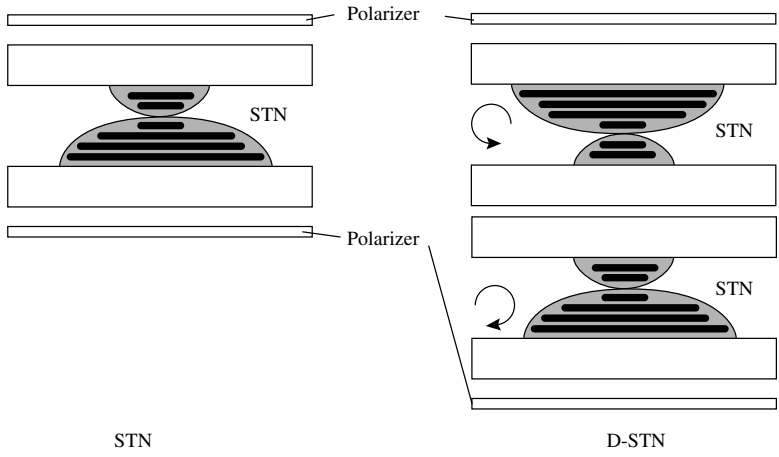


FIGURE 47. Schematic drawing of STN-LCD and D-STN-LCD

arrangement of striped transparent vertical and horizontal electrodes on the inner surface of the top and bottom glass substrates. The unequivocal advantage of the matrix techniqe is the reduced number of necessary electric contacts ($M \times N$, Figure 48). This configuration is often called the X–Y DOT matrix element and allows for the presentation of any characteristic pattern[136]. One can also depict the principle arrangement of the electrodes and the electric paths within a liquid crystal display matrix element. Without an electric field all pixels appear dark, but if voltage is applied to the electrode X_1 (column) and electrode Y_1 (row) is grounded, the cell P_{11} switches to the bright state. For all other pixels the circuit remains open and therefore they stay in the dark state. Besides the mentioned advantages of reduced bonding, this mechanism limits the number of rows and columns and, as a result, the accessible display size, the resolution and the image quality. With increasing number of columns and rows crosstalk occurs, i.e. unaddressed pixels become bright and the aspired contrast ratio decreases dramatically.

(5) *Active Matrix LCD (TFT-Technique)*: The current technique to overcome the above mentioned problems of the passive matrix display is the direct addressing of each pixel independently of each other. A thin film transistor (TFT) is located at one corner of each pixel — at the intersection of the scanning and signal electrode buses — and acts as a switch (Figures 49 and 50). The source and drain electrodes of the TFT are connected to the signal electrode bus and pixel electrode; the gate electrode is attached to the scanning electrode bus, so any interaction between different pixel elements are excluded. Full coloured TFT displays can be realized using RGB filters. Table 20 lists the present

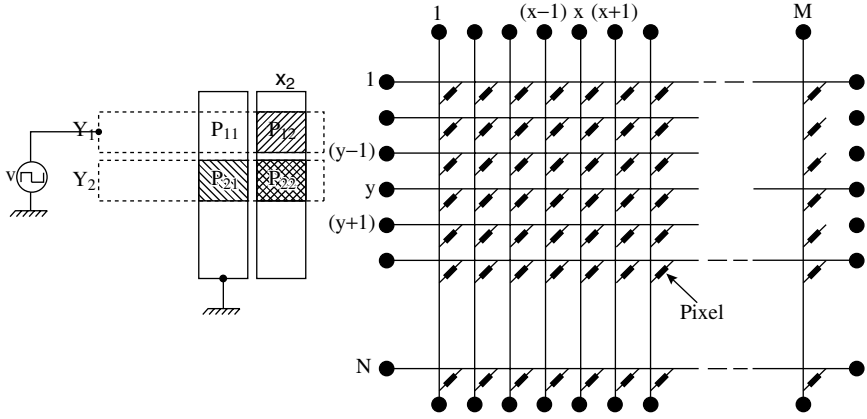


FIGURE 48. Matrix addressing and electric circuit diagram

TABLE 20. Characteristics of Sharp 14″ colour TFT module

Item	Characteristics
Display dimension	36.0 cm diagonal
DOT configuration, pitch	640 × 480 × RGB (VGA or better), 0.150 × 0.450 mm
Displayable colours	16 million
Pixel arrangement	RGB stripe configuration
Contrast ratio	>100:1 (vertical in panel)
Viewing angle	vertical and horizontal: 80 (±40°)
Module dimensions	384(H) × 285(V) × 25(D) mm
Module weight	1.8 kg

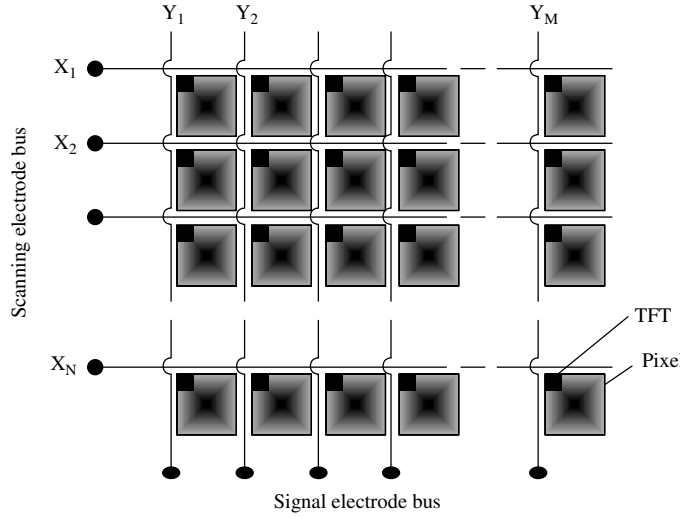


FIGURE 49. Schematic drawing of the active matrix TFT display

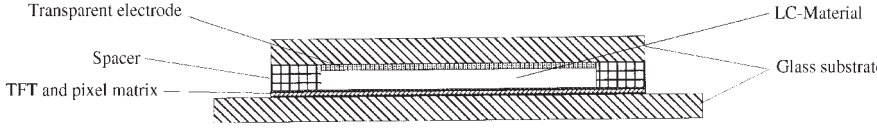


FIGURE 50. Cross section through a single TFT pixel

state of the art for a modern lc display for multimedia applications (Sharp Electronics)[125]. For the beginning of the next millenium different display characteristics are planned, depending on the various kinds of displays and the aspired applications (Table 21)[137].

B. Spatial Light Modulators

The realization of spatial light modulators for application in telecommunication has become of interest since the beginning of this decade. There is also much activity in developing flat panel devices based on ferroelectric or antiferroelectric LC's. Both are about to be introduced into the market. In principle, using nematic and ferroelectric LC's (FLC) enables many different devices to be constructed, e.g. as OASLM (optical addressed spatial light modulators), switches, shutters etc. It turned out that the nematic phase is not fast enough, therefore FLC devices are really good candidates for rapid effects. Because the linear electro-optical response of the electroclinic and DHF (deformed helicol ferroelectric) effects are compatible with the linear change in the resistivity of photoconductive layers, the sensitivity of OASLM based on these effects is much higher than in nematic liquid crystals. One great advantage is that the electroclinic and DHF effect allow the grey scale; this is not the case for SSFLC (surface stabilized ferroelectric liquid crystals) switching. OASLM consists of photosensitive layers of polycrystalline ZnSe with a thickness around 10–15 μm on one side, and amorphous hydrogenized α-Si:H in the regime of intrinsic photoconductivity was used. The ZnSe films exhibited nice spatial resolution in a thickness of 1.3–2.0 μm for the electroclinic mode and 5.5–6.0 μm

TABLE 21. Display products in 2000 (AM: active matrix, PM: passive matrix)

Characteristic	AM-LCD for office machines	PM-LCD for office machines	AM-LCD for HDTV	AM-LCD for mobile equipment	PM-LCD for mobile equipment
Screen size(″)	17	10	30	6	6
No. of pixels	1280 × 1024	640 × 480	1920 × 1035	320 × 240	320 × 240
Pixel pitch (mm)	0.27	0.30	0.345 × 0.36	0.375	0.375
Display colour	full	full	full	full	full
Contrast	100:1	30:1	100:1	100:1	40:1
Viewing angles: Up/down	90° Cone	90° Cone	90° Cone	120°	90° Cone
Left/right	(10:1)	(10:1)	(20:1)	(10:1)	
Response time (ms)	30	50	20	20	30
Screen luminance (Cd/m^2)	150	100	200	300	300
Operating temp. range (°C)	0–50	0–50	0–50	−20–80	−30–80
Storage temp. range (°C)	−20–60	−20–60	−20–60	−40–90	−40–90
Vibration (m/s^2)	15	15	15	40	40
Shock (m/s^2)	300	300	300	1000	1000
Thickness (mm)	10	6	25	6	6
Weight (g)	1000	300	7000		
Power consumption (W)	15	2	50	3	3

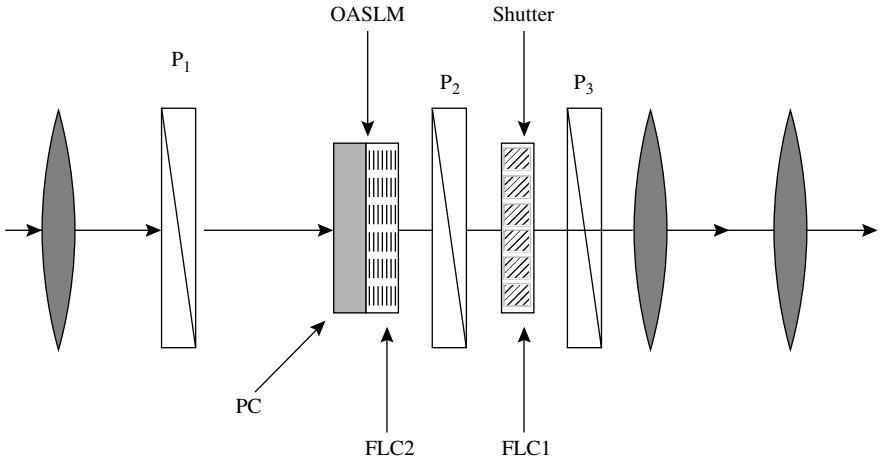


FIGURE 51. The optical scheme of a goggle with fast shutter FLC_2

for the DHF mode. Also, amorphous α-Si:H showed good effects but some problems still arise in the separation of the writing and reading light beams. The ferroelectric samples used for such experiments are mixtures with low rotation viscosities. To prepare good devices, a good surface preparation procedure is essential. OASLM can be used, e.g., as safety goggles or in general to modulate the light. One scheme is presented in Figure 51: PC is the photoconductive layer, P_1, P_2 and P_3 are polarizers, FLC_1 and FLC_2 are active cells. The best version for FLC_2 is a tilt angle Θ of 22.5°. This goggle is now in a very advanced stage[138]. An excellent overview covering this new field of application was presented by Efron[139].

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CHAPTER **10**

Pyrolysis involving compounds with C=C, C=N and C=O double bonds

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I. INTRODUCTION

In the early days of organic chemistry the action of heat alone on a newly isolated compound was often investigated as a means of obtaining information on structure and reactivity, and many important transformations were discovered in this way. In his monumental work of 1929, Hurd[1] made an attempt to collate all pyrolytic reactions reported up to that time according to the functional groups involved. Over the next 50 years only a few research groups were active in developing preparative pyrolytic methods and most of the work was concerned with gas-phase kinetic measurements. In the last 25 years there has been a great resurgence of interest in 'pyrolytic methods in organic chemistry' and this owes a lot to the monograph with this title published by Brown[2] in 1980. In this, the various experimental setups available for performing pyrolysis reactions were described, together with a detailed survey of the most important reaction types.

The technique of flash vacuum pyrolysis (FVP) has now become widely accepted by specialists as being the method of choice for carrying out many types of unimolecular thermal reaction. In more general circles, however, there are still some misapprehensions which limit its more widespread adoption. The first is that it involves extremely severe conditions and is likely to cause fragmentation, racemization or complete destruction of any reasonably complex synthetic intermediate. This arises in part from the apparently high temperatures involved (350–>1000 °C), but it must be remembered that, at the low pressures commonly used (10^{-1}–10^{-6} torr), each molecule only spends a short time in contact with the hot zone. In reality the whole range of activation energies for reaction is accessible including the mildest of conditions (250–400 °C, 10^{-3} torr) corresponding to heating in solution at little above room temperature. A second common perception is that the method is only useful for generating highly reactive products in minute quantities for spectroscopic detection. While studies of this type have been made, FVP is also useful for preparing multi-gram quantities of products for further use. So long as the success of a reaction does not depend critically on having a very low pressure, there is no reason why it cannot be scaled up to multi-kilogram scale and beyond. As is shown by many of the examples later in this chapter, pyrolytic methods in general and FVP in particular are now finding increasing use, both in the routine preparation of often sensitive compounds not readily accessible by other methods and to carry out selected steps in the course of target-directed synthesis.

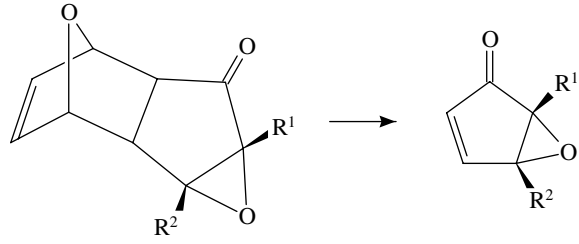
In this chapter we have attempted to present a representative selection of studies involving the pyrolysis of compounds containing C=C, C=N and C=O groups in the period since 1980. Most of the examples involve reaction in the gas phase in a flow system, but more conventional solution thermolysis is also included. In addition to Brown's monograph[2], a number of previous general reviews of pyrolytic methods contain examples from these compound classes[3–5]. There have also been more specific reviews on ketenes[6,7], α-oxoketenes[8] and carbenes and alkynes[7,9], which contain much valuable information. Although diazo compounds might be considered as containing a C=N group, they have been excluded from this chapter since thermal loss of N_2 is such a prominant feature of their chemistry that it is adequately treated in the previous volume of this series devoted to them[10].

II. COMPOUNDS CONTAINING C=C DOUBLE BONDS

A. Retro-Diels–Alder Reactions

The reverse of the Diels–Alder [4 + 2] cycloaddition reaction can be readily achieved by pyrolysis, and since one molecule of starting material generally gives two product molecules it is highly favoured by the low-pressure conditions of FVP. Care must be taken, however, that the two products do not simply undergo cycloaddition again when they are collected. This problem, which is important for reactive 1,3-dienes such as cyclopentadiene, can generally be overcome by collecting the products in separate regions of the cold trap according to their volatility. The retro-Diels–Alder reaction was comprehensively reviewed in 1978[11] and again in 1985[12] and this section only covers more recent examples.

The combination of Diels–Alder and retro-Diels–Alder reactions can be regarded as a protection–deprotection strategy for double bonds and pyrolytic extrusion of a volatile diene such as furan or cyclopentadiene is often the final step in the preparation of reactive alkenes. This has allowed the preparation of the cyclopentadienone monoepoxides **2** by pyrolytic loss of furan from **1**[13], and pyrolysis of **3** gives the strained bicyclic enone **4** which forms a mixture of stereoisomeric [2+2] dimers[14]. Pyrolysis of **5** at 430 °C and 10^{-4} torr results in loss of N_2 to give the carbene which undergoes a Wolff rearrangement to **6** and finally loses furan to afford the alkylideneketenes **7**[15]. Cyclopentadiene has been used to protect one double bond of cyclopentadienone in the adduct **8** which can then undergo benzannulation to give **9**, which is converted by FVP to the little known benz[f]indenones **10** by pyrolytic loss of cyclopentadiene[16]. The benzo analogue **11** has similarly been used as a source of indenone in work directed towards synthesis of kinamycin antibiotics[17]. FVP of **12** provides access to the cyclopentazulene **13**[18], and the corresponding enone[19] and its hydroxy derivative[20] have likewise been generated by FVP at 550 °C of **14** and **15**, respectively. Pyrolysis of the chiral adduct **16** at 320 °C and 10^{-2} torr, leading to extrusion of the diene **18** (Ar = 4-MeOC$_6$H$_4$) to afford (+)-clavularin A **17** in 84% yield, is the final



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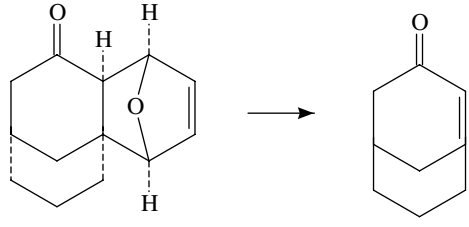
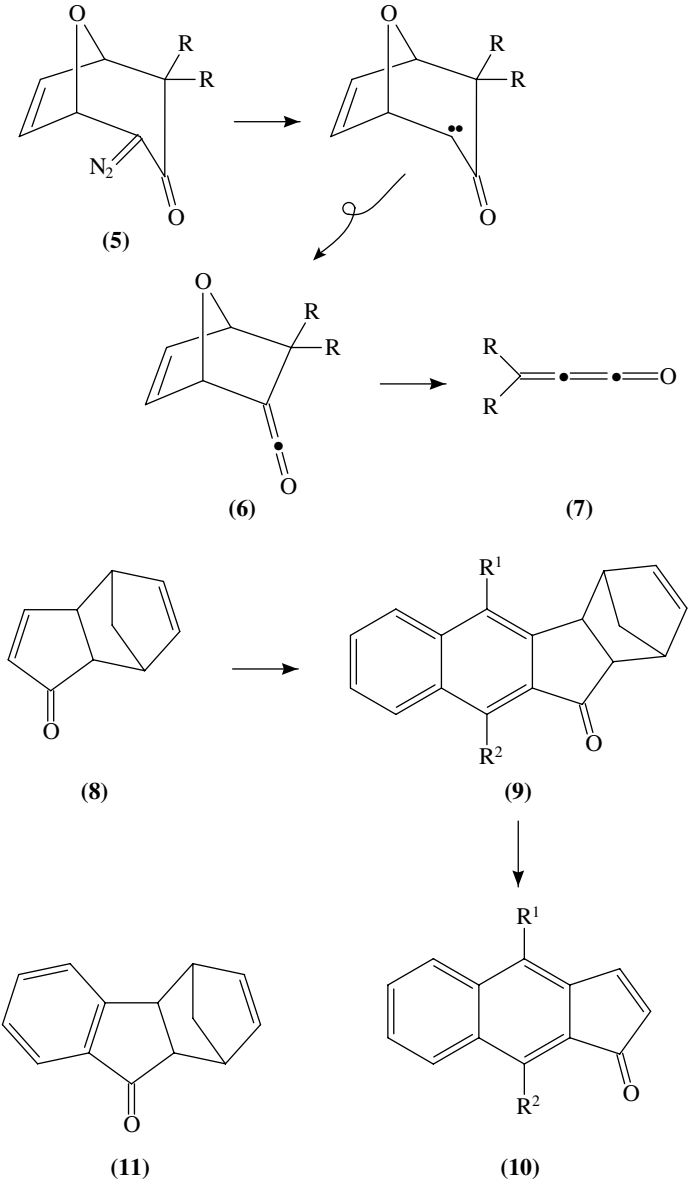
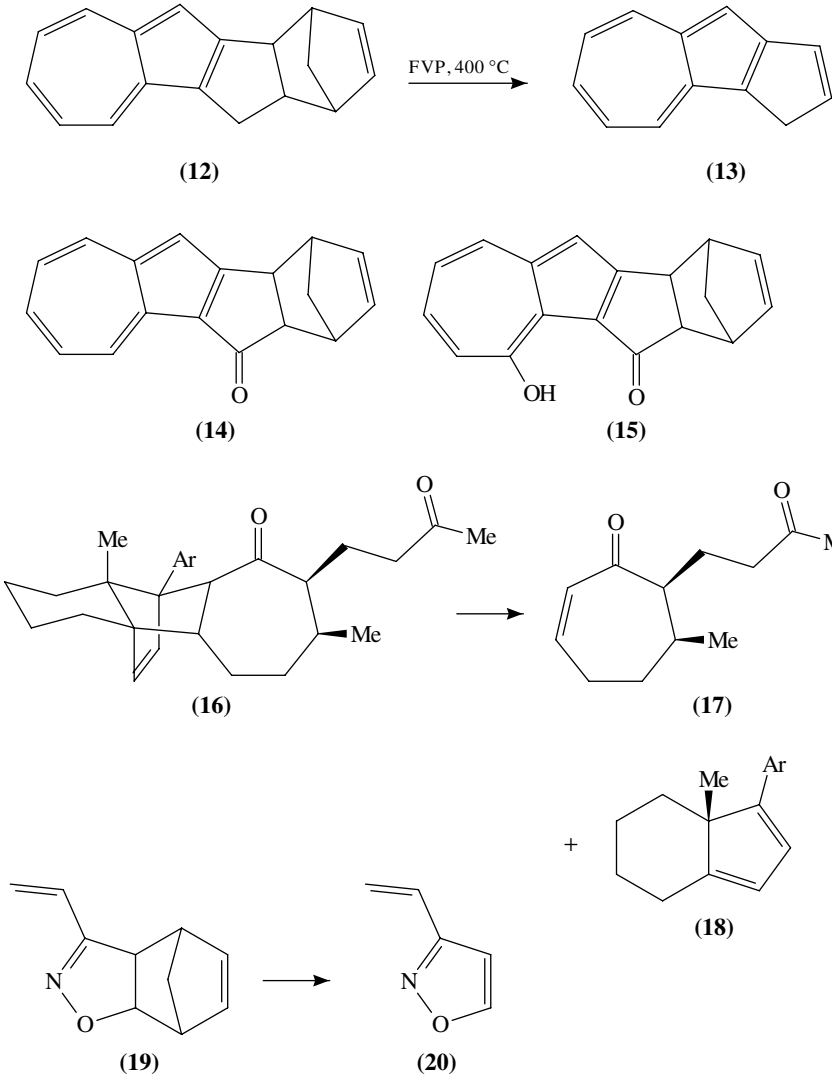


(3) **(4)**

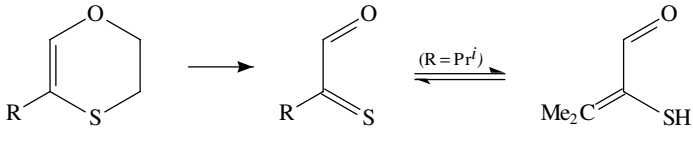
step in its six-step synthesis from cyclohepta-2,6-dienone[21]. A C≡C triple bond may also be protected by Diels–Alder reaction and norbornadiene acts in this sense as a masked form of acetylene. This has been exploited by Paton and coworkers to provide a synthesis of 3-vinylisoxazole[22]. Addition of the 1,3-dipole, acrylonitrile oxide, to norbornadiene gave **19** as a mixture of *exo* and *endo* isomers which lost cyclopentadiene to give the product **20** in virtually quantitative yield upon FVP at 350–400 °C and 3×10^{-3} torr.



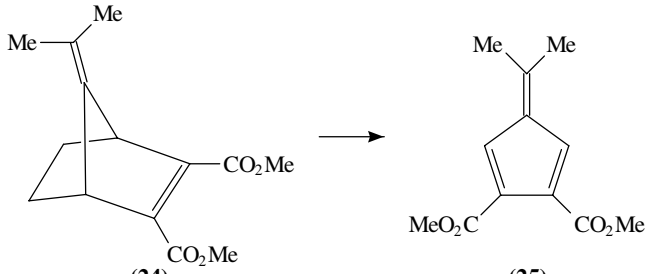


In some cases it is the diene component from the retro reaction which is the desired product and extrusion of a volatile alkene such as ethylene is then ideal. Pyrolysis of the 1,4-oxathiin systems **21** proceeds in this way to give the α-oxothiones **22** which for R = Pr^i, exists mainly as the enethiol tautomer **23**[23]. Thermal extrusion of ethylene from **24** provides convenient access to the interesting fulvene **25** in quantitative yield[24], and the corresponding reaction of **26** at 650 °C and 10^{-4} torr gives the cyclopentadienobenzopyrene **28** in 95% yield, presumably by way of the intermediate **27**[25].

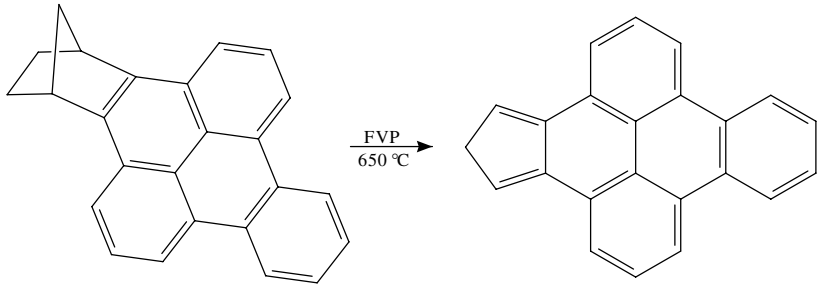
A closely related reaction is the extrusion of the bridging atom from a norbornadiene system in the form of a carbene to leave a benzenoid product. This has been examined as a function of the substituents present for a range of examples **29** and it was found that when



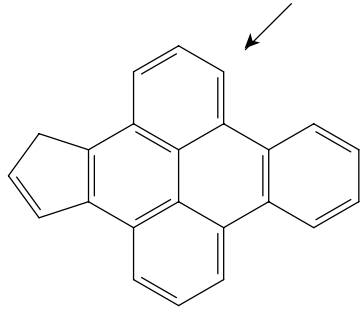
(21) R = Me, Pr^i **(22)** **(23)**



(24) **(25)**

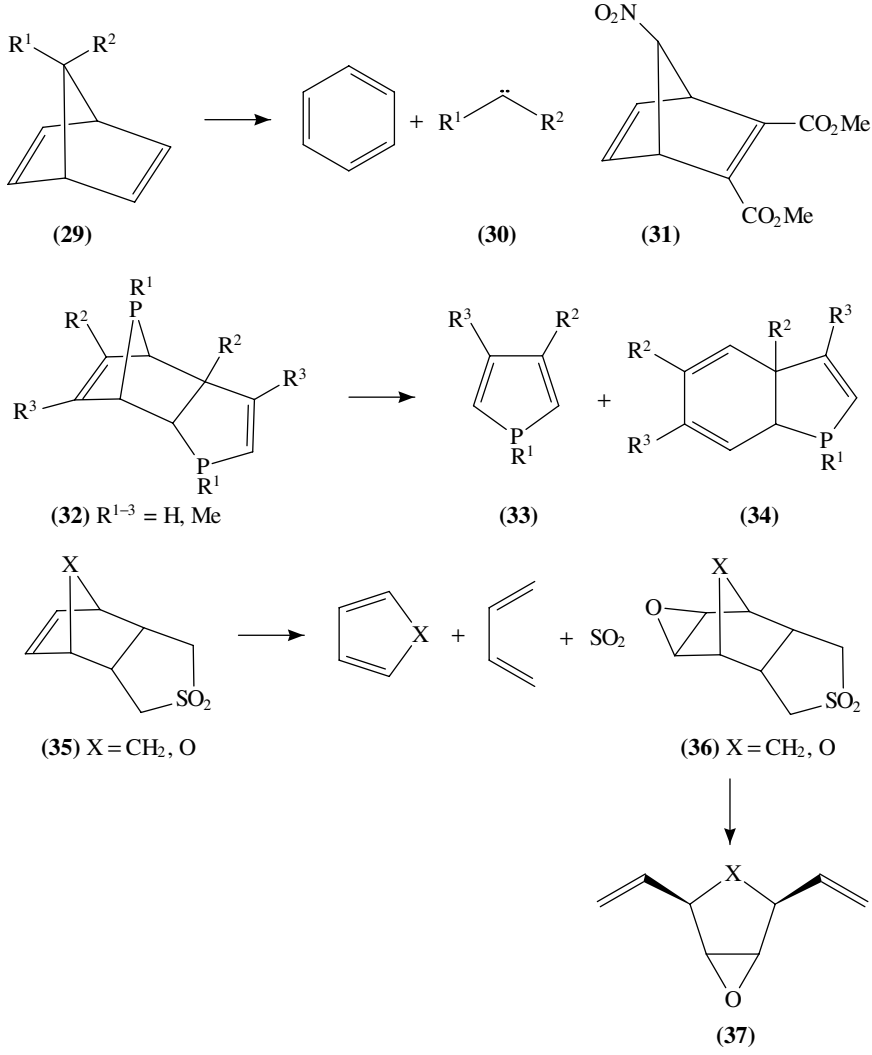


(26) **(27)**



(28)

R^1 and R^2 are weak donors a radical mechanism dominates whereas, if they are strong donors, the carbenes **30** are formed by way of a zwitterionic intermediate[26]. In some cases such as **31** the fate of the carbene is uncertain and FVP at 600 °C gave dimethyl phthalate as the only isolable product[27]. Retro-Diels–Alder reaction of the phosphole dimers **32** at 400 °C gives mainly the phospholes **33** in over 90% yield but a minor product is the dihydrophosphindole **34**, suggesting at least some extrusion of the bridge in the form of the phosphinidene R^1P:[28]. Finally, it should be noted that the retro-Diels–Alder reaction

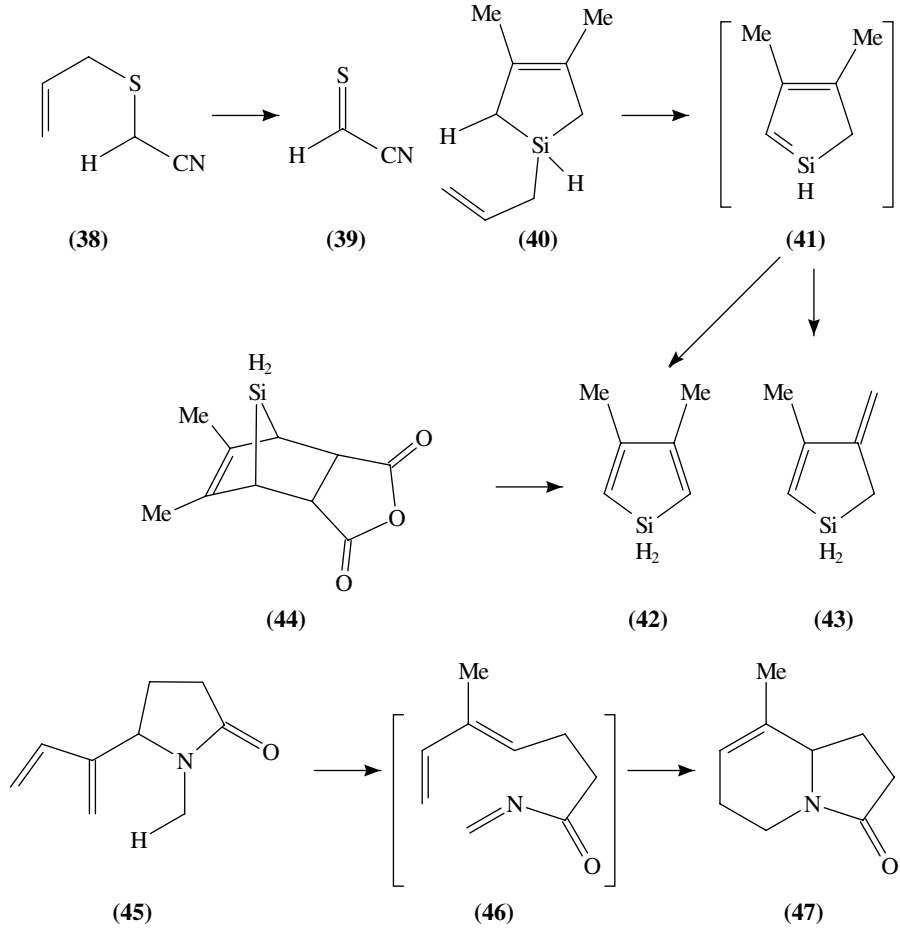


usually depends on having an intact double bond between the atoms which were C(2) and C(3) of the diene component. Modifying this double bond, for example by epoxidation, is likely to result in a complete change in the pyrolysis behaviour as illustrated by the normal retro reaction observed for the tricyclic sulphones **35** at 675 °C, but the complete change for the epoxides **36** which give the divinylepoxides **37** at 700 °C[29]. An example in which a retro Diels–Alder reaction similar to this still proceeds after modification of the double bond is described in Section IV.E.

B. Retro-ene Reactions

Only a few examples of this useful thermal reaction have been described. The elusive thioformyl cyanide **39** has been generated by elimination of propene from **38** upon FVP at

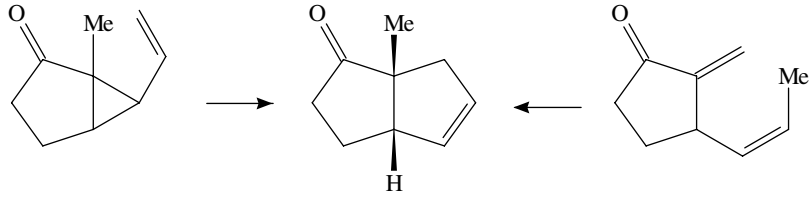
700 °C and characterized by IR in an argon matrix[30]. Similar elimination of propene from **40** at 600 °C gives a mixture of **42** and **43** by isomerization of the initial product **41**[31]. Interestingly, the silacyclopentadiene **42** can also be formed in a more conventional way by retro-Diels–Alder reaction of **44** with elimination of maleic anhydride. The retro-ene reaction can also take place intramolecularly, and the intermediate **46** resulting from FVP of **45** at 800 °C undergoes an immediate intramolecular Diels–Alder reaction to give the indolizidinone **47** as the final product[32].



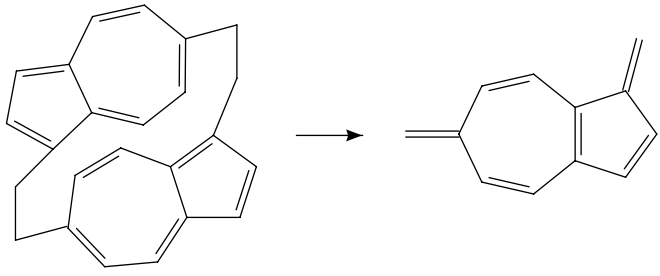
C. Miscellaneous Reactions

FVP of styrene at 850 °C gives benzene, ethylbenzene, naphthalene and other minor hydrocarbon products, while a mixture of isomeric methyl cyclohexa-1,3-dienes is converted under similar conditions mainly into benzene, toluene and ethylbenzene[33]. A vinylcyclopropane rearrangement occurs on FVP of **48** at 600 °C to give the *cis* fused cyclopentanone **49** and this product may also be prepared by FVP of the 1,4-diene **50**[34]. The highly reactive 1,6-azulylene **52** can be generated by reversible 'dedimerization' of the

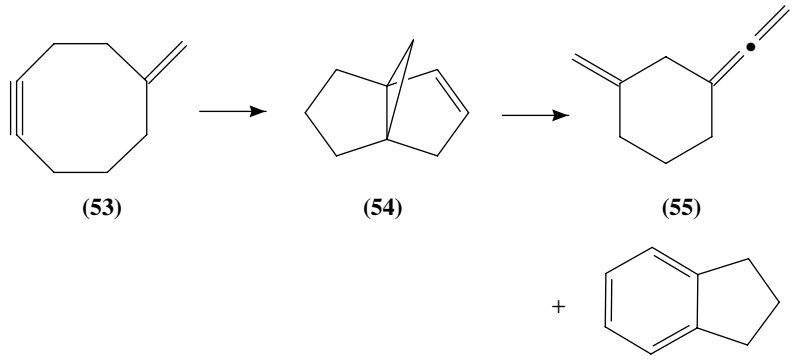
cyclophane **51** and characterized by low-temperature UV-visible spectroscopy[35]. Several mechanisms have been discussed for the unusual conversion of the methylenecyclooctyne **53** into the propellane **54** on FVP at 450 °C, and this product reacts further at 650 °C to give **55** and indane[36].



(48) **(49)** **(50)**



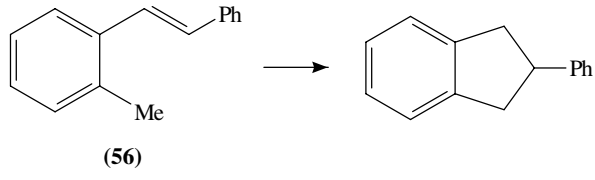
(51) **(52)**



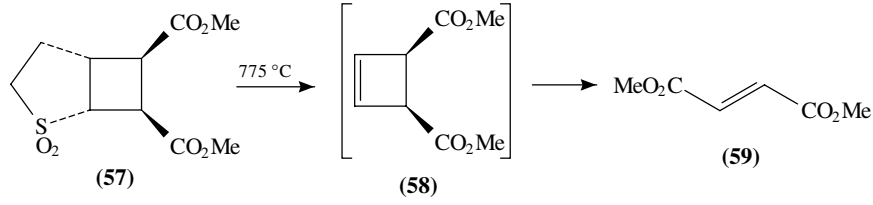
(53) **(54)** **(55)**

An important and frequently observed phenomenon in alkene pyrolysis is the ready equilibration of *E* and *Z* isomers at FVP temperatures above 500 °C. The apparently contrathermodynamic conversion of the *E* into the *Z* isomer has been quantified over the range 500–900 °C for stilbene, cinnamyl alcohol and cinnamonitrile[37]. In the last case, the proportion of *Z* isomer increases to 38% at 900 °C. In certain cases the diradical implicit in the isomerization process can be trapped by an intramolecular reaction and this is exemplified by the formation of 2-phenylindane in low yield from FVP of **56** at 700 °C[37]. The *cis* cyclobutene diester **58** is assumed to be formed as an intermediate in the FVP of the bicyclic sulphone **57** at 775 °C by loss of SO_2 and ethylene. Under these conditions, however, it reacts further to give equal proportions of the *E* diesters **59**

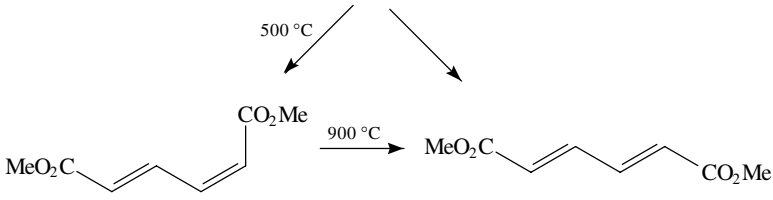
and **60**, by loss of acetylene and cycloreversion, respectively[38]. Independent pyrolysis of **58** gives the *E*, *Z* diester **61** at 500 °C but the *E*, *E* product **60** at 900 °C. The related cyclobutene **62** loses SO_2 only to give cyclohexa-1,3-diene on FVP at 450 °C[38]. This presumably involves the intermediate bicyclo[2.2.0]hexene. We have also observed the *E* to *Z* isomerization phenomenon in the styrylalkynes formed from acyl ylide pyrolysis (see Section IV,D). When these are formed by FVP at 500 °C, the double bond is exclusively *E* as in the starting materials, but by 700 °C there has been up to 50% conversion to the *Z* isomer[39]. This proved to be important in the particular cases **63** with an *ortho* methyl group present, since at the much higher temperature of 900 °C these undergo cyclization to afford 2-alkenylnaphthalenes **64**[40].



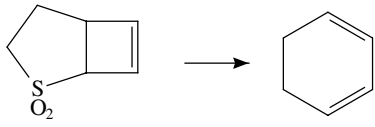
(56)



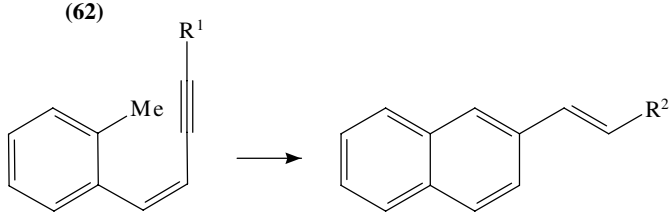
(57) **(58)** **(59)**



(61) **(60)**

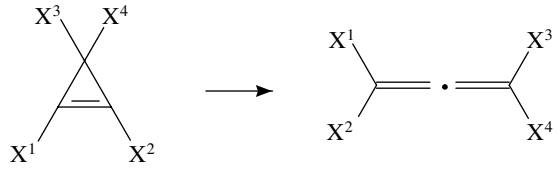


(62)

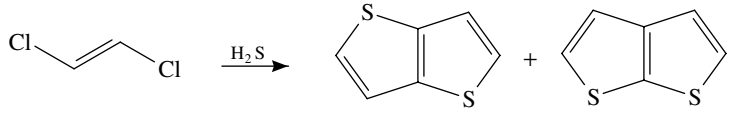


(63) **(64)**

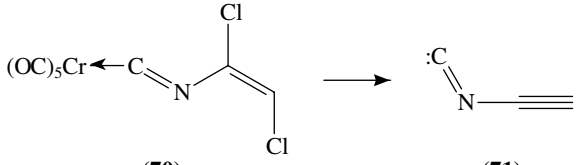
A number of interesting pyrolytic methods involving C=C compounds with halogen present have been described. A range of halogenated cyclopropenes **65** undergo ring-opening upon pyrolysis with migration of one of the groups to give the isomeric allenes **66**[41]. Pyrolysis of 1,2-dichloroethylene **67** in a stream of H_2S gives the fused thienothiophenes **68** and **69** among other products[42]. The rather unstable ethynyl isocyanide **71** has been prepared by FVP of the dichlorovinyl isonitrile chromium complex **70** at 240 °C[43].



(65) X^{1-4} = H, Cl, Br **(66)**

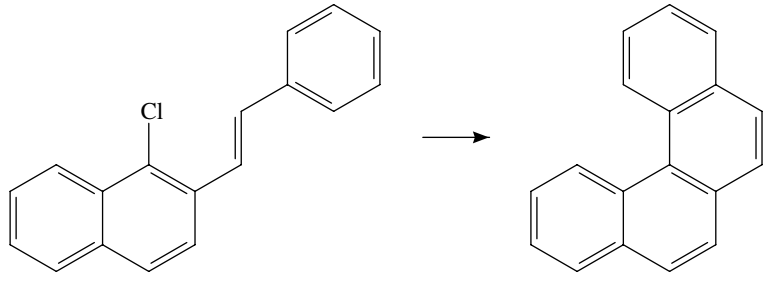


(67) **(68)** **(69)**

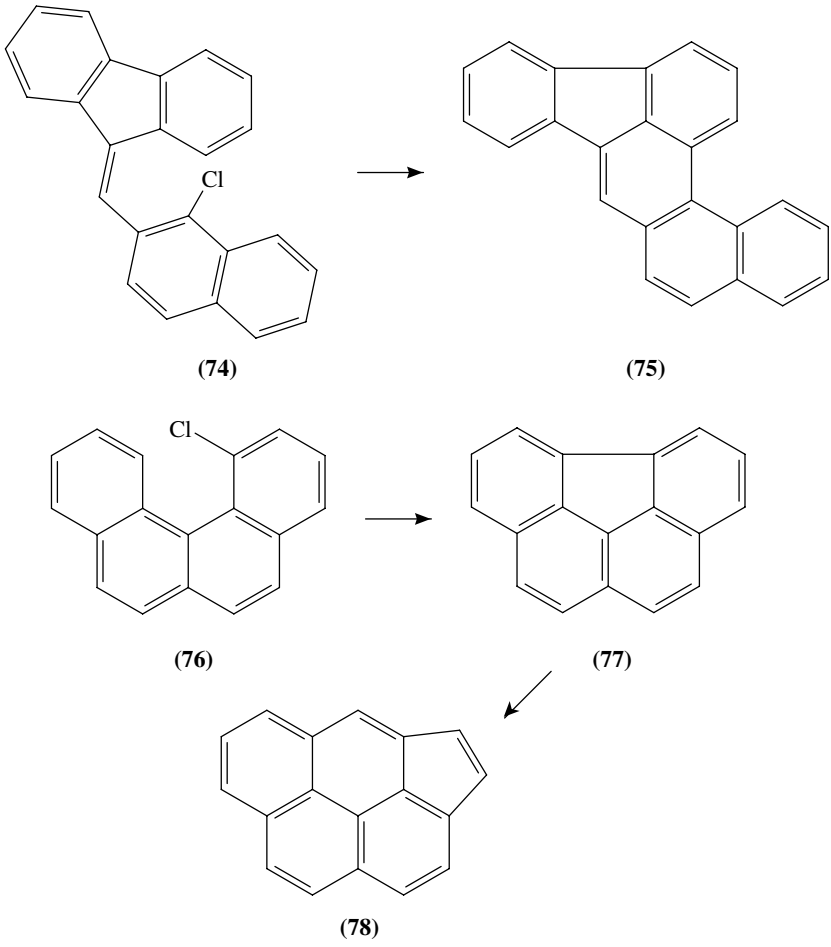


(70) **(71)**

In studies related to the stepwise synthesis of C_{60}, Plater has developed pyrolytic dehydrochlorination methods for preparation of fused polycyclic aromatic hydrocarbons. The reactions, which are thought to involve electrocyclization followed by loss of HCl, require high FVP temperatures of 950 °C. Thus **72** and **74** are converted to the products **73** and **75** at this temperature[44], while benzo[*ghi*]fluoranthene **77** is formed from **76** on FVP at 1030 °C[45]. At the even higher temperature of 1175 °C this product isomerizes to **78**.



(72) **(73)**

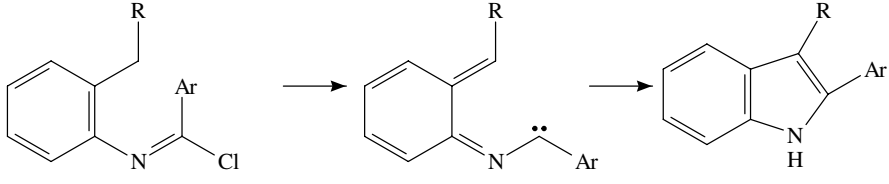


(74) **(75)** **(76)** **(77)** **(78)**

III. COMPOUNDS CONTAINING C=N DOUBLE BONDS

A. Imines, Oximes and Hydrazones

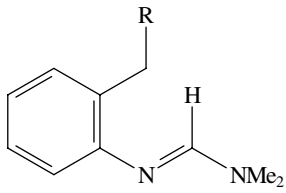
There have been relatively few recent studies in this area. FVP of the α-chloroimines **79** at 800 °C results in 1,5-loss of HCl to give the carbene **80** which cyclizes to afford the substituted indoles **81** in good yield[46]. The correspondingformamidines of the type



(79) **(80)** **(81)**

82 undergo loss of dimethylamine under similar conditions, but this is accompanied by loss of R• to give indole even in the case where R = Me. With the alkyl formamidines **83**, FVP at 900 °C results in loss of Me_2NH and both alkyl groups to give quinoline[47].

FVP of simple oximes **84** proceeds mainly by loss of OH• and fragmentation of the resulting iminyl radicals to give PhCN, RCN and products derived from Ph• and R•. A minor process involves loss of only H• from **84** and cyclization of the resulting radical to give the benzisoxazole **85**, which rearranges to the benzoxazole **86** under the conditions used[48]. The benzyl oximes **87** similarly give $ArCH_2CN$, RCN and products derived from R• and $ArCH_2$•. FVP of ferrocenyl oximes in the range 650–680 °C has been described[49]. Fc−CH=NOH gives Fc−CN and Fc−CHO while Fc−CH=NOAc gives Fc−CHO and acetic acid. The related oxime acetate Fc−C(Et)=NOAc also gives Fc−COEt. An interesting recent study involves the dimedone-derived oxime ethers **88** and **93**[50]. FVP of the former at 450–500 °C gives a mixture of the isoxazole **89**, the azirine **90** and the oxazole **91**. As will be described in Section III.C, pyrolysis of isoxazoles is known to give oxazoles by way of the azirine, but the authors suggest that the initial loss of ethanol from **88** may give the vinylnitrene **92** rather than going directly to **89**. FVP of the closely related allyl ether **93** at 300–350 °C gives the three products corresponding to **89**–**91**, but in addition the nitrile **94**.



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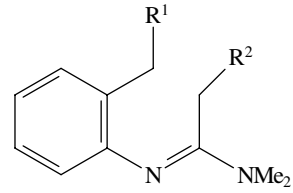

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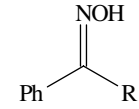

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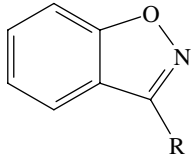

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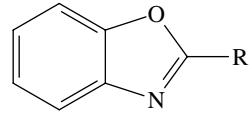

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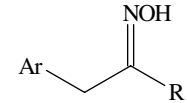
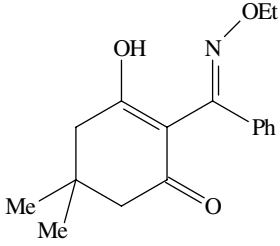


(87)

FVP of the phenylhydrazone **95** of fluorenone at 600–1000 °C proceeds by loss of PhNH• and ring-opening of the resulting iminyl radical to give **96**, which cyclizes and abstracts a hydrogen atom to afford **97**[51]. The *N*-aminoaziridine hydrazone acts as a useful thermal carbene source by loss of styrene and N_2. This method has been applied to the ferrocene system **98** which, upon FVP at 380 °C, gives the carbene **99** which undergoes intramolecular insertion to afford ferrocenocyclobutene **100**[52].

B. Pyrazoles and Indazoles

The pyrolytic behaviour of simple pyrazoles has been studied in detail by Pérez, Yranzo and coworkers. Not only have the products been identified, but in many cases



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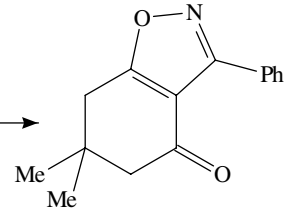

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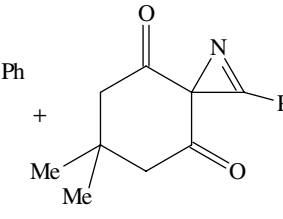

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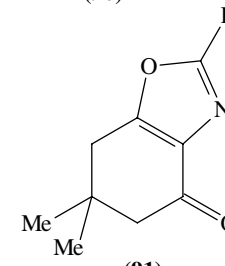

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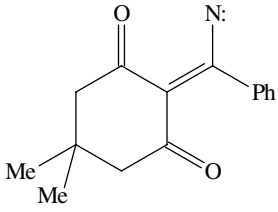

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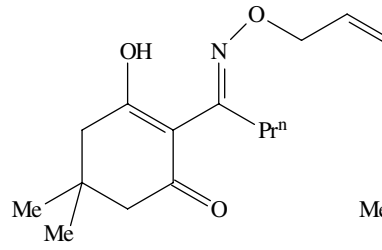

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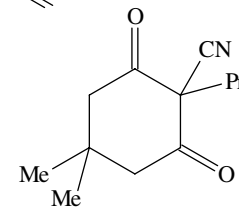

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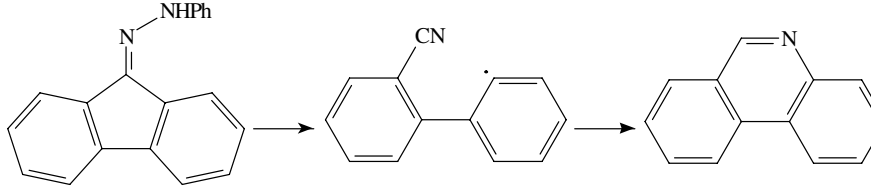
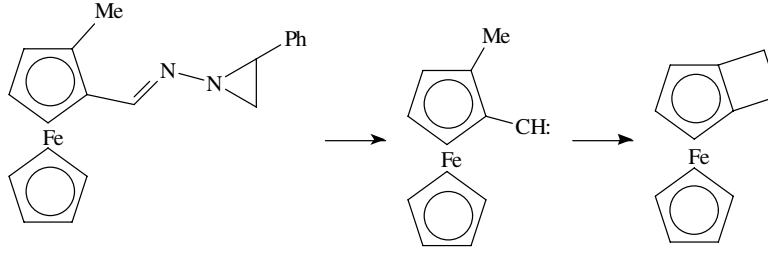
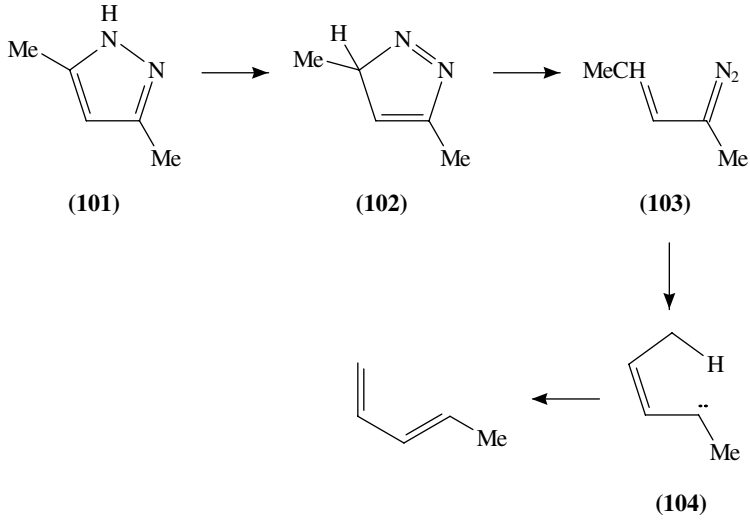


(95) **(96)** **(97)**



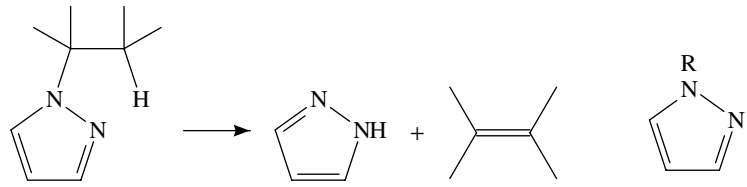
(98) **(99)** **(100)**

rate constants have been determined which may distinguish between different possible mechanisms. FVP of 3,5-dimethylpyrazole **101** at 800 °C gives penta-1,3-diene and N_2[53]. At the higher temperature of 900 °C, there is partial isomerization to penta-1,4-diene. The mechanism involves initial tautomerization to the 3H-form **102**, which ring opens to the diazo compound **103**. This is followed by loss of N_2 to give the vinylcarbene **104** which undergoes a 1,4-H shift to afford the product. The parent compound behaves similarly to give propyne and N_2[54].



(101) **(102)** **(103)** **(104)**

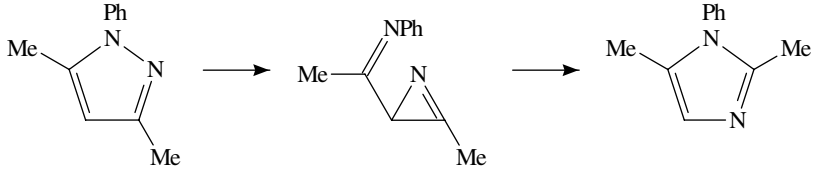
A quite different process is observed for pyrazoles **105** which bear a β-hydrogen atom containing alkyl group on nitrogen. β-Elimination occurs by way of a five-membered transition state to give an alkene and pyrazole **106**. This occurs on FVP of pyrazoles **107** with R = Et, Bu^n, Bu^s and Bu^t at 750–850 °C[55,56], for R = CH_2CH_2Cl and CH_2CH_2Br at 600–670 °C[57,58] and for R = CH_2CH_2Ph and CH(Me)Ph at 640 °C[59]. Theoretical support for the concerted mechanism has been obtained by MNDO methods[60].



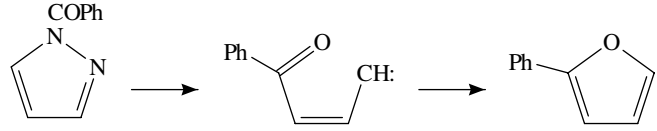
(105) **(106)** **(107)**

Other substituents on nitrogen give quite different results. FVP of *N*-phenylpyrazole at 700 °C causes ring-opening to PhNHCH=CHCN which is in equilibrium with PhN=$CHCH_2CN$, while at 900 °C, N_2 is lost to afford indene[55]. The phenyldimethylpyrazole **108** isomerizes to the imidazole **110** by way of the azirine **109** at 630 °C, while in this case reaction at 920 °C gives naphthalene[55]. FVP of *N*-benzoylpyrazole **111** at 600–720 °C proceeds as for **101** up to the stage of the carbene

112, but this can now undergo electrocyclization to afford 2-phenylfuran[61]. The products also include PhCONHCH=CHCN and its imine tautomer as for *N*-phenylpyrazole. FVP of 3,5-diphenylpyrazole at 600–800 °C involves initial tautomerization to the 3H-form which then directly loses N_2 to give 1,3-diphenylcyclopropene, while under the same conditions 3-methyl-5-phenylpyrazole gives 1-phenylbutadiene and naphthalene[62]. Pyrolysis of both 3,5-bis(trifluoromethyl)pyrazole and the 3-methyl-5-trifluoromethyl analogue leads to complex mixtures of fluorinated alkynes, dienes and enynes at 640–700 °C[63]. In contrast to these results, bis- and tris(pyrazolyl)methane undergo radical decomposition processes on FVP and, in the former case, pyrimidine is formed in low yield at 800 °C from the pyrazolylmethyl radicals produced[64].

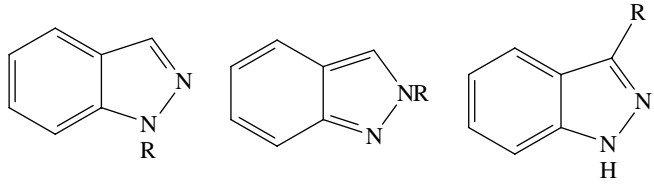


(108) **(109)** **(110)**

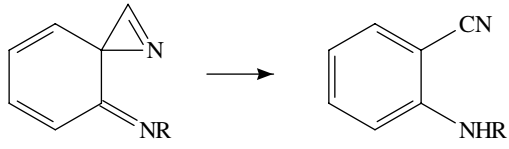


(111) **(112)**

The pyrolysis of indazoles **113–115** with bulky substituents R has also given some interesting results. For R = Ph_3C, FVP of **113** at 400 °C leads to partial conversion into **114**, while at 300 °C **114** gives **113**. The less stable isomer **115** is converted at 300 °C into a mixture of **113** and **114**[65]. For R = 1-adamantyl, **113** and **114** are again interconverted at 600 °C, while at 700 °C the new product **117** is formed from either by way of the azirine intermediate **116**[66].



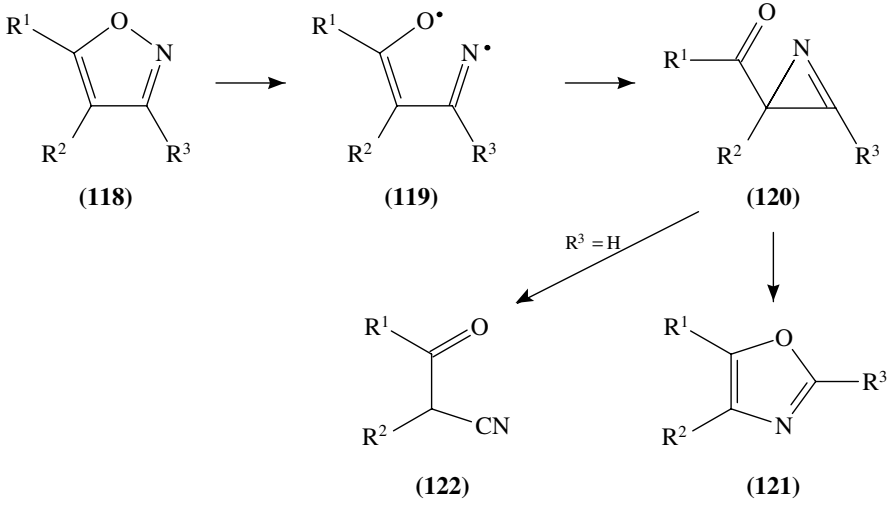
(113) **(114)** **(115)**

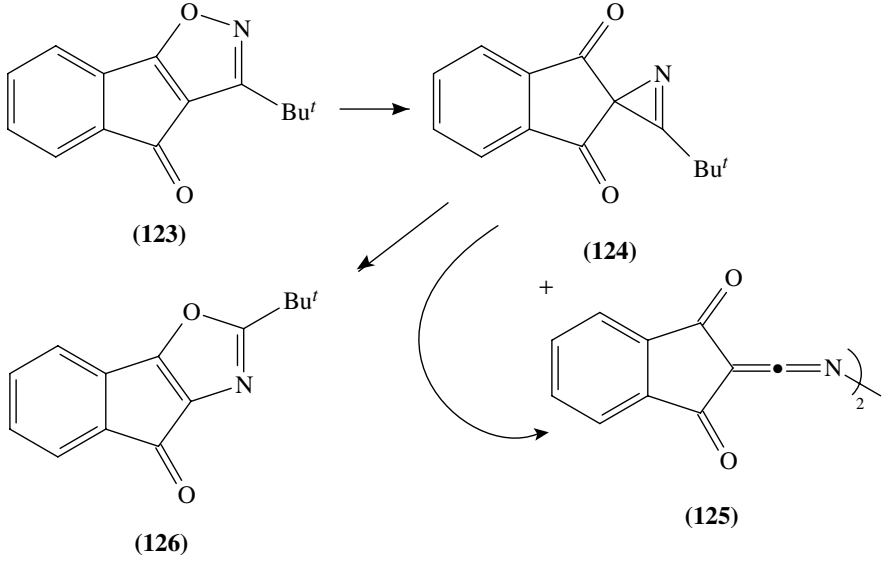


(116) **(117)**

C. Isoxazoles

The pyrolysis of isoxazoles has been examined in detail by Pérez and they show some similarities to the behaviour of pyrazoles covered in the previous section. In general, FVP of **118** leads first to homolysis of the N−O bond to give the diradical **119**, which then rearranges to the acylazirine **120**. If $R^3 = H$, this rearranges to give the nitrile **122** as the final product, whereas in other cases it rearranges to the oxazole **121**. Thus, 5-methyl- and 5-amino-4-methylisoxazole give the corresponding nitriles **122** at 550 °C and 400 °C respectively[67], as does the 4-acetyl-5-methyl compound at 400–450 °C[68]. FVP of 3,5-dimethyl- and 3-amino-5-methylisoxazole at 540–620 °C gives the corresponding

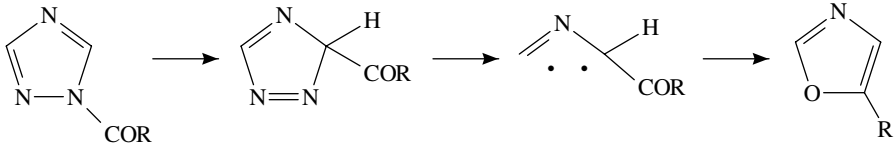




oxazoles **121**, while for the trisubstituted 5-amino-3,4-dimethyl compound at 420–500 °C, the azirine **120** is the isolated product[69]. While 5-methyl-4-nitroisoxazole undergoes the expected reaction to afford the corresponding nitrile **122**, the same product is also formed at 400 °C from the 3,5-dimethyl-4-nitro compound in a process involving anomalous loss of the 3-methyl group[70]. The indenone fused example **123** gives the azirine **124** and the unusual azine **125** at 300–400 °C, and when **124** is isolated and repyrolysed at 400 °C it gives mainly the oxazole **126**, together with a small quantity of **125**[71]. Support for the mechanism of **118** going first to the azirine **120** which can then either give **121** or **122** is provided by calculations using MNDO methods[72].

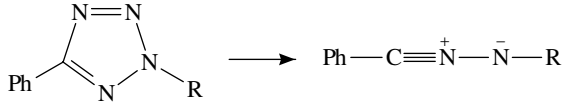
D. Triazoles and Tetrazoles

The pyrolysis of 1-acyl-1,2,4-triazoles **127** proceeds readily under flash vacuum conditions at 800 °C to provide a useful synthesis of 5-substituted oxazoles **130**[73]. The mechanism involves initial 1,2-acyl migration to give the 3H-form **128** which loses N_2 to give the diradical **129** and this then cyclizes. For aromatic R groups yields are around 90%.

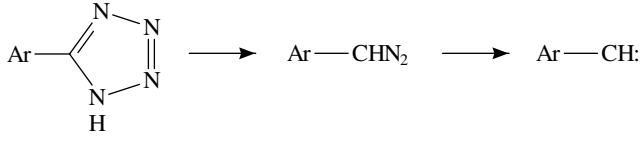


(127) **(128)** **(129)** **(130)**

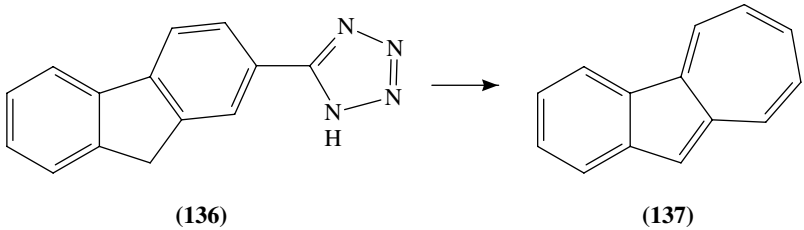
The 2,5-disubstituted tetrazoles **131** readily lose N_2 upon pyrolysis to give the nitrile imines **132**, which can be trapped by an added dipolarophile, detected spectroscopically, or in some cases isolated[74]. FVP of **131** (R = $SiMe_3$) at 440 °C, for example, gives the nitrile imine which can be isolated as a solid at liquid nitrogen temperature and trapped by cycloaddition to methyl propiolate or bis(trimethylsilyl) fumarate[75]. In contrast to this behaviour, the 1H-tetrazoles **133**, readily formed from cycloaddition of HN_3 to nitriles, act as a useful source of carbenes by loss of N_2 to give first **134** and then **135**. This method



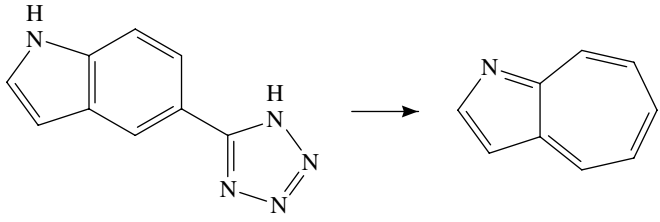
(131) **(132)**



(133) **(134)** **(135)**



(136) **(137)**



(138) **(139)**

has been applied to the synthesis of the azulene derivatives **137** and **139** by pyrolysis of **136** and **138**, respectively[76].

E. Rings Containing Sulphur or Phosphorus

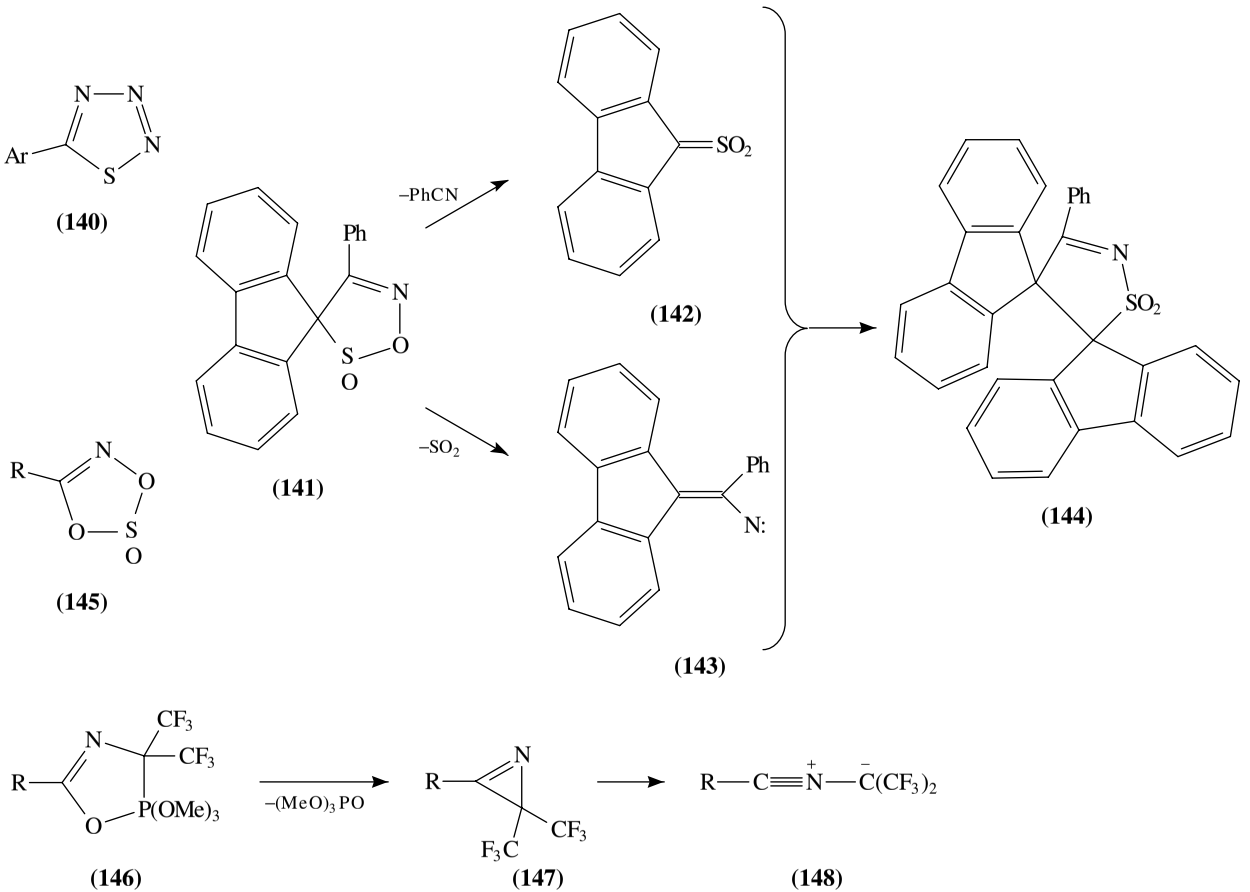
The 1,2,3,4-thiatriazoles **140** act as a convenient source of the highly reactive N_2S. FVP results in fragmentation to afford ArCN and the dinitrogen sulphide, which can be detected by IR[77]. The spiro 1,2,5-oxathiazole 2-oxide **141** formed by addition of benzonitrile oxide to 9-sulphinylfluorene decomposes on solution thermolysis in benzene both by loss of benzonitrile to give the sulphene **142** and by loss of SO_2 to give the nitrene **143**. These then combine to give **144** as the final product[78]. Pyrolysis of the dioxathiazole *S*-oxides **145** results in loss of SO_2 with concomitant migration of R to give the isocyanates, RNCO. This has been applied to the preparation of bis-isocyanates[79] and trimethylsilyl isocyanate[80].

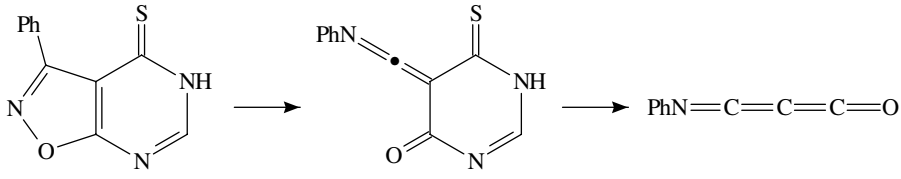
The unusual oxazaphosphole ring system **146** undergoes loss of trimethyl phosphate upon FVP at 400 °C to give the azirines **147** for R = Ph and Bu^t while, at the higher temperature of 700 °C, the nitrile ylides **148** are formed[81]. Both **147** and **148** are readily hydrolysed to give $RCONHCH(CF_3)_2$.

F. Pyrimidines and Diazepines

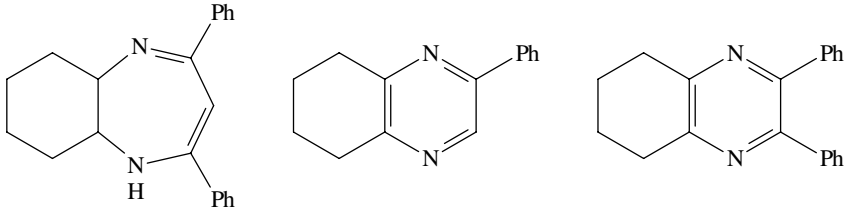
The oxazole-fused pyrimidinethione **149** has been used as a source for generation of heterocumulene **151**, an imine of carbon suboxide[82]. Under FVP conditions at 900°C, ring opening accompanied by a 1,2-phenyl shift first gives **150**, which then loses HNCS and HCN to give the product that was characterized by IR in a matrix at 18 K.

The bicyclic dihydrodiazepines exemplified by **152** and **155** undergo a variety of pyrolytic processes[83]. In the 450–500°C range, FVP results in a series of 1,5-hydrogen shifts allowing interconversion of the *cis* and *trans* ring-fused compounds while, at 750 °C, more fundamental radical processes result in the formation of pyrazines, **152** giving **153** and **154** in yields of 46 and 4% respectively, and **155** giving **156** (50%).

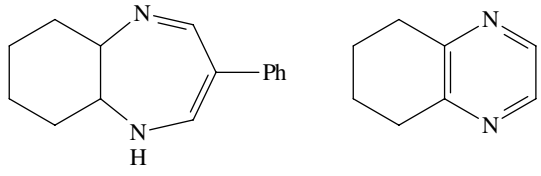

Ar
N
N
S
(140)
R
O
O
S
O
(145)
Ph
N
O
S
O
(141)
–PhCN
–SO2
SO2
(142)
Ph
N:
(143)
Ph
N
SO2
(144)
R
N
CF3
CF3
P(OMe)3
O
(146)
–(MeO)3PO
R
N
CF3
F3C
(147)
R—C≡N+—C−(CF3)2
(148)



(149) **(150)** **(151)**



(152) **(153)** **(154)**



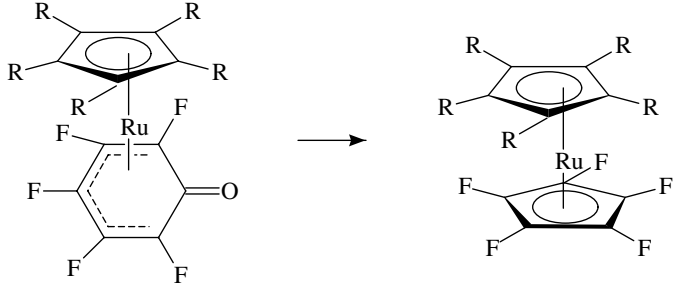
(155) **(156)**

IV. COMPOUNDS CONTAINING C=O DOUBLE BONDS

The pyrolysis of carboxylic acids and their derivatives in the period up to 1980 was reviewed in a previous volume of this series[84].

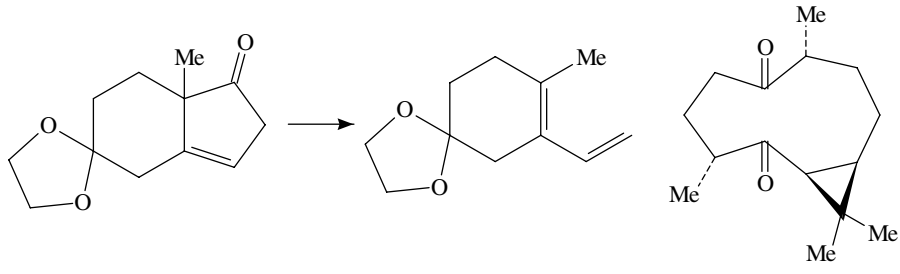
A. Aldehydes and Ketones

The characteristic thermal reaction of these compounds is decarbonylation and new examples include the formation of the ruthenocene compounds **158** by FVP of **157** at 640 °C[85], and the decarbonylation of the cyclopentenone **159** to give the synthetically

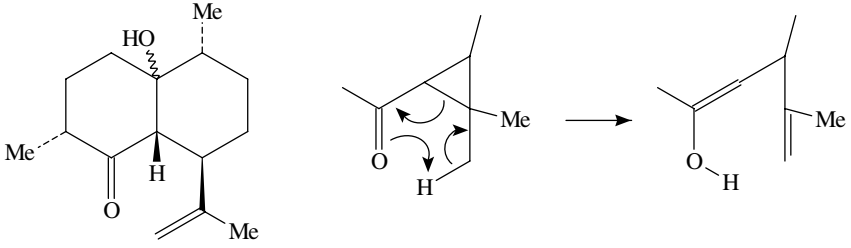


(157) R = H, Me **(158)**

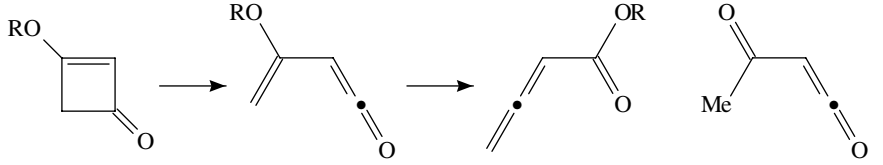
useful 1,3-diene **160** in 72% yield upon FVP at 630 °C[86]. Remarkably, if the last reaction is conducted at 740°C, there is complete degradation to give a high yield of *p*-cresol. The transannular aldol reaction which occurs upon FVP of dione **161** at 500 °C to afford **162** is explained by the electrocyclic reaction of the functions as in **163** to give the enol **164**, which is then activated towards attack on the other ketone function[87]. The alkoxycyclobutenones **165** are in equilibrium with their ring-opened vinylketene isomers **166** under FVP conditions above 400°C. At higher temperatures the alkoxy group migrates to give the corresponding allenic esters **167** and for R = Et there is also some elimination of ethylene from the enol ether function of **166** to give the acetylketene **168**[88].



(159) **(160)** **(161)**



(162) **(163)** **(164)**



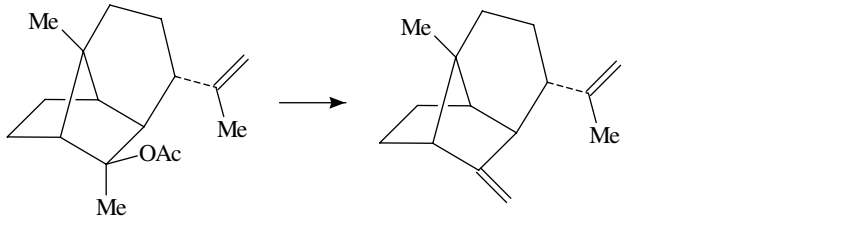
(165) R = Me, Et **(166)** **(167)** **(168)**

B. Esters and Thioesters

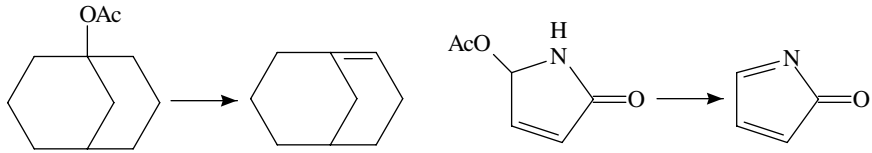
The pyrolysis of benzyl benzoate has been examined in detail under FVP conditions over the range 750–900 °C[89]. While the main products are the expected diphenylmethane, toluene, biphenyl and bibenzyl, these are accompanied by a number of interesting minor products.

The thermal elimination of acetic acid from alkyl acetates bearing a β-hydrogen atom, which proceeds by a six-membered ring transition state, has been widely used as a method

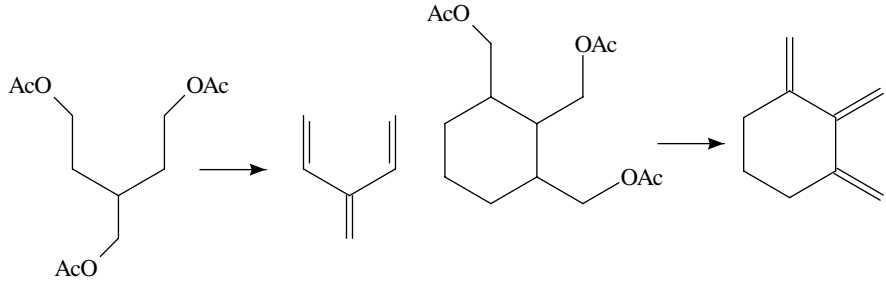
of alkene preparation as exemplified by conversion of **169** into **170** by pyrolysis at 450°C in a nitrogen stream[90], and the formation of the anti-Bredt alkene **172** from **171** at 400°C[91]. The method has also been used to form C=N double bonds in a few cases such as that of the highly reactive 2-azacyclopentadienone **174**, formed by FVP of **173** at 350°C and trapped in a matrix[92]. By the use of suitable polyacetates, dienes and trienes can be obtained and Trahanovsky has described the generation of the interesting trienes **176** and **178** by FVP of the corresponding acetates **175** and **177** at 900 °C and 860 °C, respectively[93].



(169) **(170)**



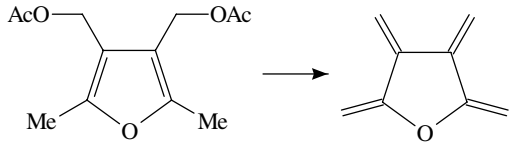
(171) **(172)** **(173)** **(174)**



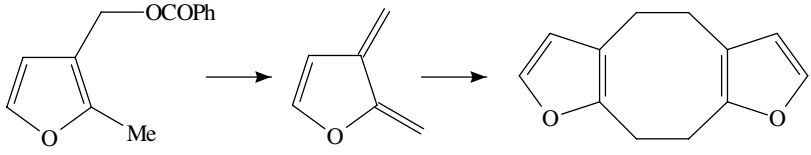
(175) **(176)** **(177)** **(178)**

Access to 1,3-dienes can also be gained by 1,4-elimination of acetic or benzoic acid from suitable ester substrates and this has been examined in detail for furan compounds by Trahanovsky and coworkers. Thus, the 'furanoradialene' **180** can be prepared in 13% yield by FVP of the diacetate **179** at 570 °C or in 30% yield from the corresponding dibenzoate at 610 °C[94]. These reactions are not as straightforward as they might appear since it is likely that migration of the acetoxy group to the 2-position by a [3,3] sigmatropic process followed by 1,2-elimination is involved rather than direct 1,4-elimination. While the benzoate **181** gives only **182**, isolated in 51% yield as its dimer **183** upon FVP at 640 °C, the isomeric compound **184** gives both **183** and the cyclobutenone **187** under similar conditions[95]. This second product results from two sequential migrations of the benzoate group to give **185**, which then suffers α-elimination of benzoic acid. The

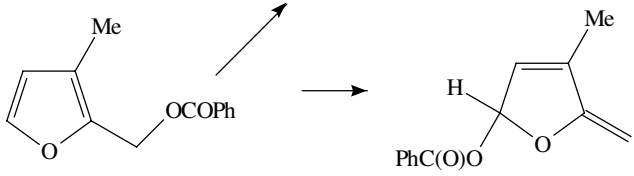
resulting allenylketene **186** finally cyclizes to give **187** in 21% yield. The benzofuran system **188** behaves in a similar way to **181**, giving **189** upon FVP at 630 °C[96], and the method has recently been extended to more hindered compounds such as **191** formed from the corresponding benzoate **190**[97]. In the absence of an adjacent methyl group as in **192**, the 1,3-migration still occurs to give **193** but this undergoes α-elimination to give the oxacarbene **194**, which rearranges to provide the first synthesis of the methylenebenzocyclobutenone **195**[98].



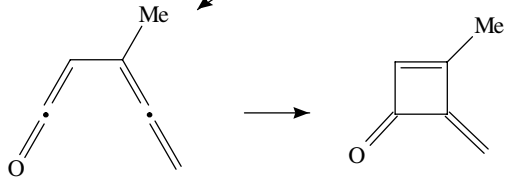
(179) **(180)**



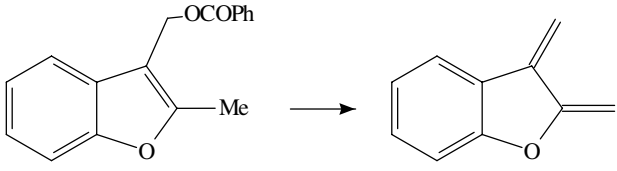
(181) **(182)** **(183)**



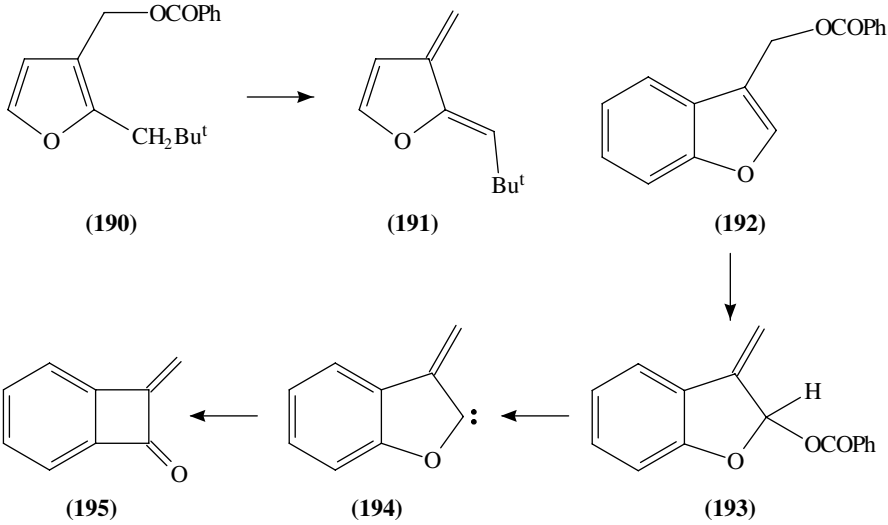
(184) **(185)**



(186) **(187)**



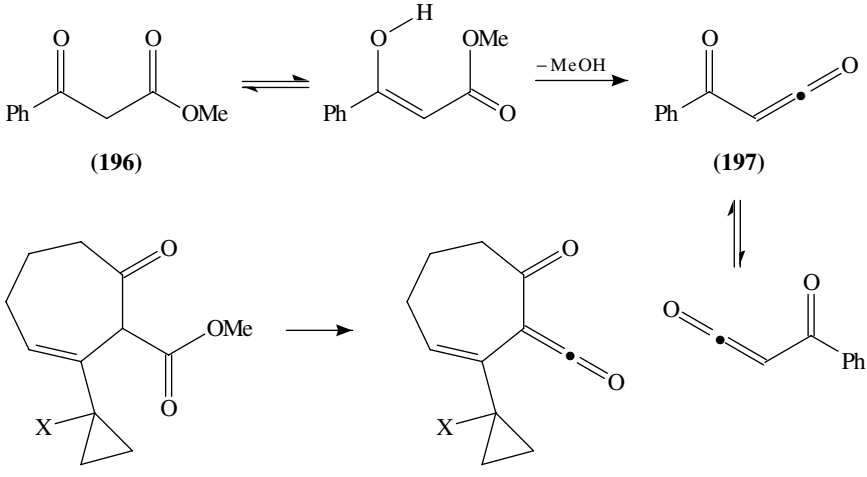
(188) **(189)**



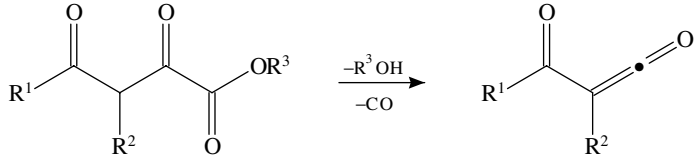
(190) **(191)** **(192)** **(193)** **(194)** **(195)**

The pyrolysis of β-oxoesters results in elimination of an alcohol to give the corresponding α-oxoketenes. Thus methyl benzoylacetate **196**, for example, loses methanol upon FVP at 700 °C to afford benzoylketene **197**, which was shown by ^{13}C labelling to undergo degenerate rearrangement by means of a 1,3-phenyl shift[99]. A similar process occurs in the cyclic case **198**, which affords the ketene **199** on FVP at 300 °C[100]. The α,γ-dioxoesters **200** also provide access to α-oxoketenes **201** with the loss of an alcohol and CO[101].

The β-enaminoesters such as **202** undergo similar loss of ethanol upon FVP and the resulting iminoketene **203** cyclizes to afford **204**[102]. Simple imidazole esters also undergo loss of an alcohol to give imidazole ketenes[103]. Thus FVP of **205** at 750–820 °C gives

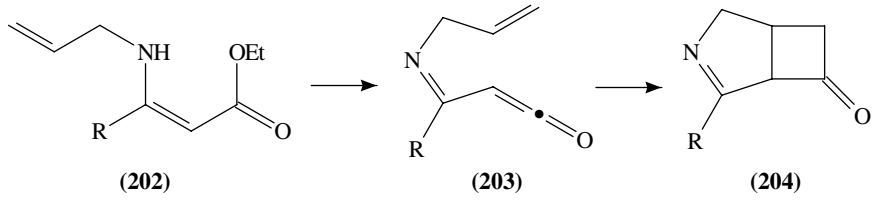


(196) **(197)** **(198)** **(199)**

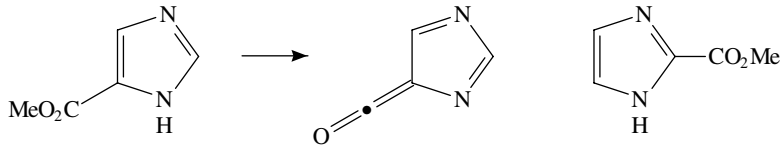


(200) **(201)**

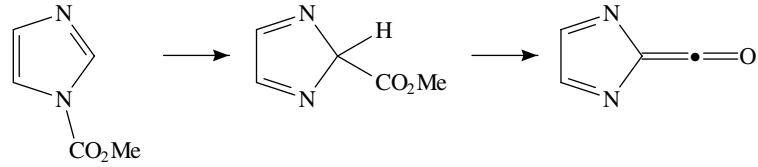
206, while, under similar conditions, the 1-ester **207** first rearranges to the 2H isomer **208** which then gives **209**, a product also accessible from **210**.



(202) **(203)** **(204)**

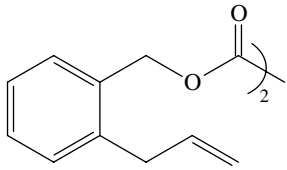


(205) **(206)** **(210)**



(207) **(208)** **(209)**

Pyrolysis of dialkyl oxalates is a well known method for the generation of alkyl radicals and FVP of **211** at 700–900 °C has been used to generate the *o*-allylbenzyl radical and examine its reactivity which is dominated by cyclization to give tetrahydronaphthalene **212**[104]. The enol ester **213** gives the bicyclic ketone **215** on FVP at 420 °C by way of initial isomerization to the 1,3-diketone **214** whose enol form is ideally set up for an intramolecular Diels–Alder reaction[105]. An intramolecular Diels–Alder reaction is the first step in the remarkable pyrolytic conversion of the perfluoronaphthyl propiolate **216** into a mixture of the isomeric naphthocyclobutenones **217** and **218** and the naphthocyclopropene **219** upon FVP at 550 °C[106]. This is then followed by loss of CO and a series of 1,2-fluorine shifts to give the observed products. A number of useful synthetic procedures based on cyclization of ester-containing phenoxy radicals have been developed. Thus,



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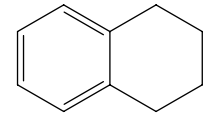

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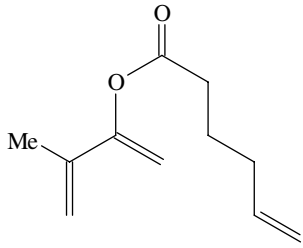

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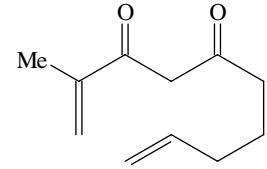

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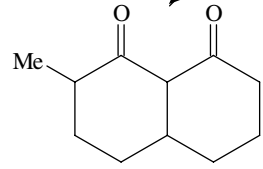

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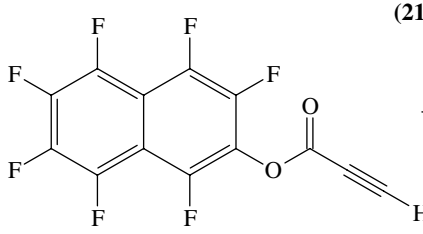

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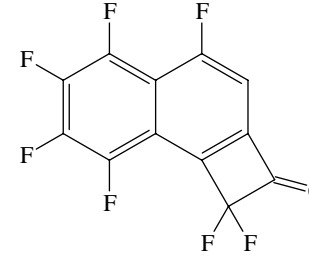

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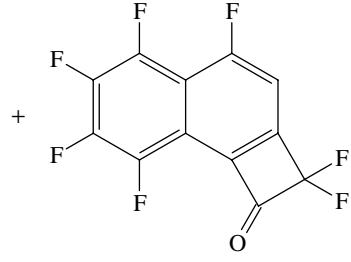

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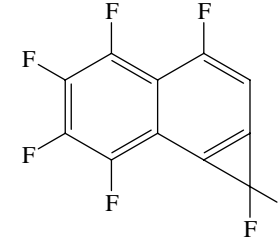
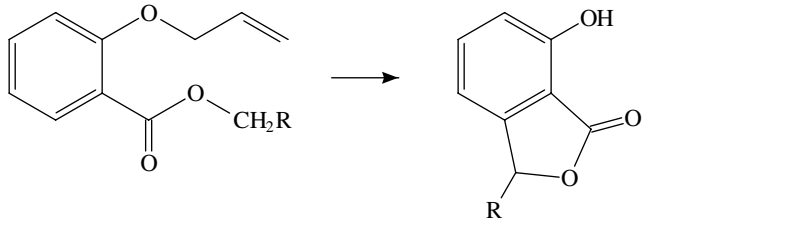
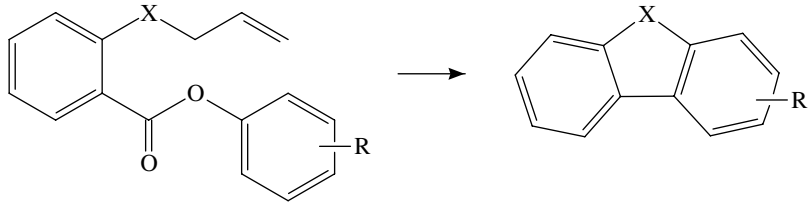


(219)

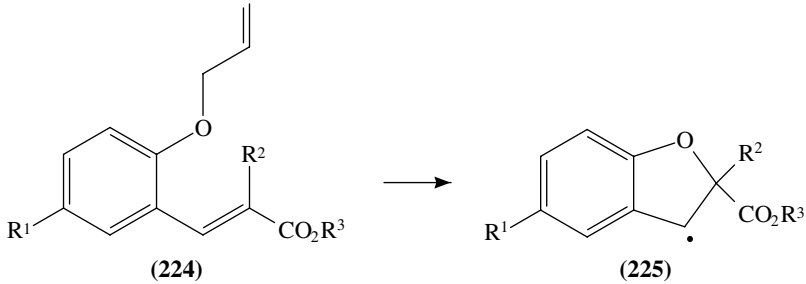
the *o*-allyloxybenzoates **220** give the substituted phthalides **221** upon FVP at 650 °C in a process involving intramolecular abstraction of a hydrogen atom from the ester by O• followed by cyclization[107]. The corresponding aryl esters **222** can similarly be used to gain access to substituted dibenzofurans and dibenzothiophenes **223** in a sequence involving initial *ipso* attack to give a spiro intermediate and loss of CO_2[108]. In the case of the cinnamates **224**, the intermediates **225** from FVP at 650 °C undergo unusual homolytic loss of the ester group (as CO_2 and $R^{3\bullet}$) to give the substituted benzofurans **226** in good yield[109]. This is to be contrasted with the behaviour of the corresponding phenols **227**, which cyclize to the coumarins **228** with loss of R^3OH on FVP at 750 °C. A surprising discrepancy in behaviour is observed for the two simple pyrrolylfumarates **229**[110]. The dimethyl compound undergoes loss of methanol and cyclization upon FVP at 700 °C to afford **230**, isolated as a mixture of stereoisomeric [2 + 2] dimers while, under the same



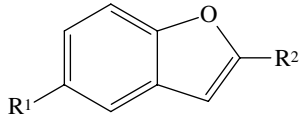
(220) R = H, Me **(221)**



(222) X = O, S **(223)**

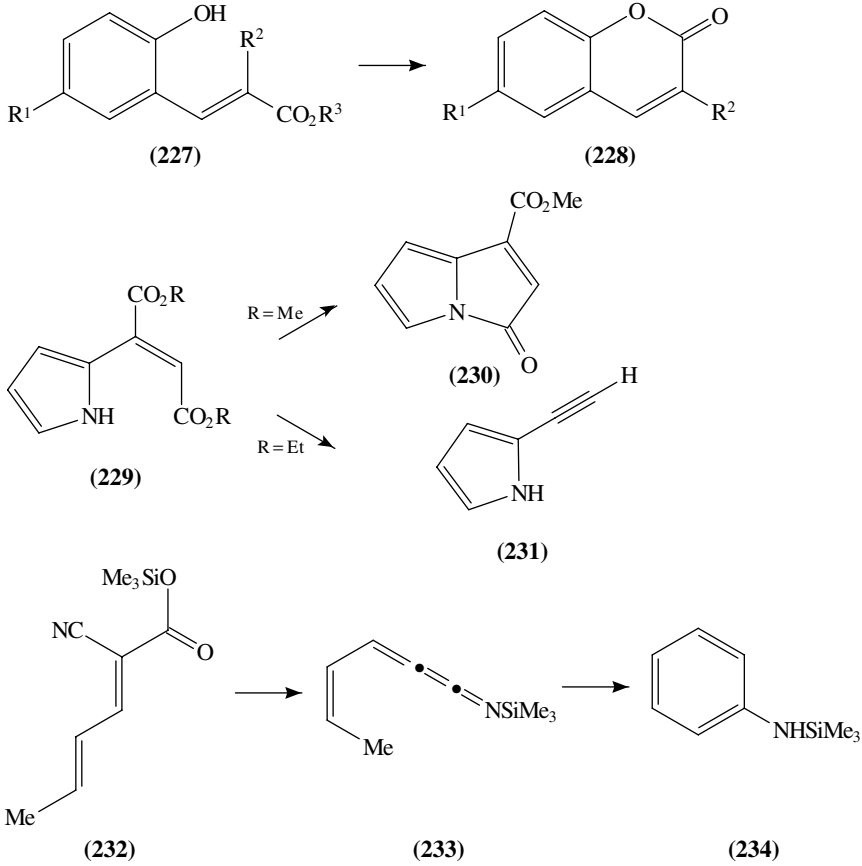


(224) **(225)**



(226)

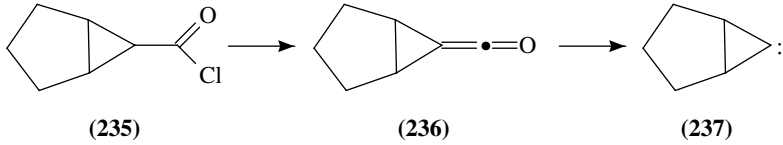
conditions, the diethyl ester fragments to give ethynylpyrrole **231**. This is explained by twofold loss of ethylene to give the diacid, which then dehydrates to the anhydride, and this loses CO_2 and CO to give the product. Complete loss of an ethyl ester group is also observed when acetylenic esters $RC{\equiv}C{-}CO_2Et$ are pyrolysed at 750 °C[111]. The formation of both $PhC{\equiv}CH$ and $PhC{\equiv}CD$ from $PhC{\equiv}C{-}CO_2CH_2CD_3$ points to a combination of different mechanisms operating. FVP of the cyano silyl ester **232** provides an unusual route to trimethylsilylaniline **234** by migration of the silyl group from O to N with loss of CO_2 to give **233**, which then cyclizes[112].



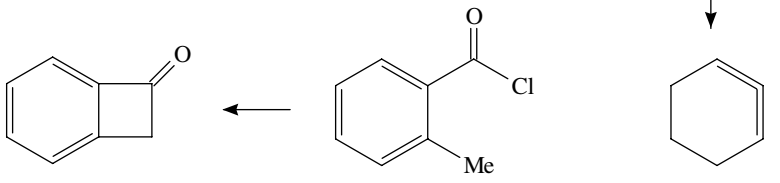
C. Acid Chlorides and Amides

The characteristic pyrolytic process for acid chlorides is loss of HCl and this occurs for the bicyclic example **235** on FVP at 800 °C to give cyclohexa-1,2-diene **238** by way of the ketene **236** and carbene **237** as shown[113]. The product can be directly observed by low-temperature IR and forms a [2 + 2] dimer on warming up. FVP of *o*-toluoyl chloride **239** at 630 °C also results in loss of HCl to provide a dependable large-scale synthesis of benzocyclobutenone **240** in excellent yield[114]. Pyrolysis of trichloroacetyl chloride, $Cl_3C{-}COCl$, over a bed of zinc at 420 °C results in dechlorination

to generate dichloroketene, $Cl_2C{=}C{=}O$, whose structure has been determined by electron diffraction[115].



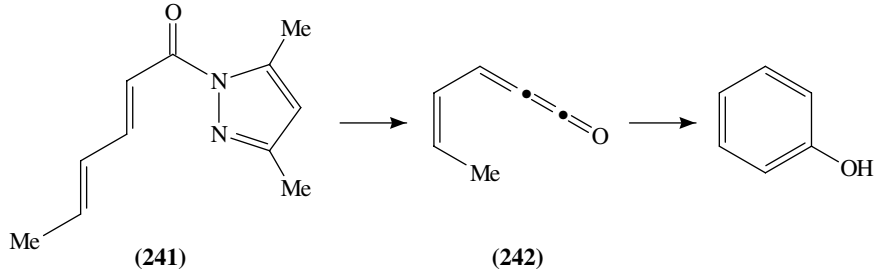
(235) **(236)** **(237)**



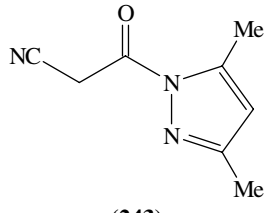
(240) **(239)** **(238)**

Amides of various types can act as a source of ketenes by pyrolytic elimination of an amine. Thus the acylpyrazole **241** undergoes loss of 3,5-dimethylpyrazole at 575 °C to give the alkylideneketene **242**, which cyclizes to phenol in direct analogy to the imine **233** mentioned above[116]. This reaction has been extended for the formation of substituted phenols and naphthols by starting with suitably substituted analogues of **241**. The cyanoacetylpyrazole **243** similarly loses dimethylpyrazole to give rise to cyanoketene upon FVP[117]. On the other hand, the pyrazolyl propiolate **244** undergoes a sigmatropic rearrangement to the alkylideneketene **245** on FVP at 650 °C and this then cyclizes to give the azaindole **246**[118].

The imidazole anilides **247** and **248** lose aniline upon FVP to give the ketenes **206** and **209**, respectively[103]. The anilides **249** also behave like their oxygen analogues **220**



(241) **(242)**



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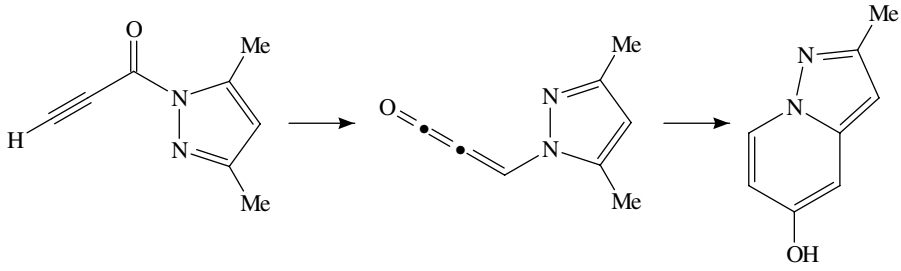
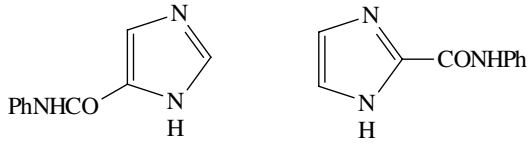
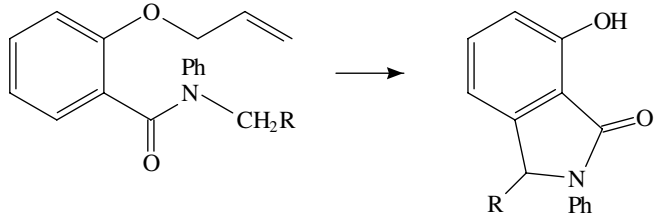


(244) **(245)** **(246)**

in undergoing loss of allyl radical, intramolecular hydrogen atom abstraction and then cyclization to the isoindolones **250**[107].



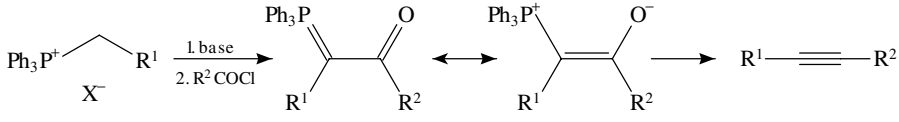
(247) **(248)**



(249) **(250)**

D. Acyl Phosphorus Ylides

The acyl phosphorus ylides of general structure **253** are unreactive crystalline solids whose stability is explained by the large contribution from the phosphonium enolate resonance form **254**. It has long been known that they undergo ready pyrolytic elimination of Ph_3PO in an 'intramolecular Wittig reaction' to give alkynes **255**. This reaction has recently been the subject of extensive investigations and a summary of the most important examples is given in Table 1. Since the starting ylides **253** are readily prepared from a



(251) **(252)** **(253)** **(254)** **(255)**

+ Ph_3PO

TABLE 1. Pyrolysis of acyl phosphorus ylides **253** to afford alkynes **255**

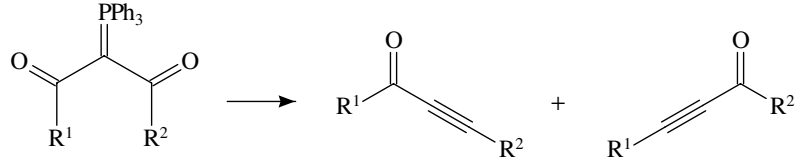
	R^1	R^2	Conditions	Reference
1.	Ph, heteroaryl	heteroaryl	heat with sand, 300 °C/10^{-4} torr	119
2.	CN	perfluoroalkyl	heat with pumice, 280 °C/10 torr	120
3.	2-Thienyl	perfluoroalkyl	heat with pumice, 220–280 °C/30 torr	121
4.	C(O)SMe	perfluoroalkyl	heat with pumice, 190–220 °C/1 torr	122
5.	$PO(OPh)_2$	perfluoroalkyl	heat with pumice, 220 °C/10^{-5} torr	123
6.	C_6F_5	perfluoroalkyl	heat at 230–260 °C/2 torr	124
7.	Polycyclic aryl	polycyclic aryl	heat at 250 °C/18 torr or boil in xylene	125
8.	Aryl	CF_3	—	126
9.	OAr	perfluoroalkyl	heat with pumice, 250–270 °C/10 torr	127
10.	SMe, SPh	aryl, alkyl	heat at 230 °C/10^{-2} torr	128
11.	SePh	aryl, alkyl	heat at 230 °C/10^{-2} torr	129
12.	Cl, Br	aryl, alkyl	FVP, 800 °C/10^{-2} torr	130
13.	H, alkyl	alkyl, aryl	FVP, 750 °C/10^{-2} torr	131
14.	CO_2Et	aryl, alkyl	FVP, 500 °C/10^{-2} torr	111
15.	CO_2Et	aryl, alkyl	FVP, 750 °C/10^{-2} torr	111[a]
16.	CO_2Et	RC≡C	FVP, 500 °C/10^{-2} torr	132
17.	CO_2Et	RC≡C	FVP, 750 °C/10^{-2} torr	132[a]
18.	Alkyl, aryl	RC≡C	FVP, 750 °C/10^{-2} torr	133
19.	H, alkyl, aryl	*E*-ArCH=CH	FVP, 500 °C/10^{-2} torr	39
20.	H, alkyl, aryl	*E*-ArCH=CH	FVP, 700 °C/10^{-2} torr	39[b]
21.	COR^1	COR^2	FVP, 500 °C/10^{-2} torr	134
22.	$COCO_2R^1$	CO_2R^2	heat at 220 °C/0.2 torr	135

[a] Terminal alkyne $R^2C{\equiv}CH$ formed.
[b] 1:1 mixture of *E* and *Z* isomers formed.

simple phosphonium salt **251** and an acid chloride **252**, this represents a valuable synthetic route to alkynes, and in many cases the widely differing volatility of Ph_3PO and the product means that using FVP they are collected in different regions of the cold trap in pure form avoiding the need for subsequent separation.

In cases where R^1 is a stabilizing group (entries 1–11) conventional pyrolysis is satisfactory, but the use of FVP has allowed the extension of the reaction to cases with R^1 = H or alkyl (entries 13, 18–20) where conventional pyrolysis does not work. For $R^1 = CO_2Et$, simply increasing the furnace temperature leads to loss of the ester group to give terminal alkynes and 1,3-diynes (entries 15, 17) as already noted in Section IV.B. The *E*–*Z* isomerization which occurs for styrylalkynes at higher temperatures (entry 20) was also noted previously in Section II.C.

It is notable that this reaction is not possible with elimination of an ester oxygen (**253**, R^2 = O–alkyl). Where there is a choice between two aldehyde or ketone carbonyls as in **256**, a mixture of the two possible isomeric products **257** and **258** is obtained[136]. In view of this, it is surprising that when an additional carbonyl group is introduced, there is good

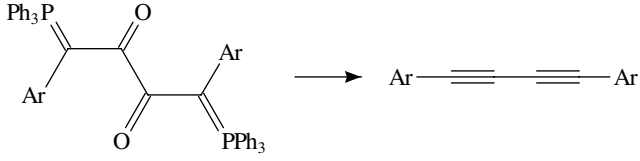


(256) **(257)** **(258)**

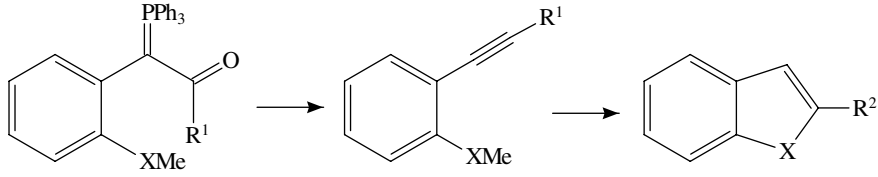
selectivity for elimination across the central position to give diacylalkynes (entry 21). With the tetraoxo ylides (entry 22), selectivity is again poor and a mixture is produced. An unusual observation in this case is that conventional pyrolysis is successful while FVP is not.

The oxalyldiylides **259** undergo twofold elimination of Ph_3PO to give diynes **260** but this requires the high FVP temperature of 900 °C and is only useful for aromatic examples[133]. In several cases ylides have been designed from which the alkynes may undergo further reactions *in situ* leading to useful syntheses. Thus, while the ylides **261** give the expected alkynes **262** upon FVP at 700 °C, increasing the temperature to 850 °C leads to benzofurans and benzothiophenes **263** by loss of $Me^{\bullet}$ followed by cyclization[137]. It should be noted here that for aliphatic groups R^1, cyclization is followed by interesting radical reactions of this group leading to products **263** with $R^2 \neq R^1$. This approach can be extended to tandem cyclization as illustrated by FVP of **264** at 850 °C to give the benzothienobenzofuran **265** and the reaction of **266** under similar conditions to afford **267**[138]. At 500 °C, FVP of ylides **268** with an *o*-methylcinnamoyl group gives the expected enynes, but at 900 °C the alkenylnaphthalenes **64** resulting from further cyclization are obtained[40].

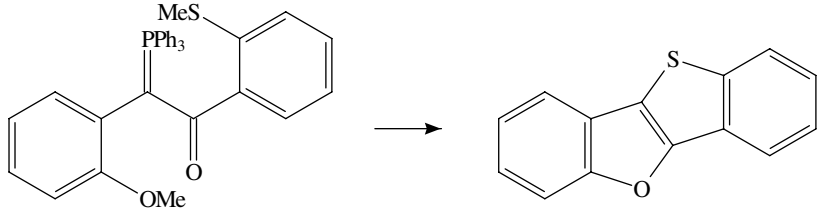
Certain classes of acyl ylides have given more unexpected results. For the amino acid derived phthalimidoacyl compounds **269**, for example, Ph_3PO is lost between the ylide and a CO of the phthalimide to give the pyrroloisoindolediones **270** upon FVP at 500 °C[139]. In the case of the benzotriazolyl tributylphosphonium ylide **271**, FVP at 450 °C results in loss of Bu^n_3P to give the acetylbenzotriazine **272** and 2-cyanoacetophenone **273**[140]. The



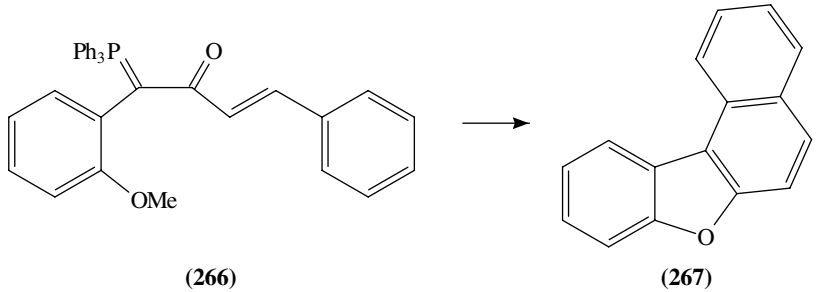
(259) **(260)**



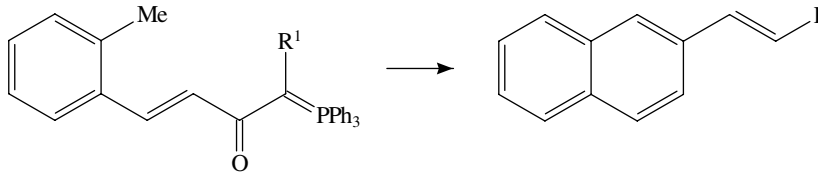
(261) X = O, S **(262)** **(263)**



(264) **(265)**

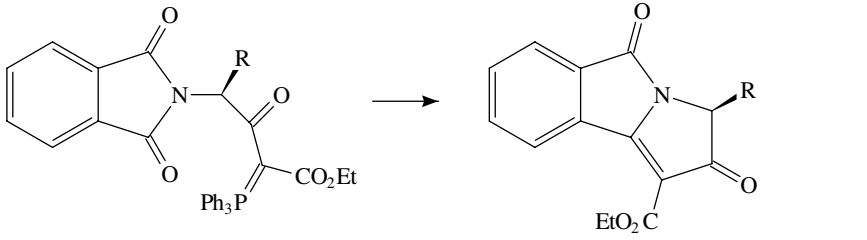


(266) **(267)**

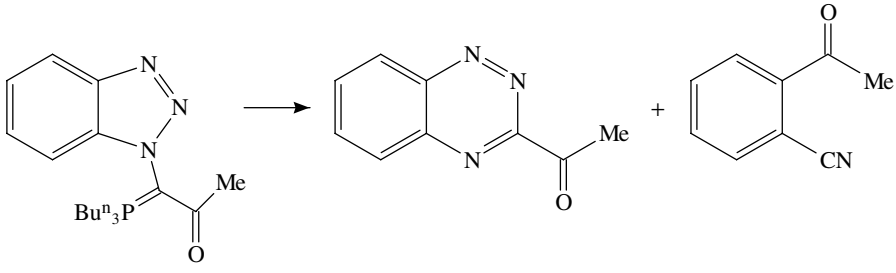


(268) **(64)**

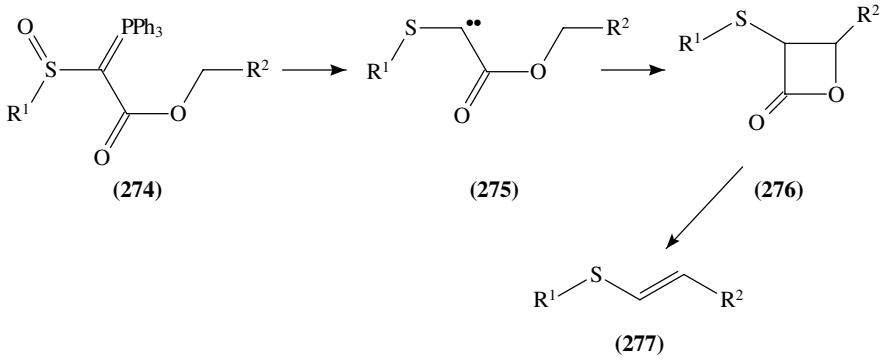
mechanism appears to involve initial formation of a carbene which can rearrange directly to **272** or the isomeric 1,2,3-benzotriazine which loses N_2 and rearranges to give **273**. The reason for the phosphine rather than the phosphine oxide being eliminated in this case is unclear. The ylides **274** stabilized by both ester and sulphinyl groups undergo loss of Ph_3PO on FVP at 600 °C to give vinylsulphides **277** as the main products[141]. The initially formed carbenes **275** apparently undergo intramolecular CH insertion to give the β-lactones **276** which readily lose CO_2.



(269) **(270)**



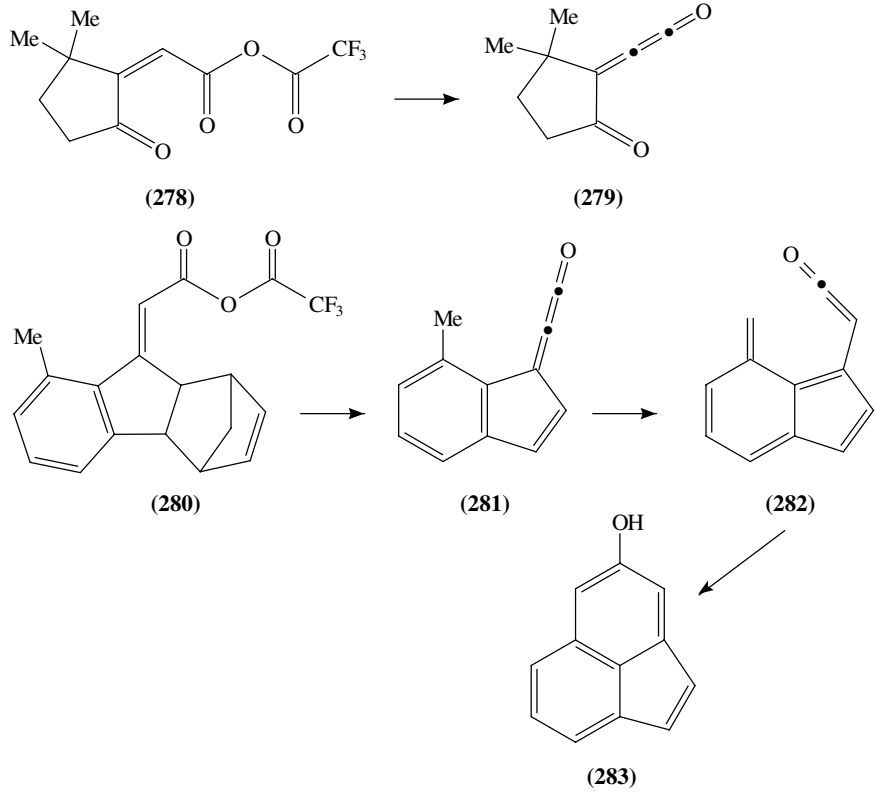
(271) **(272)** **(273)**



(274) (275) (276) (277)

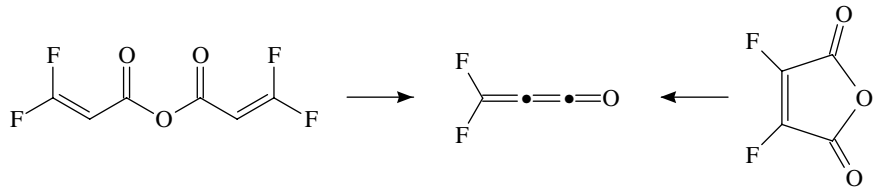
E. Acid Anhydrides

Although the majority of studies in this area involve five-membered ring cyclic anhydrides, a few pyrolytic reactions involving acyclic anhydrides have been reported. Thus, for example, FVP of **278** gives the alkylideneketene **279** with loss of trifluoroacetic acid[142], while at 650 °C **280** loses both trifluoroacetic acid and cyclopentadiene to afford the indenylideneketene **281**, which cyclizes by way of **282** to give **283**[143]. FVP of



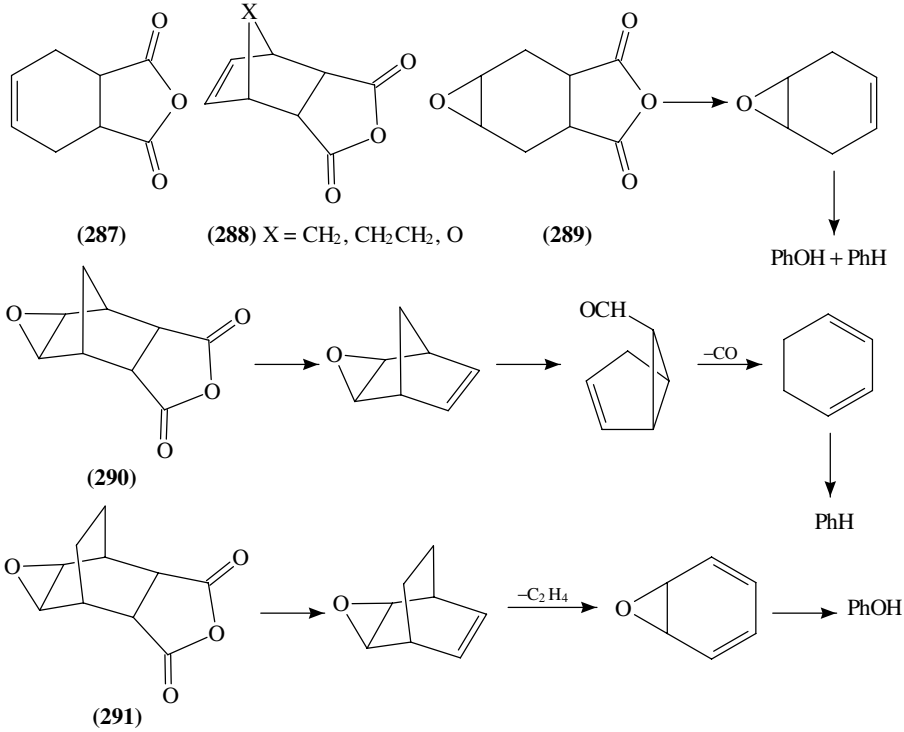
(278) (279) (280) (281) (282) (283)

difluoroacrylic anhydride **(284)** at 430 °C results in loss of difluoroacrylic acid to give difluoromethyleneketene **(285)**[144], a product also accessible from difluoromaleic anhydride **(286)** under similar conditions[145].



(284) **(285)** **(286)**

The pyrolytic behaviour of a series of bi- and tricyclic anhydrides derived from Diels–Alder adducts of maleic anhydride has been examined[146]. The adducts **287** and **288** very readily undergo the retro-Diels–Alder reaction on pyrolysis, but this is generally prevented when the double bond of these adducts is functionalized as in the epoxides **289–291**. These all fragment under FVP conditions by loss of CO_2 and CO to give diene monoepoxides, which react further under the conditions used. Thus, **289** gives phenol and benzene at 800 °C, **290** gives cyclohexa-1,3-diene and benzene at 775 °C and **291** gives phenol in 72% yield at 850 °C. The oxygen-bridged analogue **292** provides an interesting exception to this behaviour, since it undergoes a retro-cycloaddition process despite the absence of the double bond. The products at 725 °C are benzene and 1,4-dioxin, together

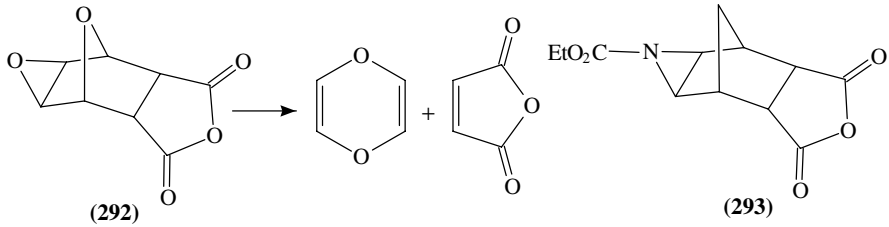


(287) **(288)** X = CH_2, CH_2CH_2, O **(289)**

(290)

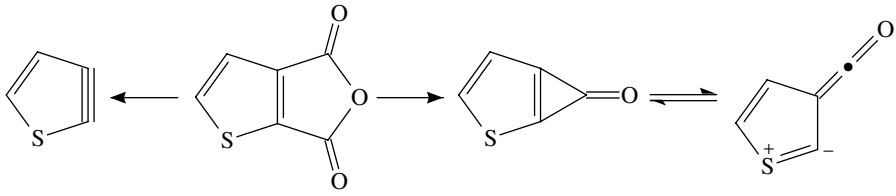
(291)

with acrolein formed by secondary fragmentation of the latter. Some evidence was also obtained for a retro-cycloaddition process in the case of the aziridine anhydride **293** which, upon FVP at 725 °C, gave equal yields of maleic anhydride and pyridine.



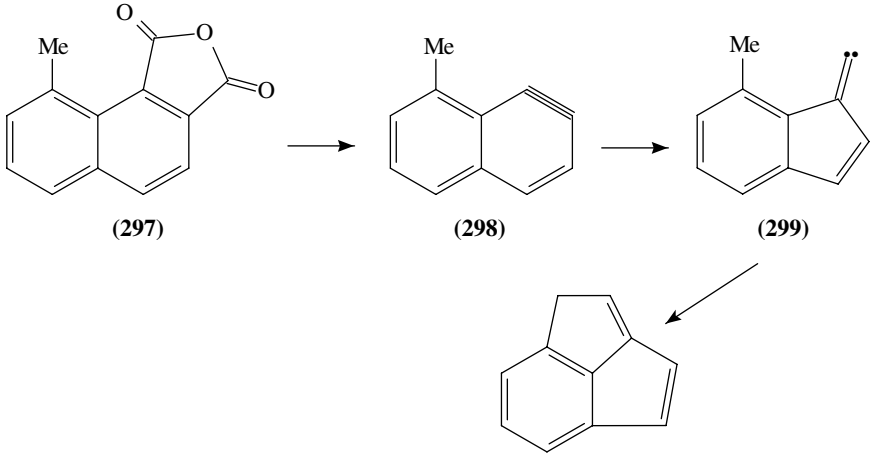
(292) **(293)**

Aromatic fused anhydrides are well known to act as a source of arynes by pyrolytic loss of CO_2 and CO. In some cases the cyclopropenone resulting from loss of only CO_2 can be trapped and this is the case for **294**, where FVP at 500 °C allows trapping of both the thienocyclopropenone **295** stabilized as the dipolar form shown, and the thiophyne **296**[147].



(296) **(294)** **(295)**

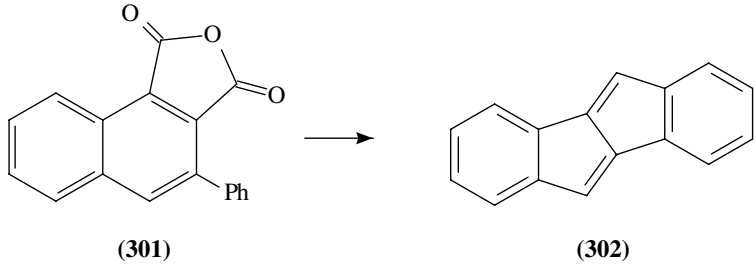
An important discovery in recent years has been that under the fairly high temperatures required for their formation from anhydrides, arynes are in equilibrium with the corresponding cyclopentadienylidenecarbenes which may be trapped by an intramolecular insertion. This is illustrated by FVP of **297** at 800 °C where the aryne **298** rearranges to the



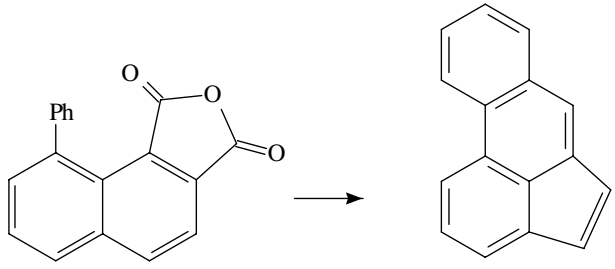
(297) **(298)** **(299)**

(300)

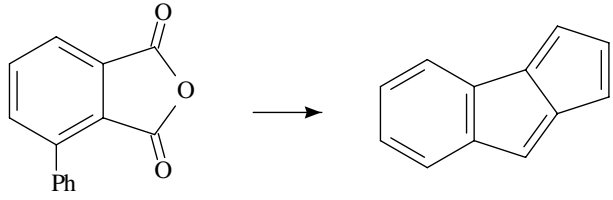
carbene **299** which can insert to give the cyclopentindene **300** in 85% yield[143]. Extension to the phenyl substituted naphthalene systems **301** and **303** is possible, giving indenoindene **302** and acephenanthrylene **304** upon FVP at 900 °C and 850 °C, respectively[148]. Similarly **305** gives mainly **306** at 900 °C[149], and **307** gives some of the expected benzindenes



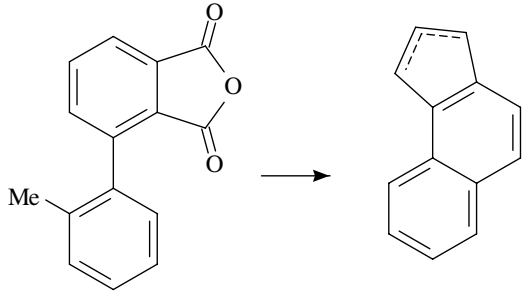
(301) **(302)**



(303) **(304)**



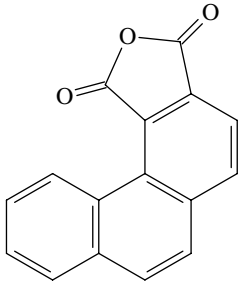
(305) **(306)**



(307) **(308)**

308 at 860 °C, but these are accompanied by a much larger quantity of the isomeric fluorene[150].

The case of the phenanthrene anhydride **309** is interesting since the carbene insertion product **310** is highly strained and undergoes ring opening under the conditions used (FVP, 870 °C) to give a mixture of the isomeric ethynylacenaphthylenes **311** and **312**[151,152]. Tetraphenylphthalic anhydride **(313)** fragments by a similar mechanism upon FVP at 840 °C with carbene insertion into a phenyl CH to give the triphenylbenzopentalene **(314)** in 74% yield[153]. By starting from quinoline-fused anhydrides, a range of nitrogen heterocycles can be obtained. Thus, FVP of **315** at 800 °C provides access to the novel indenoindole **316**[154], and under the same conditions the *o*-tolyl and benzyl compounds **317** and **319** give benzocarbazoles[155]. In the first case, **318** is formed in 77% yield, but in the second, the expected product **321** is only obtained in 30% yield and is accompanied by the isomer **320** (60%). An unexpected result is obtained for the pyridine-fused anhydride **322**[156]. FVP at 900 °C gives mainly benzonitrile and diphenylbutadiyne, PhC≡C−C≡CPh, whose formation is explained by cycloreversion of the aryne formed by loss of CO_2 and CO.



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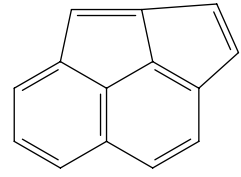

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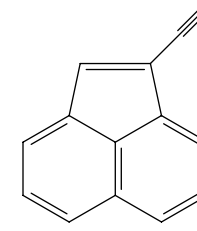

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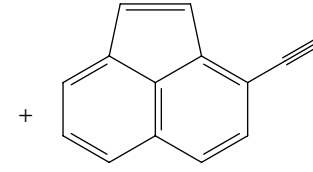

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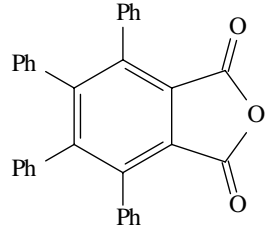

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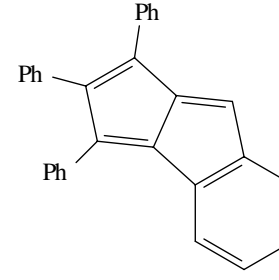

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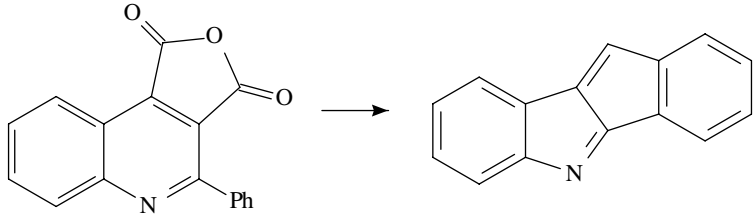
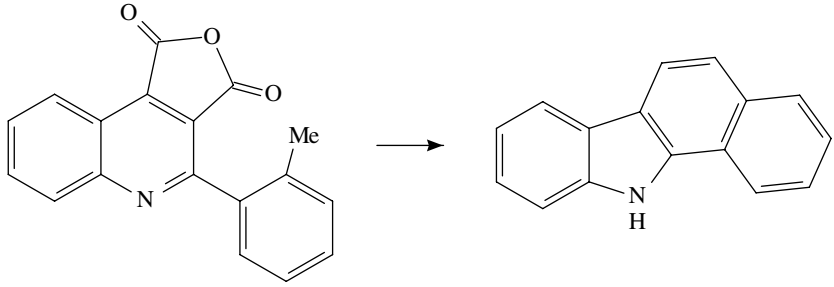
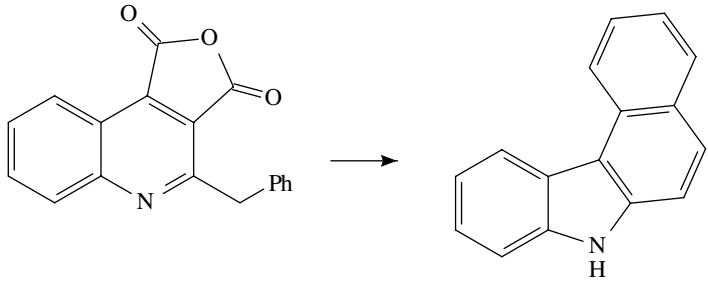


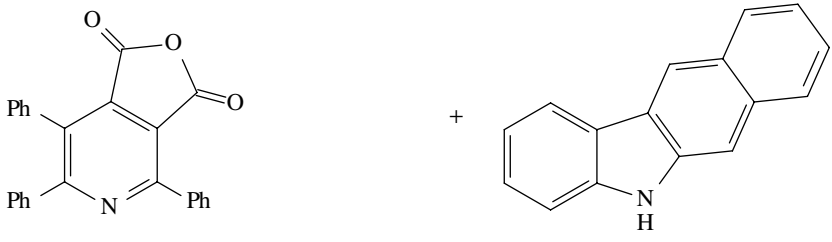
(315) **(316)**



(317) **(318)**



(319) **(320)**



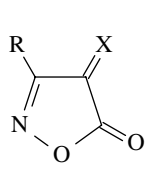
(322) **(321)**

F. Isoxazolones and Oxazolones

The pyrolysis of 4*H*-isoxazolin-5-ones of general structure **323** proceeds readily with loss of CO_2 and RCN to give the corresponding carbenes X=C:. This has provided a convenient route for the generation of fulminic acid, HO−N=C:, by pyrolysis of oximes

324[157], and for the corresponding esters $R^1O-N=C$: from the oxime ethers **325**[158]. Pyrolysis of aminoalkylidene compounds proceeds similarly to give the aminovinylidenes but, depending on the groups present, these may isomerize to aminoalkynes ('ynamines'), ketenimines or nitriles[159]. Thus, for example, FVP of **326** at 650 °C results in loss of CO_2 and MeCN to give ketenimines, $RN=C=CH_2$, as the final products, except for R = H, where the aminoalkyne, $HC\equiv C-NH_2$ is more stable. Loss of CO_2 and MeCN from **327** occurs to give the ynamine, $PhC\equiv C-NH_2$, at 750 °C, but at 850 °C the isomeric phenylacetonitrile is the product isolated in 76% yield. For the more highly substituted example **328**, FVP at 650–750 °C gives the stable ynamine **329**. A different process is observed for cases such as **330** where FVP at 300 °C results in loss of HX to give the ketenimine compounds **331**[160]. At higher temperatures these lose only CO_2 to afford the vinylnitrenes **332**, which can rearrange to either the azirines **333** or the bis-imine **334** of carbon suboxide.

With a ketene dithioacetal function in the 4-position as in **335**, FVP results in loss of CO_2 and PhCN to give **336**, which rearranges to the dithioalkyne **337**[161]. The



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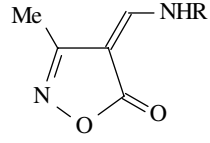

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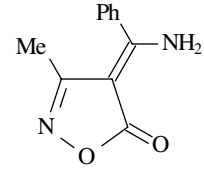
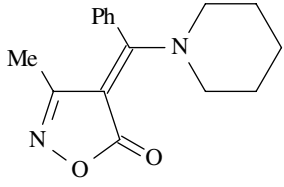
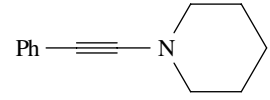


(327)

(324) X = NOH
(325) X = NOR^1



(328)



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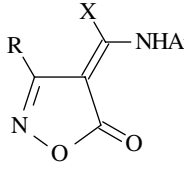
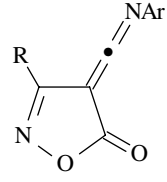


(330) X = SMe, NMe_2



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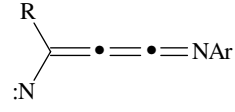

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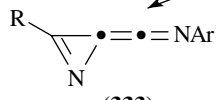

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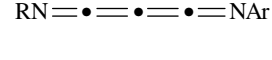
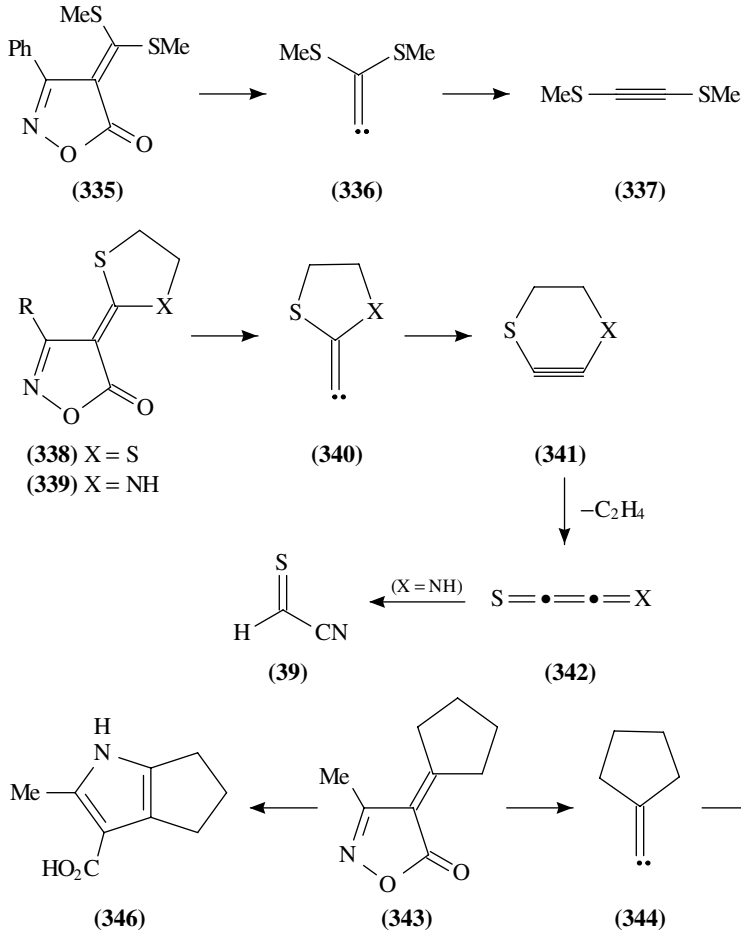


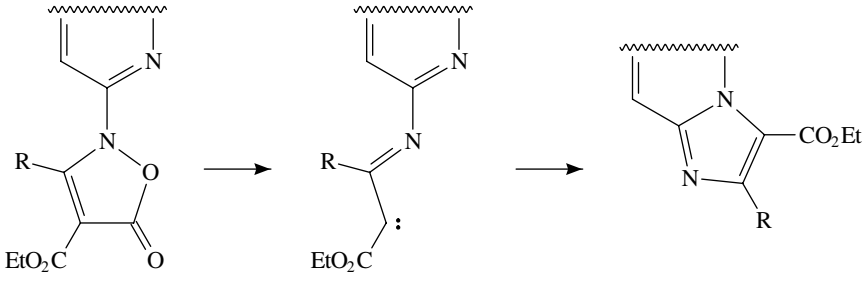
(334)

corresponding process for both the cyclic analogues **338**[162] and **339**[163] proceeds similarly to give first **340** and then the cycloalkynes **341.** However, these now eliminate ethylene to give the cumulenes **342**, which in the nitrogen case isomerizes to thioformyl cyanide **39**. Reactions of this type can sometimes take an unexpected course, and FVP of **343** at 800 °C gives only a trace of the expected cyclic trimer of cyclohexyne **345** formed via **344**. The major product is the pyrrole carboxylic acid **346**[164].

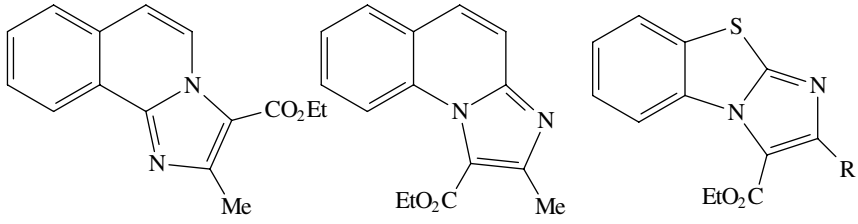


For the isomeric 2*H*-isoxazolin-5-ones **347**, elimination of a nitrile is impossible and only CO_2 is lost upon pyrolysis to give the iminocarbenes **348**, which cyclize as shown to provide a useful synthesis of fused imidazoles **349**. A wide range of examples has been examined as illustrated by the products **350–353**, which are generally formed in almost quantitative yield using FVP at 500–600 °C[165,166].

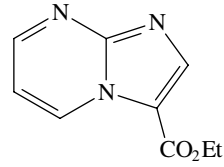
In contrast to the isoxazolones, the isomeric 4*H*-oxazolin-5-ones which lack the weak N−O bond usually lose only CO upon pyrolysis. Thus, FVP of a variety of compounds **354** at 600 °C gives the acylketenimines **355**[167]. The 2*H*-oxazolin-5-ones do lose CO_2 to give iminocarbenes, which may undergo rearrangement, as in the formation of **357** from



(347) **(348)** **(349)**



(350) **(351)** **(352)**



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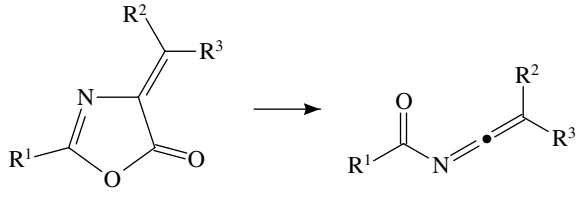
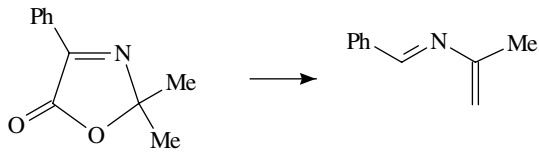
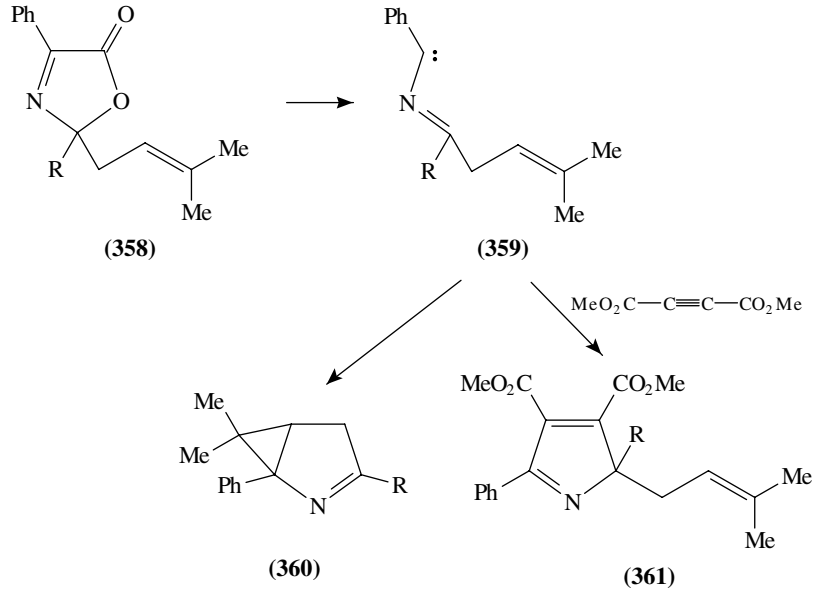


(354) **(355)**



(356) **(357)**

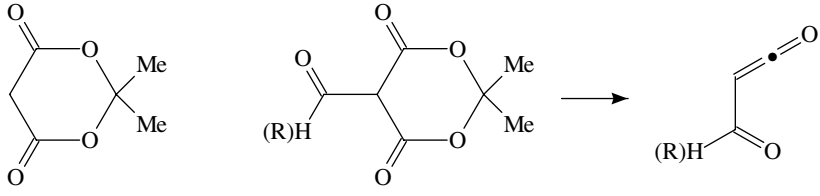
FVP of **356**[168]. Alternatively, as in the pyrolysis of **358**, the carbene **359** can be trapped by intra- or intermolecular addition to give **360** and **361**, respectively[169].



(358) **(359)** **(360)** **(361)**

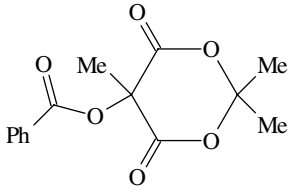
G. Meldrum's Acid Derivatives

Pyrolysis of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) **362** proceeds by loss of acetone and CO_2 to give ketene. Because of the ready availability of the starting material and the ease with which it can be functionalized at the acidic 5-position, pyrolysis of Meldrum's acid derivatives has been widely studied. Pyrolysis of the 5-formyl and 5-acyl derivatives **363** gives formyl or acylketenes **364**, which can be trapped in a number of ways[170,171]. In many cases, loss of acetone and CO_2 is accompanied by loss of CO to give a carbene, and this is illustrated by FVP of **365** at 560 °C which affords the α-diketone **368** by way of ketene **366** and carbene **367**[172].

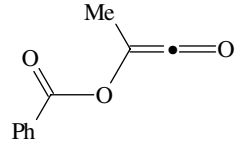


(362) **(363)** **(364)**

The majority of work has involved derivatives **369** with a double-bonded group at C-5 which provide access to either the cumulenes **370** or, by further loss of CO, the carbenes **371**. FVP of the acenaphthylene compound **372** at 860 °C gives the vinylidene, which rearranges to ethynylacenaphthylene **311**[151]. The formation of cyclopentylideneketene **374** by FVP of **373** at 500 °C is complicated by simultaneous production of the isomer **377**



(365)



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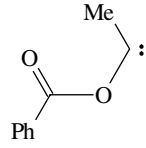

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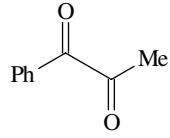
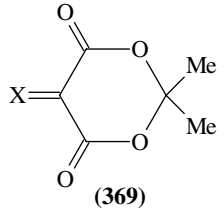


(368)



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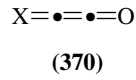

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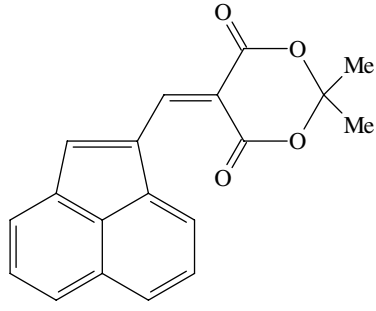
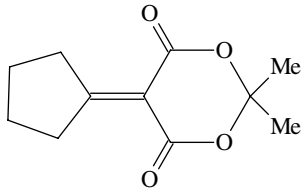


(372)

whose formation is explained by loss of acetone from the tautomeric form **375** to give **376**, which then loses CO_2. At lower temperatures **376** can be isolated[173,174]. The unsaturated analogue, cyclopentadienylideneketene **(380)** may be formed by FVP of either **378** at 650 °C[175] or **379** at 550 °C[176]. Under these conditions it loses CO to give the carbene **381** which isomerizes to benzyne, and in the latter study carrying out the pyrolysis over bitumen as a hydrogen source gave benzene.

Cyclization of a variety of alkylideneketenes generated by the Meldrum's acid method has provided a number of useful syntheses of nitrogen heterocycles. Thus, for example, FVP of **382** leads to the azepinone **383**[177], and the indole compounds **384** may give



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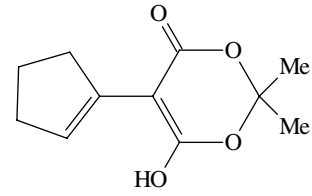

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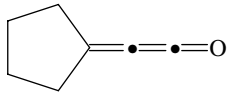

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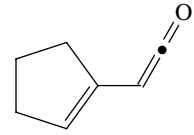

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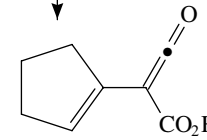

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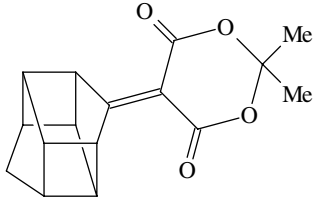

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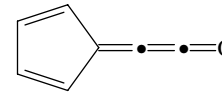

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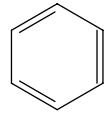

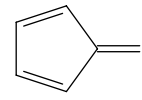

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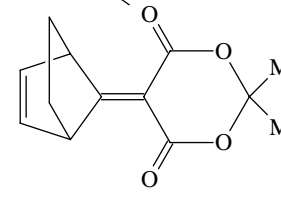

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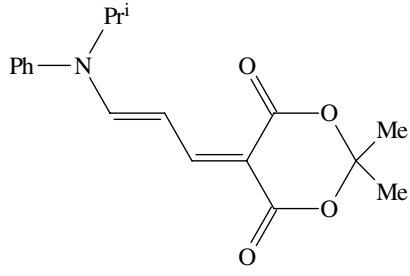

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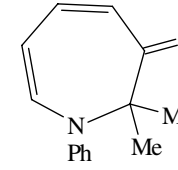
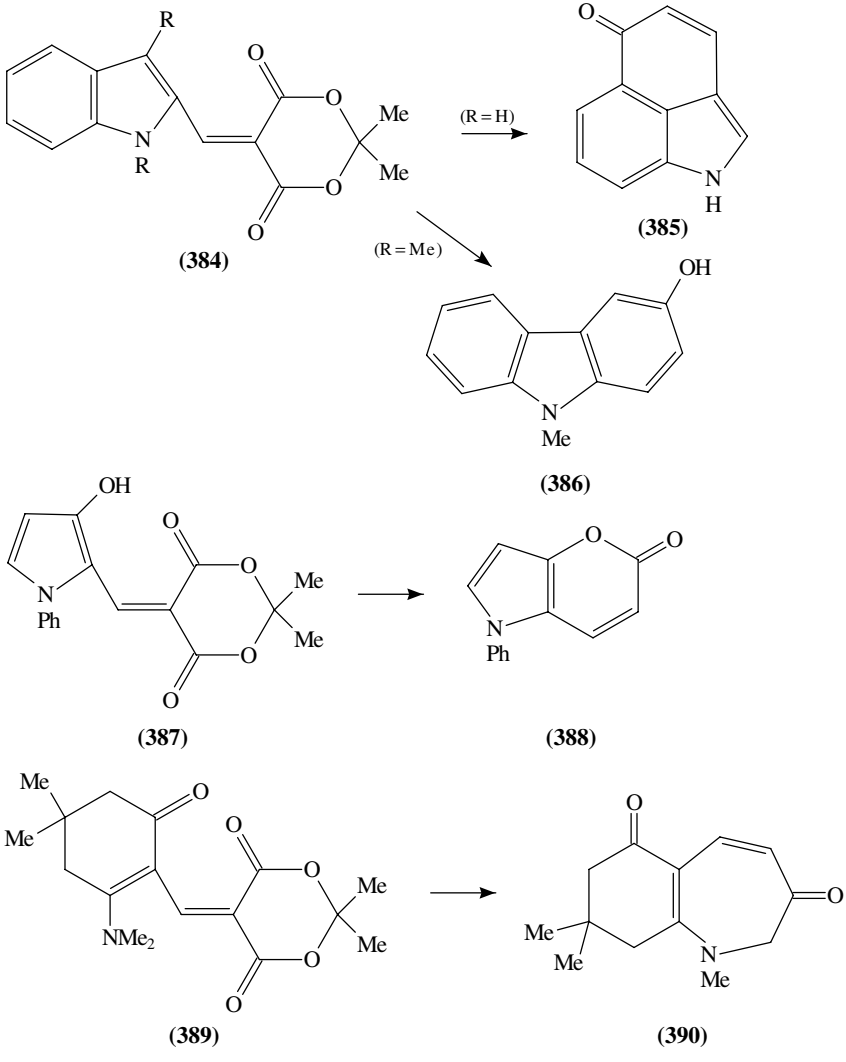
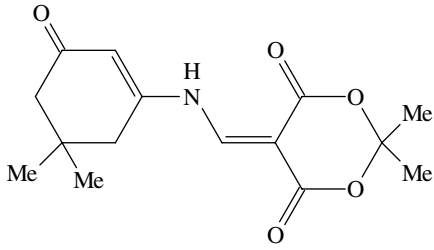


(383)

either **385** or the hydroxycarbazole **386** depending on the substituents present[178]. For a range of 3-hydroxy-2-pyrrolyl compounds such as **387** FVP at 600 °C leads mainly to the pyrrolopyranones **388**[179]. Further examples of unusual heterocyclic systems accessible by this method are the bicyclic azepinone **390**, formed in 45% yield by FVP of **389** at 600 °C, the quinolinedione **392** similarly prepared from **391**[179] and the pyrroloimidazolone **394** formed in 79% yield by FVP of **393**[180].

The pyrolysis of aminomethylene derivatives of Meldrum's acid has also been studied extensively. The parent compound **395** loses acetone and CO_2 at 400 °C to give **396**, which at higher temperatures isomerizes to **397** which loses CO to give ethynylamine **(398)**[159]. A range of cycloalkylamino compounds such as **399** reacts similarly on FVP at 500–600 °C to give the methyleneketene **400**, but under the conditions this undergoes





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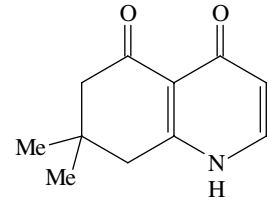

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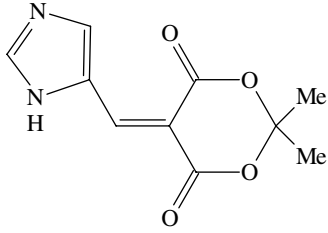

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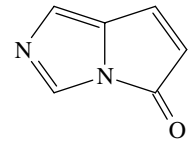

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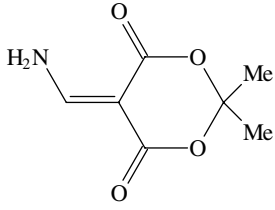

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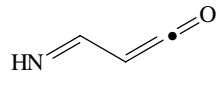

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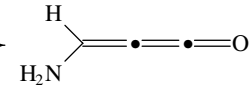

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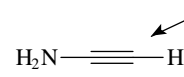

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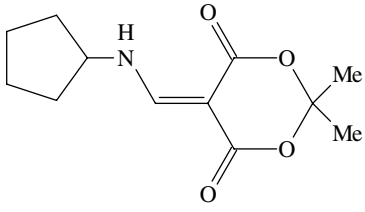

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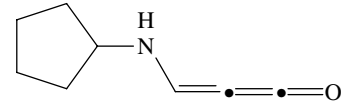

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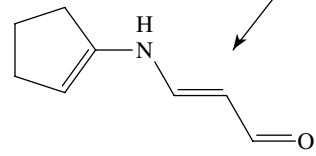
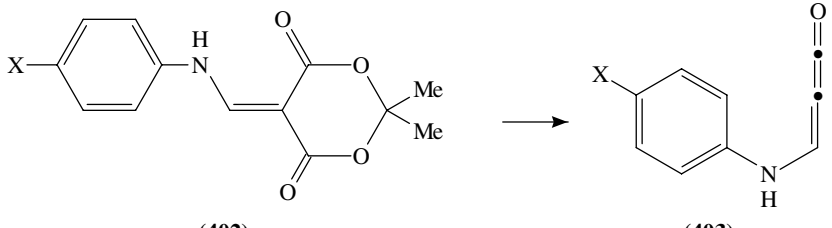


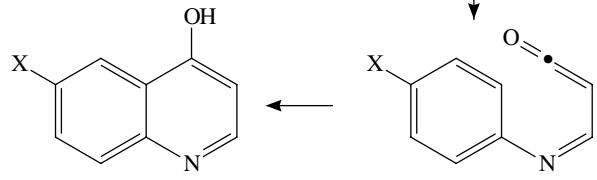
(401)

a series of hydrogen shifts to give the enaminoacrolein **401** as the final product[181]. For the *t*-butylamino analogue of **399**, isobutylene is lost to give cyanoacetaldehyde as the product of FVP above 540 °C[182].

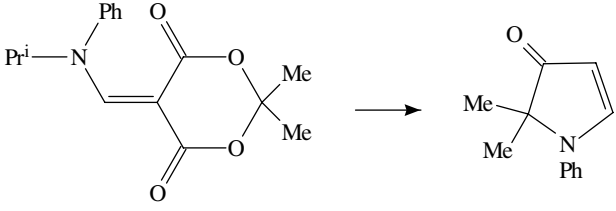
FVP of the arylaminomethylene compounds **402** at 400–600 °C gives 4-hydroxyquinolines **405** by isomerization of the initially formed aminomethyleneketenes **403** to the imidoylketenes **404**, which then cyclize[181]. Where there is a choice between an *N*-aryl and a suitable *N*-alkyl group, the ketene cyclizes onto the latter as illustrated by the formation of the pyrrolone **407** in 64% yield by FVP of **406** at 600 °C[183]. The oxazolidine compound **408** undergoes an unexpected process involving loss of formaldehyde at 600 °C to give a 2.7:1 ratio of the isomeric pyrrolones **409** and **410**[184].



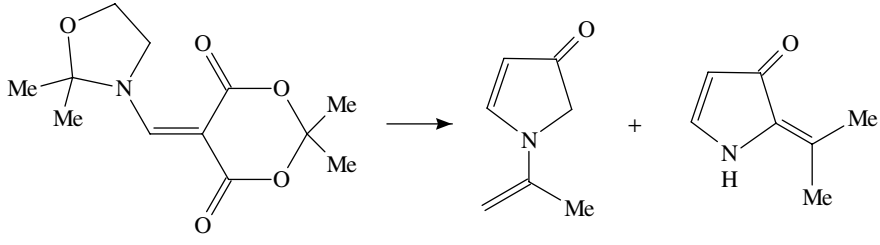
(402) **(403)**



(405) **(404)**

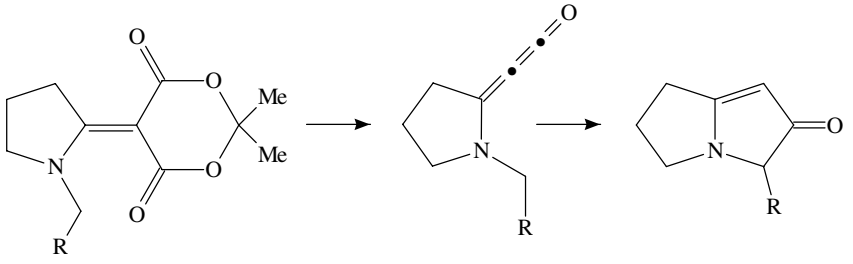


(406) **(407)**

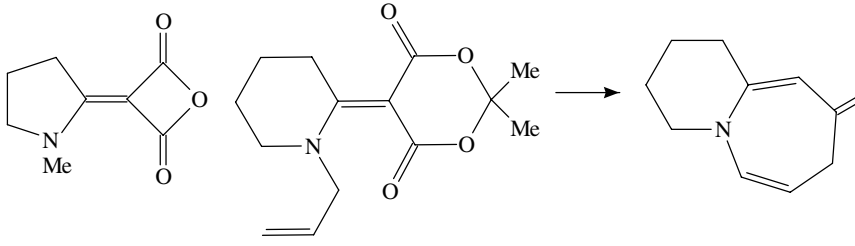


(408) **(409)** **(410)**

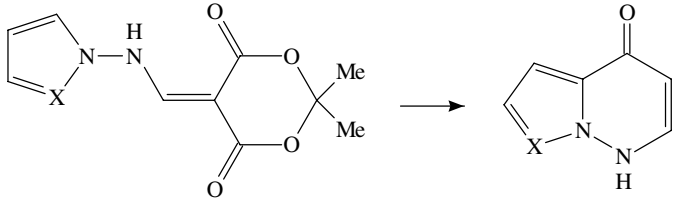
Pyrolysis of the cyclic aminoalkylidene Meldrum's acids **411** and their six-membered ring analogues at 600 °C proceeds with cyclization of the intermediate **412** on to the *N*-alkyl group to afford pyrrolizidinones **413**[185,186]. In the case of the *N*-methyl compound **411** (R = H), the unusual alkylidenemalonic anhydride **414** resulting from loss of only acetone could be detected from FVP at 450 °C[185]. FVP of the *N*-allylpiperidine compound **415** provides convenient access to the bicyclic azepinone system **416**[187]. The pyrazolyl- and pyrrolylamino compounds **417** give the fused pyridazinones **418** on FVP at 700 °C[188].



(411) **(412)** **(413)**



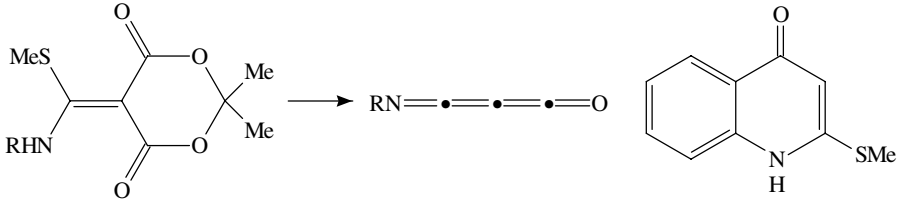
(414) **(415)** **(416)**



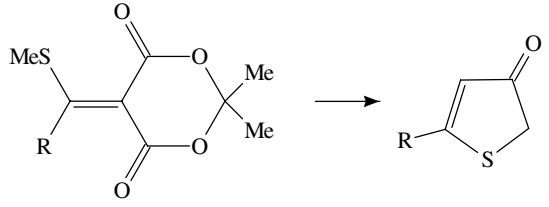
(417) X = N, CH **(418)**

The major pyrolytic process for the methylthioamino compounds **419** is loss of acetone CO_2 and MeSH to give the cumulenes **420**. For R = H this isomerizes to cyanoketene[117], while in other cases **420** can be isolated[189]. For **419** (R = Ph) an additional product is the quinolone **421**. Replacement of the amino group of **419** by Me, H or SMe leads to a change in behaviour to give dihydrothiophene-3-ones as the products, as illustrated by the conversion of **422** to **423**[190], and of **424** to **425**[190,191] on FVP at 600–625 °C.

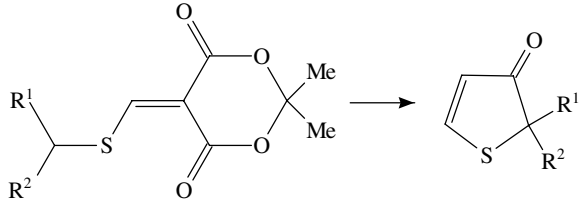
The 5-imino Meldrum's acid derivatives **426–428** have also been investigated. Heating the oxime **426** in boiling toluene provides a route to nitrosoketene, O=N–CH=C=O,



(419) **(420)** **(421)**

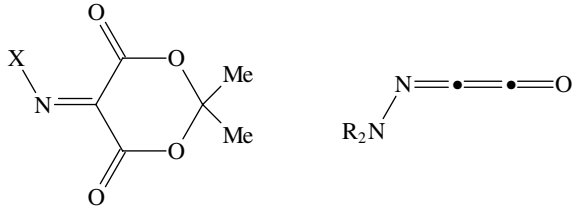


(422) R = Me, SMe **(423)**



(424) **(425)**

which can be trapped by cycloaddition to carbonyl compounds[192]. The corresponding oxime ethers **427** provide access to the unstable alkyl fulminates, RO−N=C:, which undergo further fragmentation depending on the nature of R[181]. The hydrazones **428** lose acetone and CO_2 upon FVP at 400–520 °C to give first the cumulenes **429**, which lose CO and isomerize to give the cyanamides R_2N-CN as the final products[181].



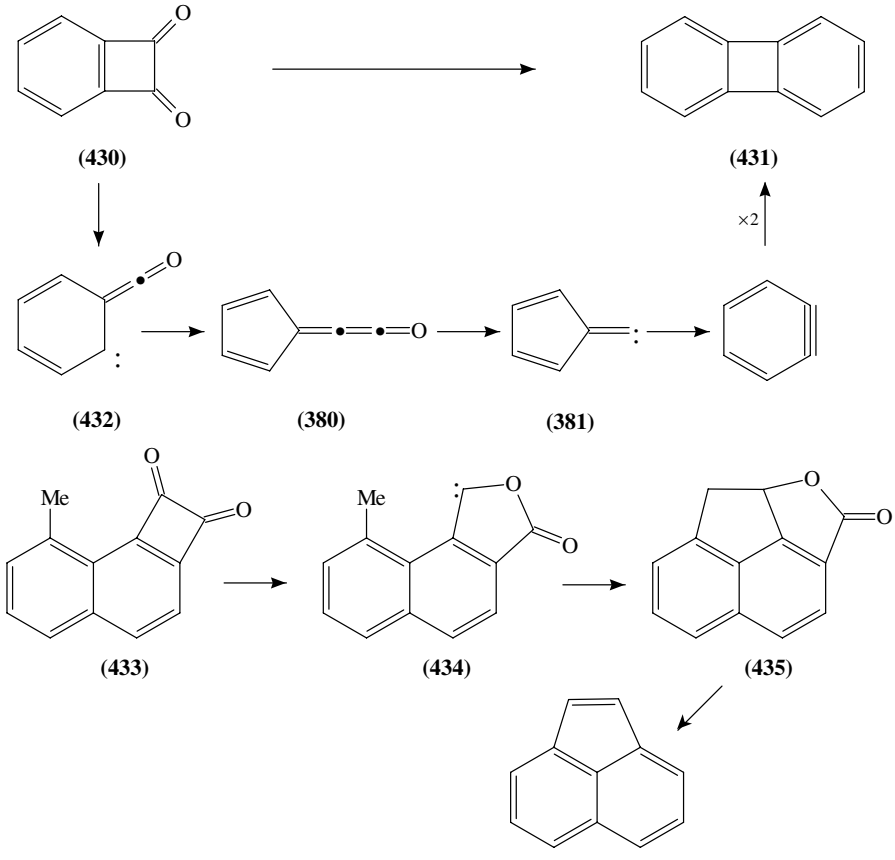
(426) X = OH
(427) X = OR
(428) $X = NR_2$

(429)

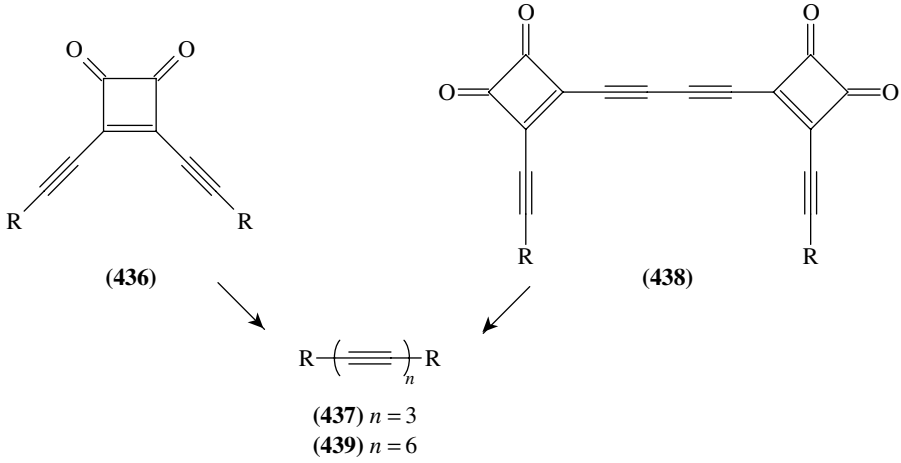
H. Cyclic 1,2-Diketones

1. Cyclobutenediones

Pyrolysis of cyclobutenediones results in loss of two molecules of CO to give the corresponding alkynes. Thus, for example, FVP of benzocyclobutenedione **(430)** at 650 °C results in formation of benzyne which dimerizes to afford biphenylene **(431)**. This process is not as straightforward as it might seem since use of the doubly ^{13}C labelled precursor shows scrambling of the label at the benzyne stage through equilibration with the ring-contracted carbene **381**[193] and benzyne is formed by the stepwise route shown involving **432**, **380** and **381**[194]. The naphthalene fused compound **433** fragments by two distinct pathways on FVP at 600–850 °C[195,196]. The first involves the expected loss of two molecules of CO to give the aryne **298**, which rearranges to the cyclopentindene **300** by way of **299** as shown earlier for the corresponding anhydride. A minor but significant competing process affords acenaphthylene by rearrangement to the oxacarbene **434**, insertion to give **435** and loss of CO_2. Simple cyclobutenediones lose two molecules of CO to give the alkyne and this has been used to particular effect by Diederich and coworkers to gain access to linear poly-ynes by using the novel technique of solution spray pyrolysis[197]. Thus, for example, treatment of **436** in this way at 650 °C gives **437**



while the more complex precursor **438**, formed by oxidative coupling, directly gives the hexaynes **439**.

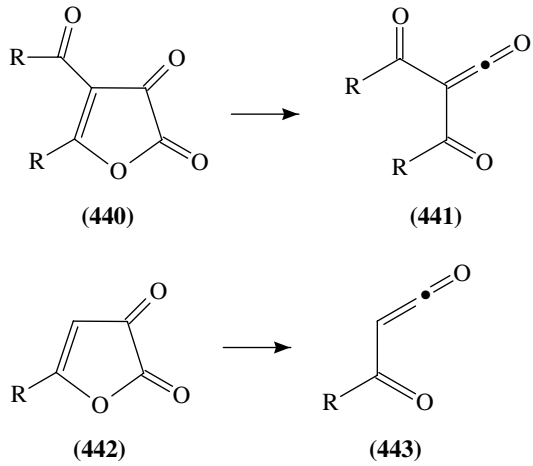


(436) **(438)**

(437) $n = 3$
(439) $n = 6$

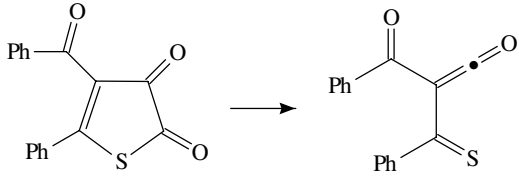
2. Furan-2,3-diones and thiophene-2,3-diones

Pyrolysis of the 4-acyldihydrofuran-2,3-diones **440** results in extrusion of one molecule of CO to give the diacylketenes **441**. These highly reactive products offer several possibilities for cycloaddition both with added dienophiles and by dimerization and their chemistry has been examined extensively for both R = Ph[198,199] and R = Bu^t[199,200]. More recently the simpler monosubstituted analogues **442** have been used to generate the acylketenes **443** for R = Me[201] and R = aryl[202]. The thiophenedione **444** also loses CO on FVP at temperatures above 300 °C to give the benzoylthiobenzoylketene **445**, which at 700 °C loses COS to afford PhCOC≡CPh[198]. The naphthalene fused thiophenedione **446** undergoes loss of CO at 700 °C to give **447** and at 900 °C this further loses CO to afford the thioketene **448**[203].

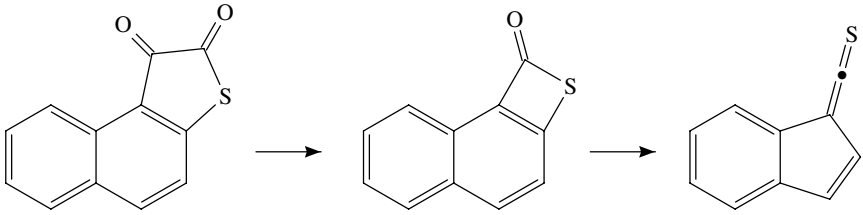


(440) **(441)**

(442) **(443)**



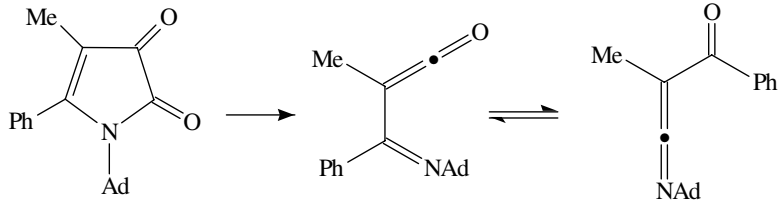
(444) **(445)**



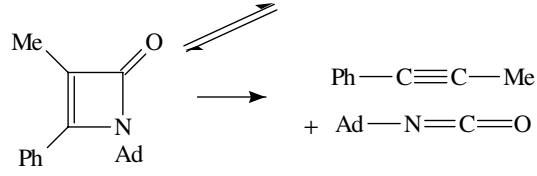
(446) **(447)** **(448)**

3. Pyrrole-2,3-diones and pyrazole-3,4-diones

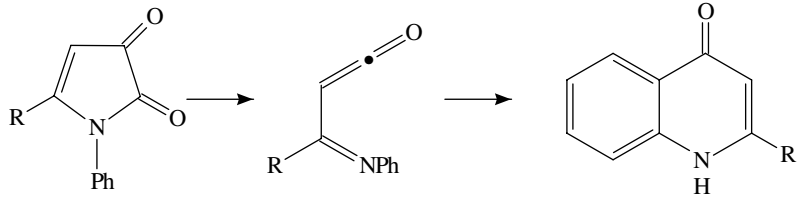
The pyrrole-2,3-diones also undergo pyrolytic loss of one molecule of CO and the resulting imidoylketenes may undergo a variety of reactions depending on the substituents present. Thus, for example, FVP of the *N*-adamantyl compound **449** at 675 °C gives the imidoylketene **450** which equilibrates with the benzoylketenimine **451** but may also cyclize to **452**, which fragments to the alkyne and adamantyl isocyanate[204]. With an *N*-phenyl group present as in **453**[205] and **454**[206,207], the imidoylketene **455** can cyclize to give the corresponding 4-quinolone **456** on FVP at 700–800 °C. In the case of **457**, FVP could not be used due to the involatility of the material, but the reaction to give **458** was successfully achieved by solution thermolysis at 180 °C in diphenyl ether[208]. FVP of the 4-benzoyl compound **459** at 500 °C gives the quinolone **460**[181]. The one pyrazoledione



(449) **(450)** **(451)**

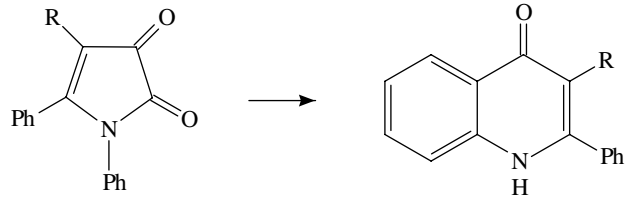


(452)

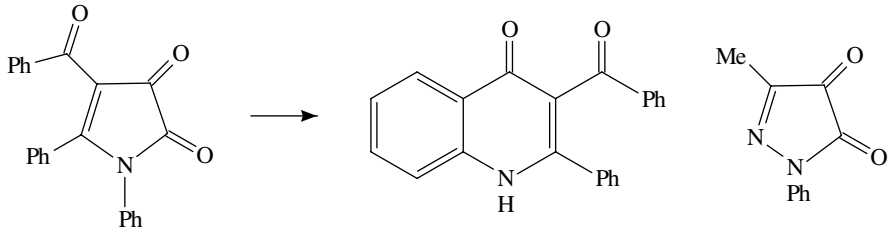


(453) R = OMe
(454) R = SMe

(455) **(456)**



(457) **(458)**

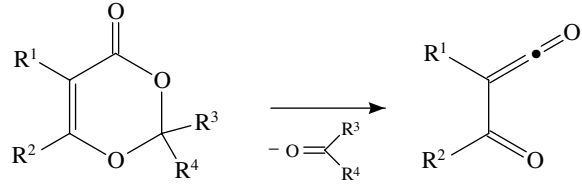


(459) **(460)** **(461)**

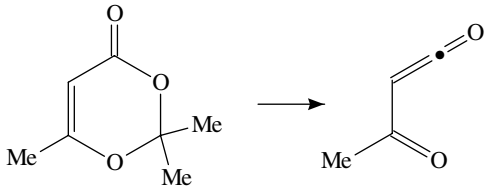
examined, compound **461**, undergoes complete fragmentation upon FVP at 750 °C to give CO, MeCN and PhNCO[209].

I. 1,3-Dioxinones and 1,3-Dioxinthiones

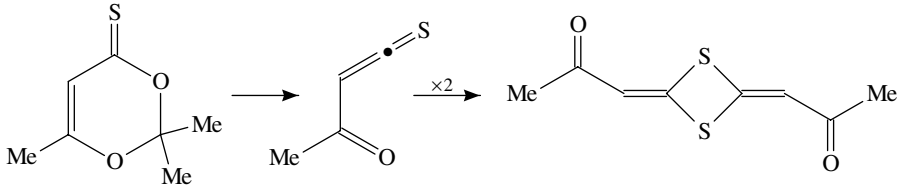
A wide range of 1,3-dioxin-4-ones **462** have been used as sources of acylketenes **463** by pyrolytic loss of acetone or another ketone. While these have generally been trapped by cycloaddition[210–216], recent work on simpler examples such as **464** has led to direct observation of the product **465** by low-temperature IR[201,217]. Heating the thione analogue **466** at 100–160 °C leads to loss of acetone to give acetylthioketene **467**, which in the absence of any trap gives the unusual dithietane dimer **468**[218].



(462) **(463)**



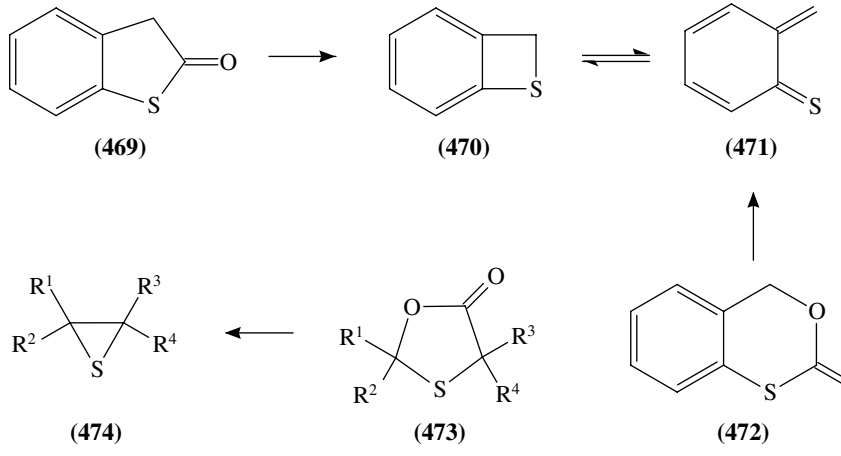
(464) **(465)**



(466) **(467)** **(468)**

J. Rings Containing Sulphur

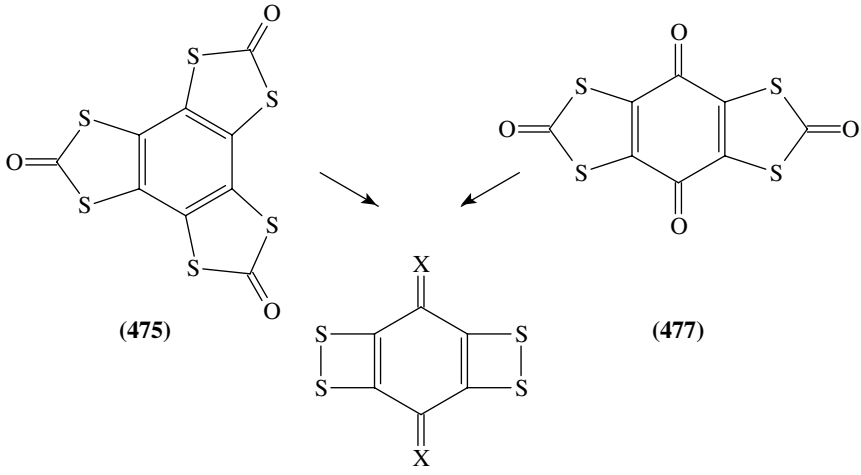
FVP of benzothiophen-2-one **(469)** at 700 °C results in loss of CO to give benzothiete **(470)**[219]. As shown, this is in equilibrium with the *o*-thioquinonemethide form **471** which can undergo Diels–Alder cycloaddition, and FVP of the six-membered ring precursor **472** at 500 °C has recently been used to gain access to **470/471** and several benzo-fused analogues for cycloaddition[220]. The 1,3-oxathiolan-5-ones **473** also undergo ready loss of CO_2 upon FVP at 600–750 °C to afford a useful synthesis of substituted thiiranes **474**[221]. The tricarbonate **475** of benzenehexathiol loses three molecules of CO upon FVP at 900 °C to give a compound which exists mainly in the dithioquinone form **476**, and **477** similarly gives the oxygen analogue **478**[222]. The cyclic sulphinic/carboxylic anhydride **479** loses SO_2 and CO on heating at 240 °C to give tetraphenylethylene[223]. Pyrolysis of the 1,3,4-oxathiazol-2-ones **480** results in loss of CO_2 to generate the 1,3-dipolar nitrile sulphides **481**[224]. The *N*-benzylthiazolidinone *S*,*S*-dioxides **482** fragment



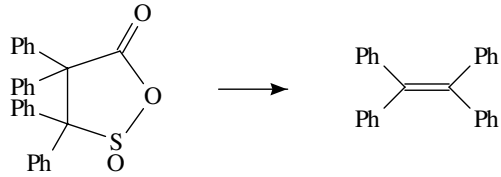
(469) **(470)** **(471)**

(474) **(473)** **(472)**

upon FVP at 650 °C mainly by loss of SO_2 to give $RCH{=}CH_2$ and benzyl isocyanate, but an unexpected minor process gives the 2-phenylthiazolines **484** and the corresponding thiazoles **485**[225]. These products are thought to arise from initial ring expansion to the sulphinic/carbamic anhydride **483**, which then loses CO_2 and rearranges with loss of water to give **484** and **485**.

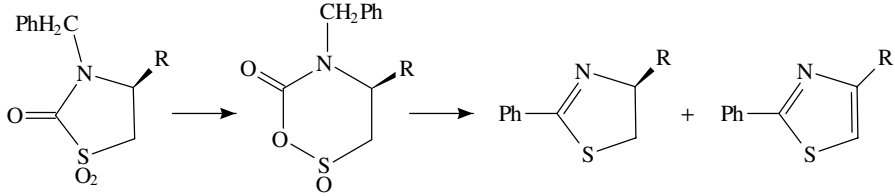


(475) **(476)** X = S **(477)** **(478)** X = O



(479)

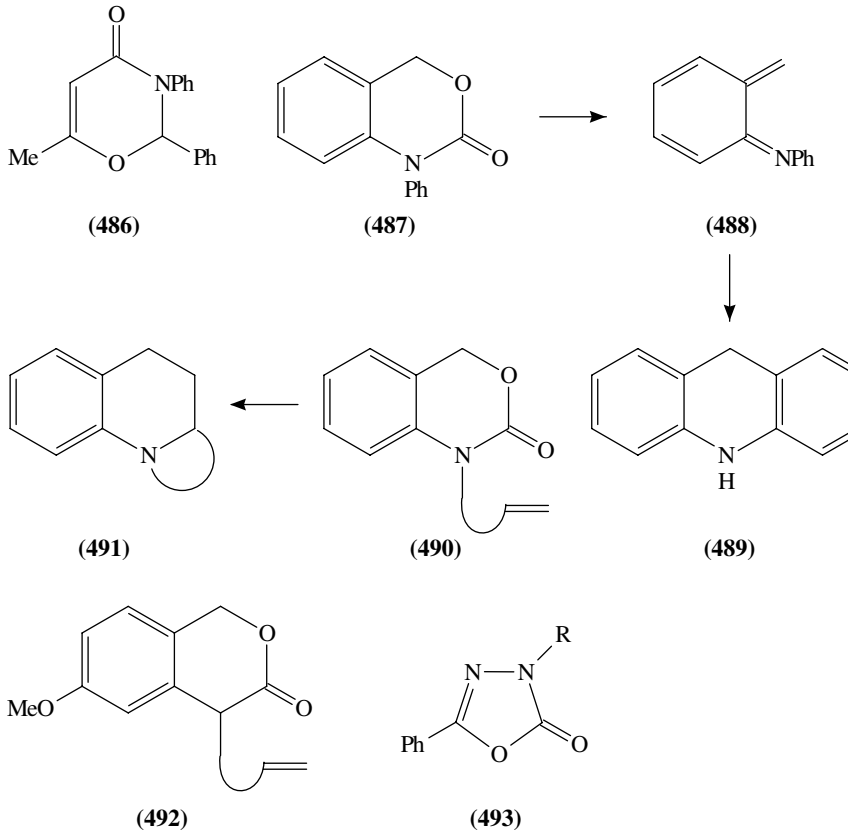
(480) **(481)**



(482) **(483)** **(484)** **(485)**

K. Miscellaneous Heterocyclic Compounds

Pyrolysis of the 1,3-oxazin-4-one **486** results in loss of benzylideneaniline to provide an alternative means of access to acetylketene **465**[201]. FVP of the 1,3-benzoxazin-2-one **487** at 650 °C results in loss of CO_2 to give **488**, which cyclizes to afford dihydroacridine **489**[226]. The *N*-alkenyl analogues **490** similarly extrude CO_2 at 600 °C to give the tricyclic products **491** resulting from an intramolecular Diels–Alder reaction in low yield. Perhaps surprisingly, attempts to extend this approach to the carbon analogues **492** were not successful[227]. A detailed study of the pyrolytic behaviour of the oxadiazolones **493** at 700 °C has been carried out and the products are largely complex mixtures of hydrocarbons whose nature depends heavily on the identity of R[228].



(486) **(487)** **(488)** **(489)** **(490)** **(491)** **(492)** **(493)**

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CHAPTER **11**

Thermochemistry of olefins, carbonyl compounds and imines

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I. INTRODUCTION: SCOPE AND DEFINITIONS

A. Thermochemistry

As has been the approach for most of the authors' other reviews on organic thermochemistry[1−8], the current chapter will be primarily devoted to the relatively restricted property, 'standard enthalpy of formation' (more commonly and colloquially called heat of formation), where we will write this quantity as ΔH_f°, instead of the increasingly more commonly used and also proper $\Delta_f H_m^\circ$. By intent, this chapter will forego discussion of other thermochemical properties such as Gibbs energy, entropy, heat

capacity and excess enthalpy. Additionally (following thermochemical convention[9]), the temperature and pressure will be tacitly assumed to be 25 °C ('298 K') and 1 atmosphere (taken as either 101,325 or 100,000 Pa), respectively, and the energy units will be kJ mol^{-1} (where 4.184 kJ ≡ 1 kcal).

Again following our earlier chapters as precedent, we will continue to view intermolecular forces as 'complications' and 'nuisances' to be avoided whenever possible. As such, unless explicitly noted to the contrary, any species to be discussed in this chapter will be assumed in the (ideal) gas phase. To interrelate these data with those for the liquid or solid state that characterizes most organic compounds as synthesized, reacted, purified and thermochemically investigated, it will be necessary to make 'corrections' to the gaseous state by using enthalpies of vaporization and of sublimation. These are defined by equations 1 and 2

$$\Delta H_{\mathrm{V}} = \Delta H_{\mathrm{f}}^{\circ}(\mathrm{g}) - \Delta H_{\mathrm{f}}^{\circ}(\mathrm{l}) \tag{1}$$

and

$$\Delta H_{\mathrm{s}} = \Delta H_{\mathrm{f}}^{\circ}(\mathrm{g}) - \Delta H_{\mathrm{f}}^{\circ}(\mathrm{s}) \tag{2}$$

where g, l and s refer to gas, liquid and solid, respectively. As always has been our practice, phase change enthalpies will be taken from whatever source available: our choice to maximize the use of gas-phase data and minimize that from the liquid or solid requires numerous expediencies. In the absence of data from experimental measurements, enthalpies of vaporization for hydrocarbons will usually be estimated using the generally accurate (±2 kJ mol^{-1}) two-parameter equation of reference 10. It is only rarely that enthalpies of sublimation will be needed.

Finally, we note that it will occasionally be necessary to use data for a species as liquid when the compound is 'normally' a solid, or as a solid when it is 'normally' a liquid. These two phases are interrelated by the enthalpy of fusion, equation 3.

$$\Delta H_{\mathrm{fus}} = \Delta H_{\mathrm{f}}^{\circ}(\mathrm{l}) - \Delta H_{\mathrm{f}}^{\circ}(\mathrm{s}) \tag{3}$$

We admit now that all phase change enthalpies should refer to determinations at 298 K. Again, for the sake of simplicity, the generally small corrections to these enthalpies to transform the temperature-dependent data to 298 K will not be made in the current study.

B. Olefins, Carbonyl Compounds and Imines

For this chapter we define an 'olefin' as any organic compound that contains but one carbon–carbon double bond and limit substitution to only 'hydrocarbyl' groups (i.e. composed of hydrogen and carbon). After all, the thermochemistry of some heterosubstituted olefins has already been the subject of specialized chapters in earlier 'Patai' volumes. Enones[2], enols[4,11] and enamines[5], and vinyl sulphides, sulphoxides and sulphones[3] have figured prominently in other 'not-so-narrow' Patai volumes. Relatedly, olefins with additional unsaturation in the form of one or more double bonds[8] and even cyclopropane rings[7] will likewise be largely ignored in this chapter.

'Carbonyl compounds' will be taken in this chapter to mean any organic compound that contains at least one carbon–oxygen double bond where we limit the substitution to only saturated aliphatic, saturated alicyclic and aryl 'hydrocarbyl' groups. Carbonyl compounds with a variety of unsaturated substituents have earlier been discussed within the context of enones[4]. Non-hydrocarbyl substituents, 'X', may be directly attached to the carbonyl and elsewhere in the molecule. The first type of species, RCOX, is alternatively identified as acyl derivatives such as carboxylic acids and their esters, halides and amides and have already been discussed in a recent Patai thermochemistry

chapter[12]. Some members of the second type have likewise been discussed as derivatives of the group 'X' (e.g. for a brief thermochemical discussion of α-haloketones, see Reference 6).

By the word 'imine' we mean a species containing at least one carbon–nitrogen double bond that is substituted only by hydrocarbyl groups. Therefore, we are omitting such C-heterosubstituted species as amidines and imidates[13], isocyanates and isothiocyanates[14], as well as N-heterosubstituted species such as diazo compounds, hydrazones, nitronates, nitrones and oximes. We are also ignoring compounds with either meaning of the term azine, both that of $>C{=}N{-}N{=}C<$ as found in benzalazine, PhCH=N–N=CHPh, and 6-membered 'benzenoid' rings containing nitrogen such as pyridazine and 1,3,5-triazine as well as pyridine and pyrimidine. After all, the first type of azine violates the hydrocarbyl group limitation. Inclusion of the second would have suggested benzene and its derivatives are to be included in discussion of trienes in Reference 8. To do so appears somewhere between nuisance and nonsense.

The choices of olefin, carbonyl compounds and imines have been made to allow for simple access to relevant data. All of these compounds contain carbon, hydrogen and possibly oxygen or nitrogen and so combustion calorimetry is relatively facile and direct[15]. As will be shown in later sections, hydrogenation and other types of reaction calorimetry can be of considerable use. We have already acknowledged that we will use relevant estimation approaches to obtain enthalpies of vaporization and sublimation to maximize the usefulness of the data available. A major simplification arises from our long-term bibliographic preferences and prejudices. We have long chosen to cite secondary and generally archival sources for enthalpies of formation[16,17] and phase changes[18] instead of primary sources. We find that this policy greatly simplifies the writing and reading of our text even as we admit the risk of offending an occasional author of a therefore uncited primary research paper.

II. ACYCLIC OLEFINS

A. Sources of Data

In a previous volume of this series[19], the author of the chapter on the thermochemistry of double-bonded compounds reported that in the period following the publication of comprehensive reviews and monographs a few years earlier[17b,20] only a small amount of experimental work had been performed. Consequently, primary attention in that chapter focused on developments in estimating enthalpies of formation by electrostatic models and group additivity. Much has been accomplished in the ensuing 20 years. Pedley and coworkers[16] have published three editions of their compendium of thermochemical data, giving easy access to much of the existing experimental enthalpy-of-formation and enthalpy-of-reaction data of interest in this chapter. Steele and Chirico[21] reviewed the thermodynamic properties of the acyclic mono-olefins beginning with C_5. The enthalpies of formation for the liquid, gas and ideal-gas state at 298.15 K were calculated for 47 compounds based on experimental enthalpy-of-combustion values. Where these authors believe there are errors in the original experimental results they suggest revised values. Jensen[22] tabulated the results of a *Chemical Abstracts* literature search through 1974 for experimental enthalpies of hydrogenation which yielded data on 225 compounds. Rogers and coworkers[23–29] have devised a method for the microcalorimetric determination of the enthalpies of hydrogenation of alkenes in dilute alkane solution, the results of which they maintain[23] are equivalent to gas-phase hydrogenation values. Contemporaneously, Wiberg and coworkers[30–32] showed that it is possible to determine the overall enthalpy of hydration of many C_4–C_8 alkenes in the liquid phase by measuring the enthalpies

of reaction of the alkene and alcohol with trifluoroacetic acid containing trifluoroacetic anhydride. In addition to determining enthalpies of formation of the alcohols, the authors suggest revisions to several of the enthalpies of formation of the alkenes based on their experimental enthalpies of isomerization.

B. Assessment of Alkene Data

Although there are abundant data for enthalpies of reaction of alkenes (combustion, hydrogenation, hydration, isomerization etc.) in the literature, some authors have expressed concern about the accuracy of the results. Jensen emphasizes in his review[22] of enthalpies of hydrogenation the requirement for careful measurement of reaction enthalpies for reliably assessing isomerization, strain and stabilization energies. In this compilation of structurally diverse compounds, he provides information regarding precision of measurement and special phase or solvent conditions. Additionally, he calculates some interesting and useful enthalpies of hydrogenation using the most precise data. The focus of recent discussion is whether the precision of the enthalpy of reaction measurements reflects the accuracy of the measurements. Various authors[23–32] state that the precision of reaction calorimetry reflects a comparable improvement in accuracy. Thus, because the enthalpy-of-hydration and -hydrogenation calorimetric measurements are inherently more precise than enthalpy-of-combustion measurements, they yield more accurate information regarding alkene energetics when used directly. Such considerations as optimum molecular weight in combustion calorimetry or undetermined, and perhaps not-quite-negligible, solvent effects in reaction calorimetry were cited as possibly affecting the accuracy of the various methods. Many of the enthalpies of formation listed by Pedley and colleagues[16] are composite values incorporating two or more separate measurements[33].

Enough data for the 1-*n*-alkenes exist to illustrate the magnitude of any differences we might expect to encounter were we to choose one set of enthalpy-of-formation data or another. Our method is first to plot the available experimentally derived enthalpies of formation for each member of the homologous series versus the total number of carbons, n_c, in the compound. Such a procedure is known to produce a reasonably straight line[34] as expressed in equation 4. A linear regression analysis using the method of weighted least squares reveals the goodness of fit and the associated uncertainty in the slope, α, and the *y*-intercept, β. Results are shown in Table 1.

$$\Delta H_f(g) = \alpha_g \cdot n_c + \beta_g \tag{4a}$$

$$\Delta H_f(l) = \alpha_l \cdot n_c + \beta_l \tag{4b}$$

The data from pedley and colleagues[16] includes $n_c = 4–8$, 10, 12 and 16 while that from Steele and Chirico[21], derived only from combustion enthalpies, comprises $n_c = 5–8$, 10, 12 and 16. The enthalpies of formation for C_8H_{16}(l), $C_{10}H_{20}$(l,g), and $C_{12}H_{24}$(l,g) used in these two regression analyses are from the same primary sources and are thus identical. Because there is *ca* 4 kJ mol^{-1} range in the enthalpies of formation for 1-hexene reported in these two references (the reason for which will be explained below), Table 1 also includes regression analyses omitting the C_6H_{12} data. Enthalpy-of-hydrogenation data[24,26,27,29] for $n_c = 5–12$, 16, 18 and the exceptionally consistent gaseous enthalpies of formation for alkanes from Pedley and colleagues[16], were used to calculate enthalpies of formation[35] according to equation 5.

$$\Delta H_f(\text{alkene, g}) = \Delta H_f(\text{alkane, g}) - \Delta H_{hyd} \tag{5}$$

Because of the precision of their alkene enthalpy of hydration measurements from Wiberg and coworkers[30,31], the authors refined the liquid enthalpies of formation for 1-pentene,

TABLE 1. Results from the linear regression analysis of equation 4 for 1-*n*-alkenes (kJ mol^{-1})

Reference	Phase	α	β
16	l	-25.59 ± 0.12	81.39 ± 0.91
16[b]	l	-25.61 ± 0.10	81.65 ± 0.761
21	l	-25.68 ± 0.16	82.03 ± 1.26
21[b]	l	-25.65 ± 0.15	81.56 ± 1.17
30, 31	l	-25.38 ± 0.006	79.96 ± 0.03
16	g	-20.60 ± 0.13	82.07 ± 0.93
16[b]	g	-20.62 ± 0.10	82.37 ± 0.73
21	g	-20.67 ± 0.16	82.54 ± 1.25
21[b]	g	-20.63 ± 0.13	81.96 ± 1.11
24, 26, 27, 29	g	-21.52 ± 0.15	82.32 ± 1.35

[a] In the least-squares analyses of equation 4, the individual enthalpies were weighted inversely as the squares of the experimental uncertainty intervals. The correlation coefficients are all greater than 0.999.

[b] Analysis of equation 4 omitting the data for 1-hexene.

1-heptene and 1-octene by combining their data and the literature combustion data in a least-squares treatment. They accepted the literature enthalpy-of-hydrogenation value for 1-hexene[36] and reduced the uncertainty by an arbitrary amount.

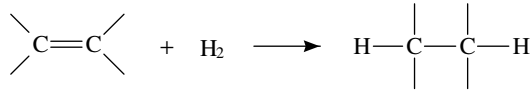
The enthalpy of formation for 1-hexene varies by *ca* 4 kJ mol^{-1} in the literature sources reviewed for this section. The enthalpy of combustion for liquid 1-hexene[37] as cited by Steele and Chirico[21] is -4005.72 ± 1.30 kJ mol^{-1} and the derived enthalpy of formation ($T = 298.15$ K, $p^\circ = 101.325$ kPa, $\Delta H_f(g, CO_2) = -393.51 \pm 0.13$ kJ mol^{-1}, $\Delta H_f(l, H_2O) = -285.830 \pm 0.042$ kJ mol^{-1}) is -70.32 ± 1.46 kJ mol^{-1}. The enthalpies of combustion of seventeen isomeric hexenes were later published only as values relative to 1-hexene[38] where the authors remark '... one does not need an accurate value of the heat of combustion of 1-hexene for the present calculations'. This is probably a repudiation of the earlier measurement because in order to calculate enthalpies of formation or combustion for the isomeric hexenes they recommend using a standard enthalpy of formation for 1-hexene (l) of -17.30 kcal mol^{-1} (-72.38 kJ mol^{-1}) based on a derived linear equation correlating the experimental enthalpies of formation of 1-*n*-alkenes with the number of included methylene groups[39]. Some authors [20,31] selected an enthalpy of formation (l, -17.29 ± 0.29 kcal mol^{-1} $= -72.34 \pm 1.21$ kJ mol^{-1}) from the weighted mean of two enthalpies of hydrogenation[36] although the latter citation indicates the enthalpy of formation is derived from combustion calorimetry. The selected enthalpies of formation for the isomeric hexenes in references 20 and 31 were all calculated from this value and the enthalpy-of-combustion ratios from Bartolo and Rossini[38]. Therefore, depending on which enthalpy of formation is chosen for 1-hexene, the calculated enthalpies of formation for the other sixteen hexene isomers differ systematically by *ca* 2 kJ mol^{-1}. Finally, Pedley and colleagues[16] incorporate not only the two enthalpies of hydrogenation from Reference 36, but also four enthalpies of isomerization from Reference 31 into a weighted-mean enthalpy of formation of -74.2 ± 1.6 kJ mol^{-1}.

The effect of excluding the enthalpy of formation of 1-hexene as determined either solely or in part from the combustion measurement[21,37] in the regression analyses improves the goodness of fit. Using these regression constants to calculate liquid enthalpies of formation for 1-hexene yields -72.01 kJ mol^{-1} from the 1-*n*-alkene data in Reference 16 and -72.34 kJ mol^{-1} from similar data in Reference 21.

Further review of the aforementioned references leads us to caution the reader not to accept uncritically the alkene enthalpy values cited throughout the literature. For example, the enthalpy of combustion for liquid *cis*-2-hexene[38] has been repeatedly cited as probably incorrect[21,26,31]. Pedley and colleagues[16] use that combustion enthalpy to determine a recommended enthalpy of formation which thus may be too negative by about 4 kJ mol^{-1}. Wiberg and Wasserman[31] also believe the enthalpy of combustion of liquid *trans*-3-hexene[38] to be erroneous. Another questionable combustion enthalpy is for either one or both of the 3-methyl-3-hexenes[40]. The results show the *cis* (*Z*) isomer to be more stable by 2.6 kJ mol^{-1}, contrary to the relative stabilities of most other isomeric *cis*–*trans* pairs. According to others[27], the *trans* (*E*) isomer probably is incorrect. In the original publication, a typographical error in the enthalpy of combustion[41] for the liquid *cis*-1-phenyl-3,3-dimethylbut-1-ene was transformed into an incorrect enthalpy of formation in Reference 16 so that the actual stabilities of the *cis* and *trans* isomers appear reversed. In subsequent sections of this chapter we will continue to explore and comment on the quality of the data.

C. Enthalpies of Hydrogenation of Alkenes

A historically useful probe of alkene energetics is the exothermic enthalpy of hydrogenation (ΔH_{hyd}) accompanying the alkene reaction to the corresponding alkane (equation 6).



(6)

A simplifying assumption is that all members of a particular category of alkene, e.g. the 1-*n*-alkenes, will have about the same enthalpy of hydrogenation and, after enthalpies for a few representative compounds have been precisely measured, the mean value is applicable to other alkenes of the same structural type. This assumption is only true, or approximately so, under well-defined circumstances; if applied indiscriminately it can lead to errors in interpreting the energetics of alkenes. The basis for the assumption is clear after recasting equation 5 in the linear form of equation 7.

$$\Delta H_{\mathrm{f}}(\text{alkane, g}) = m\bullet\Delta H_{\mathrm{f}}(\text{alkene, g}) + \text{`}\Delta H_{\mathrm{hyd}}\text{'} \tag{7}$$

Because the enthalpies of formation of homologous series of both alkanes and alkenes are linearly related to the total number of carbon atoms in their structures, the enthalpies of formation of each series are linearly related to each other. However, only in the case where the slope, α_{alkane}, from equation 4a for the alkanes is identical to the slope, α_{alkene}, from equation 4a for the alkenes (and thus $m = 1$ in equation 7) is the enthalpy of hydrogenation constant and equal to the *y*-intercept ('ΔH_{hyd}') of the equation 7 linear regression[42] (and thus to the difference in intercepts β_{alkane} and β_{alkene} from equation 4a). If the two slopes are significantly different, i.e. as the lines generated from equation 4a become noticeably non-parallel, the enthalpy of hydrogenation will not be constant for the members of the alkene series but instead will exhibit a regular increase or decrease. Thus, the indicator of consistency in measurement of enthalpies of hydrogenation for a particular class of alkene is not necessarily a close correspondence in the measured enthalpies of hydrogenation; the values may naturally be different.

In the remainder of this section we identify members of several homologous series of alkenes and apply equation 4 to their enthalpies of formation. In this way we can assess

the quality of the data as well as generate α_{alkene} to compare with the corresponding α_{alkane}. The calculation of the slopes, *m*, from equation 7 will show us in which series we might expect to find nearly constant enthalpies of hydrogenation. The difference between the *y*-intercept ('ΔH_{hyd}') and the mean experimental ΔH_{hyd} is a measure of the constancy of the enthalpy of hydrogenation for the series. When References 21 and 16 cite the same enthalpy, we will cite Reference 16 as the source. Enthalpies of hydrogenation[24–29] are used to calculate gaseous enthalpies of formation[35] according to equation 5. Because so much data is from this source and because of our previous stated preference for this phase, we will generally restrict our interest to the gaseous phase. Gaseous enthalpies of formation cited from Wiberg and coworkers[30–32] were calculated from the liquid enthalpies of formation given there and the enthalpies of vapourization[43] from Reference 16. We accept as accurate the enthalpies of formation of the alkanes from Pedley.

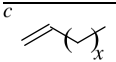
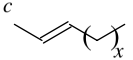
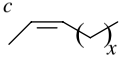
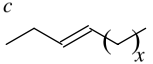
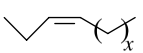
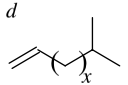
For several of the compounds considered in this section there are two or three reported enthalpies of formation, most of which are identical within experimental error. Using a weighted mean and weighted uncertainty for these measurements, or not, can significantly affect the regression analysis. The weighted uncertainty is smaller than the uncertainty of the individual measurements and may be smaller than any of the experimental uncertainties for the other members of homologous series. When used in the weighted linear regression of equation 4, the measurement with the smaller uncertainty assumes greater influence on the fit of the resulting line. Their inclusion may be justifiable if the multiple enthalpies of formation were determined using the same experimental method or if the data for all members were treated in the same way. Neither of these being the case, we calculated a simple mean and uncertainty[35] to use in the analyses.

The results of the regression analyses of equations 4a and 7 for the alkenes and the corresponding alkanes are reported in Table 2 and discussed below. The mean ΔH_{hyd} experimental enthalpies of hydrogenation in Table 2 are determined from the same data chosen for the regression analyses and were obtained either from the enthalpies of formation of the corresponding alkenes and alkanes (equation 5) or from the measured enthalpies of hydrogenation[24–29].

1. *n*-Alkenes

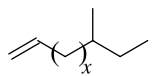
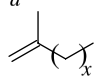
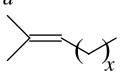
The most precise, consistent and presumably accurate enthalpies of formation in Table 1 are those for the liquid 1-*n*-alkenes from References 30 and 31. Converting to gaseous enthalpies of formation for $n_c = 5–7$ and choosing gaseous enthalpies of formation for $n_c = 4$, 8, 10, 12, 16 from Reference 16 and $n_c = 9$, 11 from Reference 24 (the only source for these two members) gives us a set of enthalpies of formation which are co-linear according to equation 4a. There are three available enthalpies of formation for *trans*-2-hexene, two of which are identical within experimental error. However, none of them is co-linear with the other members of the homologous series; instead, the enthalpies lie on either side of the series line. By averaging all three available values, the resulting enthalpy of formation was incorporated into the straight line. For the *trans*-2-alkenes, the selected values are: (C_4H_8)[16]; $(C_5H_{10} = -31.5 \pm 1.5)$[16,21,30]; $(C_6H_{12} = -52.2 \pm 2.0)$[16,26,31]; $(C_7H_{14} = -73.3 \pm 1.8)$[21,27,30]; and (C_8H_{16})[29]. For the *cis*-2-alkenes, the chosen values are: (C_4H_8)[16]; $(C_5H_{10} = -26.9 \pm 1.4)$[16,21,30]; $(C_6H_{12} = -47.8 \pm 1.4)$[26,31,43]; $(C_7H_{14} = -69.3 \pm 1.3)$[21,30]; and (C_8H_{16})[29]. A difficult choice must be made from the *trans*-3-alkene data. There are no three data points which describe a straight line with n_c, not even those three which come from the same source[26,27,29]. We accept the only enthalpy of formation for *trans*-3-octene[29]. Because Reference 31 determined the enthalpy of formation of *trans*-3-hexene from isomerization of 1-hexene, an enthalpy of formation we trust, we accept that value and the one[30] for C_7H_{14}. A plot of equation 4a

TABLE 2. Regression analyses of equations 4a and 7 for homologous series of alkenes and corresponding alkanes (kJ mol^{-1})[a]

Alkene Series	Constants from equation 4		Constants from equation 7		Experimental
	α(g)	β(g)	m(g)	'ΔH_{hyd}'(g)[b]	ΔH_{hyd} (g)[f]
[c] 					
$x = 1$–9, 13	−20.46 ± 0.11	81.20 ± 0.72	1.001 ± 0.004	−125.9 ± 0.5	−125.9 ± 0.8
[c] 					
$x = 1$–4	−20.58 ± 0.17	71.30 ± 1.11	0.999 ± 0.013	−115.1 ± 0.9	−114.9 ± 0.6
$x = 0$–4	−20.49 ± 0.09	70.64 ± 0.53	1.008 ± 0.009	−114.5 ± 0.6	−115.1 ± 0.5
[c] 					
$x = 1$–4	−20.92 ± 0.24	77.59 ± 1.55	0.987 ± 0.015	−112.0 ± 0.9	−119.3 ± 0.7
$x = 0$–4	−20.64 ± 0.17	75.70 ± 0.97	1.001 ± 0.012	−119.1 ± 0.7	−119.1 ± 0.7
[c] 					
$x = 1$–3	−21.50 ± 0.69	78.24 ± 4.69	0.980 ± 0.030	−117.2 ± 2.2	−115.8 ± 0.8
[c] 					
$x = 1$–3	−22.09 ± 0.06	85.93 ± 0.40	0.939 ± 0.006	−123.3 ± 0.5	−119.1 ± 1.4
[d] 					
$x = 0, 1, 3$	−20.48 ± 0.02	74.77 ± 0.10	1.000 ± 0.009	−126.2 ± 0.5	−126.4 ± 0.3

(*continued overleaf*)

TABLE 2. (*continued*)

Alkene Series	Constants from equation 4		Constants from equation 7		Experimental ΔH_{hyd} (g)[f]
	α (g)	β (g)	m (g)	'ΔH_{hyd}'(g)[b]	
e  $x = 0$–2	-19.20 ± 0.05	65.731 ± 0.34	1.052 ± 0.027	-119.7 ± 1.9	-123.3 ± 1.1
d  $x = 0, 2$–4	-20.74 ± 0.11	66.10 ± 0.63	0.974 ± 0.001	-117.8 ± 0.1	-116.1 ± 0.9
d  $x = 0$–2	-22.29 ± 0.26	70.34 ± 1.66	$0.921 \pm .026$	-115.9 ± 1.7	-110.9 ± 1.9

[a] In the least-squares analyses of equations 4a and 7, the individual enthalpies were weighted inversely as the squares of the experimental uncertainty intervals. The correlation coefficients are all greater than 0.999.

[b] From equation 7, the *y*-intercept in the regression analysis is interpreted as the estimated enthalpy of hydrogenation.

[c] The hydrogenation product is the corresponding *n*-alkane. The constants generated from equation 4a for the complete data set of *n*-alkanes ($n_c = 4$–12, 16, 18) are: $\alpha_{(g)} = -20.63 \pm 0.06$, $\beta_{(g)} = -43.20 \pm 0.46$ and $r^2 = 0.99994$.

[d] The hydrogenation product is the corresponding 2-methylalkane. The constants generated from equation 4a for the complete data set of 2-methylalkanes ($n_c = 4$–8, 10) are: $\alpha_{(g)} = -20.50 \pm 0.23$, $\beta_{(g)} = -51.77 \pm 1.33$ and $r^2 = 0.9995$.

[e] The hydrogenation product is the corresponding 3-methylalkane. The constants generated from equation 4a for the complete data set of 3-methylalkanes ($n_c = 6$–8) are: $\alpha_{(g)} = -20.16 \pm 0.39$, $\beta_{(g)} = -51.02 \pm 2.70$ and $r^2 = 0.99992$.

[f] The uncertainty interval was calculated as the square root of the sum of the squares of the individual enthalpies of hydrogenation.

or equation 7 shows, as do the uncertainties associated with the regression constants, that at least one of the three data points needs adjustment. A lesser problem confronts us with the data for the *cis*-3-alkenes because the enthalpies of formation for C_6H_{12} and for C_7H_{14} from various sources are the same within experimental error. The mean values are: ($C_6H_{12} = -46.6 \pm 1.8$)[16,26,31] and ($C_7H_{14} = -68.8 \pm 1.7$)[21,27,30]. Again there is only one C_8H_{16} value[29].

Figure 1 is a plot of equation 7 which helps visualize the results in Table 2 for the gaseous *n*-alkene homologous series. Although only the gaseous phase plot is presented, that for the liquid phase is almost identical except for scale and the absence of data for ethene, propene and the octenes. For visual clarity in Figure 1, lines connect the data points for the 1-*n*-, *cis*- and *trans*-2-*n*-alkene isomers only. Unlike in some other homologous series[44], the methyl-substituted functional group, $CH_3CH{=}CH_2$, does not deviate from the linear relationship. Relative to the other alkenes, ethylene is destabilized, with an enthalpy of hydrogenation[16] of -136.3 kJ mol^{-1} substantially more negative than the other alkenes. Its deviation from the 1-*n*-alkene homologous series is analogous to the deviation observed for any H–Z compound compared to the R–Z homologous series[45] and so it was not included in any of the results presented here.

2. Branched monosubstituted alkenes

It is clear from equation 7 that we should not consider as one structural category all those monosubstituted alkenes with branching in the substituent group and report an average enthalpy of hydrogenation for the group. Instead, we wish to discriminate among those subcategories wherein the branching position is progressively closer to the double bond.

In the homologous series of gaseous isoalkyl-1-alkenes, a methyl group is substituted on the penultimate carbon. The equation 4a best straight line for the four members of the series incorporates the sole C_5H_{10} point[16] and the C_6H_{12} and C_8H_{16} points from References 26 and 29. The C_7H_{14} data[16,28], which vary by 4.3 kJ mol^{-1}, lie on either side of the line. The average enthalpy of formation for 5-methyl-1-hexene from these two data (g) is -67.9 ± 1.5 kJ mol^{-1} while the interpolated value is -68.7 kJ mol^{-1}. Using the average value in the regression analysis significantly degrades the correlation of equation 4a.

Three branched 1-alkenes with a *sec*-butyl group remote from the double bond constitute another homologous series. Among the gaseous enthalpies of formation for 3-methyl-1-pentene, 4-methyl-1-hexene and 5-methyl-1-heptene derived from measured enthalpies of hydrogenation[26,27,29], one of the points is a slight outlier and the correlations from either equation 4a or equation 7 are not satisfactory. Using an alternate value[16] for 3-methyl-1-pentene which is 2 kJ mol^{-1} more negative produces a three-point series which is profoundly linear by either equation 4a or equation 7.

The 3-methyl-1-alkenes could seemingly constitute yet another series. The enthalpies of formation for (C_5H_{10})[16], (C_6H_{12})[26] and (C_7H_{14})[27] are well-correlated both with carbon number (equation 4) and with the corresponding alkanes (equation 7). Extended analysis of the alkanes reveals, however, that the first member of the corresponding alkane series, 2-methylpentane, is actually an outlier on the otherwise straight line incorporating the C_6–C_8 3-methylalkanes. Had an enthalpy value for 3-methyl-1-heptene been measured, the non-linearity would be apparent in a degradation of the alkene correlation. Of course, the C_6–C_8 3-methyl-1-alkenes and -alkanes do form homologous series, but, lacking the C_8H_{16} enthalpy, we will not perform a regression analysis on the two-point line. This example serves as a reminder that not only must there be data of good quality but also data in sufficient quantity. We are cognizant that a new measurement for a member of the

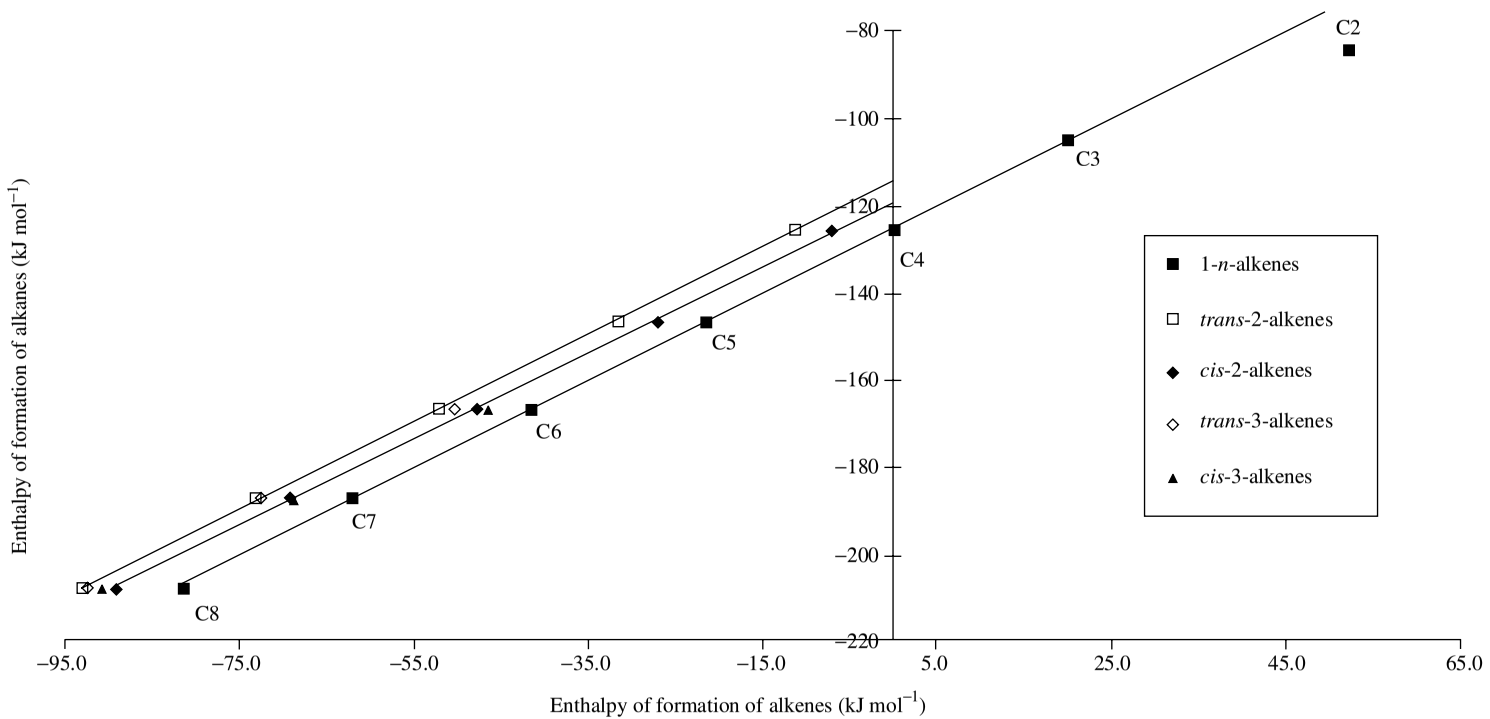


FIGURE 1. Enthalpies of formation of alkanes (g) vs alkenes (g)

series or a measurement for a new member in a series, especially if it is a fourth member, could materially affect our choice of data to include in an analysis.

There are only two members of a homologous series containing a tertiary branched group and so we will not attempt a regression analysis. The two enthalpies of formation for 3,3-dimethyl-1-butene[16,26] are essentially identical and yield an enthalpy of hydrogenation of about -125.7 kJ mol^{-1}. The two enthalpies of formation for 4,4-dimethyl-1-pentene[21,28] vary by 3.8 kJ mol^{-1}. The derived enthalpy of hydrogenation from Reference 21 is -126.4 ± 2.3 kJ mol^{-1} and the measured enthalpy of hydrogenation from Reference 28 is -122.6 ± 0.6 kJ mol^{-1}. We have no way of deciding between them.

3. 1,2-Disubstituted ethenes

There are enthalpy data for both geometric forms of four 1,2-disubstituted ethenes with one branch in one of the substituent groups (4-methyl-2-pentene, 4-methyl-2-hexene, 5-methyl-2-hexene and 2-methyl-3-hexene). Unfortunately, no three of these are homologous. We are additionally hampered because there are two enthalpies of formation for *trans*-4-methyl-2-pentene[16,26] and we have no way of deciding between them. There are not even two compounds which belong to homologous series among the various more highly branched 1,2-disubstituted ethenes for which there are data. A plot of equation 7 for the *cis* and *trans* 2- and 3-alkenes, branched and unbranched, shows the branched compounds clustered around the lines describing the *n*-alkene homologous series (except for the sterically congested *cis*-4,4-dimethyl-2-pentene and *cis*-2,2-dimethyl-3-hexene). Thus, the enthalpies of hydrogenation of the branched alkenes are similar to, but not easily derivable from, the unbranched alkenes.

4. 1,1-Disubstituted ethenes

The unbranched 1,1-disubstituted ethenes for which there are enthalpy data belong to either of two homologous series: the 2-methyl- or 2-ethyl-1-*n*-alkenes. In the latter category, there are only two members, 2-ethyl-1-butene and -pentene. As such, we will not analyse their regression characteristics. A plot of equation 4a or equation 7 for the C_4–C_8 2-methyl-1-*n*-alkenes shows a straight line incorporating all the data except that the value for 2-methyl-1-butene is a too-positive outlier. Three sources[16,21,32] give a very consistent value [mean $\Delta H_f(g) = -35.3 \pm 0.3$ kJ mol^{-1}] for this compound, all citing a fairly recent determination[46]. A value estimated from equation 7 for this species is -37.6 ± 0.3 kJ mol^{-1}, a difference of 2 kJ mol^{-1} from the literature value. The regression analysis in Table 2 does not include either of these values. Among the 2-methyl- or 2-ethyl-1-alkenes with ethyl or methyl branches for which there are data, no three compounds are homologous.

5. Trisubstituted ethenes

Of the available trisubstituted alkenes for which we have data, only three are homologous: 2-methyl-2-butene, -pentene and -hexene. Three literature enthalpy-of-formation values[16,21,32] for the C_5H_{10} compound are well within the error bars and so we have used an average (-41.4 ± 2.0 kJ mol^{-1}). A plot of equation 4a clearly shows the enthalpy of formation for C_6H_{12} derived from Reference 26 to be the best value.

6. Tetrasubstituted ethenes

There are enthalpy-of-formation data for only two tetrasubstituted ethenes (2,3-dimethyl-2-butene and 2,3-dimethyl-2-pentene). Although homologous, we will not

perform a regression analysis for only two members. Complicating any analysis are the four enthalpies of formation[16,20,26,32] for C_6H_{12} which span a range of 3.9 kJ mol^{-1}.

D. Constancy of the Enthalpy of Hydrogenation

We deduced from equations 4 and 7 that only when the slope, m, is approximately equal to 1 will the enthalpies of hydrogenation for a homologous series of alkenes be reasonably constant. Inspecting the slope and intercept data from equation 7 in Table 2, together with the actual experimental enthalpies of hydrogenation, shows our conclusion to be valid. We define for each alkene homologous series

$$\delta\Delta H_{\text{hyd}} = \Delta H_{\text{hyd}} \text{ (experimental mean)} - \text{`}\Delta H_{\text{hyd}}\text{'(y-intercept from equation 7)} \quad (8)$$

and plot $\delta\Delta H_{\text{hyd}}$ versus the slope, m, from equation 7 (Figure 2). When m is between 0.999 and 1.01 (very close to 1), $\delta\Delta H_{\text{hyd}}$ is clustered around ± 0.2 kJ mol^{-1} and the experimental ΔH_{hyd} are fairly constant. If m is less than 0.98 or greater than about 1.01, $\delta\Delta H_{\text{hyd}}$ shows a steep, nearly linear increase; the experimental ΔH_{hyd} changes monotonically. A particularly illustrative example is the *cis*-3-alkenes ($m = 0.939$). Although we used two composite enthalpies of formation in equations 4 and 7, the individual alkene enthalpies of formation, as determined by various methods, were quite consistent. The experimental, directly determined enthalpies of hydrogenation[26,27,29] by themselves show decreasing exothermicity with increasing carbon number: -121.6 ± 0.32, -118.5 ± 0.3, -117.8 ± 0.4 kJ mol^{-1}, differences which cannot be attributed to experimental error. Contrast those to such series as the 1-*n*-alkenes ($m = 1.001$) where the experimental enthalpies of hydrogenation fluctuate around the mean with increasing carbon number.

The foundation of these observations is the universal applicability of equation 4 to all known homologous series of organic compounds[34]. The regression constants in Table 2 derived from equation 4a may be used to calculate the desired enthalpy of formation for an as-yet unmeasured alkene species. The information in Table 2 also may be useful in yet another form, again derivable from equation 4. For a given homologous series, to calculate an approximate enthalpy of hydrogenation when the enthalpy of formation of neither the alkane nor the alkene is known

$$\Delta H_{\text{hyd}} = n_{\text{c}\bullet}(\alpha_{\text{alkane}} - \alpha_{\text{alkene}}) + (\beta_{\text{alkane}} - \beta_{\text{alkene}}) \quad (9)$$

E. Enthalpies of Isomerization of Alkenes

Complementary to enthalpies of hydrogenation for studying the energetics of alkenes are enthalpies of isomerization. These may be directly determined experimentally in favourable cases or derived from other enthalpies of reaction. The most accessible and general-purpose derivation is from enthalpies of formation of the alkenes of interest, as in equation 10.

$$\Delta H_{\text{isom}} = \Delta H_{\text{f}}[\text{alkene(2)}] - \Delta H_{\text{f}}[\text{alkene(1)}] \quad (10)$$

Because the enthalpies of formation of all homologous series of alkenes correlate with the number of carbons according to equation 4, any two series must correlate with each other. We can recast equation 10 in linear form as equation 11.

$$\Delta H_{\text{f [alkene(2)]}} = m' \Delta H_{\text{f [alkene(1)]}} + \text{`}\Delta H_{\text{isom}}\text{'} \quad (11)$$

Just as for the enthalpy of hydrogenation in equation 7, the enthalpies of isomerization between alkene members of two homologous series will be constant and equal to the *y*-intercept (`ΔH_{isom}') only when $m' = 1$. For homologous series with non-parallel slopes

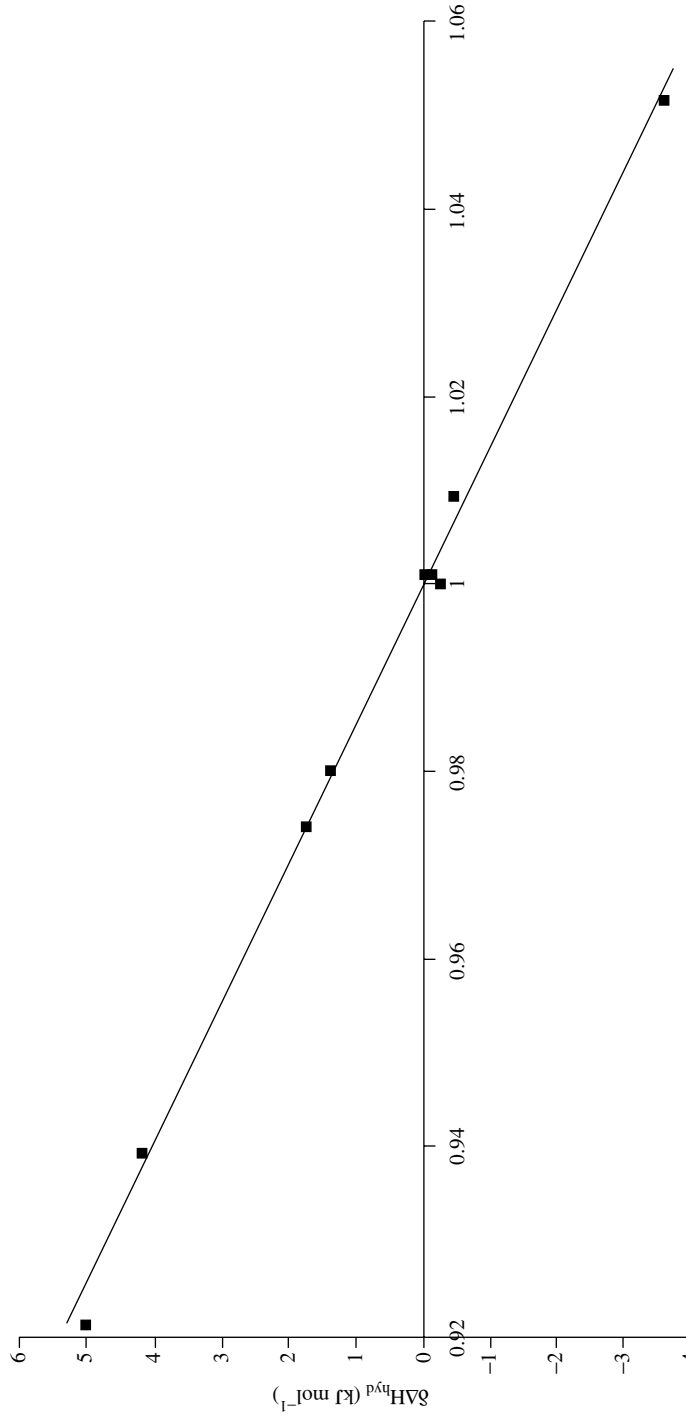


FIGURE 2. The constancy of enthalpies of hydrogenation determined from equations 7 and 8

generated from equation 4, the individual enthalpies of isomerization for the members will either increase or decrease with carbon number. The slopes, α_{alkene}, in Table 2 are such that some of the isomerization enthalpies of interest will be constant, but others will change monotonically over a greater or smaller range depending on the two compared series. A perceived limitation of this analysis is that the experimental error limits generated[35] from equation 10 are large enough seemingly to obscure any patterns in the enthalpies of isomerization. However, the individual data for members of homologous series are very well fitted by equation 4 and by equation 11 (where there are enough data) and it is the large correlation coefficients and the small uncertainties associated with the constants which determine the degree of confidence to be placed in the recognition of trends in the results.

An admitted limitation to analysis by equation 11 is the sparsity of data. Whereas all the corresponding alkane data were available to analyse with the alkenes in equation 7, the same is not true when we attempt to pair alkene isomers to analyse by equation 11. The regression constants are naturally affected by the different-sized data sets. An alternative equation for such circumstances is equation 12, which uses the best available data in each alkene series and avoids the problem of having to eliminate non-paired alkene data.

$$\Delta H_{isom} = n_{c\bullet}[\alpha_{alkene(2)} - \alpha_{alkene(1)}] + [\beta_{alkene(2)} - \beta_{alkene(1)}] \quad (12)$$

It would be helpful if there were more experimentally determined enthalpies of isomerization to provide an independent comparison with those derived from equation 11. The most recent ones are from References 30 and 31. However, as in the analysis of the enthalpies of hydrogenation, it is only because we can derive enthalpies of formation from enthalpies of combustion, isomerization and hydrogenation that we have a large enough database of compounds to confidently attempt an analysis. The same selected alkene enthalpies of formation are used for the analyses in this section as were used in the preceding section.

The trends in alkene isomer stability can be easily seen in plots of the enthalpies of formation versus the number of carbons, n_c (equation 4). For example, in Figure 3 which includes the gaseous 1-, *cis*- and *trans*-2-, and the *cis*- and *trans*-3-*n*-alkenes, the relatively more negative enthalpies of formation for the 2- and 3-*n*-alkenes show them to be more stable than their 1-*n*-alkene double bond positional isomers. (Only the C_4–C_8 1-*n*-alkene members are shown for clarity.) Another well-known relationship is depicted as well: acyclic *trans* hydrocarbons are more stable than their *cis* isomers.

1. Double-bond migration in mono- and di-substituted alkenes

Exploring all combinations of *n*-alkene isomerization reveals an apparent discrepancy within those series containing the 2-butenes. For example, consider the isomerization of the 1-*n*-alkenes to *trans*-2-*n*-alkenes. The individual enthalpies of isomerization (C_4–C_8: −11.5, −10.1, −10.6, −11.2, −11.7 kJ mol^{-1}), or equivalently, plotting the data according to equation 11, show the butene isomerization enthalpy to be anomalously negative in this otherwise increasing series. The same anomaly is present in the enthalpies of isomerization of 1-*n*-alkenes to *cis*-2-*n*-alkenes (C_4–C_8: −7.2, −5.5, −6.2, −7.2, −7.8 kJ mol^{-1}) and of *trans*-2-*n*-alkenes to *cis*-2-*n*-alkenes (C_4–C_8: −4.3, −4.6, −4.5, −4.0, −3.9 kJ mol^{-1}). However, the correlations of the *n*-alkenes according to equation 4 do not show the C_4H_8 points to be outliers[47]. We will return to this topic after considering other isomerizations involving double-bond migration.

Figure 3 also highlights some curious data which complicates our understanding of alkene stability. That is, although the enthalpies of formation of the *trans*-2-*n*-alkenes are

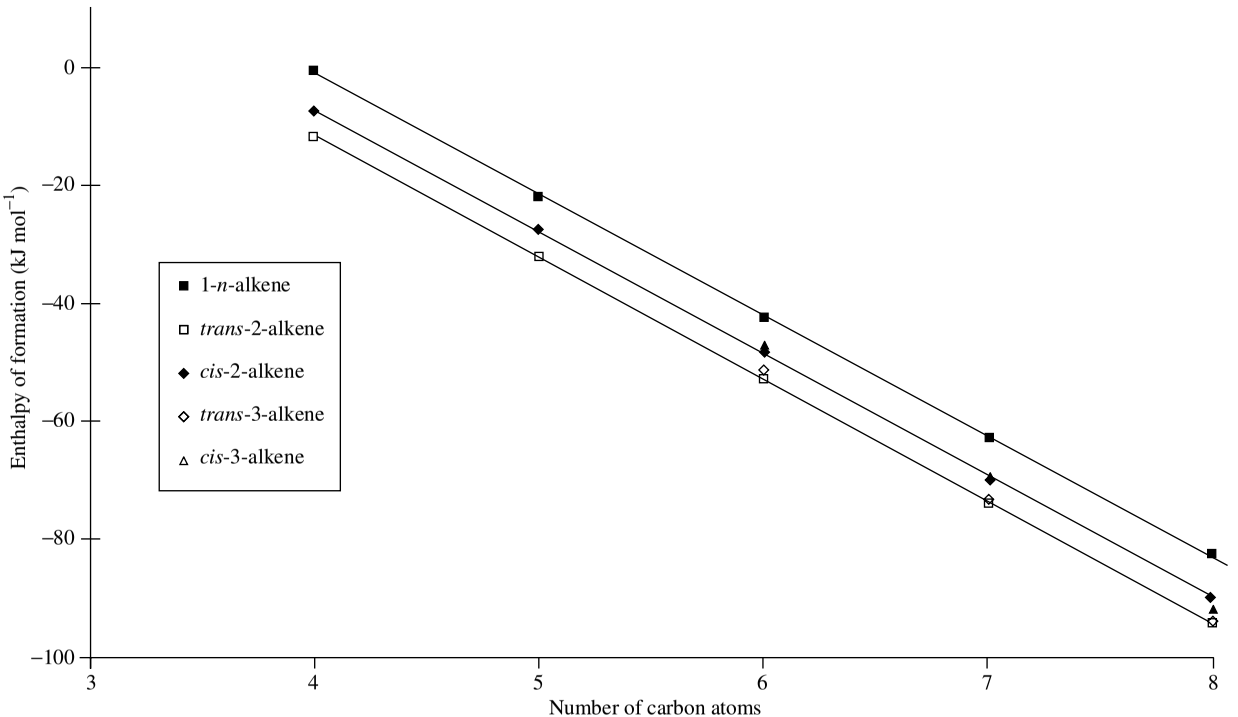


FIGURE 3. Enthalpies of formation of *n*-alkenes (g) vs number of carbon atoms

more negative than those for their *trans*-3-*n*-alkene isomers (and are thus more stable), the same is not true of the *cis*-2- and *cis*-3-*n*-alkenes. In those latter two series, the enthalpies of formation of the C_7H_{14} isomers are nearly identical, *cis*-2-hexene is more stable than *cis*-3-hexene (by *ca* 1.5 kJ mol^{-1}) and *cis*-3-octene is more stable than *cis*-2-octene (by 1.6 kJ mol^{-1}). If the lines are extrapolated, it means that for $n_c > 7$, the *cis*-3-*n*-alkenes become increasingly stable relative to their *cis*-2-isomers. Likewise, for $n_c \geqslant 9$, the *trans*-3-alkenes would be more stable than the *trans*-2-alkenes[48]. Wiberg and coworkers[30] attributed the greater stability of liquid *trans*-2-hexene and *trans*-2-heptene relative to their 3-ene isomers to the electronic effect of the methyl group and noted that the isomerization enthalpy was slightly less negative for the C_7H_{14} isomers than for the C_6H_{12} isomers. Now that there are data for the C_8H_{16} compounds, we observe continuous attenuation of ΔH_{isom} for the *trans*-3- to *trans*-2-alkenes with increasing chain length (C_6–C_8: −1.7, −0.7, −0.3 kJ mol^{-1}). Qualitatively, the diminution of ΔH_{isom} for the *cis*-3- to *cis*-2-alkene transformation mimics that for the *trans* isomers except for the reversed stability order for C_8H_{16} and presumably longer-chain *cis*-alkenes (C_6–C_8: −1.2, −0.5, +1.6 kJ mol^{-1}). Within the *n*-octene series, the *trans* double-bond migration enthalpy from C_2 to C_3 is +0.3 and from C_3 to C_4 it is −0.8 kJ mol^{-1}. The corresponding *cis* migration enthalpies are −1.6 and +0.4 kJ mol^{-1}. Overall, each of the 4-octenes is more stable than the corresponding 2-octene. Returning to the subject of the anomalous 2-butene isomerizations, it is tempting to ascribe the seeming additional stability of the 2-butenes to the presence of a second methyl group. That is, two methyl groups attached to the double bond is especially stabilizing, one methyl group on a relatively short chain is somewhat stabilizing and one methyl group on larger alkenes is either destabilizing or ineffective at off-setting some other effect. However, we acknowledge that this is only describing the phenomenon, not explaining it.

There are four pairs of 1- and 2-alkenes with branching in a substituent group for which we can examine double bond migration enthalpies[49]: 4-methyl-1- and 4-methyl-2-pentene; 5-methyl-1- and 5-methyl-2-pentene; 4-methyl-1- and 4-methyl-2-hexene; and 4,4-dimethyl-1- and 4,4-dimethyl-2-pentene. Each of the 2-enes exists in *cis* and *trans* forms. The first two pairs, which are homologous, have C_1 to *trans*-C_2 isomerization enthalpies of *ca* −13 (for two measurements of *trans*-4-methyl-2-pentene) and −14.4 kJ mol^{-1}, and C_1 to *cis*-C_2 isomerization enthalpies of −9.6 and −10.4 kJ mol^{-1}. The third pair, not homologous with any other, has a C_1 to *trans*-C_2 isomerization enthalpy of −11.5 and a C_1 to *cis*-C_2 of isomerization enthalpy of −7.1 kJ mol^{-1}. The last pair shows a *cis* repulsion steric effect in the isomerization enthalpies: from C_1 to *trans*-C_2 = −10.8 and from C_1 to *cis*-C_2 = +5.3 kJ mol^{-1}. Not much can said about the trends in the homologous series to which these compounds belong, but we can generalize concerning isomerization of the C_7H_{14} compounds: the isomerization enthalpy order for $H_2C{=}CH{-}CH_2{-}R \rightarrow$ *trans*-$CH_3{-}CH{=}CH{-}R$ is R = *iso*-Bu > *sec*-Bu, *n*-Bu > *t*-Bu. The somewhat odd substituent effect order is due to the stability orders of the two alkene sets. For the 1-alkenes the order is *n*-Bu < *iso*-Bu < *sec*-Bu < *t*-Bu and for the *trans*-2-alkenes the order is *n*-Bu < *sec*-Bu < *iso*-Bu < *t*-Bu. However, the accuracy of the enthalpy of formation of 5-methyl-1-hexene was questioned in the previous section.

Comparing the effect of the double-bond migration within the identical σ-frameworks of isomeric isoalkyl-1-alkenes and the 2-methyl-1-alkenes, we find that the individual enthalpies of isomerization for C_6–C_8 are: −10.4, −10.9 and −11.3 kJ mol^{-1}. These mono- to disubstituted isomerization enthalpies are very similar to those for isomerization of the 1-*n*-alkenes to the *trans*-2-*n*-alkenes, homologous series which also possess a common structural skeleton.

2. Cis–trans isomerization

The *cis*-to-*trans* isomerization enthalpies can be summarized with the understanding that the average given for a homologous series is the middle of a range of decreasing values and the standard deviation of the mean is an indication of the magnitude of the range of values: 2-*n*-alkenes (-4.3 ± 0.3); 3-*n*-alkenes (-3.2 ± 1.1); 4-octene (-3.2). For the branched 2-alkenes discussed above (except for the 4,4-dimethyl-2-pentenes) the average *cis*-to-*trans* enthalpy of isomerization is -3.9 ± 0.5 kJ mol^{-1}. Thus there does not seem to be any discernible steric destabilization due to branching unless the substituent is tertiary, in which case for the 4,4-dimethyl-2-pentenes, $\Delta H_{\text{isom}} = -16.1$ kJ mol^{-1}. The *cis*-to-*trans* (*Z*-to-*E*) isomerization enthalpies for three trisubstituted pairs of alkenes are less negative than or about equal to -1 kJ mol^{-1}. Using averages of the several measurements for the 3-methyl-2-pentenes[16,26,32] results in $\Delta H_{\text{isom}} = -1.0$ kJ mol^{-1}. Relying on enthalpies of hydrogenation from Reference 28 for the 3-methyl-3-hexenes and the 3,4-dimethyl-2-pentenes yields enthalpies of isomerization of -1.2 and -0.3 kJ mol^{-1}, respectively.

3. Isomerization of the sigma framework of substituted alkenes

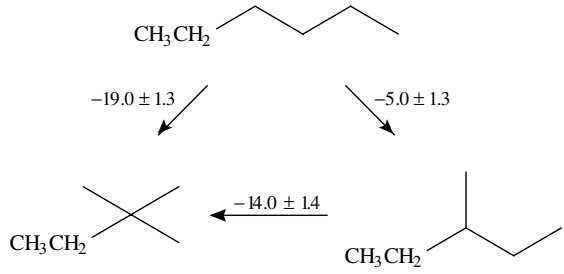
Several alkene isomers vary structurally in the position of a methyl branch on their parent 1-alkene chain. Generally, moving the methyl group from C_3 to positions further from the double bond results in an exothermic enthalpy of isomerization. That is, the isoalkyl-1-alkenes are the most stable isomers and the 3-methyl-1-alkenes are (presumably) the least stable. Because of the problematic 5-methyl-1-hexene data and the lack of data for 3-methyl-1-heptene, nothing more quantitative can be said other than each methyl re-positioning down the chain results in about 1–2 kJ mol^{-1} stabilization. A similar change in branching position from 3-methyl-*n*-alkanes to 2-methyl-*n*-alkanes releases about 3 kJ mol^{-1}.

The two main categories of trisubstituted alkenes which allow us to compare the effect of redistributing methyl substituent groups are the 1,1-dimethyl-2-alkyl ethenes, $(CH_3)_2C{=}CHR$, and the *E*- and *Z*-1,2-dimethyl-2-alkyl ethenes, $CH_3CH{=}C(CH_3)R$. The former category includes 2-methyl-2-pentene, 2-methyl-2-hexene and 2,4-dimethyl-2-pentene. The latter category includes 3-methyl-2-pentene, 3-methyl-2-hexene (*Z* only) and 3,4-dimethyl-2-pentene. Using only the enthalpies of formation derived from enthalpies of hydrogenation[26,28], in all cases the 1,1-dimethyl-2-alkyl ethenes are more stable[50]. The mean enthalpy of isomerization from the *E* isomers is -1.3 ± 0.1 kJ mol^{-1} and the mean enthalpy of isomerization from the *Z* isomers is -1.8 ± 0.1 kJ mol^{-1}. Thus, two methyl groups on the same sp^2-carbon are more stabilizing than two methyl groups on adjacent sp^2-carbons, at least for alkenes of $n_c \leqslant 7$. Because the *Z*-isomer enthalpies of isomerization are almost identical, there does not seem to be any additional steric effect due to the isopropyl group. Most interesting is to compare these results with the enthalpies of isomerization of *E*- and *Z*-3-methyl-3-hexene to 3-ethyl-2-pentene: -0.9 and -2.1 kJ mol^{-1}, respectively. The 1,1-diethyl ethene is more stable than the 1,2-diethyl ethene. From these limited examples, our empirical observation is that the more stable isomer is the one with two identical groups on the same sp^2-carbon.

A related isomerization is that of the *trans*-1,2- to 1,1-disubstituted alkenes. The only series for which there is sufficient data are for the methyl, *n*-alkyl substituents. The slope of equation 11 is 1.01 and so the enthalpies of isomerization are nearly constant, although there is some scatter in the data. The point representing the C_5 isomers is deviant in the plot, again suggestive of the unreliability of the enthalpy of formation of

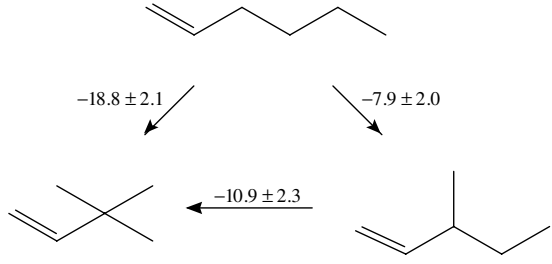
2-methyl-1-butene. Without using that data, the 2-methyl-1-alkenes are more stable by -6.1 ± 0.8 kJ mol^{-1}.

Finally, we will explore the gaseous enthalpies of isomerization of small alkyl groups substituted in 1-alkenes, *cis*- and *trans*-2-alkenes, and 2-methyl-2-alkenes which may provide insight into the electronic and steric effects in substituted alkenes. The results cannot be extended reliably to larger alkyl groups because the isomeric compounds belong to different homologous series which very likely have non-identical slopes as determined from equation 4a and thus have non-constant enthalpies of isomerization. Nevertheless, the data are useful for estimating isomerization enthalpies of small alkyl groups on more complicated alkene parent compounds. The saturated alkanes are a convenient starting point for making comparisons, and the exothermic enthalpies of isomerization for the *n*-, *sec*- and *tert*-butyl ethanes[16] are shown in Scheme 1. Not shown is the *n*-primary to secondary isomerization of *n*-pentane to 2-methylbutane (the propyl-substituted ethanes): -6.8 ± 1.3 kJ mol^{-1}.

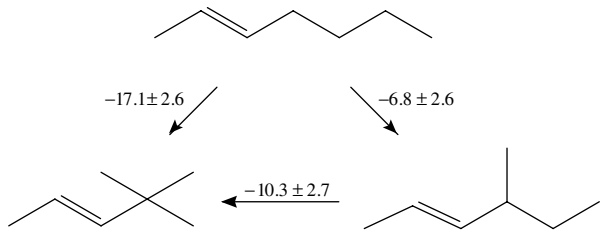


SCHEME 1

The effect on the enthalpies of isomerization upon dehydrogenating the substituted ethanes to the corresponding 1-alkenes is different for the primary-to-secondary (more negative) and the secondary-to-tertiary (less negative) rearrangements, although the overall primary-to-tertiary isomerization is the same (Scheme 2). For comparison, the enthalpy of isomerization of 1-pentene to 3-methyl-1-butene (the propyl-substituted ethenes) is -6.2 ± 0.9 kJ mol^{-1}. When the butyl groups are substituted on a double bond *trans* to a methyl group, the enthalpies of isomerization are comparable to or slightly smaller than when the methyl group is absent (Scheme 3). There are two available enthalpies of formation for *trans*-4,4-dimethyl-2-pentene which are just within each other's error bars[21,28]. Having no way to decide between them, the mean value was used. For comparison with the values shown in Scheme 3 are those for isomerization of

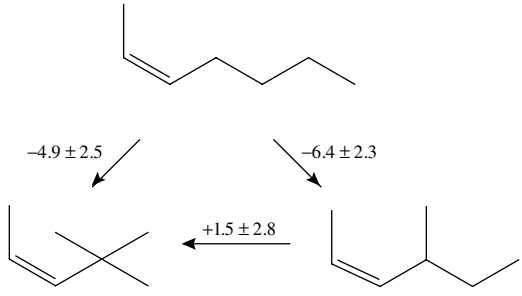


SCHEME 2



SCHEME 3

trans-3-heptene to *trans*-2-methyl-3-hexene (-6.7 ± 1.2 kJ mol^{-1}) and for *trans*-3-octene to *trans*-2,2-dimethyl-3-hexene (-14.9 ± 2.2 kJ mol^{-1}). When the butyl groups are substituted on a double bond which is *cis* to a methyl group (Scheme 4), the steric effect on the enthalpy is evident upon isomerization to the tertiary group, again using the mean value for 4,4-dimethyl-2-pentene[21,28]. Enthalpies of isomerization of *n*-Pr to *i*-Pr in *cis*-$CH_3CH{=}CHPr$ and the *cis*-$CH_3CH_2CH{=}CHPr$ are -9.9 ± 2.1 kJ mol^{-1} (using the mean value for the *i*-Pr-substituted compound[16,26]) and -7.5 ± 2.0 kJ mol^{-1} respectively, while that for butyl rearrangement in *cis*-3-octene to *cis*-5,5-dimethyl-3-hexene is $+1.5 \pm 3.2$ kJ mol^{-1}.



SCHEME 4

Unfortunately, the data are sparse for 1,1-disubstituted ethenes, and so the few values we have do not appear in a Scheme. Complicating the analysis are the multiple enthalpies of formation for 2,3-dimethyl-1-butene[16,26,32], 2,3,3-trimethyl-1-butene[21,27] and 2-ethyl-3-methyl-1-butene[16,28] where the extreme values in a set are not within each other's uncertainty intervals. We would like to compare these isomerizations with those of the corresponding *cis*-1,2-disubstituted ethenes since they are relevant to the discussion of steric effects in disubstituted ethenes, Because we have no other way of gauging the magnitude of these effects, we report the enthalpy of isomerization ranges calculated using the extreme enthalpies of formation: $H_2C{=}C(CH_3){-}n$-Pr $\rightarrow$ $H_2C{=}C(CH_3){-}i$-Pr, -3.5 ± 1.6 to -7.4 ± 2.3 kJ mol^{-1}; $H_2C{=}C(CH_3){-}n$-Bu $\rightarrow$ $H_2C{=}C(CH_3){-}t$-Bu, -6.8 ± 1.8 to -11.4 ± 1.8 kJ mol^{-1}; and $H_2C{=}C(CH_2CH_3){-}n$-Pr $\rightarrow$ $H_2C{=}C(CH_2CH_3){-}i$-Pr, -2.8 ± 2.6 to -8.2 ± 3.0 kJ mol^{-1}. Regardless of which enthalpy of formation is used, it seems that isomerization to the tertiary substituent is more favourable in the 1,1-disubstituted ethenes than in the *cis*-1,2-disubstituted ethenes. We will consider again these enthalpy-of-formation values in the context of ketone isomerizations in a later section.

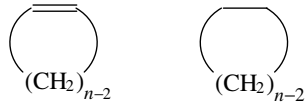
The only reported enthalpies of formation for 2-methyl-1-heptene[29] and 2-methyl-3-ethyl-1-pentene[16,21] are identical: -100.3 kJ mol^{-1}. On the one hand, we might expect at least some stabilization due to secondary branching effects as was found for the *n*-Pr to *i*-Pr example cited above. On the other hand, if the actual stabilization is at the lower end of the cited ranges for the propyl isomerizations, it may be vanishingly small for the pentyl isomerization. That is, the enthalpy of isomerization might decrease as n_c increases for these two homologous series. Lastly, the *n*-pentyl to neopentyl isomerization enthalpy, from 2-methyl-1-heptene to 2,4,4-trimethyl-1-pentene, is -10.6 kJ mol^{-1}, about half the value found for the corresponding isomerization in mono-substituted alkenes (from 1-heptene to 4,4-dimethyl-1-pentene[21,28] it is *ca* -19 kJ mol^{-1}).

III. CYCLIC OLEFINS WITH A −CH=CH− GROUP

A. *Cis*-Cycloalkenes

In this section we consider the energetics of molecules with the generic formula *cis*- or (*Z*)-cyclo-[$(CH_2)_{n-2}$ (CH=CH)] (**1**). A natural comparison of the enthalpies of formation of these olefins is with their saturated analogs, the cycloalkanes, with the generic formula, cyclo-[$(CH_2)_{n-2}$ (CH_2CH_2)] [i.e. $(CH_2)_n$, **2**]. Using equation 13, let us now define the difference quantity $\delta_{13}(n)$ as the difference of the gas-phase enthalpies of formation of the cycloalkene of interest and the related cycloalkane:

$$\delta_{13}(n) \equiv \Delta H_f^\circ(\text{cyclo-}[(CH_2)_n],\ g) - \Delta H_f^\circ(\text{cyclo-}[(CH_2)_{n-2}(CH{=}CH)],\ g) \qquad (13)$$



(1) **(2)**

Throughout our thermochemical studies, we have employed numerous difference quantities. Many have been conceptual conveniences to aid us in predicting or explaining a number of interest. Some of these difference quantities correspond to the energetics of a real reaction. In that ΔH_f° (H_2, g) is defined to be precisely equal to zero, the quantity $\delta_{13}(n)$ may be recognized as numerically equalling the enthalpy of hydrogenation of the *n*-membered ring olefin. The numerical values of the enthalpies of formation of the various cycloalkenes and the corresponding $\delta_{13}(n)$ values are found in Table 3. The values of $\delta_{13}(n)$ almost all lie between 85 and 130 kJ mol^{-1}, an admittedly large range. The sole exception to that is the $n = 3$ case, cyclopropene with $\delta_{13} = 224$ kJ mol^{-1}. This marked deviance is consistent with the *ca* 50 kJ mol^{-1} additional destabilization for each trigonal or sp^2 carbon that is introduced into a three-membered ring[52]. Other than that, it is difficult to see a pattern in terms of the ring size or parameter *n*. Cyclobutene has the next highest value of $\delta_{13}(n)$ as befits the high strain of the cycloalkane. The $n = 5$ and 7 species have nearly identical and much smaller values of strain energy in the cycloalkane[53] and nearly identical and much smaller values of $\delta_{13}(n)$. Cyclohexane shows an additional decrease in strain energy relative to the other cycloalkanes but the value of δ_{13} increases! Smaller values of $\delta_{13}(n)$ are found for $n \geqslant 8$ but no pattern is apparent. From the numerous measurements reported by Roth and coworkers[54] for the $n = 8$ case, we may expect only small revisions of the values of $\delta_{13}(n)$ for the intermediate-size 9-,

TABLE 3. Enthalpies of formation of gaseous (*Z*)-cycloalkenes, cyclo-[$(CH_2)_{n-2}$(CH=CH)], and the corresponding values of $\delta_{13}(n)$

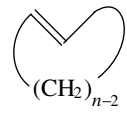
n	ΔH_f° (g)	Reference	$\delta_{13}(n)$
3	277.1 ± 2.5	[a]	-223.8 ± 2.6
4	156.7 ± 1.5	[a]	-128.3 ± 1.6
5	33.9 ± 1.4	[a]	-110.3 ± 1.6
6	-5.0 ± 0.7	[a]	-118.4 ± 1.1
7	-9.2 ± 1.1	[a]	-108.9 ± 1.5
8	-28.0 ± 1.2	[b]	-96.4 ± 0.7
9	-34.1	[c]	-98.7
10	-67.7	[c]	-86.6
12	-120.2	[c]	-110.0

[a] These values are taken from Pedley.
[b] This value is that found by hydrogenating the cycloalkene in a nonpolar hydrocarbon solvent, see Rogers and coworkers[51]
[c] These values are those found by hydrogenating the cycloalkene in glacial AcOH, see Jensen[22].

10- and 12-membered rings upon correction of the experimentally measured enthalpies of hydrogenation in glacial AcOH.

B. *Trans*-Cycloalkenes

In this section we consider the energetics of molecules with the generic formula *trans*- or (*E*)-cyclo-[$(CH_2)_{n-2}$ (CH=CH)], **3**. Again, a natural comparison of the enthalpies of formation is with their saturated analogs, the cycloalkanes, cyclo-[$(CH_2)_{n-2}$ (CH_2CH_2)] [i.e. $(CH_2)_n$]. However, we think that an even simpler comparison is with their respective *cis*- or (*Z*)-cyclo-[$(CH_2)_{n-2}$(CH=CH)] isomers because solvent effects on the hydrogenation enthalpies that interrelate cycloalkenes and cycloalkanes should more completely cancel when comparing isomeric cycloalkenes. For 'small enough' ring sizes or values of n, the (*E*)-isomer should be less stable than the (*Z*)-isomer because of the necessity of twisting the double bond in the former. For 'large enough' rings or values of n, the (*E*)-isomer should be more stable than the (*Z*)-isomer much as it is found that (*E*)-acyclic olefins with the $-CH=CH-$ substructure are more stable than their (*Z*)-counterparts. The smallest value of n for which both isomeric cycloalkenes have been thermochemically investigated is $n = 8$ for which the (*Z*)-isomer is the more stable by *ca* 47 kJ mol^{-1} if the results either from hydrogenation calorimetry in the gas phase or a hydrocarbon solvent are employed[22,51,54]. The less fundamental methodology of hydrogenation calorimetry in glacial AcOH[22] suggests a difference of only 36 kJ mol^{-1}. In the absence of thermochemical data from experiments in the former, more innocuous media, from results in the latter[22] we find that the difference has narrowed to 12 kJ mol^{-1} for $n = 9$, increased to 14 kJ mol^{-1} for $n = 10$ and fallen to 2 kJ mol^{-1} for $n = 12$. There is no use in



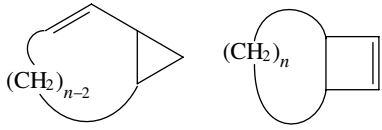
(3)

comparing the $n = 9$ and 10 values given the uncertainty in differential solvation effects, but it is safe to assume that the (*E*)-isomer is more stable for $n > 12$ species. By contrast, it is safe to assume that n becoming ever smaller will increasingly favour the (*Z*)-over its (*E*)-isomer[55].

C. Bicycloalkenes

All of the compounds of interest in this section can be described as cycloalkenes with two carbons joined by a polymethylene bridge. We can attempt to understand these species by varying the size of the cycloalkene and/or the length of the bridge, and acknowledge that occasionally there exists the possibility of varying the positions on which this bridge is affixed. Homoconjugatively derived stabilization or destabilization are distinct possibilities and so provide interesting complications[7,54]. We now consider bicyclo[*n*.1.0]alkenes — by definition of the current class of compounds, the double bond is in the larger ring.

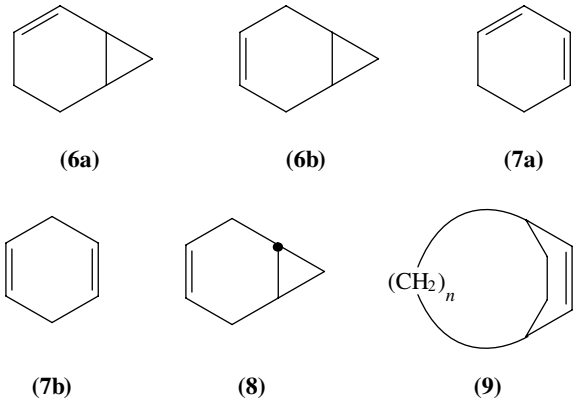
One probe is the difference of the enthalpies of formation of the bicyclo[*n*.1.0]alk-2-ene, **(4)**, and the related cycloalkene where the affixed CH_2 or monomethylene bridge has been replaced by two '−H'. For $n = 2$, 3 and 4, the differences are 177[54], 124[56] and 126[56] kJ mol^{-1}, respectively (bicycloalkene data from References 54 and 56, cycloalkene data from Pedley). Not surprisingly, it is the species with the 4-membered ring ($n = 2$) that shows a significant difference, in this case marked destabilization suggestive of homoantiaromaticity[7,54,56] as well as 'superstrain'[57] in the bicyclopentene arising from the fusion of the two, individually highly strained, rings.



(4) **(5)**

Now let us turn to the category where the length of the bridge is varied and consider the bicyclo[*n*.2.0]alkenes that are formally constructed from cyclobutene and a polymethylene bridge attached to C_3 and C_4 of that cyclobutene, cf. **5**. A logical comparison[58] entails the difference between the enthalpies of formation of these olefins with the corresponding cycloalkanes with $n = 2$ atoms in the ring, i.e. those species in which the '−CH=CH−' has been replaced by two '−H'. For example, bicyclo[2.1.0]pent-2-ene that was formed from cyclobutene and a one-carbon chain is compared with cyclopropane by loss of the two-carbon −CH=CH− unit found in all of the bicycloalkenes of the current category. For $n = 1$[54], 2[59], 3[54] and 4[54], the derived differences are 281, 233, 216 and 245 kJ mol^{-1}, respectively. While we acknowledge that the compound with $n = 1$ is again an outlier because of homoantiaromatic as well as superstrain derived destabilization, it is nontheless disconcerting how much the differences for the other bicycles fluctuate. For example, it is not obvious why the $n = 3$ bicyclic olefin is so stable. Alternatively, one may interrelate the bicyclo[*n*.2.0]alkene with the cycloalkene formed by replacing the bridgehead C−C bond by two C−H bonds. For $n = 1$[54], 2[59], 3[54] and 4[54], the derived differences are 299, 266, 148 and 147 kJ mol^{-1}. No pattern is found. In the absence of any strain or electronic effect of the double bond, one is replacing a ring of $n + 2$ atoms by one of $n + 4$ atoms. Strain in alicyclic hydrocarbons is not monotonic with the number of atoms[53,57]. As such the near-equality for the above $n = 3$ and 4 cases is not unlike the situation for the near-equality of the strain energies of 3- and 4-membered cycloalkanes: both appear

to be numerical 'accidents'. We may also vary the position of the double bond within the larger ring of the bicycloalkene. Examples are rare but it is unequivocally found with the case of the isomeric norcarenes (i.e. *syn*-bicyclo[4.1.0]hept-2- and -3-enes **6a** and **6b**, respectively). The difference as given by Roth and coworkers[54] is under one kJ mol^{-1}. However, we hesitate to generalize this near-constancy since these species are formally related to the isomeric 1,3- and 1,4-cyclohexadienes (**7a** and **7b**, respectively) for which the difference in their enthalpies of formation is still disconcertingly contentious[8]. It is quite clear, however, that *anti* fusion is destabilizing: from Roth and coworkers[54] we find that the *anti*-bicylo[4.1.0]hept-3-ene **(8)** is *ca* 100 kJ mol^{-1} less stable than its *syn*-isomer.



(6a) **(6b)** **(7a)**

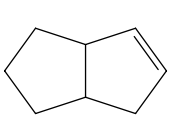
(7b) **(8)** **(9)**

In the absence of 1-carbon bridges, the possible complications of homoantiaromatic interactions are strongly minimized and thermochemical analyses would be thought simpler. An example of the effects of varying the bridge length is found with the bicyclo[*n*.2.2]alkenes **(9)** wherein the double bond is assumed to be on one of the two bridges. Again let us take the difference of the enthalpies of formation of these species with a '−CH=CH−' group and the species in which this group has been replaced by two '−H', e.g. bicyclo[2.2.2]oct-2-ene is compared with cyclohexane. For $n = 0$[59], 1[60], 2[61] and 3[54], the differences are 233, 166, 158 and 115 kJ mol^{-1}. The absence of near-constancy is not surprising: after all, the double bond being replaced is part of a 4-, 5-, 6- and 7-membered ring that is being dismembered. Nonetheless, we may argue again that the $n = 0$ species is homoantiaromatic, superstrained and therefore an outlier, and so the remaining three values are not that dissonant.

What about hydrogenation of the double bond to form the bicyclo[*n*.2.2]alkane? The respective enthalpies are 136[59], 142[60], 134[61] and 115[62] kJ mol^{-1}. The absence of near-constancy or uniform strain result is found here, although the spread of only *ca* 30 kJ mol^{-1} is quite small. The lack of uniformity is again not particularly surprising because enthalpies of hydrogenation for the simple monocyclic cycloalkenes to the saturated cycloalkane are not particularly constant either. (Recall the content of Table 3.) Furthermore, the geometries of monocyclic cycloalkene and cycloalkane rings are different from those found in their bicyclic counterparts. For example, both bicyclo[2.2.2]octene and bicyclo[2.2.2]octane 'contain' boat 6-membered rings, a conformation found in neither cyclohexene nor cyclohexane as free monocycles.

D. Polycycloalkenes

There are available measured enthalpies of formation of surprisingly few species and so attempts to find patterns are even more difficult here than before. Even if we consider the simpler quantity of the enthalpy of hydrogenation, we find that few polycyclic species qualify. To provide some semblance of conceptual unity, let us limit our attention to those polycyclic olefins in which the double bond being hydrogenated is found in a 5- or 6-membered ring. As such, we will compare the enthalpies of their hydrogenation with that of the normal, relatively strainless cyclopentene and cyclohexene, with δ_{13} equalling 110.3 ± 1.6 and 118.4 ± 1.1 kJ mol^{-1}, respectively.



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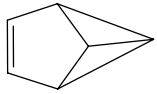

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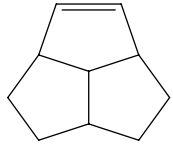

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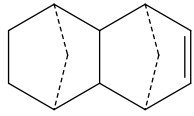

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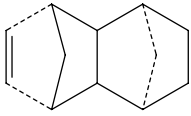

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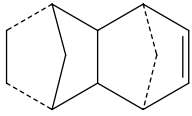

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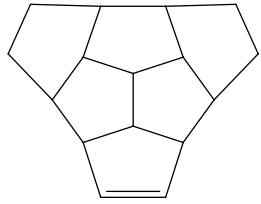

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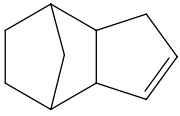

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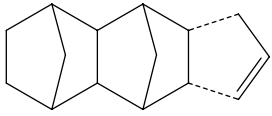

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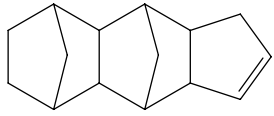

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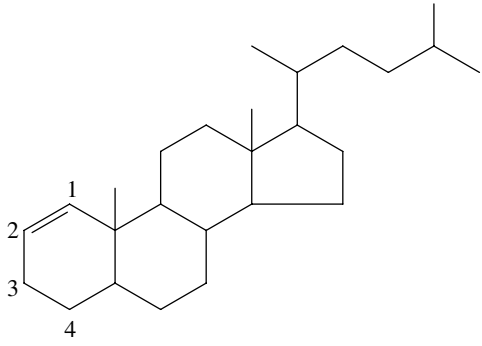


(17)

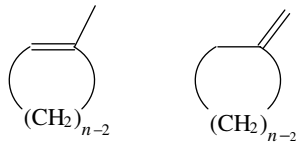
We commence with cyclopentene derivatives. *Syn*-bicyclo[3.3.0]oct-2-ene (dihydrobiquinacene, **10**) has nearly the same enthalpy[63] of hydrogenation, 112.1 ± 1.3 kJ mol^{-1}. In order of increasing number of complexity (i.e. increasing number of rings, and if constant, then increasing number of carbons), consider benzvalene **(11)**, tetrahydrotriquinacene **(12)**, three singly unsaturated derivatives of sesquinorbornene (**13a**, **13b**, **13c**) and tetrahydrohexaquinacene **(14)**. We find their hydrogenation enthalpies are 135[56], 115[64], 113[54], 156[54], 140[54] and 103[63] kJ mol^{-1}, respectively. Besides these gas-phase numbers, we also may derive the enthalpy of hydrogenation of 3*a*,4,5,6,7,7*a*-hexahydro-4,7-methanoindene **(15)** by taking the difference of Pedley's cited standard enthalpy of formation and that of the octahydromethanoindene. As solids, the δ_{13} value of interest is 89.0 ± 6.5 kJ mol^{-1}. Related examples are the so-called dihydro-α- and -β-tricyclopentadiene (**16a**, **16b**) to form the corresponding tetrahydro-α- and -β-tricyclopentadiene[65], respectively. Deriving the enthalpies of hydrogenation by taking the differences of enthalpies of formation of the corresponding solid dihydro and tetrahydro derivatives, the desired δ_{13} are found to be 101 and 107 kJ mol^{-1}. None of these numbers is particularly useful because of the medium and state of the compound being studied.

There are few cyclohexene derivatives with which to make comparison. Among them are cholest-1-ene **(17)** and its isomers, cholest-2- and -3-ene for which enthalpies of hydrogenation in glacial AcOH have been reported[22] to be 114, 108 and 119 kJ mol^{-1}, respectively. We admit that saturated polycyclic species have complexities of their own in their interplay of structure and energetics. Nonetheless, it would appear that polycyclic analogs of relatively normal olefins have additional, and likewise disconcertingly complex, thermochemical features.

IV. *EXO*- VS *ENDO*-CYCLIC DOUBLE BONDS

A. Isomeric Methylcycloalkenes and Methylenecycloalkanes

In this section we compare the enthalpy of formation of isomeric pairs of cyclic olefins, one with an exocyclic double bond and the other with the double bond endocyclic. We start with 1-methylcycloalkenes and related methylenecycloalkanes, species generically **18a** and **18b**, respectively. From prior experience with cyclopropanes and the thermochemical consequences of replacement of sp^3 carbons by sp^2 carbons in three-membered rings[52], we expect 1-methylcyclopropene to be considerably less stable than methylenecyclopropane because the former compound has two trigonal carbons within the ring while the latter has but one. And so it is found[56]: the former has a gas-phase enthalpy of formation 43.1 ± 2.2 kJ mol^{-1} more positive than the latter.



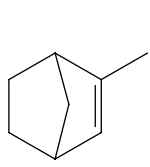
(18a) **(18b)**

Our enthalpy of formation archive lacks data for the corresponding cyclobutene/cyclobutane derivatives. Nonetheless, the enthalpy of hydrogenation[22] of both 1-methylcyclobutene and methylenecyclobutane in the same solvent (AcOH) has been reported. Because the same product, methylcyclobutane, is formed, it is not unreasonable to assume that the difference of the enthalpies of hydrogenation of the two olefins roughly equals the difference of the enthalpies of formation of the olefins[66]. It is thus found that the

exocyclic olefin is less stable than the endocyclic by only 4 kJ mol^{-1}. The hydrogenation enthalpy difference of 1-methyl-cyclopentene and methylenecyclopentane, favouring the former, is increased to 16.3 and 14.6 kJ mol^{-1} in glacial acetic acid and the innocuous hexane[67], respectively. These values are essentially indistinguishable from the differences of 15.8 ± 1.3 and 16.3 ± 1.1 kJ mol^{-1}, respectively, for the archival values of enthalpies of formation (derived from combustion calorimetry) for the gas phase and neat liquids, respectively. However, before we become too confident or merely too complacent, the difference is seen to decrease to 9.6 kJ mol^{-1} for that between 1-methylcyclohexene and methylenecyclohexane as determined by hydrogenation measurements (again in AcOH) but is 18.1 ± 3.9 and 19.9 ± 3.9 kJ mol^{-1} for the gaseous and neat liquids as determined by combustion calorimetry. For the cycloheptane case we only have hydrogenation data which suggest that the endocyclic species is less stable than its *exo* isomer by 9.6 kJ mol^{-1}.

B. Related Polycyclic Species

Can we generalize these results? Admitting the seeming exception of cyclobutene results, it would appear that the endocyclic olefin is more stable by *ca* 15 ± 5 kJ mol^{-1} than its exocyclic isomer: even the cyclopropane species obeys this conclusion if we remember to correct for the *ca* 50 kJ mol^{-1} destabilization in the 1-methylcyclopropene because of the second sp^2 carbon[52]. We now ask about bicyclic olefins. Data are quite sparse here. One example is 2-methylbicyclo[2.2.1]hept-2-ene and 2-methylenebicyclo[2.2.1]heptane, species **19a** and **19b**, respectively. Admittedly for the liquid phase — and determined by enthalpy of combustion — we find the endocyclic isomer is less stable than the exocyclic isomer by 8.6 ± 2.2 kJ mol^{-1}. By contrast, the enthalpies of formation of the isomeric bicyclo[2.2.2]octane derivatives favour the endocyclic isomer and differ by 7.5 ± 3.3 and 9.4 ± 3.9 kJ mol^{-1} for the liquid and gaseous phase, respectively, consonant with the relative stability of the monocyclic olefins. Relatedly, α- and β-pinene, the multiply methylated bicyclo[3.1.1]heptenes **20a** and **20b** respectively, have enthalpies of formation which differ by 8.7 ± 3.7 and 10.4 ± 4.1 kJ mol^{-1} favouring the endocyclic isomer for the liquid and gaseous states, respectively. We have no explanation for the discrepancy for the bicyclo[2.2.1]heptane derivatives[68].



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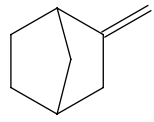

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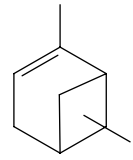

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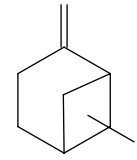
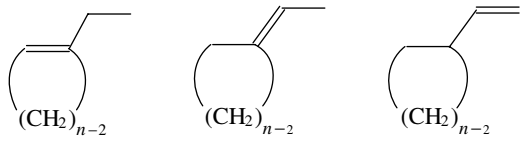


(20b)

C. Isomeric Ethylcycloalkenes, Ethylidenecycloalkanes and Vinylcycloalkanes

What about the comparison of isomeric 1-ethylcycloalkenes and ethylidenecycloalkanes, generically **21a** and **21b** respectively? This is perhaps a 'fairer' competition because both olefins are internal, i.e. neither has a $=CH_2$ group, and so it is expected that the enthalpies of formation will be closer. For the isomeric cyclopentane derivatives, the 'idene' isomer is more stable by but 1.6 ± 1.3 kJ mol^{-1}. For the isomeric olefins with a 6-membered ring, the difference is 1.9 ± 1.3 kJ mol^{-1}.

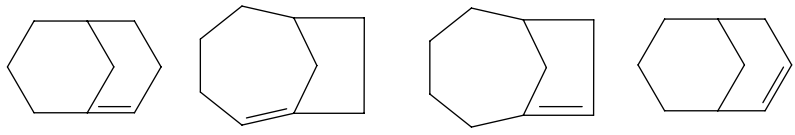


(21a) **(21b)** **(21c)**

The appendage of a two-carbon chain on a ring allows for discussion of one more isomeric type of olefin that has the same carbon framework, vinylcycloalkanes here labelled as **21c**. For the ethylidenecyclopentane/vinylcyclopentane comparison, the liquid of the former is more stable than that of the latter by 23.5 ± 1.4 kJ mol^{-1}. The enthalpies of vapourization of the two isomers should be nearly identical and so the gas-phase difference should be nearly the same. The ethylidenecyclohexane/vinylcyclohexane comparison can be made in both the liquid and gaseous phases. As liquid, the former is more stable by 14.8 ± 1.1 kJ mol^{-1}, while as gas, by 12.6 ± 1.2 kJ mol^{-1}. It is not obvious why the 'idene'/vinyl comparison is so different for the two different ring sizes. However, whether cyclopropane mimics cyclopentane or cyclohexane, prior experience on the effects of sp^2 carbons in three-membered rings[52] suggests that ethylidenecyclopropane will have a *ca* 50 kJ mol^{-1} destabilization relative to the other rings. There should thus be a *ca* 30–40 kJ mol^{-1} difference between vinylidenecyclopropane and vinylcyclopropane with the latter more stable. The difference derived from taking the enthalpies of formation of the two species suggested in Reference 56 is 34 kJ mol^{-1}, in fine agreement.

V. BREDT'S RULE, BRIDGEHEAD OLEFINS AND CYCLIC SPECIES WITH A >C=CH− OLEFINIC LINKAGE

For somewhat over seventy years, the structural proscription against bridgehead double bonds known as Bredt's rule has provided a guiding principle for strained molecules. More precisely, it is suggested that bicyclo[*m.n.p*]alk-1-enes are destabilized for small, but nonzero, *m*, *n* and *p*. The enthalpy of formation of three such species is available[54] from hydrogenation calorimetry. These are the isomeric bicyclo[3.3.1]non-1-ene **(22a)**, bicyclo[4.2.1]non-1-ene **(22b)** and bicyclo[4.2.1]non-1(8)-ene (**22c**), bicyclo[4.2.1]non-$\Delta^{1,8}$-ene) with gas-phase enthalpies of formation of 31, 74 and 50 kJ mol^{-1}, respectively. These three numbers alone inadequately address the issue of bridgehead destabilization because the alicyclic carbon skeleton is not the same for all three olefins.

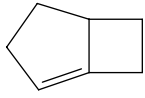


(22a) **(22b)** **(22c)** **(22d)**

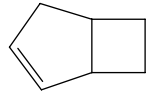
The first species may be compared with the 'normal' (i.e. non-bridgehead) olefin bicyclo[3.3.1]non-2-ene, **22d**. The former is less stable than the latter by some 80 kJ mol^{-1} even though the second species has a −CH=CH− linkage and the first has a >C=CH− linkage. (For calibration, one may compare the relative stability of the hardly strained monocyclic olefins; our primary archive shows that of the isomeric 3- and 1-methylcyclopentenes, the latter is more stable[69] than the former by 11.2 ± 1.0 kJ mol^{-1}.)

The *ca* 30 ± 10 kJ mol^{-1} higher enthalpy of formation of the bicyclo[4.2.1]non-1-enes over the bicyclo[3.3.1]non-1-ene should not be totally ascribed to differences in non-planarity, either pyramidization or twisting, or to any other distortion of the olefins. After all, molecular mechanical calculations reported elsewhere[54] show that the saturated bicyclo[4.2.1]nonane has a higher enthalpy of formation than bicyclo[3.3.1]nonane by 25 kJ mol^{-1}. As such, much of the difference between the three bicyclononenes is found in the saturated compound, and so documents the importance of the quantitative concept of olefin strain (also called OS or OSE), the difference of strain energy of the olefin and its hydrogenated counterpart[70,71]. Yet neither this new strain energy definition, per se, or anything else known to the authors allows us to understand the relative enthalpies of formation of the isomeric bicyclo[4.2.1]nonenes. As such, we reluctantly reaffirm, rather than answer, the enigma posed earlier by Warner[72] in a recent review on Bredt's rule and its violations.

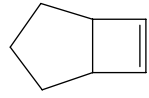
What about the case in which the double bond contains one carbon on a 0-length bridge? Such species are often considered as violating Bredt's rule. We can make but one thermochemically meaningful comparison of such a species with any other olefin that has the same alicyclic framework but lacks this Bredt-violating, strain-increasing feature. This is for bicyclo[3.2.0]hept-1-ene **(23a)** in comparison to its isomers, the -2- and -6-ene (**23b** and **23c**): **23a** is 49 and 28 kJ mol^{-1} less stable than **23b** and **23c**, respectively.



(23a)



(23b)



(23c)

What about the case in which both carbons of the double bond are on the '0' bridge? As these species lack the >C=CH− olefinic linkage that defines the key compounds of this section, such compounds are deferred elsewhere in this chapter. We merely note at this juncture that they generally have extra strain for those species in which the remaining bridges are short.

VI. CYCLIC OLEFINS CONTAINING A TETRASUBSTITUTED DOUBLE BOND

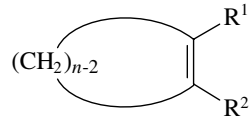
A. Monocyclic 1,2-Disubstituted Cycloalkenes

The primary examples of this class of compounds are the 1,2-dialkylcycloalkenes (**24**: n, R^1, R^2). The simplest thermochemical comparison we can make is with the corresponding unsubstituted cycloalkene, i.e. $R^1 = R^2 = H$. A suitable probe of the effect of the dialkylation is the enthalpy of the formal transalkylation reaction

$$\text{cyclo-}(CH_2)_{n-2}(RC{=}CR) + C_2H_4 \longrightarrow \text{cyclo-}(CH_2)_{n-2}(HC{=}CH) + (Z){-}RCH{=}CHR \qquad (14)$$

Small thermochemical effects of dialkylation are expected. That is, the above reaction is expected to be essentially thermoneutral because both steric and electronic differences between reactants and products are expected to be minimal. Indeed, this is found for the analogous acyclic reaction

$$Me_2C{=}CMe_2 + C_2H_4 \longrightarrow (Z)\text{-}Me_2(CH{=}CH) + (Z)\text{-MeCH}{=}\text{CHMe} = 2[(Z)\text{-MeCH}{=}\text{CHMe}] \qquad (15)$$



(24)

Using the enthalpy of formation for tetramethylethylene and that of the product (*Z*)-2-butenes from Pedley, we find reaction 15 to be endothermic by 3.6 ± 2.1 kJ mol^{-1}, a value comfortably close to the anticipated thermoneutrality.

Relevant examples of 1,2-dialkylcycloalkenes with which to test our conjecture about reaction 12 are disappointingly few. The simplest example of this class of compounds is 1,2-dimethylcyclopropene (**24**, $n = 3$, $R^1 = R^2 = Me$), and indeed, the requisite thermochemical data are available. Using the derived enthalpy of formation of 1,2-dimethylcyclopropene from Reference 56, we find this reaction to be 32 kJ mol^{-1} endothermic. *A posteriori*, we are not surprised that this reaction is endothermic. After all, if it is part of the 'folklore' of cyclopropanes that they are said to have olefinic character, then cyclopropenes are also said to have acetylenic character. Indeed, the related transalkylation reaction involving acetylenes

$$MeC{\equiv}CMe + C_2H_4 \longrightarrow HC{\equiv}CH + (Z)\text{-}MeCH{=}CHMe \qquad (16)$$

is endothermic by 23 kJ mol^{-1}. Admittedly, we would have thought that this acetylene reaction 16 would be more endothermic than reaction 12 for 1,2-dimethylcyclopropene because, for the former, the ring size is smaller (cyclopropene vs 'cycloethene'[57]) and there is greater s-ness in the C−Me bond being broken. This conceptual discrepancy between the endothermicities for cyclopropene and acetylene corroborates the suggestion in Reference 56 that the enthalpy of formation of 1,2-dimethylcyclopropene is suspect. While this last enthalpy of formation was derived using the enthalpy of hydrogenation measurements in the problematic polar solvent AcOH, the discrepancy is still disappointingly large. Regrettably, this is the sole thermochemical datum for any 1,2-dialkylcyclopropene, and indeed we admit now that this is one of the very few enthalpy-of-formation data known to the authors for any 1,2-dialkylcycloalkene!

Another sole thermochemically useful compound is the $n = 4$ case 1,2-dimethylcyclobutene, for which we must also use problematic data derived from measurements of hydrogenation enthalpies in AcOH. We also acknowledge complications generally found in the early measurements of the enthalpies of hydrogenation of tetrasubstituted olefins[73]. There is also uncertainty in the stereochemistry of the resulting 1,2-dimethylcycloalkane[74]. We are optimistic, however, that many of the above-enunciated problems with enthalpies of hydrogenation should cancel in the energetics of the following transmethylation reaction:

$$\text{cyclo-}(CH_2)_1(MeC{=}CMe) + \text{cyclo-}(CH_2)_2(HC{=}CH) \longrightarrow \text{cyclo-}(CH_2)_2(MeC{=}CMe) + \text{cyclo-}(CH_2)_1(HC{=}CH) \qquad (17)$$

More precisely, the sum of enthalpies of hydrogenation of the species on the left should equal the sum for the right. In fact, the right-hand sum is *ca* 25 kJ mol^{-1} more positive (less negative) than that on the left. This result is approaching plausiblity. Comparing established substituent effects in species with 3- vs 4-membered rings (e.g. Liebman[1]) and making simple assumptions about molecular geometries, we conclude that methyls

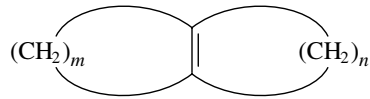
on the cyclopropene ring on the left should result in more electronic stabilization via substituent-ring interaction and less steric destabilization via inter-substituent repulsion than methyls on the cyclobutene on the right.

We now turn to the $n = 5$ case, 1,2-dimethylcyclopentene, for which there are literature enthalpy-of-hydrogenation measurements in an innocuous solvent coupled with a stereochemical analysis of the products[67]. Of all the dialkylcycloalkenes that are mentioned in this section, it is with dimethylcyclopentene that equation 14, now with $n = 5$ and R = Me, is most expected to be essentially thermoneutral. We find the reaction is endothermic by *ca* 11 kJ mol^{-1} and fail to understand the discrepancy[75].

B. Bicyclo[*m.n.*0]alkenes and Related Species

Bicyclo[*m.n*.0]alkenes (**25**: *m*, *n*) with the double bond linking the bridgehead carbons are another class of relevant compounds. Enthalpy-of-formation data are available for the $m = n = 1$ case through analysis of gas-phase acidity and electron-affinity measurements[76], and for $m = 2$, $n = 2$, 3 and 4 from hydrogenation data[54] from reaction in a thermochemically innocuous hydrocarbon solvent. Parallelling the earlier transalkylation reactions (equation 14), perhaps the simplest comparison we can make is to use the enthalpy of the reaction of the bicyclic species with ethylene to form two monocyclic ones.

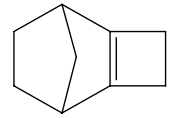
$$\mathbf{25}(m, n) + C_2H_4 \longrightarrow \text{cyclo-}(CH_2)_m(CH{=}CH) + \text{cyclo-}(CH_2)_n(CH{=}CH) \qquad (18)$$



(25)

This reaction enthalpy probes the superstrain associated with the two, trigonal, bridgehead carbons beyond that found in the individual rings. As may simply be concluded by looking at the molecular structure, the $m = n = 1$ species is clearly highly strained (quantum chemical calculations show the additional structural feature of non-planarity[77]). Experimental enthalpy-of-formation measurements of bicyclobutene show this compound to be accompanied by an exothermicity of reaction 18 of 42 ± 42 kJ mol^{-1}.

For the $m = 2$ and $n = 2$, 3 and 4 cases, equation 18 is found to be exothermic by 42, 34 and 4 kJ mol^{-1}, respectively. The large error bars for the energetics of the $m = n = 1$ case precludes comparison with these exothermicities for the 'larger' species and so it is not obvious that it is 'clearly highly strained' beyond the presence of two cyclopropene rings. The data are consistent with this $m = n = 1$ species having much more superstrain than any of the others, and the $m = n = 1$ species being somewhat less superstrained than the $m = 2$, $n = 4$ case. That reaction 18 for this last species is so close to thermoneutral suggests there is almost no additional strain or superstrain associated with ring fusion, for the corresponding acyclic reaction is the effectively thermoneutral equation 14. We can test this assumption of the absence of additional strain by considering species with more rings and thereby modulate the effective ring sizes connoted by the numbers *m* and *n*. Bridging the 2 and 4 carbons of the $m = 2$, $n = 3$ species by an ethano link to form **26** (equivalently, bridging the 2 and 5 carbons of the $m = 2$, $n = 4$ species by a



(26)

methano bridge) results in a norbornene derivative. This is expected to result in a species with superstrain intermediate to the $m = 2$, $n = 2$ and $m = 2$, $n = 3$ species[78]. Using equation 18 and the recommended norbornene enthalpy of formation from Rogers and coworkers[60] results in an exothermicity of 45 kJ mol^{-1}. While one should not conclude this norbornene derivative *must* be more strained than the $m = 2$, $n = 2$ compound, a high degree of strain is suggestive. Or one can join the 5 and 6 carbons of the '2' bridge in the $m = 2$, $n = 3$ compound by a propano or trimethylene link. Taking the enthalpy of formation of the resultant bicyclo[3.2.0]hept-5-ene from Roth and coworkers[54], an exothermicity of 33 kJ mol^{-1} suggests little change in strain by including this quite long and strainless link. This result is not particularly surprising.

We close this section with a brief discussion of how our analysis can be used to evaluate other data from the experimental literature. Consider compound **25** with $m = n = 4$. Based on the above reasoning, we expect reaction 18 to be essentially thermoneutral and so its gas-phase enthalpy is expected to be *ca* -65 kJ mol^{-1}. Let us assume that it is the same as the octahydronaphthalene cited by both Kharasch and Stull, Westrum and Sinke. If we accept the enthalpy-of-combustion data value cited in the former archive, we derive an enthalpy of formation of the liquid as -106 kJ mol^{-1}. From the latter archive, the corresponding enthalpy-of-formation value of -145 kJ mol^{-1} is found. Using our standard enthalpy of vapourization estimation protocol, we obtain a phase-change enthalpy of *ca* 50 kJ mol^{-1} and so the two 'competing' gas-phase enthalpies of formation are -56 and -95 kJ mol^{-1}. The former value is more tenable, although the 9 kJ mol^{-1} difference between theory and experiment is larger than we would have perhaps liked[79].

C. Polyhedrenes

Admittedly, not all polycyclic tetrasubstituted olefins can be so simply constructed or described as bicyclo[*m.n.*0]alkenes. Gas-phase ion–molecule experiments (combined with some judicious but non-experimentally measured numbers) allowed the derivation of[80] the formal enthalpy of hydrogenation of cubene **(27a)**, i.e. the exothermicity of reaction 19 to form the saturated cubane **(27b)**.

$$\text{cubene(g) } (\mathbf{27a}) + H_2(g) \longrightarrow \text{cubane(g) } [(CH)_8, \mathbf{27b}] \qquad (19)$$

Accepting the archival enthalpy of formation of gaseous cubane[81], we thus deduce the enthalpy of formation of cubene[80] to be 1000 ± 17 kJ mol^{-1}. It is hard to have an intuitive feel for such a large, positive enthalpy of formation. One possible probe of the energetics of cubene is the exothermicity of reaction 20

$$\text{cubene} + C_2H_4 \longrightarrow \text{tetracyclo}[4.4.0.0^{2,5}.0^{7,10}]\text{deca-3, 8-diene } (\mathbf{28}) \qquad (20)$$

which we recognize as an 'intramolecular' counterpart of equation 18. We would be disappointed if this last diene with all of its fused cyclobutane rings lacked some form of homoconjugative stabilization and/or destabilizing superstrain. As such, even were its

(27)

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enthalpy of formation known, somehow the comparison of the energetics of the polycyclic reaction 20 and of 18 for $m = n = 2$ would still be suspect as a reference energy calculation[82]. Alternatively, cubene and its fewer-ring counterpart, species **25** (with $m = n = 2$), are naturally contrasted by looking at the energetics of reaction 21.

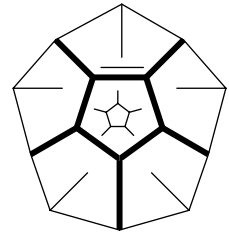
$$\textbf{27a} + \text{bicyclo[2.2.0]hexane} \longrightarrow \textbf{27b} + \textbf{25}\ (m = n = 2) \tag{21}$$

The desired number may be recognized as the difference of the enthalpies of hydrogenation of cubene and bicyclo[2.2.0]hex-1-ene and found to be *ca* 50 ± 17 kJ mol^{-1} endothermic. In that cubene is more rigid than the bicyclohexene, it is surprising that the hydrogenation enthalpy is smaller for the former than the larger. Alternatively, consider reaction 22.

$$\textbf{27a} + \text{Me}_2\text{CHCHMe}_2 \longrightarrow \textbf{27b} + \text{Me}_2\text{C=CMe}_2 \tag{22}$$

We may translate its energetics into the difference of the enthalpies of hydrogenation of cubene and the acyclic tetramethylethylene[16]. We deduce reaction 22 is some 266 ± 17 kJ mol^{-1} exothermic. This number is not particularly useful in that we have already seen there are no obvious patterns in the hydrogenation enthalpies of monocyclic alkenes. As such, why should there be patterns in the energetics of polycyclic olefins such as the various species **25**. *A forteriori*, expecting sense from the energetics of cubene could be viewed as at best premature.

Sometimes a polyhedrene is so complex that comparison is all but impossible with any but the simplest paradigm. An example is dodecahedrene **(29)**. From a different type of gas-phase ion–molecule reaction than used for cubene, it was deduced[83] that the enthalpy of hydrogenation of dodecahedrene to form dodecahedrane is some 157 ± 15 kJ mol^{-1} more exothermic than that of tetramethylethylene. We lack the standard gas-phase enthalpy of formation of this dodecahedrane, although it was recently derived from knowledge of a relatively simple derivative[84] to be *ca* 94 kJ mol^{-1}. But this is not the obstacle. We do not know how to write a meaningful reaction analogous to equation 20: the product with the resultant two $-$CH=CH$-$ groups finds them too close[85]. The simpler comparison of dodecahedrene with species **25** ($m = n = 3$) is thwarted by the absence of thermochemical information on this last, quite normal-looking, species.



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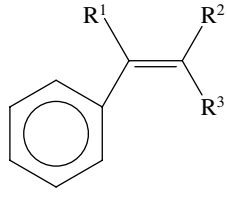
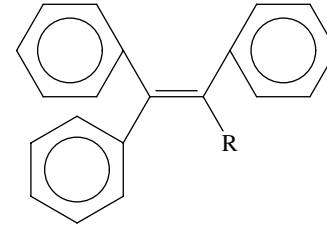
VII. OLEFINS WITH AROMATIC SUBSTITUENTS

A. Phenylated Ethylenes

The compounds discussed in this section are all of the generic type '$Ph_qH_{4-q}C_2$' and their substituted derivatives. These species may be considered to be on the boundary of acyclic and cyclic because the 'relevant' (i.e. olefinic) double bond will almost never be found in a ring, but there are 'irrelevant' (i.e. benzenoid) double bonds that are always found in rings. We also recognize these compounds as being on the borderline of compounds with a single relevant double bond and those with many because of the well-established near-constancy of the difference of enthalpies of formation of corresponding (gas-phase) phenyl and vinyl groups[86,87]. As such, these species may be said to thermochemically mimic di-, tri- and even more extended polyenes. Let us commence with the three simplest, and best characterized, members of this series of phenylated ethylenes: with 0, 1 and 2 phenyl groups, we have ethylene itself, styrene **(30a)**, and (because it is the least strained) (*E*)-stilbene **(30b)**. The relevant gas-phase enthalpies of formation are 52.5 ± 0.4, 147.9 ± 1.5 and 236.1 ± 1.3 kJ mol^{-1}. These numbers correspond to sequential enthalpies of phenylation of 95.4 ± 1.6 and 88.2 ± 2.0 kJ mol^{-1}. It is interesting to note that the second phenyl group is slightly more stabilizing than the first, i.e. the increase of enthalpy of formation upon sequential phenylation is less going from one phenyl to two than from none to one. This is in contrast to the case of the first and second methylation enthalpies of ethylene [to form propene and (*E*)-2-butene, respectively] which are identical to within experimental error. The enthalpy of formation of the *gem*-disubstituted 1,1-diphenylethylene **(30c)** is some 10 kJ mol^{-1} more positive than that of its (*E*)-1,2-isomer, while the *cis*-disubstituted (*Z*)-1,2-diphenylethylene **(30d)** is some 20 kJ mol^{-1} more positive than that of the (*E*)-isomer[88]. By contrast, (*E*)-2-butene is less stable than 2-methylpropene by *ca* 5 kJ mol^{-1} but it is 4 kJ mol^{-1} more stable than (*Z*)-2-butene. This is not particularly surprising: phenyl groups are larger than methyl groups and steric inhibition of phenyl/ethylene resonance is to be expected when two phenyls are on the same carbon atom[89].





(30a) $R^1 = R^2 = R^3 = H$
(30b) $R^1 = R^3 = H$ $R^2 = Ph$
(30c) $R^1 = Ph$ $R^2 = R^3 = H$
(30d) $R^1 = R^2 = H$ $R^3 = Ph$

(31a) R = H
(31b) R = Ph

Such destabilization is therefore to be expected for the tri- and tetraphenylethylenes (**31a** and **31b**). The enthalpy of formation is found only for the solid-phase species. The first step is to estimate their enthalpies of sublimation. Let us apply an equation explicitly designed for the study of planar aromatic hydrocarbons[90], where n_c is the total number of carbons,

$$\Delta H_s = 6.1 n_c + 2.5 \quad (23)$$

Summing the experimentally determined solid-phase enthalpies of formation of the olefin and the sublimation enthalpies predicted by equation 23 results in the desired gas-phase quantities of 358 and 473 kJ mol^{-1} for the enthalpies of formation of tri- and tetraphenylethylene. Combined with the above enthalpies of formation of ethylene, styrene and (*E*)-stilbene, our new numbers allow us to generate a reasonably straight line as a function of the number of phenyl groups:

$$\Delta H_f^\circ(\text{`}Ph_qH_{4-q}C_2\text{'}) = 44.9 + 104q \ (n = 5, r = 0.9974) \tag{24}$$

Leaving out (*E*)-stilbene — after all, why should this species be the 'representative' of the $n = 2$ compounds and not either 1,1-diphenylethylene or (*Z*)-stilbene? — we find the even more precise equation

$$\Delta H_f^\circ(\text{`}Ph_qH_{4-q}C_2\text{'}) = 50.1 + 102q \ (n = 4, r = 0.9997) \tag{25}$$

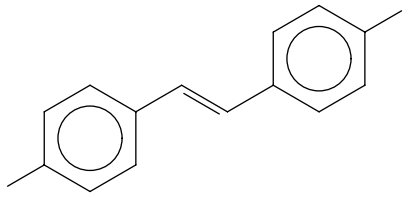
from the data for the series ethylene, styrene, triphenylethylene and tetraphenylethylene. From equation 25, we find the 'predicted' value of the enthalpy of formation of gaseous diphenylethylene, 254 kJ mol^{-1}, is plausible: it is approximately the average of the reported values for the 1,1-, (*Z*)-1,2- and (*E*)-1,2-species.

B. 'Tolylated' Ethylenes

The compounds highlighted in this section are all of the generic type '$Tol_qH_{4-q}C_2$'. The most natural comparison is with the corresponding phenylated olefins, '$Ph_qH_{4-q}C_2$', with which we define a difference quantity δ_{26}(Ph, Tol) as

$$\delta_{26}(\text{q, Ph, Tol}) \equiv 1/q\{[\Delta H_f^\circ(Ph_qH_{4-q}C_2,\ \text{s})] - [\Delta H_f^\circ(Tol_qH_{4-q}C_2),\ \text{s})]\} \tag{26}$$

For the *p*-tolyl species, we have archival enthalpies of formation for $q = 2$ [however, for only the (*E*)-1,2-isomer, **32**, are there relevant data[91]], $q = 3$ and $q = 4$. These difference quantities equal 39.5 ± 1.7, 37.4 ± 2.1 and 35.0 ± 2.2 kJ mol^{-1} and are comparable to the difference of 34.2 kJ mol^{-1}, found for the not quite 'proper' $q = 1$ case of solid benzene and solid toluene[92] used in lieu of the desired enthalpy-of-formation data for solid *p*-methylstyrene to accompany solid styrene. For the *o*-tolyl species, we have archival enthalpies of formation for $q = 2$ [again, only (*E*)-1,2- is applicable here] and $q = 3$, resulting in difference quantities of 31.0 ± 1.7 and 36.1 ± 2.1 kJ mol^{-1} and again comparable to the solid benzene/solid toluene difference. Let us assume a consensus value of δ_{26}(q, Ph, Tol) of 36 kJ mol^{-1}. Working backwards from the cited enthalpies of formation of the solid 1,1-bis(*p*-tolyl) and 1,1-bis(*o*-tolyl)ethylenes results in an enthalpy of formation of solid 1,1-diphenylethylene of 158 and 161 kJ mol^{-1}, respectively. Combining the archival enthalpy of formation of gaseous 1,1-diphenylethylene and a suggested enthalpy of sublimation from equation 23 results in the nearly identical prediction of 158 kJ mol^{-1} for this quantity. There appears to be consistency[93].

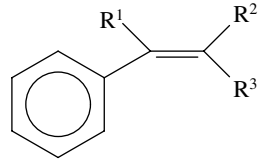


(32)

C. Alkylated Styrenes

We start with methylated styrenes. The enthalpies of formation of gaseous α-, (*E*)-β- and (*Z*)-β-monomethylstyrenes (**33a–33c**) and of β,β-dimethylstyrene **(33d)** have been ascertained by a combination of hydrogenation, rearrangement and combustion calorimetry[94] to be 115.3±2.3, 112±2, 123.0±1.3 and 86.0±1.2 kJ mol^{-1}, respectively. Interestingly, the values for the three monomethylstyrenes are almost identical to what is found by averaging the enthalpies of the correspondingly substituted dimethyl and diphenylethylenes. That is, the following reactions are nearly thermoneutral:

$$Ph_2H_2C_2 + Me_2H_2C_2 \longrightarrow 2PhMeH_2C_2 \qquad (27)$$



(33a) $R^1 = Me,\ R^2 = R^3 = H$
(33b) $R^1 = R^3 = H,\ R^2 = Me$
(33c) $R^1 = R^2 = H,\ R^3 = Me$
(33d) $R^1 = H,\ R^2 = R^3 = Me$

Relatedly, the enthalpy of formation of the dimethylstyrene is very nearly equal to that predicted assuming thermoneutrality for the reaction

$$(E)\text{-PhCH=CHMe} + (Z)\text{-PhCH=CHMe} \longrightarrow \text{PhCH=CH}_2 + \text{PhCH=CMe}_2 \qquad (28)$$

Owing to the large size of *t*-butyl groups relative to those of methyl, we do not expect thermoneutrality for the reaction

$$(E)\text{-PhCH=CHBu}^t + (Z)\text{-PhCH=CHMe} \longrightarrow (Z)\text{-PhCH=CHBu}^t + (E)\text{-PhCH=CHMe} \qquad (29)$$

This would only be achieved if the (*Z*)/(*E*)-enthalpy of formation difference of β-methylstyrene and β-*t*-butylstyrene were the same. For the former, we find the desired difference to be *ca* 13 ± 2 kJ mol^{-1}, while for the latter the difference is found[41] to be 33.2 ± 9.3 kJ mol^{-1}. Consider reaction 30 that interrelates the above two β-alkylated styrenes:

$$(E)\text{-PhCH=CHBu}^t\text{(l)} + \text{MeCH=CH}_2\text{(g)} \longrightarrow (E)\text{-PhCH=CHMe(g)} + {}^t\text{BuCH=CH}_2\text{(l)} \qquad (30)$$

If all four olefins were in the same phase then this reaction would be expected to be thermoneutral. As it is, the right-hand side has six more carbons in the gaseous phase than does the left. We thus expect the right-hand side to be automatically more positive than the left by *ca* 28 kJ mol^{-1}, the enthalpy-of-vaporization contribution of the six carbon atoms according to the estimation approach in Reference 3. In fact, making use of the data in Reference 41 for the β-*t*-butylstyrene, this reaction is seen to be exothermic by 37 kJ mol^{-1}. The 9 kJ mol^{-1} discrepancy is surprising and disappointing.

Kharasch, and Stull, Westrum and Sinke contain references to some other alkylated styrenes which we hesitate to use in the current chapter: it is well-established that styrene and many of its derivatives readily oligomerize and so we expect purity problems to plague earlier studies. Yet we briefly proceed here. For example, consider the formal reaction

$$(E)\text{-PhCH=CHEt}(*) + \text{PhPr}(*) \longrightarrow (E)\text{-PhCH=CHMe}(*) + \text{PhBu}(*) \qquad (31)$$

If $*$ corresponds to either the gas or pure liquid for each species, we might expect this reaction to be essentially thermoneutral. If:

(a) all of the enthalpies of formation are correct,

(b) our protocol for estimating enthalpies of vapourization is accurate and

(c) the assumption that numerically, enthalpies of hydrogenation of hydrocarbons are independent of the choice of gas, pure liquid, or in dilute hydrocarbon solution is valid,

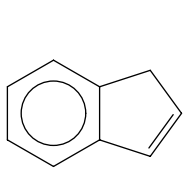
then the following reaction 32 should also be thermoneutral:

$$(E)\text{-PhCH=CHEt(l)} + \text{PhPr(g)} \longrightarrow (E)\text{-PhCH=CHMe(g)} + \text{PhBu(l)} \qquad (32)$$

Using the earlier value ignored by Pedley for the enthalpy of formation of 1-phenyl-1-butene but taken from our earlier archives, the very recent value for 1-phenylpropene[94] and the archival values for propyl and butylbenzene, we find this reaction is thermoneutral to within 2 kJ mol^{-1}!

D. 'Cyclic Styrenes'

By our definition of olefins with aromatic substituents, it appears plausible to include indene **(34)**, 1,2-dihydronaphthalene **(35)** and acenaphthylene **(36)** in this category. The natural comparison is with the saturated indane, tetralin, and acenaphthene for which the enthalpies of hydrogenation of our putative styrene derivatives are 99.1 ± 2.3 (l) and 102.7 ± 2.7 (g); 110.7 ± 2.3 (l) kJ mol^{-1}; 116.4 ± 5.3 (s) and 103.7 ± 5.6 (g), respectively. By comparison, making use of the above enthalpy of formation of gaseous (*E*)-1-phenylpropene, we derive its enthalpy of hydrogenation[95] to be 104 ± 3 kJ mol^{-1}. It would thus appear that indene, 1,2-dihydronaphthalene[96] and acenaphthylene are logically, if roughly, considered 'cyclic styrenes'[97].



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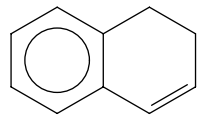

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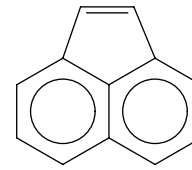

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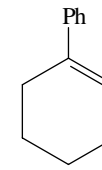


(37)

By our definition of 'cyclic styrenes', it is also logical to include 1-phenylcyclohexene **(37)** for which an enthalpy of formation has been measured and is given in our archive. In addition, its (*Z*)-/(*E*)-isomerization enthalpy is also available from experiment (cf Reference 55). Indeed, it may be argued that discussion of these species belongs in the current section of the chapter. Perhaps, but now we note that we do not consider the reported enthalpy of formation of the conventional isomer to be correct. From the proferred liquid-phase value of the enthalpy of formation of the olefin of interest, −16.8 ± 6.7 kJ mol^{-1}, and of the related saturated species, phenylcyclohexane,

-76.6 ± 1.4 kJ mol^{-1}, we deduce an enthalpy of hydrogenation of *ca* 60 kJ mol^{-1}. This value is totally incompatible with any other styrene derivative we know of, e.g. the various other unsaturated hydrocarbons enunciated earlier in this section[99]. Likewise, additionally using the enthalpies of formation of liquid 1-phenylcyclohexene and biphenyl results in an enthalpy of dehydrogenation of 132 kJ mol^{-1}, while the parent cyclohexene and its 1-methyl and 1-ethyl derivatives and their benzene analogs have enthalpies of dehydrogenation of *ca* 93 kJ mol^{-1}. The origin of the discrepancy remains unknown[99].

VIII. ACYCLIC ALDEHYDES AND KETONES

A. Assessment and Correlation of Data

All the enthalpies of formation for acyclic aliphatic aldehydes and ketones which are discussed in this section are tabulated by Pedley and coworkers[16]. The number of these carbonyl compounds whose enthalpies of formation have been measured are few compared to the abundant data available for alkenes and so there are fewer decisions to make on which data to include. However, we then lack the means to make the comprehensive analyses we would prefer. The demonstrated linearity[34] of the enthalpies of formation of the members of a homologous series vs the number of carbon atoms, n_c, in the molecules provides an excellent visual method for determining the quality of the data; any enthalpy of formation which deviates significantly from linearity is of questionable reliability. The linear relationship can be expressed as in equation 4 and the results of the regression analyses of this equation for aldehydes and ketones appear in Table 4.

When the enthalpies of formation of the *n*-aldehydes are plotted versus n_c, the pentanal point is a clear outlier in both the liquid and gaseous states. Interpolating a value from the constants given in Table 4 yields $\Delta H_f(g) = -224.5 \pm 0.9$ kJ mol^{-1} and $\Delta H_f(l) = -263.1 \pm 0.1$ kJ mol^{-1}. The methyl derivative, acetaldehyde, does not appear to deviate[44] at all from the straight line established by the $n_c = 3$, 4 and 7 members and so it is included in the regression analysis.

As for other disubstituted functional groups such as ethers[4] and sulphides[3], it is necessary to divide the non-branched aliphatic ketones into two categories: methyl *n*-alkyl ketones and di-*n*-alkyl ketones. The latter category includes examples of 3-, 5- and 6-alkanones belonging to two different homologous series, the ethyl alkyl ketones and the symmetrical dialkyl ketones; 3-pentanone is common to both series. In the methyl *n*-alkyl ketone series, the enthalpies of formation of both liquid and gaseous 2-nonanone appear about 2 kJ mol^{-1} too positive compared to the otherwise straight line incorporating the other data points. Neither the gaseous nor liquid enthalpy of formation of acetone, the methyl derivative, deviates from its respective line. The enthalpies of formation of

TABLE 4. Results from the linear regression analysis of equation 4 for aldehydes and ketones[a] (kJ mol^{-1})

	α_l	β_l	α_g	β_g
n-R(C=O)H [R = Me, Et, Pr, Hex]	-23.77 ± 0.13	-144.2 ± 0.3	-19.45 ± 0.07	-127.2 ± 0.2
n-R(C=O)Me [R = Me, Et, Pr, Bu, Hept, Dec]	-25.09 ± 0.18	-172.5 ± 1.0	-20.67 ± 0.10	-155.6 ± 0.5
n-R_2(C=O) [R = Et, Et; Bu, Bu; Pen, Pen]	-25.33 ± 0.10	-169.9 ± 0.7	-21.66 ± 0.10	-149.7 ± 0.7

[a]In the least-squares analyses of equation 4, the individual enthalpies were weighted inversely as the squares of the experimental uncertainty intervals. The correlation coefficient for each analysis is $\geqslant 0.999$.

gaseous and liquid acetone do deviate from linearity when considered as members of the symmetrical di-*n*-alkyl ketone series, their measured enthalpies being more negative than those calculated by equation 4.

B. Enthalpies of Isomerization

1. Ketone isomerization

Both 2-pentanone and 2-hexanone are more stable than their 3-alkanone isomers by 1.1 and 1.5 kJ mol^{-1}, respectively, in the gaseous state. Thus, the exothermic enthalpy of isomerization of ethyl to methyl ketones probably increases slightly with increasing n_c, as deduced from this very limited data set. However, 5-nonanone is more stable by 4.2 kJ mol^{-1} than 2-nonanone (or by 2.2 kJ mol^{-1} using an estimated value for the 2-isomer). 6-Undecanone is 4.7 kJ mol^{-1} more stable than the estimated enthalpy of formation for the unmeasured 2-undecanone (g, -382.7 ± 0.5). Because the slopes, α_g, are quite different for the methyl *n*-alkyl ketones and the symmetrical di-*n*-alkyl ketones, we expect the stability difference to increase with n_c. Both a graphical plot of the data and a calculation using the slope and intercept values in Table 4 show that the reversal in stability of the methyl *n*-alkyl ketones and the symmetrical di-*n*-alkyl ketones occurs at about C_7 (g). Recall the change in stability order for the *cis*-2- and -3-*n*-alkenes at *ca* $n_c = 7$ and for the *trans*-2- and -3-*n*-alkenes at a calculated $n_c = 9$. In contrast, the slope for the methyl *n*-alkyl ethers is nearly parallel to that of the more stable di-*n*-alkyl ethers[100,101].

2. Aldehyde/ketone isomerization

As a comparison of the enthalpies of formation of isomeric aldehydes and ketones shows, the disubstituted carbonyl compounds (ketones) are more stable than the monosubstituted carbonyl compounds (aldehydes), analogous to the stability order for the corresponding 1,1-disubstituted ethenes and the 1-*n*-alkenes. For the three aldehyde/methyl ketone isomeric pairs ($n_c = 3$–5), initially it seems that the enthalpies of isomerization are fairly constant. However, if the interpolated value for pentanal is used, the trend is clearly that of more negative enthalpy of isomerization with increasing n_c(g): -31.7, -33.9, -34.5 kJ mol^{-1}. The non-constant enthalpies are expected because the slopes, α_g, in Table 4 are quite different for aldehydes and ketones. The greater contribution to the isomerization enthalpy differences comes from the methyl ketone which is more stabilized than the aldehyde by an additional $-CH_2-$ group. The enthalpies of isomerization of the corresponding alkenes are much less exothermic (-6.1 ± 0.8 kJ mol^{-1}) than those of the carbonyl compounds.

3. Isomerization of substituent groups

Just as for the alkenes in a previous section, we would like to compare the enthalpies of isomerization of small alkyl substituents attached to the carbonyl functional group. The results are summarized in Table 5 for the isomerization reaction

$$R^1{-}X{-}R^2 \longrightarrow R^3{-}X{-}R^4 \tag{33}$$

We will also compare the carbonyl compounds with alkenes and with other oxygen-containing compounds[102] to assess steric and electronic effects on the isomerizations.

The only available aldehyde data are for isomerization of butanal to 2-methylpropanal for which $\Delta H_{isom}(g) = -11.0 \pm 1.7$ kJ mol^{-1}. The corresponding alkene isomerization enthalpy of 1-pentene to 3-methyl-1-butene is -6.2 ± 0.9 kJ mol^{-1}. Hydrogenating all

TABLE 5. Enthalpies of isomerization of aldehydes and ketones (kJ mol^{-1})

R^1-X-R^2		R^3-X-R^4		ΔH_{isom}(l)	ΔH_{isom}(g)
R^1	R^2	R^3	R^4		
n-Pr	H	*i*-Pr	H	-8.2 ± 2.1	-11.0 ± 1.7
Me	*n*-Pr	Me	*i*-Pr	-2.1 ± 1.3	-3.5 ± 1.3
Et	*n*-Pr	Et	*i*-Pr	-5.7 ± 1.3	-7.8 ± 1.3
n-Pr	*n*-Pr	*i*-Pr	*i*-Pr	-2.9 ± 1.3[a,b]	-5.0 ± 1.3[a,b]
Me	*n*-Bu	Me	*t*-Bu	-6.6 ± 1.3	-10.9 ± 1.5
n-Bu	*n*-Bu	*t*-Bu	*t*-Bu	7.1 ± 1.8[b]	-0.5 ± 1.8[b]

[a]Calculated from an estimated value for 4-heptanone using equation 4 and the constants in Table 4.
[b]Statistically corrected for two isomerizing alkyl groups.

of these entities produces enthalpies of isomerization for the corresponding alcohols of -8.1 ± 1.0 kJ mol^{-1} and for the corresponding alkanes of -6.8 ± 1.3 kJ mol^{-1}. This is perhaps not the best comparison of substituent isomerization effects because in the aldehydes the isomerization is from an *n*-primary to a secondary substituent attached to the carbonyl group, while in the alcohol the isomerization is from an *n*-primary to a branched primary substituent group attached to the hydroxyl group. The more closely related enthalpy of isomerization[103] of *n*-propanol to isopropanol is -17.7 ± 0.7 kJ mol^{-1}.

Two ketone pairs provide experimental data for an *n*-primary-to-secondary isomerization but both contain only propyl substituents. Estimating the enthalpy of formation of 4-heptanone from equation 4 and the constants in Table 4 gives a third pair. All of these enthalpies of isomerization are less negative than the propyl isomerization in aldehydes. Ketones, more stable than aldehydes generally, thus seem less susceptible to the stabilizing effect of increased branching in the substituent group, although they are stabilized more than aldehydes per $-CH_2-$ group. The propyl isomerization enthalpy is somewhat affected by the nature of the other substituent bonded to the carbonyl (Me, Et or *n*-Pr). One ketone pair yields a single *n*-butyl-to-*tert*-butyl isomerization enthalpy, while a second pair gives us partial insight into the effects of di-tertiary branching and steric hindrance: the gaseous enthalpy of isomerization of di-*n*-butyl ketone to di-*t*-butyl ketone is only -0.9 ± 1.8 kJ mol^{-1}. Although there is an experimental enthalpy of formation for ethyl *t*-butyl ketone, there is none for its isomer, 3-heptanone. We can roughly estimate a value for the latter from the methylene enthalpy increment between 3-pentanone and 3-hexanone which is -20.4 kJ mol^{-1}. Using the derived enthalpy of formation (-298.7 kJ mol^{-1}), the approximate gaseous enthalpy of isomerization for the ethyl butyl ketone pair is *ca* -15 kJ mol^{-1}, compatible with that of the methyl butyl pair in Table 5 and presumably not too different from one butyl isomerization in di-*n*-butyl ketone. Thus, if *ca* -15 kJ mol^{-1} is released during the first rearrangement to the more stable tertiary substituent with presumably minimal steric interference, then *ca* $+14$ kJ mol^{-1} is required for the second rearrangement. To produce such a net endothermicity in the hypothetical second isomerization, the enthalpy effect of unfavourable steric hindrance must be about $+29$ kJ mol^{-1}, assuming additivity of the favourable branching effect. Even if the first butyl isomerization is closer to -11 kJ mol^{-1} (as for the gaseous methyl butyl ketones), the endothermic steric enthalpy would be about $+21$ kJ mol^{-1}. To assess the importance of tertiary branching (even though not adjacent to the functional group) but with a presumably smaller steric effect, consider the isomerization of di-*n*-pentyl ketone to di-neopentyl ketone: $\Delta H_{isom}(g) = -33.8 \pm 3.0$, or -16.9 for each pentyl group rearrangement, similar to the single primary-to-tertiary isomerization enthalpy derived above.

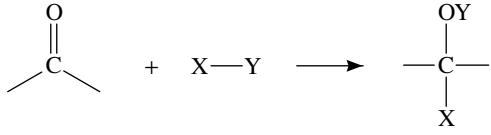
The more negative enthalpies of isomerization of ethers are presumably a consequence of the greater electronegativity of the oxygen atom compared to the carbonyl group[103]. For example, the gaseous enthalpy of isomerization for the methyl propyl ethers is -13.8 ± 1.2 kJ mol^{-1} and that for methyl *n*-butyl to methyl *t*-butyl ether is -25.4 ± 1.6 kJ mol^{-1}. The magnitude of the steric interaction in the ether can be assessed in the same way as for the ketones. Tertiary branching of the first primary group in di-*n*-butyl ether is favourable by -27.6 kJ mol^{-1}. Assuming additivity of the branching enthalpy[104], the total isomerization of di-*n*-butyl ether to di-*t*-butyl ether would be -55.2 kJ mol^{-1}. That the actual enthalpy of isomerization is -28.6 kJ mol^{-1} means that $+26.6$ kJ mol^{-1} are lost, presumably to destabilizing steric interactions. The methyl ether series provides the only example of an *n*-pentyl to *t*-pentyl isomerization, -26.8 ± 2.0 kJ mol^{-1}, which is indistinguishable from the single butyl isomerization in di-*n*-butyl ether. From this comparison of ketones and ethers, it seems the steric effects on the enthalpy of isomerization are nearly the same in the two families of compounds.

We now reconsider from a previous section the multiple gaseous enthalpies of formation available for the 1,1-disubstituted ethenes corresponding to the aforementioned ethyl and methyl ketones with one branched substituent: 2,3-dimethyl-1-butene[6,26,32], 2-ethyl-3-methyl-1-butene[16,28] and 2,3,3-trimethyl-1-butene[21,27]. The calculated ranges for the alkene enthalpies of isomerization for the methyl/propyl and ethyl/propyl substituted pairs were respectively -3.5 ± 1.6 to -7.4 ± 2.3 kJ mol^{-1} and -2.8 ± 2.6 to -8.2 ± 3.0 kJ mol^{-1}, and for the methyl/butyl pair, -6.8 ± 1.8 to -11.4 ± 1.8 kJ mol^{-1}. If ketones are analogous to aldehydes with respect to their larger exothermicity of isomerization relative to alkenes, then the $H_2C{=}C(CH_3)Pr$ enthalpy of isomerization value of -3.5 kJ mol^{-1}, at the lower end of the range (compared to -3.5 ± 1.3 kJ mol^{-1} for the corresponding ketones), is more accurate[26]. For the $H_2C{=}C(CH_2CH_3)Pr$ and $H_2C{=}C(CH_3)Bu$ alkenes, no choice can be made because any of the isomerization enthalpies could be rationalized as correct. There are no data for the corresponding 1,1-disubstituted ethenes to compare with the enthalpies of isomerization for the other ketones.

C. Enthalpies of Reaction

The chemical reactivity of the carbonyl group is such that several reaction types are applicable to exploring the energetics of aldehydes and ketones[105,106]. It might be interesting and useful here to computationally interrelate a few common carbonyl reactions especially as we continue to investigate the behaviour of homologous series with respect to the constancy, or lack of it, in their interconversions.

A typical reaction of aldehydes and ketones is addition to the C$-$O π bond. Examples of addition reagents are H_2 (resulting in reduction to the corresponding alcohol), ROH (to give a hemiacetal or hemiketal) and RM (yielding a metal alkoxide). Only the hydrogenation reaction produces an addition product for which there is any useful quantity of thermochemical data, however. Equation 34 represents an overall reaction of the carbonyl compound with a (hypothetical) reagent XY, an equation which includes any reaction, subsequent to an initial addition reaction, to form products for which there are sufficient data.



(34)

TABLE 6. Linear analysis of equation 36 for several carbonyl addition reactions (kJ mol^{-1})[a]

Carbonyl compound >C=O	Product >C(OX)Y		m(l)	'ΔH_{rxn}'(l)	m(g)	'ΔH_{rxn}'(g)
	X	Y				
n-R(C=O)H [R = Me, Et, Pr, Hex]	H	H	0.955 ± 0.005	73.3 ± 1.6	0.966 ± 0.006	60.8 ± 1.7
n-R(C=O)H [R = Me, Et, Pr]	H	CH_3	0.967 ± 0.005	116.0 ± 1.6	0.925 ± 0.025	86.0 ± 7.2
n-R(C=O)H [R = Me, Et, Pr]	CH_3	OCH_3	0.989 ± 0.015	223.7 ± 6.9		
n-R(C=O)Me [R = Me, Et, Pr, Bu[b]]	H	H	0.998 ± 0.007	69.0 ± 2.6	0.997 ± 0.037	54.2 ± 10.9
n-R(C=O)Me [R = Me, Et]	H	CH_3	1.250	200.8	1.168	147.6
n-R(C=O)Me [R = Me, Et, Pr]	CH_3	OCH_3	1.019 ± 0.013	221.2 ± 6.4		

[a]The correlation coefficients for all equations are ⩾0.999.
[b]Enthalpy of formation (g) of 2-hexanol is not available.

For example, aldehydes and ketones react with excess alcohol to produce acetals or ketals, and organometallic additions followed by hydrolysis produce alcohols. The formal reagents X−Y for formation of acetals/ketals and substituted alcohols are thus ROR and RH, respectively. Equation 34 is a clean chemical equation, as opposed to the real chemical reactions with the accompanying complicating effects of reagents, by-products and solvents. Equation 35 expresses the reaction thermochemically.

$$\Delta H_{rxn} = \Delta H_f[>C(OY)X] - \{\Delta H_f[>C{=}O] + \Delta H_f[XY]\} \quad (35)$$

Since ΔH_f [XY] is a constant in Equation 35, we can further simplify the analysis by not including it and writing Equation 36:

$$\Delta H_f[>C{=}O] = m\bullet\Delta H_f[>C(OY)X] - \text{'}\Delta H_{rxn}\text{'} \quad (36)$$

Its obviously linear form lends itself to analysis by the plotting and regression techniques introduced previously for equations 7 and 11. For homologous series in which the enthalpy of reaction is more-or-less constant for all members, the slope of equation 36 is close to 1 and the y-intercept, 'ΔH_{rxn}', is approximately equal to the mean experimental enthalpy of reaction, ΔH_{rxn}. The direction of deviation of the slope from unity for any carbonyl/product pair indicates whether the hypothetical reaction enthalpy will increase or decrease for the series. Inclusion of the enthalpies of formation of the appropriate XY reagent (or a combination of reagents and/or by-products) shows whether the reaction is actually endo- or exothermic. Some results are summarized in Table 6.

1. Reduction to alcohols

In the hydrogenation reduction reaction of non-branched aldehydes to primary alcohols, for both liquids and gases the enthalpy of hydrogenation becomes more negative with increasing n_c. The range of gaseous reaction enthalpy is −69.1 to −72.6 kJ mol^{-1} for acetaldehyde through heptanal. With increasing n_c, the alcohol becomes slightly more stabilized than does the aldehyde from which it is formed. The hydrogenation enthalpy of the branched aldehyde, 2-methylpropanal, is 1–2 kJ mol^{-1} less negative than its isomer.

For methyl n-alkyl ketones, both liquid and gaseous enthalpies of hydrogenation to secondary alcohols[107] are essentially constant, as predicted by the almost unit slope of

equation 36 [mean values: $\Delta H_{rxn}(l) = -69.8 \pm 0.33$; $\Delta H_{rxn}(g) = -55.1 \pm 0.8$ kJ mol^{-1}]. The reduction of 3-methyl-2-butanone is *ca* 3 kJ mol^{-1} less exothermic than the reduction of 2-pentanone, its unbranched isomer. Almost all of this difference is due to the -3.5 kJ mol^{-1} difference in stability of the two gaseous methyl ketones because the stability of the two alcohol reduction products are nearly identical [$\Delta H_{isom}(g) = -0.6$ kJ mol^{-1}]. This contrasts with the one example of an *n*-alkyl *sec*-alkyl ketone, 2-methyl-3-pentanone, whose enthalpy of hydrogenation is virtually identical to its di-*n*-alkyl isomer, 3-hexanone. (There are not enough alcohol data to assess the other di-*n*-alkyl ketone reduction enthalpies.) However, the enthalpy of reduction of liquid 3,3-dimethyl-2-butanone (-105.4 kJ mol^{-1}) is much greater than for the other ketones. This is because the difference in stability of liquid 3,3-dimethyl-2-butanol[17b] (*ca* -42 kJ mol^{-1}) and its unbranched isomer is very much greater than the stability difference for the corresponding ketones (-6.6 kJ mol^{-1}).

Hydrogenation of an aldehyde or ketone results in the corresponding primary or secondary alcohol; a Grignard reaction with methylmagnesium iodide, for example, followed by hydrolyis produces a secondary or tertiary alcohol with a methyl group bonded to the carbinol. The overall reaction is tantamount to adding CH_3–H to the carbonyl π bond. This enthalpy of reaction for aldehydes to the corresponding 2-alkanols is slightly increasingly negative with larger n_c as it was for the hydrogenation, but for the ketones, the exothermic enthalpies of reaction decrease substantially with n_c. The range for C_2–C_4 gaseous aldehydes is -106.7 to -109.8 kJ mol^{-1} and the values for gaseous acetone and 2-butanone are -95.2 and -92.1 kJ mol^{-1}, respectively. Both of these results are predicted by a comparison of the relevant slopes generated from equation 36. The aldehydes are reduced to the secondary alcohols of slightly steeper slope (*ca* -20.1) and so the difference between them increases with n_c. The ketones are reduced to tertiary alcohols with a less steep slope (*ca* -18.3) and so the difference decreases with increasing n_c. The reaction enthalpy for 2-methylpropanal is fully 10 kJ mol^{-1} less exothermic than its isomer, while the reaction enthalpy for 3-methyl-2-butanone, -94.5 kJ mol^{-1}, is presumably more exothermic than that of its unbranched isomer.

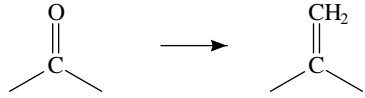
2. Acetal and ketal formation

Most measured acetal and ketal enthalpies of formation are for the dimethyl derivatives in the liquid phase. The slopes of equation 36 for the formation of 1,1-dimethoxyalkanes[108] from aldehydes and for the formation of 2,2-dimethoxyalkanes[109] from methyl ketones are in the region where constancy of the enthalpy of reaction is indeterminate. Although the acetalization for $n_c = 2$–4 is overall increasingly exothermic (mean $= -228.4 \pm 0.5$ kJ mol^{-1}), and the ketalization for $n_c = 3$–5 is overall decreasingly exothermic (mean $= -212.2 \pm 0.6$ kJ mol^{-1}) as predicted by their slopes, neither enthalpy range is large enough, nor are there data enough, to define a trend. The ketalization of methyl isopropyl ketone is about 1 kJ mol^{-1} more negative than ketalization of its *n*-propyl isomer while the ketalization of methyl *t*-butyl ketone is about 15.6 kJ mol^{-1} more positive than ketalization of its *n*-butyl isomer[110]. This large difference is due mainly to the endothermic isomerization of 2,2-dimethoxyhexane to 2,2-dimethoxy-3,3-dimethylbutane (*ca* +9 kJ mol^{-1}).

3. Methylenation

Earlier we compared the enthalpies of isomerization of small substituent groups in aldehydes and ketones with those of the correspondingly substituted alkenes. We now

consider the enthalpy of reaction which converts the carbonyl-containing compounds into those alkenes. The overall reaction may be written as



(37)

which corresponds to, for example, a Wittig reaction with methylene triphenylphosporane, $Ph_3P{=}CH_2$ (the reverse of equation 37 might be an ozonolysis reaction). Since any reactants and/or by-products for this reaction will be constants in the thermochemical equation, we can restrict consideration to just the alkene and the carbonyl, as in equation 36. The *n*-aldehydes exhibit a decreasing endothermicity of methylenation (n_c = 2–4, 7) with a range of 186.1 to 182.4 kJ mol^{-1}. The enthalpy of reaction for 2-methylpropanal is 4.8 kJ mol^{-1} more endothermic than its unbranched isomer. Immediately we see that the reaction enthalpy should be constant for the methyl ketones and the 2-methyl-1-*n*-alkenes since their slopes from equation 4a are virtually identical (Tables 2 and 4). Indeed, from a linear regression of equation 36 the slope is 1.008 and the *y*-intercept ($-$'ΔH_{rxn}') is 200.2. The average enthalpy of reaction calculated from the experimental enthalpies of formation is the nearly constant $+200.6 \pm 0.3$ kJ mol^{-1}. The reaction enthalpies of the two 3-*n*-alkanones are also constant and only 1 kJ mol^{-1} more endothermic.

When the enthalpies of reaction between branched ketones and the corresponding 1,1-disubstituted alkenes are calculated using the multiple enthalpies of formation available for the latter, the following ranges are obtained: Me/*i*-Pr, 196.6 to 200.5; Et/*i*-Pr, 201.2 to 206.6; and Me/*t*-Bu, 200.5 to 205.1 kJ mol^{-1}. Perhaps it is reasonable to conclude that the reaction enthalpies for the branched compounds either will be approximately constant, as for the unbranched ketone/alkene conversions, or will be more endothermic with branching, as in the branched aldehyde/alkene conversions. In either case, the least endothermic reaction enthalpy for the Me/*i*-Pr conversion above seems inconsistent and therefore the enthalpies of formation for 2,3-dimethyl-1-butene from References 16 or 26, which are essentially identical, should be selected. These enthalpies were also selected in a previous section. However, there is too much inconstancy, as well as too much uncertainty, in the replacement reactions of carbonyls and olefins to be more definitive in our conclusions.

IX. ALICYCLIC KETONES

A. Monocyclic Ketones

We start with the unsubstituted cycloalkanones **(38)**, compounds of the generic formula cyclo-[$(CH_2)_{n-1}CO$]. The gas-phase enthalpies of formation of all of these species from n = 3 to 12, 15 and 17 are available from experiment. An obvious comparison is with the corresponding *n*-membered ring cycloalkanes, cyclo-[$(CH_2)_n$]. Consider equation 38 in which the difference quantity $\delta_{38}(n)$ is defined as the difference of the gas-phase enthalpies of formation of the ketone of interest and the related cycloalkane.

$$\delta_{38}(n) \equiv \Delta H_f^\circ(\text{cyclo-}[(CH_2)_n],\ \text{g}) - \Delta H_f^\circ(\text{cyclo-}[(CH_2)_{n-1}CO],\ \text{g}) \qquad (38)$$

The numerical values of the enthalpies of formation of the various cycloalkanones and the corresponding $\delta_{38}(n)$ values are found in Table 7.

The values of $\delta_{38}(n)$ almost all lie between 100 and 150 kJ mol^{-1}. The two exceptions to that are the n = 3 case, cyclopropanone, and the n = 17 case, cycloheptadecanone. That the first is deviant is consistent with the *ca* 50 kJ mol^{-1} general additional destabilization

(38)

TABLE 7. Enthalpies of formation of gaseous cycloalkanones and the corresponding values of $\delta_{38}(n)$

n	ΔH_f (g)	Reference	$\delta_{38}(n)$
3	16 ± 4	[a]	37 ± 4
4	-101.3 ± 1.3	[b]	129.7 ± 1.5
5	-194.8 ± 1.7	[b]	118.4 ± 1.9
6	-227.8 ± 1.9	[b]	104.4 ± 2.1
7	-248.1 ± 1.3	[b]	130.0 ± 1.6
8	-272.2 ± 1.8	[b]	147.8 ± 2.1
9	-279.7 ± 1.7	[b]	146.9 ± 2.3
10	-305.1 ± 1.9	[b]	150.8 ± 2.5
11	-322.0 ± 2.2	[b]	142.6 ± 2.8
12	-349.1 ± 2.3	[b]	118.9 ± 2.6
15	-414.5 ± 9.2	[c]	113.1 ± 9.4
17	-460.3 ± 10.9	[c]	96.0 ± 11.2

[a] See Reference 111 for cyclopropanone.
[b] See Reference 112 for the cycloalkanone data.
[c] See Pedley.

of three-membered rings upon introduction of a trigonal carbon[52]. This correction results in the value for the $\delta_{38}(n)$ of cyclopropanone to appear 'almost normal', and thereby legitimizes the enthalpy of formation as well despite its unconventional non-calorimetric, origin[113]. The $n = 17$ case is not sorely out of line, but we note that doubts have been raised about the accuracy of the measurement of the enthalpy of formation of the appropriate cycloalkane, cycloheptadecane[114]. Although the two outliers have now been tended to, no apparent pattern in the 100–150 kJ mol^{-1} difference quantity, $\delta_{38}(n)$, is to be found. Nonetheless, the cyclopropanone case aside, low values seem to accompany the most strain-free cycloalkanes, $n = 6$ and 17.

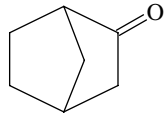
B. Bicyclic and Polycyclic Ketones

For these species, we consider the difference quantity δ_{39} which is defined as the difference of the gas-phase enthalpies of formation of the ketone of interest and the related hydrocarbon — there is no single parameter such as the ring size n to provide a conceptual framework. Letting $*$ denote the phase,

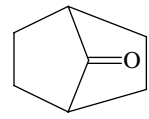
$$\delta_{39}(*) \equiv \Delta H_f^\circ(>CH_2, *) - \Delta H_f^\circ(>CO, *) \tag{39}$$

(If no phase is explicitly given, the reader is implicitly told that the data and the difference quantity are for the gas.)

We thus start with the smallest and simplest systems for which we have thermochemical data, the isomeric 2- and 7-bicyclo[2.2.1]heptanones (the norbornanones, **39a** and **39b**). Our intuition suggests that the latter species is more strained since the increased geometric constraints of a single-carbon bridge over those for a two-carbon bridge are



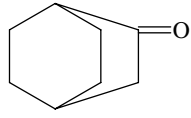
(39a)



(39b)

expected to be more sterically severe or destabilizing for a trigonal than tetrahedral carbon because of the larger endocyclic >C angle for the former[115]. This is realized by the enthalpy-of-formation data on these bicycloheptanones: the former ketone is more stable than the latter by 36.5 ± 5.8 kJ mol^{-1}. The enthalpy of formation for the single bicycloalkane which corresponds to both ketone isomers is -54.9 ± 4.7 kJ mol^{-1} from which we find δ_{39} values of 115.7 ± 6.8 and 79.2 ± 5.6 kJ mol^{-1}, respectively. Unlike the case for the monocyclic ketones, the smaller value of δ_{39} is found for the more strained ketone. This value is not merely 'smaller' — it is quite astonishing how small δ_{39} is for 7-bicyclo[2.2.1]heptanone when compared with any of the monocyclic ketones or its 2-isomer.

Consider now bicyclooctanones. Of the nine possible species, there are three for which the desired thermochemistry is available in the literature: bicyclo[2.2.2]octanone[116,117], and the *cis*- and *trans*-bicyclo[3.3.0]octan-2-ones, species **40a**, **40b** and **40c**, respectively. We find the following δ_{39} values: 119, 137.2 ± 5.3 and $140.1 \pm$



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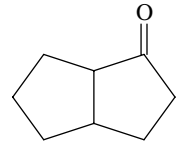
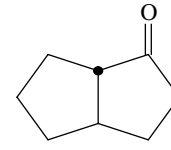
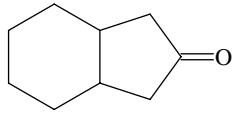


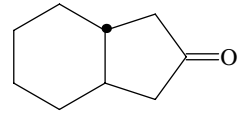
(40b)



(40c)



(41a)



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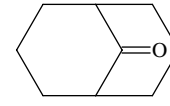
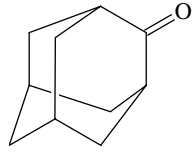


(41c)



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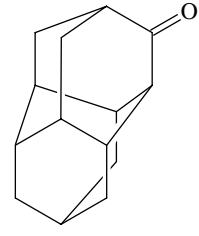


(43)

5.4 kJ mol^{-1}. Interestingly, the δ_{39} values for the two bicyclo[3.3.0]octanones are quite comparable despite the *ca* 25 kJ mol^{-1} difference in strain between these latter ketones.

Bicyclononanones are represented by *cis*- and *trans*-hexahydro-2-indanone, **41a** and **41b**, which like the above bicyclo[3.3.0]octan-2-ones are fused cyclopentanones. The values of δ_{39} are 122.5 ± 2.4 and 117.8 ± 2.7 kJ mol^{-1}. Another example is bicyclo[3.3.1]nonan-9-one[126] **(41c)**, for which δ_{39} equals *ca* 112 kJ mol^{-1}.

We now consider adamantanone **(42)** and diamantanone **(43)**. The two values of δ_{39} are rather close, 96.0 ± 5.1 and 90.6 ± 3.2, and both values are rather much smaller than for their monocyclic six-membered ring relative, cyclohexanone (104.4 ± 2.1 kJ mol^{-1}).

C. Comparison of Alicyclic Ketones and Their Methylene Analogs

Before commencing our comparison we now define the methylene analog of a ketone to be that species in which the >C=O of the former is replaced by the isoelectronic and isosteric >C=CH_2 group, the erstwhile Wittig reaction of a previous section. Starting with 1-ring species, it might have been thought that these methylenecycloalkanes (**18b**, now redrawn as **44**, cyclo-[$(CH_2)_{n-1}$C=CH_2]) would be good 'mimics' of the cycloalkanones. After all, they both have a trigonal carbon replacing a >CH_2 in the alicyclic cycloalkane ring. Consider now the difference quantity $\delta_{40}(n)$ which is defined as the difference of the gas-phase enthalpies of formation of the cycloalkanones and the related methylenecycloalkanes:

$$\delta_{40}(n) \equiv \Delta H_f^\circ[\text{cyclo-}[(CH_2)_{n-1}C{=}CH_2,\ g] - \Delta H_f^\circ(\text{cyclo-}[(CH_2)_{n-1}CO]),\ g] \quad (40)$$

(44)

The numerical values of the enthalpies of formation of the cycloalkanones and the corresponding $\delta_{40}(n)$ values are found in Table 8. Admittedly, the enthalpies of formation of the desired gas-phase methylenecycloalkanes are only available for $n = 3$–7. However, while the difference, $\delta_{40}(n)$, clusters between 200–220 kJ mol^{-1}, a pattern is disappointingly just as absent for the derived values of $\delta_{40}(n)$ as for those of $\delta_{38}(n)$.

The thermochemical data are likewise sparse for the methylene derivatives of the bicyclic and polycyclic ketones. For these species, we consider the difference quantity δ_{40} which is defined as the difference of the gas-phase enthalpies of formation of the ketone of interest and the related hydrocarbon:

$$\delta_{34} \equiv \Delta H_f^\circ(>C{=}CH_2,\ g) - \Delta H_f^\circ(>CO,\ g) \quad (41)$$

We thus start with the smallest and simplest systems. For bicyclo[2.2.1]heptan-7-one, δ_{41} is deduced to be 194.2 ± 3.8 kJ mol^{-1}. No immediate comparison from experiment is available for the -2-one and its methylene analog for the gas-phase enthalpy of formation of the latter species, 2-methylenebicyclo[2.2.1]heptane **(45a)**, remains unmeasured for want of the enthalpy of vaporization. We are not, however, particularly thwarted. From our standard enthalpy-of-vaporization protocol, we would predict a value of 40 kJ mol^{-1},

TABLE 8. Enthalpies of formation of gaseous cycloalkanones and the corresponding values of $\delta_{40}(n)$

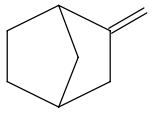
n	$\Delta H_f^\circ(g)$	Reference	δ_{40}
3	16 ± 4	[a]	184 ± 4
4	-101.3 ± 1.3	[b]	222.8 ± 1.5
5	-194.8 ± 1.7	[b]	206.8 ± 1.8
6	-227.8 ± 1.9	[b]	202.6 ± 4.3
7	-248.1 ± 1.3	[c]	210

[a] See Reference 111 for cyclopropanone.

[b] See Reference 112 for the cycloalkanone data.

[c] The enthalpy of formation of cycloheptanone was obtained from Reference 112. The enthalpy of formation of methylenecycloheptane was obtained by combining the directly measured enthalpy of hydrogenation (Reference 22) to form methylcycloheptane and the suggested gas-phase enthalpy of formation of this latter hydrocarbon from Reference 8.

nearly identical to that of the vaporization enthalpy for the 7-methylene isomer **(45b)** from the experimental literature. From this we deduce a value of 206 kJ mol^{-1} for δ_{41}. The δ_{41} value for methylenebicyclo[2.2.2]octane **(46)** is 213.0 ± 6.0 kJ mol^{-1}. No further comparison is now possible for there are no reported enthalpies of formation of the remaining methylene derivatives of any of the bicyclic or polycyclic ketones for comparison.



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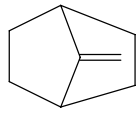

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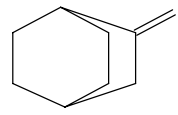
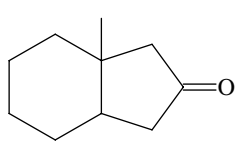


(46)

D. Methylated Cyclic Ketones

Ketones are a relatively common and widespread class of natural products: we recognize camphor, carvone, chlorophyll, cortisone, estrone, δ-ketolevulinic acid and testosterone as examples. We now discuss if there are any simple rules for estimating the enthalpies of formation of cyclic ketones upon methylation. There are problems as soon as we consider monocyclic species. Using solely liquid-phase data so as not to need estimates of enthalpies of vaporization, we find 2-methylation of cyclopentanone is accompanied by the enthalpy of formation becoming more negative by 29.9 ± 5.7 kJ mol^{-1} while the corresponding 2-methylation of cyclohexanone results in a change of but 17.9 ± 3.9 kJ mol^{-1}. *Trans*-hexahydro-2-indanone and its 8-methyl derivative **(47)** differ by 28.2 ± 2.7 kJ mol^{-1}. A difference of 25 kJ mol^{-1} allows for rough consistency between all three results. The enthalpy of formation changes upon methylating cyclopentane, cyclohexane and *trans*-decalin (on C_2) are 32.8 ± 1.1, 33.7 ± 1.3 and 34.3 ± 2.9 kJ mol^{-1}. Consistency is achieved with a difference of 34 kJ mol^{-1}. We are thus forced to conclude there is a *ca* 9 kJ mol^{-1} difference between the enthalpies of methylation of cyclic ketones and of cycloalkanes. Alternatively, it is more plausible that the reported enthalpy of formation of 2-methylcyclohexanone is in error. However, it is disturbing because this is a 'normal' compound that we would not have expected to be plagued by calorimetric complications.

Let us briefly consider camphor **(48)** and compare it with its 'nor' derivative, bicyclo[2.2.1]heptan-2-one that lacks its 1,7,7-trimethyl substitution. The enthalpies of



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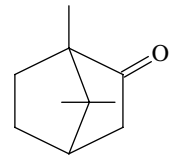


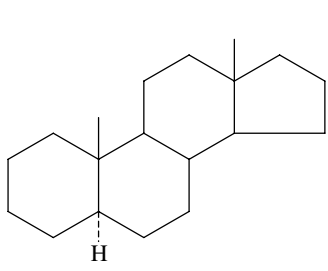
(48)

formation of both of these substances are available both as solids and gases. We want liquids here, and so need to correct either the solid- or gas-phase data. The latter is simpler: direct application of the logic in Reference 118 would suggest that the enthalpy of vaporization of their putative liquid forms would differ by the contribution of one non-quaternary carbon and two quaternary carbons, namely 7 kJ mol^{-1}. Accordingly, the difference of formation of the gas-phase compounds, 96.9 ± 5.6 kJ mol^{-1} 'favoring' the trimethylated species, gets amplified to *ca* 104 kJ mol^{-1} for the liquids. If it is assumed that introduction of the 1-methyl and the two 7-methyls into the 'nor' species corresponds to methylation of a ketone and a cycloalkane respectively, the difference would have been *ca* 93 kJ mol^{-1}. Given we have blithely ignored any strain incumbent on methylation, that the difference between the two values is but 11 kJ mol^{-1} is encouraging.

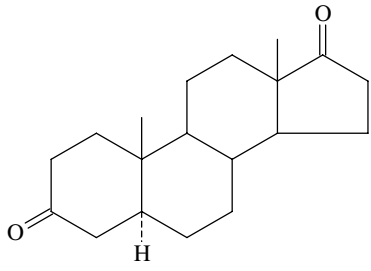
E. Solid Cyclic Ketones

What can be said about the thermochemistry of methylated cyclic ketones in any phase other than liquid? In that we would have discussed gas-phase species if the data were available, what we are really asking is: 'what can be said about the species of interest as solids?', Let us generalize this to see what can be said about the thermochemistry of cyclic ketones as solids. In that the cyclic ketones in the previous section were all formally quite strain-free derivatives of cyclopentanone or cyclohexanone, let us now consider only such species and their cycloalkane analogs. There are no enthalpy-of-fusion data available for cyclopentanone. For cyclohexanone, the temperature-uncorrected fusion enthalpy is about 1.3 kJ mol^{-1} — we arbitrarily ignore in this discussion enthalpies of any crystal → different crystal phase enthalpy. The same treatment for cyclohexane discloses the fusion enthalpy of 2.7 kJ mol^{-1}. Accordingly, the earlier reported value of $\delta_{38}(6) = 104.4$ for the gas phase is sequentially modified to *ca* 115 kJ mol^{-1} for the liquid and to 113 kJ mol^{-1} for the solid. For 2-norbornanone, adamantanone and diamantanone (**39a**, **42** and **43**), the gas-phase differences of 115.7 ± 6.8, 96.0 ± 5.1 and 90.6 ± 3.2 become for the solids 124.4 ± 6.8, 116.9 ± 4.5 and 97.8 ± 3.1 kJ mol^{-1}. Very roughly, δ_{39}(*) is some 10 kJ mol^{-1} more positive for solids than for gases and δ_{39}(s) is about 113 kJ mol^{-1} for all of the solids discussed here.

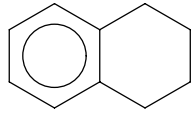
The above is such a coarse analysis that it may appear unlikely it could be of any use until it is remembered that many compounds of interest lack thermochemical data except as solids. Agreement with our suggested difference quantity suggests 'consistency' and 'plausibility'. Marked discrepancy from our suggested difference quantity suggests either error or a 'new phenomenon'. To illustrate this, consider the polycyclic hydrocarbon 5α-androstane **(49a)** and its 3,17-dione **49b**. The enthalpies of formation of both were reported nearly 30 years ago[119] and chronicled by Domalski, but ignored by Pedley. These values, −314 and −544 kJ mol^{-1} respectively, result in the normalized value (i.e. divided by the number of keto groups) of δ_{39}(s) of 115 kJ mol^{-1}. We thus conclude that these data are, at least, consistent and plausible. An example of the latter



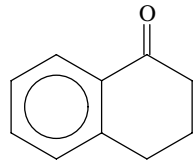
(49a)



(49b)



(50a)



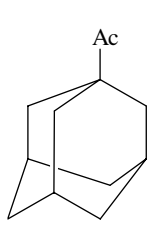
(50b)

involves tetralin **(50a)** and its 1-ketone **50b**. Combining the archival enthalpy of formation of the former as liquid and an uncorrected enthalpy of fusion results in ΔH_f° $(C_{10}H_{12},\ s) = -41\ kJ\,mol^{-1}$. The archival enthalpy of formation of solid tetralone is $-209.6 \pm 20.9\ kJ\,mol^{-1}$. This suggests $\delta_{39}(s)$ equals 160 $kJ\,mol^{-1}$, i.e. much more stabilization of the ketone relative to its corresponding hydrocarbon than expected. Something is either wrong and/or incomplete here. Could this additional stabilization arise from conjugation of the ketone with the benzene ring? Aromatic ketones are discussed elsewhere in this chapter.

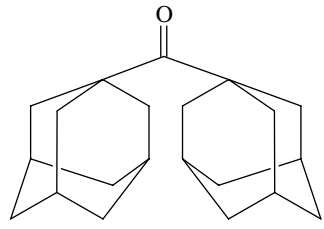
F. Adamantyl Ketones

In this section we are considering cyclic ketones in which the >CO group is not part of the ring. The two compounds of greatest interest here are 1-adamantyl methyl ketone[120] **(51a)** and bis(1-adamantyl)ketone[121] **(51b)** with their respective gas-phase enthalpies of formation of -298.3 ± 3.2 and $-367.8 \pm 5.0\ kJ\,mol^{-1}$. Abboud and coworkers[121] considered formal reaction 42

$$2RCOMe \longrightarrow RCOR + MeCOMe \qquad (42)$$



(51a)



(51b)

for both $R = {}^t$Bu and 1-Ad, and found for the latter group that it was *ca* 7 kJ mol^{-1} less endothermic. Equivalently, 1-admantyl appears to be a smaller group than *t*-butyl. Is this general? Let us define the adamantyl/*t*-butyl difference quantity

$$\delta_{43}(\text{X; 1-Ad, } {}^t\text{Bu}) \equiv \Delta H_f^\circ(\text{1-AdX, g}) - \Delta H_f^\circ({}^t\text{BuX, g}) \tag{43}$$

For X = 1/2(CO), this quantity equals 11.0 ± 2.6 kJ mol^{-1}: two 1-adamantyl groups repel each other less than two *t*-butyl groups. For the small X = H and Me, the difference all but vanishes, 0.4 ± 2.4 and 2.3 ± 2.9 kJ mol^{-1}. For the larger, and isoelectronic and essentially isosteric, X = COMe and $CONH_2$ (see Reference 121 for the latter compound), the differences are the comparable 7.6 ± 3.4 and 5.9 ± 2.8 kJ mol^{-1}. Larger groups need more room and so have greater steric interactions with other affixed groups. However, the largest X we will cite, $CONMe_2$ (see Reference 94), returns us to a vanishing value for δ_{43}, namely 0.0 ± 3.4 kJ mol^{-1}. It would be highly useful to have enthalpies of formation where X = COPr^i, where affixed to the carbonyl are large, but effectively electronically innocuous, groups.

X. CARBONYL COMPOUNDS WITH ARYL SUBSTITUENTS

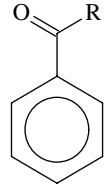
A. The Choice of Phase

The obvious answer is 'gas' based on the reasons given in the beginning of this chapter and those of our other thermochemical chapters. Yet, for almost all aromatic carbonyl compounds, the available enthalpy-of-formation data from the literature is only for the liquid. Rather than estimating enthalpies of vaporization for almost every compound discussed, we have decided to employ only liquid-phase data in the current section.

B. Alkyl Phenyl Ketones

As beginning examples of aromatic ketones, we discuss compounds with the generic formula, PhCOR (**52**) where R = H, Me, Et, ^{i}Pr and ^{t}Bu. The first comparison we will make with the PhCOR species is the difference between the enthalpies of formation of these compounds and MeCOR, δ_{44}(Ph, Me; R):

$$\delta_{44}(\text{Ph, Me; R}) \equiv \Delta H_f^\circ(\text{PhCOR, l}) - \Delta H_f^\circ(\text{MeCOR, l}) \tag{44}$$



(52)

For R = H, Me, Et, ^{i}Pr and ^{t}Bu, δ_{44}(Ph, Me; R) equals 104.8 ± 2.2, 105.6 ± 1.2, 106.1 ± 1.4, N.D. (no data) and 119.7 ± 2.4 kJ mol^{-1}. The first three numbers are essentially identical. That the last is some 14 kJ mol^{-1} larger attests to considerable repulsion between an α-methyl of the R = ^{t}Bu- group with the benzene ring. Accordingly, we 'roughly' define a universal $\delta_{44}(\text{Ph, Me}) \approx 106 \pm 2$ kJ mol^{-1}. Had the Me affixed to the carbonyl not been

so much smaller and/or so different from other hydrocarbyl groups, then the R = ^{t}Bu species might not have been such an outlier. Therefore, instead of contrasting the effects of Ph with those of Me, let us contrast those of Ph with ^{t}Bu instead. The related difference quantity δ_{45}(Ph, ^{t}Bu; R)

$$\delta_{45}(\text{Ph, }^t\text{Bu; R}) \equiv \Delta H_f^\circ(\text{PhCOR, l}) - \Delta H_f^\circ(^t\text{BuCOR, l}) \tag{45}$$

is very much more of a constant over the choice of R groups as seen from the values N.D., 186.1 ± 1.9, 188.9 ± 1.8, N.D. and 182.2 ± 2.6 from the same five R groups. Accordingly, we 'roughly' define a universal δ_{45}(Ph, ^{t}Bu) $\approx 186 \pm 2$ kJ mol^{-1}.

Consider now the following 'disproportionation' reaction involving benzophenone (**52**, R = Ph):

$$1/2[\text{RCOR} + \text{PhCOPh}] \longrightarrow \text{PhCOR} \tag{46}$$

For the R groups of interest, this reaction 46 is exothermic by N.D., 10.3 ± 0.8, 10.8 ± 0.9, N.D. and 5.2 ± 1.7 kJ mol^{-1}. A 'constant' value, δ_{46}(Ph) of 9 ± 2 kJ mol^{-1}, is 'roughly' consistent with all of the data.

Let us use the new δ quantities to make thermochemical estimates and fill in the above blanks and omissions in the data. To begin with, what do we find for the enthalpy of formation of isobutyrophenone, PhCOPr^i? From δ_{44}(Ph, Me) and ΔH_f°(MeCO^{i}Pr, l) = -299.4 ± 0.9 kJ mol^{-1}, we obtain ΔH_f°(PhCO^{i}Pr, l) ≈ -193 kJ mol^{-1} while from δ_{45}(Ph, ^{t}Bu) and $\Delta H_f^\circ(^t\text{BuCO}^i\text{Pr, l}) = -381.6 \pm 1.3$ kJ mol^{-1}, we obtain the nearly identical ΔH_f°(PhCO^{i}Pr, l) ≈ -196 kJ mol^{-1}. From δ_{46} and the liquid-phase enthalpies of formation of benzophenone[122] and i-Pr$_2$CO, -16.3 and -352.9 ± 1.2 kJ mol^{-1}, a value of -194 kJ mol^{-1} is found. We thus conclude ΔH_f°(PhCO^{i}Pr, l) $\approx -194 \pm 2$ kJ mol^{-1}. Relatedly, from δ_{45}(Ph, ^{t}Bu) and ΔH_f°(PhCHO, l) $= -87.0 \pm 2.1$ kJ mol^{-1} we obtain $\Delta H_f^\circ(^t\text{BuCHO, lq}) \approx -273$ kJ mol^{-1}. Finally, the use of the putative constant δ_{45} allows us to derive enthalpies of formation and vapourization of liquid formaldehyde to be *ca* -140 and -31 kJ mol^{-1}, respectively.

The above logic does not determine how much resonance stabilization there is for alkyl phenyl ketones but rather asserts that any additional stabilization is largely independent of the alkyl group flanking the carbonyl. We now present two admittedly contradictory analyses. The first notices that the location of the ketone hardly affects enthalpies of formation of acyclic ketones. At least, that is the case for 2- and 3-hexanone for which the former is more stable than the latter by 1.8 ± 1.4 kJ mol^{-1} for the liquid and 1.5 ± 1.4 kJ mol^{-1} for the gas. Likewise, the standard enthalpies of formation of 2- and 3-pentanone differ by 0.8 ± 1.3 and 1.1 ± 1.3 kJ mol^{-1} for the liquids and gases, respectively. By contrast, the non-conjugated phenylacetone is 15.3 ± 2.3 and 8.0 ± 3.6 kJ mol^{-1} less stable than its conjugated isomer, propiophenone, in the liquid and gas phases, respectively. That the location of the carbonyl group has such a dramatic effect on the enthalpy of formation for the alkyl phenyl ketones and essentially none for the aliphatic species is suggestive of the effects of conjugation. Furthermore, the enhanced enthalpy of vapourization of propiophenone over phenylacetone is suggestive of the importance of dipolar resonance structures.

However, an alternative probe of conjugation energy in alkyl phenyl ketones is to identify this additional stabilization with the exothermicity of reaction 47,

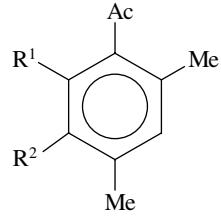
$$\text{PhCOR}^1 + \text{R}^2\text{CH}_2\text{R}^3 \longrightarrow \text{PhCH}_2\text{R}^1 + \text{R}^2\text{COR}^3 \tag{47}$$

For example, for R^1 = R^2 = Me and R^3 = Bu, we find reaction 47 to be endothermic by 4.0 ± 2.1 and 6.9 ± 1.9 kJ mol^{-1} for gaseous and liquid species, respectively. Both numbers

are small, and statistically can be equated. So doing suggests that the conjugation energy of interest is small and the importance of dipolar resonance structures quite negligible. On the other hand, that the value for the liquid can be considerably greater than for the gas suggests PhCOR may well be considerably more stabilized as liquid than the acyclic 2-hexanone.

C. Alkyl Acetophenones

There are two compounds in this category for which there are reported enthalpies of formation, the 2,4,5-trimethyl and the 2,4,6-trimethylacetophenone (**53a** and **53b**). From these data we may derive that the latter is more stable than the former in the liquid phase by 15.0 ± 5.2 kJ mol^{-1} and by 15.9 ± 5.9 kJ mol^{-1} as gases. That the difference is essentially independent of phase vindicates our decision above to use enthalpy-of-formation values in the liquid phase. But is the relative stability plausible? Consider replacing the COMe group by COOH in the above compounds. The difference of the gas-phase enthalpies of formation[123] of the related 2,4,5-trimethyl and 2,4,6-trimethylbenzoic acids is of comparable magnitude but with the opposite sign, -11.8 ± 1.8 kJ mol^{-1}. Save to suggest experimental error, we fail to understand why the relative isomer stabilities for trimethylacetophenones and trimethylbenzoic acids are so different[124].

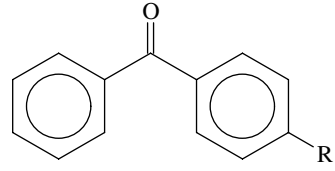


(53a) $R^1 = H$, $R^2 = Me$
(53b) $R^1 = Me$, $R^2 = H$

D. Alkyl Benzophenones

In this section, we will discuss compounds with the generic formula, $PhCOC_6H_4-p$-R **(54)** where R = H, Me, Et, ^{i}Pr and ^{t}Bu. For most of these compounds, the available enthalpy-of-formation data from the literature is only for the liquid. We have the same options as in the first subsection. The simplest difference quantity we can define is $\delta_{48}(PhCOC_6H_4, Ph; R)$,

$$\delta_{48}(PhCOC_6H_4, Ph; R) \equiv \Delta H_f^\circ(PhCOC_6H_4R, l) - \Delta H_f^\circ(PhR, l) \qquad (48)$$



(54)

where implicitly the substituent is on the 4-position of the benzophenone. The derived values are −65.3 (cf Pilcher and coworkers[131]), N.D., −52.0 ± 2.3, −77.5 ± 2.4 and −64.9 ± 2.5 kJ mol^{-1}. We fail to understand why these values are so un-constant given their small error bars, and thus we are very hesitant to assign any universal value for the related δ_{48}(PhCOC$_6$H$_4$, Ph).

XI. POLYCARBONYL COMPOUNDS

So far all of the discussion in this chapter has been devoted to the thermochemistry of compounds with one C=C double bond or one C=O double bond. What about compounds with more than one double bond? In fact, there have been 'Patai' volumes, and associated thermochemistry chapters, devoted to compounds containing at least one apiece of these types of double bonds[4] and to more than one C=C double bond[8]. We know of no such chapter and volume — published, in press or in preparation — that deals with compounds with more than one C=O double bond. The thermochemistry of such species is briefly discussed in this section.

We start with α-dicarbonyl compounds, R^{1}COCOR^2. Data are sparse: enthalpies of formation are seemingly limited to R^1 = R^2 = H, Me and Ph, and R^1 = Me, R^2 = H. It was recently noted[125] that the formal gas-phase reaction

$$R^1CHO + R^2CHO \longrightarrow R^1COCOR^2 + H_2 \qquad (49)$$

is very close to thermoneutral for the hydrogen and methyl cases. For these three sets of R groups above, this reaction 49 is endothermic by 5.2 ± 1.1, 5.1 ± 1.5 and 3.7 ± 4.8 (for R^1 = R^2 = H; R^1 = R^2 = Me; R^1 = Me, R^2 = H respectively). For the case with R^1 and R^2 both equal to phenyl, the endothermicity has increased to 17.9 ± 5.1 kJ mol^{-1}. This suggests considerable phenyl/carbonyl repulsion, and thus it would be useful to know the enthalpy of formation of the mixed R^1 = Ph, R^2 = H and Me compounds. What about for the liquid phase? The only compound for which all of the necessary data have been directly measured is R^1 = R^2 = Me. In this case, the endothermicity has increased to 17.8 ± 1.1 kJ mol^{-1} for the liquid! R^1 = R^2 = Ph, using a temperature-uncorrected enthalpy of fusion of the diketone, results in an endothermicity of 44 kJ mol^{-1}. And for the mixed Me, H case using the roughly estimated enthalpy of formation of liquid formaldehyde from a previous section, an endothermicity of 23 kJ mol^{-1} is found. These findings suggest that the enthalpy of vaporization of α-diketones is significantly reduced compared to monoketones — a conclusion suggested by the analysis in Reference 126, and that the near-additivity of the vapourization substituent constants for numerous −COX (see Reference 127) is sorely violated here. But is there any destabilization associated just with the adjacent carbonyl groups? To test this, by analogy with the question of the magnitude of stabilization[8] associated with adjacent carbon–carbon double bonds, one may consider the enthalpies of the formal gas phase reactions

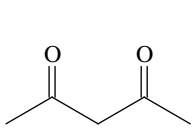
$$R^1COCH_2R^2 + R^1CH_2COR^2 \longrightarrow R^1COCOR^2 + R^1CH_2CH_2R^2 \qquad (50)$$

for the four cases of R^1 = R^2 = H, Me and Ph, and R^1 = Me, R^2 = H. These reactions 50 are endothermic by 36.4 ± 1.1, 24.7 ± 1.9, 43.3 ± 7.9 and 27.2 ± 4.9 kJ mol^{-1}. Indeed, all of these reactions are significantly endothermic — the diphenyl most of all — and so we may conclude that α-diketones are significantly destabilized.

What about β-diketones where we mean species that explicitly have the −CO−C−CO− substructure, and not the hydroxyenones[4] with the −C(OH)=CH−CO− substructure that usually 'answer to this name'. We now consider what is probably the best known of the

β-diketones, $MeCOCH_2COMe$, and resist calling it either acetylacetone or even pentane-2,4-dione[128]. Nonetheless, there are measurements[129] of the enthalpy of formation of this minority, as written[130], tautomer **55a** as well as **55b**. For the liquid and gas, the enthalpies of formation are -416.3 ± 1.1 and -374.4 ± 1.3 kJ mol^{-1}, respectively. To discern any destabilization associated with the two carbonyl groups being quite close, we consider the energetics of reaction 51 by analogy to the above reaction 50,

$$MeCOCH_2CH_2Me + MeCH_2CH_2COMe \longrightarrow MeCOCH_2COMe + MeCH_2CH_2CH_2Me \qquad (51)$$



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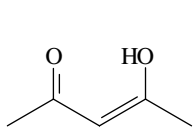
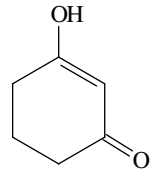
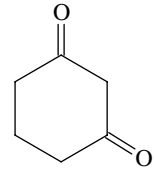


(55b)



(56a)



(56b)

Some amount of destabilization is seen, 4.8 ± 2.0 and 8.3 ± 2.1 kJ mol^{-1}, respectively, for the liquid and gaseous β-diketone. Not surprisingly, there is less destabilization for the β-diketone than for α-diketones.

Cyclohexane-1,3-dione is an interesting, but problematic, β-diketone. Calculational, (cited) spectroscopic and calorimetric studies[131] show that it exists as the hydroxyenone **56a** in the intermolecularly hydrogen-bonded solid and is most stable as the diketone **56b** in the gas. From the experimentally measured enthalpy of formation of this dione at -335.6 ± 1.6 kJ mol^{-1}, we find that reaction 52

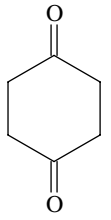
$$2[\text{cyclo-}(CH_2)_5CO] \longrightarrow [\text{cyclo-}(CH_2)_6] + \text{cyclo-}[1,3\text{-}(CH_2)_4(CO)_2] \qquad (52)$$

is exothermic by -6.8 ± 3.5 kJ mol^{-1}. We would have thought that this mimics the endothermic reaction 51 and fail to see any mechanism for stabilization of cyclohexane-1,3-dione. Let us now turn to the 4,4- and 5,5-dimethyl derivatives of cyclohexane-1,3-dione. Consider the 'transmethylation' reaction 53

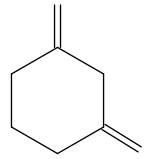
$$\text{cyclo-}[(CH_2)_5CMe_2] + \text{cyclo-}[1,3\text{-}(CH_2)_4(CO)_2] \longrightarrow [\text{cyclo-}(CH_2)_6] + \text{cyclo-}[x,x\text{-}CMe_2\text{-}1,3\text{-}(CH_2)_3(CO)_2] \qquad (53)$$

From measured enthalpies of formation, we find this reaction to be *exo*thermic by 7.3 ± 4.0 kJ mol^{-1} for the 4,4-dimethyl isomer and *endo*thermic by 9.5 ± 3.6 kJ mol^{-1} for its 5,5-isomer. Why the 4,4-isomer should be stabilized and the 5,5-isomer destabilized relative to the unmethylated diketone is enigmatic. So is the nearly 17 kJ mol^{-1} difference in their enthalpies of formation[132].

We now discuss γ-diketones. Pilcher and coworkers[131] show cyclohexane-1,4-dione **(57)** to have a gas-phase enthalpy of formation of -332.6 ± 1.2 kJ mol^{-1}, i.e. 3.0 ± 2.0 kJ mol^{-1} less stable than its 1,3-isomer. This, too, is quite inexplicable but is reproduced by their quantum chemical calculations, and by the relative stability of species **58a** and **58b**, the related bis-exomethylenecyclohexanes[133]. The only other γ-diketone for which we have enthalpy-of-formation data is solid 1,4-diphenylbutane-1,4-dione, **59**.



(57)



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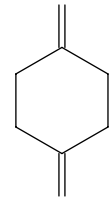

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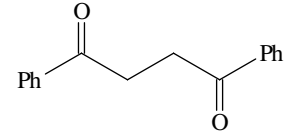

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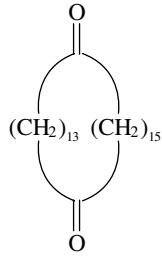
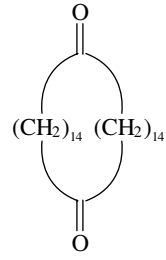


(60a)



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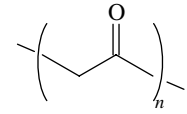


(61)

The difference between this value and solid 1,4-diphenylbutane is -122.8 ± 1.4 kJ mol^{-1}. This value is reasonable, especially given some aryl-ketone stabilizing interaction.

We now note the calorimetric measurements of the enthalpies of combustion of the isomeric 1,15- and 1,16-cyclotricontanediones (**60a** and **60b**, respectively) or, more precisely, a solid-phase mixture of the two[134]. From the reported values, we deduce that the formal dimerization reaction

$$2[\text{cyclo-}(CH_2)_{14}CO)] \longrightarrow \text{1,15- and 1,16-[cyclo-}(CH_2)_{28}(CO)_2] \qquad (54)$$

is exothermic by *ca* 10 kJ mol^{-1}. Given ambiguities as to the nature of the sample, and intrinsic complications of solids, the near-thermoneutrality is encouraging[135].

What about polyketones where poly means 3 or more? Experimental data are lacking. Nonetheless, the enthalpy of formation[136] of a putative gas-phase polymer [**61**, i.e. $(CH_2CO)_n$] was discussed from which a cumulative error — experimental, conceptual and calculational — of but 8 kJ mol^{-1} was found from that predicted assuming thermoneutrality for reaction 55

$$1/n[(CH_2CO)_n] + \text{MeCOMe} \longrightarrow \text{MeCOCH}_2\text{COMe} \qquad (55)$$

This suggests very little additional destabilization arising from an 'array' of β-diketones. Equivalently, there is insignificant enthalpic consequence of ε- or greater separation on the energetics of ketones, a finding consonant with the energetics of reaction 54.

XII. IMINES

A. Definition and Organization

By the word 'imine' we remind the reader that we mean a species containing at least one carbon–nitrogen double bond that is not part of an aromatic ring and attached only

to hydrocarbyl groups. We now proceed through the various imines that qualify by the aforementioned definition. Because the measurements of the enthalpies of formation of the various imines have involved so many distinct techniques and remain so confused and conflicted, the organizing principle of this section is one of increasing carbon number. Whenever possible, we will attempt retrospective cross-referencing, i.e. later compounds may refer to earlier ones. As such, the treatment of imines is perhaps relatively longer than anticipated. To date we lack rules and regularities for understanding these species that allow for sweeping generalities and/or edifying examples.

B. Methylenimine

We start with formally the simplest species, CH_2NH, which has been also been called formalidimine. Perhaps because it is the simplest imine, it has been studied by a variety of unconventional and non-calorimetric techniques. To illustrate the complexities we will devote more time and space than otherwise — yet, we are still unable to say from these experiments[137]: 'Formerly, it was confusing. Now it is not.' The first measurement[138] of its enthalpy of formation involved bracketing the energy of gas-phase hydride transfer to $HCNH^+$ and resulted in a value of 110 ± 13 kJ mol^{-1}. The next study[139] involved the ionization and appearance energies of CH_2NH relative to azetidine **(62a)**, thereby resulting in 88 ± 13 kJ mol^{-1}. From various radical and radical ion processes, the enthalpies of formation of the isomeric $CH_3NH\bullet$ and $CH_2NH_2\bullet$ were determined, and from the latter, that of CH_2NH was deduced[140] to be 105 ± 6 kJ mol^{-1}. In what was anticipated to be the simplest and most direct study[141], radical ion fragmentation from primary amine radical cations and proton transfer bracketing from $CH_2NH_2{}^+$ resulted in the dissonant value of 69 ± 8 kJ mol^{-1} being obtained. Finally, in a more accurately measured appearance energy reprise[142] of Reference 139 [and also using azetidine as well as the alternative precursor, propargylamine **(62b)**], a value of 82 ± 13 kJ mol^{-1} was reported. It is disconcerting that over a 40 kJ mol^{-1} range of values has been reported for the enthalpy of formation of CH_2NH. Is it perhaps too pessimistic to wonder what values would be obtained for most other gas-phase species if they were to be scrutinized as closely as this 5-atom molecule? Most of the species below have been studied but once and so such exquisite comparison and extensive doubts will not be exercised. It is too much an exercise in masochism to do so. We will be pleased with approximate self-consistency of the results.

(62a)

$HC{\equiv}CCH_2NH_2$

(62b)

C. Methylated Methylenimines

There are two isomers, CH_2NMe and MeCHNH. We know of but one measurement for the enthalpy of formation for the N-methylated isomer, that found in Reference 141, where a value of 44 ± 8 kJ mol^{-1} was reported. Even if we were to feign knowledge of CH_2NH, a simple estimation based on change of an N−H to an N−Me bond would be hard to achieve. The enthalpy-of-formation change going from $MeNH_2$ to Me_2NH is $+4.4 \pm 0.9$ kJ mol^{-1} while that from Me_2NH to Me_3N is -5.1 ± 1.0 kJ mol^{-1}. These are 'sp^3' nitrogens. What about 'sp^2' nitrogens? Admitting now that the enthalpy of formation of PhNHMe is uncertain — two values of 85 and 95 kJ mol^{-1} have been offerred[143] — the change from $PhNH_2$ to this secondary amine is either *ca* -2 or $+8$ kJ mol^{-1} and from

PhNHMe to $PhNMe_2$ is either *ca* +20 or +10 kJ mol^{-1}. We fail to reconcile or even rationalize the -25 ± 11 kJ mol^{-1} change reported elsewhere[144]. There are two values reported for the C-methylated isomer, MeCHNH, 24 ± 8[141] and 8 ± 17 kJ mol^{-1}[144] both from ion–molecule chemistry. These values, consistent with each other because of large error bars, are also consistent with the result in the beleagured Reference 141 for the parent CH_2NH. The -45 or so kJ mol^{-1} enthalpy-of-formation change on C-methylation of sp^2-containing CH_2NH to form MeCHNH sensibly interpolates the *ca* -61 and -24 kJ mol^{-1} changes for sp-containing HCN[9] and MeCN[145], and sp^3-containing $MeNH_2$ and $EtNH_2$, respectively.

D. Unsaturated Imines: Propenaldimine

The sole representative of this class of compounds for which there is an experimentally measured enthalpy of formation is $CH_2CHCH{=}NH$, alternatively called propenaldimine and vinylimine[146]. The literature value, 125 ± 11 kJ mol^{-1}, was obtained by measurement of the appearance energy for formation of its protonated ion from the radical cation of cyclopentylamine (reaction 56), and then bracketing experiments to deprotonate (reaction 57) this ion to the imine of interest.

$$\text{cyclo-}(CH_2)_4CHNH_2^{+\bullet} \longrightarrow C_2H_5\bullet + CH_2CHCHNH_2^{+} \tag{56}$$

$$CH_2CHCHNH_2^{+} + B \rightleftharpoons CH_2CHCHNH + BH^{+} \tag{57}$$

Is this 125 kJ mol^{-1} value plausible? In Reference 125 it is suggested that the reaction of two terminal olefins to form an unstrained conjugated diene is endothermic by *ca* 4 kJ mol^{-1}.

$$R^1CH{=}CH_2 + R^2CH{=}CH_2 \longrightarrow R^1CH{=}CHCH{=}CHR^2 + H_2 \tag{58}$$

while the reaction of a terminal olefin and formaldehyde to form an α,β-unsaturated aldehyde is exothermic by *ca* 10 kJ mol^{-1}

$$RCH{=}CH_2 + CH_2{=}O \longrightarrow RCH{=}CHCH{=}O \tag{59}$$

By interpolation, the reaction of a terminal olefin with methylenimine to form an unsaturated imine

$$RCH{=}CH_2 + CH_2{=}NH \longrightarrow RCH{=}CHCH{=}NH \tag{60}$$

will be exothermic by *ca* 3 kJ mol^{-1}. Accepting the literature value for propenaldimine suggests that $\Delta H_f^\circ(CH_2NH, g)$ equals 76 ± 11 kJ mol^{-1}, a value consistent with all of the above values because of the excruciatingly large error bars for all of the imine measurements.

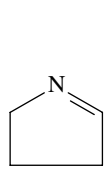
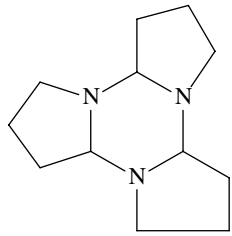
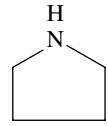
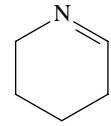
E. Cyclic Imines: 1-Azacyclopentene

The sole representative of this class of compounds for which there is an experimentally measured enthalpy of formation is species **63**, alternatively called 1-azacyclopentene and Δ^1-pyrroline[147]. The literature value, 64.0 ± 1.3 kJ mol^{-1}, was obtained by measurement of the enthalpy of hydrogenation of its trimer, **64a**, to form pyrrolidine **64b**

$$\mathbf{64a} + 3H_2 \longrightarrow 3[\mathbf{64b}] \tag{61}$$

and equilibration of that trimer with the imine

$$\mathbf{64a} \rightleftharpoons 3[\mathbf{63}] \tag{62}$$

(63) **(64a)** **(64b)** **(65)**

We would think that the following formal reactions are approximately thermoneutral:

$$MeCH{=}NH + CH_2NMe \longrightarrow MeCH{=}NMe + CH_2NH \quad (63)$$

$$MeCH{=}NMe + \text{cyclo-}[(CH_2)_3CH{=}CH] \longrightarrow MeCH{=}CHMe + 300 \quad (64)$$

Accepting the enthalpies of formation given by Jackman and Packam[150] for all three imines results in a value of 40 ± 14 kJ mol^{-1}, considerably lower than experiment[148]. In principle, clarification of this discrepancy could be achieved by related studies on other 1-azacycloalkenes. However, except for an unsuccessful attempt[148] for the corresponding 1-azacyclohexene (alternatively, Δ^1-piperideine or 3,4,5,6-tetrahydropyridine) **65** — its trimer fails to monomerize — we do not know of any such study.

F. 'Simple' Acyclic Aldimines

This class of compounds, generically $RCH{=}NR^1$, is surprisingly well-represented in the thermochemical literature although superficial reading does not appear to support this conclusion. For example, our archive presents but two enthalpies of combustion, both for $^{i}PrCH{=}NBu^{n}$, and having chosen the later one, results in an enthalpy of formation of the liquid imine[149] of -132.8 ± 3.4 kJ mol^{-1}. To convert the earlier value to that for the gas phase, we invoke a protocol for the enthalpy of vapourization (cf Reference 128) that extends our standard approach for hydrocarbons. We then assume that an imine nitrogen contributes the same as a pyridine nitrogen, i.e. 12.1 kJ mol^{-1}. The resulting gas-phase enthalpy of formation is *ca* -80 kJ mol^{-1} with a plausible ± 6 kJ mol^{-1} uncertainty.

Almost 40 years ago[150], the enthalpy of hydride transfer to a collection of N-substituted aldimines $R^1CH{=}NR^2$ was reported and compared with the reaction enthalpy of the same (complex metal) hydride with the corresponding amine $R^1CH_2NHR^2$; reactions 65 and 66, respectively.

$$R^1CH{=}NR^2 + \text{'}H^-\text{'} \longrightarrow R^1CH_2N^-R^2 \quad (65)$$

$$R^1CH_2NHR^2 + \text{'}H^-\text{'} \longrightarrow R^1CH_2N^-R^2 \quad (66)$$

From

(a) the difference of the measured hydride reaction numbers,

(b) group increment estimates of enthalpies of formation of product gaseous amines and

(c) the difference of the vapourization enthalpies for corresponding imines and amines [i.e. ΔH_v(imine) $-$ ΔH_v(amine)] set equal to 2.1 kJ mol^{-1},

the following gas-phase enthalpy of formation values were deduced[151]: $MeCH{=}NPr^{n}$, -5; $EtCH{=}NEt$, 0; $EtCH{=}NPr^{n}$, -34; $EtCH{=}NPr^{i}$, -40; $^{i}PrCH{=}NEt$, -31 kJ mol^{-1}. Alternatively, we may derive the quite similar values below by use of

(d) the difference of the measured hydride reaction numbers,

(e) the CH_2, NH enthalpy increment[143], $\delta(sec/R, R^1)$ [defined as $\Delta H_f^\circ(RCH_2R^1) - \Delta H_f^\circ(RNHR^1)$] and corrected for the types of alkyl groups in the amine and

(f) the difference of the vapourization enthalpies for corresponding imines and amines set equal to 3.3 kJ mol^{-1} as we had for the discussion of ^{i}PrCH=NBu^n.

The new numbers are −2, 3, −31[152], −37 and −30 kJ mol^{-1}, very similar to the earlier ones.

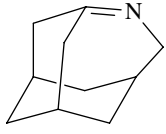
Some 20 years ago, a new set of reduction enthalpies of imines by catalytic hydrogenation was reported[153] but derived from direct solution-phase hydrogenation calorimetry: for MeCH=NPr^i, 91.6 ± 4.3; MeCH=NBu^t, 96.4 ± 5.9; ^{n}PrCH=NBu^n, 86.2 ± 2.6 kJ mol^{-1}. From the '(d), (e) and (f)' set of vapourization and amine enthalpy of formation assumptions, the enthalpies of formation of these new imines are −7, −41[154] and −65[155] kJ mol^{-1}, respectively. All of these values are roughly plausible. Although the *ca* 30 kJ mol^{-1} difference between the enthalpies of formation of MeCH=NPr^n and EtCH=NPr^n seems large, it is reproduced by the difference between MeCH=NPr^i and EtCH=NPr^i. The almost 50 kJ mol^{-1} difference between those of ^{i}PrCH=NEt and of ^{i}PrCH=NBu^n, and 15 kJ mol^{-1} between ^{n}PrCH=NBu^n and ^{i}PrCH=NBu^n seem large also, although they are 'almost' precedented by other pairs of ethyl vs butyl and isopropyl vs propyl differences[156].

G. Aliphatic and Alicyclic Ketimines

This class of compounds, $RR^1C{=}NR^2$, is much more poorly represented in the thermochemical literature. Only two species qualify, although the method of determination appears as general as it is novel. It is well-established that tertiary-alkyl azides, $RR^1R^2CN_3$, unambiguously photolyse to form aliphatic ketimines, reaction 67:

$$RR^1R^2CN_3 \longrightarrow RR^1C{=}NR^2 + N_2 \tag{67}$$

Photoacoustic calorimetry cleanly gives the enthalpy of rearrangement and thus knowledge of the enthalpy of formation of the azide gives the corresponding data for the imine[157]. The first species so characterized has all of the affixed alkyl groups equalling ethyl. The resulting enthalpy of formation for 3-pentanone ethylimine is −66 ± 20 kJ mol^{-1}. This number is seen to be plausible by comparing α-ethylation enthalpies of Et*CH*=CH_2 and Et*CH*=O with those of Et*CH*=NEt. The former two values are −56.1 ± 1.8 and −72.3 ± 1.2 kJ mol^{-1}. The last ethylation enthalpy is *ca* −66 kJ mol^{-1}, with conservatively 5 kJ mol^{-1} error bars. Nitrogen interpolates carbon and oxygen successfully. Imines interpolate, as might be expected, olefins and carbonyl compounds. The second compound relatedly is an alicyclic ketimine, the twisted, anti-Bredt, 4-azahomoadamant-3-ene **(66)**, with an enthalpy of formation of 121±13 kJ mol^{-1}. Disappointingly, thermochemical comparison cannot be made with the corresponding



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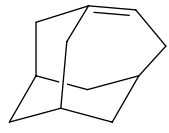
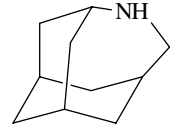


(67a)



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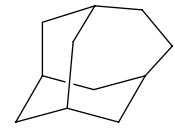
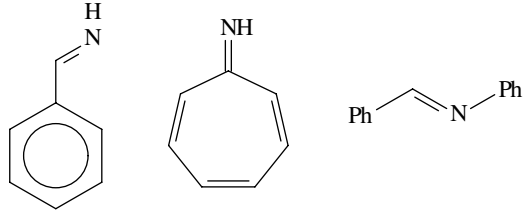


(67c)

olefin **(67a)**, saturated amine **(67b)** or even saturated carbocycle **(67c)**, for enthalpies of formation of any of these more conventional species have yet to be determined.

H. Aromatic Aldimines

There are but two members of this class of compounds that have been studied with explicit interest as to their enthalpies of formation[158]. The first is benzaldimine **(68a)**, studied by gas-phase ion–molecule reactions[141] for which the alternative possibility of troponimine **(68b)** was considered plausible. It is unequivocal that the enthalpy of formation of PhCHX is significantly more negative than that of cyclo-$(CH{=}CH)_3CX$ for both the archival X = O and the newly generated value of X = CH_2, cf Reference 8. X = NH is expected, as before, to interpolate the ketone and olefinic cases and so benzaldimine is most assuredly more stable than troponimine. However, this species was 'synthesized' by deprotonation of the corresponding cation and protonated troponimine is probably more stable than protonated benzaldimine[159]. If it is the former ion that was seen in Reference 141, simple deprotonation is not expected to yield benzaldimine.

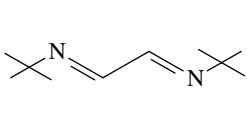


(68a) **(68b)** **(69)**

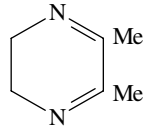
The second species is *N*-phenylbenzaldimine **(69)**, very commonly known as benzalaniline. Our archive cites an earlier study that resulted in an enthalpy of formation of 253.6 ± 7.4 kJ mol^{-1}, while more recently[160] a value of 278.7 ± 2.2 kJ mol^{-1} was reported. This result may be compared with earlier data. We earlier cited the enthalpy of formation of propenaldimine of *ca* 125 kJ mol^{-1}. We can employ the standard[86] *ca* 30 kJ mol^{-1} increase accompanying the transformation of ViX to PhX and so conclude the enthalpy of formation of benzaldimine is *ca* 155 kJ mol^{-1}. Or alternatively acknowledging unresolved difficulties with unsaturated and conjugating groups X[87], we may assume the same increase from $CH_2{=}CHCH{=}NH$ to $PhCH{=}NH$ as from $CH_2{=}CHCH{=}CH_2$ to $PhCH{=}CH_2$. This 'fine-tuning' will be assumed but needn't be made. This results in a value of *ca* 163 kJ mol^{-1}. Either way, as a result of N-phenylating benzaldimine, let us assume that the same increase of enthalpy of formation accompanies this process as from ethyl amine to EtNHPh, or *ca* 113 kJ mol^{-1}. We thus predict an enthalpy of formation of benzalaniline of 276 kJ mol^{-1}, essentially identical to the recently measured enthalpy of formation. The results and reasoning are both found to be credible and that is what we endeavoured to show.

I. Polyimines

The key question for such species is whether two imine groups will provide intramolecular stabilization or destabilization. There are three examples of these species for which there are relevant thermochemical data: **70a**, the conjugated glyoxal bisimine, ^{t}BuN=CHCH=NBu^t (see Reference 153); **70b**, the cyclic and likewise conjugated



(70a)



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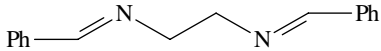
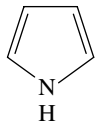


(70c)

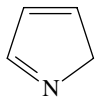
biacetyl bis-imine 2,3-dimethyl-5,6-dihydropyrazine (see Reference 153); and **70c**, the non-conjugated ethylenediamine bis-anil PhCH=N$(CH_2)_2$N=CHPh from our archive. The first two species were investigated using hydrogenation calorimetry, the last by combustion calorimetry. We wish to put all three species on a common footing with each other and preferably with the mono-imines earlier discussed. Enthalpies of hydrogenation would appear to be such an approach: after all, any stabilization energy of bis-imines is reflected in an enthalpy of hydrogenation smaller than twice that of a mono-imine, or *ca* $2 \times 90 = 180$ kJ mol^{-1}. The measured values for the first two species — without any phase-change correction — are 188.1 ± 1.6 and 169.4 kJ mol^{-1}, respectively. For conjugated bis-imines it would thus appear there is an effect of *ca* 0 ± 10 kJ mol^{-1}, suggestive of comparatively little stabilization. To investigate the last species it is necessary to estimate the enthalpy of formation of the saturated diamine *N*,*N*′-dibenzylethylenediamine, $PhCH_2NH(CH_2)_2NHCH_2Ph$. This may be facilely estimated by twice adding the δ(*sec*/*prim*, *prim*) methylene/amine increment of -73 kJ mol^{-1} from Reference 143 to the enthalpy of formation of $Ph(CH_2)_6Ph$ and deriving this by adding the enthalpy of formation of four strainless methylene groups to that of 1,2-diphenylethane. The enthalpy of formation of the saturated diamine is *ca* 205 kJ mol^{-1}. This corresponds, to an enthalpy of hydrogenation of the bis-imine of *ca* 150 kJ mol^{-1} or *ca* 30 kJ mol^{-1} stabilization. That the enthalpy of hydrogenation of the non-conjugated bis-imine is less than either of the conjugated species seems most unreasonable. However, it is then remembered that the same authors who investigated this bis-imine had erred by *ca* 30 kJ mol^{-1} for both benzalaniline and the alicyclic ^{i}PrCH=NBu^{n}. Assuming the same error results in the non-conjugated bis-imine lacking either stabilization or destabilization. We admit the numbers are not likely to be as precise as we have written them. Too many estimates have been made. However, the conclusion remains valid — there is but a small enthalpic consequence of the interaction of imines with other imines.

J. Unusual Tautomers

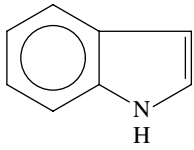
Numerous well-known nitrogenous heterocycles have unconventional tautomers that are formally imines: e.g. pyrrole and 2*H*-pyrrole (**71a** and **71b**), indole and 3*H*-indole (**72a** and **72b**), imidazole and 4*H*-imidazole (**73a** and **73b**), purine, 6*H*- and 8*H*-purine (**74a**, **74b** and **74c**). Of all of the diverse species we can posit, the only tautomeric imine we will discuss is 3*H*-indole. This is the last imine, indeed the last compound, that we will discuss in the current chapter. Generated[161] by photochemical reactions of both *N*-phenacyl-indolenine **(75a)** and of the parent heterocycle (**75b**, with added ketone), its aqueous-phase Gibbs energy of isomerization to the more conventional (1*H*)-indole is 33 ± 1 kJ mol^{-1}. If one presumes to equate Gibbs energies and enthalpies, and aqueous and gaseous media, then one may derive an enthalpy of formation of gaseous 3*H*-indole given the enthalpy of formation of the conventional 1*H*-indole tautomer. While both of these assumptions are unequivocally invalid, nonetheless they are simple and useful and a value of *ca* 190 kJ mol^{-1} was suggested. Additionally, this value was shown to be numerically



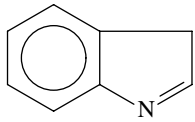
(71a)



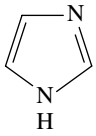
(71b)



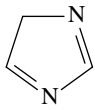
(72a)



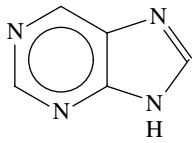
(72b)



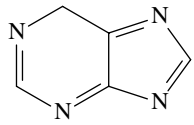
(73a)



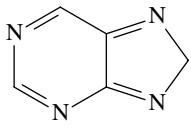
(73b)



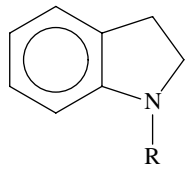
(74a)



(74b)



(74c)



(75a) R = $PhCOCH_2$
(75b) R = H

plausible by reproducing it within 15 kJ mol^{-1} upon assuming that thermoneutrality for the following reactions;

$$\text{indene} + \text{Py} \longrightarrow 3H\text{-indole} + \text{PhH} \tag{68}$$

$$\text{indene} + \text{PhCH=NPh} \longrightarrow 3H\text{-indole} + \text{PhCH=CHPh} \tag{69}$$

These equations are appealing, but suffer from the debits that both pyridine and benzalaniline have the imine group flanked by unsaturated carbon on both sides while 3*H*-indole is better described as a cyclic N-alkylbenzaldimine with unsaturated carbon only on one side of the imine functionality. In that the following reaction is thermoneutral to 2 kJ mol^{-1}:

$$\text{cyclo-}(CH)_4CH_2 + \text{indane} \longrightarrow \text{cyclo-}(CH)_2(CH_2)_3 + \text{indene} \tag{70}$$

we are optimistic that the following reaction is likewise essentially thermoneutral as well[162]:

$$\Delta^1\text{-pyrroline} + \text{indene} \longrightarrow \text{cyclo-}(CH)_2(CH_2)_3 + 3H\text{-indole} \tag{71}$$

This results in a predicted enthalpy of formation of 3*H*-indole of 193 kJ mol^{-1}. That this value is so close to that suggested in the literature gives credence to the enthalpies of formation of both 3*H*-indole and the earlier one cited above for Δ^1-pyrroline. We are encouraged[163].

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17. We will also occasionally take data from
    (a) E. S. Domalski, *J. Phys. Chem. Ref. Data*, **1**, 221 (1972).
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    These last three sources will usually be referred to as 'Domalski', 'Stull, Westrum and Sinke' and 'Kharasch', respectively.
18. Admittedly unreferenced phase-change enthalpies are taken from any of the following sources:
    (a) J. S. Chickos, in *Molecular Structure and Energetics, Vol. 2 (Physical Measurements)* (Eds. J. F. Liebman and A. Greenberg), VCH Publishers, Deerfield Beach, 1987.
    (b) W. E. Acree, *Thermochim. Acta*, **189**, 37 (1991); **219**, 97 (1993).
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43. The enthalpies of vapourization of interest found in Reference 16 and Reference 21 vary no more than 0.1 kJ mol^{-1}, except for the values for *cis*-2-hexene which differ by 0.7 kJ mol^{-1}. We chose $\Delta H_v = 32.2$ kJ mol^{-1} from the latter source.
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48. We have often wondered if there is a 'large enough' n_c such that equation 4 exhibits a break or curvature and the bond additivity changes within a homologous series to become essentially the same as for the n-alkanes. If such a change were to occur in the 2- and 3-n-alkenes at n_c *ca* 7–9, it might avoid the current conundrum of reversed stability order.

49. The enthalpy data for the 2-alkenes come from References 16, 21, 26 and 28. Where more than one enthalpy of formation for a compound is available a simple average is taken. The enthalpy data for the 1-alkenes are those specifically cited in the previous section.
50. The enthalpy of formation of 2,4-dimethyl-2-pentene from Reference 21 is less negative than that of 3,4-dimethyl-2-pentene and would be the only one of the three 1,1-dimethyl-2-alkyl ethenes to be less stable than its 1,2-dimethyl-2-alkyl isomer.
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66. We consider this plausible assumption somewhat suspect. Admitting ignorance as to the difference in solvation energies of the two cyclic olefins and the methylcycloalkane, we note that summing the enthalpies of hydrogenation and formation of liquid methylenecyclobutane results in a value of the enthalpy of formation of liquid methylcyclobutane of *ca* -29 kJ mol^{-1}, in marked contrast to the archival value of -44.5 ± 1.4 kJ mol^{-1}. The source of the discrepancy is not apparent.
67. N. L. Allinger, H. Dodziuk, D. W. Rogers and S. N. Naik, *Tetrahedron*, **38**, 1593 (1982).
68. Our further analysis of the enthalpy of formation of 2-methylbicyclo[2.2.1]heptene only worsens the disparity. That is, we find methylation of one doubly bonded carbon in gaseous cyclopropene, cyclopentene and cyclohexene is accompanied by a decrease in enthalpy of formation of 34, 38 and 38 kJ mol^{-1}, i.e. 36 ± 2 kJ mol^{-1}. The recommended enthalpy of formation of bicyclo[2.2.1]heptene (see Reference 60) is 90 kJ mol^{-1} and so we would predict an enthalpy of formation of its gaseous 2-methyl derivative of $90 - 36 \approx 54$ kJ mol^{-1}. Using our standard enthalpy of vapourization estimation protocol we would predict a phase-change enthalpy of 40 kJ mol^{-1} for this species, and so derive an enthalpy of formation of liquid 2-methylbicyclo[2.2.1]heptene of *ca* $54-40 \approx 15$ kJ mol^{-1}. That is, if anything, the exocyclic species is 'too' stable if we compare this derived value with 4.5 ± 1.8 kJ mol^{-1} derived from the available combustion calorimetric data.

That 2-methylenebicyclo[2.2.1]heptane and 2-methylbicyclo[2.2.1]heptene have the same carbon skeleton suggests some experiments that can directly give information as to their enthalpy-of-formation difference. The first suggested experiment is the measurement of hydrogenation to 2-methylbicyclo[2.2.1]heptane. On the assumption that the same *exo*/*endo* ratio is found and that the two olefins have the same enthalpy of solution, the difference of the enthalpies of hydrogenation equals the numerical negative of the enthalpies of formation. The second suggestion notes that deprotonation of both olefins yields the same carbanion: it is reasonable to assume that the two olefins have nearly identical enthalpies of solution here as well. Such a deprotonation study was performed on the isomeric 1- and 2-propenylbenzenes [E. Taskinen and N. Lindholm, *J. Phys. Org. Chem.*, **7**, 256 (1994)]. The last approach notes that protonation of both olefins gives the same carbocation. This would parallel the investigation of the thermochemistry of the acid-catalysed interconversion of 2-ethylbicyclo[2.2.2]oct-2-ene and 2-ethylidenebicyclo[2.2.2]octane [cf G. Van Binst and Y. Hera, *Tetrahedron Lett.*, 3897 (1967)] that showed the latter to be more stable by 5.4 ± 0.1 kJ mol^{-1}. Alternatively, measurement of the low-temperature solution phase reaction enthalpies of these olefins with HCl to form 2-chloro-2-methylbicyclo[2.2.1]heptane [cf E. M. Arnett and N. J. Pienta, *J. Am. Chem. Soc.*, **102**, 3329 (1980)] would allow for direct numerical determination of the difference of enthalpies of formation. Relatedly, and even more directly, is to measure the (gas phase) proton affinities of the two olefins. In principle, this should give us the numbers that are the most trustworthy to subtract. Both numbers are available [cf the archival review by S. G. Lias, J. F. Liebman and R. D. Levin, *J. Phys. Chem. Ref. Data*, **13**, 695 (1984)] but we are thwarted in our comparison because the necessary 'bracketing data', which are effectively calibration experiments, are lacking for the exocyclic isomer.

69. In turn, our archive shows that 3-methylcyclopentene has been reported to be 7.2 ± 2.1 kJ mol^{-1} more stable than the 4-isomer. Interestingly, hydrogenation calorimetry (cf Reference 67) shows the 1,3-isomer difference to be 14.1 kJ mol^{-1} but no data is available to compare the 3- and 4-isomers. We also note that 1-methylcyclohexene (as liquid) is found to be 6 ± 4 kJ mol^{-1} more stable than its 4-isomer as shown by the archival enthalpy of formation of the former and the measurement of B. Lebedev and H. Smirnova, *Macromol. Chem. Phys.*, **195**, 35 (1994).
70. W. R. Maier and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **103**, 1891 (1981); A. B. McEwen and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **108**, 3951 (1986).
71. Z.-H. Li and M. Jones, Jr., *Tetrahedron Lett.*, **28**, 752 (1987).
72. P. M. Warner, *Chem. Rev.*, **89**, 1067 (1989).
73. D. W. Rogers and F. J. McLafferty, *Tetrahedron*, **27**, 3765 (1971). In particular, the enthalpy of hydrogenation of 1,2-dimethylcyclopropene is *ca* 180 kJ mol^{-1}, a value considerably higher than the acyclic tetrasubstituted paradigm. We recall that cyclopropanes with trigonal carbons are additionally strained beyond that of the saturated ring (cf Reference 7), and so that this enthalpy of hydrogenation is large is not particularly surprising. Indeed, the value for 1,2-dimethylcyclopropene is quite small compared to the *ca* 220 kJ mol^{-1} for both the parent and 1-monomethylated cyclopropene that we derive from the data in Reference 57.
74. The reader may wonder why we did not present the energetics of reaction 14 in the text for the currently discussed $n = 4$ case. We acknowledge that we do not know the precise *cis*/*trans* composition of the resulting 1,2-dimethylcyclobutane but the difference of the enthalpies of these isomers is expected to be less than 10 kJ mol^{-1} by analogy with other dimethylcycloalkanes. As probed by the deviation from thermoneutrality for the reaction 2 cyclo-[$(CH_2)_{n-1}$CHMe] $\rightarrow$ cyclo-[1,2-$(CH_2)_2(CHMe)_{n-2}$] + cyclo-[$(CH_2)_n$] for other cycloalkanes (*ca* 6 ± 6 kJ mol^{-1} endothermic), steric repulsion is expected to be small. The enthalpy of formation of 1,2-dimethylcyclobutane is achievable from that of the parent and monomethylated cyclobutanes. Experimentally measured enthalpy-of-formation data for methylcyclobutane is limited to that of the liquid, but our estimation protocol for enthalpies of vapourization easily ameliorates that deficiency. From all of the above data and assumptions, we derive enthalpies of formation of gaseous 1,2-dimethylcyclobutane and 1,2-dimethylcyclobutene to be *ca* -60 and 50 kJ mol^{-1}, respectively. Accordingly, we find the desired reaction energy to be *ca* 50 kJ mol^{-1} endothermic. This value makes little sense — the origin of the very large deviation from thermoneutrality evades us.
75. Although the data are from the recent source, Allinger and coworkers[67], the reader may still be bothered by results for hydrogenation in different solvents being discussed in this section. There are two reasons for our policy. The first is that we lack the exquisite collection of species that

characterized our discussion of the acyclic alkenes in an earlier section. The second is that within an admittedly greater tolerance for discrepancies, the differences are seemingly quite small: recall our earlier discussion of the monosubstituted 1-methylcyclopentene and methylenecyclopentene.
76. P. K. Chou and S. R. Kass, *J. Am. Chem. Soc.*, **113**, 697 (1991).
77. W. J. Hehre and J. A. Pople, *J. Am. Chem. Soc.*, **97**, 6941 (1975). This olefinic non-planarity of derivatives of **35** is quite general; cf W. T. Borden, *Chem. Rev.*, **89**, 1095 (1989).
78. The reader is reminded of the suggested interpolation of norbornyne between cyclobutyne and cyclopentyne discussed in Greenberg and Liebman[53].
79. The origins of the 9 kJ mol^{-1} error and the much larger discrepancy between the two literature results is not obvious. However, we do note that for both naphthalene and 1,2,3,4-tetrahydronaphthalene, much better known hydrocarbons with the same carbon skeleton as the $m = n = 4$ species, our primary archive cites alternative enthalpy-of-formation measurements that deviate by *ca* 10 and 40 kJ mol^{-1} from those recommended by this source.
80. P. D. Staneke, S. Ingemann, P. Eaton, N. M. M. Nibbering and S. R. Kass, *J. Am. Chem. Soc.*, **116**, 6445 (1994).
81. Our analysis accepts the archival enthalpy of formation of cubane, although we admit there is some 40 kJ mol^{-1} disagreement over this value; see D. R. Kirklin, K. L. Churney and E. S. Domalski, *J. Chem. Thermodyn.*, **21**, 1105 (1989).
82. An example of the problem with species with multiple four-membered rings is seen in the inorganic chemical literature involving −P< in lieu of −CH<. The standard form of elemental phosphorus is P_4 with 60° P−P−P angles. Trivalent phosphorus 'enjoys' angles of somewhat over 90°. So, why is cubic P_8 with P−P−P angles of 90° less stable than P_4? Theorists have found this last question of considerable interest. See the nearly contemporaneous papers:
(a) M. W. Schmidt and M. S. Gordon, *Inorg. Chem.*, **24**, 4503 (1985).
(b) G. Trinquier, J.-P. Daudey and N. Komiha, *J. Am. Chem. Soc.*, **107**, 7210 (1985).
(c) R. Alrichs, S. Brode and C. Ehrhardt, *J. Am. Chem. Soc.*, **107**, 7260 (1985).
(d) K. Raghavachari, R. C. Haddon and J. S. Binkley, *Chem. Phys. Lett.*, **122**, 219 (1985).
83. J. Kiplinger, F. R. Tollens, A. G. Marshall, T. Kobayashi, D. R. Lagerwall, L. A. Paquette and J. E. Bartmess, *J. Am. Chem. Soc.*, **111**, 6915 (1989).
84. The standard enthalpy of formation of dodecahedrane remains unmeasured. However, standard enthalpies of formation of a bis-carbomethoxy derivative of the isomeric pagodane, and pagodane are available in the literature: H.-D. Beckhaus, C. Rüchardt, D. R. Lagerwall, L. A. Paquette, F. Wahl and H. Prinzbach, *J. Am. Chem. Soc.*, **116**, 11775 (1994), from which these authors suggested a value of 94 ± 5 kJ mol^{-1} for the desired quantity.
85. This problem does not arise in the cubene study because one can transform the 'proper' or 'directly synthesized' product 'all-*syn*'-tetracyclo[4.4.0.0^{2,5}.0^{7,10}]deca-3,8-diene, species **28**, to its all-*anti*-isomer without particularly compromising our model. No such option exists for the 'decacyclodocosadiene' product that would be formed from the related, formal dodecahedrene/ethylene reaction.
86. (a) J. F. Liebman, in *Molecular Structure and Energetics: Studies of Organic Molecules* (Eds. J. F. Liebman and A. Greenberg), VCH, Deerfield Beach, 1986.
(b) P. George, C. W. Bock and M. Trachtman, in *Molecular Structure and Energetics: Biophysical Aspects* (Eds. J. F. Liebman and A. Greenberg), VCH, New York, 1987.
87. Y.-R. Luo and J. L. Holmes, *J. Phys. Chem.*, **96**, 568 (1992) and *J. Phys. Org. Chem.*, **7**, 403 (1994).
88. From the tables of recommended values in Pedley, we find gaseous (*E*)-1,2-diphenylethylene 16.2 ± 2.6 kJ mol^{-1} more stable than its (*Z*)-isomer, while E. L. Eliel and J. J. Engelsman, *J. Chem. Educ.*, in press, recommend a difference of 22.8 ± 2.8 kJ mol^{-1}. These values are not altogether that different. However, it is quite seemingly accidental that these values are as close as they are because the recommended enthalpies of sublimation of the (*E*)-isomer differ by nearly 13 kJ mol^{-1} in the two sources while individually professing error bars less than 0.5 kJ mol^{-1}.
89. Furthermore, given the phenyl/vinyl comparison, we also note interesting features of the energetics of cross-conjugated vs conjugated 2-vinylbutadiene and 1,3,5-hexatriene (see Reference 8).
90. S. E. Stein, D. M. Golden and S. W. Benson, *J. Phys. Chem.*, **81**, 314 (1977).
91. We have enthalpy-of-formation data for both 1,1- and (*Z*)-1,2-bis(*p*-tolyl)ethylene as solids. What is lacking are the corresponding data for the diphenylethylenes, or equally useful, the enthalpies of fusion of these two hydrocarbons.

92. The values for the enthalpies of formation of solid benzene and toluene were obtained by summing the archival enthalpies of formation of the liquid hydrocarbons and temperature-uncorrected enthalpies of fusion.
93. Nonetheless, we are troubled because we fail to understand or even reconcile the following:
(a) the enthalpy of formation of solid (*E*)-1,2-bis(*p*-tolyl)ethylene is *ca* 17 kJ mol^{-1} lower than that of its solid (*E*)-1,2-bis(*o*-tolyl)ethylene isomer,
(b) the enthalpy of formation of solid (*Z*)-1,2-bis(*p*-tolyl)ethylene is *ca* 12 kJ mol^{-1} higher than that of its solid (*Z*)-1,2-bis(*o*-tolyl)ethylene isomer.
94. J.-L. Abboud, P. Jiménez, M. V. Roux, C. Turrión, C. Lopez-Mardomingo, A. D. Pododensin, D. W. Rogers and J. F. Liebman, *J. Phys. Org. Chem.*, **8**, 15 (1995).
95. This is not the precise value for the hydrogenation enthalpy as reported by Abboud and coworkers[94], 105.9 ± 1.2 kJ mol^{-1}, but, as indicated above in the text, a composite value was used to generate the enthalpy of formation of the unsaturated hydrocarbon. As such, the hydrogenation enthalpy employed here was the difference of the suggested enthalpy of formation of (*E*)-1-phenylpropene from this source and the archival value for propylbenzene.
96. It is interesting to note that the archival enthalpies of formation of 1,2- and 1,4-dihydronaphthalene differ by 12.7 ± 2.3 kJ mol^{-1} and those of their 1-ring 'de-benzoated' counterparts 1,3- and 1,4-cyclohexadiene have been suggested to be nearly identical (see Reference 8).
97. An interesting test of our logic relates to phenanthrene and its 9,10-dihydro derivative. Phenanthrene is occasionally described as having two benzenoid rings and that its 9,10-bond is almost a localized double bond. If this were an accurate description, then phenanthrene could be considered a cyclic styrene. From S. H. Lee-Bechtold, I. A. Hossenlopp. D. W. Scott, A. G. Osborn and W. D. Good, *J. Chem. Thermodyn.*, **11**, 469 (1979), we find the enthalpy of gas-phase 9,10-dihydrophenanthrene is 155.2 kJ mol^{-1}, while from our primary thermochemical archive, that of phenanthrene is 207.5 ± 1.7 kJ mol^{-1}. The hydrogenation enthalpy is thus *ca* 52 kJ mol^{-1}, less than for styrene and the above cyclic analogs, so that we conclude phenanthrene is not a 'cyclic styrene', but a three-ring aromatic species.
98. For example, consider hydrogenation enthalpies. Besides the multi-ring species just discussed, our analysis also includes the variously phenylated and tolylated ethylenes presented in the beginning of this section.
99. One might have thought that phenylcyclohexene might be contaminated by polymer and/or biphenyl, both formed by free-radical processes. In both cases, the apparent dehydrogenation enthalpy would be smaller, not larger, than for the alkylcyclohexenes.
100. See Reference 4 for enthalpies of formation of other oxygen-containing compounds.
101. For comparison, the regression equations for the ethers are:

$$\Delta H_f(n\text{-ROMe, g}) = -20.57n_c - 155.3 \text{ and } \Delta H_f(n\text{-R}_2\text{O, g}) = -20.34n_c - 170.8.$$

102. The alkene data are the same as used in previous sections of this work.
103. Enthalpies of isomerization of small alkyl groups are roughly related to the electronegativity of the attached functional group: the more electronegative the group, the larger the enthalpy of isomerization. See, for example, K. Wiberg, *J. Org. Chem.*, **56**, 544 (1991); Y-R. Luo and S. W. Benson, *J. Am. Chem. Soc.*, **111**, 2480 (1989).
104. The secondary branching effect in ethers is nearly additive: $\Delta H_{isom}[n\text{-PrOMe} \rightarrow i\text{-PrOMe}] = -13.8$ kJ mol^{-1}; $\Delta H_{isom}[n\text{-Pr}_2\text{O} \rightarrow i\text{-Pr}_2\text{O}] = -26.3$ kJ mol^{-1}, and $\Delta H_{isom}[n\text{-Bu}_2\text{O} \rightarrow sec\text{-Bu}_2\text{O}] = -27.5$ kJ mol^{-1}.
105. The enthalpies of hydrolysis of alkyl-substituted dimethyl acetals and ketals are reported in K. B. Wiberg and R. R. Squires, *J. Am. Chem. Soc.*, **103**, 4473 (1981).
106. The hydration of carbonyl compounds, along with hemiketal and ketal or hemicacetal and acetal formation, were studied in K. B. Wiberg, K. M. Morgan and H. Maltz, *J. Am. Chem. Soc.*, **116**, 11067 (1994).
107. The enthalpy of formation for liquid and gaseous 2-pentanol[16] is probably incorrect by about 2 kJ mol^{-1} as shown by a plot of equation 4. More reliable values, −367.1±0.8 (l) and −314.6± 1.5 kJ mol^{-1} (g), are found in Cox and Pilcher[20]
108. The regression analysis of equation 4b for the 1,1-dimethoxyalkanes is (kJ mol^{-1}):

$$\Delta H_f(n\text{-RC(OMe)}_2\text{H, l}) = -24.28n_c - 322.8.$$

109. The regression analysis of equation 4b for the 2,2-dimethoxyalkanes is (kJ mol^{-1}):

$$\Delta H_f(n\text{-RC(OMe)}_2\text{CH}_3, \text{l}) = -24.14n_c - 340.2.$$

110. The enthalpy of formation of 2-hexanone was estimated from Table 4. The enthalpy of formation of 2,2-dimethoxyhexane was estimated from Reference 109.
111. The enthalpy of formation of cyclopropanone, $n = 2$, is taken as that suggested by Liebman and Greenberg[56], accepting the analysis of the appearance energy threshold ion measurements of the fragmentation of cyclopropanone radical cation into ethylene radical cation + carbon monoxide, H. J. Rodrigues, J.-C. Chang and T. F. Thomas, *J. Am. Chem. Soc.*, **98**, 2027 (1976), but using more recent ancillary data.
112. G. Wolf, *Helv. Chim. Acta*, **55**, 1446 (1972). We have chosen the enthalpies of formation of the $n = 5-8$ cycloalkanones from this source, rather than from the archival value by Pedley, so as to provide a greater uniformity of origin for the chosen data. In any case, that the values are the same within the proferred error bars suggests little difference will arise by using the data from either source. For the same reason of uniformity of data, we have also chosen the value for the $n = 4$ species from Wolf rather than from J. Roček and A. E. Radkowsky, *J. Am. Chem. Soc.*, **95**, 7123 (1973), or by estimating it by assuming that the following reaction is thermoneutral:

$$\text{PhCH(CH}_2)_2\text{CO} + \text{C}_3\text{H}_8 \longrightarrow \text{PhPr-i} + (\text{CH}_2)_3\text{CO}$$

using the phenylcyclobutanone data from R. R. Krall and J. D. Roberts, *Am. Chem. Soc., Div. Petr. Chem. Symp.*, B-63 (1958). In both of the latter cases, a nearly 10 kJ mol^{-1} discrepancy is incurred relative to Wolf's data.
113. Reference 111 employed ionization and appearance energy measurements, and not the 'conventional' combustion- or solution-phase reaction calorimetry used to obtain most enthalpies of formation reported in the literature.
114. Prof. Ernest L. Eliel, personal communication to the authors.
115. It is not obvious how to deconvolute the above reasoning with one that considers the 7-isomer as having the carbonyl part of a 5-membered ring and the 2-isomer as having it part of a less strained 6-membered ring.
116. P. Müller, J. Blanc and D. Lenoir, *Helv. Chim. Acta*, **65**, 1212 (1982) cite an unpublished gas-phase enthalpy of formation of this species.
117. We note the earlier paper by Becker and Roth[65] that presented a value for bicyclo[2.2.2]octanone (herein named *endo*-ethylenecyclohexanone) that differed from the just-cited more recent one[116] by *ca* 4 kJ mol^{-1}.
118. J. S. Chickos, D. G. Hesse, J. F. Liebman and S. Y. Panshin, *J. Org. Chem.*, **54**, 3424 (1988).
119. D. Paoli, J.-C. Garrigues and H. Patin, *Compt. Rend.*, **C268**, 780 (1969).
120. J.-L. M. Abboud, P. Jiménez, M. V. Roux, C. Turrión, C. Lopez-Mardomingo and G. Sanz, *J. Chem. Thermodyn.*, **24**, 217 (1992).
121. J.-L. M. Abboud, P. Jiménez, M. V. Roux, C. Turrión and C. Lopez-Mardomingo, *J. Chem. Thermodyn.*, **21**, 859 (1989).
122. This value was obtained by summing the temperature-uncorrected enthalpy of fusion of benzophenone and the archival enthalpy of formation of the solid.
123. We use here the gas-phase data of M. Colomina, P. Jiménez, M. V. Roux and C. Turrión, *J. Chem. Thermodyn.*, **19**, 1139 (1987), although the difference for the standard enthalpies of formation of the solid trimethylbenzoic acids is again in the reverse direction to that of the acetophenones, 17.8 ± 1.6 kJ mol^{-1}.
124. What adds to our suspicion is that the steric effect of Me and COOH in substituted benzenes are so comparable: M. Colomina, C. Turrión, P. Jiménez, M. V. Roux and J. F. Liebman, *Struct. Chem.*, **5**, 141 (1994). It seems very unlikely that the steric effects of COMe and COOH could be that different.
125. J. F. Liebman, *Struct. Chem.*, **3**, 449 (1992).
126. J. S. Chickos, D. G. Hesse and J. F. Liebman, *J. Org. Chem.*, **54**, 5250 (1989).
127. We recall the use of the substituent constants for the relevant >CO and X groups from the preceding reference for generating near-additivity for enthalpies of vapourization of many other types of −COX species, J. F. Liebman and J. S. Chickos, *Struct. Chem.*, **1**, 501 (1990).
128. We note that even *Chemical Abstracts* persists in calling the intramolecularly hydrogen-bonded isomer $CH_3C(OH)=CHCOCH_3$ pentane-2,4-dione and leaves the diketone compound of interest in the current context without a name or even a registry number.

129. J. M. Hacking and G. Pilcher, *J. Chem. Thermodyn.*, **11**, 1015 (1979).
130. H. Y. Afeefy and J. F. Liebman, unpublished analysis, find it useful to affix to the name حق (derived from the Arabic حقيقى meaning 'as it is written' or else the transliterated Km from 'K'makotep').
131. G. Pilcher, O. G. Parchment, I. H. Hillier, F. Heatley, D. Fletcher, M. A. V. Ribeiro da Silva, M. L. C. C. H. Ferrão, M. J. S. Monte and F. Jiye, *J. Phys. Chem.*, **97**, 243 (1993).
132. Our ignorance is only compounded when the keto and enol groups are stripped off and a comparison is made between the enthalpies of formation of 3,3- and 4,4-dimethylcyclohexene. Pilcher and coworkers[131] chronicle that the former has a higher enthalpy of hydrogenation than the latter by but 4.6 kJ mol^{-1}. In that the solvent was the same for both measurements (glacial AcOH) and that the product is the same (1,1-dimethylcyclohexane), we have lost a plausible 'excuse' for the difference of stability of the isomeric dimethylcyclohexane-1,3-diones. Furthermore, the difference of hydrogenation enthalpies between either dimethylcyclohexene and that of cyclohexene in this medium is only 3 kJ mol^{-1}. The profound lack of thermoneutrality of reactions 53 remains disconcerting.
133. Note, as discussed in Reference 8, 1,3-dimethylenecyclohexane is some 10 kJ mol^{-1} more stable than its 1,4-isomer. The 1,3- and 1,4-dimethylene compounds are stabilized relative to the monomethylene compound by 19 and 9 kJ mol^{-1}, respectively, while the corresponding diketones are stabilized relative to the monoketone by some 7 and 4 kJ mol^{-1}. These results are consonant with the 1,3-bis-sp^2 cyclohexanes being more stabilized than their 1,4-counterpart, but electrostatic destabilization affecting the β-diketone and not particularly the bismethylene compound.
134. L. Ruzicka and P. Schläpter, *Helv. Chim. Acta*, **16**, 162 (1933).
135. We must admit, however, that the corresponding formal solid-phase dimerization reaction of cyclopentadecane to cyclotriacontane shows no such near-thermoneutrality, suggestive of unenunciated complications with the study of these large rings.
136. J. F. Liebman, in *Fluorine-containing Molecules: Structure, Reactivity, Synthesis and Applications* (Eds. J. F. Liebman, A. Greenberg and W. R. Dolbier, Jr.), VCH, New York, 1988.
137. B. J. Smith, J. A. Pople, L. A. Curtiss and L. Radom, *Aust. J. Chem.*, **34**, 285 (1992), using calculational theory at the G2 level, provide what has been taken to be a definitive answer, 86 ± 10 kJ mol^{-1}. As an example of such enthusiasm applied to more generally substituted, and thus more complicated imines, see M. B. Seasholtz, T. B. Thompson and N. G. Rondan, *J. Phys. Chem.*, **99**, 17838 (1995).
138. D. J. DeFrees and W. J. Hehre, *J. Phys. Chem.*, **82**, 391 (1978).
139. W. A. Tarasenko, A. A. Tishenov, V. G. Zaikin, V. V. Volkova and L. E. Gulsel'nikov, *Izv. Ser. Chim. (Engl. Transl.)*, **35**, 2196 (1986).
140. M. A. Grela and A. J. Colussi, *Int. J. Chem. Kinet.*, **20**, 713 (1988).
141. R. A. L. Peerboom, S. Ingemann, N. M. M. Nibbering and J. F. Liebman, *J. Chem. Soc., Perkin Trans. 2*, 1825 (1990).
142. J. L. Holmes, F. P. Lossing and P. M. Mayer, *Chem. Phys. Lett.*, **198**, 211 (1992).
143. See the discussion in Liebman, Campbell and Slayden[62].
144. M. R. Ellenberger, R. A. Eades, M. W. Thomsen, W. Farneth and D. A. Dixon, *J. Am. Chem. Soc.*, **101**, 7151 (1979).
145. X.-W. An and M. Månsson, *J. Chem. Thermodyn.*, **25**, 287 (1983).
146. G. Bouchoux, J.-Y. Salpin, D. Leblanc, C. Alcaraz, O. Dutuit and H. Palm, *Rapid Commun. Mass Spectrom.*, **9**, 1195 (1995).
147. K. B. Wiberg, D. Y. Nakaji and K. M. Morgan, *J. Am. Chem. Soc.*, **115**, 3527 (1993).
148. It is easy to disparage Reference 141. However, we note that we did not say whether we are considering (*Z*)- or (*E*)-MeCHNMe. Should we wish to invoke calculational results — those of Reference 147 — we find that reaction 64 is approximately thermoneutral (*ca* 2 kJ mol^{-1} discrepancy) as anticipated. However, unlike the isoelectronic 2-butene for which the (*E*)-isomer is only 4.3 ± 1.4 kJ mol^{-1} more stable than its (*Z*)-isomer (from experiment), these same literature calculations show that (*E*)-MeCHNHMe is almost 18 kJ mol^{-1} more stable than the (*Z*)-isomer that is implicitly needed for the above reaction. We would thus predict the enthalpy of formation of 1-azacyclopentene to be *ca* 58 ± 14 kJ mol^{-1} and so the data in Reference 141 is also consistent with the literature experimental data on this new heterocycle.

149. The earlier reference results in a value of -161.0 ± 10.0 kJ mol^{-1}. Undetected, and so uncorrected, hydrolysis and/or polymerization could result in the observed difference.
150. L. M. Jackman and D. I. Packam, *Proc. Chem. Soc.*, 349 (1957).
151. S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).
152. We used the theoretical value of the enthalpy of formation of dipropylamine for consistency. The archival experimental value is but 1 kJ mol^{-1} dissonant.
153. G. Häflinger and L. Steinmann, *Angew. Chem., Int. Ed. Engl.*, **16**, 47 (1977). We thank Prof. G. Häflinger for sending us a copy of L. Steinmann's doctoral thesis.
154. Following the procedure in Liebman, Campbell and Slayden[62], we derived the new δ (*sec/prim*, *tert*) enthalpy increment, numerically equal to 65 kJ mol^{-1}.
155. We used the theoretical value of the enthalpy of formation of di-*n*-butylamine for consistency. The archival experimental value is but 2 kJ mol^{-1} dissonant.
156. This is derived from reasoning based on the enthalpies of formation of other pairs of EtX and ^{n}BuX, and of ^{n}PrX and ^{i}PrX species. For example, let us take X = NH_2 and CN. For amines, the ethyl/butyl difference is 44.6 ± 1.4 while for nitriles it is 41.0 ± 1.5 kJ mol^{-1}. For amines, the isopropyl/*n*-propyl difference is 13.6 ± 0.7 kJ mol^{-1} while for nitriles it is 10.3 ± 1.6 kJ mol^{-1}.
157. G. S. Wayne, G. J. Snyder and D. W. Rogers, *J. Am. Chem. Soc.*, **115**, 9860 (1993). In this paper, the enthalpies of formation of the requisite azides were determined by hydrogenation to the amine and estimation of the latter enthalpies of formation. While far less is known about the enthalpies of formation of azides than amines, this approach seems without additional complication or significant error.
158. Were we to relax our restriction to consider solely hydrocarbyl substituents and accept both benzenoid and non-benzenoid aromatic imines, we would find other relevant compounds. For example, there is *N*-*t*-butyl-*p*-nitrobenzaldimine with a gas-phase enthalpy of formation of 49.4 ± 3.6 kJ mol^{-1} from W. E. Acree, Jr., J. J. Kirchner, S. A. Tucker, G. Pilcher and M. D. M. C. R. Ribeiro da Silva, *J. Chem. Thermodyn.*, **21**, 443 (1989) and *N*-methyl-7-(methylamino)-troponimine (misnamed in our principal archive, Reference 16) with a gas-phase enthalpy of formation of 211.2 ± 4.2 kJ mol^{-1}. Another relevant species is ammonium murexide with its 100-year-old enthalpy of formation of -1212 kJ mol^{-1} as chronicled by Domalski. These three compounds are interesting, but it is precisely the non-hydrocarbyl part of these species that confounds simple comparison with other interesting species in this chapter.
159. From the gas-phase ion–molecule literature we find the isomeric protonated tropone and protonated benzaldehyde to be nearly isoenergetic, while the parent (i.e. not methylated) tropylium ion is more stable than benzyl cation by *ca* 50 kJ mol^{-1}; cf S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin and W. G. Mallard, 'Gas-Phase Ion and Neutral Thermochemistry', *J. Phys. Chem. Ref. Data*, **17**, Supplement 1 (1988).
160. J. J. Kirchner, W. E. Acree, Jr., G. Pilcher and L. Shaofeng, *J. Chem. Thermodyn.*, **18**, 793 (1986).
161. I. G. Gut and J. Wirz, *Angew. Chem., Int. Ed. Engl.*, **33**, 1153 (1994).
162. We do not have to concern ourselves with aniline-like conjugation of the π-electrons of the benzene ring with the nitrogen lone-pair electrons because the π- and n-orbitals are geometrically perpendicular and so do not overlap. We also do not concern ourselves with the 5 kJ mol^{-1} discrepancy in the values of the enthalpy of formation of cyclopentadiene as found in Roth and coworkers[54] and that which we take from our major data archive.
163. We note that for the case of keto/enol interconversion, it is simple, useful and remarkably accurate to equate the difference of Gibbs energies in aqueous media of the two tautomers and the difference of enthalpies of formation in the gas; J. R. Keefe and A. J. Kresge, *J. Phys. Org. Chem.*, **5**, 575 (1992). We are pleased.

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CHAPTER **12**

The electrochemistry of the C=C, C=O and C=N groups

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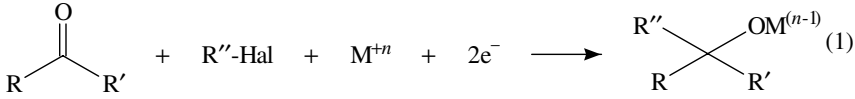
I. INTRODUCTION

This review describes the electrochemical behavior of compounds containing the C=C, C=O and C=N functional group. The review covers both anodic oxidation and cathodic reduction of such compounds. The electrochemistry of these functionalities was reviewed in an earlier volume of this series[1]; this article updates the previous one but does not include the material included there. The Kolbe oxidation of carboxylic acids has

been adequately reviewed elsewhere[2] and is not included here. This review also focuses primarily on reactions in which a compound containing a C=X (X = C, N or O) undergoes chemical transformation at an electrode, in distinction to processes wherein the C=X substance undergoes reaction with a reagent formed at an electrode. Thus we exclude from discussion here the cathodic hydrogenation of alkenes and alkynes at noble metal electrodes[3] and aldehydes at carbon paste/palladium hybrid electrodes[4]; no matter how valuable it may be synthetically this reaction is basically a conventional surface catalytic process using electrochemically generated hydrogen. We also exclude a number of very useful and interesting processes[5] in which the elements of X−Y are added to a C=C bond through addition of an anodically generated electrophilic species 'X^+', followed by reaction with a nucleophile Y. Such processes do not involve the alkene itself at the electrode in any way. However, sometimes it is not easy to make this distinction; it may not be evident just what the actual electroactive species is in a particular transformation. This is particularly so in the case of electrochemically driven 'Grignard-type' processes, where cathodic reduction of a mixture of an alkyl halide, a carbonyl compound and an inorganic salt results in addition of the alkyl group to the carbonyl (equation 1). In principle, any one of the three components might be the electroactive species in such reactions. For this reason and also because this area has not been previously reviewed, a variety of such transformations are included herein even though some do not strictly speaking fit the criterion mentioned above.



(1)

II. GENERAL CONSIDERATIONS

The elementary electrochemical process exhibited by compounds containing the C=X functional group is electron exchange with the electrode: addition of one or more electrons to the LUMO at the cathode or removal of an electron from the HOMO at the anode, depending on whether one is carrying out a reduction or oxidation, respectively. Our knowledge from chemical experience of the dependence of LUMO and HOMO energies on structure will serve us well here. Thus we know that it is easier to add electrons to aldehydes and ketones than to alkenes because of the presence of the electronegative oxygen atom, and that alkenes bearing electron-withdrawing groups are more readily reduced and less readily oxidized than isolated alkenes. Likewise, conjugated species are more reactive toward both oxidation and reduction because the extended conjugation both lowers the LUMO energy and raises the HOMO energy relative to the corresponding unconjugated species. For these reasons, we may expect that for certain of the groups we discuss here cathodic reduction may be the predominant mode of electrochemical reaction; for others, the observed electrochemistry may be essentially completely anodic oxidation. In fact, with some exceptions, the chemistry discussed in this chapter involves the anodic oxidation of alkenes on one hand and cathodic reduction of carbonyl compounds on the other. Electrochemical reductions of alkenes and oxidations of carbonyl compounds are rare indeed.

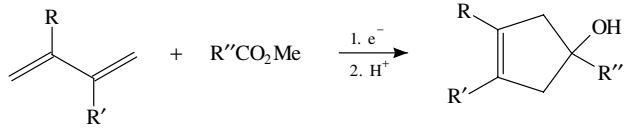
The previous review in this series[1] discussed the variations which can be expected in the structure and reactivity of electrochemically generated anion radicals and cation radicals as the group X in C=X is varied through C, N and O. The reader is referred to the previous review for that discussion, which will not be repeated here.

III. ALKENES (C=C COMPOUNDS)

A. Cathodic Reduction

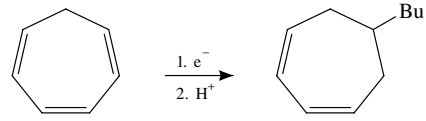
Direct reduction of simple alkenes is difficult because their LUMO energy is very high. Normally, before a sufficiently negative electrode potential can be reached to effect electron transfer from the electrode to the alkene, some other constituent of the medium, such as the solvent or the supporting electrolyte, is found to be more easily reduced. Generally speaking, reduction of isolated double bonds is possible only under rather special conditions, for example, (a) electrolysis at a platinum or other noble metal electrode in a protic medium, in which case the reduction is effectively a catalytic hydrogenation[4], or (b) electrolytic reduction under conditions which favor ion-pairing, such as with a lithium salt as electrolyte and/or in a relatively nonpolar solvent[6]. In this case, electron transfer to the alkene to form the corresponding radical anion is made more thermodynamically favorable by ion-pairing of the cation of the supporting electrolyte to the incipient radical anion.

Reduction of conjugated C=C bonds is, however, much more readily accomplished because the LUMO energy of such substances is lowered considerably by conjugation. This is especially so in the case of alkenes bearing one or more strongly electronegative groups such as carbonyl, cyano, nitro etc., but the electrochemical behavior of such so-called 'activated alkenes' has already been adequately reviewed recently[7,8]. Such substituents are however not necessary: conjugated polyenes are also reducible at potentials which are readily accessible under electrochemical conditions. For example, reduction of 1,3-dienes in the presence of carboxylic esters results in cyclic alcohols (equation 2)[9]. To be sure, unusual experimental conditions are required: magnesium cathode and anode and a lithium perchlorate/THF solvent system. Almost certainly this reaction depends on strong ion-pairing of the diene anion radical to magnesium and/or lithium for its success.



(2)

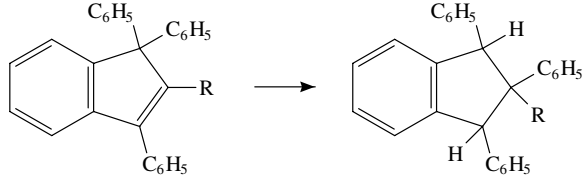
In the same vein, reduction of tropilidene **(1)** in the presence of butyl chloride results in reductive alkylation (equation 3). The reaction was employed in a synthesis of *β*-thujaplicin[10].



(3)

(1)

Farnia and coworkers have described a novel 1,2-phenyl shift which takes place during the electrochemical reduction of the indenes **2** (equation 4)[11]. Mechanistic experiments demonstrated that rearrangement takes place at the dianion stage.



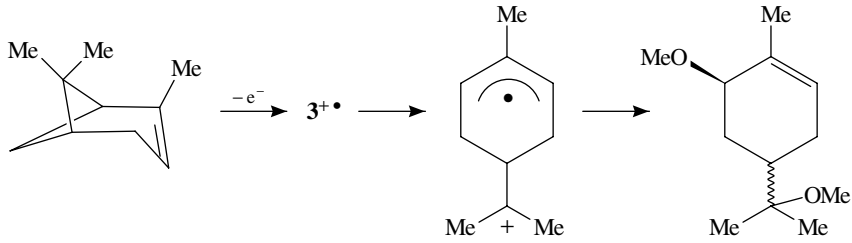
(4)

(2) R = H or Me

B. Anodic Oxidation

It is easier to oxidize an alkene electrochemically than to reduce it, because it is easier to reach powerfully oxidizing anode potentials[12] (at which one can remove an electron from the HOMO of the alkene) without interference from the solvent or electrolyte than it is with reductions, where one can normally not achieve sufficiently negative cathode potentials to be able to add an electron to the LUMO. Even so, anodic oxidation of alkenes is relatively rarely observed; almost always the alkene is part of a conjugated system or it bears an electron-supplying substituent, which raises the HOMO energy.

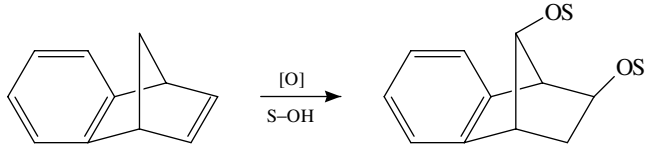
Oxidation of hydrocarbons, even alkanes and arenes, generally proceeds by removal of an electron from the hydrocarbon by the anode to afford a radical cation. Depending on the experimental conditions, the radical cation can react with a nucleophilic component of the medium or lose a proton or alkyl group. Either type of reaction affords a neutral radical. The radical is in general easier to reduce than the starting hydrocarbon because in the case of the radical the electron is being removed from a nonbonding molecular orbital, whereas with the starting hydrocarbon the electron being removed is in a bonding orbital. The product of this second electron transfer is a carbocation, which can undergo reaction(s) typical of such species. The oxidation of α-pinene **(3)** in methanol[13] is typical of such oxidations (equation 5). The initially formed radical cation can relieve ring strain by bond cleavage to afford an allylic radical cation **(4)**. Further oxidation of **4** and nucleophilic attack by the solvent lead to the observed products **(5)**, which are stereoisomeric derivatives of the corresponding diol, sobrerol. Interestingly, a cathodic equivalent to the conversion of **3** to **5** has been observed previously[14].



(5)

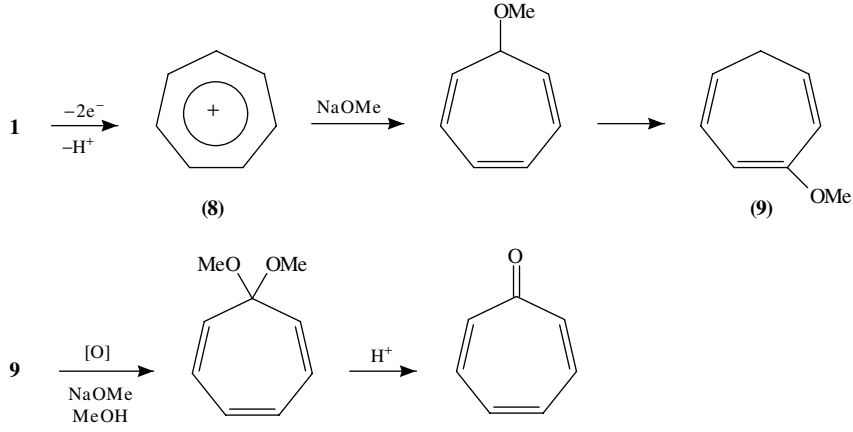
(3) **(4)** **(5)**

Anodic oxidation of **6** represents a variant on this scheme. Ring opening by cleavage of the bridge bond as observed for the radical cation of **3** does not take place. Instead, the 1,2-shift characteristic of these bicyclo[2.2.1] ring systems takes place to afford, ultimately, **7** stereospecifically[15] (equation 6). Oxidation of tropilidene **(1)** affords the tropylium ion **(8)**[16]; when the reaction is carried out in NaOMe/MeOH the product is tropyl methyl ether, which can be treated with acid to regenerate **8** or heated to induce rearrangement to **9**[17]. The latter can be oxidized further, followed by acid catalyzed hydrolysis, to afford tropone in good yield (Scheme 1). This work has been extended to a synthesis of 4-substituted tropones[18].

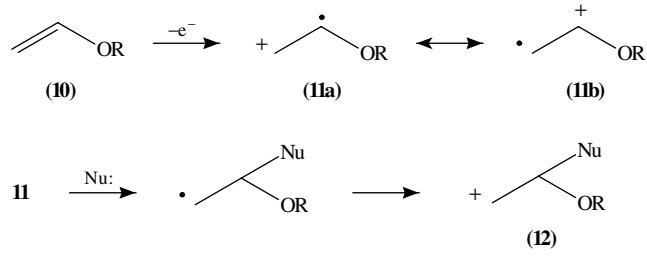


(6)

(6) **(7)**



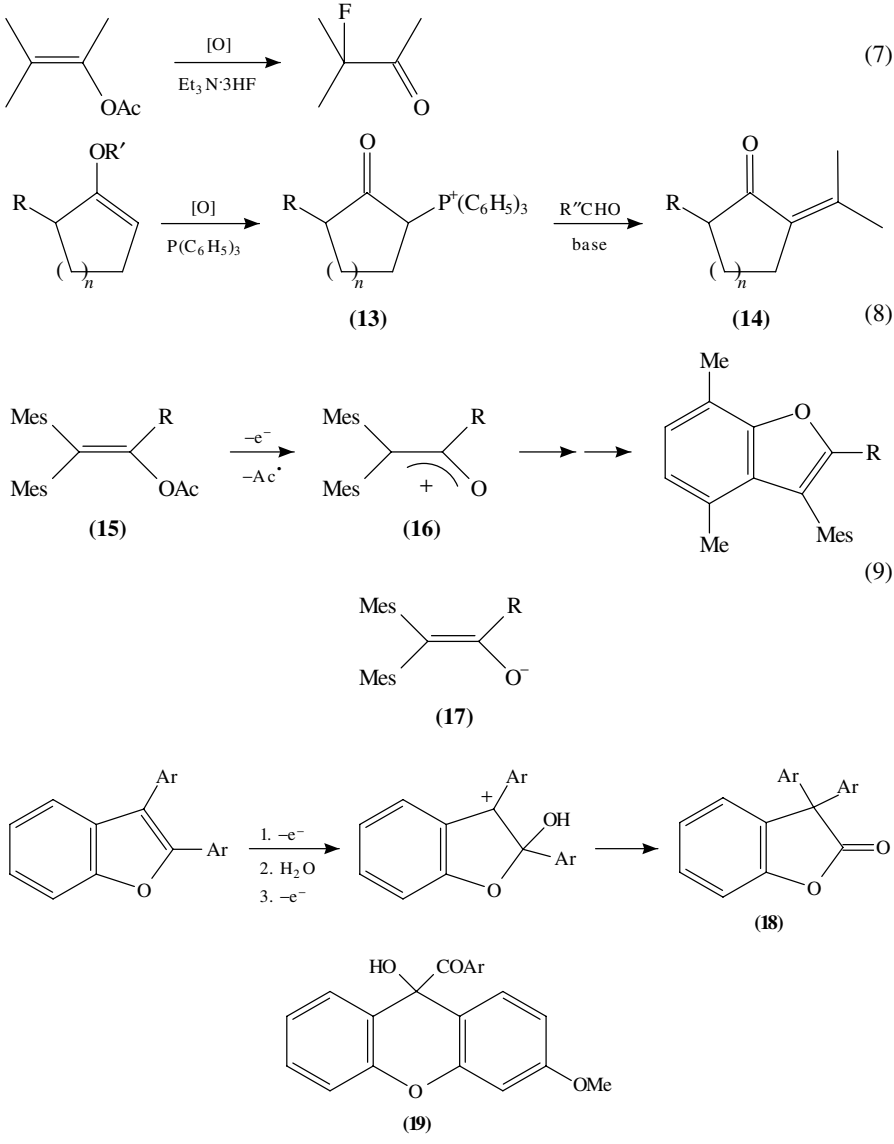
SCHEME 1



SCHEME 2

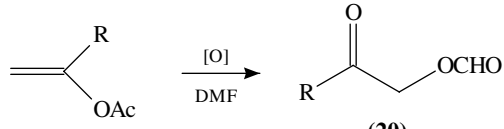
Anodic oxidation of alkenes is more readily accomplished when the double bond bears an electron-supplying group. Enol ethers, acetates and even a few enols have been studied. Removal of an electron from an enol derivative **(10)** affords a radical cation in which the major resonance contributor is presumably structure **11b**, in which the positive charge is localized on the atom bearing the oxygen atom. Loss of a proton or alkyl group from **11** or reaction with a nucleophilic component of the medium leads to a neutral radical, which generally suffers further oxidation to a carbocation. Anodic oxidation thus converts the normally nucleophilic enol derivative **10** to at least two highly electrophilic species, **11** and **12**. (Scheme 2). Synthetic applications can be designed to take advantage of this *umpolung* of reactivity of the enol derivative. Oxidation of enol acetates in the presence of a source of fluoride affords α-fluoroketones (equation 7)[19]. Two processes must take place: nucleophilic attack by fluoride and deacetylation, which probably also involves nucleophilic attack by fluoride on the carbonyl group. Plausible mechanisms may be written in which these two steps can take place in either order. Similarly, oxidation of cyclic enol derivatives in the presence of triphenylphosphine affords α-triphenylphosphonioketones **(13)**, which can readily be converted into α-alkylidene ketones **(14)** (equation 8)[20]. On the other hand, oxidation of the dimesitylvinyl acetates **15** in the absence of an added nucleophile results in formation of benzofurans. It was suggested that the radical cation of **15** decomposes to an acetyl radical and cation **16**. Intramolecular electrophilic attack on the adjacent arene ring, followed by methyl rearrangement, would lead to the observed products (equation 9)[21]. Evidence for this mechanism is the concomitant formation of biacetyl

and the fact that the same benzofurans are also formed[22] upon two-electron anodic oxidation of enolate **17**; this should also afford **16**. Benzofurans themselves are a type of enol derivative and Simonet has shown that they too undergo anodic oxidation. Two main types of products are formed: lactones **(18)** and xanthene derivatives **(19)** (Scheme 3)[23]. Attack of water on the oxygen-bearing carbon atom of the radical cation and a subsequent pinacol-type reaction involving migration of an aryl ring[23] would afford **18**. The origin of **19** is less clear; the authors suggested a phenoxonium ion as intermediate.



SCHEME 3

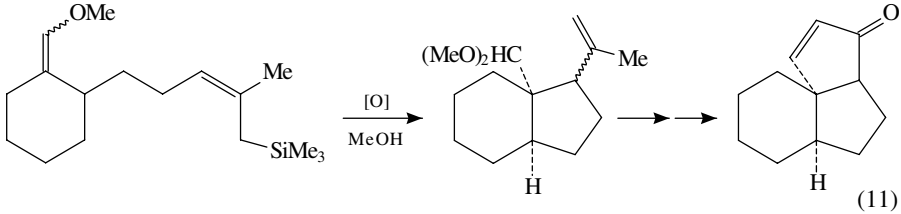
Barba and coworkers reported that the anodic oxidation of vinyl acetates in DMF affords *alpha*-formyloxy ketones **(20)** (equation 10)[24]. A novel feature of this reaction is the fact that the formyloxy carbonyl group of **20** is derived from the DMF solvent[24].



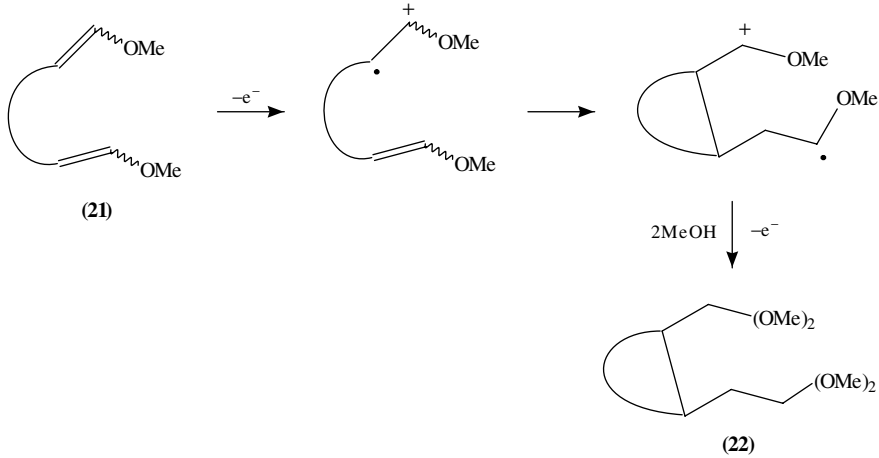
(10)

(20)

Moeller has carried out an extensive series of studies of the electrochemical oxidation of electron-rich *bis*-alkenes. One olefinic component is an enol ether, which is converted into an electrophilic center upon oxidation; this center then attacks the other site intramolecularly. The anodic oxidation of the *bis*-enol ethers **21** in methanol[25] exemplifies the course of such reactions (Scheme 4). The products are *bis*-acetals **(22)**, formed in 50–70% yield in many cases. The cyclization can be used to produce quaternary[25] and angularly fused[26] bicyclic and tricyclic structures (equation 11). In its original form, this work involved oxidation of a mono-enol ether bearing a nearby styrene-type double bond[27].



(11)



(21)

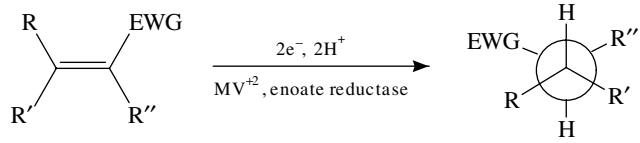
(22)

SCHEME 4

C. Electroenzymatic Synthesis

Simon and collaborators have described a novel stereoselective electroenzymatic reduction of alkenes of type **23** (equation 12)[28]. The enzyme enoate reductase is the reductant

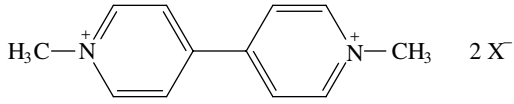
of the double bond in this process; the actual electroactive species is the methyl viologen dication **(24)** which is reduced at the cathode to the corresponding monocation, which then participates as an electrocatalyst in the enzymatic reduction process. This is representative of an increasing number of electroenzymatic processes which have been studied in recent years in an effort to combine the high degree of selectivity of enzymatic processes with the relatively low cost of electricity compared with that of redox coenzymes such as NADPH and NADH (see Section V.C).



(12)

(23)

EWG = electron-withdrawing group

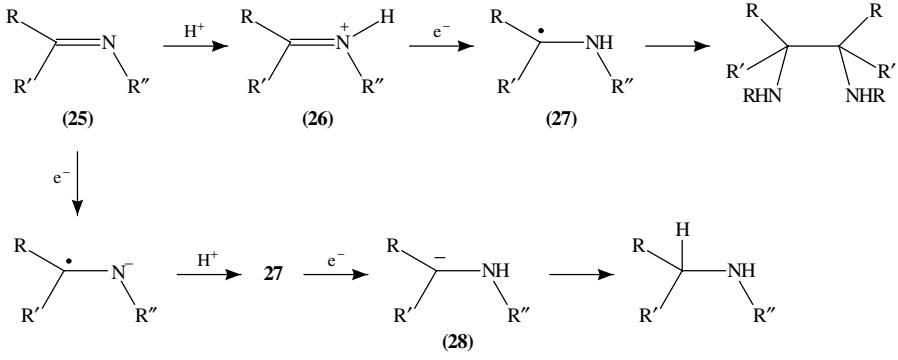


(24)

IV. C=N COMPOUNDS

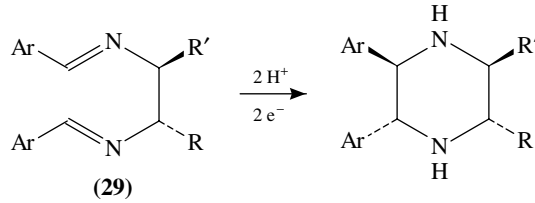
A. Cathodic Reduction

Electrochemical reduction of imines (**25**; Schiff bases) in acidic media proceeds via the iminium species, i.e. the protonated imine **(26)** (Scheme 5)[29]. Since **26** bears a positive charge, it is very easily reduced, so much so that the resulting neutral radical **(27)** is formed at a potential *positive* of its reduction potential. The products are therefore derived from **27** rather than the corresponding carbanion **(28)**. This stands in contrast with the electrochemical behavior of imines in neutral media, where **27** is immediately reduced to **28**[30]. Thus, cathodic reduction of *bis*-imines of 1,2-diamines **(29)** in DMF containing methanesulfonic acid affords tetrahydropyrazines (equation 13)[31]. A similar reaction can

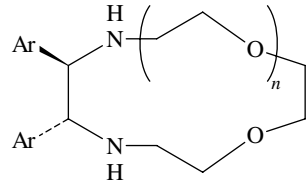


SCHEME 5

be used to prepare *bis*-azacrown ethers **(30)**[32]; the imine can be prepared *in situ*.

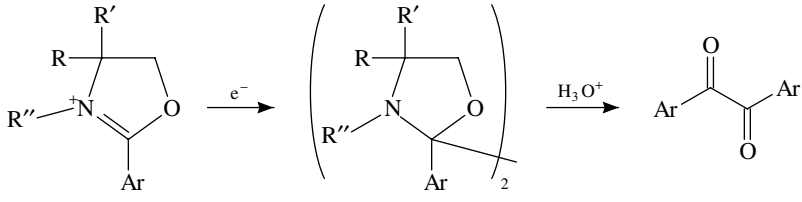


(29) (13)

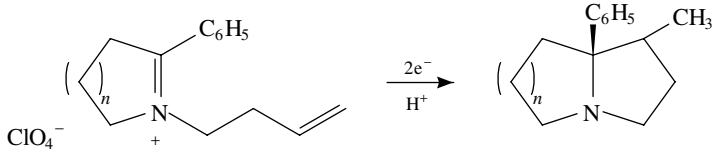


(30) $n = 0-4$

Reduction of *N*-alkyl iminium salts also ought to afford radical-derived products. Indeed, reduction of oxazolinium salts **(31)** results in isolation of the corresponding dimers, which can in turn be converted to the corresponding benzils by acid hydrolysis[33] (equation 14). In a similar vein, electrochemical reduction of *N*-butenyl iminium salts **(32)** affords cyclopentane derivatives (equation 15)[34].



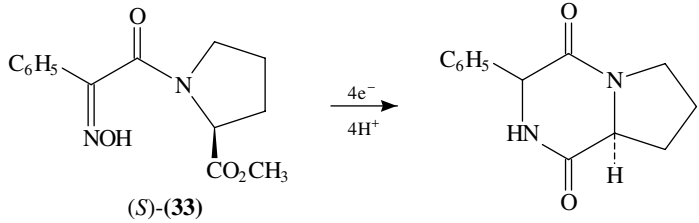
(31) (14)



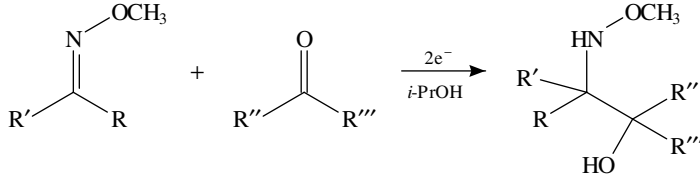
(32) (15)

It is known that electrochemical reduction of oximes in protic media occurs in two steps: the N−O bond is first reduced to form an imine and the latter is then reduced to afford a primary amine[1,29]. Tallec has shown that the amine from oxime **33** can be trapped intramolecularly (equation 16)[35]. Interestingly, the SS diastereomer predominates; the chiral pyrrolidine ring derivative serves to control the stereochemistry of formation of the new benzylic chiral center. Electrochemical reductive cross-coupling of *O*-methyl oximes with carbonyl compounds in isopropanol at a tin cathode affords adducts (equation 17) which can be reduced further to 2-amino alcohols[36]. In this fashion, menthone could

be condensed with acetaldehyde *O*-methyl oxime to afford a chiral adduct which was effective as a promoter for the enantioselective addition of diethylzinc to aldehydes.

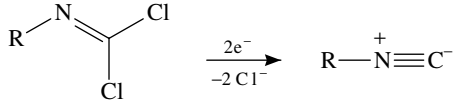


(*S*)-(**33**) (16)



(17)

Finally, reduction of 1,1-dichloroimines leads to formation of isocyanides in good yield (equation 18)[37].



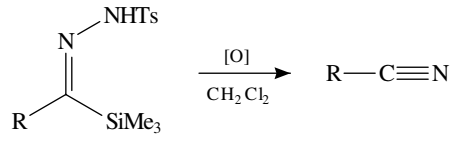
(18)

B. Anodic Oxidation

Compounds containing the C=N functional group derivatives undergo anodic oxidation when the nitrogen atom bears an electron-rich heteroatom. Perhaps the simplest such species are aldoximes, which are anodically oxidized to nitrile oxides (**34**)[38]. The reaction was carried out in an undivided cell[39], hence the species **34** underwent immediate reduction to a nitrile (equation 19). However, since nitrile oxides are 1,3-dipolar species, one could in principle carry out the oxidation in a divided cell in the presence of a good 1,3-dipolarophile[40] to effect the synthesis of substituted heterocycles.

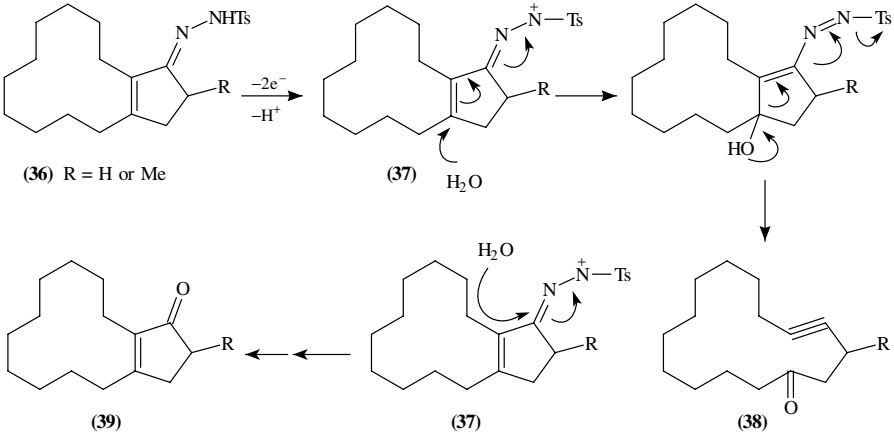
$$\mathrm{RCH{=}NOH} \xrightarrow[\text{anode}]{[O]} \underset{\textbf{(34)}}{\mathrm{R{-}C{\equiv}\overset{+}{N}{-}O^-}} \xrightarrow[\text{cathode}]{[H]} \mathrm{R{-}C{\equiv}N} \tag{19}$$

Oxidation of silyl tosylhydrazones (**35**) in an aprotic medium (dichloromethane) also results in the formation of nitriles, but in this case the conversion is apparently a true anodic process[41] in which the key difference from the anodic behavior of oximes is the presence of the *p*-toluensulfonyl group, which facilitates cleavage of the N−N single bond (equation 20).

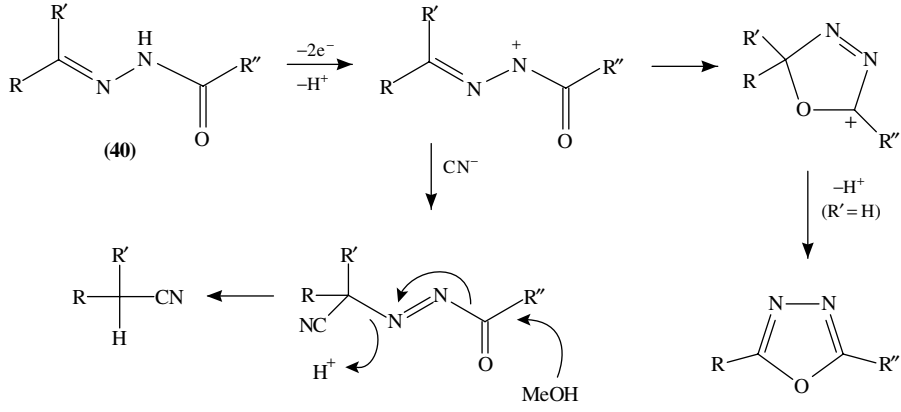


(**35**) (20)

Oxidation of the unsaturated tosylhydrazones **36** affords a mixture of ring-cleaved **(38)** and hydrolyzed **(39)** products (Scheme 6)[42]. The formation of **38** and **39** can be explained in terms of a common intermediate **(37)**. Oxidation of acylhydrazides **(40)** follows an apparently mechanistically similar course to afford cyclized materials[43] except in the presence of cyanide, in which case nitriles are formed[44] (Scheme 7).



SCHEME 6



SCHEME 7

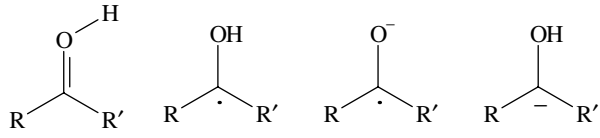
V. CARBONYL (C=O) COMPOUNDS

A. Cathodic Reduction

1. Aldehydes and ketones

Earlier studies on the electrochemical reduction of aldehydes and ketones have been summarized in several reviews[1,29,45]; the reader should refer to those reviews for background material to the discussion which follows. Nevertheless, a short outline of the cathodic behavior of these substances will be helpful.

One of the primary issues in the electrochemical reduction of any carbonyl compound is the nature of the electroactive species under a particular set of experimental conditions, of which the proton donor ability of the solvent is paramount. The behavior of diaryl ketones is best understood in this respect. In acidic media (pH < 5), the species undergoing reduction is the protonated carbonyl compound **(41)** and the reduction affords a neutral ketyl radical **(42)**. Dimerization of the latter affords benzpinacols, which generally rearrange to benzpinacolones under the acidic reaction conditions. In neutral and weakly basic media (pH from 5 to 11), the neutral carbonyl compound is reduced to a radical anion **(43)**, which is protonated rapidly; the resulting ketyl radical usually immediately accepts a second electron and proton, and the product is the secondary alcohol. Reduction in strongly basic or aprotic media affords **43**, which dimerizes to a pinacol. Aryl alkyl ketones and aldehydes have been generally believed to exhibit similar behavior (but see next paragraph). Dialkyl ketones and aliphatic aldehydes are not reducible at all under aprotic conditions; the LUMO of these substances is apparently too high to be accessible. These compounds are however reducible in protic media, e.g. alcohol solvents. Under these conditions the electroactive species is probably an alcohol–carbonyl hydrogen-bonded complex. These types of compounds are generally reduced to alcohols; the intermediate ketyl radical is apparently reduced to an anion **(44)** at the very negative potentials at which reduction must be carried out, and protonation of **44** to afford the alcohol is undoubtedly fast.



(41) **(42)** **(43)** **(44)**

Attention has turned recently to the mechanistic details underlying these processes. Probably the most significant development in this area in recent years is the discovery that the ketyl radical produced by electrochemical reduction of benzaldehyde in buffered neutral ethanol is *harder* to reduce than benzaldehyde itself[46]. All previous discussions had assumed that the ketyl radical would be reduced as quickly as it is formed, but fast scan cyclic voltammetry demonstrated the existence of a short-lived intermediate, apparently the ketyl radical. Computer simulation of the voltammograms showed that the radical dimerizes at a rate *ca* 10^6 M^{-1} s^{-1}.

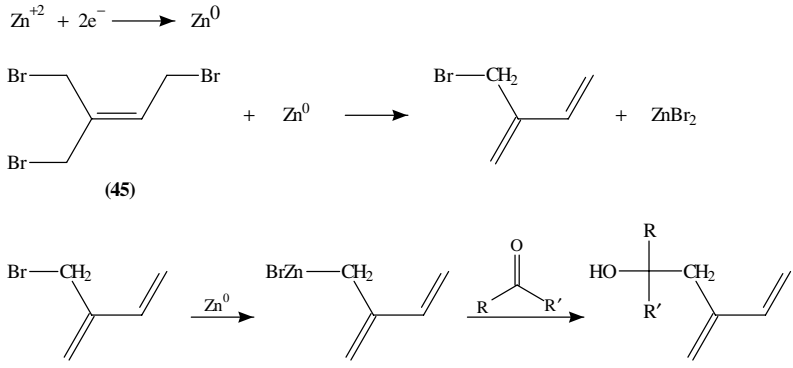
Many aliphatic aldehydes exist primarily as hemiacetals in alcoholic solvents. It has been well understood for many years[47] that the actual reducible species, or 'electrophore', in such media is not the hemiacetal but rather the small amount of the carbonyl compound itself (actually a hydrogen-bonded complex; see above) present at equilibrium. Thus reduction is kinetically controlled; that is, the overall rate of reduction is governed by the rate of conversion of the hemiacetal to the aldehyde. More recently, this has been confirmed and studied for formaldehyde and acetaldehyde in water at different pH levels[48] and the kinetics of the reduction process have been studied for glucose, galactose and lactose[49].

Synthetically, the question of which product is formed from a given carbonyl compound, the pinacol or the alcohol, is obviously of great interest. We have already noted the critical importance of the proton-donating ability of the medium in this respect. Attention has turned to the effect of other variables on the pinacol/alcohol ratio. Formaldehyde can be reduced cleanly to ethylene glycol at an electrode composed of a special type of carbon, in a process of potential commercial significance[50]. Nonaka and coworkers have found that reduction of aldehydes proceeds more selectively to aldehydes at nickel–Teflon–silica gel composite electrodes[51]. Nonaka and coworkers have also shown that for aromatic

aldehydes in aqueous methanol this ratio is sensitive to stirring conditions[52]: the ratio is in the range 2–3 when the electrolysis solution is stirred magnetically, but 24–34 under ultrasonic stirring. Presumably, highly efficient stirring (ultrasonic irradiation) removes the ketyl radical from the electrode surface before it can undergo further reduction. It would appear desirable to study the effect of ultrasonic stirring on a number of other electrode reactions.

Several studies have been made of the effect of added metal ions on the pinacol/alcohol ratio. Addition of antimony(III) chloride in catalytic amounts changes the product of the electrochemical reduction of acetophenone in acidic alcohol at a lead electrode from the pinacol in the absence of added metal salt to the secondary alcohol in its presence[53]. Antimony metal was suspected to be an intermediate in the reduction. Conversely, addition of Sm(III) chloride to DMF solutions of aromatic aldehydes and ketones[54] and manganese(II) chloride to DMF solutions of hindered aromatic ketones[55] results in selective formation of pinacols in excellent yields. When considering these results one should keep in mind the fact that aromatic ketones tend to form pinacols in DMF even in the absence of added metal ions[1,29,45].

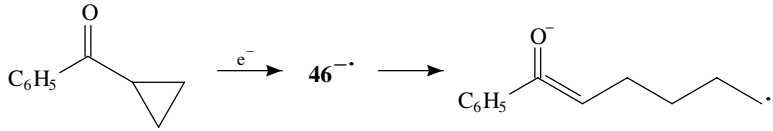
A number of investigators have studied the possibility of effecting electrochemical Grignard-type reactions by reducing a mixture of an alkyl halide and a carbonyl compound in the presence of a metal salt (or, equivalently, in a cell containing a readily oxidizable metal anode, thus generating the metal ion as current is passed) (equation 1, Section I). While these reactions have frequently been successful, it is not always clear whether the chemistry involves reduction of the carbonyl compound or the alkyl halide, or indeed perhaps of the metal ion. Examples include reduction of bromoesters in the presence of ketones in a cell containing an indium anode to afford Reformatsky-type products[56], reduction of a mixture of an allylic halide and ketone in the presence of a catalytic amount of zinc bromide[57], similar reductions involving a zinc anode and a catalytic amount of Ni(II)(bipyridine)[58], the zinc anode alone[59] and a magnesium anode and a small amount of samarium(III) chloride[60]. The latter reaction is thought to involve Sm(II) as the reactive species; the reactions involving zinc species are thought to involve a highly active form of zinc metal electrodeposited on the electrode surface, except for the Ni(II)(bipyridine) chemistry, which probably involves a low-valent nickel species. It has been established that a highly active form of zinc prepared by reduction of Zn(II) chloride by sodium in liquid ammonia readily effects the condensation of allyl halides with ketones[61]. The conversion of a mixture of an aldehyde or ketone and the tribromide **45** to an isoprenylated derivative by electrolysis in a cell with zinc anode is interesting



SCHEME 8

because the electrogenerated zinc effects both dehalogenation of **45** and addition of the resulting monobromide to the carbonyl group (Scheme 8)[59].

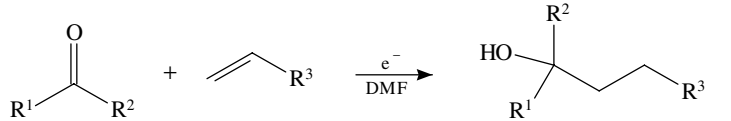
Tanko has shown that electrochemical reduction of ketone **46** affords a radical anion which undergoes conversion to an open chain species (Equation 21)[62]. Ring-opening was shown to be reversible; for this reason, ketones such as **46** are unreliable probes for electron transfer processes. Likewise, electrochemical reduction of aromatic aldehydes proceeds selectively to the corresponding benzyl alcohols in DMF containing a trialkoxysilane[63]. However, this process is thought to involve a catalytic cycle involving pentacoordinate hydrosilane intermediates; it is not a true electrochemical reduction and in fact consumes only a small amount of current.



(21)

(46)

Much of the development of new reactions in modern synthetic chemistry rests on trapping intermediates in known chemical reactions in order to force the reaction into new pathways. This idea has been used to expand the range of usefulness of the electrochemical reduction of carbonyl compounds. We have seen that these reductions involve a variety of reactive intermediates **(41–44)**. Ketyl radical **42** and radical anion **43** can be trapped by added good radical traps, though it is not always clear which of these species is involved in a particular process. As a rough rule of thumb we may expect **43** to be involved in aprotic or highly basic media, and **42** to be involved under neutral conditions. Alkenes serve particularly well as trapping agents. Reduction of ketones in DMF at a carbon electrode in the presence of alkenes affords alcohols in fair-to-good yields (equation 22)[64]. Intramolecular versions of this reaction result in cyclization, as in equation 23[65] and equation 24[66].



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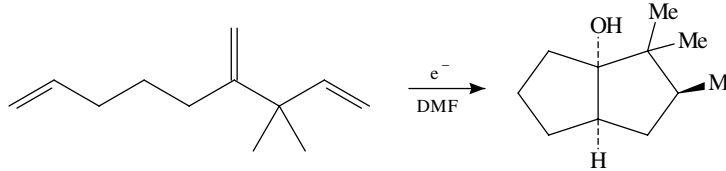

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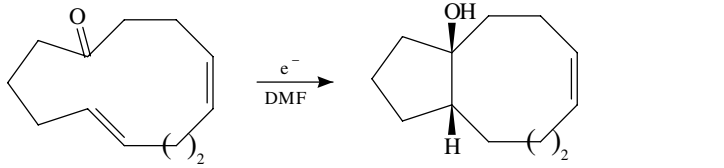
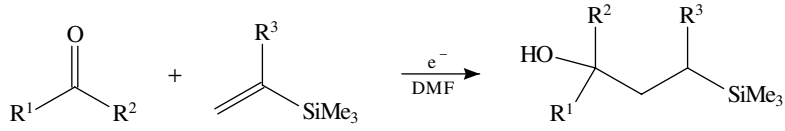


(24)

Addition to a vinylsilane takes place regioselectively (equation 25)[67]. A trialkylsilyl group can be used in this way to direct ring formation so as to form a six-membered ring (equation 26) in opposition to the usual preference for five-membered ring formation in

radical-type cyclizations[67]. These reactions undoubtedly involve attack of a radical anion on the C=C bond.



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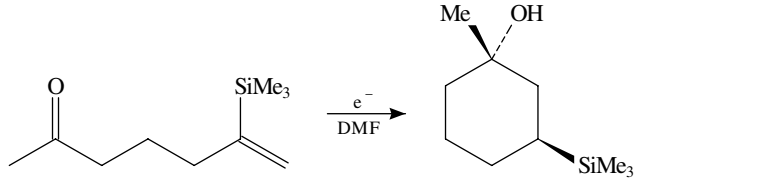
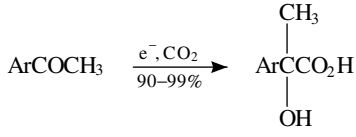


(26)

The radical anion is probably the reactive intermediate in the reductive carboxylation of aromatic ketones in DMF in a cell containing a sacrificial aluminum anode (equation 27)[68]; conceptually, this is better seen as a nucleophilic attack of radical anion **43** on the electrophile CO_2. It is not clear whether the electrochemical cyclizations which have been observed onto a benzene nucleus[69] and onto a cyano group[70] (equations 28 and 29, respectively) involve **42** or **43**, inasmuch as the reactions are carried out in the presence of a proton donor, albeit a rather poor one. Reduction of **47** is temperature-dependent: the hydroxy ketone **(48)** is the major product at room temperature, but **49** is the major product at 65 °C. The authors suggest that **49** arises by dehydration of **48** to an α,β-unsaturated ketone **(50)** and subsequent reduction of the latter. This seems unlikely; reduction of **50** should afford a hydrodimer[7,8], not **49**. More likely, **48** is probably converted directly to **49** at the higher temperature by electrochemical cleavage of the activated carbon–oxygen bond[71].



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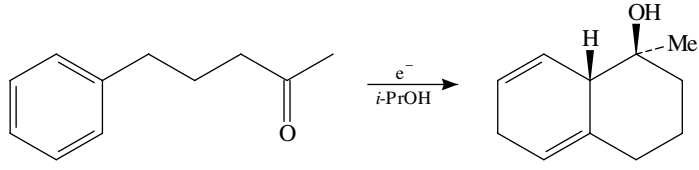
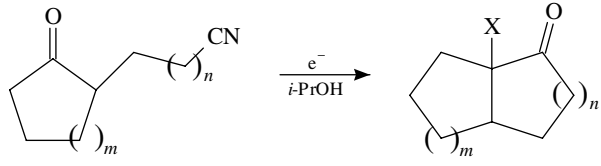


(28)

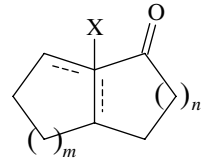


(29)

(47)

(48) X = OH

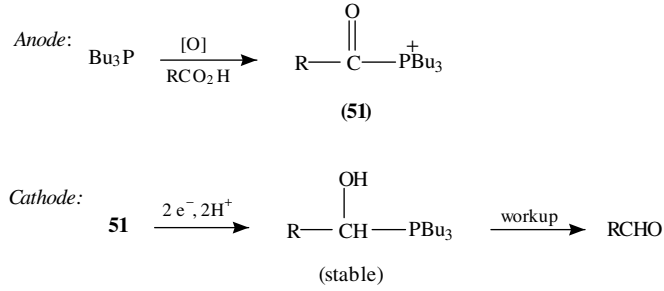
(49) X = H



(50)

2. Carboxylic acids and acid derivatives

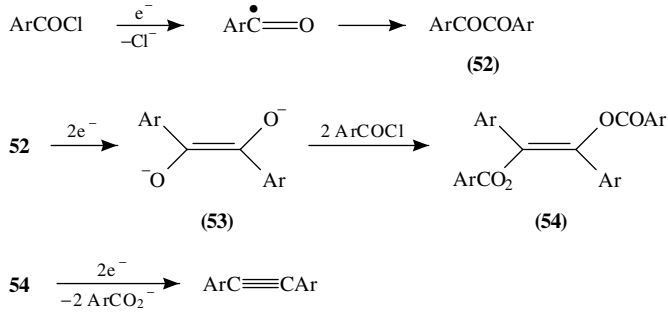
Carboxylic acids cannot normally be reduced directly electrochemically[1]; they can however be reduced to aldehydes by electrolysis in an undivided cell containing tributylphosphine and methanesulfonic acid[72]. The conversion involves an interesting combination of anodic and cathodic reactions (Scheme 9).



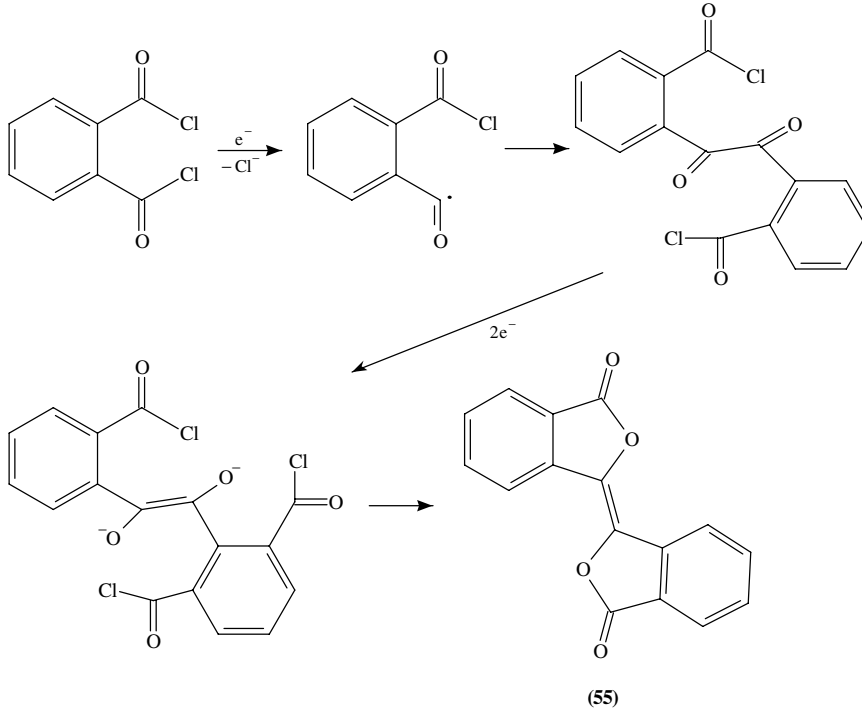
SCHEME 9

Aroyl chlorides undergo an interesting electrochemical reduction to afford 1,2-dibenzoyloxystilbenes **(54)**[73–75]. The reaction appears to involve reductive dimerization to benzil **(52)** (Scheme 10). The latter is readily reduced to a stilbenediolate **(53)**. Reaction of **53** with unreacted aroyl chloride affords **54** (*trans:cis* = 2 : 1). Alkene **54** can be further reduced to a diphenylacetylene by electrolysis at a more negative cathode potential[74]. Benzoyl fluoride undergoes the same conversion to **54**[74]. Voltammetric investigations and careful product analysis have revealed the fact that these reactions are actually more complex than suggested by Scheme 10. Typically, at least two voltammetric waves are observed[74,75]. The most positive is that of the acid chloride itself. A second wave is usually seen for the corresponding benzaldehyde. Small amounts of the corresponding aldehyde also accompany **54** in the preparative electrolysis. Other electrolysis products include the corresponding carboxylic acid and anhydride; these presumably arise by reaction of the acid chloride with traces of moisture in the solvent[74,75]. Electrolysis of thiophene-2-carbonyl chloride in the presence of D_2O and CD_3CN gave products suggesting the intermediate formation of the benzoyl *anion*[75b]. Reduction of phthaloyl chloride affords **55** in 65% yield[76]. In this system, the enediolate intermediate is trapped intramolecularly (Scheme 11). On the other hand, electrochemical reduction of terephthaloyl chloride (*para*-substituted) and its derivatives affords linear polyterephthaloylenes in good yield (95% for the parent compound)[77].

Reduction of aliphatic acid chlorides follows a roughly similar course[78]. That is, tetrameric products similar to **54** are the major products, together with small amounts of the corresponding aldehyde. The latter has been suggested to be formed from both acyl radical



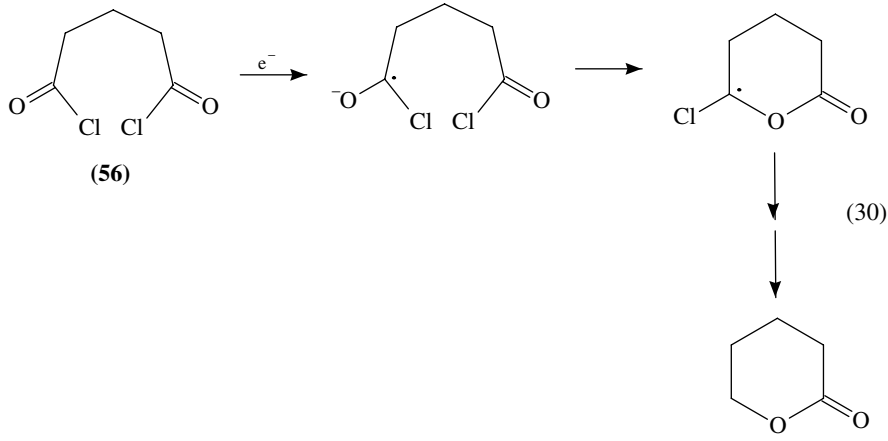
SCHEME 10



SCHEME 11

and acyl anion intermediates[78a]. On the other hand, reduction of 1-adamantanoyl chloride in CD_3CN (a good hydrogen atom donor but a poorer proton donor) affords the deuterated aldehyde in high yield, suggesting that the critical intermediate is the 1-adamantanoyl radical[78c]. Presumably dimerization of the radical is sterically inhibited, permitting the hydrogen atom abstraction to dominate. Electrochemical reduction of glutaryl chloride **(56)** affords a γ-lactone (equation 30)[78b]. This appears to suggest that the first intermediate, a radical anion formed by addition of one electron to the carbonyl group of **56**, cyclizes faster than it can eject chloride. It would be interesting to know whether glutaryl bromide

would take a different course because of the better leaving group ability of bromine.



(56) (30)

The electrochemical reduction of acid chlorides takes a very different course when carried out in an undivided cell equipped with nickel cathode and anode[79]. The product is a symmetrical ketone (**57**); **57** is formed by a complex sequence involving both electrodes (Scheme 12). This is really a chemical reaction induced by a highly reactive form of nickel produced by dissolution of the anode and plated onto the cathode. We have already encountered similar chemistry involving highly reactive zinc (Section V.A.1).

Anode:

$$Ni - 2e^- \longrightarrow Ni^{2+}$$

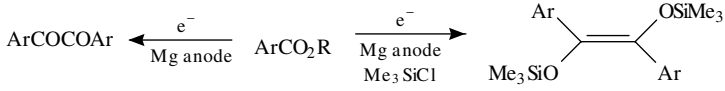
Cathode:

$$Ni^{2+} + 2e^- \longrightarrow Ni^\circ \xrightarrow{RCOCl} RCONiCl$$

$$2\,RCONiCl \longrightarrow Ni^{2+} + 2\,Cl^- + (RCO)_2Ni$$

$$(RCO)_2Ni \longrightarrow \underset{\displaystyle CO}{RCONi{-}R} \longrightarrow \underset{\textbf{(57)}}{RCOR} + Ni^\circ + CO$$

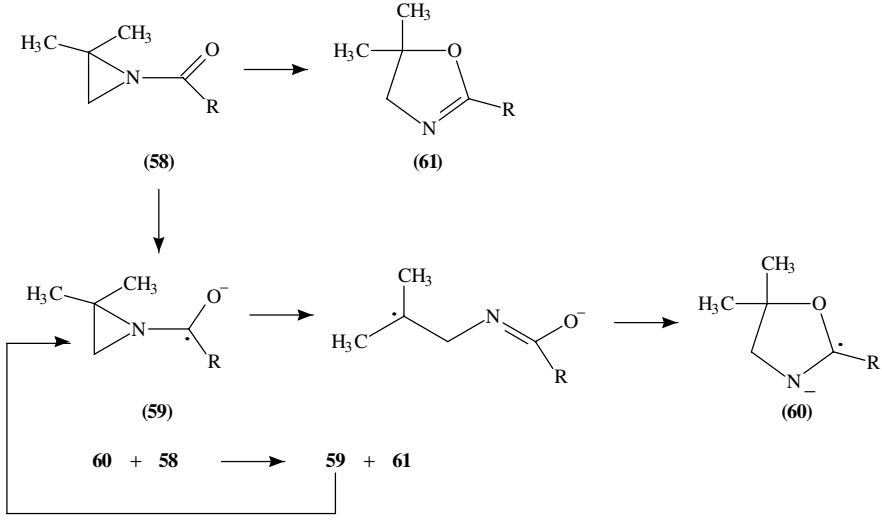
SCHEME 12



SCHEME 13

Esters undergo conversion to 1,2-diketones when reduced in a cell containing a magnesium anode[80]. Reduction in the presence of chlorotrimethylsilane affords an enediol *bis*-silyl ether (Scheme 13)[80]. Coordination of the chlorosilane probably activates the diketone for reduction[80]. The effect of the magnesium anode is less clear; coordination of magnesium ion to the diketone may stabilize it against further reduction; magnesium ions

liberated at the sacrificial anode can presumably also facilitate reduction of the starting ester. This interpretation is bolstered by work of Pletcher and Slevin[81], who showed that in DMF benzoate esters undergo alkyl-oxygen cleave to afford benzoate ion, whereas coupling is fast in the presence of added magnesium ion[81]. The role played by experimental conditions on these reactions still leaves much to be resolved. Thus, electrochemical reduction of esters and *N*, *N*-dialkyl amides takes a very different course when carried out in a *t*-BuOH/THF mixture in a cell containing magnesium anode and cathode; the ester is reduced to the primary alcohol stage[82]. Substitution of *t*-BuOD results in formation of RCD_2OH from RCO_2R'. Ring-opening is observed with amide **58**[83], the isomerization of which to **61** is initiated electrochemically, but for which there is *no net consumption of current* (Scheme 14).



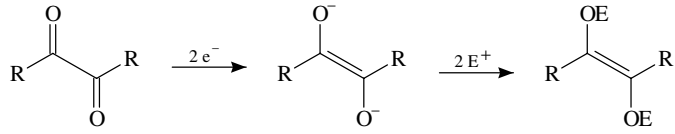
SCHEME 14

The electrochemical reduction of 2,6-pyridine diesters and *S*-thioesters shows interesting contrasts. The first step in each case is conversion to a short-lived radical anion, but the esters undergo alkyl-oxygen cleavage (cf Reference 81), whereas the *S*-thioesters undergo cleavage of the C(O)−S bond[84]. The latter mode of cleavage is reasonable, inasmuch as *S*-thioesters resemble acid chlorides chemically more than they do esters.

3. 1,2-Dicarbonyl compounds

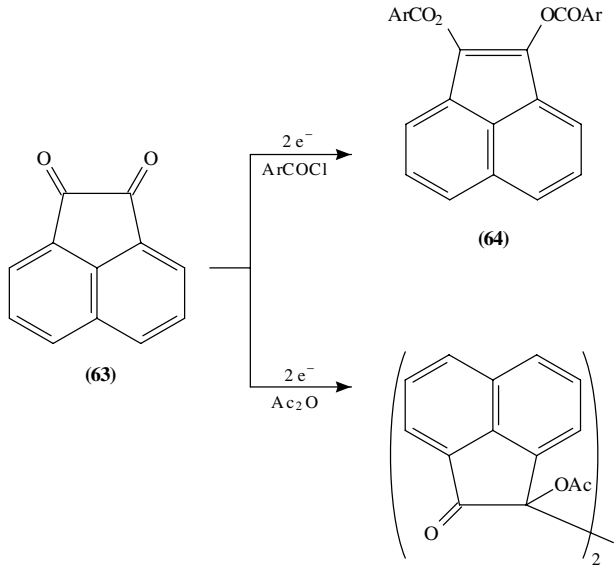
1,2-Diketones are easily reduced electrochemically because of the mutual electron-withdrawing effect of one carbonyl group on the other. Two-electron reduction usually takes place to afford an enediolate **(62)**, which can then react with an electrophile E present in the medium (equation 31; see also Schemes 10 and 13); an *alpha*-hydroxy ketone is formed by subsequent tautomerization when E = H[1,85,86]. An unusual exception to the generalization that these substances undergo two-electron reduction is the electrochemical behavior of acenaphthenequinone **(63)**, which is converted to the expected enediol dibenzoate **(64)** in the presence of aroyl chlorides but affords the dimeric substance **65** (shown to be the *meso* diastereomer by X-ray crystallography) in the presence of acetic

anhydride (Scheme 15)[87].



(31)

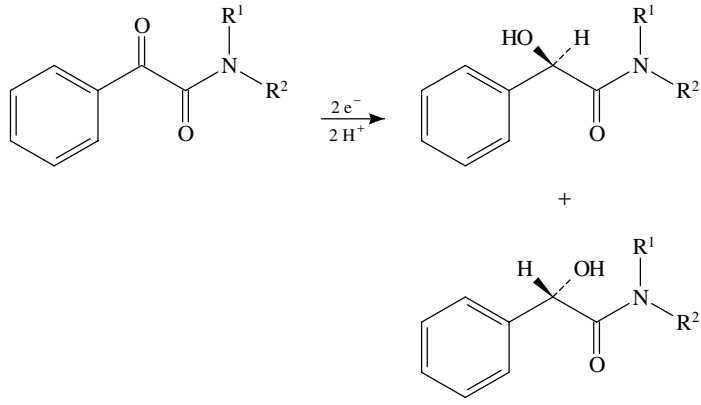
(62)



(63) **(64)** **(65)**

SCHEME 15

Schäfer examined the effect of chiral auxiliaries on the stereochemistry of reduction of a series of α-ketoamides (equation 32)[88]. Diastereomeric excesses ranged from 42 to 81%.

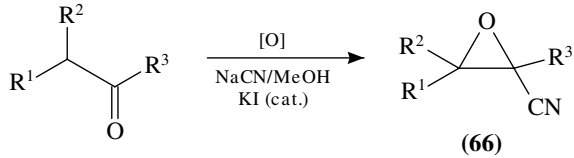


(32)

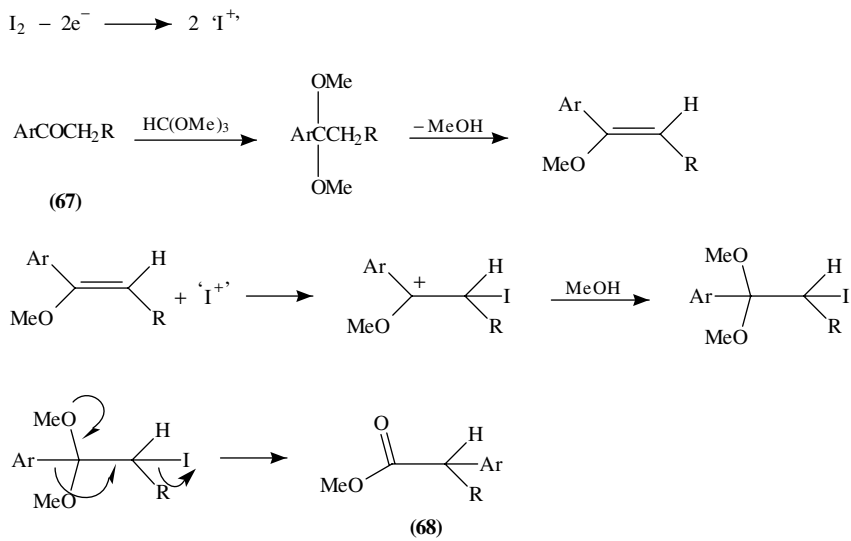
B. Anodic Oxidation

1. Aldehydes and ketones

Direct electrochemical oxidation of ketones and even aldehydes is difficult to achieve, paralleling their chemical resistance to oxidation. A number of reports have however appeared in which chemical transformation of ketones is effected by anodically generated positive halogen species. Previous work in this area has been reviewed[89]. Typically, oxidation of a halide ion produces a halogenating agent (the exact chemical structure of which is often uncertain) which reacts with the carbonyl compound to afford an *alpha*-halo derivative. Usually the latter undergoes a follow-up reaction; a surprising variety of the latter have been observed, depending on experimental conditions, the identity of the halide ion and the structure of the carbonyl compound. Recent examples of this type of chemistry include the anodic conversion of methyl ketones to methyl esters in methanol containing sodium bromide (an electrochemical haloform reaction)[90], the oxidative conversion of ketones into epoxy nitriles **(66)** in the presence of sodium cyanide and potassium iodide (equation 33)[91] and the oxidative rearrangement of arylalkyl ketones **(67)** to esters **(68)** in the presence of iodine and trimethyl orthoformate[92]. The mechanism shown in Scheme 16 for the conversion of **67** to **68** appears simpler than that proposed by the group of Shono[92].



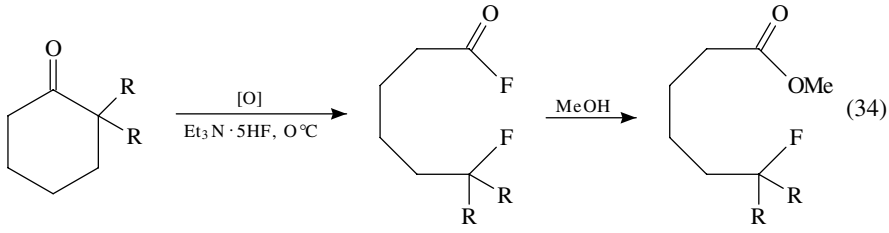
(66) (33)



SCHEME 16

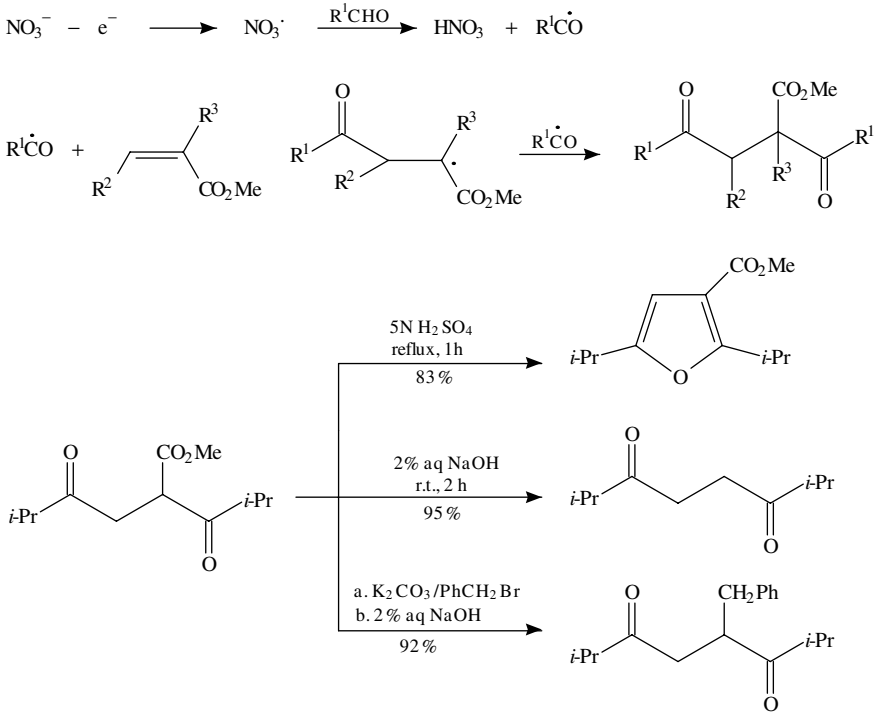
One of the few anodic transformations of ketones in the presence of halogen derivatives which appears to involve anodic oxidation of the carbonyl compound itself is shown in

equation 34[93]. The stability of the uncommon tertiary fluoride functionality in methanol is noteworthy.



(34)

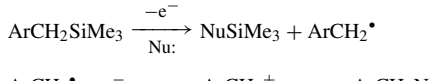
Anodic oxidation of a mixture of an aldehyde and an activated ester in aqueous acetonitrile containing lithium nitrate results in addition of two acyl groups derived from the aldehyde across the C=C double bond. These diacylated substances exhibit a diverse chemistry (Scheme 17)[94].



SCHEME 17

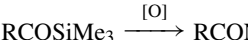
2. Other carbonyl compounds

The high electropositivity of silicon means that the carbon–silicon bond is readily oxidized. Yoshida has carried out an extensive study of the anodic oxidation of benzyl and allyl silanes[95]. Oxidation converts the silane to a carbocation, which then reacts with a nucleophilic component of the medium (Scheme 18). Yoshida has shown that the reaction

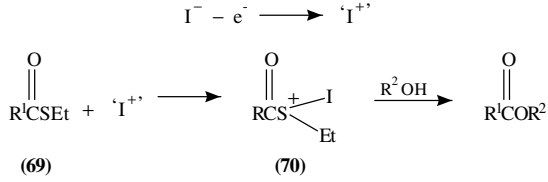


SCHEME 18

can be extended to the anodic oxidation of acyl silanes in the presence of a variety of nucleophiles (equation 35)[96] A somewhat related study involves the oxidation of thioesters **(69)** in an alcohol solvent containing an iodide salt[97]. Replacement of sulfur by the alcohol takes place, perhaps via an activated iodosulfonium species **(70)** (Scheme 19).

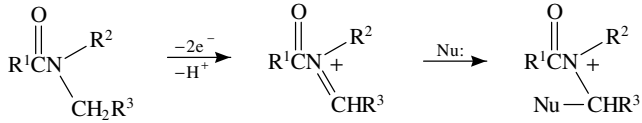


(35)



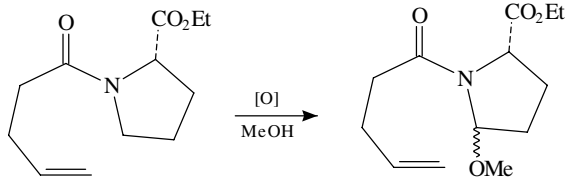
SCHEME 19

Shono and others have shown that electrochemical oxidation of amides in nucleophilic media results in incorporation of the nucleophile into the *alpha*-position of the N-alkyl group via an intermediate iminium species (equation 36). This so-called 'anodic *alpha*-functionalization' reaction has been shown to be of considerable synthetic value. The reaction has been extensively reviewed[98].



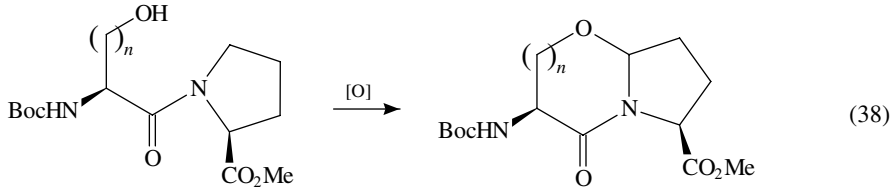
(36)

Moeller has more recently contributed a series of reports describing the further use of this reaction in synthesis. Oxidation of the unsaturated amide **71** in methanolic acetonitrile afforded a substance **72** (equation 37) which could subsequently be converted into conformationally restricted peptide mimics[99]. Further, anodic oxidation of **73** resulted in intramolecular cyclization to afford **74** (equation 38), which could be converted into bicyclic reverse-turn peptidomimetics[100]. A similar intramolecular anodic cyclization of **75** into **76** (equation 39) was employed as the key step in total syntheses of the natural products (−)-A58365A and (+)-A58365B[101].



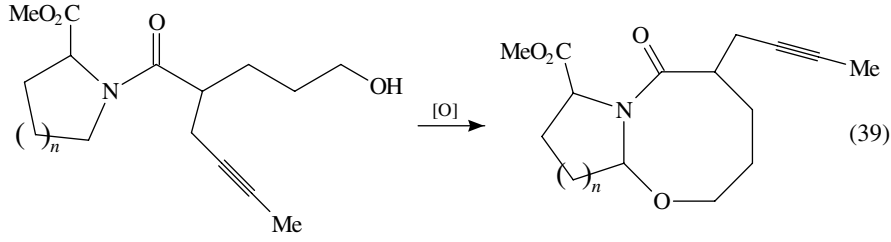
(37)

(71) **(72)**



(38)

(73) **(74)**



(39)

(75) **(76)**

C. Electroenzymatic Synthesis

There is much interest at the present time in the possibility of using electric current to regenerate the cofactors, especially NAD(P)+ and NADH(P), required by enzymes which catalyze redox processes. If successful, this concept would combine the high degree of selectivity of the enzyme with the electrode as an inexpensive source of reducing (or oxidizing) power. The essential concept is illustrated in Scheme 20 for oxidation of an alcohol to the corresponding carbonyl compound. The electrode would oxidize the cofactor (in this case NADH) to the form (NAD^+) needed for the enzymatic synthesis. After the desired conversion has been carried out, the NADH would return to the electrode to be oxidized again and begin the cycle anew. The idea is conceptually simple, but can be difficult to implement in practice. The very high cost of these redox cofactors (NADH costs more than $20,000/mole in bulk in 1996) requires that practical syntheses of this type exhibit turnover numbers of 1000–10,000 or higher. Furthermore, the reverse process, reduction of a carbonyl compound to an alcohol, generally fails because electrochemical reduction of NAD^+ affords not NADH but an inactive dimer[102]. It is therefore necessary to employ an electrocatalyst to insure that NAD^+ is converted to NADH at the electrode. This catalyst is typically a combination of a second enzyme, lipoamide dehydrogenase (LiDH; diaphorase), which catalyzes the NAD^+ NADH interconversion, with an electron-transfer mediator, for example of the viologen **(24)** type[103]; certain organometallic complexes can effect the same conversion nonenzymatically[104]. Whitesides was one of the first to reduce these concepts to practice. His procedure[105] for stereoselective L-lactate dehydrogenase (LDH)-catalyzed conversion of pyruvate to L-lactate involving passage of a current through a solution containing LiDH, LDH, **24**, pyruvate and NAD^+ (catalytic amount) is shown in Scheme 21. Other syntheses can be carried out by replacing pyruvate and LDH with the appropriate substrates and enzymes[105].

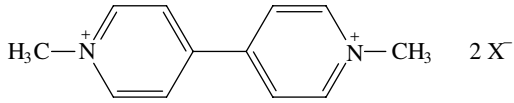
Steckhan has reviewed progress in the area of electroenzymatic synthesis[106]. His review constitutes an excellent summary of previous work in this area. A few recent advances should be mentioned here. There is much interest in improving the practicality of these electroenzymatic conversions. Although Scheme 21 above proves the essential validity of the concept, it is highly impractical for large-scale operation because (a) the two enzymes

$$NADH - 2e^- \longrightarrow NAD^+ + H^+$$

$$NAD^+ + R_2CHOH \longrightarrow NADH + R_2C{=}O + H^+$$

Net : $R_2CHOH - 2e^- \longrightarrow R_2C{=}O + 2H^+$

SCHEME 20



(24)

$$\mathbf{24}^{2+} + e^- \longrightarrow \mathbf{24}^{1+}$$

$$2\ \mathbf{24}^{1+} + LiDH_{ox} \longrightarrow 2\ \mathbf{24}^{2+} + LiDH_{red}$$

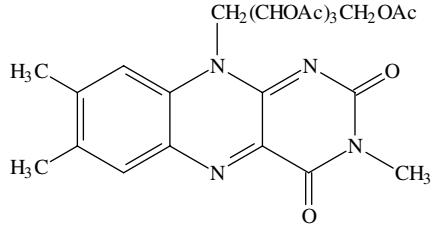
$$NAD^+ + LiDH_{red} \longrightarrow LiDH_{ox} + NADH$$

$$NADH + \text{pyruvate} \xrightarrow{LDH} NAD^+ + \text{(+)-lactate}$$

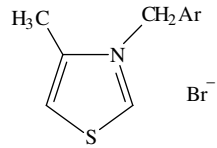
LiDH = lipoamide dehydrogenase; LDH = L-lactate dehydrogenase

SCHEME 21

are short-lived (half-lives less than two days), (b) viologen derivatives **24** are highly toxic and represent unacceptable potential contaminants, (c) the fact that all of the components are in solution makes separation of the desired product difficult and (d) any attempt to isolate the product will probably destroy the two redox enzymes. Any successful scheme for electroenzymatic synthesis must address all of these problems. One attractive approach is to replace the redox mediator LiDH with a synthetic catalyst. This is the approach taken by Steckhan, who uses a rhodium complex to convert NAD^+ to NADH[104,106]. Similarly, Diederich has shown that the conversion of substituted benzaldehydes to methyl esters can be accomplished by electrochemical oxidation of a mixture of the aldehyde, a flavin derivative **(77)** and a thiazolium salt **(78)** in methanol (Scheme 22)[107]. The thiazolium salt first condenses with the aldehyde. The reduced form of the flavin ($\mathbf{77}_{red}$), a mimic of the redox enzyme active site, is oxidized at the anode to its active form ($\mathbf{77}_{ox}$), which then oxidizes the thiazolium adduct to an acyl thiazole, which in turn reacts with the solvent to afford the ester.



(77)



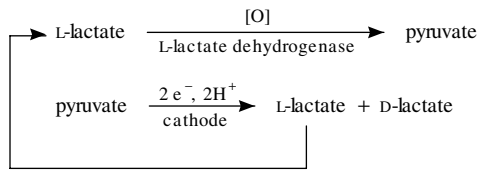
(78)

SCHEME 22

An alternate approach to solving the problems (a)–(c) cited in the previous paragraph seeks to retain the two enzymes and redox mediator **24** of Scheme 21, but somehow both extend the lifetime of the two enzymes and isolate them and also **24** from the bulk of solution so that separation of the product in a pure form, uncontaminated by **24**, is easier. Substantial progress on this problem has recently been made by Fry and Sobolov and their collaborators. It was found that LiDH and **24** can be co-immobilized on a carbon electrode under an insoluble cation exchange membrane[108,109], thus simplifying the composition of the electrolysis solution. A side benefit turned out to be a better than tenfold enhancement of the lifetime of LiDH when so immobilized. Unfortunately **24** slowly leaks into solution from the electrode under these conditions. This problem was addressed in two alternative ways: (a) chemically binding a viologen derivative to the enzyme[110] and (b) incorporating LiDH and an oligomeric viologen derivative into a complex copolymer on the electrode surface[111]. The twin problems of the instability of LDH in solution and the difficulty of separating it from the electrolysis product were solved by resorting to the use of so-called 'cross-linked enzyme crystals'[112] or CLCs. The concept of a CLC is based on the facts that (a) enzymes retain their activity for long times in the crystalline state and that (b) components of a solution within which the crystal is placed can freely diffuse into and out of the crystal. An enzyme is crystallized from concentrated salt solution and the crystals are treated with a cross-linking agent, usually glutaraldehyde, which forms Schiff base linkages with lysine amino groups on the exterior of the crystal. The product is a CLC: an insoluble solid which retains the high activity of the original enzyme for very long times. Typically, CLCs have lifetimes measured in years in contrast with the lifetime (days) of the enzyme in solution. Fry and Sobolov and coworkers prepared CLCs of LDH[113]. These LDH-CLCs could be placed in a permeable pouch made of dialysis tubing. The enzyme is thus easily removed from the solution at the end of electrolysis for later re-use. All of these experimental variations could be incorporated into a single experiment in which an electrode coated with either the LDH-**24** copolymer was immersed in a solution containing pyruvate, a trace of NAD^+, the LDH-CLC (in its dialysis pouch). Passage of current resulted in efficient production of L-lactate and ready isolation of the latter at the conclusion of electrolysis[113]. These concepts are readily incorporated into electrochemical flow cells designed for continuous electrolysis[114].

Matsue's group has immobilized *both* LiDH and alcohol dehydrogenase (ADH) on a single electrode[115]. The electrode was immersed in a solution containing methyl viologen **(24)**, NAD^+ and any of several cyclohexanone derivatives and current was passed. The ketones were reduced to the corresponding alcohols with good current efficiency. The course of the reduction is very similar to that of Scheme 21, except for the replacement of LDH and pyruvate by ADH and ketone and the fact that the viologen was in solution, not on the electrode. The efficiency of the process derives at least in part because the two enzymes are in close physical proximity; NADH and NAD^+ merely have to shuttle back and forth between the two enzymes. A similar concept was introduced by Fry, Sobolov and coworkers, who co-crystallized the two enzymes LiDH and LDH and then cross-linked the resulting crystals to create *cross-linked dual enzyme crystals*[116]. These prove to be highly efficient for conversion of pyruvate to lactate, again because the two enzymes are in close physical proximity.

The characteristic stereospecificity of enzymes has been exploited in the design of an electrochemical cell for the conversion of L-lactate to D-lactate (Scheme 23)[117]. Enzymatic oxidation of L-lactate by L-lactate dehydrogenase affords pyruvate. Pyruvate is then reduced electrochemically to racemic lactate. A second enzymatic oxidation of the latter by L-lactate dehydrogenase selectively converts L-lactate to pyruvate, leaving D-lactate behind. The ingenious feature of this system is the fact that pyruvate can be re-reduced



SCHEME 23

to racemic lactate, so that after several cycles one effects essentially complete overall conversion of one enantiomer to the other.

VI. ACKNOWLEDGMENTS

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CHAPTER **13**

Photochemistry of compounds containing C=C double bonds

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I. INTRODUCTION

The photochemistry and photophysics of C=C double bonds have been extensively investigated since the 1960s, especially when new spectroscopic techniques such as

laser flash spectroscopy, ESR spectroscopy and others have provided powerful tools for precise investigation of photochemical reactions. Much effort is currently focused on the photoisomerization and photodimerization of C=C double bonds conjugated to aromatic substituents, on mechanistic studies and on synthetic applications of stereoselective *inter*- and *intra*molecular photocycloadditions of C=C double bonds to enones.

This chapter summarizes and discusses the recent advances in the organic photochemistry of C=C double bonds. Special attention is focused on the photocycloaddition of alkenes to cyclic enones, including the mechanism, regio- and stereoselectivity and synthetic applications of the reaction.

II. EXCITED STATES

The ultraviolet spectroscopy and the electronic excited states of C=C and C=O chromophores is well discussed in several recent books and reviews[1–6]. However, it is necessary to start by presenting some UV properties of these chromophores in unconjugated and conjugated structures. Simple alkenes are known to undergo $\pi \rightarrow \pi^*$ transition to the lowest singlet excited state S_1 upon UV absorption at the range of 170–210 nm, which is strongly affected by substituents on the C=C bond. In simple C=O chromophores, two possible excitations take place. The first one is excitation of an electron from the nonbonding orbital on the oxygen to the antibonding π orbital ($n \rightarrow \pi^*$), with typical UV absorption of unconjugated carbonyls at 290–330 nm, when this forbidden transition is observed with a very small extinction coefficient ($\varepsilon = 10\text{–}10^2$ $mol^{-1}\,cm^{-1}$) and corresponds to excitation to the lowest energy excited state S_1 (Figure 1). The next transition occurs by $\pi \rightarrow \pi^*$ excitation upon absorption at 180–220 nm.

Mixed chromophores with both C=C and C=O moieties such as α,β-unsaturated enones are one of the most investigated chromophores in organic photochemistry. Conjugation of the two chromophoric moieties results in lowering the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ energy levels relative to the unconjugated chromophores. UV absorption spectra of selected alkenes, ketones and enones are presented in Table 1.

The lowest vibrational level of the S_1 state is the origin in most of the known photoreactions. The average lifetime of the S_1 excited state before fluorescence radiative decay is $10^7\text{–}10^{10}$ s^{-1}. Competing processes, chemical reactions or intersystem crossing (ISC) to the triplet excited state T_1 must take place at a faster rate than the $S_1\text{–}S_0$ decay. The T_1 lifetime is significantly longer (*ca* 10^6 s^{-1}) than the S_1 state.

Direct excitation of C=C bonds to the T_1 state can be achieved via transfer of triplet excitation from electronically excited sensitizers. Selected singlet and triplet energies

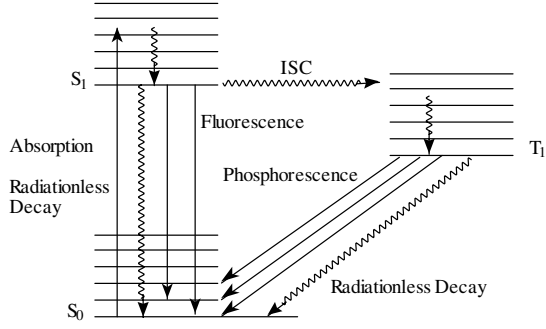


FIGURE 1. Modified Jablonski diagram. Reproduced by permission of Academic Press, Inc. from Ref. 3

TABLE 1. UV absorption spectra of selected C=C and C=O chromophores[1]

Chromophore	λ_{max}(nm)	ε_{max}	Transition type
C=C	180	10,000	π,π^*
C=C−C=C	220	20,000	π,π^*
Benzene	260	200	π,π^*
Naphthalene	310	200	π,π^*
C=O	280	20	n,π^*
C=C−C=O	350	30	n,π^*
C=C−C=O	220	20,000	π,π^*

TABLE 2. S_1 and T_1 energies of C=C bonds and related chromophores[1]

Compound	S_1	T_1
CH_2=CH_2	120	82
CH_2=CMe_2	95	81
Acetone	84	78
Acetophenone	80	74
Benzophenone	76	69
CH_2=CH−CHO	74	70
Cyclopentenone	83	74
Cyclohexenone	80	75(n,π^*)
		74(π,π^*)
2-Methylcyclohexenone	*ca* 76	76(n,π^*)
		74(π,π^*)
Benzene	115	85
Naphthalene	90	61

(kcal mol^{-1}) of C=C bonds and related chromophores are summarized in Table 2.

III. *Z*–*E* ISOMERIZATIONS

Photochemical $Z \leftrightarrows E$ isomerization of C=C double bonds is one of the typical reactions of acyclic alkenes which can occur by direct or sensitized excitation. The mechanism and the potential energy surfaces of this isomerization have been extensively investigated since the sensitized isomerization studies of stilbenes, first reported by Hammond, Saltiel and coworkers in the 1960s[7–9]. In most cases the isomerization process takes place by excitation of either Z or E alkene to its first excited singlet state (S_1), generally agreed to be responsible for the isomerization, followed by rapid decay to the ground state (S_0), which is faster in most alkenes than the alternative intersystem crossing to the corresponding excited triplet state (T_1). The isomerization process can proceed at either the S_1 or T_1 excited state via twisting motion on the C=C bond until it reaches a corresponding geometry, crossed at the potential energy surface with radiationless decay, after which it decays to the S_0 ground state as could be generally described by the typical potential energy surfaces in Figure 2.

Photoisomerization of alkenes via the triplet excited state is known to be possible by triplet sensitization, usually efficient in conjugated C=C bonds that fulfill the requirement of possessing triplet excited energies below those of the typical triplet sensitizers such as acetone, acetophenone, benzophenone, etc. (Table 2). Sensitization with the opposite order of triplet excited energies is possible in cases with strong electronic or strong

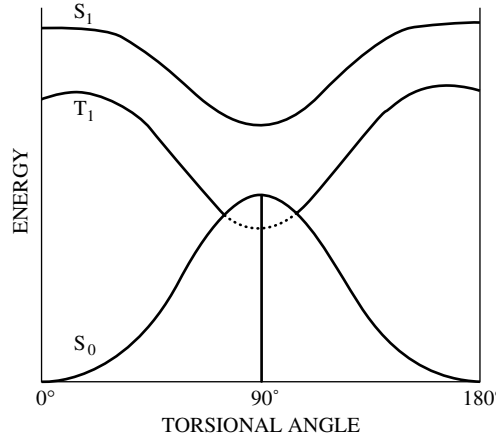
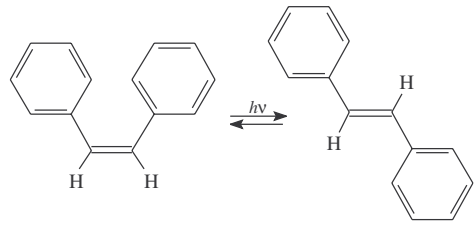
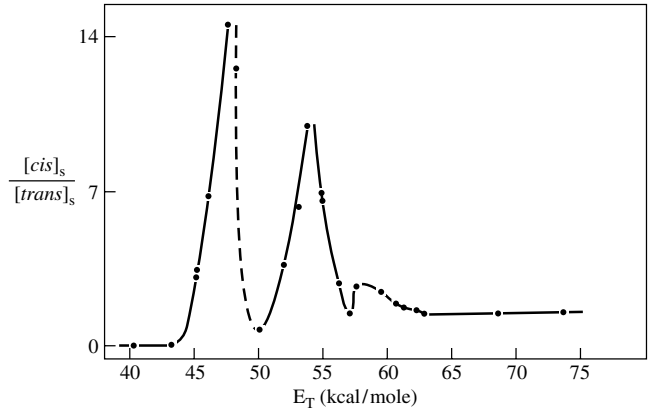


FIGURE 2. Potential energy surfaces of S_1, T_1 and S_0 states of alkenes and their dependence on the torsional angle. Reprinted with permission of Academic Press, Inc. from Ref. 3



(1) **(2)**

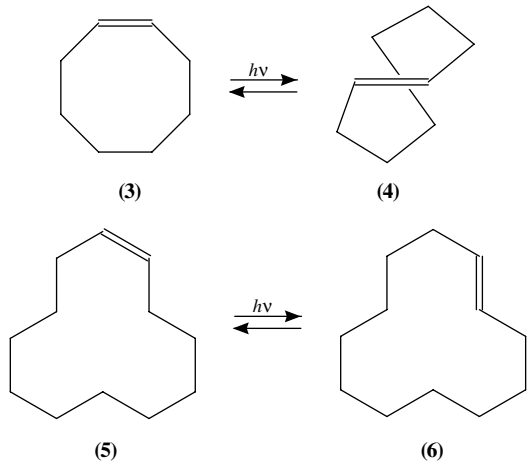


SCHEME 1. The effect of the triplet excitation energy of the sensitizer on the *Z*/*E* isomerization of stilbene at the photostationary state. Reprinted with permission from Ref. 7. Copyright (1964) American Chemical Society

spin–orbit interactions between the sensitizer and the alkene[10]. The ratio of the isomers at the photostationary state depends on the triplet excitation energy of the sensitizer (Scheme 1). This was examined by Hammond and coworkers and best demonstrated by the $Z \leftrightarrows E$ isomerization of stilbene with various triplet sensitizers[7].

A. Isomerization of Cyclic Alkenes

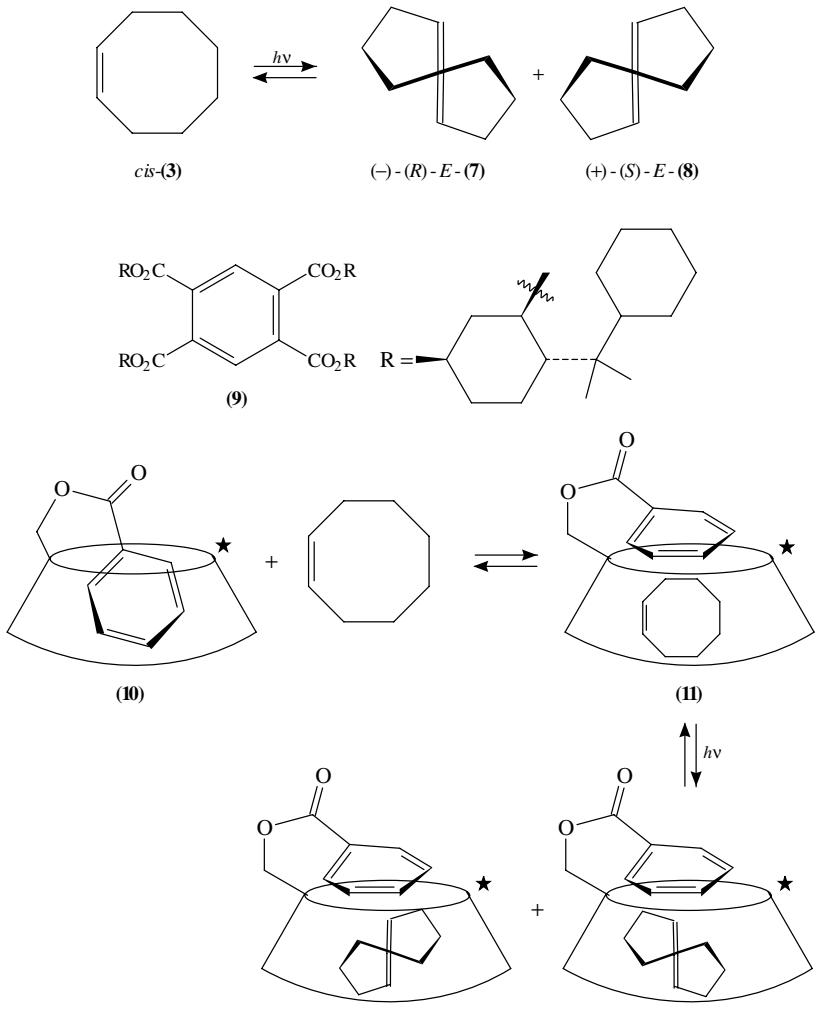
Cyclic alkenes undergo geometrical photoisomerization in medium and large ring systems upon either sensitized or direct irradiation. Cyclooctene was the smallest cycloalkene possessing an *E* double bond which has been isolated. Isomerization studies on cyclooctene using different triplet sensitizers ($E_t \geqslant 74$ kcal mol^{-1}) revealed the *Z*-alkene as the major product in a mixture with the corresponding *E*-isomer[11], and a similar result was obtained in the isomerization of cyclododecene (**5** $\leftrightarrows$ **6**)[12]. However, direct irradiation (185 nm) of cyclooctene[11b] affords a photostationary state mixture with an *E*/*Z* ratio of approximately unity[11b,13,14] and provides a convenient method for the preparation of the corresponding *E*-isomer **4** (Scheme 2). However, it should be noted that among the best yields, the *E*-isomer was obtained[13] in about 37% yield in a mixture with methylenecycloheptane and bicyclo[5.1.0]octane.



(3) **(4)** **(5)** **(6)**

SCHEME 2

E-Cyclooctene has two enantiomeric forms **7** and **8** (Scheme 3). Interestingly, sensitized photoisomerization of cyclooctene using chiral sensitizers afforded (*R*)-(−)-*E*-cyclooctene **7** with *ca* 4% enantiomeric excess[15]. Studies on the asymmetric photoisomerization of *Z*-cyclooctene with simple β-cyclodextrins via direct irradiation at 185 nm in the solid state or in water suspension afforded in the photostationary state *E*/*Z* mixtures with negligible optical activity (<1%) in the *E*-isomer[16]. However, enantioselective photoisomerization of cyclooctene has been achieved[17] in high optical purity (64%) upon irradiation via sensitization with optically active benzopolycarboxylates **9** affording *E*-**7**. Recently Inoue and coworkers[18] have employed β-cyclodextrin 6-*O*-monobenzoate **10** as a novel photosensitizer host molecule carrying a chiral cavity. Irradiation of 1:1 complex of *Z*-cyclooctene with cyclodextrin **11** in water–methanol solutions afforded the best ratios of *E*/*Z* (0.8) and enantiomeric excess (6%) in 50% MeOH solution. The enantiomeric



SCHEME 3

excess (ee) was found to be affected by the solvent composition and the irradiation period with preferential formation of the (*R*)-*E*-isomer **7**; the best ee was obtained in *ca* 11% ee in very low $Z \rightarrow E$ conversions.

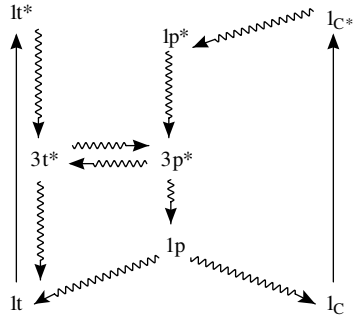
Photoisomerizations of cycloheptenes and cyclohexenes are known as well, and photosensitized excitation and isomerization of these have been directly detected using nanosecond flash photolysis techniques[19] and time-resolved photoacoustic calorimetry[20].

B. Isomerization of Aryl Alkenes

1. Two-way ($Z \leftrightarrows E$) geometrical isomerization

Extensive investigations on the $Z \leftrightarrows E$ isomerization of stilbenes have revealed that stilbene undergoes mutual isomerization in the singlet or triplet manifold on direct or

triplet sensitization, respectively[7–9,21]. Polar substituents on the phenyl rings of stilbene have shown no considerable effect on the mutual isomerization as found by Gorner and coworkers[22]. A typical mechanistic scheme for the $Z \leftrightarrows E$ isomerization of 4-nitrostilbene is shown in Scheme 4.



SCHEME 4. Reprinted with permission of VCH from Ref. 22g

On excitation of the *E* and *Z* ground states (^1t and ^1c respectively) into their corresponding first excited singlet states, the lowest triplet states are populated by the intersystem crossing (ISC) steps $^1t^*$–$^3t^*$ and $^1c^*$–$^1p^*$–$^3p^*$. The planar and twisted ($^3p^*$) triplet configurations form a rapidly established $^3t^* \leftrightarrows {}^3p^*$ equilibrium[23]. Radiationless decay of $^3t^*$ to ^1t is important in highly viscous solutions but does not play a role at room temperature. However, decay of the triplet occurs predominantly via the twisted configuration, followed by conversion to the ground state. In solutions, ISC of the twisted triplet $^3P^*$ is the main process. In accordance with these results, along with Mulliken's calculations of the potential energy surface of the excited and ground state of ethylenes along the rotation of the C=C bond linkage, it had long been accepted that the olefins generally would undergo isomerization mutually between their corresponding *Z*–*E* configurations. However, in the last decade a one-way isomerization of aryl olefins was extensively investigated by Tokumaru and coworkers[9].

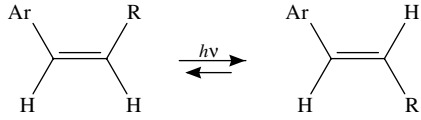
2. One-way (*Z* → *E*) geometrical isomerization

In comparison to the conventional two-way isomerization ($Z \leftrightarrows E$) of stilbene and other aryl alkenes **12** (Scheme 5), a novel one-way isomerization ($Z \rightarrow E$) of C=C double bonds was achieved upon replacing a phenyl group of stilbene by a 2-anthryl group[9a,c]. Tokumaru and coworkers found in isomerization studies on substituted anthracenes[9] that substitution at the C=C bond resulted in complete isomerization of the *Z*-isomer to the corresponding *E*-isomer upon irradiation, via a quantum chain process. Interestingly, the isomerization takes place as an adiabatic process in the triplet manifold on both direct and triplet sensitized irradiations.

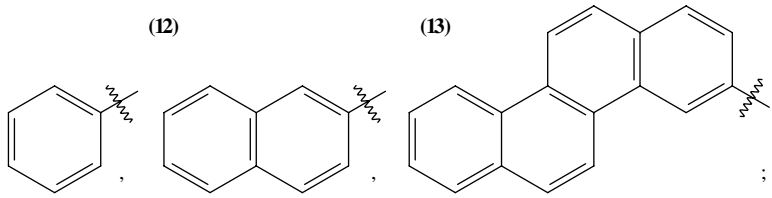
Typical potential energy surfaces proposed for one-way (a,c) and two-way (b) isomerizations of olefins are described in Figure 3.

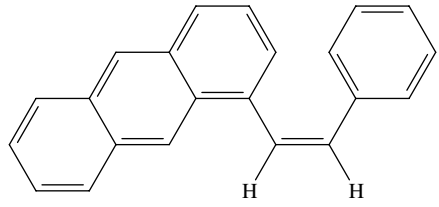
3. One-way (*E* → *Z*) geometrical isomerization

Photoisomerization of *E*-C=C double bonds substituted with heteroaromatic groups that allow intramolecular hydrogen bonding were found to afford one-way $E \rightarrow Z$

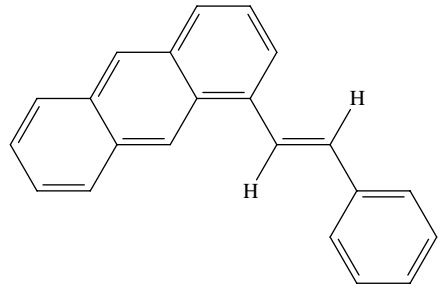


(12) **(13)**

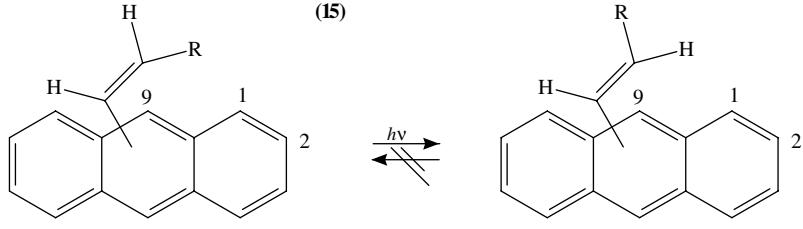
Ar =  ; R = *t*-Bu, Ph



(14)



(15)



(16) **(17)**

R = Ph, *t*-Bu

SCHEME 5

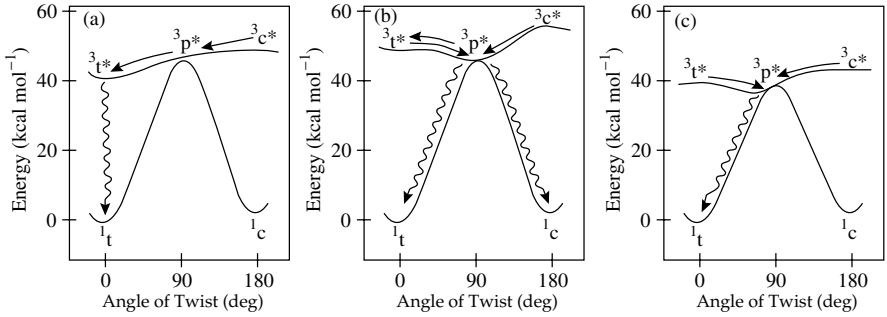
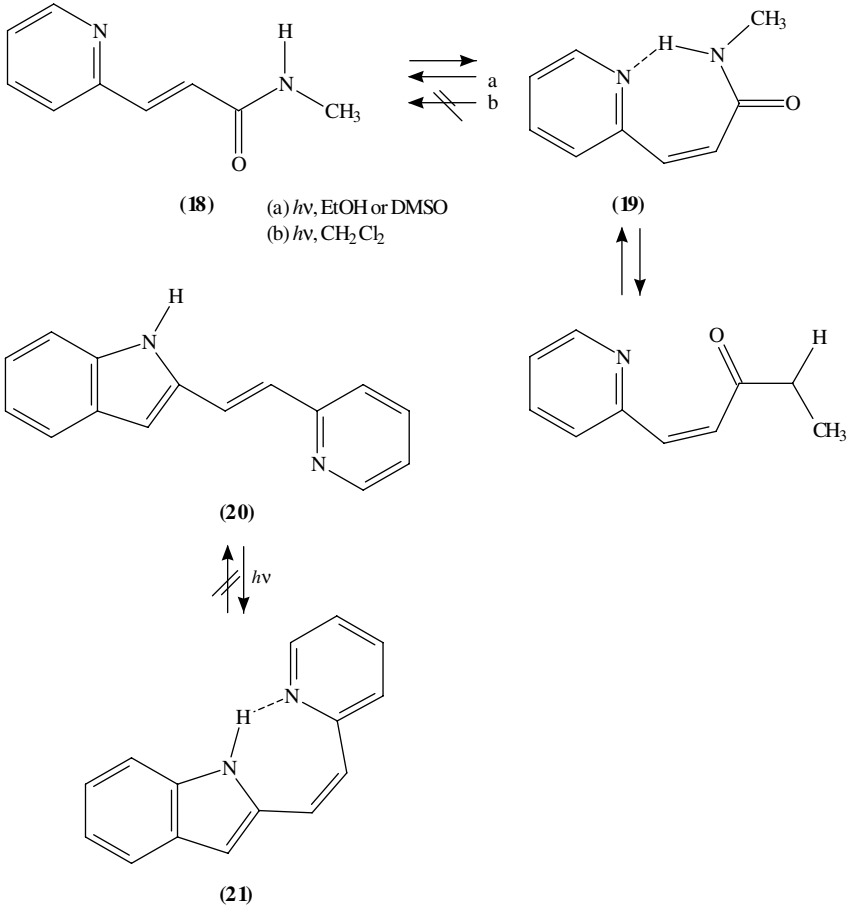


FIGURE 3. Potential energy surfaces proposed for one-way (a,c) and two-way (b) isomerization of alkenes. Reprinted with permission from Ref. 9c. Copyright (1993) American Chemical Society



SCHEME 6

isomerization. For example[24], direct irradiation of **18** affords complete isomerization to the corresponding Z-isomer **19** in methylene chloride as solvent, while irradiation in ethanol or DMSO provides two-way isomerization (Scheme 6). Another example was found[25] in the irradiation of **20** to **21**. In general, such isomerizations take place upon direct irradiation in nonpolar solvents presumably via the first excited singlet state.

The effect of intramolecular hydrogen bonding plays an important role in the $Z \rightarrow E$ photoisomerization, e.g. in the (4*Z*, 15*Z*) equilibrium of **23** (Scheme 7), the final metabolic product of hemoglobin in living bodies[26]. Isomerization studies in solvents with different polarity[27] revealed that the more the intramolecular hydrogen bonds are weakened, the more efficient the $Z \rightarrow E$ isomerization at C-4 becomes, and this isomerization is necessary for the cyclization of **26** to **24**. In human serum albumin (HSA) **23** undergoes specific photoisomerization to the *ZE*-isomer **22** induced by intermolecular hydrogen bonding or salt bridges with the amino acid residues of HSA.

The geometric isomerization of olefins via photochemical electron transfer is well known[28,29] and can be divided into two categories: (a) isomerization via the radical cation, in which case the olefin is the donor in the presence of an excited electron acceptor; (b) isomerization via the radical ion pair, which leads to the triplet-excited olefin, and in this mechanism the olefin is the acceptor. This subject is not discussed in this chapter because of space limitations. However, several reviews[30] can be consulted in this regard.

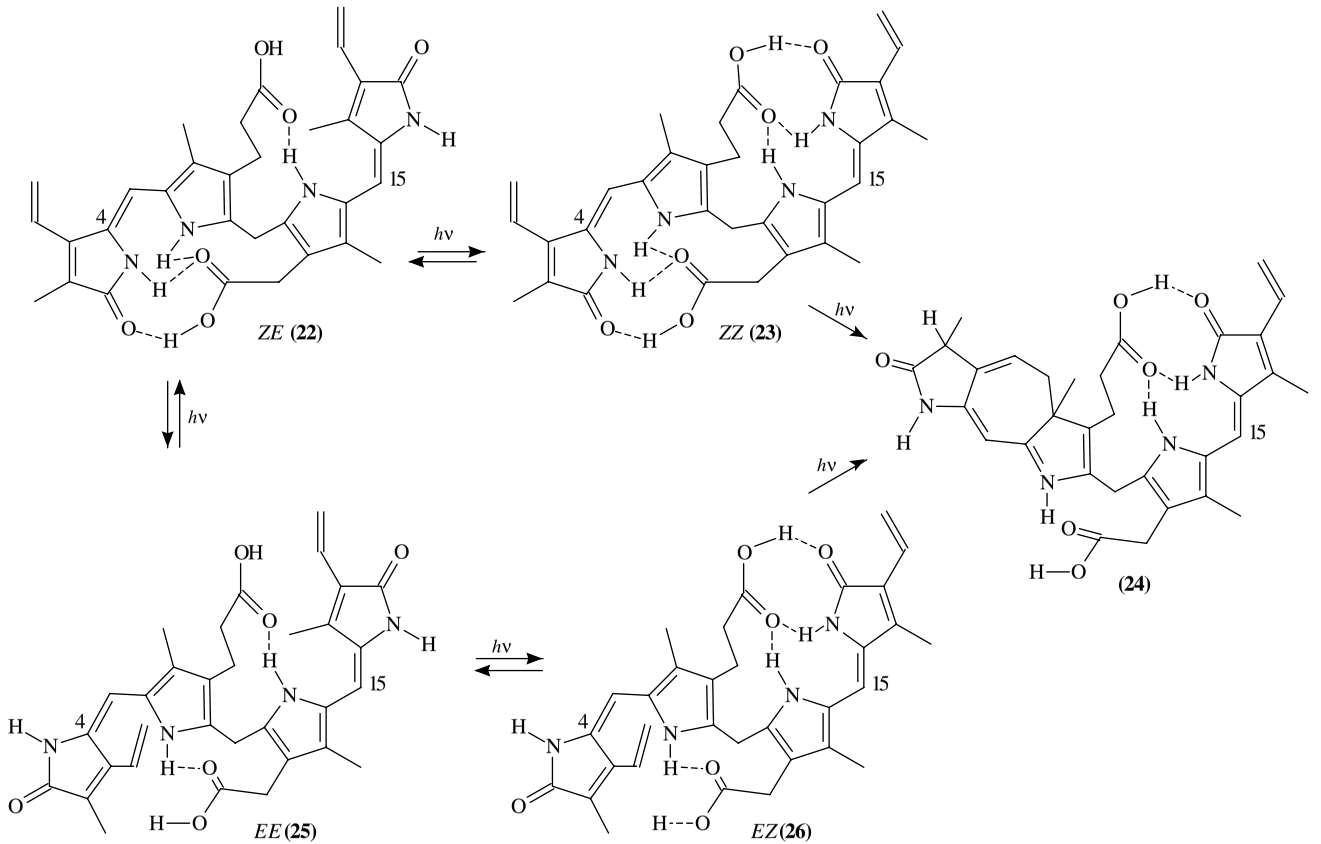
IV. [2 + 2] PHOTODIMERIZATIONS

The intermolecular photodimerization of alkenes is known to take place via addition of the triplet or singlet excited state of the C=C double bond to the ground state alkene. The dimerization in the former mechanism is a competing reaction with the photoisomerizations of acyclic or large cycloalkenes ($n \geqslant 8$) discussed above. Acyclic, exocyclic and large-ring alkenes do not undergo photosensitized dimerization, presumably due to the fast relaxation of the triplet excited state via its orthogonal geometry[2]. However, direct irradiation of acyclic and large-ring cyclic alkenes provided photodimerization.

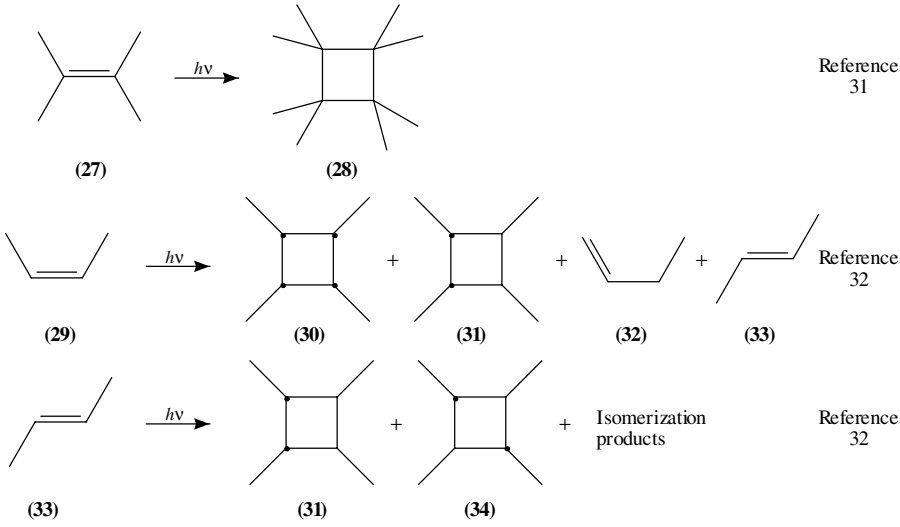
A. Dimerizations of Unconjugated Alkenes

Direct irradiation of tetramethylethylene **27** afforded octamethylcyclobutane **28** (Scheme 8) in good yield[31]. Stereospecific dimerization was obtained in the irradiation of concentrated solutions of *Z*- and *E*-2-butenes **29** and **33**, respectively[32]. Irradiation of **29** afforded a mixture of the all-*cis* product **30** and the *cis–anti–cis* **31** along with double bond migration **(32)** and $Z \leftrightarrows E$ isomerization **(33)**. Irradiation of *E*-2-butene **33** afforded **31** and *trans–anti–trans* **34** as the dimeric products.

Photosensitized dimerization of small-ring alkenes using acetone and/or acetophenone as triplet sensitizers is an efficient reaction. Typical examples are summarized in Scheme 9. Dimerization of cyclopropene **35** afforded head-to-head (H,H) **36** and head-to-tail (H,T) **37** isomers in good yield[33]. Much lower yields were obtained in the dimerization of acyclic and larger cyclic alkenes[34,35] **38** and **40**. Interestingly, cyclohexene[36,37] undergoes an efficient sensitized photodimerization affording three isomeric dimers **43**, **44** and **45** in 92% total yield. Bridged bicyclic alkenes that could not undergo efficient $Z \rightleftarrows E$ isomerization provide the corresponding dimers in acceptable to good yields. The dimerization of 2-norbornene **46**, which was first reported by Sharf and Korte[38] and later examined in a large number of solvents and sensitizers[39], afforded in all cases isomeric mixtures of **47** and **48** in good yields.



SCHEME 7. Reprinted with permission from Ref. 9a. Copyright (1995) John Wiley & Sons, Inc.



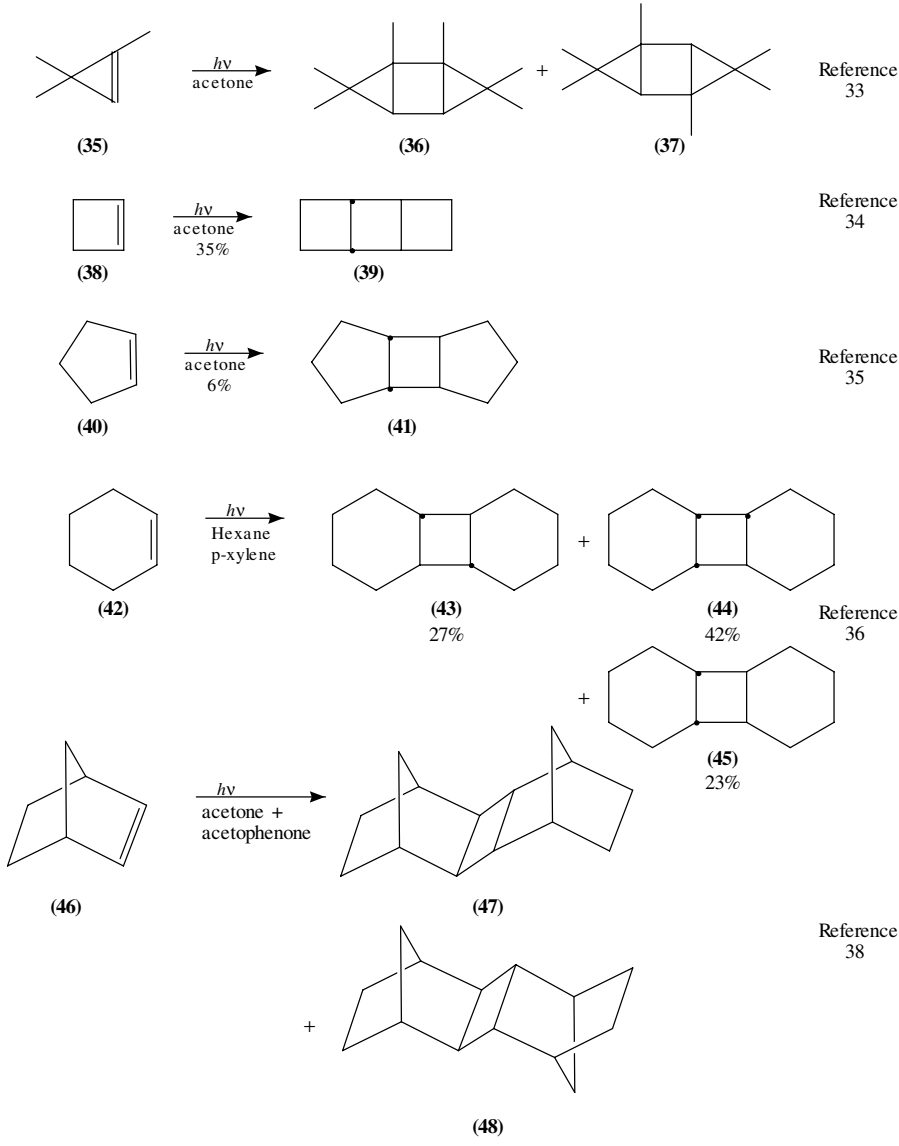
SCHEME 8

Considerably improved dimerization of medium–small ring alkenes was obtained in copper(I) salt catalyzed irradiations. Interestingly, the dimerization of small[37] and bridged bicyclic[40] alkenes **40** and **46**, respectively, afforded the corresponding *cis–anti–cis* dimers as major products, whereas dimerization of cyclohexene and cycloheptene[37] afforded the *trans–anti–trans* dimers **43** and **51**, respectively (Scheme 10). These results are consistent with the suggested mechanism for the cases of catalyzed photoisomerizations to the *E*-alkene that undergo stereoselective dimerization with a *Z*-alkene affording the *trans–anti–trans* geometry in the produced dimer.

B. Dimerizations of Vinylaryls

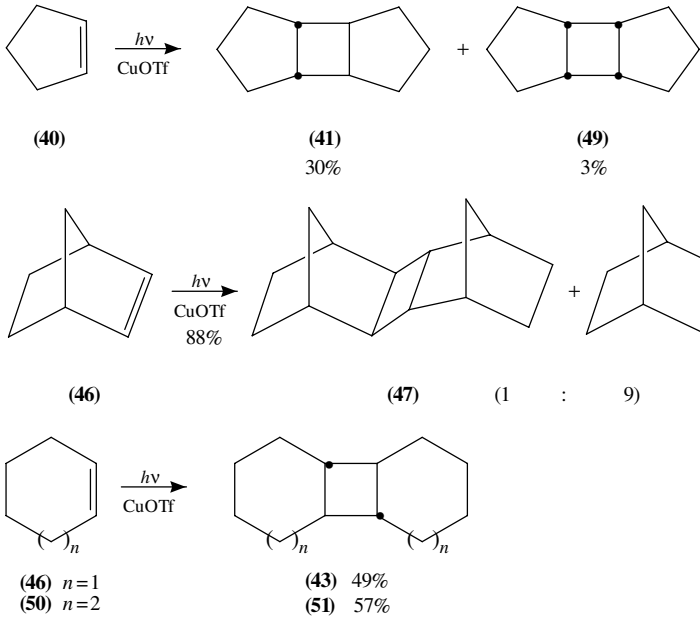
The photodimerization of *trans*-stilbene was first discovered by Ciamician[41] at the beginning of the twentieth century; however, the structures of the major product **52** and the minor isomer **53** (Scheme 11) were determined much later[42]. The mechanism of the photoaddition was extensively investigated and recently discussed by Meier[43]. Due to the fact that intersystem crossing of alkenes and polyenes is generally inefficient from S_1 to its corresponding T_1, the reaction proceeds stereospecifically upon direct irradiation, via the singlet excited state by diffusion-controlled formation of nonfluoresent singlet excimers, which transfer to the minima D_1 of the doubly excited singlet state for a pericyclic geometry of the intermediate and are rapidly deactivated to the ground state of the products[44]. Excimers and pericyclic minima determine the regioselectivity (H,H vs H,T) and the stereoselectivity (*syn* vs *anti*) of the cycloaddition reaction. However, predicting the regiochemistry is difficult as noted by Meier[43], since according to the perturbation theory, the head-to-head adducts should give the most stable excimers and the head-to-tail adducts the most stable pericyclic minima[44].

The photodimerization is a reaction competing with the previously discussed photoisomerization (Section III). The quantum yields of photodimerizations are affected by the concentration of the photosubstrate ($c \geqslant 0.1\ \mathrm{mol\,L^{-1}}$) and the polarity of the

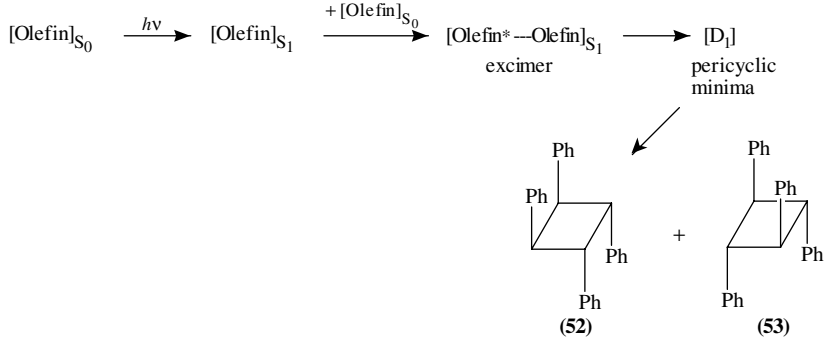


SCHEME 9

solvent. Fixed geometrical arrangement of the photosubstrates affects the regioselectivity of the photodimerization reaction. In a study[45] of the photodimerization of (*E*)-2,4-dichlorostilbene in solution a mixture of (H,H) and (H,T) isomers was obtained. However, irradiation of this compound in the solid state afforded selective dimerization to the (H,H) product. Other examples could be seen in the photodimerization of several cinnamic acid derivatives in the crystal form, studied by Schmidt[46], which were found to afford selective formation of cyclophanes. The photocyclization reaction

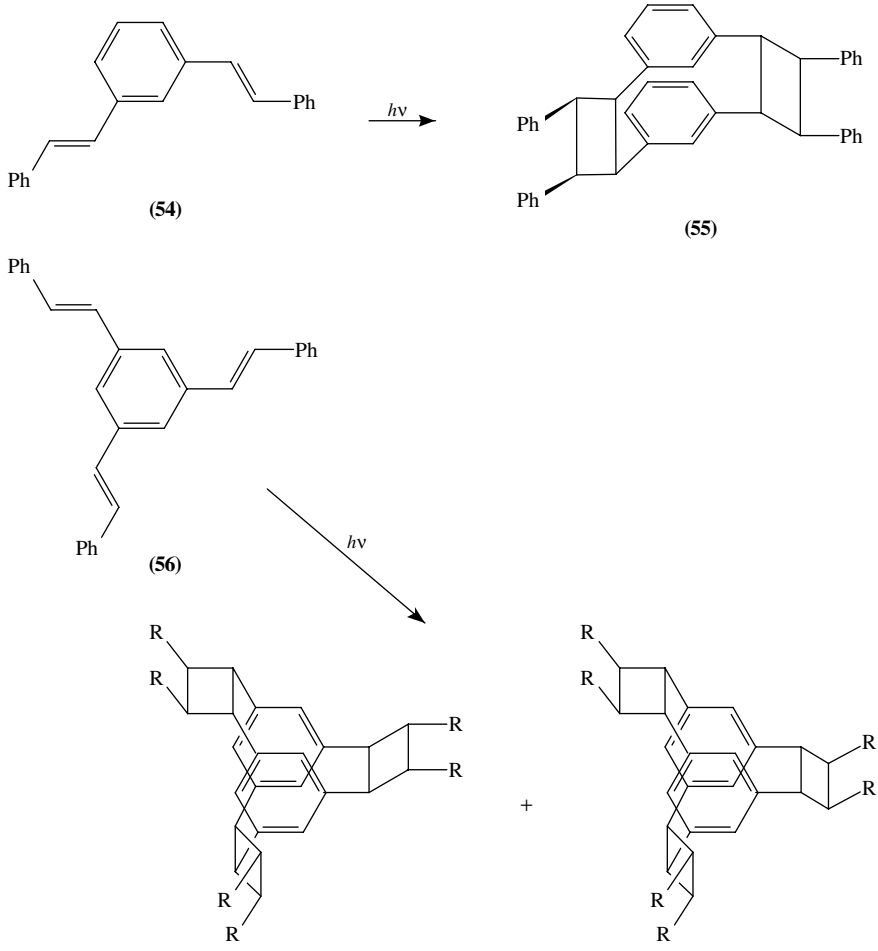


SCHEME 10



SCHEME 11

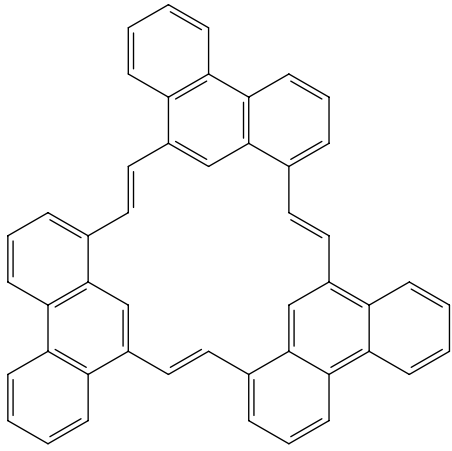
becomes the method of choice for the preparation of various cyclophane systems, especially in the intramolecular cases (discussed later). Meier and coworkers[43] obtained highly stereocontrolled photodimerization of substituted vinylbenzenes **54** and **56a** in concentrated solutions, affording the corresponding cyclophanes **55** and **57a** + **58a** (30:1), respectively (Scheme 12). Similar results were obtained later by Nishimura and coworkers[47] upon irradiation of trivinylbenzene **56b** to afford the corresponding cyclophanes **57b** and **58b** in a 26:74 ratio, respectively. Both the stereoselectivity (affected by the steric hindrance) and the regioselectivity obtained indicate selective arrangement of the reactants that was probably determined by the formation of excimers. A fascinating example that demonstrates the utility of the photodimerization reaction in the synthesis of cyclophanes was recently obtained[48] in the successful synthesis of the belt cyclophane **60**.



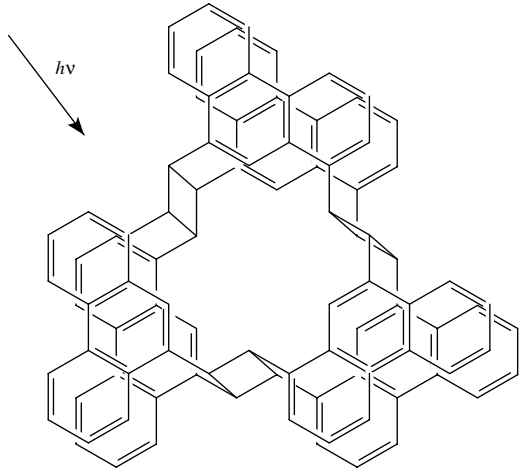
	(57)		(58)
(a) R=Ph	30	:	1
(b) R=H	26	:	74

SCHEME 12

Nishimura and coworkers[49] have systematically examined the photodimerization of divinylnaphthalenes and found that 1,3-, 1,7-, 2,3-, 2,6- and 2,7-divinylnaphthalenes afforded the corresponding [2.2]naphthalenophanes, whereas 1,4-, 1,5- and 1,6-divinylnaphthalenes gave polymeric material with no detection of [2.2]naphthalenophanes. The best yields of this reaction were found in systems **61b** and **61c**, indicating the effect of substituents on the efficiency of the photoaddition (Scheme 13). Although no mechanistic work has been done yet, the observation of half-cyclized products was considered to indicate a stepwise mechanism[49]. Further application of this chemistry took place in the preparation of various [2.2]biphenylophanes of type **64** and its regioisomer **65**. Intermolecular photocycloaddition of the corresponding divinylbiphenyls **63** afforded two

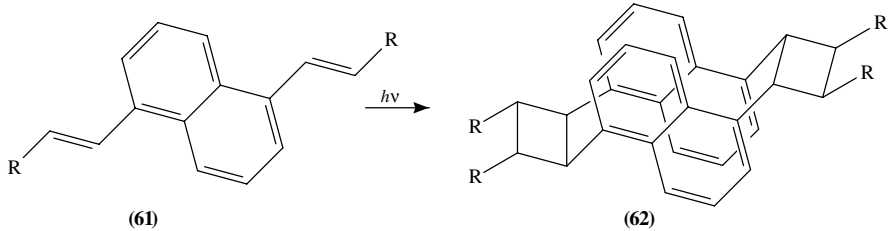


(59)



(60)

SCHEME 12. (*continued*)



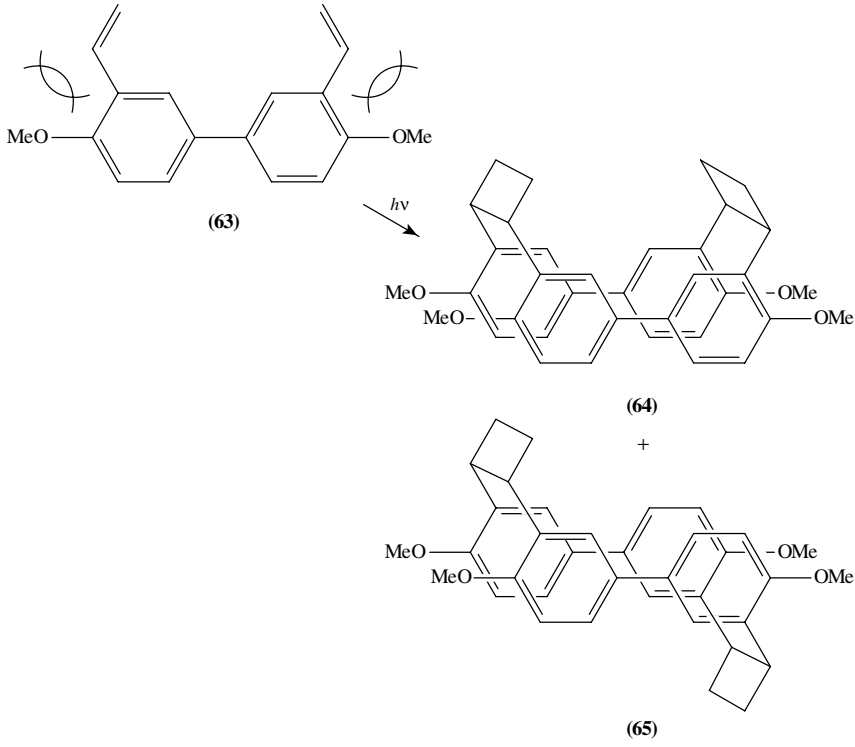
(61)

(a) R = H
(b) R = Ph
(c) R = CO_2Et

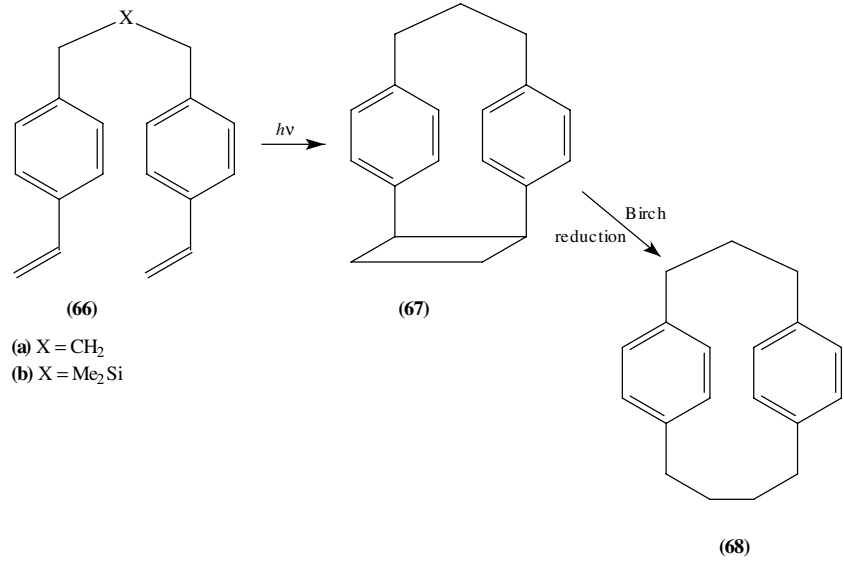
(62)

0% yield
42% yield (100% *exo*, *exo*)
47% yield (100% exo, exo)

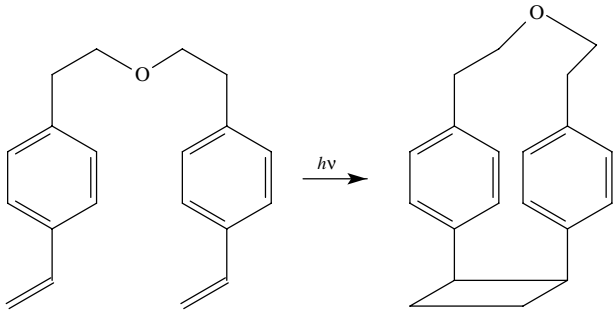
SCHEME 13



SCHEME 13. (*continued*)



SCHEME 14



(69) **(70)**

SCHEME 14. (*continued*)

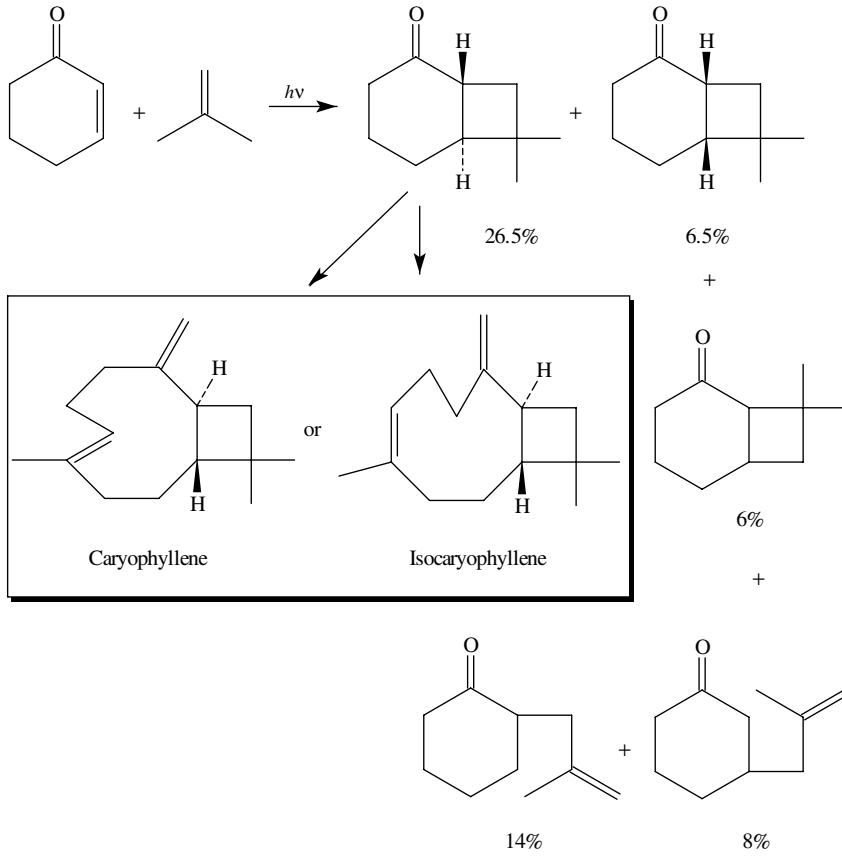
out of the six possible dimers (*endo*,*endo*; *endo*,*exo*; *exo*,*exo* of each regioisomer) in *ca* 10% yield.

Intramolecular photocyclodimerizations of styrene systems of type **66** have been applied[50] for the synthesis of cyclophanes (Scheme 14). The irradiation of compound **66a** afforded straight photoproducts **67**, subsequently transformed, upon reductive cleavage of the produced four-membered ring, to cyclophane **68**. The approach seems successful for longer chains between the styrene units and allows introduction of heteroatoms such as oxygen[51,52] **(69)** and silicon[53] **(66b)**.

V. [2 + 2] PHOTOCYCLOADDITIONS OF ALKENES TO ENONES

The inter- and intramolecular [2 + 2] photocycloadditions of C=C bonds, affording four-membered ring structures, became the method of choice for the synthesis of cyclobutane systems. Extensive investigation on the mechanistic aspects and synthetic applications[54–58] were carried out during the past three decades. The successful control in the regio- and stereoselectivity of the photocycloaddition, especially in the intramolecular cases[56,57], prompted many research groups to apply this reaction as the key step for the formation of strained four-membered rings, which in many cases were followed by subsequent selective fragmentation to afford stereoselective synthesis of polycyclic or macrocyclic structures. It should be noted that there are still open questions on the nature of the excited chromophore, especially of conjugated systems (conformation, polarity etc.), and its effect on the stereoselectivity of the photocycloaddition process. Thus, the stereoselectivity of this reaction, which probably could be considered as the most successful contribution by far of photochemistry to organic synthesis, could not yet be predicted for any given case. However, in some cases, good predictions can be made based on current knowledge and experimental data available.

The photodimerization of unconjugated alkenes, discussed above, could be regarded as the most synthetically useful photocycloaddition of C=C double bonds in the *intermolecular* photocycloadditions. Mixed photocycloadditions between two different C=C double bonds generally give mixtures when both possess similar photoreactivity. In fortunate cases, one of the possible isomers may predominate. A special category of mixed alkene photoaddition that is generally selective is the reaction of α,β-unsaturated ketones (enones) with unconjugated C=C double bonds via selective excitation of the enone chromophore. This has been investigated extensively for mechanistic studies and synthetic applications, especially after Corey's elegant synthesis of caryophyllene and isocaryophyllene (Scheme 15) using this reaction as the key step in the synthetic sequence[59].



SCHEME 15

A. Regioselectivity

1. Intermolecular photocycloadditions

Based on systematic investigation of this reaction, Corey and coworkers[60] proposed the formation of an 'oriented π-complex' (exciplex) between the excited enone and the alkene in its ground state. The reaction proceeds via formation of a 1,4-diradical that cyclizes to the corresponding four-membered ring (Figure 4a). Following some kinetic studies, Loutfy and de Mayo[61] suggested that the proposed triplet exciplex is formed irreversibly and is short-lived. The exciplex gives rise to a 1,4-diradical that can either cyclize to produce a four-membered ring or revert back to the starting materials. Its modified mechanistic scheme is presented in Figure 4b.

The proposed exciplex orientation, suggested to dictate the regioselectivity of the photoaddition, is consistent with the orientation of the dipolar attraction between the electronically n,π^* excited triplet enone and the ground state alkene. Generally, electron acceptor substituents on the alkene provide preferential formation of the head-to-head (H,H) products, whereas electron donor substituents provide preferential formation of the head-to-tail (H,T) photoproducts[55] (Scheme 16).

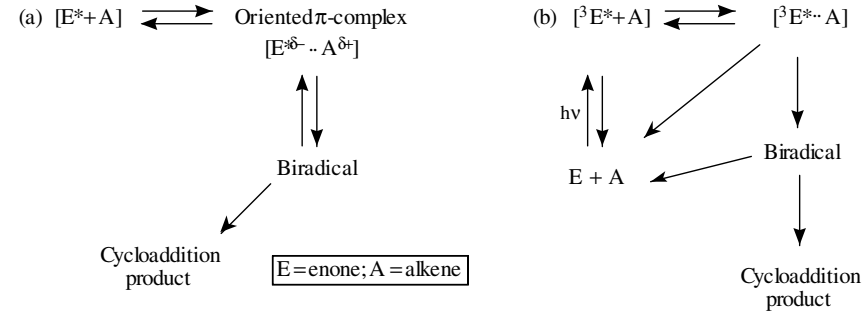
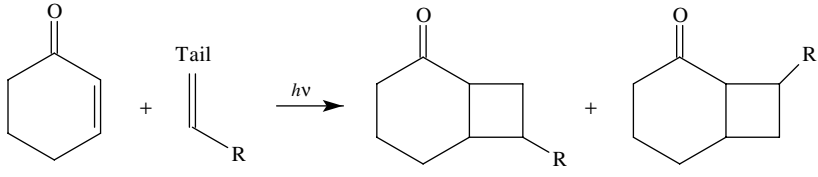
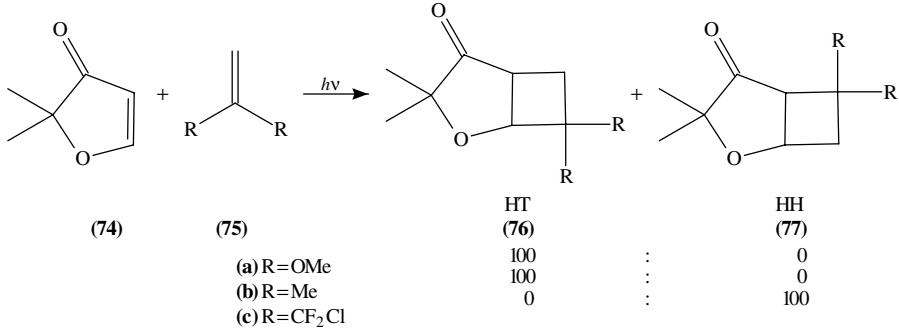


FIGURE 4. (a) Corey's proposed mechanism; (b) de Mayo's proposed mechanism



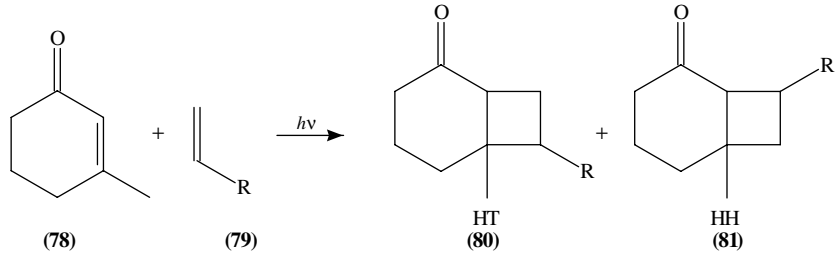
SCHEME 16



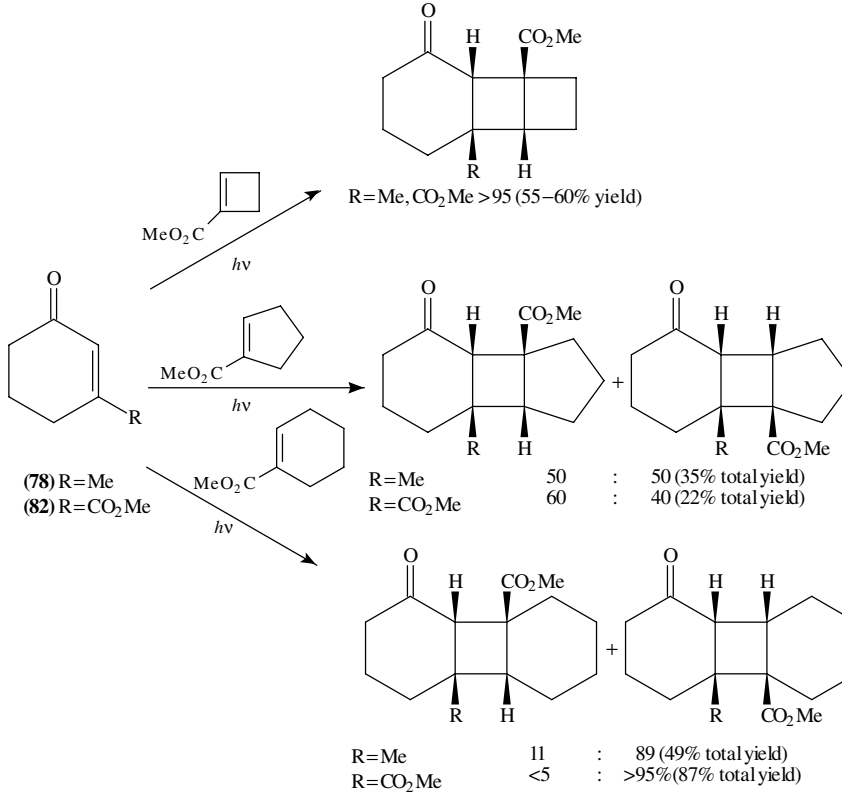
SCHEME 17

The effect of the alkene's substituents on the regioselectivity of the photocycloaddition could probably be best presented in the photoaddition of **74** to various alkenes[62] **75** (Scheme 17).

High regioselectivity was found as well in the intermolecular photoaddition of cyclohexenone **78** to alkenes **79**. The regioselectivity was examined by several research groups[63] and found to be affected by the solvent polarity, the temperature and steric effects[55] (Scheme 18).



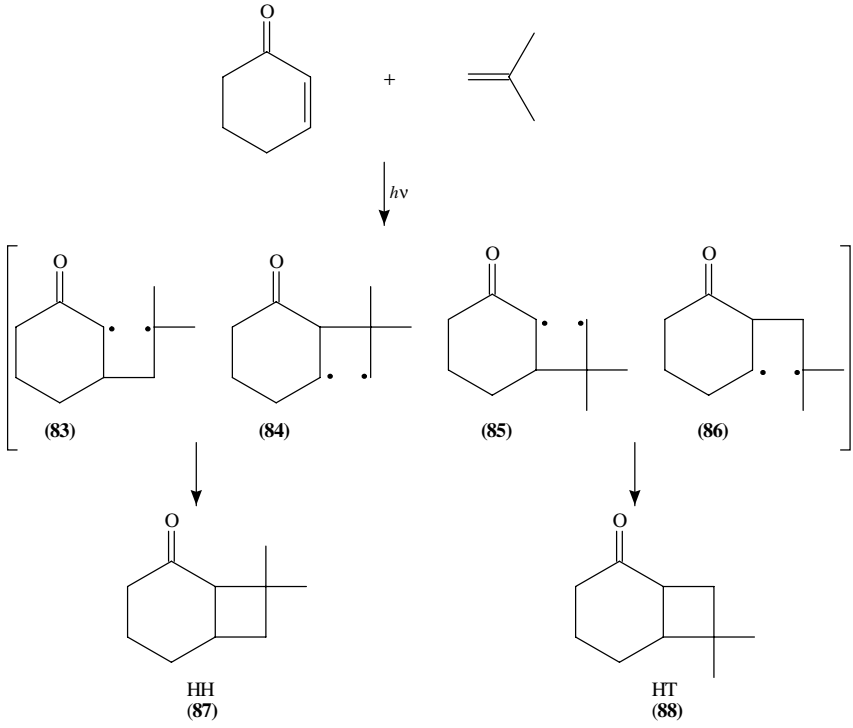
SCHEME 18



SCHEME 19

However, the groups of Tada[64] and of Lange[65] have obtained photoadditions with opposite regioselectivity rationalized by the oriented π-complex. Lange and coworkers[65] have systematically examined the effect of the ring size in the alkene on the regioselectivity of its photoaddition to cyclohexenones **78** and **82** (Scheme 19). The reversal of regioselectivity with increasing ring size of the alkene is not consistent with the oriented π-complex model.

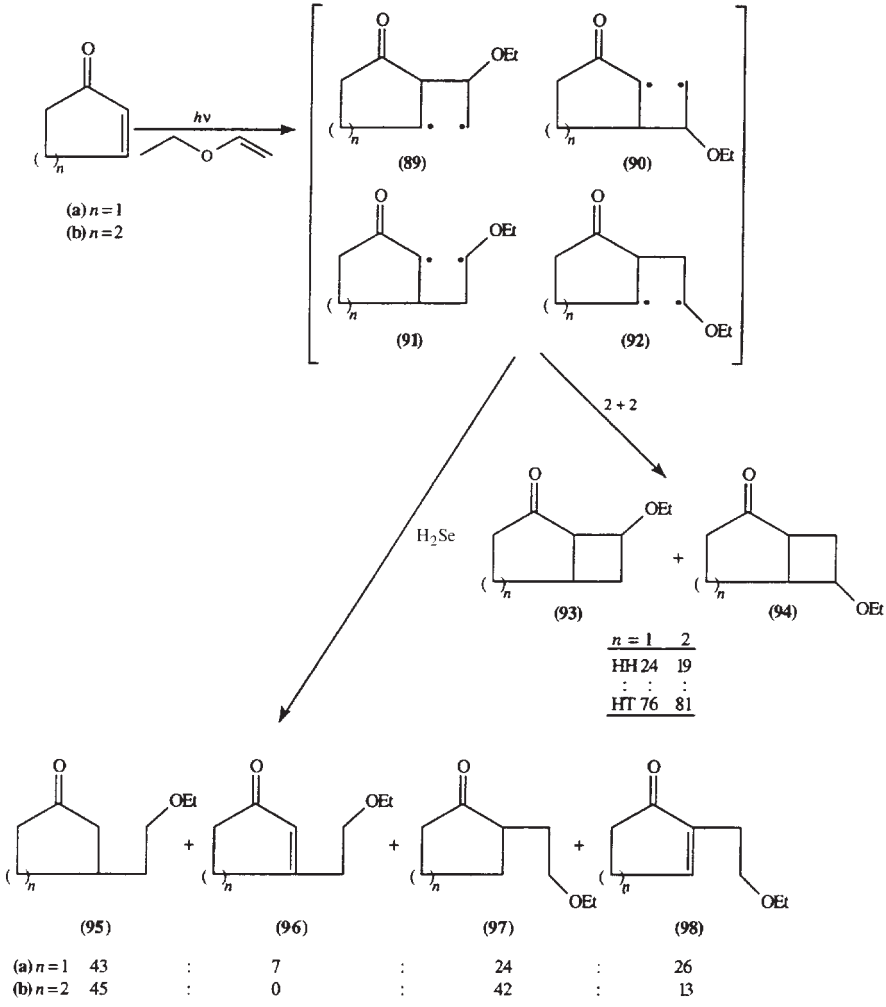
Alternatively, Bauslaugh[66] proposed that the regiochemistry in [2 + 2] photocycloadditions of enones could be explained without invoking exciplexes, by considering the partitioning of 1,4-diradicals between cyclization and fragmentation pathways. For example, in the photoaddition of cyclohexenone to 2-methylpropene, four possible diradical intermediates **(83–86)** could be considered. Based on the relative diradical stabilization, he proposed that **84** was unlikely to be formed and **83** was formed by the fastest rate; however, it most likely undergoes efficient fragmentation to the starting materials due to its relative stability. Thus cyclization occurred preferentially from diradicals **85** and **86** affording the corresponding H,T **(88)** photoproduct (Scheme 20).



SCHEME 20

Recent studies by Schuster and collaborators[67,54], based on nanosecond laser flash techniques, revealed important conclusions, including: (a). The enone excited state responsible for the photocycloaddition is the π–π^* which possesses different polarization than the n-π^* state, considered in rationalizing the effect of the oriented π-complex. (b) Direct measurement of the reactivity scale of alkenes measured by nanosecond flash photolysis provided different results from those obtained with no consideration of the diradical fragmentation to starting materials.

Further experimental support for the effect of the fragmentation of the 1,4-diradical intermediates on the regioselectivity of the photocycloaddition was recently reported by Weedon and coworkers[68,69], who obtained different H,H/H,T ratios between the photocycloproducts [H,H **(93)** and H,T **(94)**] and the trapped products **95–98**, upon irradiation in the absence of H_2Se in the former case and complete trapping of the diradical intermediates in the presence of H_2Se in the latter case (Scheme 21).



SCHEME 21

Schuster's and Weedon's results support Bauslaugh's proposed mechanism that emphasizes the effect of the ratio between cyclization and the alternative fragmentation pathway of the diradical intermediate, on the regioselectivity in the *intermolecular* photocycloadditions, and propose *not to consider* the oriented π-complex (exciplex) as an intermediate in the mechanistic pathway of the $[2+2]$ photocycloaddition of enones to alkenes.

Recent theoretical studies on the regioselectivity of photocycloadditions of triplet cyclohexenones to alkenes have been carried out by Houk and coworkers[70], using *ab initio* theory implemented in the GAUSSIAN programs to locate the transition states for the formation of regioisomeric biradicals and to investigate the influence of substituents on the rates. UMP4(SDTQ)/6-31G* single-point calculations on the planar and twisted conformers of the $n\pi^*$ and $\pi\pi^*$ triplet states of acroleine, as a model for the enone

TABLE 3. PMP3/6-31G*//UHF/3-21G relative energies (kcal mol^{-1}) for addition of $\pi\pi^*$ triplet acrolein to substituted alkenes. Reprinted with permission from Ref. 70. Copyright (1995) American Chemical Society

Alkene	Calcd (kcal mol^{-1}) $\Delta\Delta E^* = E(\alpha) - E(\beta)$	Expt (kcal mol^{-1}) $\Delta\Delta G^*$	Expt HH/HT ratio
Acrylonitrile	0.9	> 1.1	>5.7:1
Allene	0.6	> 2.0	*ca* 100:0
Ethylene	0.3	—	—
Isobutene	−0.5	−0.5	1:3.3
Methyl vinyl ether	−1.7	< -2.0	*ca* 0:100

chromophore, show that the twisted $\pi\pi^*$ triplet is the global minimum, the planar $n\pi^*$ triplet is higher by 9.9 kcal mol^{-1}, the planar $\pi\pi^*$ triplet by 13.2 kcal mol^{-1} and the twisted $n\pi^*$ triplet by 23.4 kcal mol^{-1}. The calculated charges of the planar $n\pi^*$ triplet show that the β-carbon, as proposed by Corey, bears more negative charge than the α-carbon. However, in accord with experimental data, the lowest energy is the $\pi\pi^*$ triplet and possesses opposite polarity to that found in the planar $n\pi^*$ triplet.

Houck and coworkers postulate that the origin of the regioselectivity is at the biradical-forming step and directly affected by the polarity of the alkene. The β-carbon, considered as nucleophilic, adds rapidly to the less substituted side of the electron-deficient alkene, whereas a position considered as an α-acyl radical (more electrophilic than an alkyl radical) adds rapidly to the less substituted side of electron-rich alkenes. The calculated relative energies for the addition of $\pi\pi^*$ triplet acrolein to different substituted alkenes at the first bond-forming step (Table 3) are found to be in good agreement with experimental values determined in the photoaddition of cyclohexenone to the related alkene.

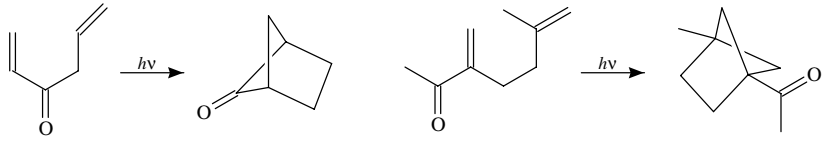
Prediction of the regioselectivity in the *intermolecular* photocycloaddition of enones to alkenes following this method provides similar results to those rationalized by the oriented π-complex. However, it is in contrast with Weedon's previously discussed trapping results which indicate no selectivity in the first bond formation at the α- or β-carbon positions in cyclic enones.

2. Intramolecular photocycloadditions

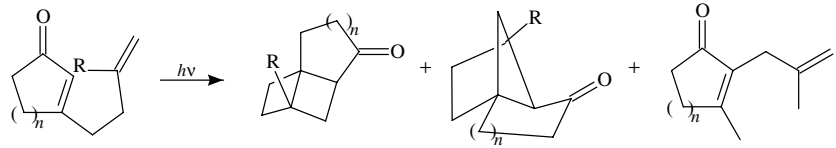
The regioselectivity in the intramolecular photocycloadditions can be controlled to some extent due to geometrical constraints. The effect of substituents and chain length between the reacting alkenes has been extensively investigated in the photoaddition of alkenes to enones and well documented in several excellent reviews[54–58]. In some cases, the regioselectivity can be predicted based on the empirical 'rule of five'[71], which postulates that the first bond formation will favor closure to a five-membered ring, unless structural or conformational factors interfere. If a five-membered ring cannot be formed (short or long tethered), a six-membered homolog is favored.

Wolff and Agosta[72] have investigated the regioselectivity in a large number of acyclic and cyclic enones to tethered alkenes of types **99–102**. These compounds generally form cross 1,5-photoproducts. Two factors were found to play an important role in the regioselectivity toward 1,6-parallel addition: (a) placement of a substituent on the C-5 position of the alkenyl chain and (b) incorporation of the conjugated double bond in a five- or six-membered ring. Selected examples are presented in Scheme 22.

Homologation of the alkenyl side chain was extensively examined in compounds of type **103** and **105**. In all cases, only straight and all *cis*-fused photoproducts were obtained (Scheme 23).



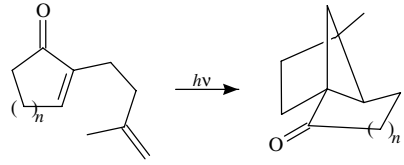
(99) 88% (crossed) **(100)** 12% (crossed)



(101) (straight) (crossed)

$n = 1, 2$

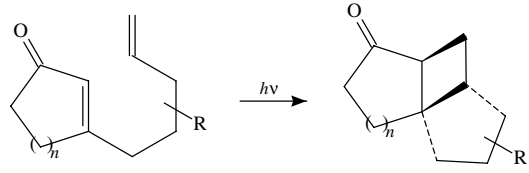
(a) $n = 1$, R=H	56%	:	7%	:	8%
(b) $n = 1$, R=Me	84%	:	0%	:	4%
(c) $n = 2$, R=H	20%	:	49%	:	2%
(d) $n = 2$, R=Me	76%	:	11%	:	2%



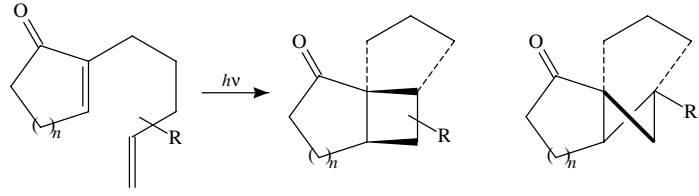
Other isomers obtained in less than 6% yield.

(102) $n = 1, 2$ major (50-70%)

SCHEME 22

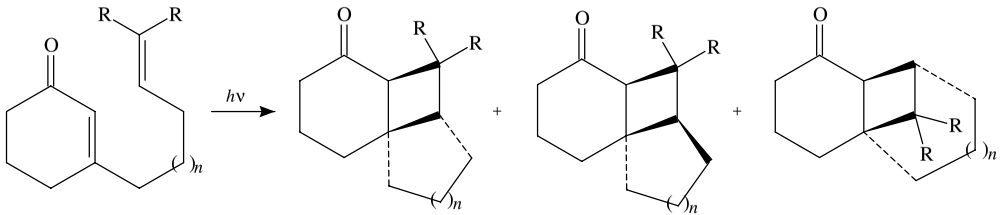


(103) $n = 1, 2$; R = H, Me, *i*-Pr, *t*-Bu straight **(104)**



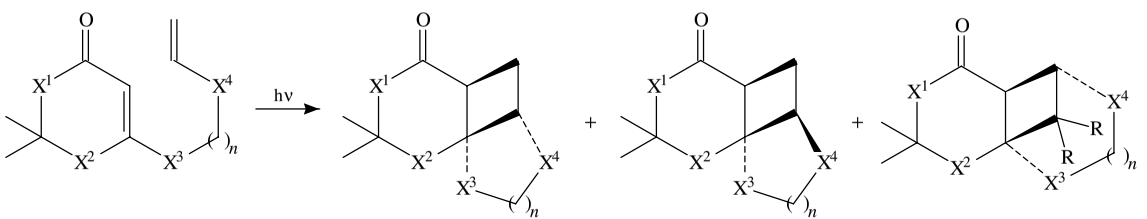
(105) $n = 1, 2$; R = H, Me, *t*-Bu straight **(106)** (Sole or major) crossed **(107)** (minor obtained with n = 1, R = Me, *t*-Bu)

SCHEME 23



	straight	straight (twisted approach)	crossed
(a) $n = 1$, R = H or CH_2 (allene)	100	0	0 (>95%, Reference 73)
(b) $n = 2$, R = H	66	? 17	? 17 (>90%, Reference 74)
(c) $n = 2$, R = CH_2 (allene)	85	0	15 (>95%, Reference 73)

SCHEME 24



	straight	straight (twisted approach)	crossed
(a) n = 1or2, $X^1 = X^2 = 0, X^3 = X^4 = H$	100	0	2 (>73%, Reference 75)
(b) $n = 2, X^1 = X^2 = X^4 = H, X^3 = O$	100 (straight photo products)		0 (60%, Reference 76)
(c) $n = 2, X^1 = X^2 = X^3 = H, X^4 = O$			(>95%, Reference 77)
(d) $n = 2, X^1 = X^3 = X^4 = H, X^2 = O$	80	20	0 (80%, Reference 78)

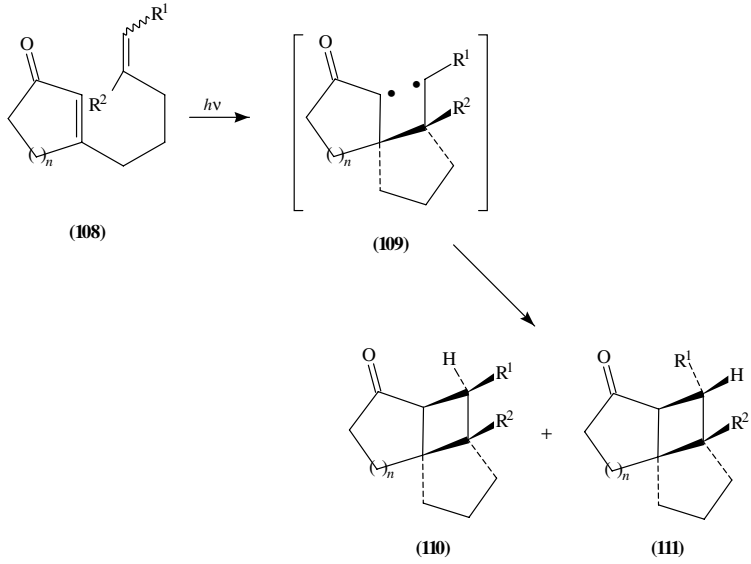
SCHEME 25

Further homologation of the alkenyl side chain affects the regioselectivity, as could be seen in the examples in Scheme 24.

Interestingly, incorporation of an oxygen heteroatom at any allylic position in these systems strongly affects the regioselectivity of the photocycloaddition and in all cases, summarized in Scheme 25, straight products were obtained as the sole products.

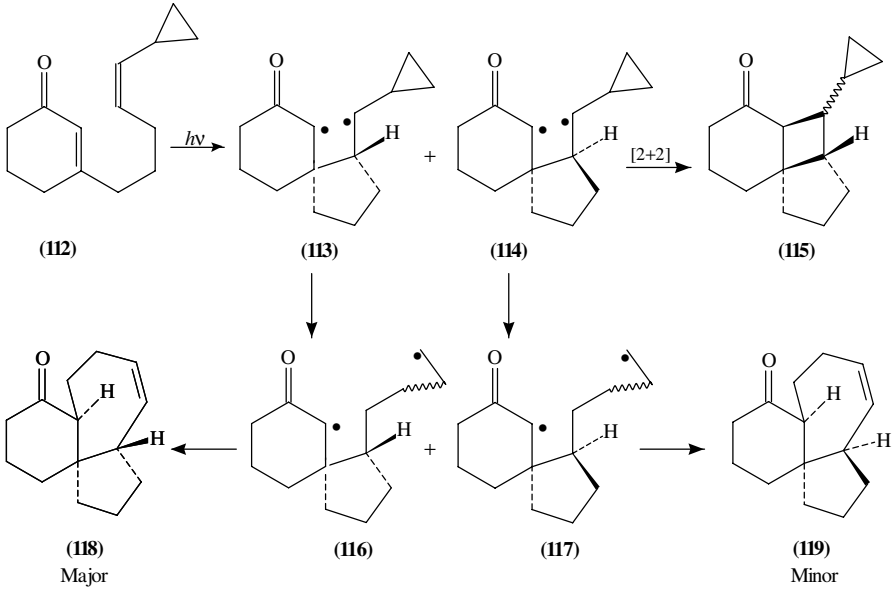
The regioselectivity of the photocycloaddition is strongly affected by the relative stability of the possible diradical intermediates and the relative rate of cyclization vs cleavage of the corresponding diradical intermediate to the starting material. The order of the first bond formation of the alkene to the α-carbon or the β-carbon of the enone chromophore plays a major role in the regioselectivity, in cases where the fragmentation of the diradical intermediate to the starting compounds is a neglectable process.

Becker and coworkers[79] have systematically investigated the photoaddition of substituted enones **108**. Irradiations of *Z*- or *E*-**108** afforded a similar ratio of *endo* **(110)** to *exo* **(111)** isomers with minor geometrical isomerization of the alkene in the starting material **108** during the irradiation (less than 10%). Based on these results, they reached the conclusion that first bond formation in these compounds follows the 'rule of five' and takes place exclusively via diradical **109**. Different ratios were obtained in the photoaddition of the corresponding cyclopentenone systems[80]. However, the similar *endo*/*exo* ratio obtained in the photocycloaddition of *Z* and *E* alkenes is in full agreement with the diradical intermediate **109** in which the obtained ratio is affected by steric effects in the cyclization step of the diradical to the corresponding [2 + 2] photoproducts (Scheme 26).

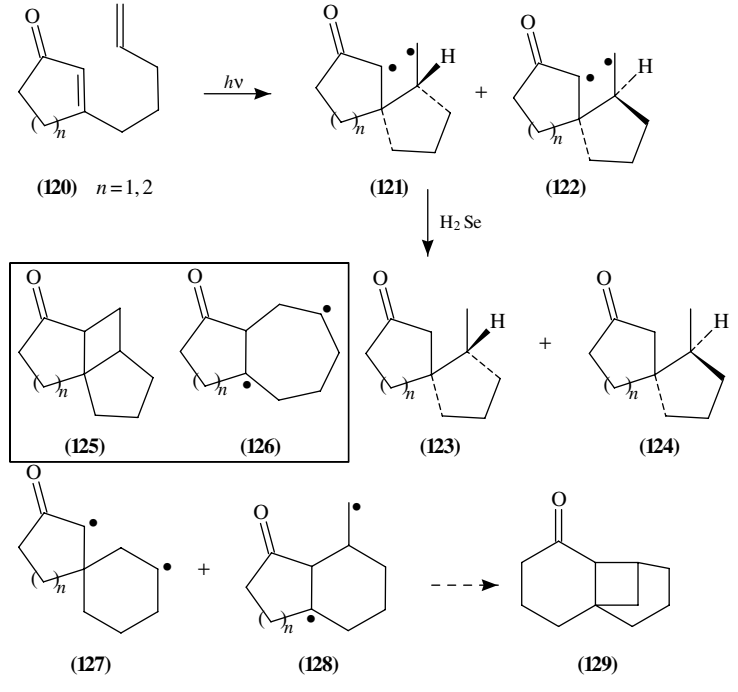


(a) R1 = *Z*-Me, *E*-Me, *E*-*i*-Pr, R2 = H, *n* = 2;	*endo*	1	:	1	*exo*
(b) R1 = R2 = D, *n* = 2;	*endo*	1	:	1	*exo*
(c) R1 = *Z*-Me, R2 = H, *n* = 1;	*endo*	1	:	2	*exo*
(d) R1 = *E*-Me, R2 = H, *n* = 1;	*endo*	1	:	2	*exo*
(e) R1 = *Z*-*t*-Bu, R2 = H, *n* = 1;	*endo*	1.1	:	1	*exo*
(f) R1 = *E*-*t*-Bu, R2 = H, *n* = 1:	*endo*	1.1	:	1	*exo*

SCHEME 26



SCHEME 27



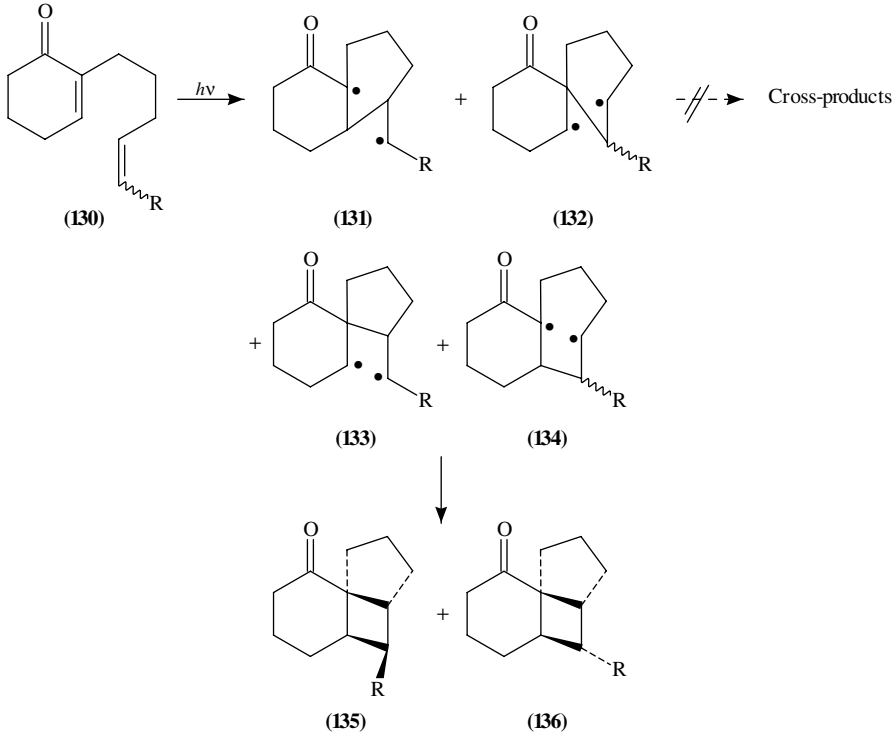
SCHEME 28

Furthermore, Becker and coworkers[81] have succeeded in trapping the 1,4-diradical intermediates **113** and **114** in the irradiation of compound **112** providing direct evidence for these intermediates and support for the regioselectivity in the first bond formation (Scheme 27).

Further support was recently obtained by Maradyn and Weedon[82] on complete trapping of diradicals **121** and **122** with hydrogen selenide (H_2Se) affording products **123** and **124**. The absence of cross-products **129**, of [2 + 2] photoproduct **125** and of other trapped products, precludes the formation of diradical intermediates **126–128** and provides further evidence for the selectivity in the formation of the first bond as predicted by the 'rule of five' (Scheme 28).

Irradiation of cyclohexenones **130** possessing the alkenyl side chain at the α-carbon have been systematically examined by Becker and coworkers[79,80] and found to afford different ratios of *endo* **(135)** and *exo* **(136)** photoproducts. It is generally accepted that in these systems diradicals **133** and **134** could be formed; however, the absence of cross-products clearly rules out diradical intermediates **131** and **132** (Scheme 29).

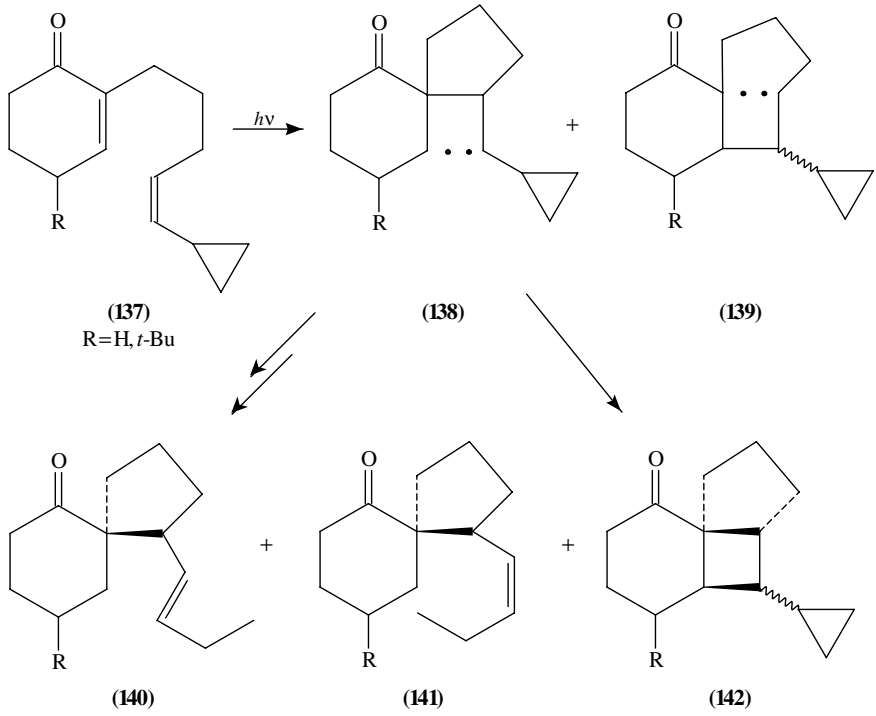
Trapping experiments on cyclic enones which possess the alkenyl side chain at the α-carbon were examined by Becker and coworkers[83] via the irradiation of compounds



(a) R=*Z*-Me	5.8	1
(b) R=*E*-Me	35	1
(c) R=*Z*-*i*-Pr	14	1
(d) R=*E*-*i*-Pr	3.8	1

SCHEME 29

137. Formation of trapping product **140** in over 54% yield provides strong support for preferential formation of the first bond at the α-carbon, as could be predicted by the 'rule of five'. Higher trapping yield (65%) was obtained in the irradiation of **137** (R = *t*-Bu) at 50 °C. Formation of the *Z*-trapped product **141** and the *E*/*Z* ratio of the trapped products **140/141** (52:13 respectively) could be attributed to an equilibrium between the cyclopropylcarbinyl radical **138** and its corresponding homoallyl radical. However, further studies are required to verify this assumption (Scheme 30).

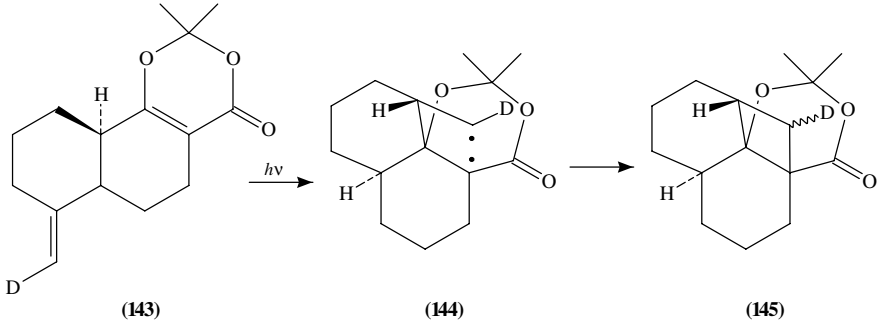


SCHEME 30

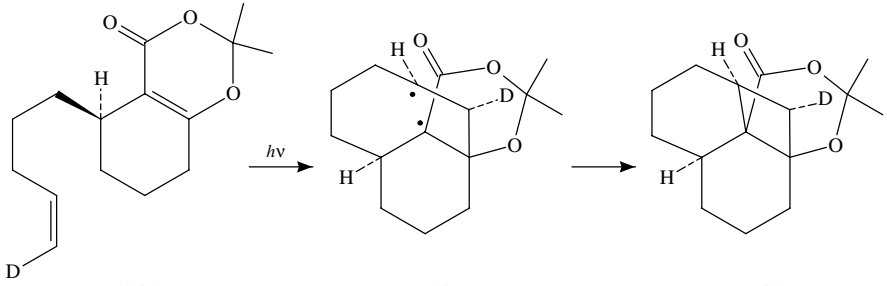
The steric effect of R-substituents at C-4 in the cyclohexenone was found to affect the diastereofacial selectivity of the photocycloaddition[84].

Winkler and Shao[85] have examined the first bond formation in the photoaddition of labeled dioxinones **143** and **146**. Irradiation of **143** afforded an epimeric mixture of the more strained photoproducts **145**, while irradiation of **146** gave **148** as a single product. These results are consistent with diradicals **144** and **147** as the intermediates in the photoaddition of **143** and **146**, respectively, pointing out that the first bond formation in both cases takes place exclusively at the β-carbon of the dioxinone chromophore (Scheme 31).

The role of the dioxinone chromophore on the selectivity in the first bond formation, was examined by comparison to the enone analogs **149** and **151**, lacking the β-oxygen found in the dioxinone chromophore. Irradiation of **149** and **151** afforded only the *trans*-fused photoproducts **150** and **152** respectively, which indicates that in contrast to dioxinones, the first bond formation in the enone photocycloadditions can take place from either the α- or β-carbon of the enone via six-membered ring of the corresponding diradical intermediate (Scheme 32).

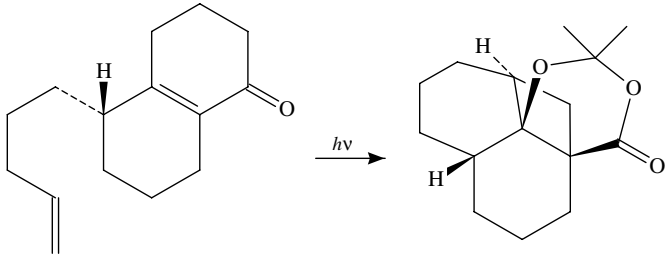


(143) **(144)** **(145)**

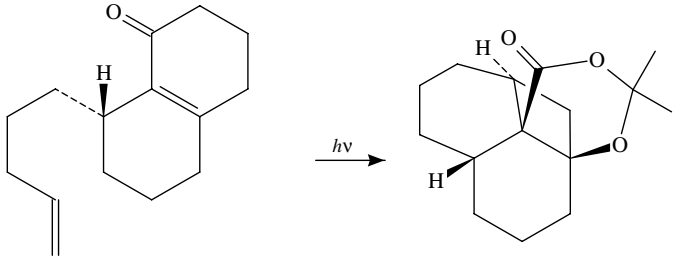


(146) **(147)** **(148)**

SCHEME 31



(149) **(150)**



(151) **(152)**

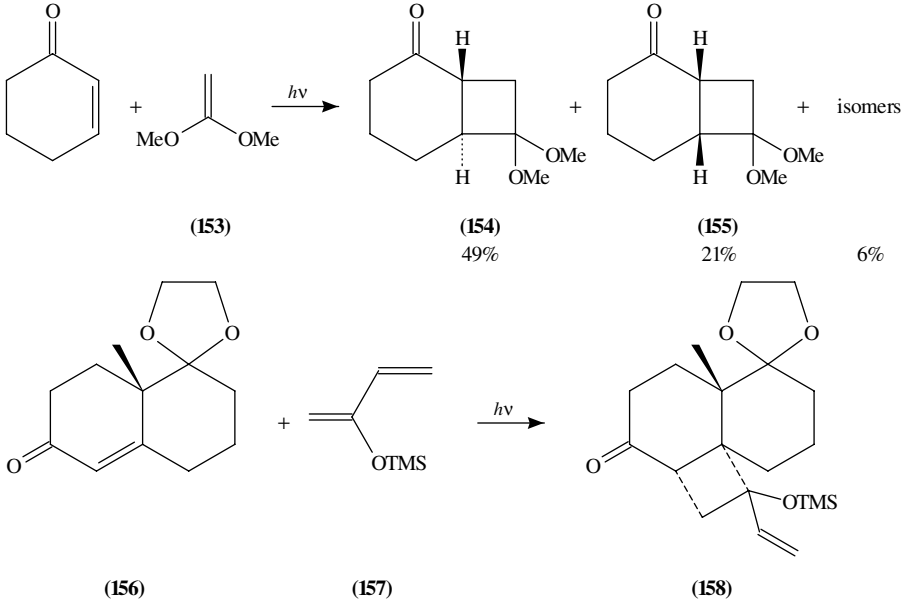
SCHEME 32

B. Stereoselectivity and Synthetic Applications

1. Intermolecular photocycloadditions

The intermolecular photocycloaddition of alkenes to cyclic enones was found to afford *cis*- and *trans*-fused bicyclic systems. This stereoselectivity and the diastereofacial selectivity of chiral alkenes and/or enones is discussed below.

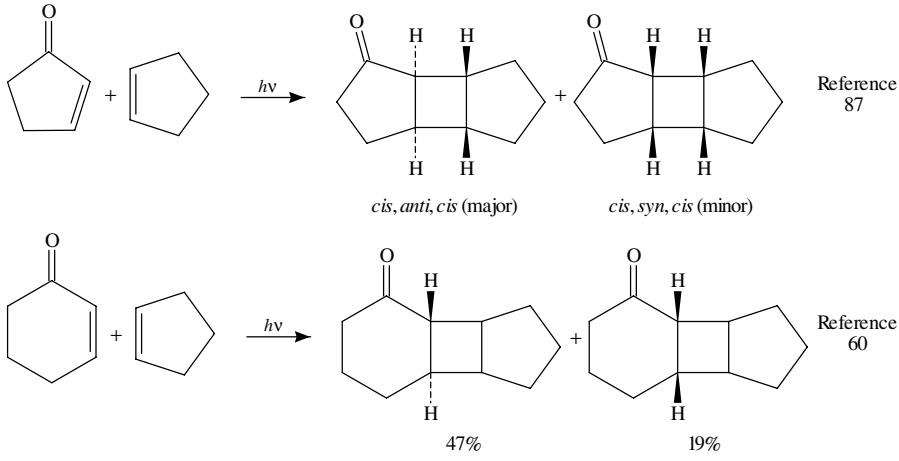
a. Ring fusion selectivity. The ring fusion stereoselectivity is affected by the ring size of the cyclic enone and the nature of the alkene (cyclic, substituted etc.). In most cases, photocycloaddition of cyclopentenones provide *cis*-fused bicyclic products with acyclic alkenes with loss of the alkene configuration via the diradical intermediate, usually providing a mixture of the corresponding *endo*- and *exo*-isomeric products. Intermolecular photoaddition to cyclohexenones usually provides *trans*-fused bicyclic products with acyclic alkenes as obtained in one of the early examples reported by Corey on the photoaddition of **153** to cyclohexenone[60]. However, *cis*-fused photoadditions have also been obtained as the major or exclusive photoproduct as found in the photoaddition of **156** to the silylenolether **157**[86] (Scheme 33).



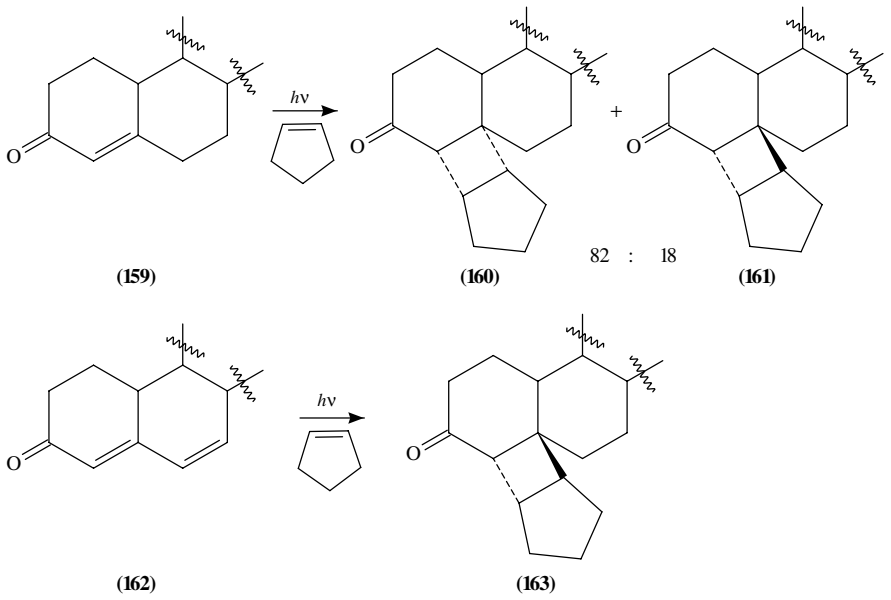
SCHEME 33

Cis,*anti*,*cis* products are favored in the intermolecular photocycloaddition of cyclopentenones with cyclic alkenes[87] (Scheme 34). However, intermolecular photoaddition of some cyclohexenones provided preferred *trans*-fused product as the major product with cyclic alkenes[60]. From the large number of examples presented in Schemes 37, 42, 43, 45, 46, 48 and other examples, it could be concluded that *cis*-fused products are usually preferred.

The structure of the cyclic enone affects the stereoselectivity in the formation of the four-membered ring, as could be seen in the photoaddition of testosterone derivatives **159** and **162** to cyclopentene. Rubin and colloborators[88] reported favored *cis*-fused product



SCHEME 34

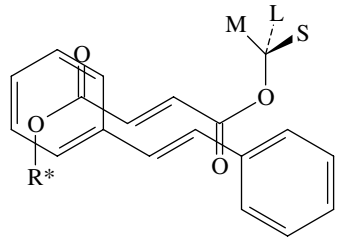


SCHEME 35

160 in the irradiation of **159** while the *trans*-fused product **163** formed exclusively in the irradiation of **162** (Scheme 35).

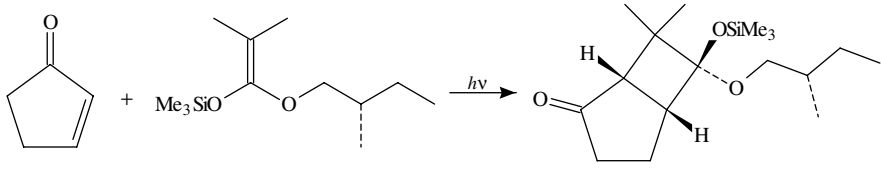
b. Diastereofacial selectivity. Considerable attention in organic photochemistry in recent years has been given to inducing a chiral auxiliary on the alkene, enone or both and their efficiency on the diastereofacial differentiation for the preparation of enantiomerically pure or enriched materials. One of the most efficient asymmetric photocycloadditions, leading to chiral cyclobutanes, was obtained in an early example by Ali and Tolbert[89]

in the addition of *trans*-stilbene to an optically active fumarate ester in 94% ee. This stereofacial selectivity was claimed to be due to extensive π-stacking giving rise to a rigid exciplex **164**.



(164)

Another example involves photoaddition of the chiral acetal **165** to cyclopentenone, affording the photoproduct **166** in a considerable enantiomeric excess[90] (Scheme 36).

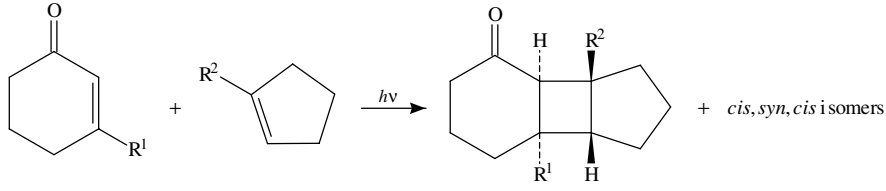


(165) **(166)** 33% ee

SCHEME 36

Further studies, on the same principle, were carried out by Lange and coworkers on the intermolecular photocycloadditions of cyclohexenones **167** to alkene **168**, possessing different chiral auxiliaries at the enone[91] or alkene[92]. Diastereomeric mixtures of *cis*,*anti*,*cis* **169** and *cis*,*syn*,*cis* isomers were obtained in low to moderate diastereomeric excess (Scheme 37).

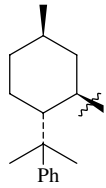
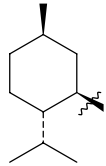
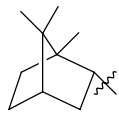
Chiral auxiliary on rigid cyclic enones could be expected to afford good facial selectivity. Based on a fairly large number of examples, Wiesner and coworkers[93] have proposed two models that allow, to some extent, prediction of the preferred facial selectivity in the intermolecular [2 + 2] photocycloadditions of alkenes or allenes to chiral cyclohexenones. In the first model, they proposed that the excited cyclohexenone adopts a half-chair conformation in its reactive excited state, with a trigonal α-carbon and pyramidal β-carbon capable of adapting the more stable configuration and orbital overlap. In the second model, Wiesner assumed a planar excited state in which the β-carbon is pyramidalized in the process of reacting with the olefin, and the more stable biradical, formed at the β-carbon, leads to the product. He also pointed out that the diastereofacial selectivity could be predicted from the selectivity obtained by an alkali metal–ammonia reduction of the cyclic enone. Photoaddition of decalone **170** with allene afforded **172** stereoselectively and in 95% yield. The obtained diastereofacial selectivity from the α-side is consistent with the transoid anion **173** being responsible for the formation of **174** while structure **171** that presents the triplet excited state with pyramidalization at the β-carbon points to the α-side with similar steric and conformational considerations. Further examples could be seen in the irradiation of compounds **175–177** in which all present exclusive or preferred diastereofacial selectivity consistent with the selectivity obtained with similar or related compounds on Li/NH_3 reduction (Scheme 38).



(167) **(168)** **(169)**

(a) $R^1 = Me, R^2 = CO_2R^*$

(b) $R^1 = CO_2R^*, R^2 = Me$

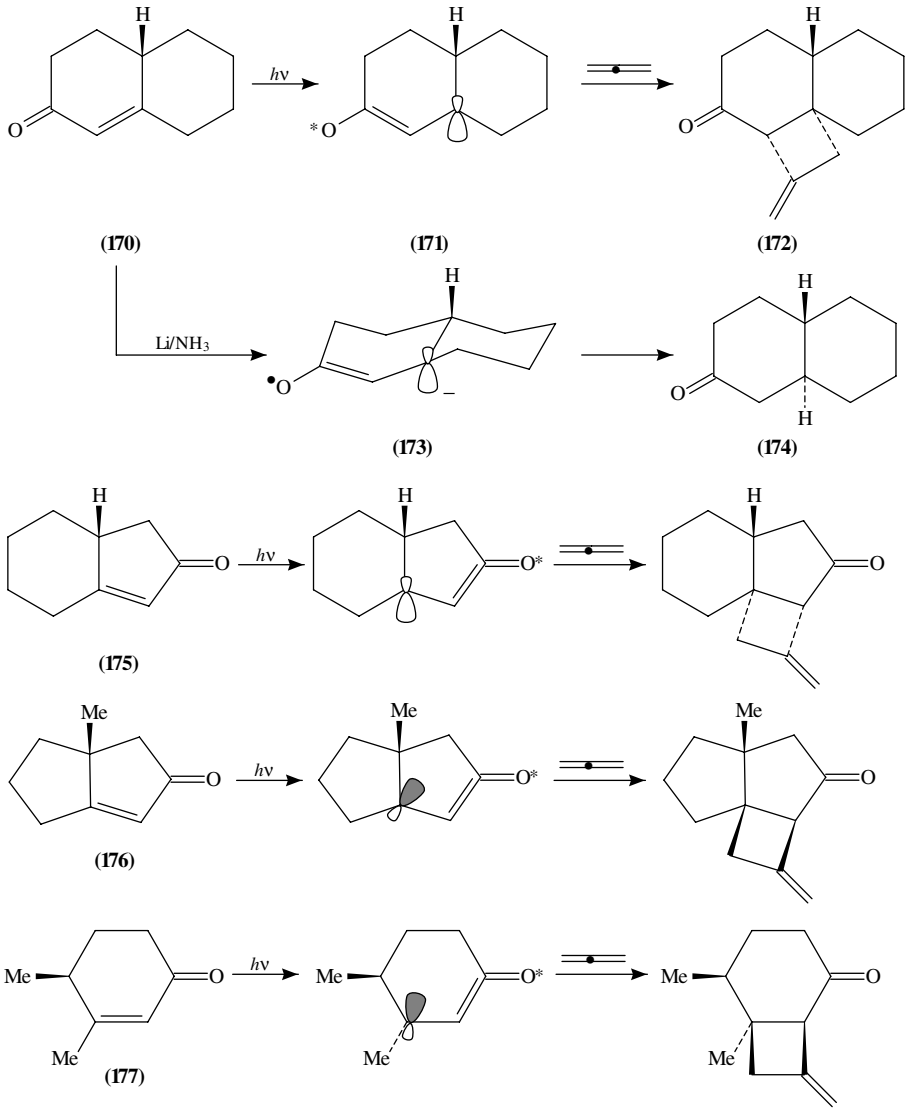
R*		**169a**	**169b**	*cis, syn, cis* isomers
	de	56%	20%	–
	ee	57%	30%	79
	de	13%	40%	–
	ee	12%	18%	25
	de	19%	66%	–
	ee	18%	14%	–

ee: after hydrolysis

SCHEME 37

Wiesner and coworkers have emphasized that while the equilibrium constants between the two diastereomeric photoexcited states and anionic intermediates respectively should be similar, there is no reason to expect that they must be numerically identical. Small differences in equilibrium constants could in some cases reverse the stereoselectivity of photocycloaddition with respect to metal reduction. The group of Cargill[94] examined the validity of Wiesner's models by the photoaddition of *tert*-butylcyclohexenone **178** with ethylene. Irradiation at low temperature (−78 °C) afforded a mixture of three isomers **179–181**, in which the photoproduct **179** is the major product while isomer **180**, expected to be the major one based on the first model, was obtained as the minor isomer. This result seems to rule out the first model (it does not take into consideration the reversibility of the first bond formation in the intermolecular photoadditions), however, it is consistent with the second model (Scheme 39).

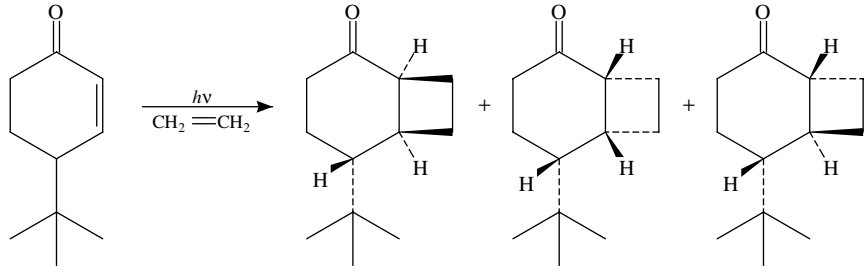
The first model was used later on to rationalize the experimental fact that photocycloaddition of ethylene to the *trans*-fused enone **182** proceeded smoothly while the *cis*-fused



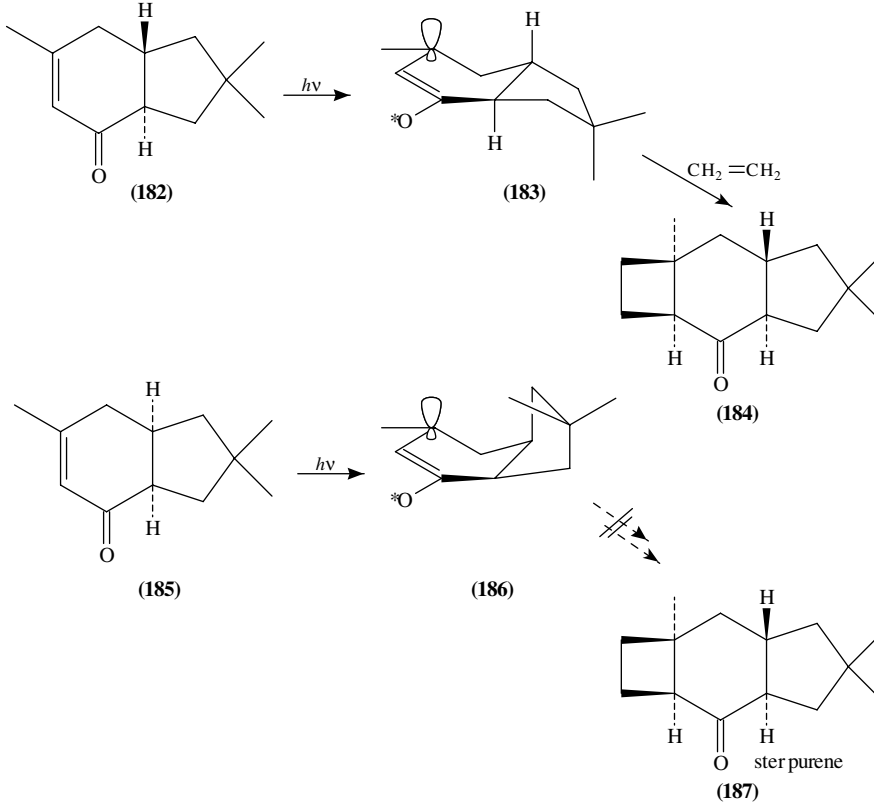
SCHEME 38

isomer **185**, planned as the key step for the synthesis of sterpurene **187**, proved unreactive under the same conditions[95]. Representing the corresponding excited states **183** (for the *trans*-fused) and **186** (for the *cis*-fused), wherein the β-carbon is pyramidal and the methyl substituent is oriented pseudo-equatorial, the unreactivity of **185** was attributed to the hindered approach of ethylene to **186** (Scheme 40).

High diastereofacial selectivity (84% de) was obtained in the photoaddition of ethylene to the chiral bicyclic lactam **188** with preferential approach from the expected convex side[96]. The photoproduct was used as the key step in the synthesis of enantiomerically



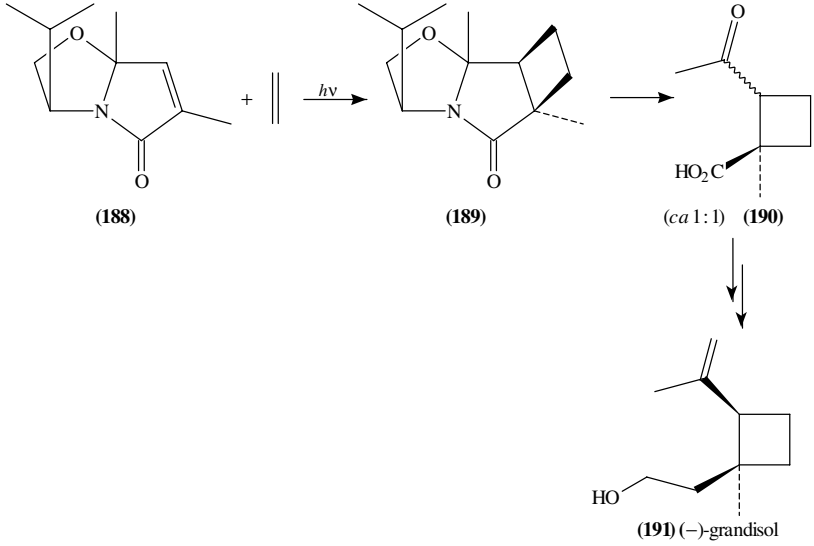
SCHEME 39



SCHEME 40

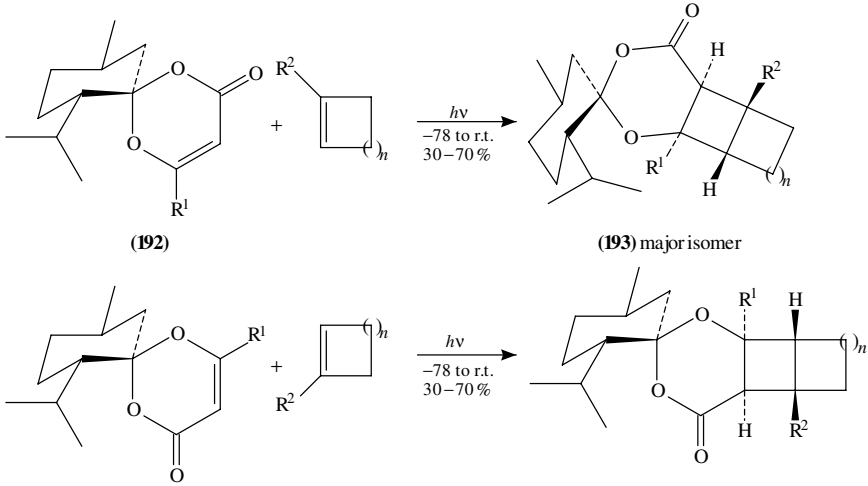
enriched grandisol **191**. Subsequent hydrolysis of the chiral auxiliary under strong acidic conditions resulted in epimerization of the acetyl group in **190** (Scheme 41).

An alternative approach was developed by the group of Demuth[97], based on the intermolecular photoaddition of chiral 1,3-dioxin-4-ones **192** and **194** possessing the (−)-menthone auxiliary that could smoothly be removed after the photoaddition step. The results of Demuth's pioneering studies into the reactions of chiral dioxinones with cyclic



(188) **(189)** (*ca* 1 : 1) **(190)** **(191)** (−)-grandisol

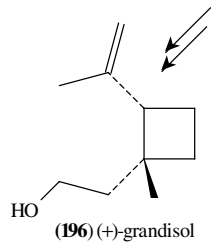
SCHEME 41



(192) **(193)** major isomer

(194) **(195)** major isomer

n = 1-3;
R^1 = H, Me
R^2 = H, Me

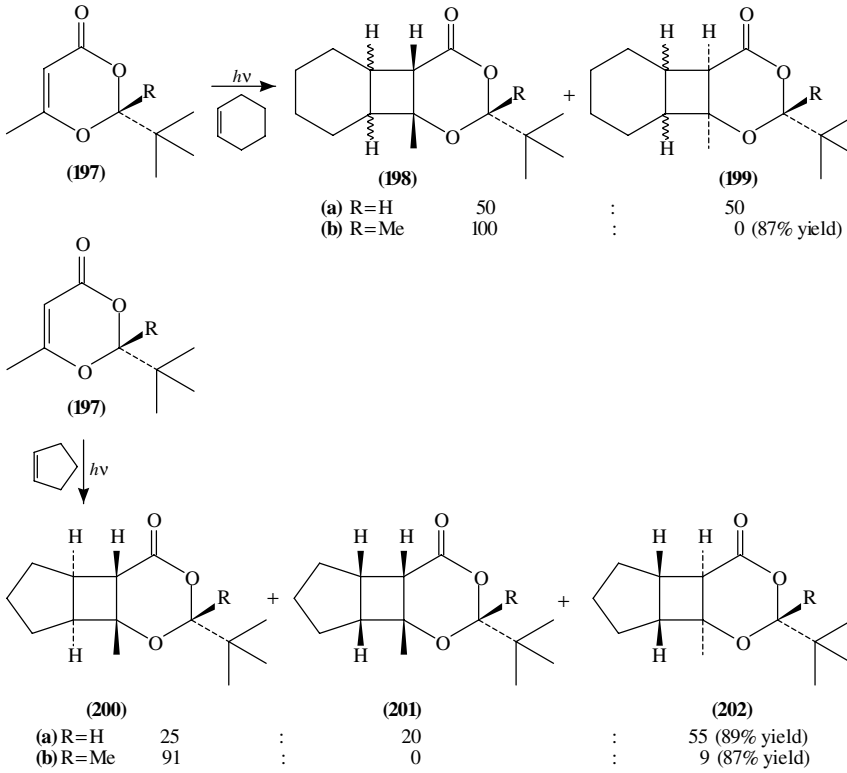


(196) (+)-grandisol

SCHEME 42

alkenes afforded *ca* 80% de in both isomers **193** and **195** in a head-to-head fashion and *cis*,*anti*,*cis*-fused products (Scheme 42).

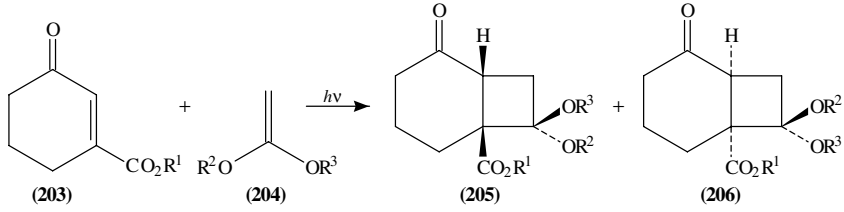
The high facial selectivity found in the thermal and photochemical reactions of chiral 1,3-dioxin-4-ones have triggered increasing interest in both their mechanistic aspects and synthetic applications. Poor facial selectivity was obtained in the intermolecular photoaddition of dioxinone **197a** with various alkenes. However, Lange and coworkers[98] have succeeded in achieving high facial selectivity in the *intermolecular* photoaddition of dioxinone **197b** with preferred approach of the alkene from the equatorial *tert*-butyl side. The observed stereoselectivity was attributed to the steric hindrance of the axial methyl at the ketal center (Scheme 43).



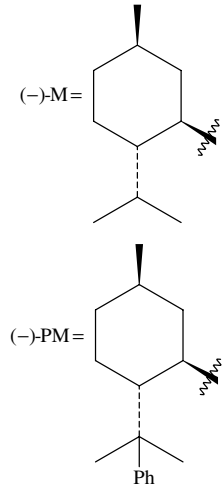
SCHEME 43

The above examples have presented a better induction effect when the chiral auxiliary was located at the enone molecule. Double auxiliary induction has been examined by Scharf and coworkers[99]. Systematic study on the photoaddition of chiral enones **203** to chiral ketene acetals **204** provides examples of matched (45% de) and mismatched (9% de) double stereo differentiation (Scheme 44).

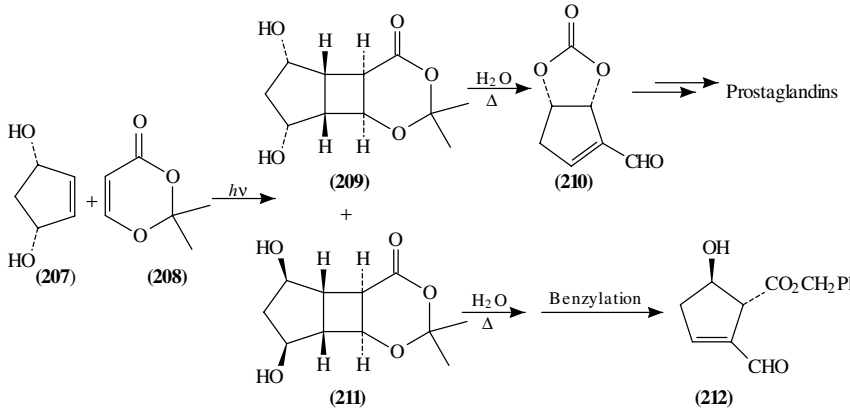
Stereoselective *intermolecular* photoadditions of alkenes to enones have been elegantly utilized in the synthesis of naturally occurring compounds or compounds of special interest. Sato and collaborators[100] have applied the photoaddition of dioxinone **208** to the chiral *cis*-diol **207** for a one-pot synthesis of the Corey lactone **210**, which possesses considerable utility in the preparation of prostaglandin derivatives (Scheme 45).



R^1	R^2	R^3	de (%)	Excess of
Me	(−)-M	Me	27	**206**
(−)-M	Et	Et	14	**206**
(−)-M	(−)-M	Me	45	**206**
(+)-M	(−)-M	Me	17	**206**
(−)-PM	(−)-M	Me	74	**206**
(+)-PM	(−)-M	Me	9	**205**

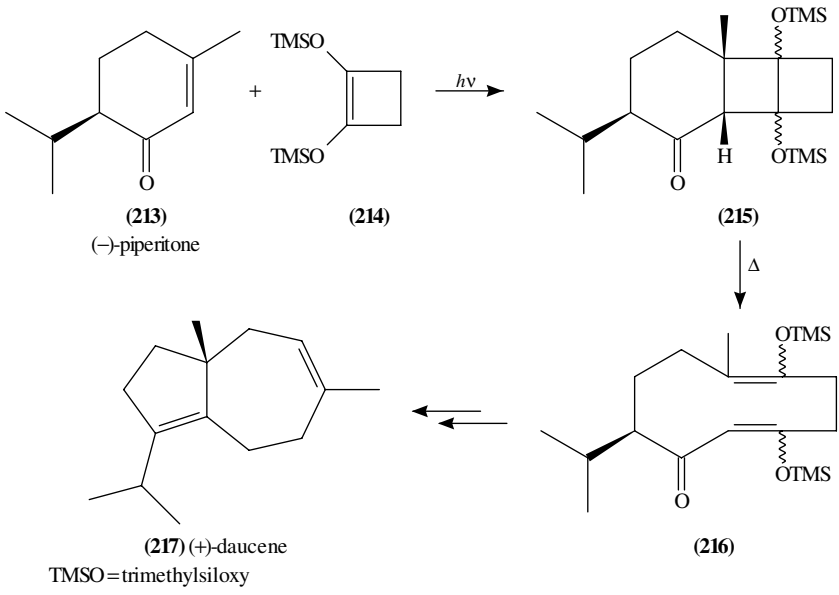


SCHEME 44



SCHEME 45

Photoaddition of 1,2-bis(trimethylsiloxy)cyclobutene **214** to various cyclohexenones followed by subsequent fragmentation of the produced four-membered ring was elegantly applied for the synthesis of various sesquiterpenes and diterpenes[101]. The photoaddition of **214** was applied[102] in the total synthesis of the sesquiterpene (+)-daucene **217**, which was obtained in a three-step sequence from the naturally occurring (−)-piperitone **213** (Scheme 46).



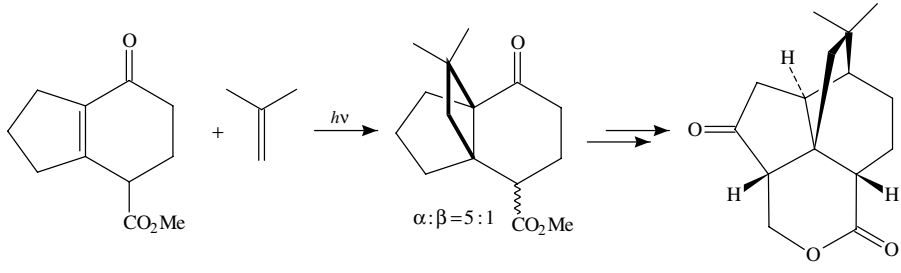
(213) (−)-piperitone **(214)** **(215)**

(217) (+)-daucene **(216)**

TMSO = trimethylsiloxy

SCHEME 46

The first enantiomerically pure synthesis of the antitumor compound quadrone has been developed by Smith and coworkers[103], via photoaddition of isobutylene to **218** followed by epimerization affording the desired photoproduct **219**α in 5:1 ratio with its diastereomer in 74% yield. The synthesis of (+)-enantioquadrone was completed via kinetic resolution of **219**α (Scheme 47).

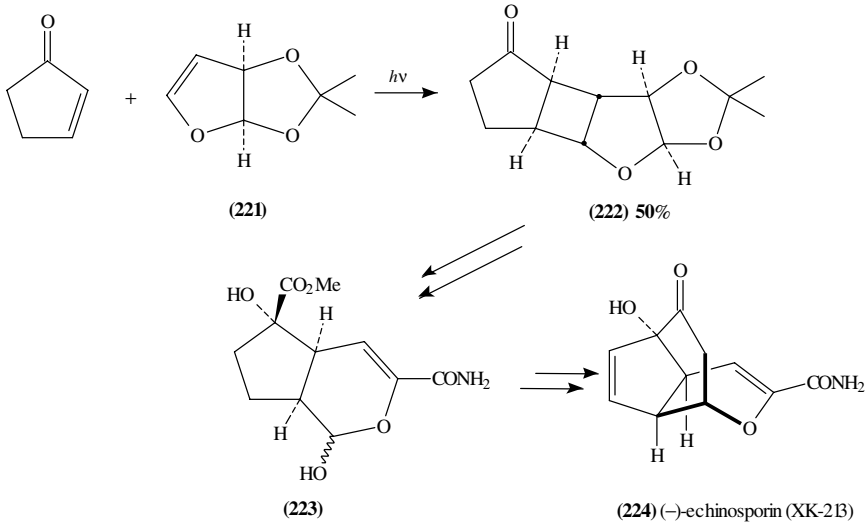


(218) **(219)** **(220)** (+) enantioquadrone

SCHEME 47

Recently, the same group[104] has reported the first total synthesis of the novel antitumor metabolite (−)-echinosporin **224**. The synthesis is based on an asymmetric [2 + 2] photocycloaddition, which constitutes the cornerstone of the synthetic strategy (Scheme 48).

The presented examples on the synthetic utility of the discussed reaction certainly do not include all the cases which reported in the recent literature because of space limitation. However, excellent reviews[54–58] can be consulted in this regard.



SCHEME 48

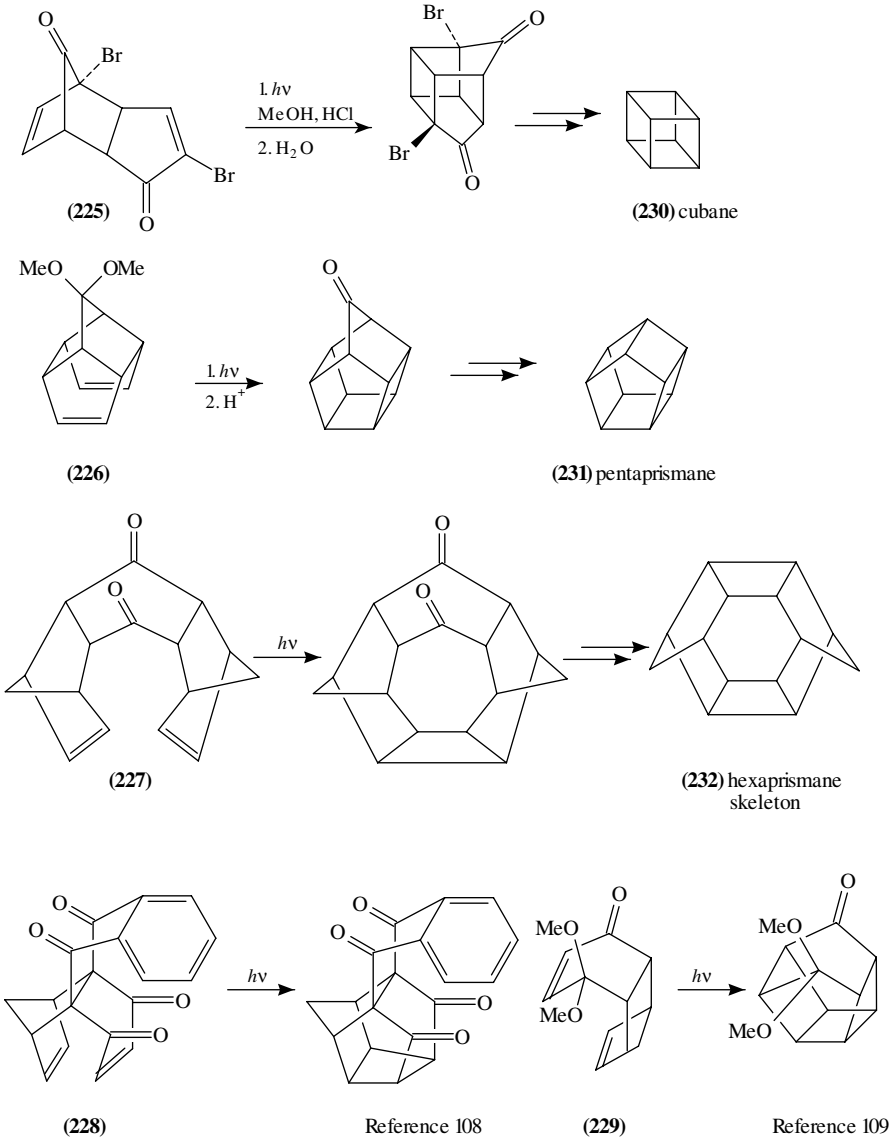
2. Intramolecular photocycloadditions

The stereoselectivity in the intramolecular photocycloadditions of mixed alkenes can be controlled to some extent by geometrical constraints. The effect of substituents and chain length in the reactants has been extensively investigated in the photoaddition of alkenes to enones. In many cases, the selectivity can be predicted on rigid structures possessing the reacting alkene at an appropriate distance. For instance, the photocyclization of cage compounds **225–229** is used as the key step in the synthesis of cubane[105] **230**, pentaprismane[106] **231**, hexaprismane skeleton[107] **232**, and other highly strained compounds[108–110] (Scheme 49).

Demonstration of the unique synthetic utility of the [2 + 2] photocycloaddition reaction of enones to alkenes and the success in controlling the stereoselectivity, to some extent, in the intermolecular additions (discussed above) prompted further studies and development of new synthetic applications in the intramolecular photoadditions during the last decade. In most cases that have been studied, the alkene was tethered to the cyclic enone by three carbon units or two carbons and one heteroatom.

High stereoselectivity was found in the first example of intramolecular [2 + 2] photocycloaddition discovered by Ciamician and Silber[111] in the irradiation of camphor **233** to carvon camphor **234**. Generally, if the tethered alkenyl side chain is connected to the enone via an asymmetric center, the configuration of this center plays an important role on the diastereofacial selectivity. For example, high stereoselectivity was found in the irradiation of the diketone **235** or its corresponding enol acetates[112], when substituents on the alkenyl side chain affect the selectivity of the enolization of **235** but not the diastereofacial selectivity (Scheme 50).

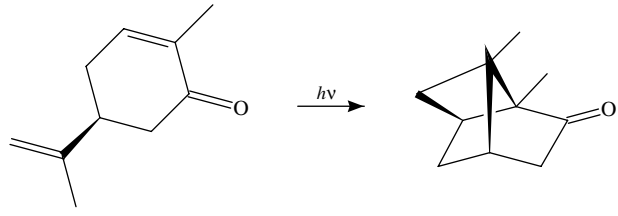
One of the first examples of high asymmetric induction in the intramolecular [2 + 2] photocycloaddition in which the chiral center located at the side chain found in Winkler and coworkers[113] approach to the synthesis of (−)-histrionicotoxin alkaloid **240**. Irradiation of **237** is the key step in the synthetic strategy. The isomer **238** was formed in



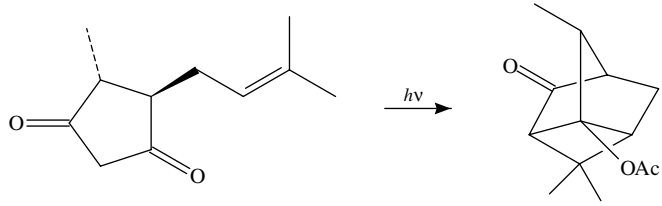
SCHEME 49

quantitative yield and was then transformed to the corresponding spirostructure **239** upon reduction with $NaBH_4$ (Scheme 51).

Another example is Crimmins and Gould's[114] total synthesis of (±)-laurenene **243** via the intramolecular photoaddition of enone **241**, affording an epimeric mixture with very high facial selectivity, followed by subsequent transformations (Scheme 52).

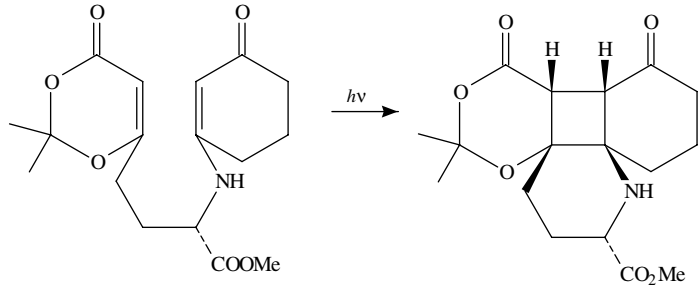


(233) **(234)**

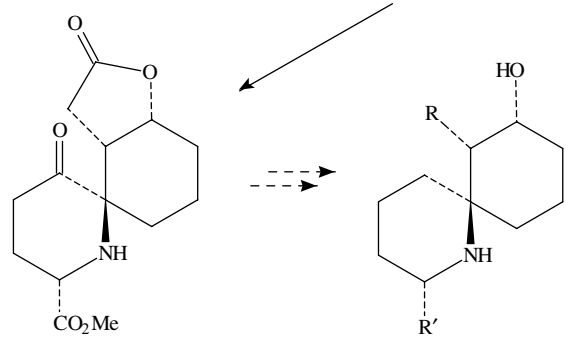


(235) **(236)**

SCHEME 50

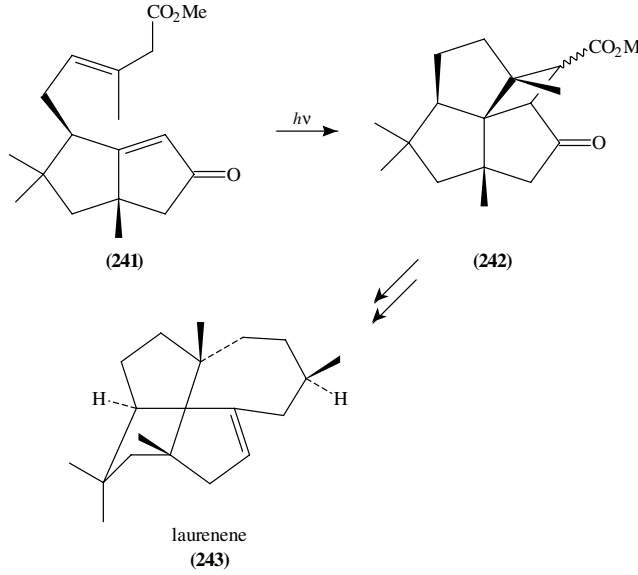


(237) **(238)**



(239) histrionicotoxin **(240)**

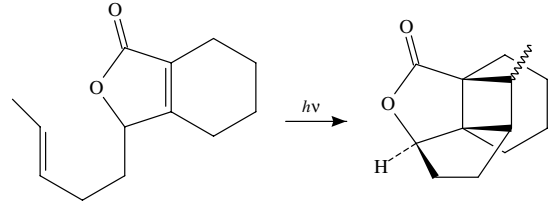
SCHEME 51



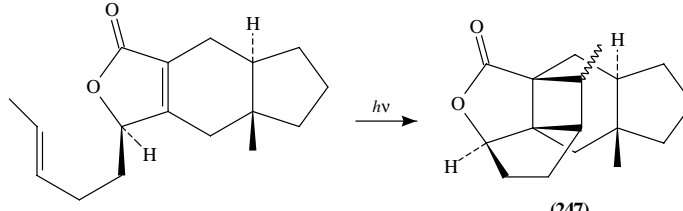
(241) **(242)**

laurenene
(243)

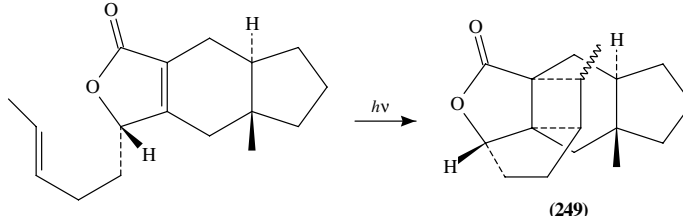
SCHEME 52



(244) **(245)**



(246) **(247)**

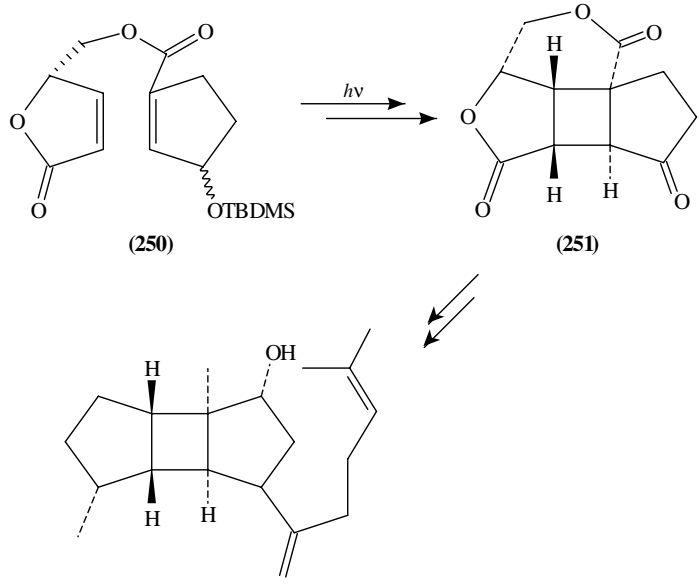


(248) **(249)**

SCHEME 53

Very high diastereofacial selectivity was obtained in the intramolecular photoadditions of the chiral unsaturated lactones[115] **244**, **246** and **248** (Scheme 53).

Koga's group described the first example of an asymmetric total synthesis of stoechospermol using the photoaddition of **250** as the key step in the synthetic sequence. Irradiation followed by deprotection of the silyl ether and subsequent oxidation afforded the single product **251**, indicating the high regio- and stereoselectivity of the photocycloaddition[116] (Scheme 54).



(250) **(251)**

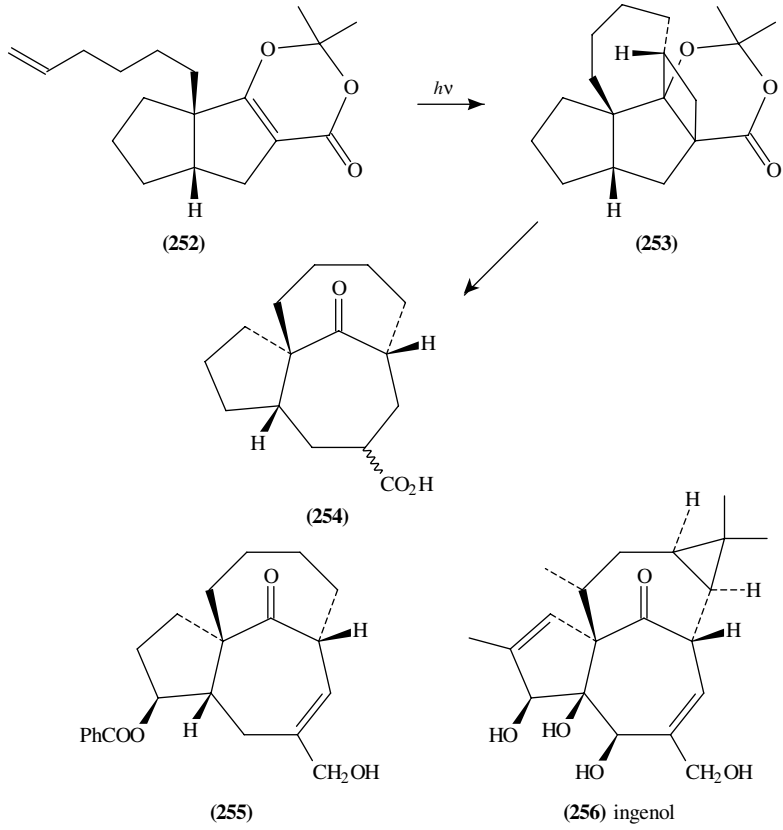
Stoechospermol

SCHEME 54

Winkler and coworkers[117] have elegantly applied the intramolecular photoaddition of the tricyclic dioxinone photosubstrate **252** in the first synthesis of the ingenane tricyclic ring system **254**. The work has recently been extended to the preparation of ingenane **255**, the first analog of ingenol **256** to have high affinity for protein kinase C[118] (Scheme 55).

Another successful application of the photoaddition fragmentation strategy of dioxinones, with complete stereoselectivity, defined by the configuration of the stereogenic center connecting the alkenyl side chain and by the orientation of the alkene in the first bond-forming step, was found in the photoaddition of dioxinone **257**, which afforded the single diastereomer **258**. Fragmentation under basic conditions gave the *cis*-bridged ketoester **259** with the desired configuration at the stereogenic centers as found in the target molecule taxol **260**[119] (Scheme 56).

All the above examples share high stereofacial selectivity defined by the configuration of the stereogenic center that connects the enone chromophore with the alkenyl side chain. However, chiral induction at the enone and/or the alkenyl tethered must be introduced to achieve stereofacial selectivity in the more general systems in which the alkene is connected at the α-carbon or β-carbon of the enone. One of the successful early examples is found in Pirrung's[120] synthesis of (±)-isocomene **263**. Irradiation of **261** afforded the single product **262**, which was transformed to isocomene in a two-step sequence.



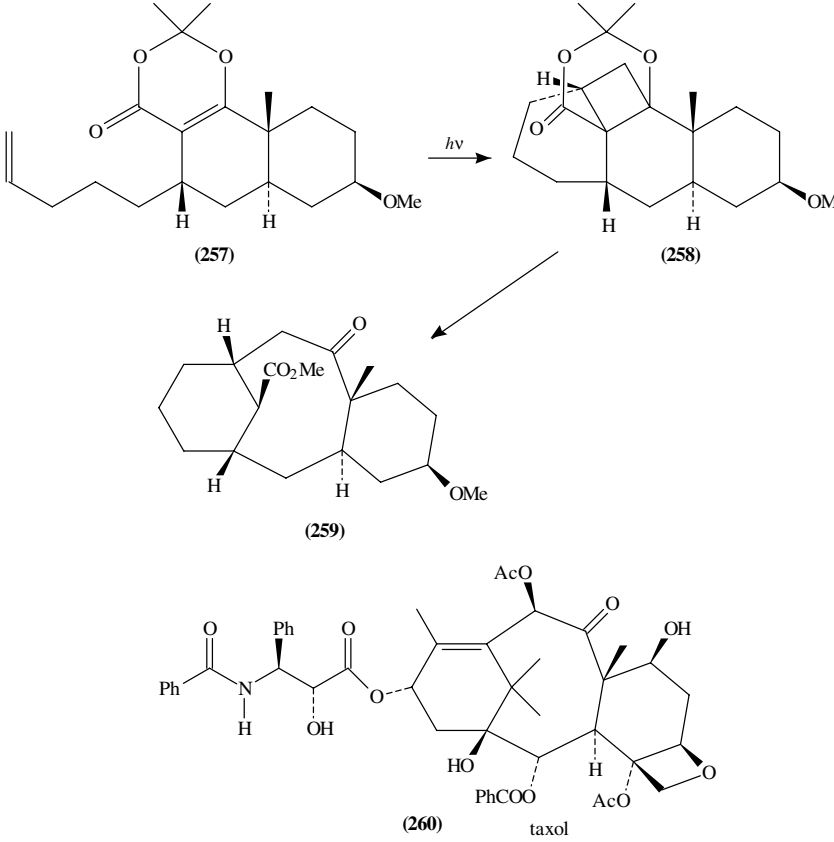
SCHEME 55

Minor structural variations were found to affect the stereoselectivity of the photoaddition. Irradiation of **264** under similar conditions afforded a mixture of four isomers and the facial selectivity was reduced to 3:1 (Scheme 57).

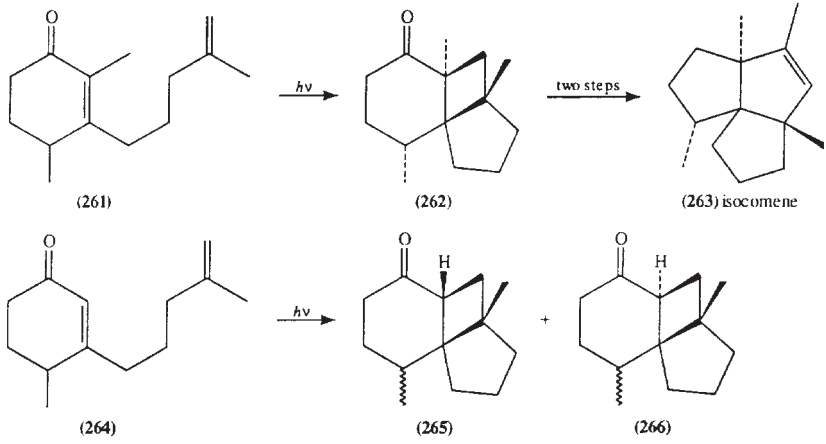
Similar diastereofacial selectivity was found in the photoaddition of **267** affording a mixture of **268** and **269** in 4:1 ratio respectively. This reaction was used as the key step reaction in the synthesis of (±)-cedrene **269**[121] (Scheme 58).

The effect of substituents at the α-carbon of the enone on the stereoselectivity was examined on compounds **270**, with the stereogenic center located at the alkenyl side chain. Crimmins and DeLoach[122] found that the stereoselectivity encountered upon irradiation of **270** depends on the degree of steric hindrance associated with the ester group linked to the double bond. The ratio of the two epimeric centers at the C-9 position varied from 13:1 (R = Me) to 17:1 (R = Et), then 20:1 (R = *i*-Pr). These results demonstrate that steric effects play an important role in controlling the stereofacial selectivity in these and related systems. Fragmentation of the photoproduced four-membered ring and simple transformations afforded synthesis of (±)-pentalene **274**, (±)-pentalenic acid **275** and (±)-deoxypentalenic acid **276** (Scheme 59).

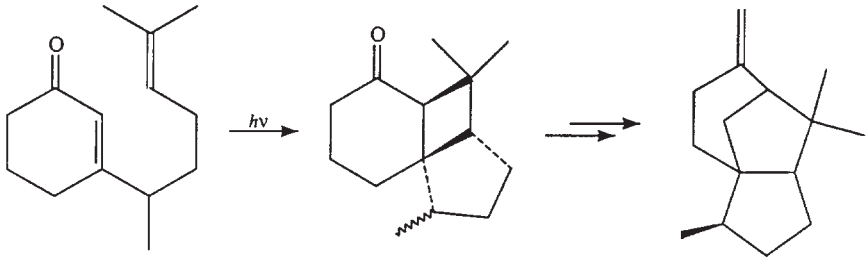
High facial selectivity was also achieved in systems with the alkenyl side chain at the α-carbon of the enone. Irradiation of **277** afforded a single stereoisomer **278** in 98% yield, which was used as a key compound in the synthesis of (±)-epi-precapnelladiene[123] **279**.



SCHEME 56

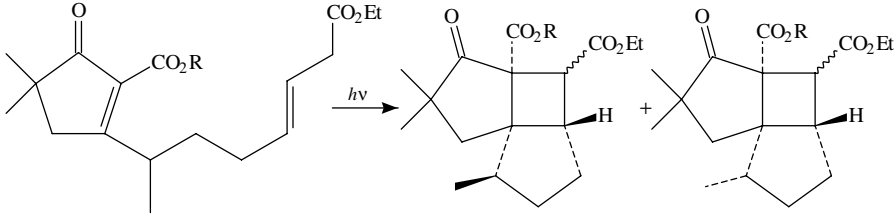


SCHEME 57



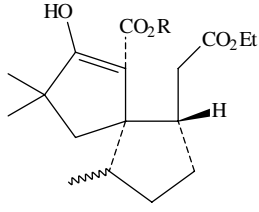
(267) (268) (269) cedrene

SCHEME 58

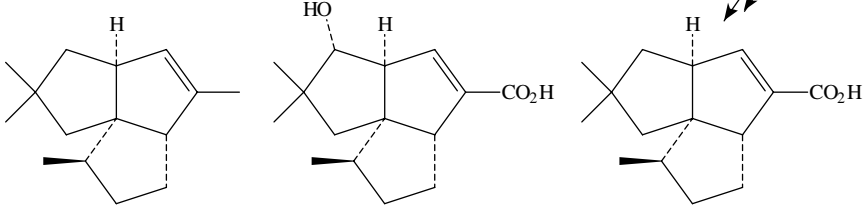


(270) (271) (272)

(a) R=Me	13	:	1	
(b) R=Et	17	:	1	Li / NH_3
(c) R=*i*-Pr	20	:	1	



(273)



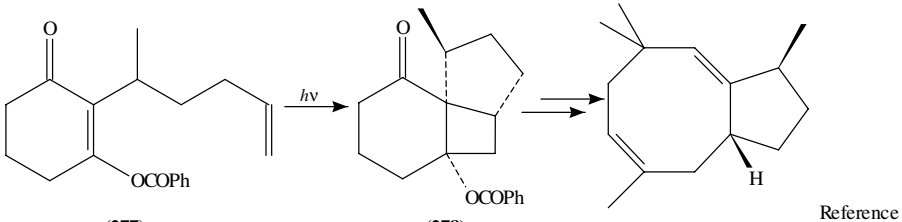
(274) pentalene

(275) pentalenic acid

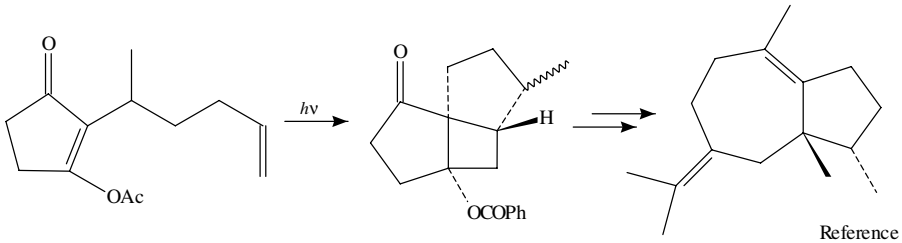
(276) deoxypentalenic acid

SCHEME 59

The high stereoselectivity was attributed to a repulsive interaction between the methyl group on the side chain and the benzoate enol ether group. Unfortunately, the extremely high stereoselectivity obtained in this system is rather exceptional as could be seen from the irradiation of the related compound **280**, elegantly used as the key reaction in a synthesis of β-bulnesene[124] **282** (Scheme 60).

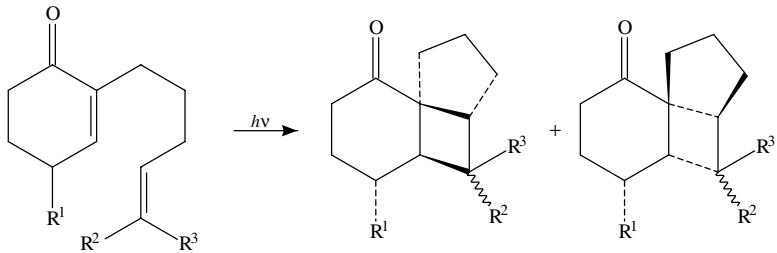


(277) **(278)** **(279)**
epi-precapnelladiene



(280) **(281)** **(282)**
β-Me/α-Me = 3.3 β-bulnesene

SCHEME 60



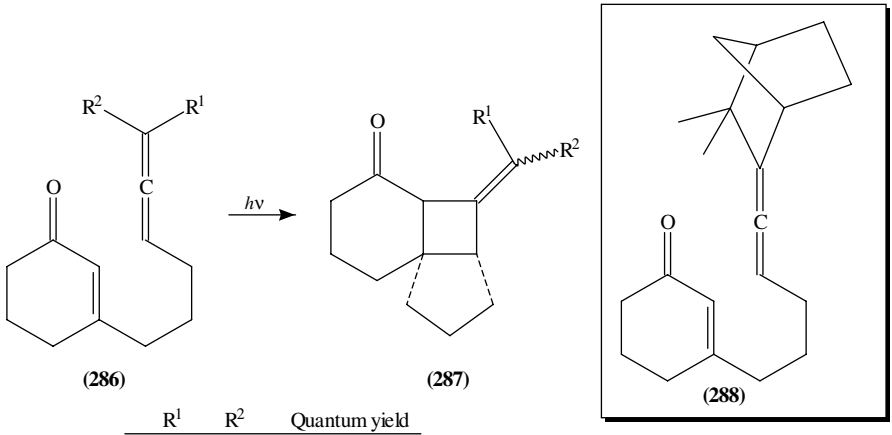
(283) **(284)** **(285)**

(a) $R^1 = t\text{-Bu}, R^2 = R^3 = Me$	100	:	00
(b) $R^1 = t\text{-Bu}, R^2 = Me, R^3 = H$	94	:	06
(c) $R^1 = t\text{-Bu}, R^2 = R^3 = CH_2$ (allene)	100	:	00
(d) $R^1 = t\text{-Bu}, R^2 = R^3 = H$	70	:	30
(e) $R^1 = R^2 = R^3 = Me$	80	:	20

SCHEME 61

The effect of substituents on the stereoselectivity of the intramolecular photocycloadditions of alkenes to cyclohexenones was systematically examined by Becker and coworkers[84] who obtained high stereofacial selectivity in compounds **283a–c**. However, small changes in the position, geometry or steric effect of the substituents have dramatically affected the selectivity, indicating the complexity in predicting the stereoselectivity in such system (Scheme 61).

Becker and coworkers[125] have examined the intramolecular photoaddition of chiral allenes **286** and **288** to cyclohexenone. Based on the quantum yields of the disubstituted allenes **286a** (0.81), **286b** (0.63) and **286c** (0.6) and of the trisubstituted allene **286d** (0.11) they concluded that the disubstituted allenes approach the cyclic enone in a highly stereoselective manner in which the hydrogen points toward the enone and the substituent points in the opposite direction. Preliminary investigations on the irradiation of the chiral allene **288** afforded poor chiral induction and low ee was obtained (Scheme 62).



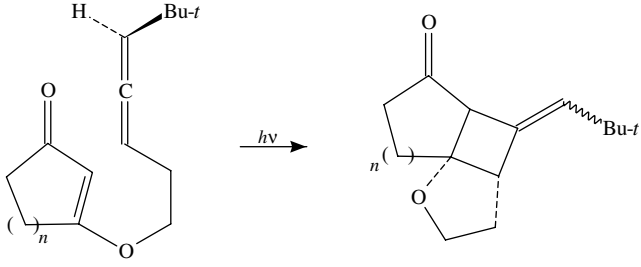
(286) **(287)** **(288)**

	R^1	R^2	Quantum yield
(a)	H	H	0.81
(b)	Ph	H	0.63
(c)	*t*-Bu	H	0.60
(d)	Me	Me	0.11

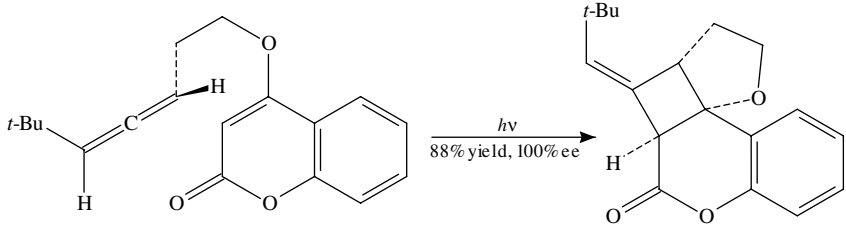
SCHEME 62

Recently, Carreira and coworkers[126] obtained very high asymmetric induction (83–100%) in intramolecular [2+2] photocycloadditions of 1,3-disubstituted allenes with enones **289** and **290** (Scheme 63).

Stereoselective intramolecular photocycloaddition of alkenes to enones with a chiral auxiliary located at the enone chromophore is not a well explored approach. The use of conformationally rigid chiral dioxinones, found to provide good diastereofacial selectivity in the intermolecular photoadditions, are described in Scheme 43. The first successful example of very high stereofacial selectivity in the intramolecular photocycloaddition of alkenes to chiral dioxinones have recently been reported by the group of Sato[127] on the irradiation of compound **291**. The single product **292** was obtained in the irradiation of **291b** in 90% yield via selective approach of the alkene from the more exposed side of the dioxinone. Interestingly, a 1:1 mixture of isomers was obtained when the side chain was reduced by one carbon. The authors attribute the lack of diastereofacial selectivity in the photoaddition of **291a** to additional geometrical constraints imposed on the reaction sites which mainly determine the preferential site by kinetic control irrespective of the

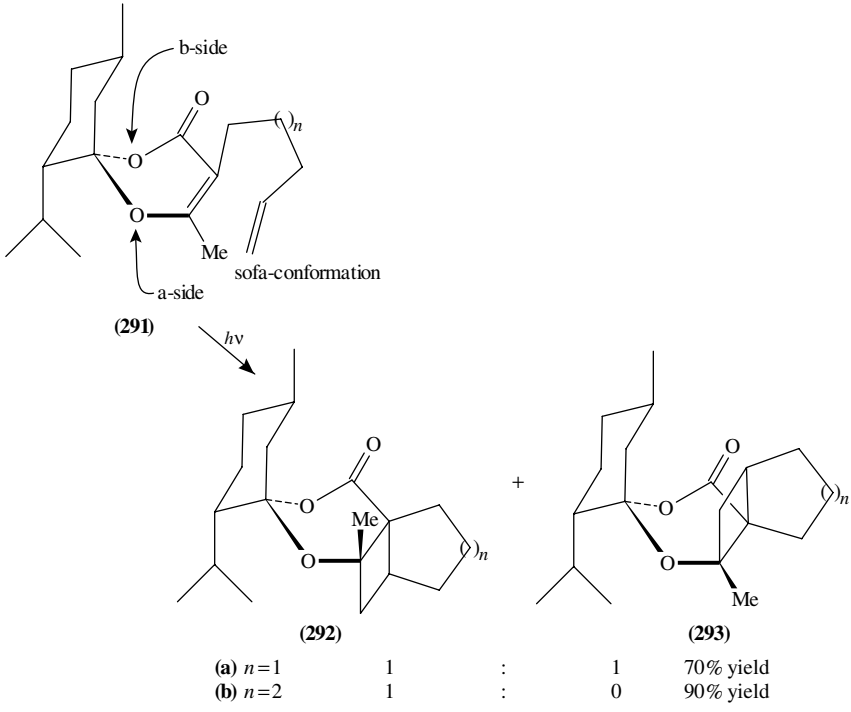


(289) **(a)** $n=2$ 89% yield, >99% ee
(b) **n**=1 72% yield, >83% ee



(290)

SCHEME 63



(a) $n=1$	1	:	1	70% yield
(b) $n=2$	1	:	0	90% yield

SCHEME 64

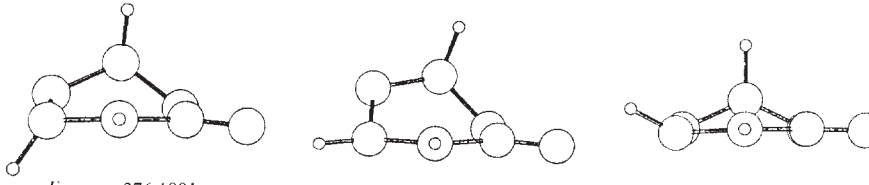
conformation of the dioxinone, whereas homologation of the alkenyl side chain **(291b)** reduces the geometrical constraint and the facial selectivity is strongly affected by the dioxinone conformation while the approach of the alkene is preferable from the more exposed side, as found in the intermolecular cases (Scheme 43). In this regard the authors suggest that the dioxinones exist as the sofa-conformation in the excited state, just like in the ground state (Scheme 64).

The fact that diradical intermediates formed in the intramolecular photocycloaddition of alkenes to cyclic enones does not cleave efficiently to the starting material, as pointed out by several research groups[77,79,85], suggests that the conformation of the cyclic enone at the reactive triplet excited state and the order of the first bond formation play an important role in the diastereofacial selectivity of the photocycloaddition of cyclic enones under kinetically controlled conditions. Alternatively to the sofa-conformation of dioxinones in the triplet excited state, suggested by the groups of Demuth[97] and of Sato[127], strong pyramidalization was found in the *ab initio* calculations of the triplet excited states of dioxinone conformations **294**, **295** and **296**, reported by Seebach and coworkers[128] who suggested, in accordance with Wiesner's model, that pyramidalization of β-carbon in the triplet excited state of chiral 1,3-dioxin-4-ones is strong and could be the origin of the observed stereoselectivity (Figure 5).

Systematic study on the diastereofacial selectivity in the intramolecular photocycloaddition of alkenes to chiral dioxinones was recently reported by Haddad and coworkers[129] on compounds of type **298**. Preferred pyramidalization in the direction of the less exposed side (the axial methyl at the acetal center) described in structure **298b**, and first bond formation at this position (found to be the case in dioxinones **143** and **146**, Scheme 31), are essential features for obtaining selective photocycloadditions of alkenes to chiral dioxinones from this side, leading to the kinetically favored products. In such cases the preferred approach is not necessarily from the more exposed side (Figure 6).

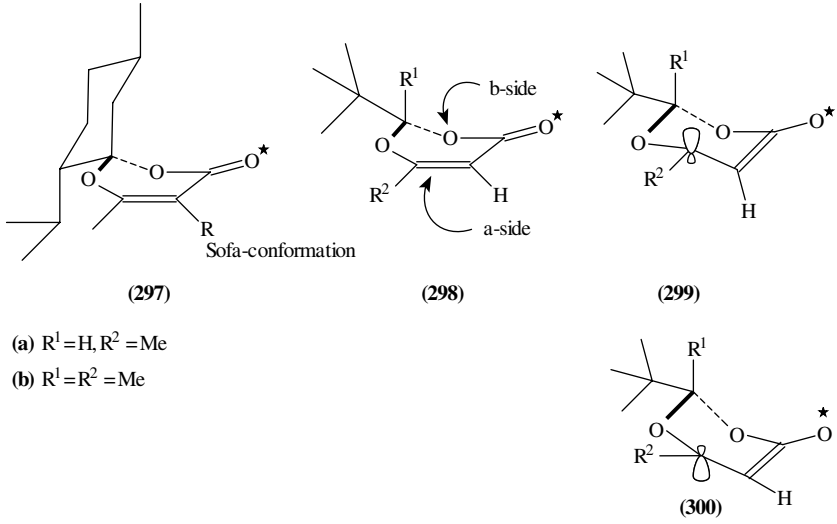
The preferred facial selectivity from the less exposed side (b-side) obtained in the irradiation of **301** under kinetically controlled conditions (entry 4) cannot be explained only on the basis of steric effect; however, it is consistent with the direction of pyramidalization in structure **299**. The increase in the facial selectivity from the same side, upon reducing the steric effect in compound **301d**, emphasizes that steric effects cannot be neglected in rationalizing the facial selectivity in these or related systems (Scheme 65).

General and stereoselective synthesis of spiroethers and less thermodynamically stable spiroketals have recently been developed by Hadded and coworkers[129,130]. The key step is the intramolecular photocycloaddition of chiral dioxinones of type **305** to dihydropyrones. Subsequent fragmentation of the produced four-membered ring provides, after oxidative enlargement of the cyclic ketone, the thermodynamically less stable spiroketal **310** (R = H) as was demonstrated on photoproduct **308** (Scheme 66).



(294) **(295)** **(296)**

FIGURE 5. 3-21G triplet states energies and related conformations of 1,3-dioxon-4-one system. Reprinted with permission from Ref. 128. Copyright (1988) American Chemical Society



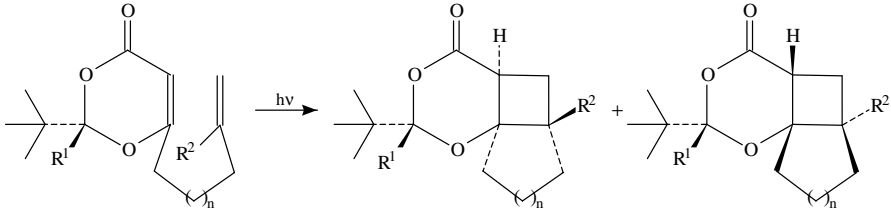
(297) **(298)** **(299)**

(a) $R^1 = H, R^2 = Me$

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

(300)

FIGURE 6. Possible triplet conformations of chiral 1,3-dioxin-4-ones



(301) **(302)** **(303)**

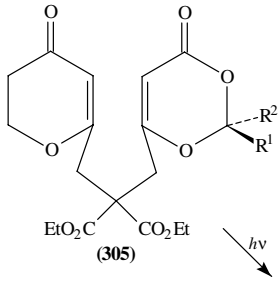
Racemic Racemic

(a) $R^1 = Me, R^2 = H, n = 1$; **(b)** $R^1 = R^2 = Me, n = 1$; **(c)** $R^1 = Me, R^2 = H, n = 2$; **(d)** $R^1 = R^2 = H, n = 2$

Entry	Compound	Products (ratio)	T(°C)
1	**301a**	**302a** (1.0), **303a** (2.0)	0
2	**301b**	**302b** (1.0), **303b** (2.4)	0 or –70
3	**301c**	**302c** (1.0), **303c** (1.0)	0
4	**301c**	**302c** (1.8), **303c** (1.0)	–70
5	**301d**	**302d** (3.3), **303d** (1.5), **304** (1.0)	0
6	**301d**	**302d** (17), **303d** (3.7), **304** (1.0)	–70

(304)

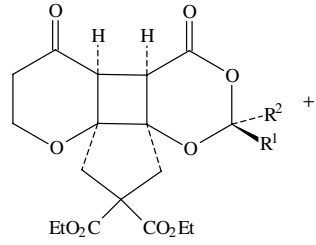
SCHEME 65



(305)

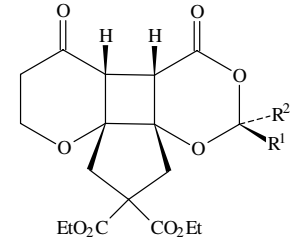
a: $R^1 = H, R^2 = t\text{-Bu}$
b: $R^1 = Me, R^2 = Ph$

hν



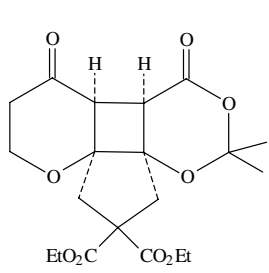
(306)

+



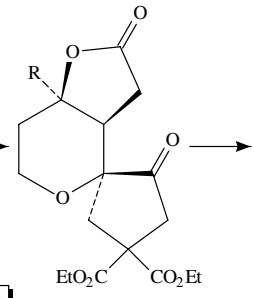
(307)

$R^1 = H, R^2 = t\text{-Bu}$	1.8	:	1	85% yield	reference 130
$R^1 = Me, R^2 = Ph$	1.0	:	0	70% yield	reference 131

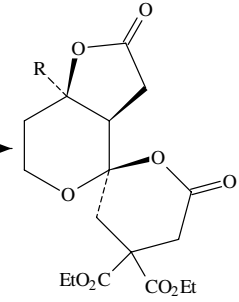


(308)

R=H, EtO



(309)



(310)

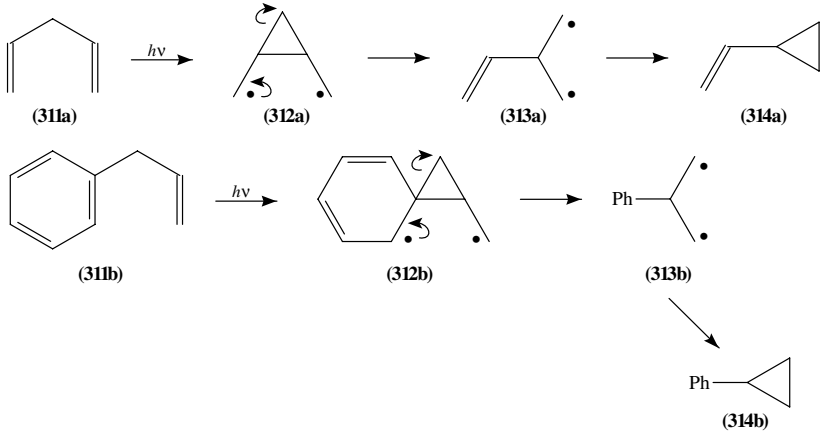
SCHEME 66

VI. DI-π-METHANE REARRANGEMENT

One of the important photoreactions of C=C bonds is the di-π-methane rearrangement. Because of space limitation, the azadi-π-methane[132] and the oxadi-π-methane[133] rearrangements are not reviewed in this chapter, and we briefly summarize the principles and typical examples of the di-π-methane rearrangement which was recently reviewed by Zimmermen[134], the principal researcher of the process[135].

The di-π-methane rearrangement, takes place on structures that possess two π-groups connected with a single carbon (the 'central' carbon), upon direct and/or sensitized irradiation of a C=C double bond chromophore, affording vinylcyclopropane products. Zimmerman proposed a stepwise cyclization of the excited π-system via a 1,4-diradical of

type **312** (Scheme 67) that rearranges to the corresponding 1,3-diradical **313**, followed by cyclization to the cyclopropyl ring **314** as described in the typical examples in Scheme 67.



SCHEME 67

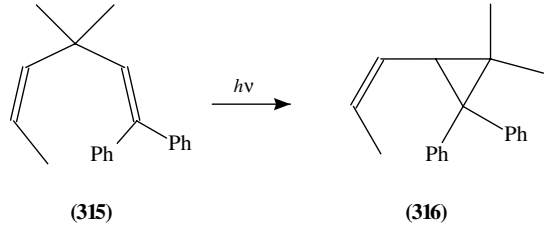
Generally, the di-π-methane rearrangement proceeds efficiently via the singlet excited state[136] in acyclic systems such as **315**. Triplet excitation of such systems, using typical triplet sensitizers (benzophenone, acetophenone or acetone), reveals an alternative $Z \leftrightarrows E$ isomerization, usually found to proceed more efficiently than the di-π-methane rearrangement. However, inhibition of the free rotation in the $Z \leftrightarrows E$ isomerization by either increasing the steric hindrance on the 'central' carbon or incorporating the di-π-methane system in cyclic structures[137] revealed an efficient di-π-methane rearrangement as shown with compounds **318** and **320**. A similar effect was achieved upon substitution of the 'central' carbon by strongly odd-electron stabilizing groups such as cyano[138], phenyl[139] or carbomethoxy[140] as illustrated in Scheme 68.

Substituents were found to play an important role in controlling the regioselectivity of the di-π-methane rearrangement in compounds **324a** and **324b**[141]. Electron-withdrawing groups (W) and electron-donating groups (D) promote isomerization of the 1,4-diradical **325** via the (a) pathway, in which the (W) group ends up at the cyclopropyl part as shown by structure **327**. This selectivity could be rationalized by formation of the more stable[142] 1,3-diradical **326** (Scheme 69).

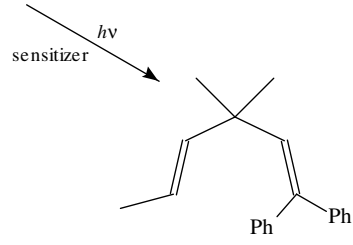
Zimmerman and Baum[143] obtained selective rearrangement in compound **324c**, which was rationalized by preferred formation of the delocalized homoallylic radical **326c**, followed by subsequent cyclization of this radical to the corresponding cyclopropyl product. Interestingly, this delocalization effect was also demonstrated in the di-π-methane rearrangement of the bicyclic α-naphthobarrelene **330** labeled by deuterium at the bridged positions[144]. Sensitized irradiation of **330** afforded the more delocalized diradical **331** that underwent rearrangement to **332**, followed by two possible cyclizations to give **335** and **336**. The positions of the labeled carbons preclude the alternative mechanism via diradical **332a** (Scheme 70).

The application of the di-π-methane rearrangement in organic synthesis could be expected to increase. Pattenden and Whybrow[145] have applied this rearrangement as a key step in the total synthesis of (±) desoxytaylorione **341** (Scheme 71).

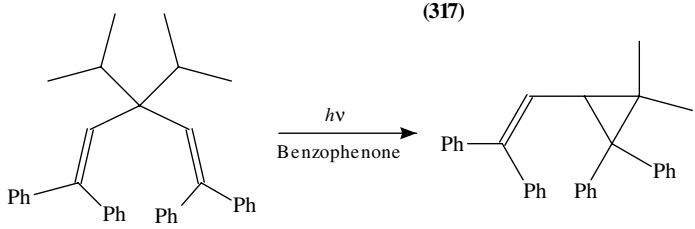
Interestingly, much attention has been paid to the di-π-methane rearrangement in solid state chemistry[146].



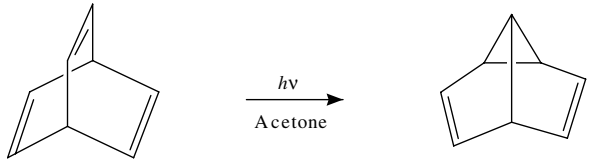
(315) **(316)**



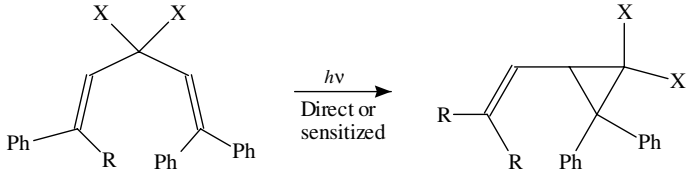
(317)



(318) **(319)**



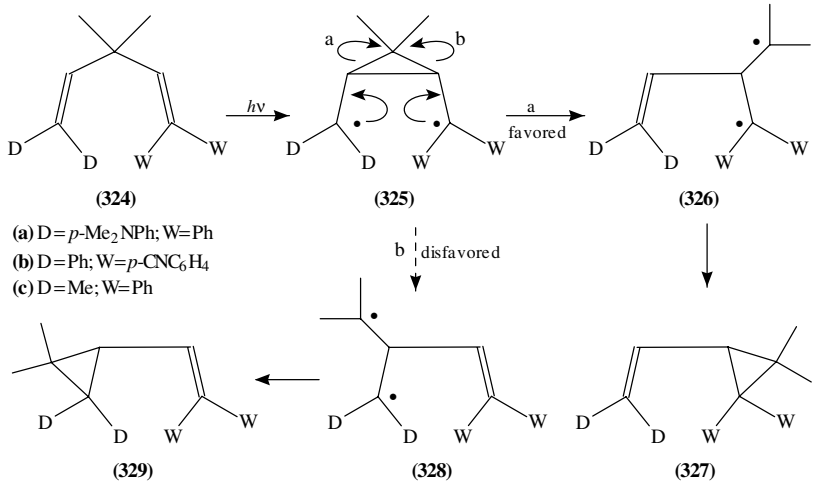
(320) **(321)**



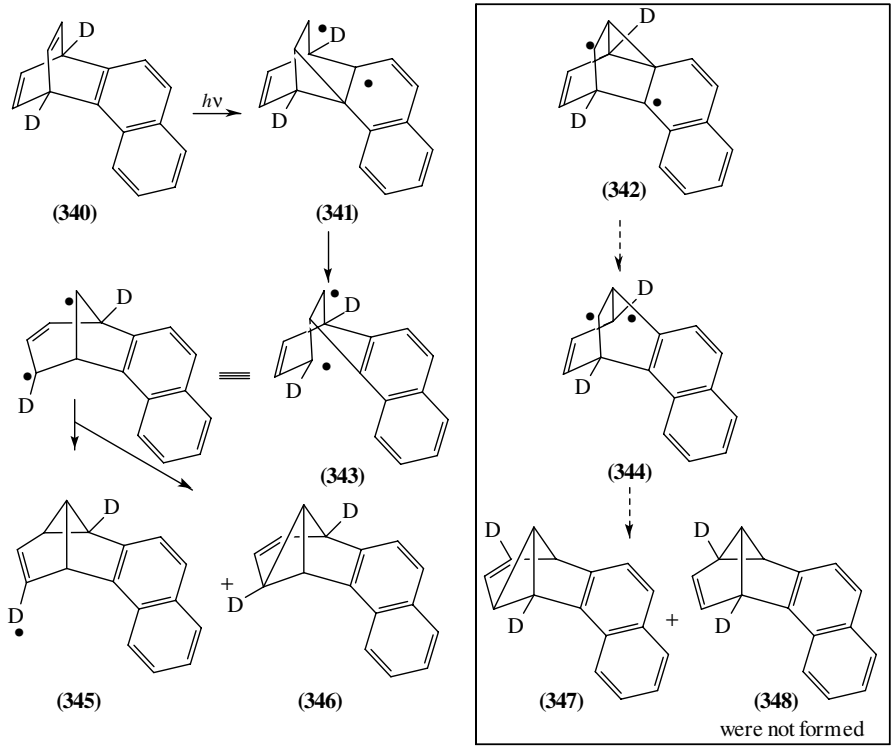
(322) **(a)** X=Ph, R=Me
(b) X=CN, R=Ph
(c) X=CO_2Me, R=Ph

(323)

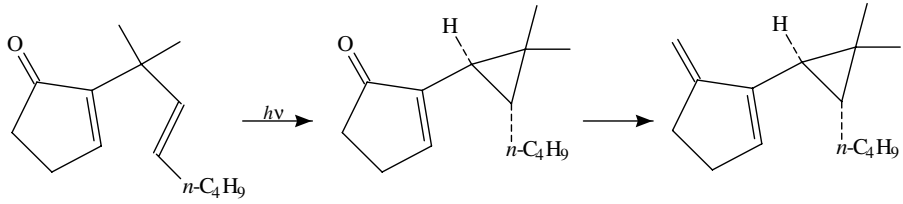
SCHEME 68



SCHEME 69



SCHEME 70



(339) **(340)** **(341)**

SCHEME 71

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Supplement A3: The Chemistry of Double-Bonded Functional Groups. Edited by Saul Patai

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CHAPTER **14**

Some synthetic uses of double-bonded functional groups

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I. INTRODUCTION

Modern organic synthesis requires that polyfunctional molecules be transformable into synthetic targets by simple and mild reactions with total stereocontrol. Although this ideal is not always attained, it is a goal that is strived for by most of the world's major synthetic organic chemistry groups. Synthetic organic chemists are challenged by this goal which stimulates the development of new reaction strategies using old procedures in novel ways and the development of new reaction pathways.

A cursory glance at a recent volume of any journal or book which covers organic synthesis will convince the reader of the central importance of double-bonded functional groups as sources of starting materials, as key intermediates and as synthetic target molecules. In particular, the reader is referred to the excellent *Art in Organic Synthesis*[1] which chronicles key syntheses that have been successfully completed over the last several decades.

Functional group transformations from alkenes, imines, carbonyl compounds and other double-bonded functional groups may be easily performed in high yield. In this review, transformations as a result of oxidation (Section II) and reduction (Section III) are covered. The reader is urged to consult the excellent *Comprehensive Organic Transformations* by Larock[2] for in-depth listings of functional group interconversions for double-bonded functional groups. The major synthetic importance of these functionalities arises from the ease by which compounds that contain these groups may be used in C−C bond-forming reactions (Section IV) and in the preparation of heterocyclic compounds (Section V).

In this review, the above-mentioned useful synthetic processes will be discussed in detail with examples mainly taken from the chemical literature since 1990.

The intent of this review is not to cover all aspects of the use of double-bonded functional groups in synthesis but rather to cover recent developments that are hopefully of interest to the synthetic community at large. Other chapters in the present volume cover some other reactions of double-bonded functional groups.

This chapter does not cover Diels–Alder and other pericyclic reactions, in any detail, since these have been the subject of several recent reviews[3−8]. Nor is the chemistry of double-bonded functional groups involving allenes or carbenes covered in any great detail.

The present review covers the chemical literature up to the beginning of 1995.

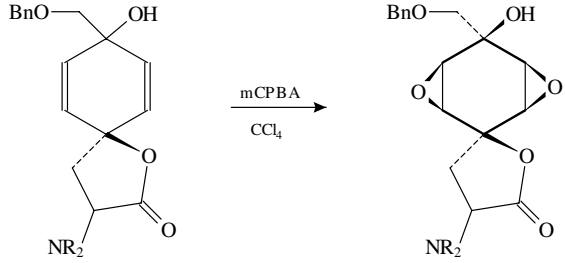
II. OXIDATION

Oxidation of double bond-containing functional groups is a key method in synthesis which is used to form other functional moieties, especially in a stereocontrolled fashion. In this section the epoxidation and dihydroxylation of alkenes are covered in some detail. These are particularly common methods used for stereocontrolled elaboration of organic molecules.

A. Epoxidation of Alkenes

Epoxides are useful synthetic intermediates or targets which can be readily prepared by many routes from the corresponding alkenes. Traditionally, this process was performed using hydrogen peroxide and organophosphorus electrophiles[9–12] or peroxy acids catalyzed with transition metal salts[13], but safety concerns with these methodologies have also caused workers to develop many other new routes. However, it is noteworthy that the commercial synthesis of propylene oxide (more than 1 million tonnes annually worldwide) occurs via hydroperoxide oxidation[14].

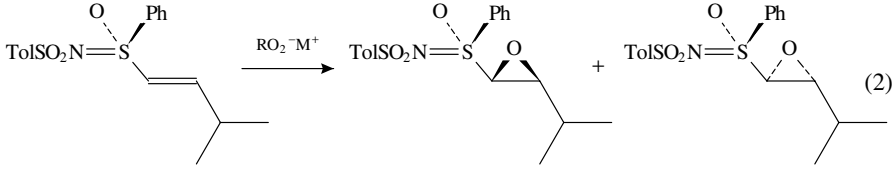
Notwithstanding this safety aspect, mCPBA continues to be used as an epoxidizing agent. In one such reaction, a diepoxidation (equation 1) was brought about as a key step in the synthesis of the spirocyclic core of aranorosin[15], which is a novel antibiotic. A radical inhibitor was added in order to achieve an acceptable yield of 46%.



(1)

tert-Butyl hydroperoxide acts as a very useful oxidant in the presence of vanadium pentoxide and titanium complexes as catalysts[16,17]. This method suffers from safety drawbacks due to the toxicity of vanadium oxide dust. Use of a titanium complex gives somewhat improved yields and significantly reduces the safety problems[18]. This methodology has been used in the asymmetric synthesis of (*S*)-fenfluramine, an important anorectic agent[19].

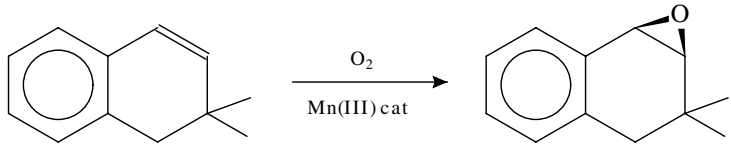
Oxidation by a hydroperoxide (generated *in situ* from oxygen and a cobalt salt) enables unfunctional alkenes to be epoxidized in reasonable yield[20]. A very attractive and much improved methodology for forming epoxides is by use of an oxidant which is regenerated *in situ*, so as to reduce the amount of oxidant required. This has been performed using oxygen with a sacraficial aldehyde catalyzed by $Ni(dmp)_2$[21–23], metalloporphyrins[24], or 'clayniac' (which is a clay supported nickel complex)[25,26]. These reactions occur in high yields and in a stereocontrolled manner (in some cases) for a wide range of alkenes. Metal alkylperoxides also give a highly diastereoselective epoxidation of *N*-tosylvinylsulfoximines, under low temperature conditions (equation 2)[27,28]. The yields are very high and the degree of selectivity depends upon the metal cation being used. Vinyl sulfones also undergo stereocontrolled epoxidation with these reagents.



(2)

Unfunctionalized alkenes have been epoxidized in 40–80% yield by an aerobic process that is catalyzed by salen-manganese(III) complexes at room temperature (equation 3).

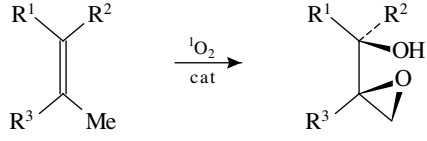
The reaction occurs with some enantioselectivity and requires the presence of pivaldehyde (which is also oxidized)[29,30]. The reaction occurs for many other alkenes using transition metals coordinated to 1,3-diketone type ligands[31–34]. Use of a cobalt(II) complex and aldoacetal in place of the Mn(III) compound and pivaldehyde gives a novel method for the synthesis of acid-sensitive epoxides[35].



(3)

Oxygen may also be used as the oxidant for epoxidation. For example, a selective epoxidation, in the absence of metal ions, has been performed in excellent yield by treatment of alkenes with oxygen in the presence of a large excess of benzaldehyde[36]. Photooxygenation of alkenes, in the presence of transition metal catalysts, is a very general and synthetically useful reaction which leads to hydroxy-epoxidation (equation 4)[37–39].

The reaction exhibits excellent stereocontrol in most instances, with the major exception being simple alkenes. The reaction has been improved so that even these latter substrates give the desired products, by initial preparation of vinylsilanes (equation 5)[40]. The reaction occurs in good yields and the Me_3Si group can be easily removed at the end of the synthetic sequence.



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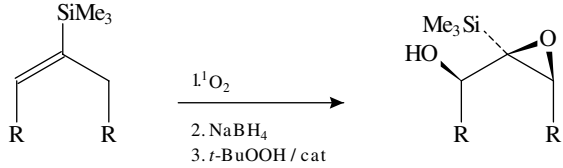
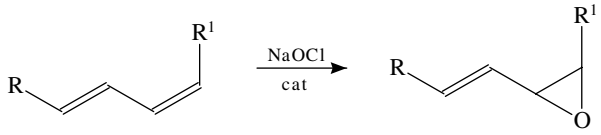


(5)

Sulfonic peracids, synthesized *in situ* from arylsulfonyl imidazolides and hydrogen peroxide, are also efficient reagents for the epoxidation of a wide range of alkenes[41]. Substituents in the aryl group affect the selectivity of this reagents and this reaction occurs in an alkaline medium.

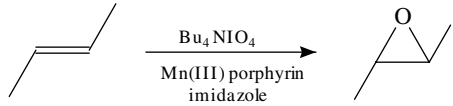
A very useful asymmetric epoxidation reaction of *cis*-alkenes, in the presence of *trans*-alkenes, has been developed using sodium hypochlorite (Chlorox bleach) and catalyzed by a complex manganese(III) salt (equation 6)[42,43]. PhIO may also be used as the oxidant[44]. This type of selectivity for epoxidation of *cis*-alkenes has been seen in other epoxidation reactions[45–47]. The enantiomeric excess of the product is 80–90% and overall yields are reasonable. A similar epoxidation process has been used with a wide range of other alkenes, especially those which lack polar directing groups, to generate optically active synthetic intermediates[48–55]. The reaction is also catalyzed by porphyrins[56–59]. Other asymmetric oxidations of alkenes have been performed by Jacobsen and coworkers using

hypochlorite and iodosoaromatic compounds[60–62].



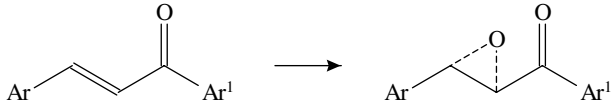
(6)

Alkenes may be epoxidized in an efficient manner by the use of tetrabutylammonium periodate, catalyzed by a manganese porphyrin[63] in the presence of imidazole (equation 7)[64]. Sodium periodate may also be used as oxidant in a similar system[65].



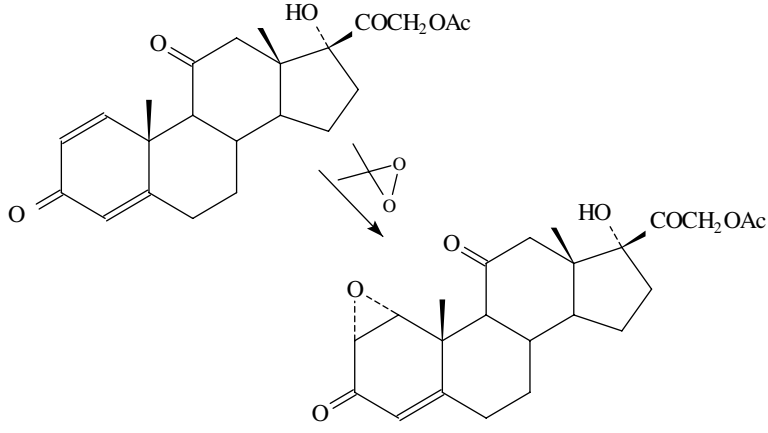
(7)

In the synthesis of optically active aryl glycidic esters, Julia[66] type epoxidation (triphasic system of NaOH/aqueous hydrogen peroxide, hexane and a polyamino acid) of an unsaturated ketone gives excellent yields of the required epoxide[67]. A potent and selective leukotriene antagonist (SK&F 104353) has been synthesized by a route where one of the key steps is this type of epoxidation (equation 8)[68].

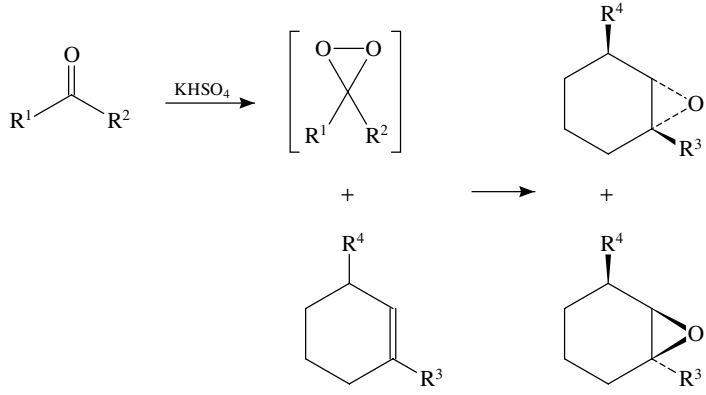


(8)

Dimethyldioxirane has also been used as the epoxidizing agent in a key step in the synthesis of A-norsteroids[69,70]. The reaction occurs in dichloromethane-acetone and is highly regio- and stereoselective as shown in equation 9. Dioxiranes may also be generated *in situ*, by reaction of potassium monoperoxysulfate (sold commercially as OXONE) and cyclohexanones. In this case, cyclohexene derivatives may be smoothly epoxidized in 40–100% yields (equation 10)[71].

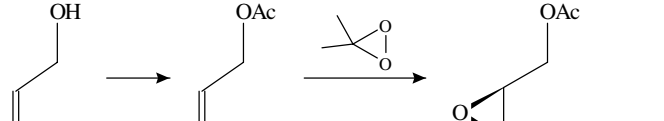


(9)



(10)

Epoxidation of allylic alcohols can be achieved by first protecting the alcohol functional group. The reagent of choice for this process is dimethyldioxirane, which is usually generated *in situ* (equation 11)[72]. If the alcohol group is not protected then it is the preferred site of oxidation[73]. This methodology has been used to prepare the important synthetic intermediates, 1,2-anhydro sugars (glycal epoxides) from glucals (equation 12)[74–77].



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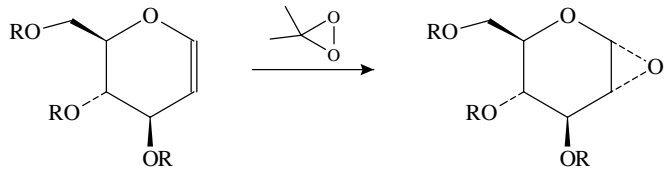
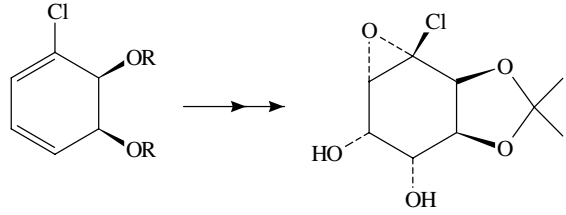


(12)

An unusual regiocontrolled oxidation (epoxidation and dihydroxylation) of 1-halo-1,3-dienes (equation 13) has been accomplished by use of potassium permanganate–$MgSO_4$, after initial treatment with 2,2-dimethoxypropane[78]. The preferred epoxy diol is formed with the epoxide being adjacent to the chloro substituent. Further elaboration of these molecules yields highly sought after inositols with controlled stereochemistry.

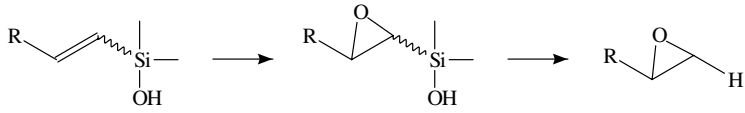


(13)

Electrochemical epoxidation of electron-poor alkenes can be accomplished by the use of silver(III) bipyridine-based redox mediators[79]. The reaction proceeds in aqueous

acetonitrile at room temperature, in high synthetic yields. Enantioselective epoxidation of unfunctionalized alkenes has recently been reported using hydrogen peroxide with antibody 20B11 as catalyst[80]. This is the first reported example of an antibody-mediated oxidation at carbon, *in vitro*.

Finally, even with all the above methods available to the organic chemist, it is still fairly difficult to prepare simple epoxides. One route has been developed recently which uses Sharpless epoxidation[81,82] procedures on alkenylsilanols (equation 14)[83]. This reaction produces an epoxysilanol which is readily converted to the epoxide in good yields by treatment with fluoride ions.

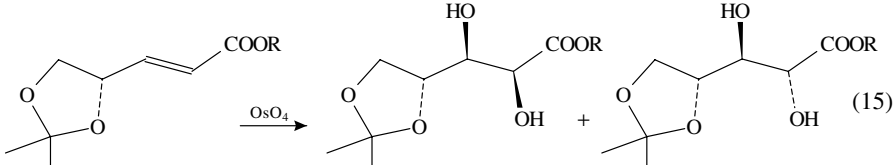


(14)

B. Dihydroxylation of Alkenes

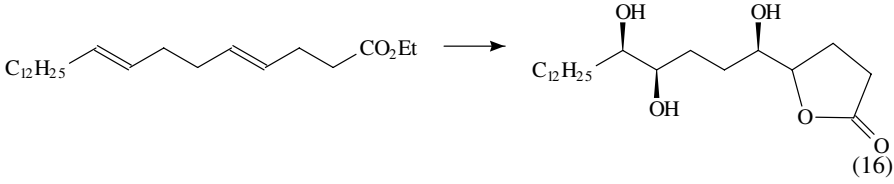
Dihydroxylation (especially asymmetric reactions) of alkenes is a very important synthetic tool for the introduction of a new functionality into organic molecules. The reader is referred to recent reviews on the synthetic utility and mechanisms of asymmetric dihydroxylation for useful background material regarding synthetic outcomes[84–88].

Catalyzed osmium tetraoxide mediated, asymmetric dihydroxylation (AD) of alkenes has become a very useful means of distereoselective functionalizing alkene-containing molecules, which contain a wide-range of neighboring stereogenic centers[89–93]. In this reaction the choice of oxidizing agent-coordinating ligands is extremely critical in determining which diastereomers are produced. For example, compound **1** (equation 15) was the major product when phthalazine ligands[94–96] were used, whilst compound **2** was the major product when pyrimidine analogues[97] were the ligand of choice. The latter ligands are particularly useful in the dihydroxylation of terminal olefins. A key step in the total synthesis of solamin and reticulatacin (naturally occurring acetogenins) was performed using this methodology (equation 16)[98]. A polymer-bound quinine derivative has also been used recently in the enantioselective dihydroxylation of olefins[99]. However, in some reactions of this type[100–107] the diastereoselectivity is not as good as that achieved by titanium-catalyzed epoxidations[108].



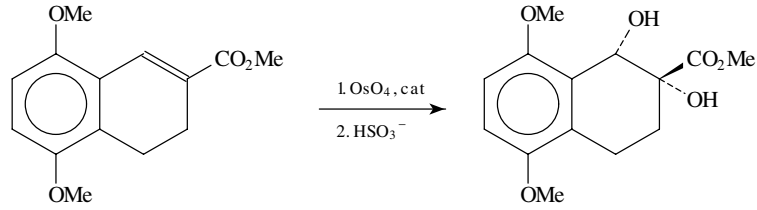
(15)

(1) **(2)**



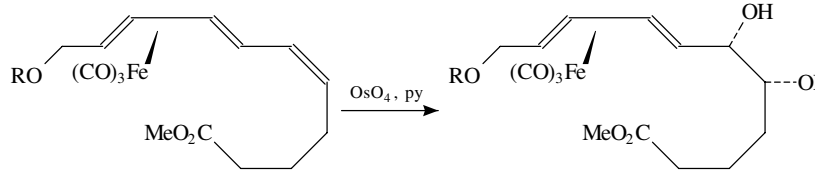
(16)

Enantioselective dihydroxylation of *trans*-alkenes has been performed, with a high degree of selectivity, by catalysis of the oxidation process by chiral diamines[109–113]. In this way an anthracycline has been prepared via a short-step process, the key step being a catalyzed dihydroxylation (equation 17) which occurred in 85% enantiomeric excess. Asymmetric dihydroxylation of sulfur(II)-containing olefins has been performed successfully, with excellent chemoselectivity[114]. This is somewhat surprising, but is due to the selectivity of the AD reagents and to the relatively slow oxidation reaction which OsO_4 and sulfur(II) atoms undergo.



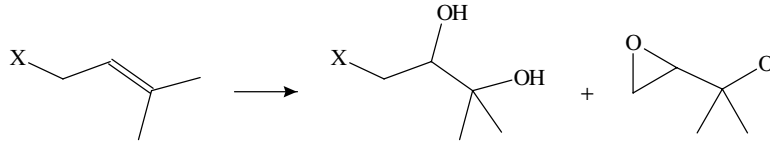
(17)

In the synthesis of polyhydroxylated polyenes, osmium tetroxide induced dihydroxylation of an alkene adjacent to a coordinated iron atom has been used as the key synthetic step[115]. The reaction has been shown to be highly diastereoselective for *E*-alkenes and diastereospecific for *Z*-alkenes. With both types of alkene, the reaction occurs *anti* to the coordinated iron group (equation 18).



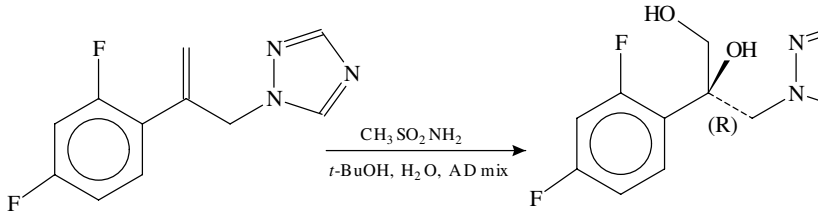
(18)

Primary allylic halides may be efficiently asymmetrically dihydroxylated in 40–98% ee. The products may be readily converted into epoxy alcohols in high yields, by treatment with NaOH in THF (equation 19)[116].



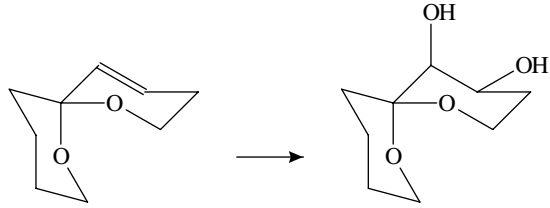
(19)

The key step in the synthesis of novel azole antifungal agents has been performed by asymmetric dihydroxylation[117] using a modified AD-mix[118–120] (equation 20). The reaction occurs in excellent yields at room temperature in *t*-BuOH–water as solvent.



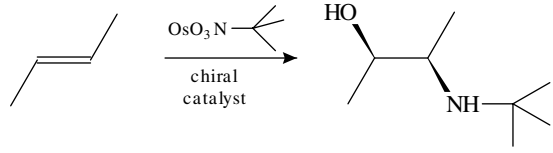
(20)

Spiro acetals can also be stereoselectively hydroxylated, in high yield, with osmium tetraoxide and a catalyst. The resultant diol is formed by *syn*-hydroxylation from the least hindered side of the alkene moiety (equation 21)[121].



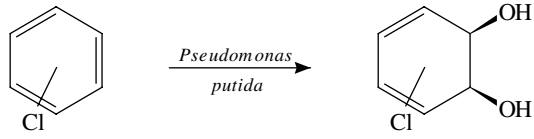
(21)

A vincinal amino alcohol grouping is present in a fair number of natural products which possess useful biological activity, such as antibiotics[122]. Such a functionality has been produced from alkenes via osmium-mediated aminohydroxylation (equation 22)[123]. The reaction proceeds in 40–97% yield and is enantioselective if chiral osmium-*Cinchona* alkaloid complexes are used to mediate the reaction.



(22)

In a rather obscure, but synthetically very useful reaction, the biooxidative hydroxylation of chloro-benzenes (equation 23) has been used as a key step in the synthesis of inositols[124]. Cyclohexadiene *cis*-diols are produced and similarly functionalized compounds may also be obtained from quinolines and isoquinolines[125]. These reactions have been exploited for the synthesis of a number of natural products[126,127].



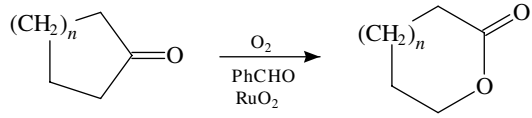
(23)

C. Baeyer–Villiger Oxidations

The regioselectivity of the migration in Baeyer–Villiger oxidation of ketones is very dependent upon substituents attached to carbon atoms adjacent to the ketone. In a study[128] of the MCPBA oxidation of polyhydroxycyclohexanone derivatives, the regioselectivity of the reaction has been carefully identified. This should prove useful to synthetic chemists when planning to use this type of reaction, since cyclitols are important synthons in natural product synthesis.

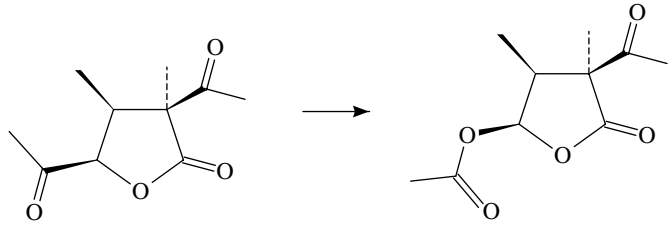
Baeyer–Villiger oxidation of ketones to esters or lactones is a very useful synthetic technique which has been used for many years[129,130]. Variations of this reaction have recently been performed with molecular oxygen using Fe_2O_3[131], nickel(II) complexes[132], and benzaldehyde with a nickel[133] or ruthenium[134] complex as catalysts. The last of these reactions (equation 24) is noteworthy since it occurs in the absence of ionic metal

catalysts, thus giving a new, milder alternate methodology for this established oxidation process.



(24)

Baeyer–Villiger oxidation has been used to selectively oxidize one of two methyl ketones (to esters) in the final step of a stereoselective synthesis of (−)-acetomycin, an antibiotic with potential anti-leukemia activity (equation 25)[135]. This reaction was accomplished using MCPBA as oxidant, with an excess of sodium bicarbonate and 5-*tert*-butyl-4-hydroxy-2-methyl phenyl sulfide as a radical inhibitor.

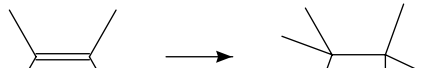


(25)

D. Reductive-Oxidation Processes

This section covers the hydroboration–oxidation of alkenes to give alcohols. The author chooses to include this under oxidation since an oxygen atom is introduced into the molecule. This reaction can be performed in a stereocontrolled fashion and it is these methods that are highlighted here. In addition, one similar reductive-oxidation reaction is included, since it is an extremely facile route to benzyl alcohols and α-hydroxyalkanoic acids.

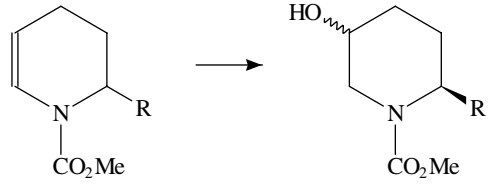
Hydroboration of a wide range of alkenes using catecholborane (and similar boranes), catalyzed by samarium(III)[136,137], palladium[138,139], iridium[140,141] and other transition metal and lanthanide complexes[142–145], gives good to excellent yields of alcohols (equation 26). The process is regioselective and is dependent upon the catalyst used[146]. However, in the presence of some functional groups there is a significant yield of alkane (via hydrogenation) and aldehyde (after the oxidative work-up step)[147]. The normal regiochemistry can be inverted if allylic sulfones are used. In such a case, rhodium-catalyzed hydroboration gives the Markovnikov product (equation 27)[148]. In the absence of catalyst, a mixture of products is obtained. Similar inversion of selectivity is also obtained by rhodium-catalyzed hydroboration of styrenes[149–151].



(26)

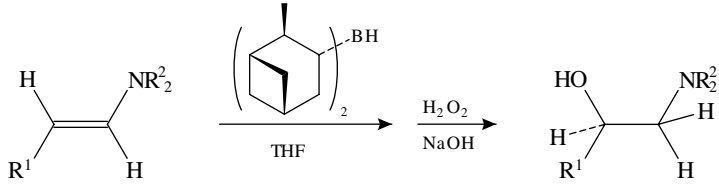
(27)

Hydroboration-oxidation of enecarbamates with borane-dimethylsulfide complex gives reasonable yields of β-hydroxycarbamates (equation 28) with some diastereoselectivity, depending upon what other functional groups are present in the starting material[152].



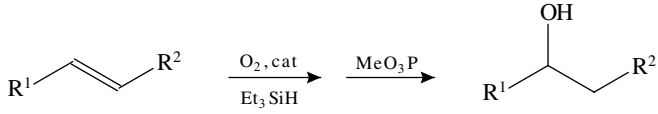
(28)

Asymmetric hydroboration of enamines with chiral diboranes, followed by oxidation with hydrogen peroxide, in aqueous sodium hydroxide, gives β-amino alcohols in good yields and high ee (equation 29)[153]. The products of this reaction are useful in medicinal applications and as synthons for further synthetic elaboration.



(29)

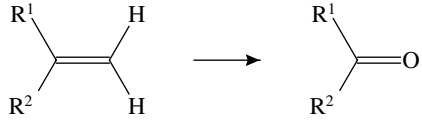
A range of aromatic alkenes and acrylic acid derivatives have been converted into benzyl alcohols and α-hydroxyalkanoic acids in good yields by a 'reductive oxidation' process. This reaction is accomplished by reaction with oxygen and triethylsilane with a cobalt(II) catalyst, followed by treatment with trialkyl phosphites (equation 30)[154]. The aromatic olefins may also be converted into the corresponding acetophenone in a modified procedure where the trialkyl phosphite is removed[155]. In a similar reaction 2,4-alkadienoic acids are converted into 4-oxo-2-alkenoic acids[156].



(30)

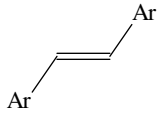
E. Oxidative Cleavage

This is a useful route for the preparation of aldehydes and ketones from alkenes, and is covered in this section. Photosensitized oxidative cleavage of alkenes occurs in reasonable yield using *p*-dimethoxybenzene in the presence of oxygen (equation 31)[157]. The products are aldehydes or ketones depending upon substrate structure.

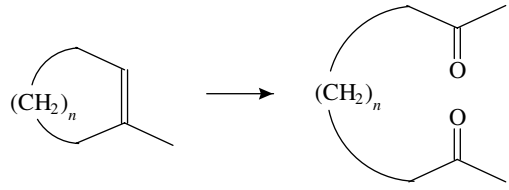


(31)

Trans-substituted diarylalkenes undergo oxidative cleavage upon treatment by potassium permanganate in the presence of moist alumina as a solid support (equation 32)[158]. Under the same conditions, cyclic alkenes, with medium-sized rings, give acyclic dialdehydes (equation 33).



(32)

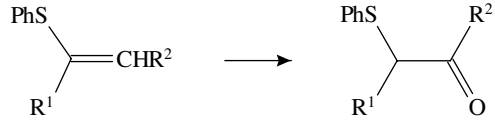


(33)

F. Other Oxidations

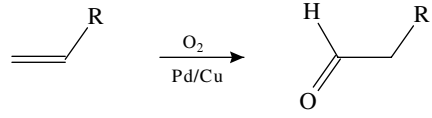
1. Formation of ketones and related functionalities

Phenyl vinyl sulfides undergo one-electron transfer reactions with oxygen to give reasonable yields of α-ketosulfides (equation 34)[159].

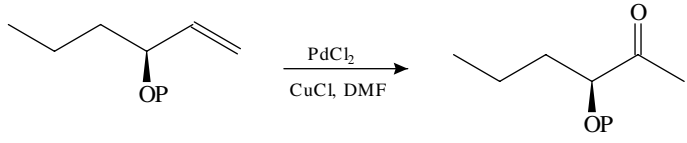


(34)

Terminal alkenes can be selectively oxidized to aldehydes by reaction with oxygen, using a palladium-copper catalyst in tertiary butanol (equation 35)[160]. This reaction is contrary to the normal oxidation process which yields a ketone as the major product. The palladium(II) oxidation of terminal alkenes to give methyl ketones is known as the Wacker process. It is a very well established reaction in both laboratory and industrial synthesis[161,162]. The Wacker oxidation of alkenes has been used in the key step in the synthesis of the male sex pheromone of *Hylotrupes bajulus* (equation 36)[163].



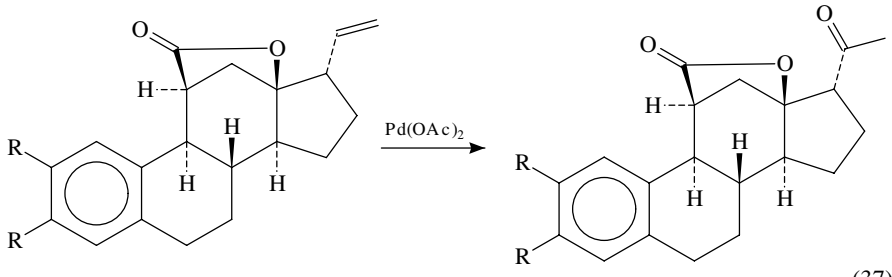
(35)



(36)

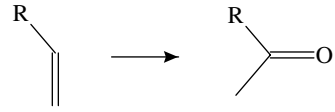
The reaction can also be carried out under electrochemical conditions[164,165]. The reaction is somewhat unpredictable since in some cases the aldehyde is produced together

with the ketone. However, in some cases the two products may easily be separated by recrystalization. Thus, this reaction has been used for the preparation of estratriene derivatives in up to 89% yield (equation 37)[166]. The stereochemistry of the lactonic bridge in this molecule is crucial to the synthetic outcome.



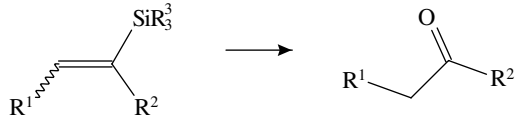
(37)

Terminal olefins may be oxidatively cleaved by hydrogen peroxide, catalyzed by a palladium(0) complex, to give methyl ketones in almost quantitative yields (equation 38)[167]. This methodology is an alternative to the well established Wacker protocol using palladium(II) complexes.

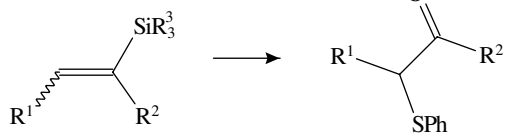


(38)

Alkenylsilanes have been used as precursors of carbonyl compounds as depicted in equation 39. Traditionally, the carbonyl group may be produced by epoxidation followed by an acid-catalyzed rearrangement. More recently this process has been achieved by oxygenation in the presence of *N*-benzyl-1,4-dihydronicotinamide, catalyzed by tetraacetylriboflavin[168]. The reaction has also been performed using cobalt(II) catalyzed oxygenation[169]. All these reactions suffer from regioselectivity problems, where the resulting ketone is unsymmetrical and specific α-functionalization is sought as the target molecule. This problem has been elegantly solved in a process that involves electro-initiated oxygenation of alkenylsilanes, in the presence of thiophenol (equation 40)[170,171]. A similar result is also obtained if the alkenylsilane is replaced by an alkenyl sulfide[172].



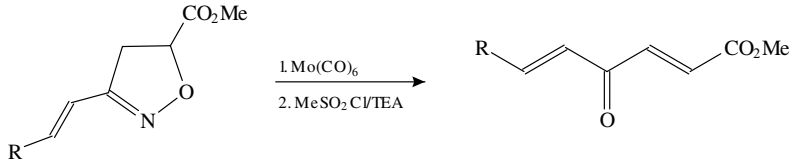
(39)



(40)

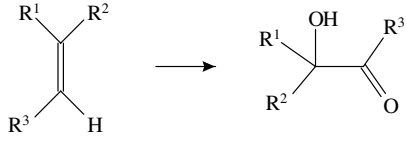
The synthesis of 4-oxo-2,5-hexadienoates (which is a functionality which has received some attention due to its presence in some anti-tumor compounds[173,174]) may be accomplished in high yield from isoxazolines. This reaction is performed by reaction with

molybdenum hexacarbonyl in acetonitrile–water, which affords an intermediate β-hydroxy ketone which is readily dehydrated by standard methodology (equation 41)[175].



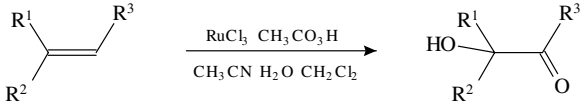
(41)

Peracid oxidation of alkenes, catalyzed by osmium trichloride, produces α-ketols which are extremely versatile synthetic intermediates. The reaction occurs for a range of mono- and disubstituted alkenes (equation 42)[176].



(42)

α-Ketols may be formed from trisubstituted alkenes by treatment with peracetic acid, catalyzed by ruthenium trichloride in a mixed solvent system (equation 43)[177]. These products are very useful synthons and this functionality is the target in cortisone and adriamycin derivatives. Similar transformations have also been performed using potassium permanganate-copper sulfate[178] and with isobutylaldehyde, oxygen and osmium tetraoxide, with nickel catalysts[179].



(43)

α-Diketones or α-hydroxyketones may also be formed from alkenes by oxidation using potassium permanganate on an inert support, which has been coated with *tert*-butanol[180]. α-Hydroxyketones are also formed in the osmium tetraoxide catalyzed AD of alkenes[181].

2. Formation of acids and their derivatives

Aldehydes may be readily oxidized giving carboxylic acids in very good yield. This reaction has recently been performed using sodium perchlorate in aqueous acetonitrile (equation 44)[182]. Aldehydes may also be converted into methoxymethyl (MOM) esters, an interesting synthetic sequence that involves the initial formation of an organostanane followed by oxidation with ozone at $-78\,^{\circ}C$ (equation 45)[183]. The α-alkoxyesters produced in this later reaction seem to be potentially very useful synthons for further synthetic elaboration.

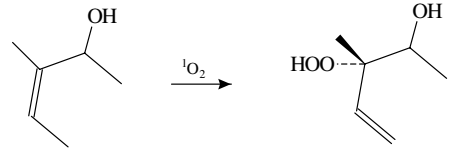
$$\mathrm{RCHO} \xrightarrow[\mathrm{MeCN\ aq}]{\mathrm{NaClO_4}} \mathrm{RCOOH} \tag{44}$$

$$\mathrm{RCHO} \xrightarrow[\begin{array}{l}2.\ \mathrm{MOMCl}/i\text{-}\mathrm{Pr_2NEt}\\ 3.\ \mathrm{O_3/CH_2Cl_2}\end{array}]{1.\ \mathrm{Bu_3SnLi}} \mathrm{RCOOCH_2OCH_3} \tag{45}$$

Selective oxidation of thioamides into amides can be brought about by several reagents including mCPBA[184,185], ozone[186], phase-transfer oxidation methods[187] and dimethyldioxirane[188]. These reactions give varying success, depending upon the substrate being oxidized.

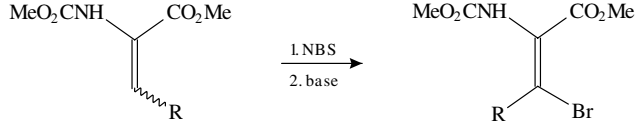
3. Others

Oxidation of allylic alcohols with singlet oxygen has been used as a route to prepare allylic peroxides in a stereoselective fashion (equation 46)[189].



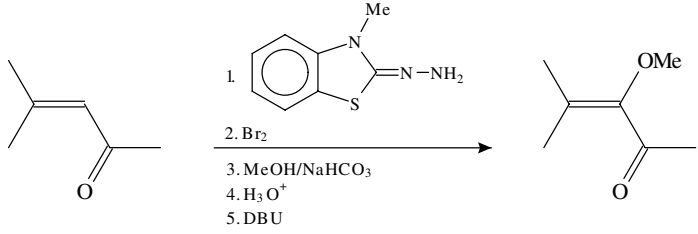
(46)

Stereoselective bromination of dehydroamino acids is a useful reaction of further functionalizing such a compound. The reagent of choice is NBS and good yields are obtained under stereocontrolled conditions (equation 47)[190]. This reaction has been used as a key step in the synthesis of azinomycin A and B, which are valuable antitumor agents[191].

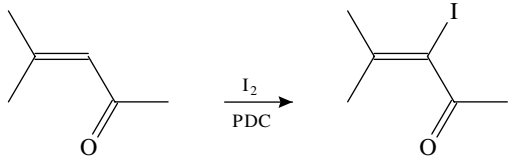


(47)

α-Methoxylation of an α,β-unsaturated carbonyl compound is potentially a very useful method in the synthesis of natural products. This reaction can be readily brought about by formation of a hydrazone followed by treatment with bromine and then $NaHCO_3$, and then aqueous acid and finally DBU (equation 48)[192]. Using a different hydrazone reagent, or by the initial formation of semicarbazones, β-substitution is also possible[193,194]. Formation of an α-iodoenone is also easily attained by treatment of α,β-unsaturated ketones with pyridinium dichromate (PDC) and iodine (equation 49)[195].

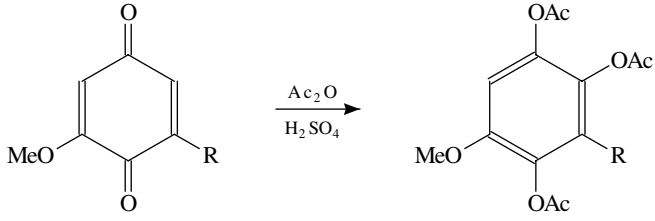


(48)



(49)

Finally, Thiele acetoxylation of quinones, by treatment with acetic anhydride and sulfuric acid, is another excellent method of introducing functionality at an alkene carbon atom, for further synthetic elaboration (equation 50)[196]. This reaction was recently used as a key synthetic step in the total synthesis of metachromin-A, a useful sesquiterpene quinone moiety[197].



(50)

III. REDUCTION

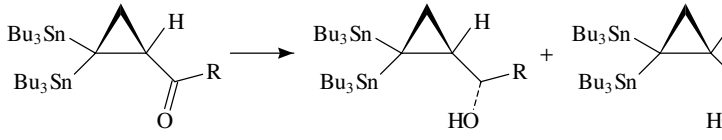
The reduction of double bond-containing functionalities, especially alkenes and carbonyl compounds, is an important methodology used in synthetic elaboration. In this section the stereocontrolled reduction of aldehydes, ketones and C=N-containing compounds and the catalytic hydrogenation of alkenes are covered, among other reductions. The emphasis here is placed on stereocontrolled reactions.

A. Reduction of Ketones and Aldehydes to Alcohols

The production of alcohols by the reduction of aldehydes and ketones is probably one of the most useful and fundamental steps in the synthetic chemist's arsenal. Although there are many well developed methods for the reduction of ketones and aldehydes to alcohols, there is still much interest in developing new or improved methodologies which are milder and can be brought about under special conditions, especially in the presence of other reducible functional groups. Of particular interest to the modern synthetic organic chemist are the aldehyde and ketone reductions which are accomplished in an enantioselective fashion. Advances in this field up to 1992 have been the subject of a review by Singh[198]. The present section covers very recent work in this area.

1. Using hydride transfer and related reagents

This section covers the reduction of aldehydes and ketones, in complex molecules using hydride transfer reagents. Many of these are complex reagents designed specifically for particular reactions. LAH has been used for the reduction of cyclopropyl ketones[199]. Trialkyltin moieties in the cyclopropane ring cause diastereoselective reduction to occur (equation 51).



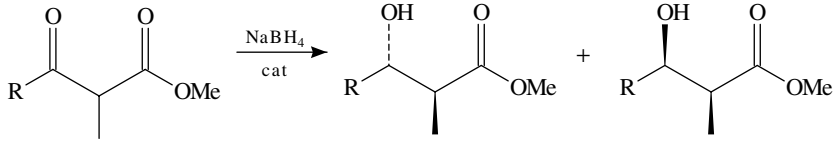
(51)

17:1

Enantiomerically pure α-hydroxy esters may be prepared by the stereoselective reduction of the corresponding α-keto esters, by $LiAlH(OCEt_3)_3$ in THF in the presence of chiral

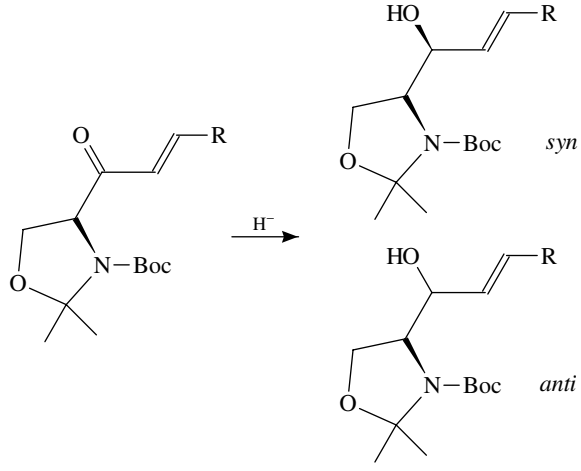
borneol auxiliaries[200]. The auxiliaries may be easily removed under mild, saponification conditions, giving the free acid as the final product.

The synthesis of 3-hydroxy-2-methyl esters and amides in a stereoselective manner is a challenge which needs to be met due to the prevalence of these moieties in natural products[201]. This has been accomplished by using sodium borohydride, catalyzed by manganese(II) chloride or by tetrabutylammonium borohydride (equation 52)[202,203].



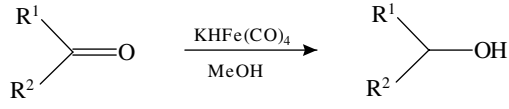
(52)

The synthesis of α'-amino allylic alcohols is particularly difficult, yet this functionality is important in natural products (such as sphingosine) or as a synthon for further elaboration to amino sugars. In synthetic studies of this moiety[204], the corresponding enones, with adjacent stereocenters, have been efficiently reduced to the allylic alcohol in quantitative yields and in both a regiocontrolled (1,2) and a stereocontrolled fashion (equation 53). The *syn*:*anti* ratio of the product depends upon the hydride reductant and solvent being utilized. A 4:1 ratio was obtained with L-selectride and a 1:6 ratio obtained by the use of DIBAL in toluene.



(53)

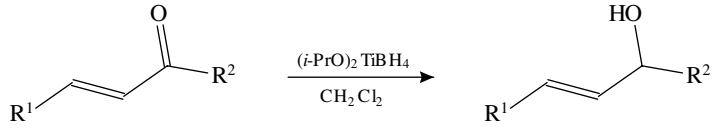
Potassium tetracarbonylhydridoferrate is a hydride transfer agent that may be used to reduce ketones selectively in high yields (equation 54)[205]. With diketones a hydroxy ketone is produced.



(54)

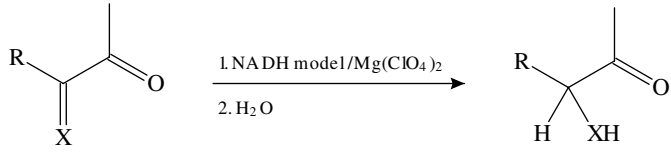
Allylic alcohols have also been obtained in excellent (90%) yields by reduction of enones with diisopropoxytitanium(III) tetrahydroborate (equation 55)[206]. The reaction

occurs in only a few minutes, in dichloromethane at −20 °C.



(55)

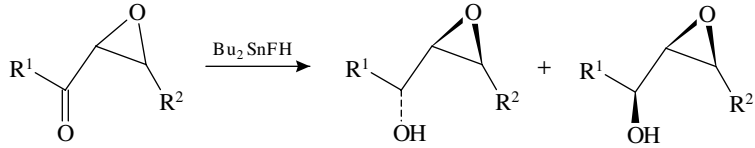
α-Ketoesters and α-methoxycarbonylimino esters may be efficiently reduced, with good enantioselectivity, by the use of C-4 methylated NADH model compounds in the presence of magnesium perchlorate (equation 56)[207]. This reaction may also be brought about, in good yield and with up to 87% ee, by catalytic hydrogenation with Pt/Al_2O_3 and a chiral catalyst[208].



(56)

X = NCO_2Me or O

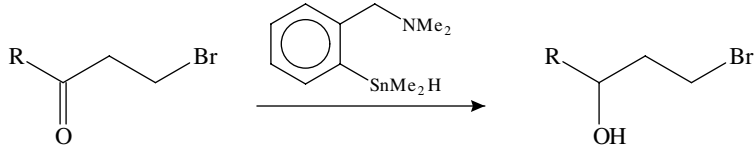
The reduction of aldehydes and ketones to alcohols by tri-*n*-butyltin hydride gives a yield of up to 95% when carried out in the presence of silica gel[209] or Lewis acids[210]. Modified tin hydrides have also been employed for this reduction[211–213]. For example, α,β-epoxyketones may be reduced, in excellent yields, in a selective manner to give the *anti* epoxy alcohol as the major product, by reaction with Bu_2SnFH[214] and similar tin hydrides[215] (equation 57). A similar *anti*-selectivity is obtained upon reduction of α-alkoxy ketones[216].



anti *syn*

(57)

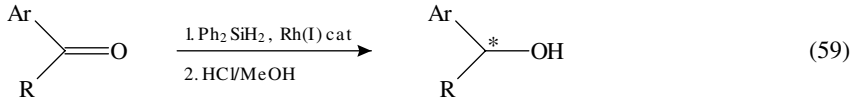
Tin hydrides that are internally activated have also proved extremely useful for the mild reduction of a wide range of ketones containing alkoxy, halogen and alkyne groups (equation 58)[217]. Careful choice of solvent is needed in order to eliminate halogen reduction.



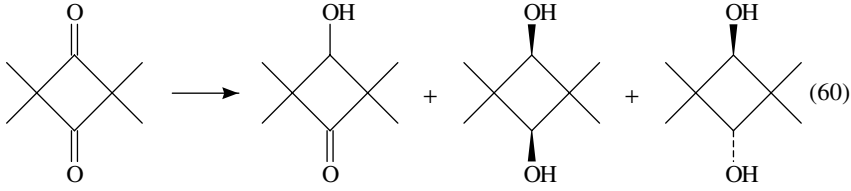
(58)

Rhodium(I) catalyzed asymmetric hydrosilation of ketones is an excellent route to chiral alcohols in reasonable chemical yields. The reaction occurs by treatment of alkyl

aryl ketones with diphenylsilane at 0 °C (equation 59)[218]. Similar reactions have been performed using lithium hydride/trimethylsilyl chloride as the hydrosilation reagent[219] and using a chiral titanium complex as the catalyst[220]. Reaction of 2,2,4,4-tetramethyl-1,3-cyclobutanedione with hydrosilanes, catalyzed by rhodium(I) complexes, results in either one or two carbonyl groups being reduced, to the alcohol, depending upon the silane employed[221]. This reaction can be controlled to give either the *cis*-diol or the *trans*-diol exclusively. The three products resulting from this reaction are shown in equation 60. Other metals and their complexes also catalyze the reduction of diketones[222–224].



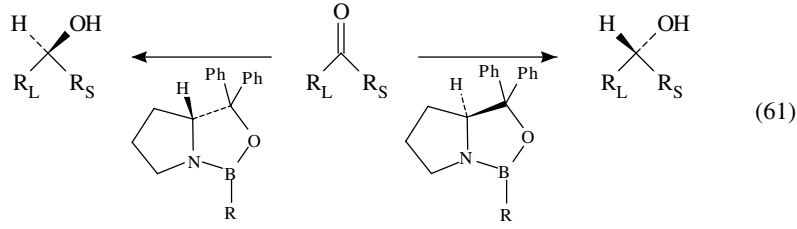
(59)



(60)

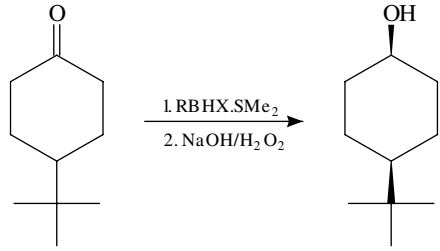
2. Using boron-containing reagents

Enantioselective reduction of ketones can be accomplished by the use of BH_3 and catalytic quantities of chiral oxazaborolidines, in THF at low temperature[225–236]. The enantiomer produced depends upon the choice of reducing agent (see, for example, equation 61), and in most cases the alcohol is produced in high enantiomeric excess. This reaction has been used as the key step of enantioselective synthesis of a dopamine D1 agonist[237], which has found use in the treatment of Parkinson's Disease. The reaction is successful in the presence of halogens and sulfur and nitrogen atoms[238–242], thus making this particular reduction procedure very useful in the elaboration of more complex molecules. Imines[243,244], imides[245] and oximes[246] may also be reduced by this mild methodology. Borane reduction of ketones may also be catalyzed by β-hydroxysulfoximines giving enantioselectivity of up to 93%[247].



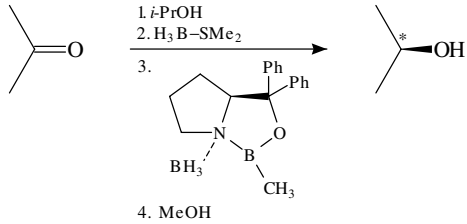
(61)

Cyclic ketones may be reduced by thexylchloroborane-dimethyl sulfide (ThxBHCl.SMe_2) and the related bromo and iodo compounds, in a stereoselective manner (equation 62)[248]. The selectivity increases with increasing halogen size. These reagents give much better selectivity than many of the more traditional ones, such as ThxBH_2.



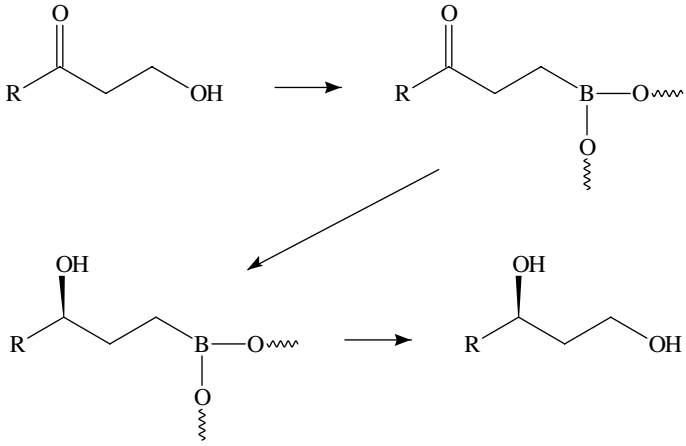
(62)

The enantioselective reduction of ketones using oxazaborolidine-borane complexes is a useful synthetic route to chiral alcohols (equation 63). Additives such as simple alcohols have been found to enhance the enantioselectivity of the process, and the reaction has been used in the large-scale synthesis of an important drug with anti arrhythmic properties[249].



(63)

Directed asymmetric reduction of a ketone has been brought about by the use of an intramolecular homochiral boronate ester[250]. The latter was readily introduced at a hydroxyl group in the molecule and has allowed the production of the enantiomeric alcohol, from the ketone by use of BH_3-complex as the reductant (equation 64). The boronate ester may be readily removed by treatment with hydrogen peroxide–sodium hydroxide, using standard methodology. Other similar reductions have also been reported[251–253].

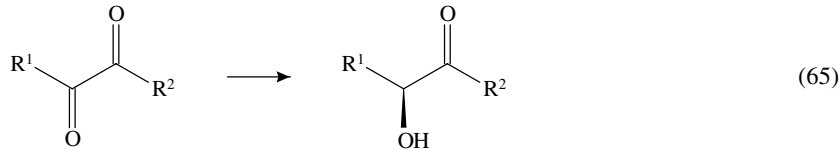


(64)

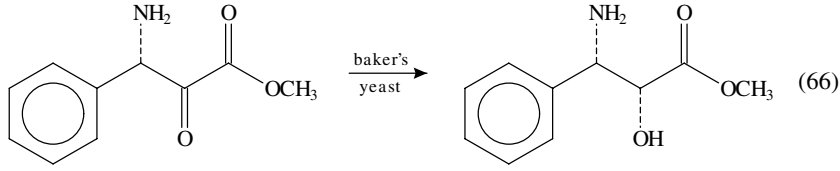
Finally, it is noteworthy that Lewis base adducts of gallane ($LGaH_3$) reduce cyclic ketones, enones and α-haloketones to the corresponding alcohols in excellent yields[254]. These reagents show some promise as a new extension of the boron-type reductions of carbonyl compounds.

3. Using baker's yeast

Baker's yeast reduction of organic compounds, especially carbonyl compounds, is an extremely useful method of obtaining chiral products[255–257]. Recently, much effort has been expended to improve the ee obtained in this process. In one very useful example, 1-acetoxy-2-alkanones have been reduced enantioselectively into (*S*)-1-acetoxy-2-alkanols in 60–90% yields and with 95–99% ee[258]. The reaction readily occurs in a variety of solvents, both aqueous and nonaqueous. The reduction is fairly selective and so may be brought about in the presence of α-amide, ether, ester and other acid functional groups, in reasonable yields and with excellent ee (equation 65)[259–261]. Thus, in the synthesis of the C-13 side chain of taxol, the key step was the reduction of a α-ketoester to the corresponding alcohol in 72% overall yield (equation 66)[262].

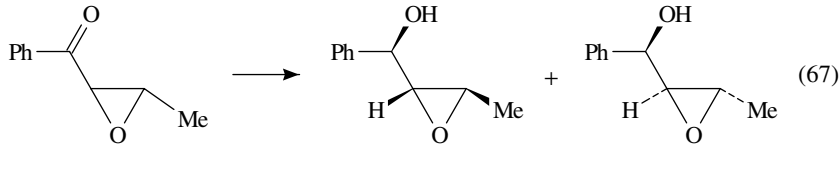


(65)

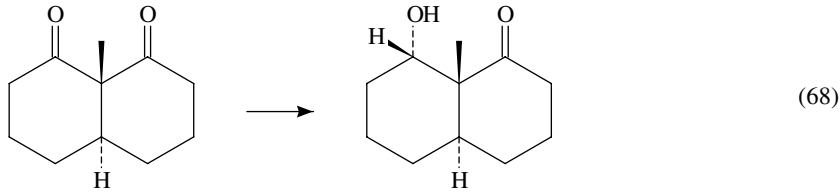


(66)

γ-Ketoacids[263] and β-ketoesters[264–273] have also been reduced enantioselectively by baker's yeast, in good to excellent ee (It seems that pretreatment of the yeast may improve the stereochemical control of the reaction[274].) In this case a chiral lactone is usually formed. Nitro-containing ketones[275–277], epoxyketones (equation 67)[278–280] and acetophenones[281] may also be reduced in a similar fashion. Also, in the case of diketones it is sometimes possible to obtain selective reduction of just one ketone group[282–284] (equation 68)[285].



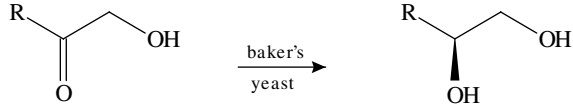
(67)



(68)

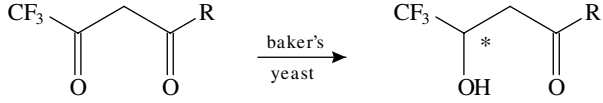
α-Hydroxyketones (and other oxygenated groups) are also readily tolerated by the reaction conditions, giving very good to excellent yields of the corresponding diols, with one alcohol as part of a chiral center (equation 69)[286–288]. Whether the stereocenter is

R or *S* is very much dependent upon the reaction conditions and upon the substrate structure[289]. This is probably due to the several dehydrogenase enzymes that are present in baker's yeast.



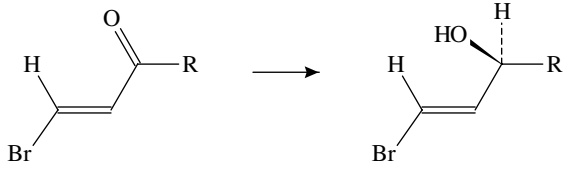
(69)

Fluorinated α-diketones are reduced by baker's yeast in a regioselective fashion giving reduction chiefly at the ketone which is adjacent to the fluorine atoms (equation 70)[290]. The enantiomer in excess can be selected by manipulation of the rest of the molecular structure.



(70)

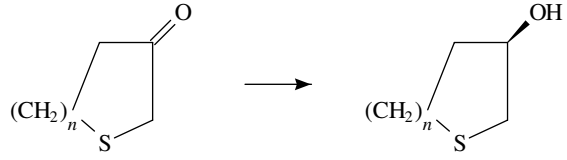
Finally, (*S*)-coriolic acid (a metabolite of linoleic acid) has been synthesized, in an enantiospecific fashion, by the use of the alcohol dehydrogenase enzyme from baker's yeast in the presence of NADPH. In the key step of this synthesis, the supported enzyme/NADPH was used to reduce a bromovinyl ketone enantiospecifically (equation 71)[291].



(71)

4. Other methods

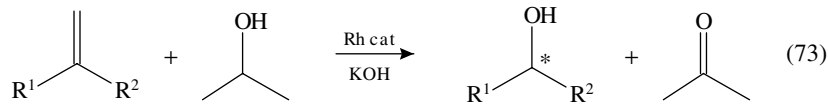
Some other methods used for the stereocontrolled reduction of aldehydes and ketones are discussed below. Catalytic hydrogenation, under mild conditions using rhodium-based catalysts, is a very facile means of reducing a wide range of aldehydes and ketones[292]. Asymmetric reduction of α-dicarbonyl compounds may be performed selectively at a ketone in the presence of an ester or amide, by hydrogenation using achiral binaphthalene (BINAP) ruthenium complex. The resulting 2-hydroxy ester (amide) is typically obtained in excellent yield and in high ee[293–295]. Similar catalysts may be used to reduce β-ketoesters[296] and cyclic alkanones and β-thiacycloalkanones (equation 72)[297], with hydrogen, in the same controlled fashion.



(72)

Catalytic reduction of unsymmetrical ketones into alcohols by concomitant oxidation of 2-propanol to acetone (Meerwein–Ponndorf–Verley reduction, MPV), with rhodium

catalysts, has been a very successful methodology that has resulted in excellent selectivity (equation 73)[298,299]. Recently, this selectivity has been improved by the use of C_2-symmetric 1,2-diamines as chiral ligands[300,301]. This reaction may also be brought about using trivalent lanthanide compounds, with chiral ligands, as catalysts[302–305]. Other improved MPV reductions have been performed using either hydrous zirconium oxide[306], or a new silica-supported zirconium complex[307] as the catalyst. These reactions result in excellent yields of the corresponding alcohol, under mild and neutral conditions.



(73)

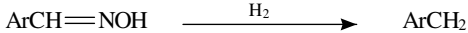
Metals in protic solvents have also been used to reduce ketones to alcohols. One such process employs cadmium chloride and magnesium in THF–water. This reagent efficiently (85–95%) reduces aldehydes and ketones to their corresponding alcohols[308]. Sodium supported on alumina has also been used as an excellent means of ketone reduction[309]. In this reaction a proton donor such as isopropanol is employed. This reaction gives good yields and affords a moderate selectivity in the case of ketones containing chiral centers in close proximity. The synthetic utility of this reagent is due to the ease by which the sodium-supported reductant may be prepared and wax-coated, thus allowing the material to be stored ready for use at a later date.

Reduction of benzaldehydes with Raney nickel, under alkaline conditions, gives good to excellent yields of the corresponding alcohol[310]. Reduction of the same substrates under acidic conditions, using an amine-cyanoborane complex as the reducing agent, also gives very good yields[311].

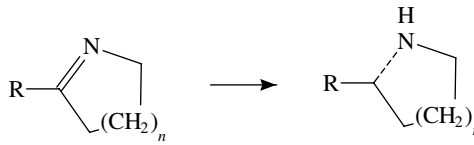
B. Reduction of C=N Containing Compounds

The reduction of imines to the corresponding amino compounds is a synthetically useful and very important means of introducing this latter group into organic compounds[312,313].

Aromatic aldoximes have been smoothly reduced to their corresponding acylamides by ammonium formate-palladium-carbon catalyzed hydrogenation, in either ethanoic or propanoic acid solution in 65–85% yield (equation 74)[314]. Catalyzed hydrogenation has also been successful for the formation of amines from cyclic ketimines[315]. In this reaction a highly enantiomerically enriched cyclic amine, an important functionality in natural products[316], is produced by the use of a chiral titanocene catalyst. The reaction occurs in good yields and is general for 5- to 7-membered cyclic imines (equation 75). Other asymmetric hydrogenations have also led to enantiomeric amines[317–323].



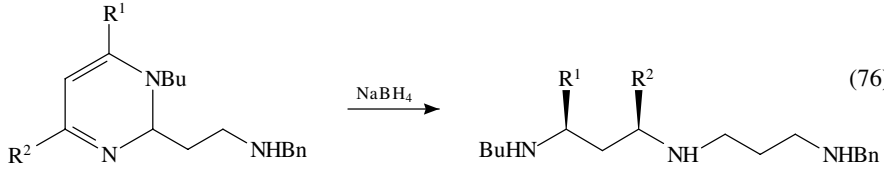
(74)



(75)

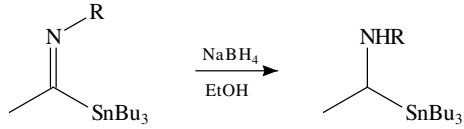
$n = 1–3$

Reduction of dihydropyrimidines by the use of excess sodium borohydride in methanol, at 60 °C, has been used as a route to substituted polyamines (equation 76). The reaction occurs in a stereocontrolled fashion and gives reasonable yields. These latter molecules are synthetic targets due to their potential in chemotherapy.



(76)

Imidoylstannanes may also be cleanly reduced to α-stannylamines in good yields by the use of sodium borohydride in ethanol at ice temperatures (equation 77)[324]. The same reagent may be used to reduce α,α-dihalo ketimines (equation 78) to β,β-dialkoxyamines (which are α-amino keto acetals)[325]. The products from this reaction are extremely useful intermediates for the synthesis of a wide variety of heterocyclic molecules.



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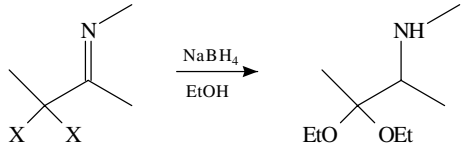
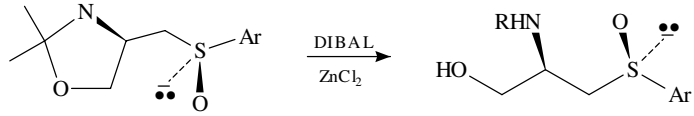


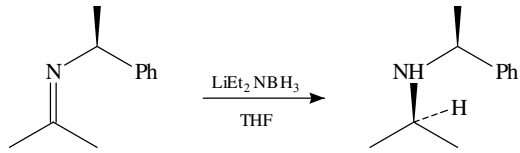
(78)

Chiral sulfoxides are useful both as intermediates and target molecules of synthetic elaboration. The β-amino-γ-hydroxysulfoxide moiety is one type of chiral sulfoxide which is the intermediate target in the synthesis of (*S*)-(+)-sparsomycin. In the key step in this synthesis, the sought after moiety was produced by asymmetric reduction of an oxazoline using DIBAL, in the presence of zinc chloride and at −78 °C (equation 79)[326].



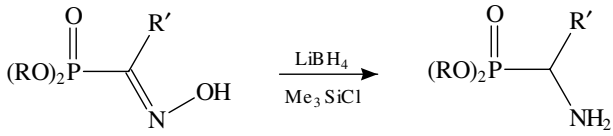
(79)

Lithium aminoborohydrides, which are readily obtained by reaction of *n*-BuLi with amine-boranes[327,328], are excellent reagents for the reduction of imines to their corresponding secondary amines (equation 80)[329]. If the substrate possesses chirality, then there is considerable diastereoselectivity in this reaction (up to 90%).



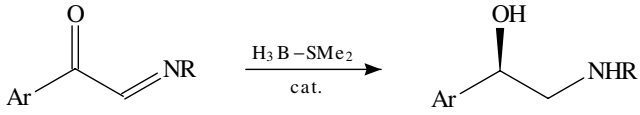
(80)

O,*O*-Dialkyl 1-aminoalkanephosphonates, which are moieties in peptide analogues, with antibacterial activity, and important inhibitors of aminopeptidases[330] have been synthesised from oximes in THF (equation 81)[331].



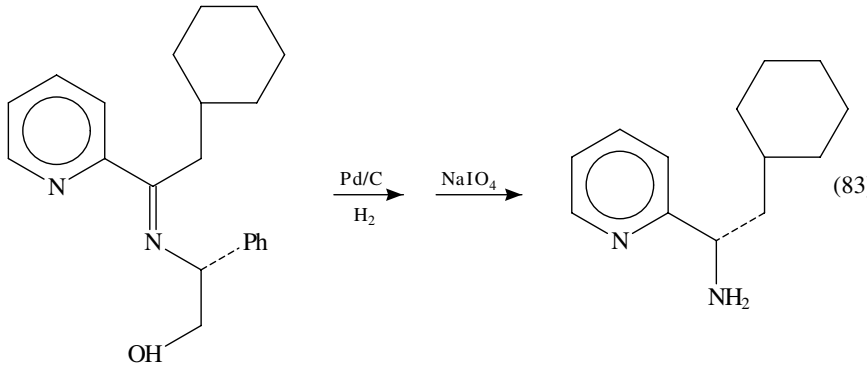
(81)

Asymmetric reduction of aryl α-ketoimines, by the use of oxazaborolidine catalysts, gives a good ee of the resultant alcohol (equation 82)[332]. The product is an arylethanolamine which is a synthetic target (e.g. β-blockers) and a useful intermediate.



(82)

Catalytic reduction of chiral 2-(2-pyridyl)-1,3-oxazolidines and of 2-pyridyl imines, which are easily produced by standard synthetic means, followed by oxidation, results in the formation of chiral secondary amines as shown in equation 83[333]. The reaction occurs with a reasonable diastereoselectivity.



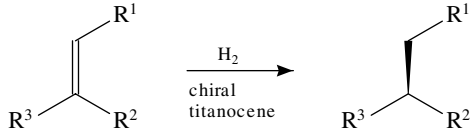
(83)

C. Catalytic Hydrogenation of Alkenes

The reduction of alkenes to alkanes is a reaction that is often used as a key part of a synthetic sequence. In some cases this reaction is performed in an attempt to introduce chirality into a molecule. The emphasis here is on the stereocontrolled reduction of alkenes in complex molecules.

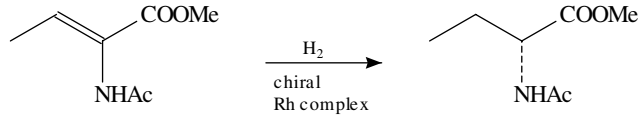
Asymmetric hydrogenation has been reported to occur in excellent yield and ee when a trisubstituted alkene is hydrogenated with a chiral titanocene catalyst (equation 84)[334]. A similar reaction, but with variable enantioselectivity, may also be obtained with chiral Rh, Ru and Co catalysts[335–338]. Disubstituted alkenes (mainly 1,1-disubstituted) may also be

asymmetrically hydrogenated with various chiral catalysts[339–342].



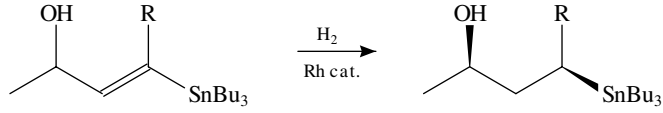
(84)

The rhodium-chiral phosphine catalyzed asymmetric hydrogenation of protected enamides, and other unsaturated amino acid derivatives (equation 85), gave almost 100% ee of the corresponding chiral α-amino acid derivative[343,344].



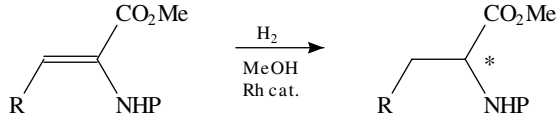
(85)

γ-Hydroxy vinylstannanes also undergo catalytic hydrogenation, using chiral rhodium complexes, in this case giving diastereoselectivities of 60:1 and greater[345]. The reaction occurs under high hydrogen pressures in dichloromethane for 24–36 hours (equation 86).



(86)

Chiral rhodium catalysts have also been used to affect the homogeneous asymmetric hydrogenation of protected 2-aminoacrylates (equation 87)[346–350]. The chiral protected α-amino esters formed are extremely useful for further synthetic elaboration.



(87)

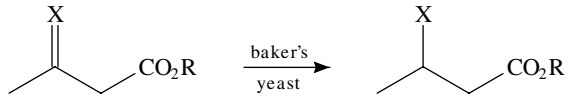
Finally, of note is the hydrogenation of α,β-unsaturated carboxylic acids. This may be accomplished in a highly diastereoselective manner by the use of ruthenium(II)–BINAP complexes (equation 88)[351]. The chemical yields are high (83–99%) and the reaction occurs in up to 97% ee. This type of hydrogenation has been used as the key step in a synthesis of building blocks for protease inhibitors and has been performed on a 100 g scale[352].

(88)

D. Other Reductions

Baker's yeast has been used to reduce selectively the thioketone moiety in a β-thioketo ester[353]. Whilst a mixture of alcohol and thiol containing products are obtained, the ee is

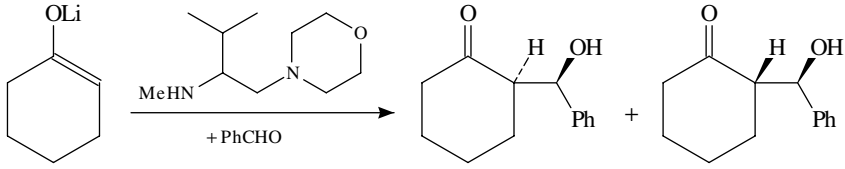
up to about 90%, thus making this process a valuable one (equation 89).



(89)

X = OH, SH

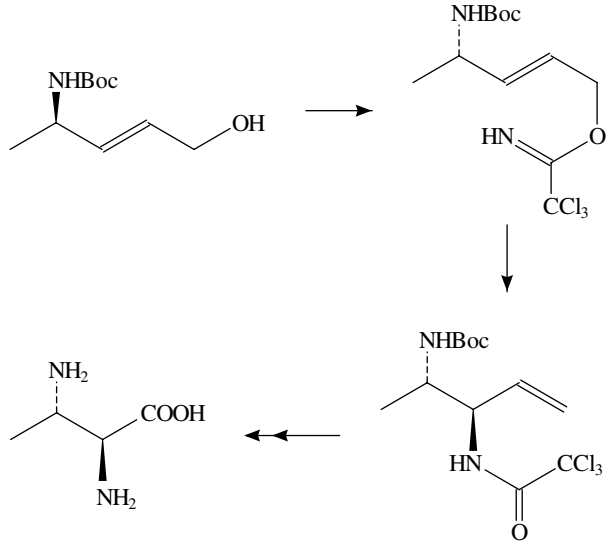
The enantioselective aldol and Michael additions of achiral enolates with achiral nitroolefins and achiral aldehydes, in the presence of chiral lithium amides and amines, was recently reviewed[354]. The amides and amines are auxillary molecules which are released on work-up (equation 90 shows an example of such a reaction).



(90)

30 70

Lastly, 1,2-diamines, which are extremely useful in the synthesis of many natural products, may be readily produced in good yields and with excellent diastereoselectivity via the aza-Claisen rearrangement reaction, catalyzed by palladium(II) chloride[355]. In this reaction sequence the starting amino-containing, allylic alcohol is converted into the corresponding trichloroacetimidate. Following aza-Claisen rearrangement, the 1,2-diamine is produced by an oxidation–reduction work-up (equation 91).



(91)

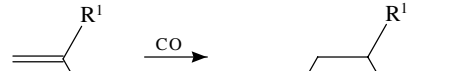
IV. C−C BOND-FORMING REACTIONS

C−C bond-forming reactions using double-bonded functional groups are very facile synthetic processes. In the present work only C−C bond formations directly at the carbon atoms of the double bond-containing group are considered.

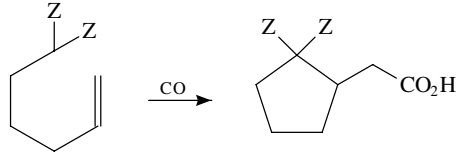
The subdivision of this topic is somewhat arbitrary, but is used in an attempt to group similar C−C bond-forming reactions together.

A. Carbonylation and Related Reactions

Carbonylation is a very useful synthetic process[356,357]. Synthetically, these reactions are usually high yielding methods for the preparation of a wide range of functionalities, covered below. Palladium acetate catalyzed carbonylation of a wide range of alkenes gives good to excellent yields of the homologous acid, in the presence of a proton donor (equation 92)[358−363]. Other catalysts have been used, but these tend to give lower yields of the desired products[364,365]. Further, the carbonylation of appropriately functionalized alkenes, in the presence of transition metal acetates, produces reasonably good yields of multifunctional cyclopentanes (equation 93), which are extremely useful synthetic intermediates[366,367].

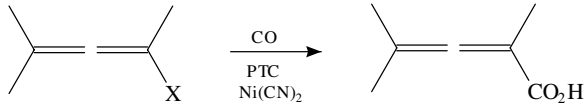


(92)



(93)

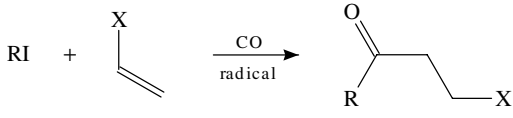
In a similar process, nickel compounds also catalyze the carbonylation of allenyl halides, under phase-transfer conditions (PTC), to give allenyl acids in poor to reasonably good yields (equation 94)[368].



(94)

X = Br, Cl

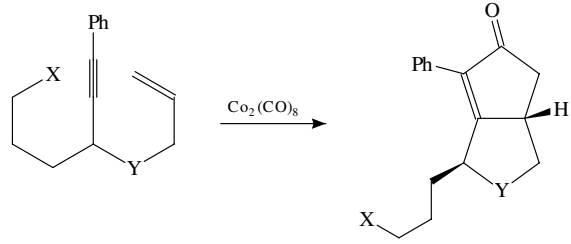
The carbonylation of functionalized alkenes in the presence of alkyl bromides and iodides under radical producing conditions gives good yields of β-functionalized ketones (equation 95)[369,370]. These compounds may be formed with cyano, ester and aldehyde groups attached directly to the alkene.



(95)

X = CN, CHO, CO_2R

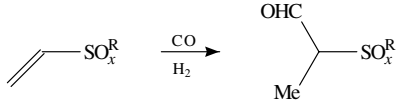
The Pauson–Khand reaction is an extremely useful method of construction of 5-membered rings[371,372]. The reaction proceeds by carbonyl insertion (mediated by cobalt-carbonyl complexes) into an enyne. The products are usefully functionalized cyclopentenones (equation 96)[373–377]. The reaction is promoted by the addition of tertiary amine N-oxides[378,379], DMSO[380] or phosphites[381]. It has also been reported that appropriately placed sulfur or oxygen moieties, within the alkene, also speed up the reaction[382]. This reaction has been used as the key step in the total synthesis of (−)-α-kainic acid, a potent neuronal exitant[383], the synthesis of bis-heteroannulated pyranosides[384] and also in the synthesis of the D and E rings of xestobergsterol[385].



(96)

Y = CH_2, O, NAc

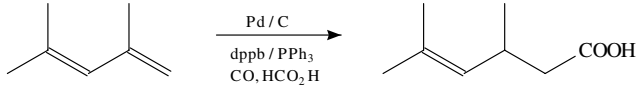
Upon hydroformylation with carbon dioxide and hydrogen, vinylic sulfoxides and sulfones give reasonable yields of branched-chain aldehydes in a regioselective manner (equation 97)[386]. This reaction also occurs, with Rh catalysis, for a wide range of substituted alkenes[387–392].



(97)

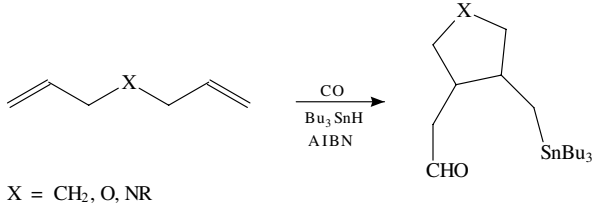
x = 1, 2

Direct hydrocarboxylation of conjugated dienes with carbon monoxide and formic acid, using Pd–C catalysis and in the presence of triphenylphosphine and 1,4-bis(diphenylphosphino)butane (dppb), gives good yields of what is essentially addition of formic acid to the terminal alkene (equation 98)[393]. This is an extremely useful synthetic route to γ,δ-unsaturated acids.



(98)

Lastly, stannylformylation has been used to synthesize both homocyclic and heterocyclic five-membered rings[394]. The reaction occurs by the treatment of 1,6-dienes with tin hydride and AIBN, under CO pressure at elevated temperatures (equation 99).

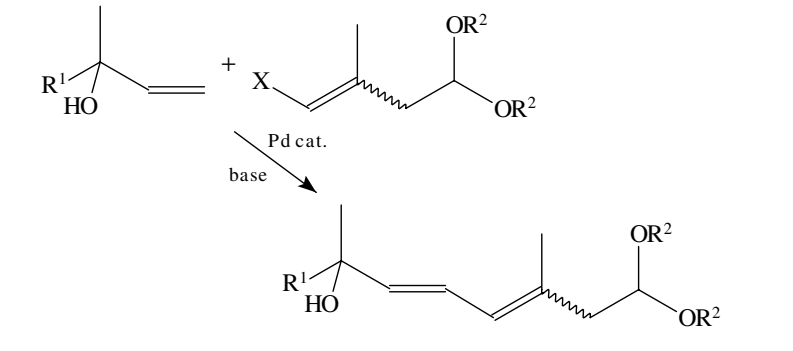


(99)

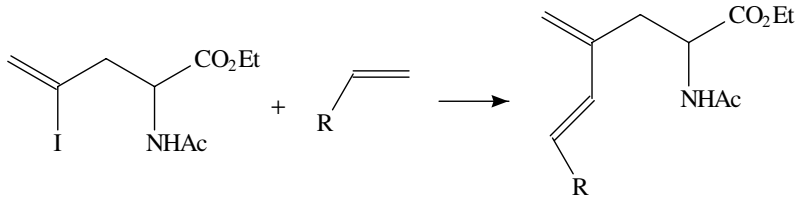
X = CH_2, O, NR

B. Vinylations

The introduction of vinyl groups is described in this section. Palladium(0) catalyzed intermolecular vinylation of a wide range of organic compounds by vinyl halides is an important C−C bond-forming reaction[395−399]. As a key step in the synthesis of retinal, an allylic alcohol has been coupled with a vinyl halide to give excellent yields of the adduct (equation 100)[400]. The side chains of protected α-amino acids have also been extended in a similar way, via Pd catalyzed coupling of a vinyl iodide with an alkene (equation 101)[401]. In some cases the reaction can be carried out at significantly lower temperatures by increasing the pressure[402].

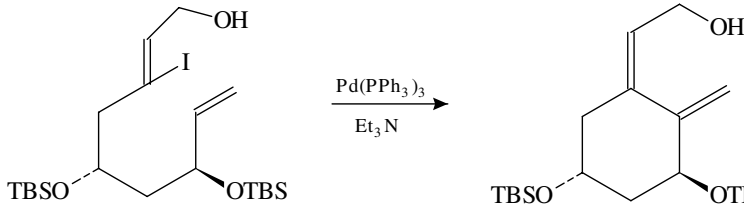


(100)



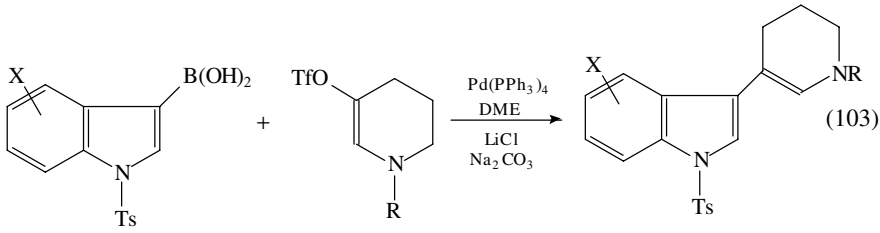
(101)

The equivalent intramolecular Heck-type vinylation of a ω-vinyl-(*Z*)-iodoalkene has been used as the key step in the synthesis of A-ring synthons for 1α,25-dihydroxyvitamin D_3 and its analogues[403]. The reaction takes place under reflux in acetonitrile in the presence of one equivalent of triethylamine[404] and gives a 81% yield (equation 102).



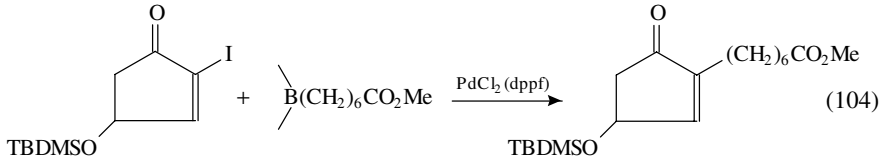
(102)

The palladium catalyzed cross-coupling of vinyl triflates with boronic acids is also a very facile means of introducing a vinyl group into a wide range of molecules. The reaction occurs under mild conditions, is highly regiospecific and requires easily prepared starting materials. Thus, this methodology has been employed to introduce a vinyl group at the 3-position of indoles[405], as shown in equation 103.



(103)

In a similar fashion, vinyl halides have been used in C−C bond formation, giving good to excellent yields in the synthesis of prostaglandins, as exemplified in equation 104[406]. Other similar syntheses have been performed with great success[407−411]. A similar coupling reaction may also be performed by using vinylzinc and vinyltin reagents[412−414].



(104)

C. Reactions with Organometallic Reagents

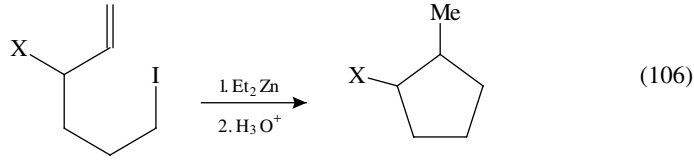
The formation of new C−C bonds by reaction of double-bonded functional group-containing compounds with organometallic reagents is a useful method in organic synthesis. Alkylation at an anionic center adjacent to a CO group is a very useful means by which more complex organic compounds may be synthesized. However, this reaction is not covered in the present work and the reader is referred to the excellent *Annual Reports in Organic Synthesis* series for recent advances in this area.

1. With alkenes

In a useful intermolecular carbozincation process, a vinylzinc reagent reacts with allyl halides to give good to excellent yields of the unconjugated 1,4-diene (equation 105)[415]. The reaction is highly regioselective and occurs at room temperature in 10–20 minutes.

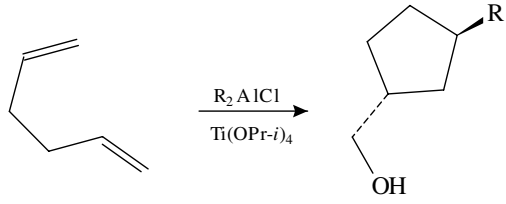
(105)

Carbozincation of alkenes is a very facile method for the formation of new C−C bonds. A smooth intramolecular reaction occurs when functionalized 5-hexenyl iodides are treated with diethylzinc in ether, followed by acid work-up (equation 106)[416].

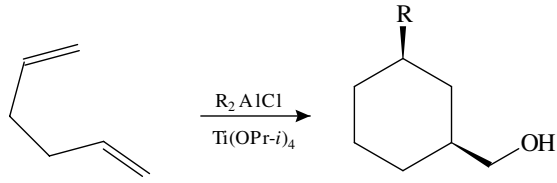


(106)

1,5- and 1,6-Dienes may be cyclized in high yields by reaction with dialkylaluminum compounds. The reaction is catalyzed $Ti(OiPr)_4$ and proceeds via carboalumination and surprisingly occurs in a *trans*-selective manner for 5-membered rings and in a *cis*-selective manner for 6-membered rings (equations 107 and 108)[417]. Trienes are also cyclized to give bicyclic products, however the mixtures formed are not synthetically very useful.

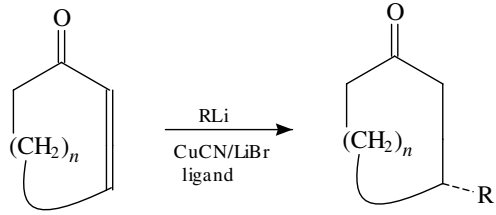


(107)



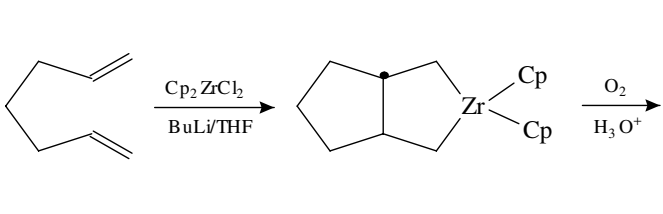
(108)

Conjugate addition of organocopper reagents (generated *in situ*) to cycloalkeneones, using a bound, chiral amidophosphine ligand, allows for the high-yield preparation of 3-substituted cycloalkanones in 68–95% ee (equation 109)[418,419]. This type of asymmetric reaction may also be performed using CO compounds with chiral auxiliaries[420,421], or metal thiolates and amides as chiral components of the organometallic reagent[422–426]. This whole area of synthesis has been recently reviewed[427,428].



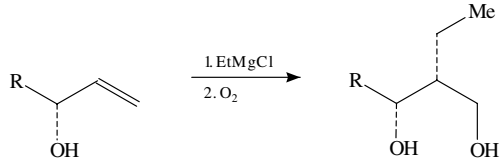
(109)

Alkene cyclozirconation is a really useful means by which 1,2-*trans* difunctionalized cyclopentane rings can be produced. The initially formed cyclometallic species is decomposed in the presence of oxygen and aqueous acid to give the desired product (equation 110)[429–433].



(110)

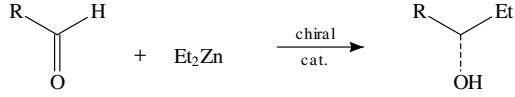
Finally, C−C bond formation occurs through regio- and stereospecific reaction between allyl alcohols and ethyl magnesium chloride, in the presence of complex zirconium catalysts, followed by treatment with oxygen (equation 111)[434]. In this reaction the alkene functionality is lost.



(111)

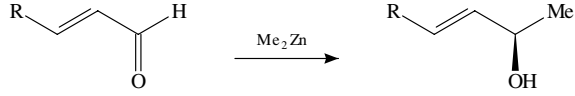
2. With carbonyl compounds

The catalytic asymmetric synthesis of γ-hydroxy ketones and aromatic hydroxy ketones by alkylation of keto aldehydes with dialkylzincs is a very useful method of obtain these target molecules (equation 112)[435,436]. The reaction requires a chiral amine[437], such as *N*,*N*-dibutylnorephedrine, as catalyst. Chiral diols[438−440] and other bidentate[441−443] and tridentate[444] ligands have also been successfully used as the catalyst. Reaction yields are very good and ee is typically 85%. This is a much more versatile route to γ-hydroxy ketones than the asymmetric aldol reaction. If the zinc reagent contains an alkene moiety, then asymmetric alkenylation may be easily accomplished[445]. Other functional groups, such as esters, halides, silanes, stannanes and protected amines and alcohols, may also be present in the dialkyl zinc reagent[446−449]. These organozinc compounds are readily available via hydroboration of the corresponding alkene followed by transmetallation.



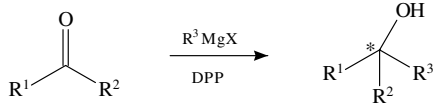
(112)

Unsaturated aldehydes undergo catalytic enantioselective addition to give secondary allylic alcohols in good to excellent yields and up to 98% ee. (equation 113)[450−456].

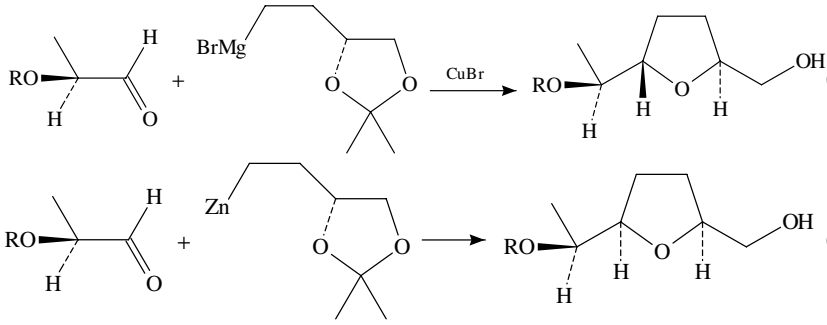


(113)

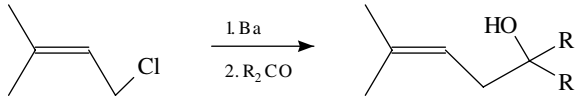
Prochiral CO compounds react with Grignard reagents, in the presence of a chiral diamine, such as (5a*S*,10a*S*-octahydro-1*H*,5*H*-dipyrrolo[1,2-a:1′,2′-d]pyrazine (DPP), to give good to excellent yields of chiral tertiary alcohols in 35−97% ee (equation 114)[457]. Under chelation conditions, using CuBr, chiral Grignard reagents undergo addition with aldehydes containing a chiral auxiliary, to give good yields of alcohols with excellent diastereoselectivity (equation 115)[458−463]. This reaction has been used as the key step in the synthesis of the bis-THF moiety in (+)-rolliniastatin[464]. Use of organozinc reagents, in place of the Grignard, is also stereocontrolled but a different optically active product is realized (equation 116)[465].



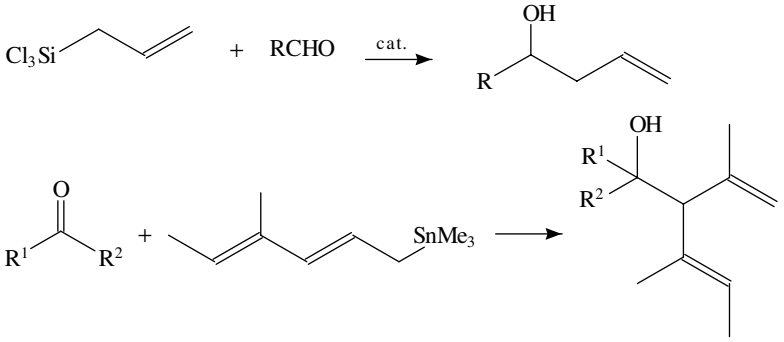
(114)



Allylbarium reagents (generated *in situ* from allyl halides and barium salts) have been used to perform stereoselective allylation at a CO group. The reaction occurs in THF at −78 °C and the resultant homoallylic alcohols are produced in very good yields with a high degree of regio- and stereoselectivity (equation 117)[466]. A similar product is formed if a CO compound is stirred at room temperature in THF or DMF, with an allylic halide and germanium iodide[467] or chromium(II) chloride[468].

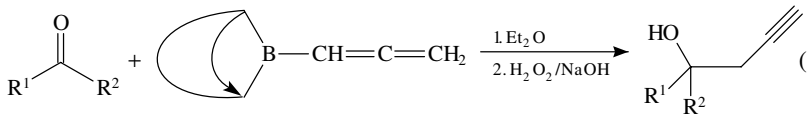


Aldehydes may also undergo asymmetrical allylation by reaction at room temperature with allylic trichlorosilanes in the presence of chiral phosphoramides. Yields are very good and there is some modest ee (equation 118)[469]. The yields in this reaction are significantly improved by using DMF at 0 °C, with no added catalyst[470]. Allylstannanes, in the presence of tin(IV) chloride and other catalysts, may also be used to allylate aldehydes asymmetrically[471–474]. The reaction has also been carried out with a pentadienyltin reagent and zinc chloride as catalyst. In this case an unconjugated 1,4-diene is selectively produced in almost quantitative yields (equation 119)[475]. Allylation with stannanes is tolerant of the presence of an epoxy group[476].



The direct coupling of allenic boranes with aldehydes and ketones affords reasonably good yields of homopropargylic alcohols[477–480] (equation 120), which are extremely valuable intermediates in organic synthesis. Enynes and enediynes have been made in this

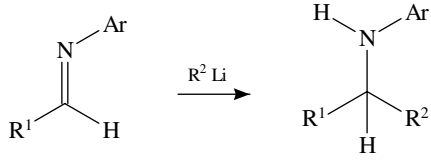
fashion in combination with dehydration processes[481].



(120)

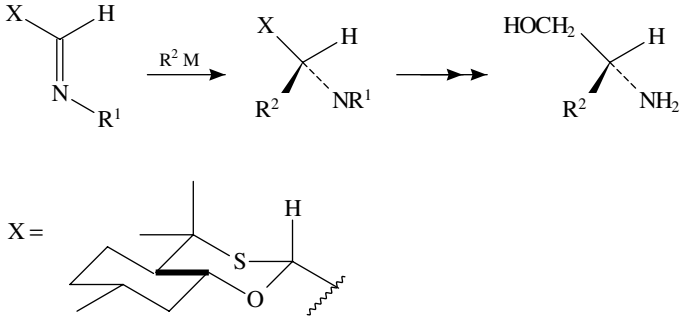
3. With imines

Imines undergo asymmetric addition with organolithium reagents in the presence of catalysts with chiral ligands[482–485]. In general, these methods are restricted to non-enolizable imines and they require large amounts of expensive catalysts. Recently, a reaction sequence has been developed using bis-oxazoline ligands, which allow the reaction to occur for a wider range of imines (equation 121)[486]. The reaction occurs in very good to excellent yields and in up to 91% ee.



(121)

Imines with an adjacent chiral auxiliary undergo diastereoselective addition of organometallic reagents in a similar fashion, as discussed above (equation 122)[487]. The products are readily converted into enantiomeric β-amino alcohols, which are useful in further synthetic sequences or the target moiety in some natural products. Other such syntheses have been performed via additions to both imines[488–490] and the related hydrazone moiety[491–493].



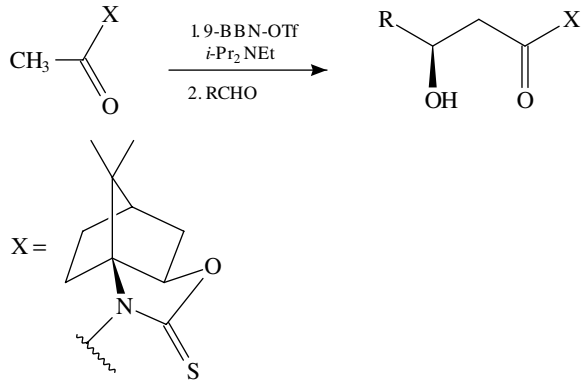
(122)

D. 1,2-Additions to Carbonyl Compounds

Intermolecular aldol-type 1,2-addition reactions are an important means by which stereocontrolled chain elaboration can be performed. Such reactions are widely used in synthesis of complex molecules and some leading examples are herein provided.

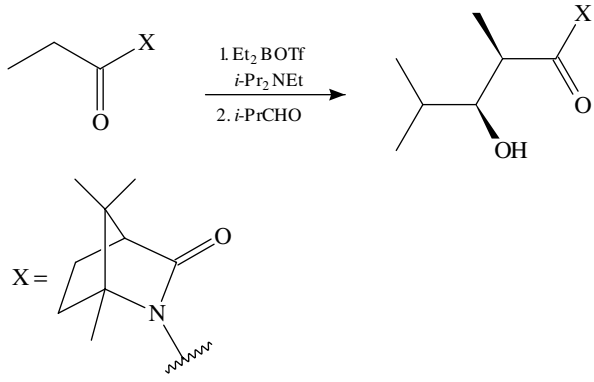
Considerable efforts have been directed towards the development of a system to maximize enantiomerically pure diastereomers from aldol reactions. The most effective systems

found to date involve the use of α-substituted boryl enolates[494,495]. Also, the use of chiral, boron-containing Lewis acid catalysts has also shown significant promise[496–499]. Similar control has also been affected by the careful choice of a chiral carbonyl-containing compound and an achiral boryl triflate (equation 123)[500]. In this latter reaction the yields are reasonable (50–90%) and the diastereoselectivity is excellent.

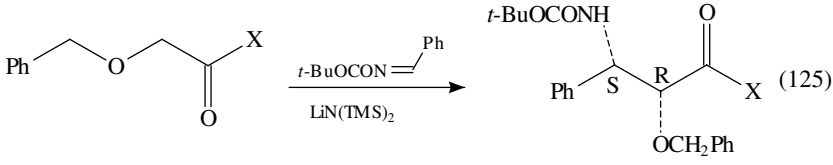


(123)

A camphor lactam imide auxiliary has also been used in a similar fashion (equation 124)[501]. Using this type of protocol, but replacing the aldehyde with an imine, the docetaxel (an important anticancer compound related to taxol) side chain has been prepared in 66% yield and 99% ee, as shown in equation 125[502].



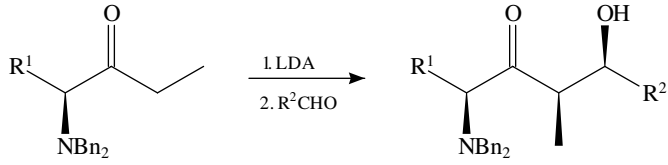
(124)



(125)

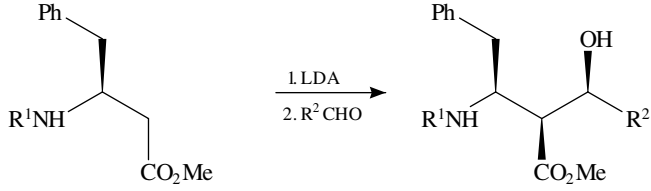
Quantitative yields are realized when α-(*N*,*N*-dibenzylamino) ethyl ketones undergo aldol reactions with aldehydes. The reaction proceeds in a highly diastereoselective manner

and results in the exclusive formation of the *syn* adduct (equation 126)[503,504].



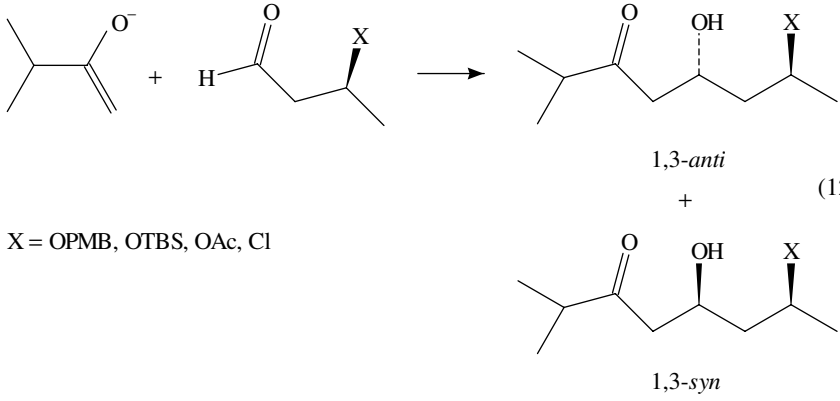
(126)

The reaction of N-protected-3-amino-4-phenylbutanoic esters with aldehydes[505], after lithiation, gives good yields of products which are essentially 2-substituted 1-hydroxyethylene building blocks — the central moiety of HIV-1 protease inhibitors (equation 127)[506].



(127)

1,3-Asymmetric induction in the aldol reaction of enolsilane and metal enolate nucleophiles with β-substituted aldehydes gives rise to both excellent yields and good diastereoselectivities (equation 128)[507]. The best diastereoselectivity was obtained using a trimethylsilyl enolate in the presence of boron trifluoride-etherate (92:8; *anti*:*syn*). The key step in the synthesis of the N-terminal amino acid analogue of nikkomycin B and Bx (nucleoside peptide antibiotics) has been performed using this type of methodology[508].

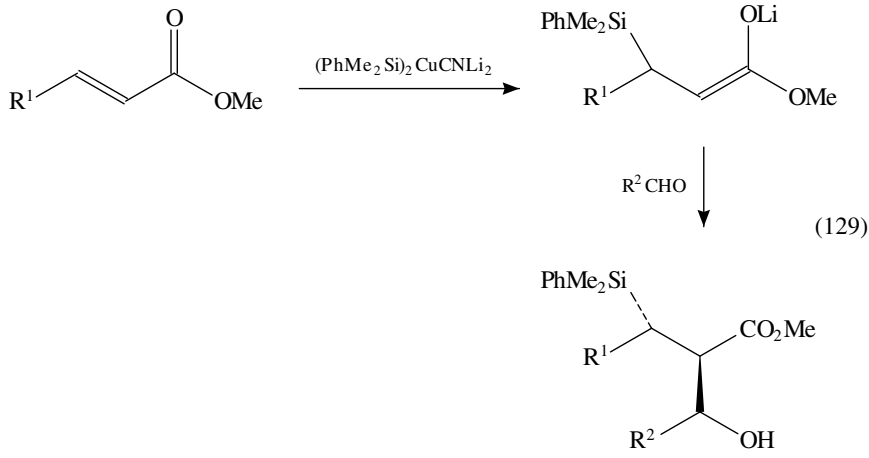


X = OPMB, OTBS, OAc, Cl

(128)

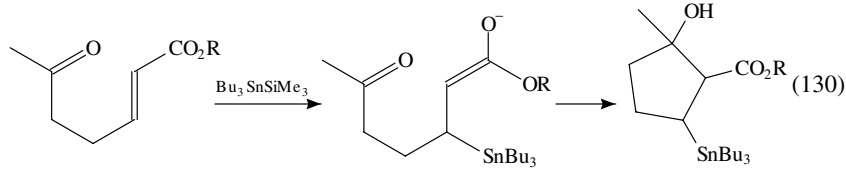
The conjugate addition of lithium bis(phenyldimethylsilyl)cuprates to α,β-unsaturated esters forms enolates, which readily react with aldehydes to give 2-substituted 3-silyl esters (equation 129)[509]. The products are useful as intermediates in the synthesis of allylsilanes and natural products. Yields of this reaction may be significantly increased by

replacing the cuprates with ilyl(dialkyl)zincates[510].



(129)

A novel cyclization, producing a polyfunctional cyclopentane ring system, has been reported to occur starting from a ε-keto-α,β-unsaturated ester. Reaction with $Bu_3SnSiMe_3$, in the presence of fluoride ions, gives a Michael addition product, which then undergoes Dieckmann condensation (equation 130)[511]. The product is formed in reasonably good yields and bicyclic compounds may be accessed from starting materials which possess a cyclic ketone.

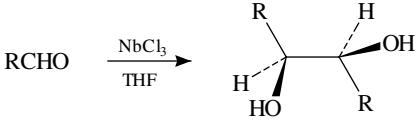


(130)

E. Reductive Coupling of Carbonyl and Related Compounds

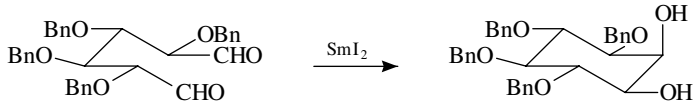
The reductive coupling of carbonyl-containing compounds is an important route for the synthesis of vicinal diols and alkenes. In addition, a C−C bond is being formed, making this type of reaction one that is much used in the building of complex organic molecules. In particular, there is a continuous search for methodology which gives a stereocontrolled vicinal diol moiety.

The pinacol-type coupling of aliphatic aldehydes, in the presence of niobium(III) salts, occurs, with a high *anti* diastereoselectivity (equation 131)[512]. In the case of aromatic aldehydes and ketones the alkene product is sometimes formed[513]. In both cases the cyclic acetals may also be formed.

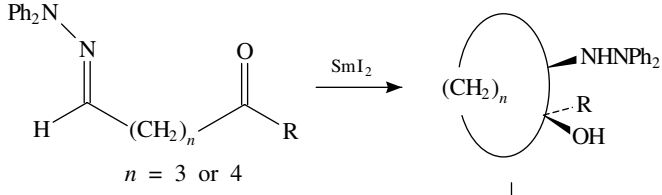


(131)

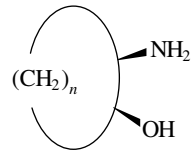
Reductive coupling of dialdehydes may also be accomplished by use of samarium(II) iodide[514]. The reactions is stereoselective and has been used to prepare myo-inositol derivatives (equation 132)[515]. The equivalent reaction, using low-valent titanium species as catalysts, results in a mixture of products[516]. The production of cyclic β-amino alcohols may be accomplished in good yields, and with a high degree of *cis* selectivity by the treatment of carbonyl hydrazones with samarium(II) iodide (equation 133)[517]. This reaction is effectively equivalent to an aza-Barbier reaction.



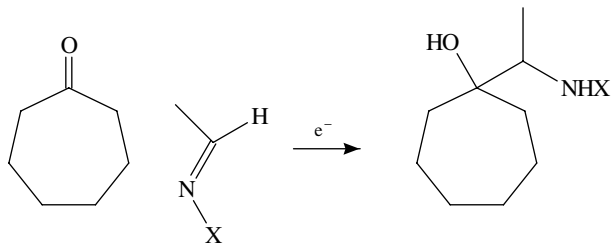
(132)



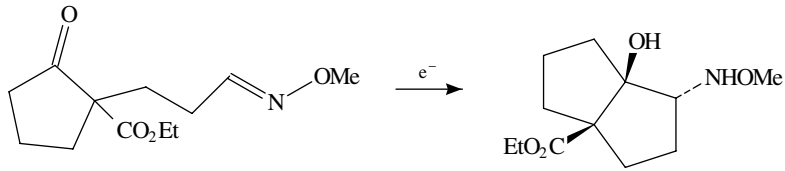
(133)



In a rather surprising, but synthetically very useful, intermolecular reaction, ketones may be electroreductively coupled with a range of C=N-containing compounds to give very good yields of masked β-aminoalcohols (equation 134)[518]. If the reaction is performed intramolecularly, then cyclic products are formed with a high degree of stereocontrol, giving the *trans* product (equation 135).



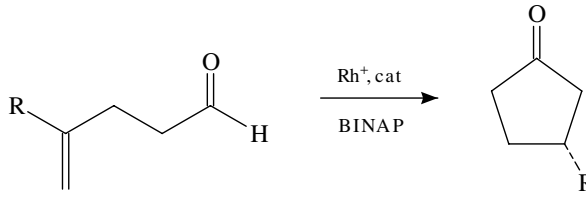
(134)



(135)

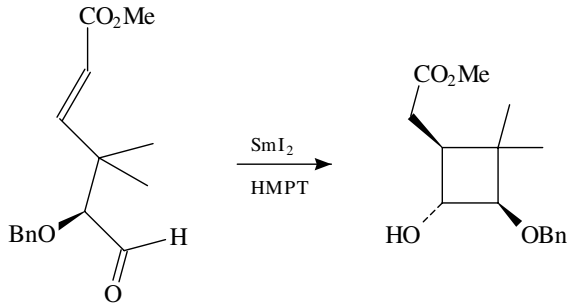
F. Coupling of Alkenes and Carbonyl Compounds

Alkenes and carbonyl-containing molecules may be coupled in various ways to give new C−C bonds in high yields. Intramolecular hydroacylation is a very versatile method for the production of cyclic ketones. Although many Rh complexes cause a significant yield reduction, due to decarbonylation, chiral Rh(diphosphine) catalysts apparently give good yields of cyclopentanones from a wide range of starting 4-pentenals, with reasonable ee (*ca* 60%) (equation 136)[519].

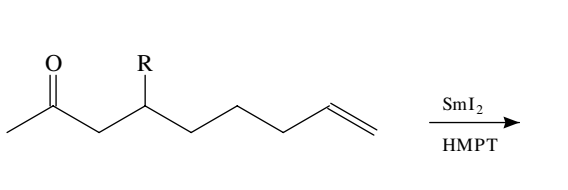


(136)

Intermolecular coupling of ketones and alkenes, promoted by SmI_2, occurs with excellent stereochemical control. In one such reaction, samarium(II) iodide has been used to prepare cyclobutanones and cyclobutanols from chiral, 6-oxohex-2-enoates (equation 137)[520]. The reaction is performed in THF in the presence of HMPT and occurs in good yield with excellent stereocontrol. If appropriately located carbonyl and alkene moieties are present in a molecule, then SmI_2-HMPT can be used to form cyclooctanols by a radical cyclization process; in some cases there is a reasonable degree of diastereoselectivity (equation 138)[521,522].



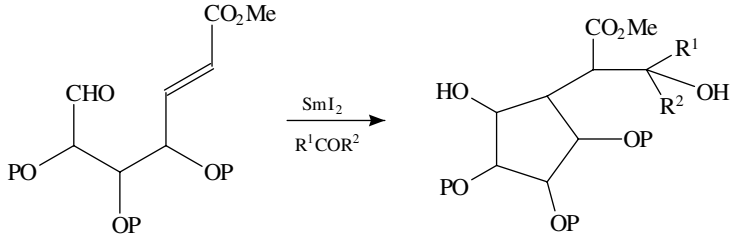
(137)



(138)

The intramolecular coupling of an aldehyde and alkene at −78 °C, promoted by SmI_2, in the presence of a ketone, has led to a tandem coupling–addition process. This reaction has proved to be synthetically very useful for the preparation of poly-oxygenated compounds (equation 139)[523]. This reductive coupling process may also be promoted in dry methanol,

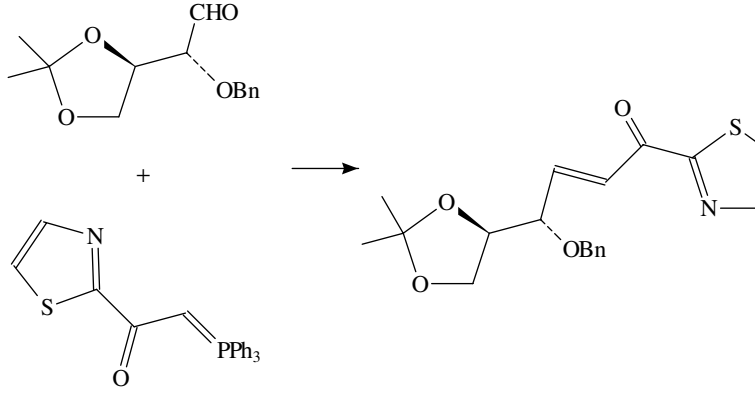
using Mg metal and a trace amount of mercuric chloride[524] and by electroreduction[525].



(139)

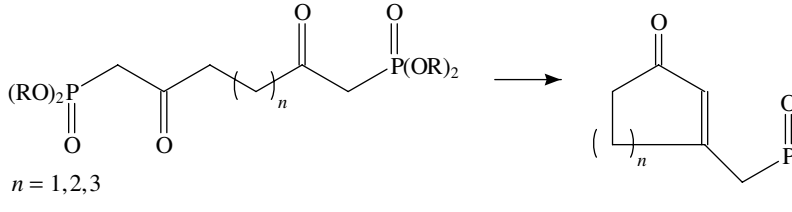
G. Wittig-type Reactions

The Wittig-type reaction is a key synthetic process by which alkene functionalities are introduced, using CO compounds as the key synthons. Thus, during the synthesis of carbohydrates, the Wittig reaction has been used as the key step for the introduction of a masked pyruvate moiety into a highly oxygenated substrate (equation 140)[526]. The alkene formed has *E*-geometry in this case. In other Wittig olefinations a mixture of *E* and *Z* isomers are often produced and this may be overcome, giving almost entirely *E* isomers, by photolytic irradiation[527,528].



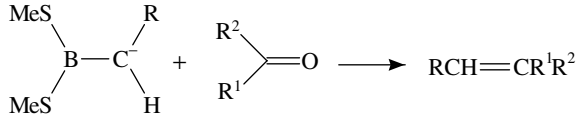
(140)

Wittig-type reactions may also be performed intramolecularly to give cyclic alkenones in good to excellent yields. Thus bis-β-ketophosphonates have been cyclized under Horner–Wittig conditions to give 5-, 6- and 7-membered rings which contain a 3-phosphorylmethylene group that can be used for further synthetic elaborations (equation 141)[529].



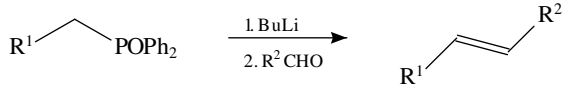
(141)

Under very mild conditions, the Wittig-type reaction of dimesitylboron stabilized carbanions with arylketones and aldehydes yields alkenes in good yields (equation 142)[530]. The stereochemistry of the alkene produced may be controlled, depending upon conditions.



(142)

Using an aldehyde as the key synthon, a reaction, which is termed an anti-Wittig reaction[531], has been performed. In this process a benzyl phosphine oxide is treated with butyllithium followed by an aldehyde, to give exclusively an *E*-alkene in high yield (equation 143)[532].

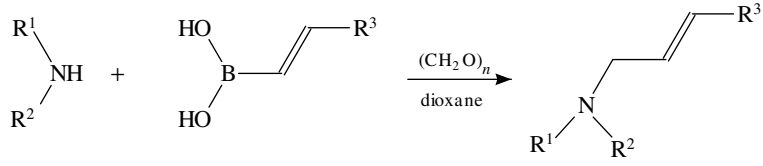


(143)

H. Others

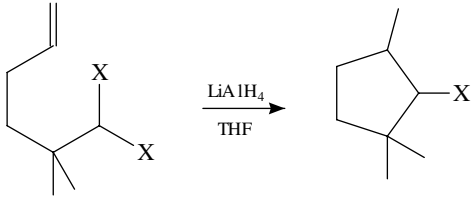
Recently, there have been several reactions which do not fit into the sections above, but which are important means by which C−C bonds are formed using double-bonded functional groups as the key synthons. Some of these reactions are outlined below.

Reaction of vinylboranes with secondary amines produces very good yields of allylamines (a useful functionality with antifungal properties), when the starting materials are heated in dioxane, at 90 °C, together with paraformaldehyde (equation 144)[533]. An intramolecular variant of this process uses a vinylsilane as the precursor[534].



(144)

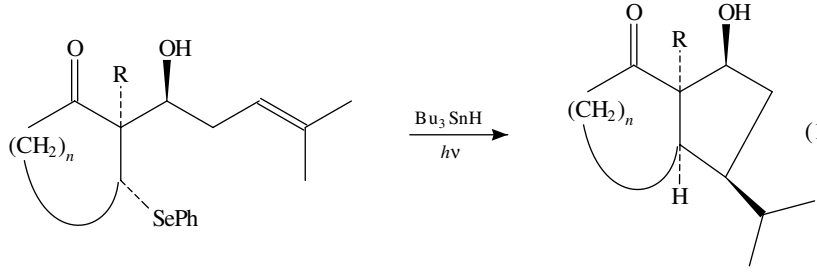
Radical cyclization of 6,6-dihaloalkenes promoted by LAH in THF is a useful route to halocyclopentanes (equation 145)[535,536]. A small quantity of the dehalogenated alkene is also produced.



(145)

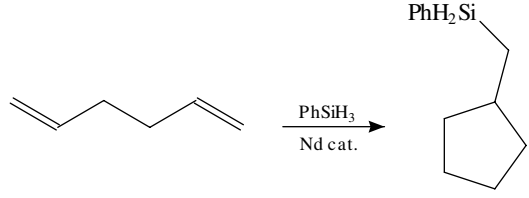
The formation of bicyclo compounds by the radical cyclization of alkenes with strategically placed phenylseleno groups, promoted by Bu_3SnH, occurs in high yields and gives

stereocontrolled products (equation 146)[537]. The reaction requires photochemical initiation and the starting materials are readily prepared by aldol condensation in the presence of PhSeH.



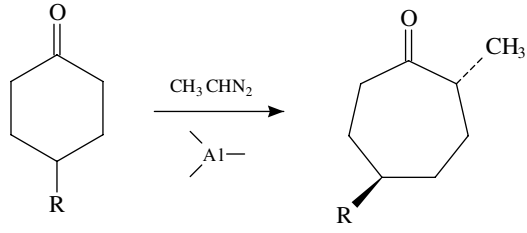
(146)

Hydrosilation of 1,5- and 1,6-dienes, catalyzed by a chiral neodymium complex, leads to intramolecular bond formation and results in the formation of silylated methylcyclopentanes (equation 147)[538]. This reaction is in stark contrast to the reaction catalyzed by group VIII complexes, which gives a range of silanes but no carbocyclic compounds[539,540].



(147)

Finally, ring expansions of cyclic ketones are an important method for the preparation of carbocyclic systems. Diazoalkanes allow this reaction to occur and involve C−C bond formation. When combined with carefully chosen organoaluminum compounds, this process can be performed in a highly stereoselective fashion (equation 148)[541].



(148)

V. PREPARATION OF HETEROCYCLES

One of the major uses of double-bonded functional groups in organic synthesis is the preparation of heterocyclic compounds. These compounds are either target molecules of a particular synthetic sequence, or are key intermediates in organic synthesis. This section covers the synthesis of heterocyclic compounds by carbon–heteroatom bond formation or by C−C bond formation. Epoxidation of alkenes is not covered here, but in Section II.A. Subdivision, for ease of reading, is by ring size, for the most part.

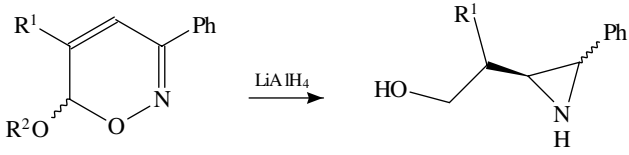
A. Heterocycles with a Single Heteroatom

In this section, the syntheses of lactams and other nitrogen-containing heterocycles, from double-bonded functional groups, are discussed. This is an extremely important area of synthesis, especially given the present interest in developing new antibiotics to combat bacteria which are resistant to traditional treatments. In addition, a wide variety of heterocycles containing a single oxygen atom may be prepared from double-bonded functional groups, the most important of which are probably lactones. Lactones exhibit many useful properties, especially in the field of pharmaceutical synthesis. They are a very prevalent structural feature in natural products and are key intermediates in many synthetic sequences. There has been much interest and effort exerted in the development of strategies for the synthesis of these and other oxygen-containing heterocycles from double-bonded functional groups. There have been many reviews concerning the synthetic utility of lactones, for example of halolactones[542] and of the synthesis of target lactones, such as macrolide antibiotics[543], and the reader is referred to these sources for further details.

1. Three- and four-membered rings

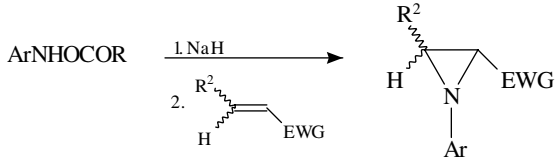
This section covers the synthesis of aziridines, oxiranes, β-lactams and oxetanes. Aziridines are fairly important moieties in bioactive molecules and thus new routes for their synthesis are constantly being developed. β-Lactams are probably the most important heterocyclic compounds that contain a single nitrogen atom, due to their importance in penicillin and cephalosporin chemistry. Their synthesis and chemistry has received much attention and much of this work has been reviewed[544]. The oxygen-containing heterocycles are much less commonly synthesized from double-bonded functional groups.

6*H*-1,2-Oxazines (which can be readily formed from nitrosoalkenes and methoxyallene derivatives[545]) may be converted into aziridines by reduction with LAH. The reaction occurs in moderate yield, giving a preponderance of the *cis* product (equation 149)[546].



(149)

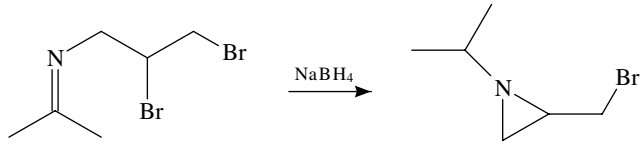
Electron-deficient alkenes react with hydroxamic acids to give 2-functionalized *N*-arylaziridines in good yields (equation 150)[547].



(150)

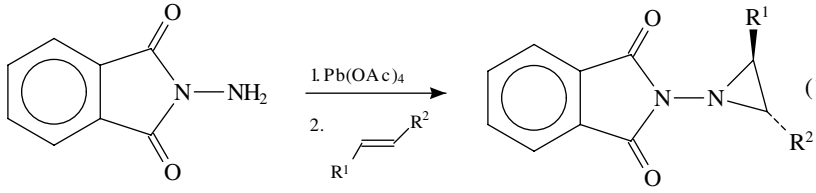
EWG = electron withdrawing groups

N-(γ-Haloalkyl) imines undergo cyclization to aziridines upon treatment with sodium borohydride in methanol[548]. Dibromoketimines can be readily cyclized to give (2-bromomethyl)aziridines in good yields under similar conditions (equation 151)[549].



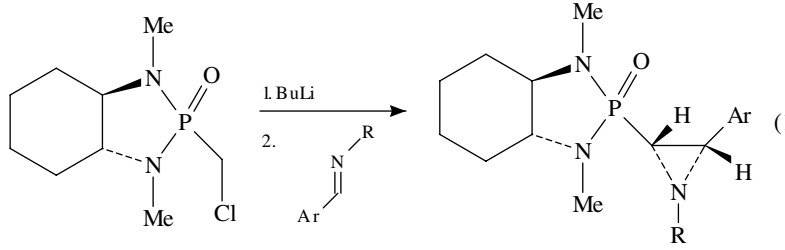
(151)

N-Phthalimidoaziridines may be obtained by reaction of alkenes with *N*-aminophthalimide which has been treated with lead tetraacetate (equation 152)[550–554]. These compounds are useful in the synthesis of α-hydrazino acid derivatives which are inhibitors of amino acid metabolising enzymes.



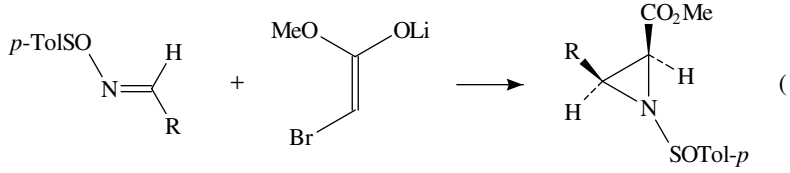
(152)

The synthesis of chiral α-amino phosphonic acids (analogues of natural amino acids) may be accomplished from imines. The key step in this synthesis is the formation of an aziridine by reaction of a phosphonamide with an imine (equation 153)[555]. The reaction occurs in very good yield in THF, at $-78\,^{\circ}C$ with BuLi.



(153)

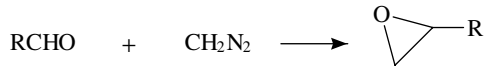
There are many routes available for the synthesis of aziridine 2-carboxylic acids, however there are few reactions which yield enantiomerically pure products. These compounds (especially those with *cis*-stereochemistry) are especially useful for the synthesis of bioactive molecules[556]. There is thus significant effort in this area of synthesis[557,558], but most methods are lengthy multistep procedures. Recently, a simple, one-pot procedure, utilizing imines, has been developed for the asymmetric synthesis of *cis*-N-substituted aziridine-2-carboxylic acids via a Darzens-type reaction (equation 154)[559].



(154)

Treatment of aldehydes with diazomethane, in the presence of organoaluminum reagents, in dichloromethane at $-78\,^{\circ}C$, gives very good yields of oxiranes

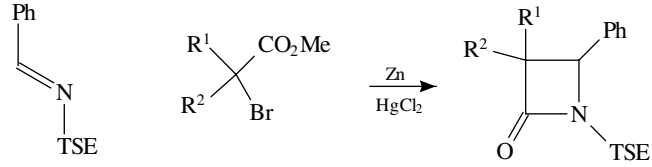
(equation 155)[560]. The reaction also occurs with rhodium acetate and dimethyl sulfide as catalyst[561]. A wide range of oxiranes may be readily prepared using this type of methodology.



(155)

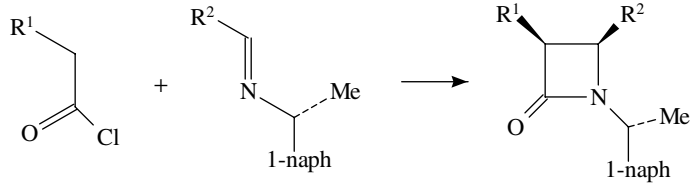
Due to the increasing resistance of bacteria to β-lactams, new syntheses and novel structural variants are continuously being sought[562,563]. Some recent examples are described below.

β-Lactams may be synthesized from N-protected β-tosylethyl (TSE) imines by reaction with α-bromoesters, in the presence of zinc and $HgCl_2$ (equation 156)[564]. The TSE group is readily removed by stirring with *t*-butoxide for a few hours.

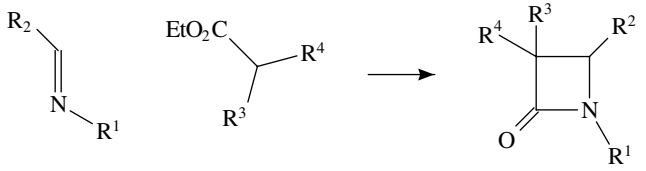


(156)

The Staudinger reaction[565], the cyclization of an imine with an acyl halide, in the presence of base, is an extremely useful method of β-lactam preparation. In this reaction it is possible to get asymmetric induction by use of chiral auxiliaries in either starting material. However, a chiral auxiliary attached directly to the imine nitrogen is generally more useful since, if it is removed, it allows for a greater range of useful products. With this strategy in mind, diastereomeric *cis*-lactams have been prepared in good yields (equation 157)[566,567]. Replacing the imine with an azine gives good yields of *N*-imino-β-lactams[568]. Imines also react with esters, upon treatment with *t*-butoxide, to give good yields of β-lactams (equation 158)[569–571].



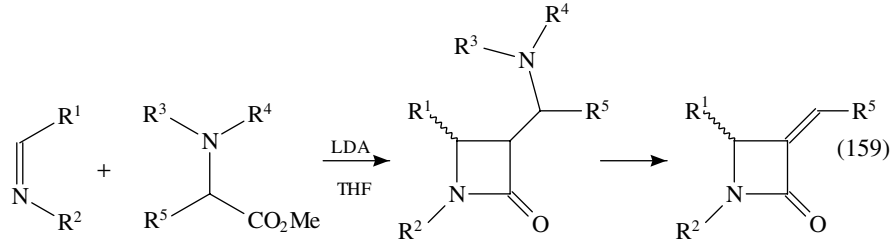
(157)



(158)

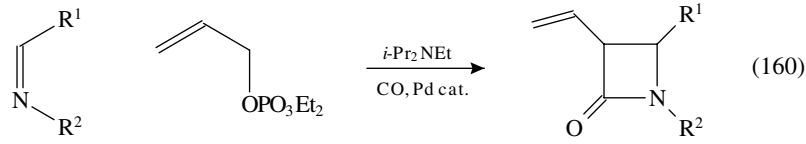
The so-called 'ene-type' β-lactams are an important group of compounds which contain a α-alkylidene side chain in the lactam moiety, and which are also useful both as antibiotics and as synthetic intermediates. A recent simple synthesis of these compounds has been

reported in which imines are reacted with the lithium enolates of 3-(dialkylamino) esters (equation 159)[572,573]. Dehydroamination is affected by treatment with silica gel in toluene or methyl iodide in methanol followed by DBU in benzene. The resultant β-lactams are produced in good overall yields.



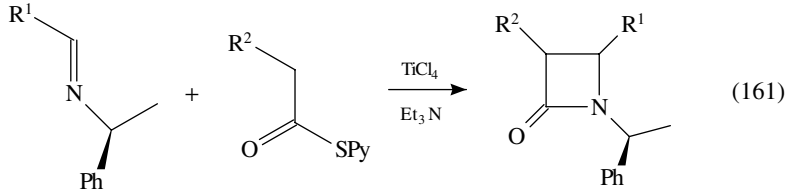
(159)

The palladium-catalyzed carbonylation reaction of allyl diethyl phosphate, in the presence of imines, gives either *cis*- or *trans*-3-vinyl-β-lactams, in high yields and in a stereoselective fashion (equation 160)[574,575]. The reaction is a [2 + 2] cycloaddition process which occurs under simple and mild conditions and has significantly more potential than the reaction of imines with ketenes (due to the more forcing conditions that are usually required to form the ketene intermediates). This reaction, however, only proceeds in low yield if the allyl phosphate is replaced with allyl acetate[576].



(160)

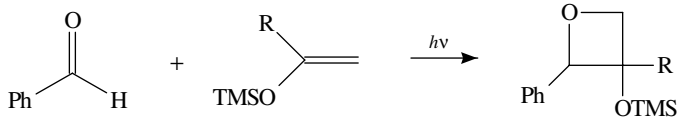
β-Lactams are also prepared in a highly stereoselective fashion, in good yields, by treatment of imines with titanium enolates of 2-pyridylthioesters (equation 161)[577–580] and similar compounds[581,582].



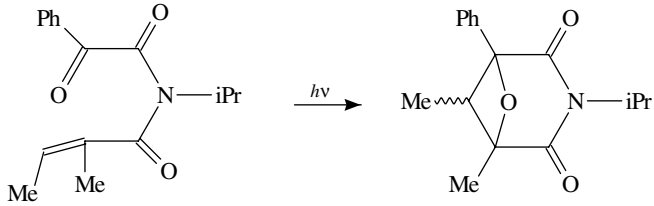
(161)

The Paterno–Buchi reaction for the formation of oxetanes by a photochemical [2 + 2] process, from an alkene moiety and a carbonyl-containing compound, is a well-established synthetic route[583]. Reaction of benzaldehyde with a range of silyl enol ethers, under photolytic conditions, gives rise to oxetanes in reasonable yields and with excellent regioselectivity and some diastereoselectivity, the latter of which parallels the bulkiness of the R group (equation 162)[584,585]. Other workers have also performed this type of reaction with excellent regio-[586] or stereocontrol[587–590], or both[591,592]. One notable reaction of the latter type is an internal [2+2] reaction which occurs in very high yield and a *syn*:*anti*

ratio of 2.1 (equation 163)[593].



(162)

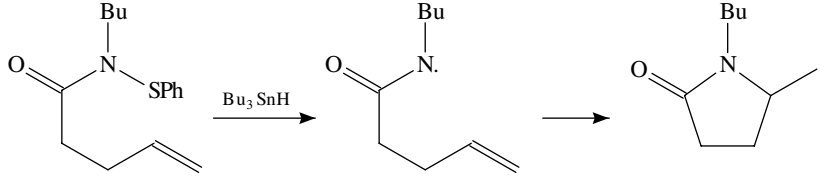


(163)

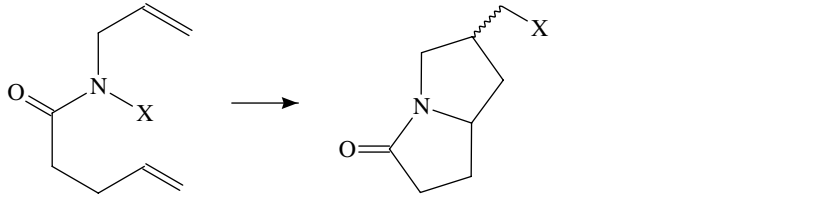
2. Five- and six-membered rings

Five- and six-membered heterocycles, containing either a nitrogen or oxygen atom, and in particular pyrrolidine rings, are very important in natural products synthesis. There are many methods by which all these compounds may be synthesized and new routes to this target are constantly being sought.

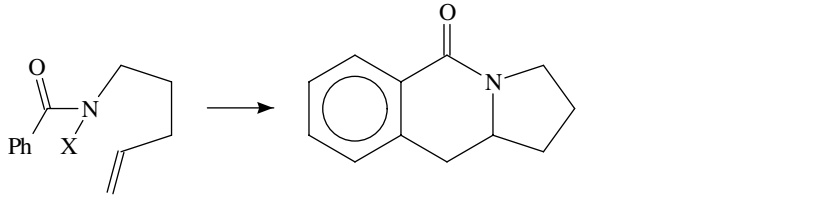
γ-Lactams may be formed by intramolecular reaction of an alkene with an amidyl radical (equation 164)[594,595]. The radical is formed from the *N*-(phenylthio) amide by treatment with Bu_3SnH. If the molecule has a second, strategically placed alkene moiety, tandem cyclizations occur to give either pyrrolizidinones (equation 165) or 3,4-benzoindolizidinones (equation 166)[596]. In all cases, yields were very good to excellent.



(164)

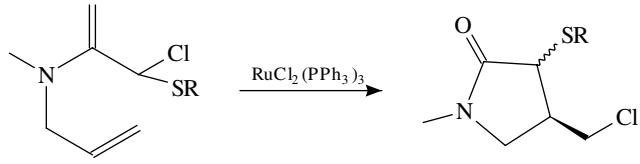


(165)



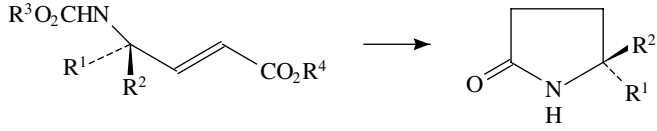
(166)

Cyclization of N-allylic α-chloro-α-thioacetamides, catalyzed by Ru complexes, gives rise to five-membered lactams (equation 167). This reaction has been used as a key step in the synthesis of several natural products[597]. Other similar Ru-catalyzed cyclizations have been used to prepare 2-pyrrolidinones[598,599]. This methodology is preferable over the equivalent Bu_3SnH-mediated radical cyclization[600,601] when a halogen atom is required in the target molecule.



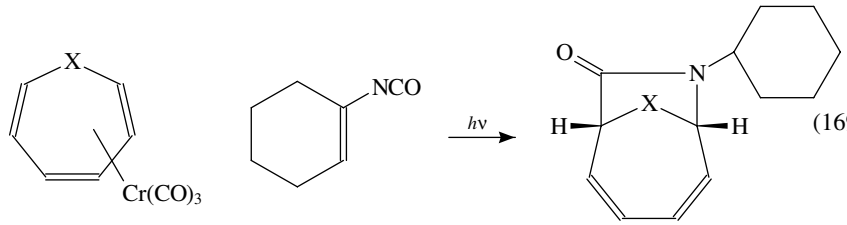
(167)

2-Pyrrolidinones with a chiral C-5 atom have been prepared in a very simple, one-pot synthesis, by treatment of *N*-alkoxycarbamoyl γ-amino α,β-unsaturated carboxylates with Mg in methanol (equation 168)[602]. The products are formed in 87–95% yield, with high optical purity (96–99% ee). Since this γ-lactam is very important, as an intermediate and target in the synthesis of natural products, this simple reaction is a very useful addition to the synthetic chemist's arsenal. Most other preparations of this target usually lead to racemic mixtures[603–606].



(168)

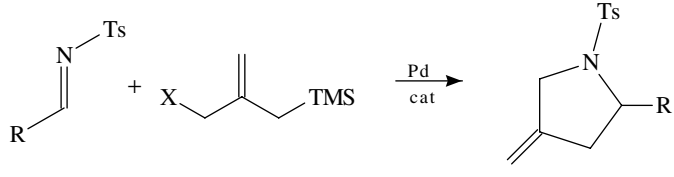
Alkyl and aryl isocyanates (and ketenes) can be used in a [6+2] cycloaddition process, promoted by chromium(0) species under photolysis, to give useful bicyclo compounds (equation 169)[607]. In this process the yields are 20–45%, which is a great improvement over other attempts at metal-mediated [6 + 2] cycloaddition reaction[608–610].



(169)

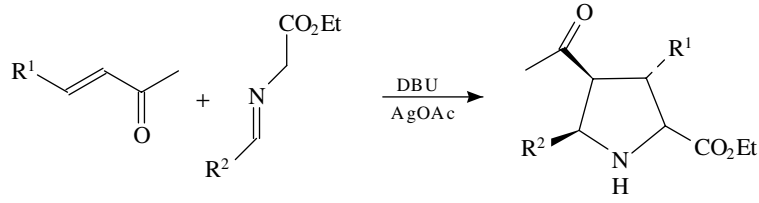
X = CH_2 or NCO_2Me

An interesting [3+2] cycloaddition reaction, of imines with TMS allyl esters catalyzed by Pd complexes, has been developed and produces pyrrolidine rings in good to excellent yields under mild conditions (equation 170)[611].



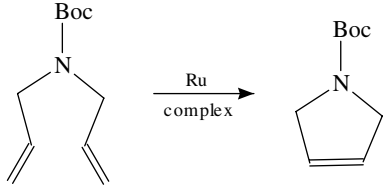
(170)

Another synthesis of pyrrolidines, in this case with high enantioselectivity, has seen several enones with a chiral alkoxy or amino substituent in the γ-position react with azomethine yields (derived from glycine imine derivatives) upon treatment with DBU/AgOAc (equation 171)[612–614]. This reaction may also be done using other alkene-containing substrates[615,616].

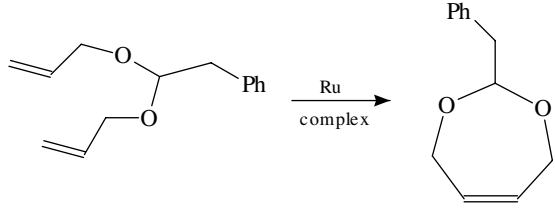


(171)

The catalytic ring-closing metathesis of functionalized dienes is an important means of preparing heterocyclic and carbocyclic compounds. Both ruthenium[617] and molybdenum[618–620] carbene complexes catalyze this process, giving good to excellent yields of cyclized products. In this way dihydropyrroles, dihydrofurans and larger oxygen-containing heterocycles can be produced (viz equations 172 and 173). A wide range of oxygenated functional groups can be tolerated in the diene.

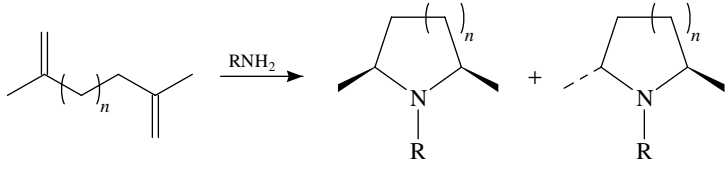


(172)



(173)

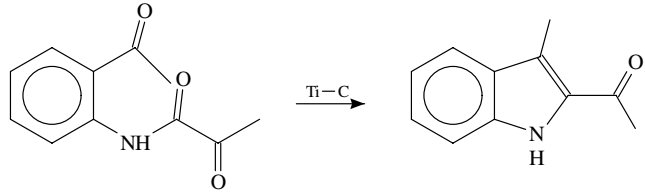
Reductive amination of 2,5- and 2,6-hexanedione moieties, with ammonia and primary amines in the presence of sodium cyanoborohydride, gives 5- and 6-membered rings with some diastereoselectivity (equation 174)[621]. As the bulk of the nitrogen substituent is increased, so greater amounts of *cis*-pyrrolidines and *trans*-piperidines are produced. This methodology has been exploited in the synthesis of azasugars from dicarbonyl sugars[622]. A similar synthesis may also be performed using other reducing agents[623–626].



(174)

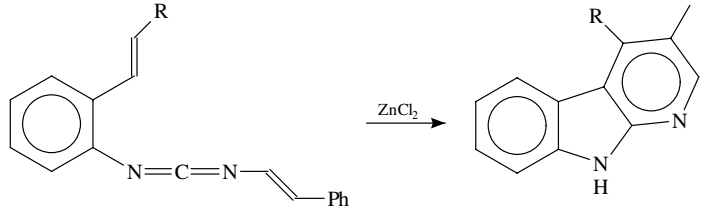
n = 1,2

Furan or pyrrole rings may be readily formed by the Ti-induced coupling of CO groups, producing an alkene (McMurry reaction)[627,628]. This reaction gives good yields and can also be used to prepare carbocyclic ring systems[629]. One example of the use of this reaction is in the synthesis of salvadoricine as shown in equation 175[630].



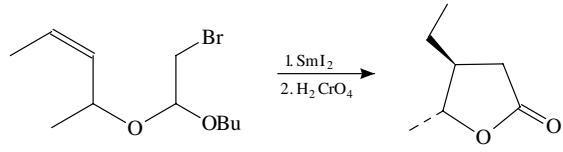
(175)

Intramolecular Diels-Alder reaction (with high periselectivity and good yields) of conjugated carbodiimides, catalyzed by Lewis acids, affords a simple procedure for the construction of pyrido[2,3-*b*]indole and indolo[2,3-*b*]quinoline ring systems (equation 176)[631]. This procedure is superior to the often mixed reactions that occur in the absence of the Lewis acid[632–635]. It is interesting to note that Lewis acids also improve yields and selectivity in intermolecular reactions of this type[636].



(176)

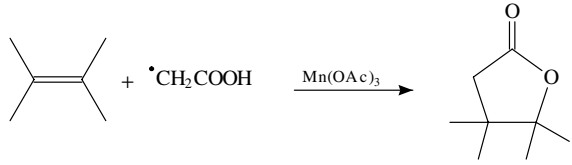
The formation of γ-lactones, by intramolecular radical coupling of haloalkenes, is usually a very efficient means of converting acyclic compounds into cyclic target molecules. The reagent of choice for promoting this reaction is usually Bu_3SnH[637]. The replacement of this promotor with samarium(II) iodide allows for a more functionalized target molecule to be produced[638,639]. In this way, unsaturated haloacetals may be smoothly converted into γ-lactones upon treatment with SmI_2, followed by Jones oxidation, in 50–99% overall yields (equation 177)[640].



(177)

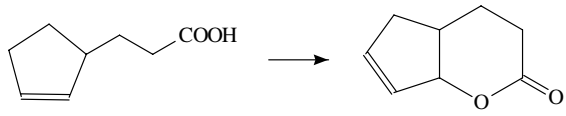
Formation of γ-lactones by lactonization of alkenes, with carboxyalkyl radicals, is a useful synthetic reaction which involves single-electron transfer. This process gives particularly good yields when performed at low temperature with ultrasonic irradiation, in the presence of manganese(III) acetate (equation 178)[641]. In general, the reaction is useful for alkenes possessing electron-donating groups and enol ethers. This reaction gives superior yields for these alkenes as compared with the thermal route[642]. Notwithstanding this, the thermal route to lactonization has been used as a key step in the synthesis of the β-glucoside paeoniflorin which is a component of the Chinese paeony, widely used

in traditional medicine[643].



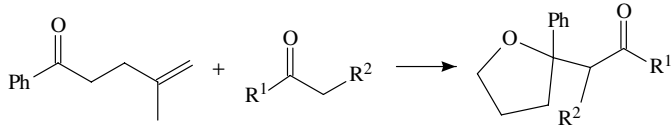
(178)

A wide range of 5- and 6-membered lactones may be synthesized in high yields from alkenoic acids upon treatment with palladium(II) acetate, sodium acetate and oxygen (equation 179)[644]. The reaction has advantages (most notably, higher yields and lower required temperatures) over the normal two-step processes used to form lactones such as halolactonization followed by dehydrohalogenation[645], sulfenolactonization followed by oxidation[646] or selenolactonization followed by oxidation[647–651].



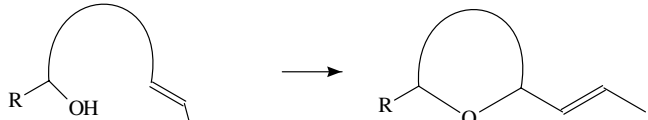
(179)

Substituted 2-(β-oxoalkyl)tetrahydrofurans have been prepared in acceptable yields by a one-step aldol-type reaction of allyl ketones and 4-methyl-1-phenyl-4-penten-1-one, catalyzed by a rhodium(I) complex–tin(II) chloride mixture (equation 180)[652]. This type of catalyst mixture has also been used for both linear[653] and cyclic[654] codimers in a similar fashion.

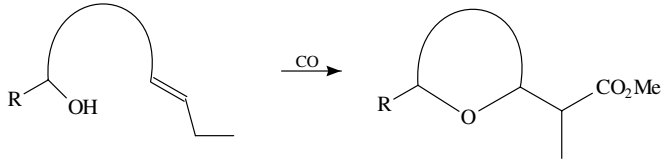


(180)

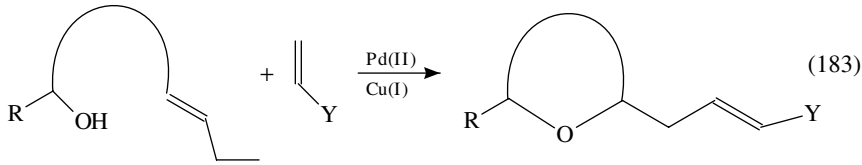
Catalytic oxy-palladation is an extremely useful method for the synthesis of functionalized THF and tetrahydropyran moieties. This reaction is brought about simply by treating a 1,4- or 1,5-hydroxy alkene with 0.1 mol-eq of Pd(II) salts and copper(I) chloride in DMF, with oxygen (equation 181)[655]. If this reaction is carried out in the presence of carbon monoxide in methanol, then an ester moiety is introduced into the product molecule (equation 182)[656–658]. If an alkene is introduced in place of the CO, then a tandem vinylation reaction also takes place (equation 183)[659].



(181)

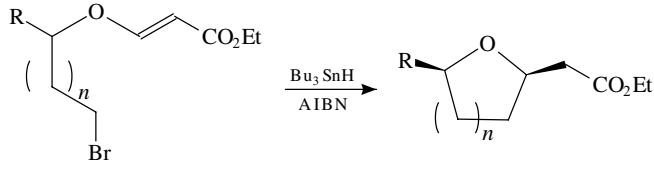


(182)



(183)

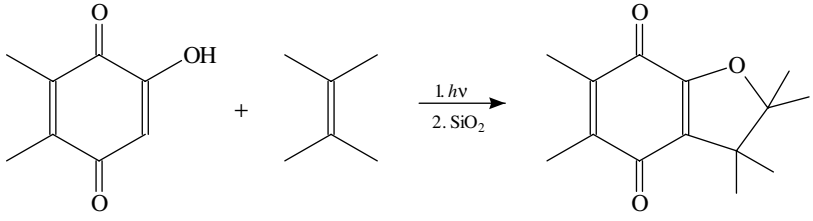
The intramolecular, radical-mediated cyclization of ω-halo-β-alkoxyacrylates (formed from propiolates and ω-halo alcohols) gives nearly quantitative yields of THF and tetrahydropyran ring systems (equation 184)[660]. The reaction is performed in refluxing benzene in the presence of Bu_3SnH and AIBN. The functionalization in the 2-positions allows for further structural elaboration. Other similar radical cyclizations have also been performed as the key step in natural product synthesis[661–663].



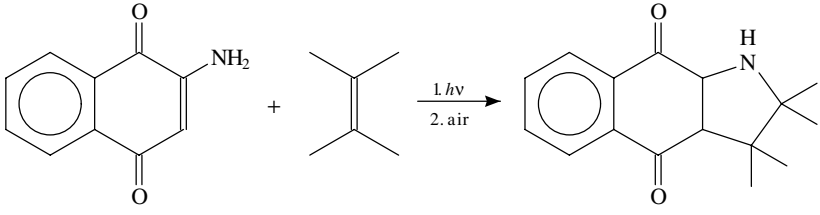
(184)

$n = 1, 2$

Benzofuran-4,7-diones have been synthesized regioselectively by [3 + 2] photoaddition of 2-hydroxy-1,4-benzoquinones with a range of alkenes (equation 185)[664]. The reaction occurs in 30–60% yield and is a useful method for the synthesis of the benzofuran ring system, which is important in natural products like acamelin[665]. Substituted naphthoquinones may also be used in this reaction[666,667] and this has lead to a very simple two-step synthesis of maturinone. In a similar reaction, a [3 + 2] photoaddition reaction of 2-amino-1,4-naphthoquinones with electron-rich alkenes gave 13–82% yields of 2,3-dihydro-1*H*-benz[*f*]indole-4,9-diones in a single-step process which involved photolysis followed by oxidation (equation 186)[668,669].



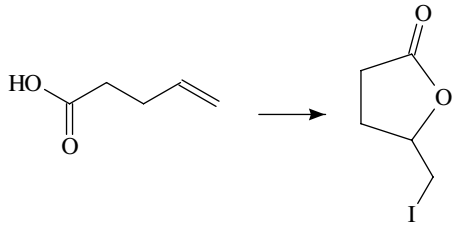
(185)



(186)

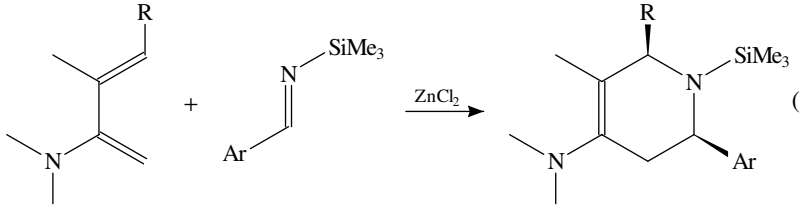
Iodolactonization of salts of unsaturated carboxylic acids, using potassium iodide, which has been oxidized by sodium persulfate *in situ*, gives rise to high product yields in very

short reaction times (equation 187)[670].



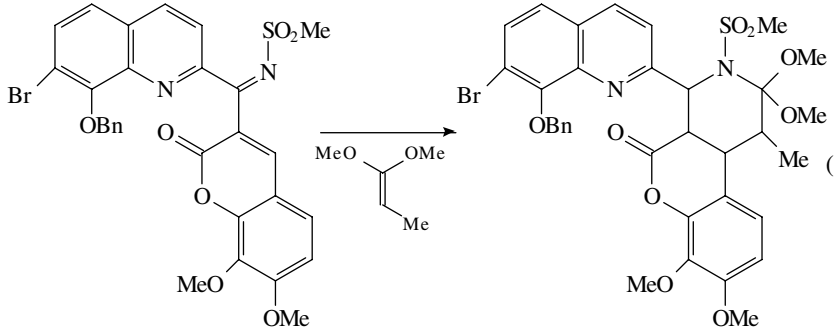
(187)

The [4 + 2] cycloaddition reaction of 2-aminobutadienes with *N*-silylimines is an extremely useful means by which cyclic eneamines may be produced[671–673]. The reaction (equation 188) takes place at −80 °C to room temperature and is catalyzed by Lewis acids, such as $ZnCl_2$. Chirality in the 2-amino group is maintained and is useful for further synthetic elaborations. Alternatively, the eneamine moiety may be replaced by a ketone by passing the product through a column of damp silica, thus affording 4-pyridinones as the final synthetic target. A similar reaction can be performed by replacing the amino group on the butadiene with a siloxy group[674,675] or by replacing the silylimine with an acyl[676–678], sulfonyl[679–682] or substituted alkyl[683] imine.



(188)

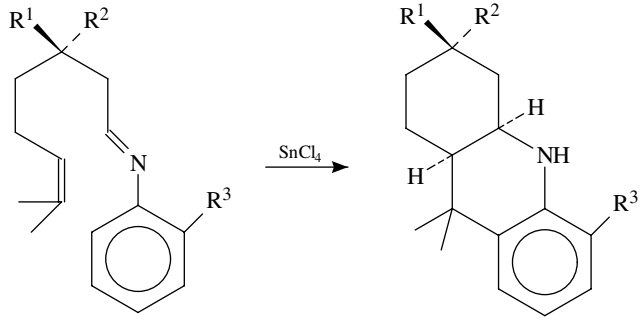
The functionalities in the previously described reaction may be reorganized so that the imine is part of the diene moiety, which is then reacted with an alkene. This particular arrangement of functionality has been used as one of the key steps in the total synthesis of streptonigrone (equation 189)[684].



(189)

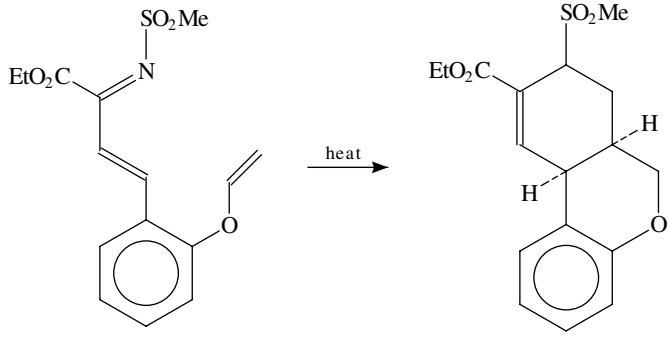
Diels–Alder reactions are a very versatile means of synthesizing several ring systems in a single-step process. This protocol has been used to form octahydroacridine derivatives by taking *N*-arylimines which contain a nonactivated alkene functionality appropriately

placed within the molecule, and subjecting them to Diels-Alder conditions in the presence of a Lewis acid (equation 190)[685]. Control of *cis* versus *trans* selectivity can be achieved by variation of substituents within the molecule. Previously, electron-rich dienophiles had been required in order for this type of reaction to occur in useful yields[686–688].



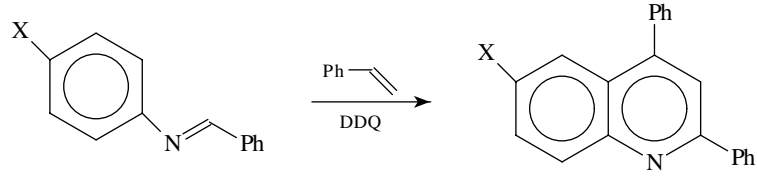
(190)

A similar reaction, with functionalities reorganized, may also be used to form tricyclic compounds. Thus, sulfonylimines (as part of a diene system) react by [4+2] intramolecular cycloaddition with an appropriately placed alkene moiety as shown in equation 191[689]. Some aromatization of the nitrogen-containing ring also occurs. This problem of a mixed product can be overcome by treating the reaction mixture with DBU/DDQ, which gives the aromatized product in 84% yield.



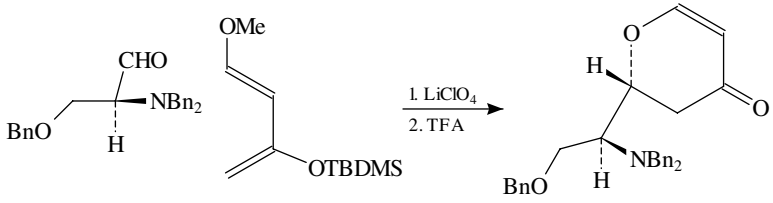
(191)

A nonconcerted pathway by which *N*-arylimines react with alkenes to give quinolines has been described (equation 192)[690]. The reaction takes place at room temperature, in acetonitrile, and is catalyzed by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ); final processing involves bubbling ammonia into the reaction mixture. Yields are low (10–65%) but in many cases only a single product is formed, and purification from starting materials is a relatively simple matter.



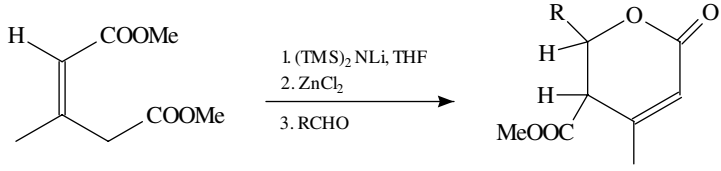
(192)

The [4+2] cycloaddition of butadienes to the carbonyl group in a N-protected α-amino aldehyde is an extremely useful means by which complex amino sugar antibiotics may be accessed. Such reactions have been performed using ultrahigh-pressure conditions[691,692] or Lewis acid catalysis[693,694] to promote the Diels–Alder process. A milder process involving catalysis by lithium perchlorate in ether has also been used[695] which gives good yields of dihydropyrones and with controlled stereochemistry (equation 193)[696].



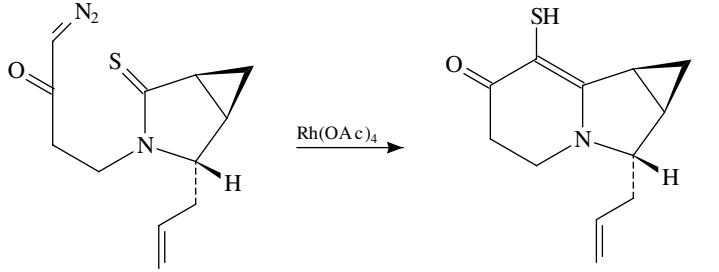
(193)

The 5,6-dihydro-α-pyrone ring is present in several biologically active molecules[697,698]. This ring system may be usefully prepared, in a one-pot procedure, via a directed aldol-type condensation followed by cyclization (equation 194)[699]. The products are usefully functionalized with a carboxylic ester group in the 3-position which allows further synthetic elaboration.



(194)

In the total synthesis of indolizomycin[700], one of the key steps involved the cyclization of a thiolactam with an intramolecular α-diazoketone moiety, catalyzed by rhodium acetate (equation 195). The molecule is desulfurized by treatment with Raney nickel, giving a good yield of the required target.

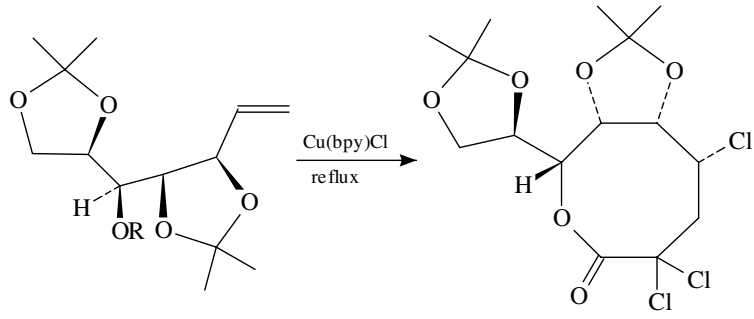


(195)

3. Larger rings containing a single heteroatom

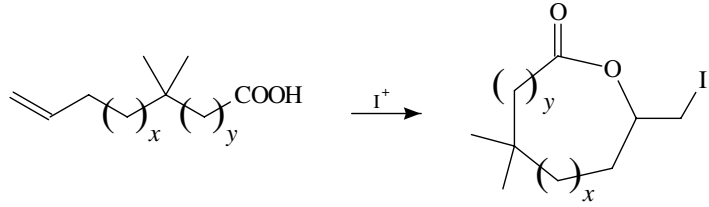
Medium-sized lactones have become significant targets of synthesis due to their regular occurrence as biologically active natural products[701–703]. Various synthetic methods utilizing the alkene moiety have been developed recently for the preparation of these compounds. Medium-sized lactones have also been very successfully prepared, with

some unexpected diastereoselectivity, by the copper(I)-catalyzed cyclization of ω-alkenyl trichloroacetates. For example, the reaction shown in equation 196 proceeded in 74% yield, producing only a single diastereomer[704]. The catalyst, Cu(bpy)Cl, has been used with other substrates to induce radical cyclizations which produce 8- and 9-membered lactones[705,706].



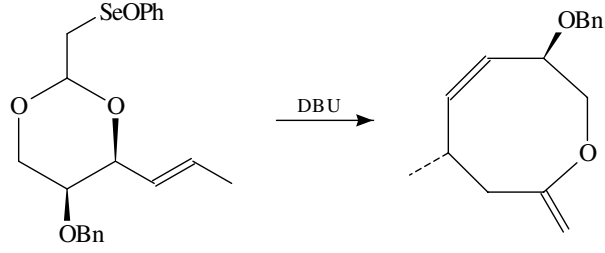
(196)

ω-Alkenoic acids have also been used to form 7- to 11-membered lactones, in useful yields, in a reaction that is induced by iodine(I) compounds at room temperature (equation 197)[707,708]. The reaction has been employed as the key step in the formation of a natural product that has been isolated from the East African tree, *Conyza hypoleuca*, which has yielded some useful bioactive compounds[709].



(197)

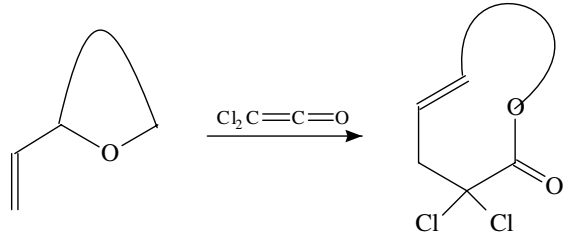
Further, medium-sized lactones have been prepared by a thermal elimination–Claisen rearrangement sequence, of unsaturated selenoxide cyclic acetals (equation 198)[710]. The reaction affords reasonable yields of these useful lactones upon treatment with DBU and a siloxy species at 185 °C. The reaction has been used as the key step in the synthesis of (+)-laurencin, which contains an 8-membered cyclic ether moiety[711].



(198)

Finally, using a variant of the Claisen rearrangement (Malherbe–Bellus[712]), nine-membered lactones may be synthesized in reasonable yields with some stereocontrol.

This reaction has been used as the key step in the synthesis of some important bioactive marine metabolites by treatment of readily available 2-vinyltetrahydrofurans with dichloroketene (equation 199)[713].

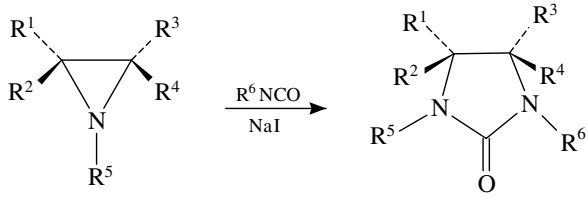


(199)

B. Heterocycles with Multiple Heteroatoms

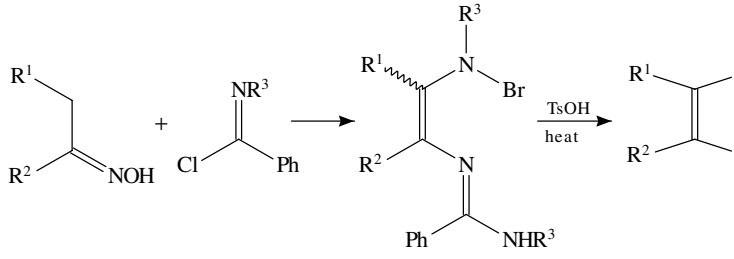
Heterocyclic compounds containing two nitrogen atoms within the ring are very useful both as synthetic intermediates and as target molecules. A range of such heterocycles may be prepared from double-bonded functional groups. In addition, other heterocycles may be prepared by the use of double-bonded functional groups as key starting materials. Recent examples of these syntheses are described in the section below.

Isocyanates react with a wide range of aziridines, in the presence of NaI, to give imidazolidinones, which are quite difficult to synthesize by other means. The reaction usually gives a stereocontrolled product in up to 60% yield (equation 200)[714,715].

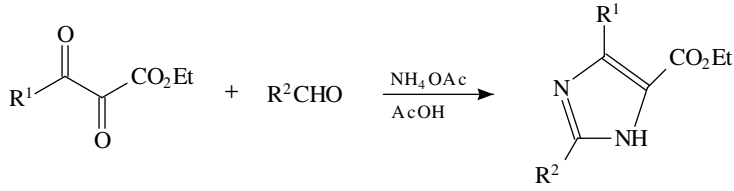


(200)

Carboximidoyl chlorides may be reacted with oximes to give 30–65% yield of amidines, which may then be used to form imidazoles in good yields, by treatment with TsOH (equation 201)[716]. Highly substituted imidazoles may be prepared in a simple one-pot synthesis by treating vicinal tricarbonyl compounds with an aldehyde and ammonium acetate (equation 202)[717]. The reaction occurs in 66–90% yield and seems to be general in scope.

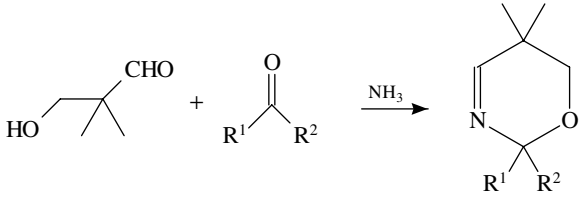


(201)



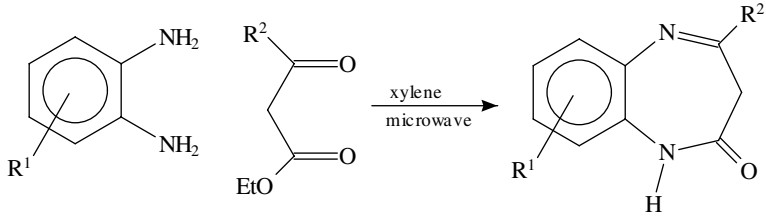
(202)

Asinger-type condensations allow the synthesis of a wide range of 5-, 6- and 7-membered heterocyclic compounds, such as 2,5-dihydro-1,3-oxazolines[718] and 5,6-dihydro-2*H*-1,3-oxazines[719]. In the latter, a β-hydroxyaldehyde is treated with a ketone (or aldehyde) and ammonia, giving up to 50% yields of the useful heterocyclic product (equation 203).



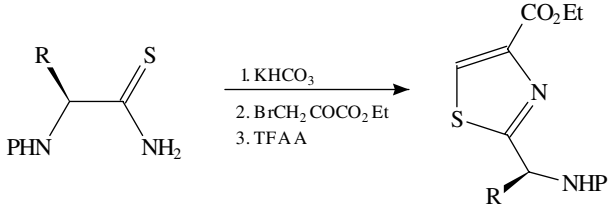
(203)

Condensation of *ortho*-aryldiamines with β-ketoesters by irradiation with microwaves in xylene gives very good yields of 1,5-arylodiazepin-2-ones by a novel and simple route (equation 204)[720].



(204)

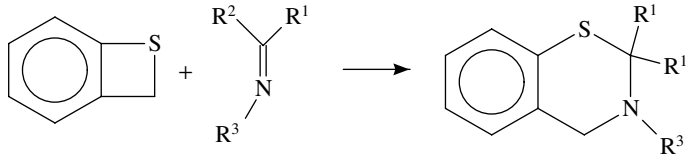
Thiazoles may be prepared by a Hantzsch-type process, by reaction of N-protected thioamino acids with bicarbonate and $BrCH_2COCO_2Et$, followed by TFAA in 2,6-lutidine (equation 205). This reaction has been used as one of the important steps in the total synthesis of (−)-bistatramide C[721].



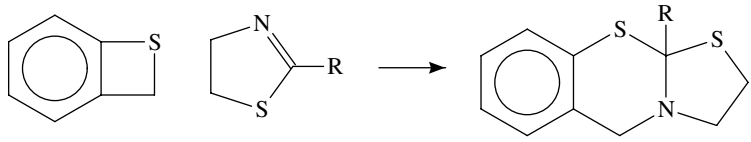
(205)

Treatment of benzothiete with a wide range of C=N-containing compounds gives good yields of 1,3-benzothiazines (equation 206)[722]. If the C=N double bond is already part of

a heterocyclic system, then useful tricyclic compounds may be produced (equation 207).

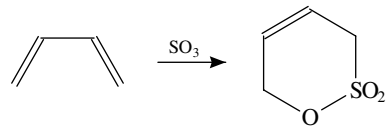


(206)



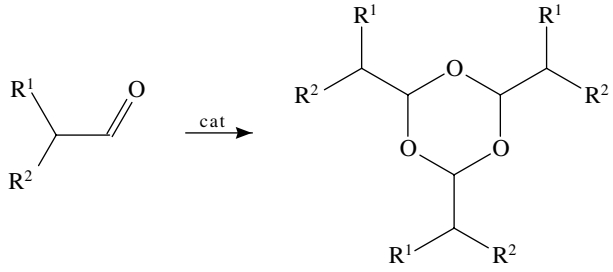
(207)

δ-Sultones are useful heterocycles which may be synthesized, in up to 80% yield, simply by treatment of conjugated dienes with sulfur trioxide at low temperatures (equation 208)[723]. Other alkene-containing molecules react with sulfur trioxide to give α- and β-sultones[724].



(208)

Finally, 1,3,5-trioxanes are heterocyclic systems that are seeing increasing use in industrial chemical applications, for example as stabilizers in color photography[725] and in polymers[726]. Many syntheses of these compounds give low yields under rather extreme conditions. A new, mild and high yielding synthesis has been developed for symmetrical 1,3,5-trioxanes which simply involves treatment of aldehydes with bentonitic earth (equation 209)[727].



(209)

VI. ACKNOWLEDGMENTS

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CHAPTER **15**

Hydrogenation of compounds containing C=C, C=O and C=N bonds

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I. INTRODUCTION

This chapter will review developments in the area of hydrogenation of C=C, C=O and C=N bonds which have been reported in the last ten years or so, thereby providing an update of past volumes in this series. In the area of asymmetric hydrogenation, one outstanding publication provides a comprehensive survey of the area up to 1985[1]. The emphasis will be on synthetic implications rather than the detailed mechanistic analysis of the reactions under study. However, important developments in our understanding of the mechanism of hydrogenation will be described. The synthesis of hydrogenation ligands will not be described in detail, unless the method discussed is a very general one. Coverage will be restricted to the addition of hydrogen across double bonds rather than reduction by other methods such as hydride reagents. Transfer hydrogenation will be included in the review.

Many of the major developments in hydrogenation chemistry in the last decade have been in the area of asymmetric catalysis, and the level of coverage in this review will reflect this important area. In preparing this review it became apparent that many specific catalytic systems may be employed for the reductions of several different classes of double-bonded substrate. To afford maximum utility to the reader as a reference text, the contents have been arranged by type of double bond reduced.

Attention is drawn at this point to a number of excellent reviews of hydrogenation reactions which have recently been published and which will be cited throughout this text.

II. HYDROGENATION OF C=C BONDS

A. Homogeneous Methods

1. General comments

The high level of research in methods for homogeneous hydrogenation of carbon–carbon double bonds originates mainly from the use of the chlorotris(triphenylphosphine) rhodium(I) complex which was first reported by Wilkinson[2] and others[3,4] in 1965. This review will not seek to define the reaction profile of Wilkinson's catalyst, since this has been done adequately elsewhere[5,6]. The Wilkinson catalyst has a very wide substrate range, although less hindered alkenes are reduced more rapidly. It has been demonstrated that the reduction of an alkene takes place in all cases with a *syn* selectivity, i.e. hydrogen is added to one face of the double bond.[5–7] Many modified variants of the Wilkinson catalyst have been reported, some of which benefit from improved substrate selectivity[8–18]. The chloride atom may be replaced, for example with another halide[8], or hydride[12b], as may the phosphines. The latter modification provides the greatest scope for productive catalyst modification; dimeric or trimeric phosphines may be employed, including homochiral ligands, as will be described in more detail in a later section. Trialkylarsine and -stibine ligands[11] may also be employed in place of phosphines to give active hydrogenation catalysts (Figure 1).

Aqueous solubility may be imparted on the complex most commonly by the incorporation of sulphonic acid groups into the aromatic rings of the phosphine[14,19]. This method benefits from the particular advantage that it does not interfere with the desirable structural features of many valuable ligands, particularly chiral ligands, as will be described in later sections. Whilst sulphonic acids provide anionic groups to aid solvation, cationic groups based on quaternary amine[20] or phosphine[21] salts may be employed to the same effect. Another class of water-soluble hydrogenation complexes to be reported recently are those derived from the 1,3,5-triaza-7-phosphaadamantane ligand **1**[22]. Complexes of this ligand with rhodium or ruthenium have been shown to be highly effective water-soluble ligands for the hydrogenation of C=C and C=O bonds and for the reduction of enones to

Rh

$[RhCl(PPh_3)_3]$[2–4] $[RhBr(PPh_3)_3]$[8a] $[RhI(PPh_3)_3]$[8a]

$[Rh(NO)(PPh_3)_3]$[9] $[Rh(OCOMe)(PPh_3)_3]$[10] $[RhCl(AsPh_3)_3]$[11] $[RhCl(SbPh_3)_3]$[11]

$[Rh(H)(CO)(PPh_3)_3]$[12b] $[RhCl_3(py)_3]$[13] $[RhCl(TPPTS)_3]$[14c]
(TPPTS = $P(m\text{-}SO_3H)C_6H_4$)

$[Rh(COD)(MeCN)_2]BF_4$[15]

$[Rh_2(\mu\text{-}Cl)_2(CO)_2CH_2(PPh_2)_2]^+$[16] $[RhCl(py)_2(DMF)(BH_4)]Cl$[17]

$[Rh_6(CO)_{10}(PPh_3)_6]$[18]

Ru

$[RuCl_2(PPh_3)_3]$[26,5b] $[RuHCl(PPh_3)_3]$[26] $[RuH_2(PPh_3)_4]$[27]

$[RuH(NO)(PPh_3)_3]$[28] $[RuCl_2(AsPh_3)_3]$[29] $[Ru(OAc)_2(PPh_3)_2]$[30]

$[RuCl(Ph_2PCH_2CH_2PPh_2)(MeCN)_3]PF_6$[31] $[Ru_3(NCO)(CO)_{10}]^-$[32]

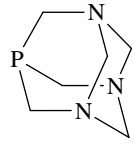
Os $[OsHBr(CO)(PPh_3)_3]$[34d]

Ir $[IrCl(CO)(PPh_3)_3]$[25e]

Co$[CoH_3(PPh_3)_3]$[35]

Pt $[PtCl_2(PPh_3)_2]$[37]

FIGURE 1. Organometallic complexes used in hydrogenation reactions
[a] Higher activity than chloro compound.
[b] Terminal alkenes are reduced selectively.
[c] Water and air stable complex.
[d] Suitable for reduction of conjugated dienes to monoenes.
[e] Vaska's compound.



(1)

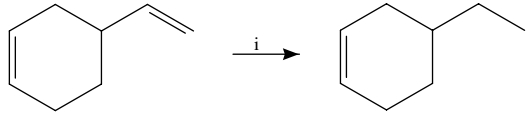
aldehydes or ketones. In certain cases the use of a two-phase system is advantageous. The attachment of water-soluble sugar units may also be employed as a strategy to aid water solubility[23]. The area of water-soluble ligands has been extensively reviewed recently[24].

Whilst rhodium complexes have perhaps been the most widely studied reagents for homogeneous hydrogenations, complexes of many other metals have been demonstrated to be highly valuable catalysts. From the point of view of synthetic chemistry complexes based on iridium[6,25], ruthenium[6,26–32] and osmium[6,3,34] are of particular importance and will be discussed in detail throughout this report. Whilst a comprehensive summary of available catalysts is not possible in a review of this type, representative examples of hydrogenation complexes are given in Figure 1. Some of the metals, for example palladium and platinum, are also commonly associated with heterogeneous catalysis, and will be discussed in a later section.

Recent years have seen the introduction and development of metallocene complexes based on early transition metals for hydrogenation. Of complexes of the general formula

$[Cp_2MR^1R^2]$ (R^1, R^2 = H, alkyl) those derived from zirconium, titanium and hafnium have been most exploited[6,38]. The catalysts are most conveniently prepared by the action of an excess of a Grignard reagent upon zirconium dichloride complexes[39]. Many applications of this class of reduction have been reported, including the selective reduction of conjugated dienes to alkenes[40], and the mechanism has been studied in some detail[39,40]. Hydrozirconation has been employed as a method for the reduction of C_{60} to $C_{60}H_2$[41]. The well-defined structure of the cyclopentadienyl groups and their homochiral derivatives have led to applications of metallocene complexes to asymmetric synthesis, as will be discussed in later sections.

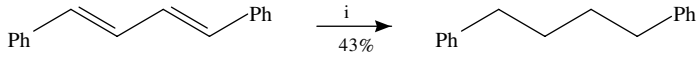
Actinide and lanthanoid complexes have been employed for hydrogenation reactions, for which they often generate dramatic rate increases and high numbers of turnovers[42]. Many of these complexes exhibit good selectivity for preferential reduction of the less hindered alkene in situations where more than one is present in a substrate (Scheme 1)[43].



Reagents: (i) 1% $[Cp^*_2, YMe(THF)]H_2$

SCHEME 1

Reductions of conjugated alkenes to saturated hydrocarbons may be achieved using a number of methods[6]. The reduction of dienes conjugated to aromatic rings has been achieved using a binuclear palladium complex pretreated with oxygen (Scheme 2)[44]. Reductions which stop at the alkene stage are in principle more valuable since a functionality is retained in the molecule. Again there have been several reported methods which achieve this including the use of ferrocenyl amino sulphide and selenide complexes[45] and by tricarbonyl chromium arene complexes[46]. Isomerization of the remaining alkene is often observed and optimal conditions can often only be achieved by careful modifications of the conditions. Many of these processes have been described in detail elsewhere[6].



Reagents: (i) 1% $[(Bu^tPh)Pd(PBu^t_2)]_2$, THF, rt, 1 atm H_2, 15 min

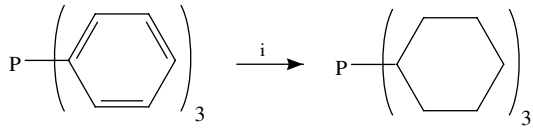
SCHEME 2

In general, electron-poor double bonds are hydrogenated most rapidly in homogeneous catalytic reactions. This observation greatly facilitates the selective reduction of carbon–carbon double bonds in enones and related compounds. The catalyst developed by Wilkinson, $[RhCl(PPh)_3]$, has a wide substrate scope in this respect[2,6,47], although in the case of aldehydes it can also promote decarbonylation reactions[48]. One of the most impressive examples of selectivity is in the reduction of unsaturated nitro compounds, without reduction of the nitro group itself, which is normally highly susceptible to reduction[48a]. The rhodium complex $[(PCy_3)_2Rh(H)Cl_2]$ has been employed in a chemoselective biphasic enone reduction system which is highly selective for the C=C bond[49]. Catalysts based on ruthenium ($[RuCl_2(PPh_3)_3]$[26b,c] and osmium $[OsHBr(CO)(PPh_3)_3]$[34] work well in the reduction of enones to saturated ketones. Crabtree's catalyst, $[Ir(COD)(PCy_3)(Py)]PF_6$

and related complexes, are especially effective for this application[50] as are certain arene chromium tricarbonyl complexes[51]. Certain cobalt complexes have been used as catalysts for the reduction of enones to saturated ketones[6]. In one recent report the use of cyclodextrin as a phase transfer catalyst in conjunction with hydridopentacyanocobaltate proved to be a highly effective combination for the reduction of α,β-unsaturated acids to the saturated derivatives[52a]. Other methods are described in detail elsewhere[6].

The selective reduction of α,β-unsaturated carbonyl compounds can be achieved using a palladium complex, $[(t\text{-}Bu_2PH)Pd(t\text{-}Bu)_2]_2$, pretreated with oxygen[53]. Vinylic sulphones and phosphates can be reduced selectively to the saturated products using the same remarkable catalyst[54] as can double bonds adjacent to epoxides. In the latter case the epoxide remains undamaged[55].

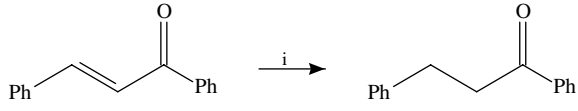
Hydrogenation of aromatic rings will not be described in detail in this review since it is mostly concerned with isolated double bonds. This is however an area of active research, as recently demonstrated by the use of catalytic niobium complexes for the selective hydrogenation of aryl phosphines (Scheme 3)[56].



Reagents: (i) $[Nb(OC_6H_3Pr^i_2)_2]$, 4 Bu^nLi, ...

SCHEME 3

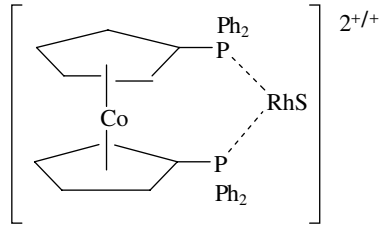
Transfer hydrogenation provides a useful alternative to the use of high-pressure hydrogen gas; hydrogen is in this case usually provided by an alcohol such as isopropanol or by formic acid[57]. Many examples will feature throughout this review, however at this stage simple reductions of the C=C bond in enones will be featured (Scheme 4). The use of microwaves can greatly accelerate this process[58]. Transfer hydrogenation *without* the use of a transition metal catalyst can also be achieved using 9,10-dihydroanthracene as a source of the hydrogen[59]. In this case it is likely that a radical mechanism operates. Transfer hydrogenation of Buckminsterfullerene (C_{60}) and its derivatives has been achieved using this method[60]. Although a mixture of products is formed, it is possible to maximize the formation of certain reduction species, such as $C_{60}H_{36}$.



Reagents: (i) $(RuCl_2(PPh_3)_3]$, $PhCH_2OH$, 180 °C, 1h

SCHEME 4

The reactivity of a transition metal catalyst can be modified by redox modification of its oxidation level. In a remarkable example the complex **2**, which is formed by the hydrogenation of a precursor complex, may be switched between the +1 and +2 from by the use of an electrode. The +2 form is highly effective at the hydrogenation of alkenes, whilst the +1 complex is more effective for other applications such as the hydrosilylation of ketones[52b].

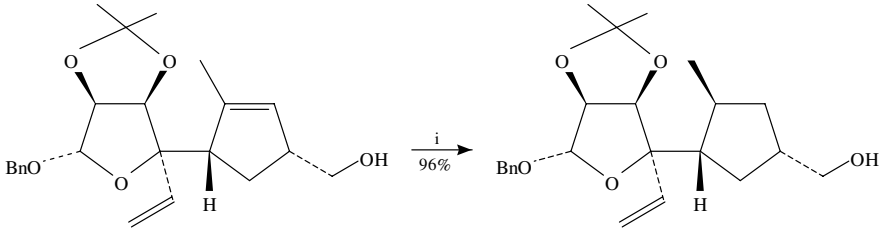


(2)

2. Diastereoselective reductions

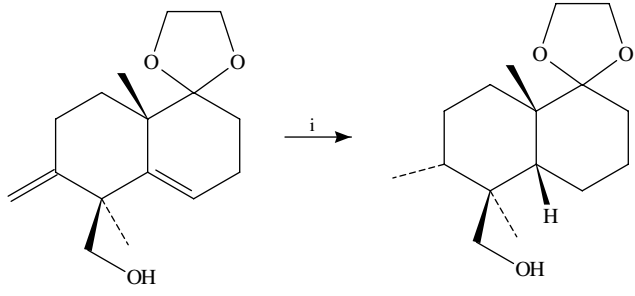
Many functional groups can co-ordinate to the metal of a hydrogenation catalyst, thereby playing an important part in the directing of diastereoselective reductions of proximal double bonds[61]. Particularly effective groups in this respect are alcohols, amides, ester and carboxylic acids. Many of these processes have been studied in great detail.

Looking first at alcohol-directed reductions[62], it is apparent that there have been many studies of the reduction of allylic and homoallylic alcohols using both the neutral and cationic reduction complexes based on rhodium, iridium etc. In the case of cyclic substrates where an alcohol is located on one side of a ring, the hydrogen is simply delivered *cis* to the alcohol function[63]. This is illustrated by key reduction steps in the synthesis of monensin (Scheme 5)[64] and the marine natural product arenarol (Scheme 6)[65]. In each



Reagents: (i) $[Rh(COD)Diphos]BF_4$, 640 psi H_2

SCHEME 5

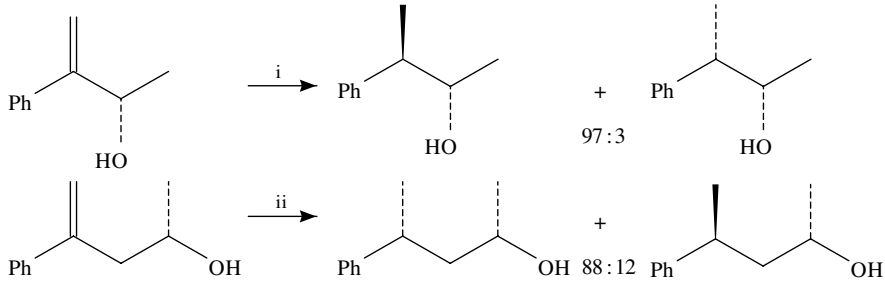


Reagents: (i) $[Ir(COD)(PCy_3)py]BF_4$, 1000 psi H_2

SCHEME 6

case a cationic complex, based on rhodium and iridium respectively, was employed. Although neutral compounds often work very well in this type of process, the use of the correct cationic complex can be critical in some cases for the full control of diastereoselectivity[66].

For the reduction of acyclic allylic and homoallylic alcohols a high level of diastereocontrol can be generated in a predicted direction. The general directing effects observed are summarized in Scheme 7 using as an example a cationic rhodium complex as catalyst[67]. In the case where there is an α-chiral centre bearing a co-ordinating group the selectivity is generally observed to be *anti*, as illustrated. The product formation is believed to take place via a structure such as that illustrated in Figure 2, in which steric eclipsing effects etc are minimized[62,68]. Although asymmetric reactions will be described in depth in the next section, the potential for kinetic resolution of racemic substrates by matching the effects of chiral ligands to the stereodirecting effects of substituents will be highlighted here. In the example of the carbamate reduction shown in Scheme 8 (the stereodirecting effect is illustrated using an achiral ligand), enantioselectivity ratios (i.e. relative rate of reaction of each enantiomer) of around 20:1 were typical using the chiral ligand DiPAMP (see below) with rhodium in an equivalent cationic complex[62,68].



Reagents: (i) $[Rh(NBD)(Diphos)]BF_4, H_2, CH_2Cl_2$, (ii) $[Rh(NBD)(Diphos)]BF_4, H_2$, THF

SCHEME 7

The complexes may be applied to some very demanding and complex transformations as illustrated by a key step in the synthesis of Bafilomycin A1 (Scheme 9), in which a neutral rhodium catalyst was employed[69]. In contrast, a cationic iridium-based complex was the catalyst of choice in an exacting selective homoallylic alcohol reduction to achieve a vital inversion of configuration in the synthesis of Brevetoxin B[70]. Functionalized alkenes may also be effectively reduced, significantly trialkylstannanes which

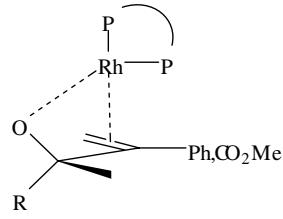
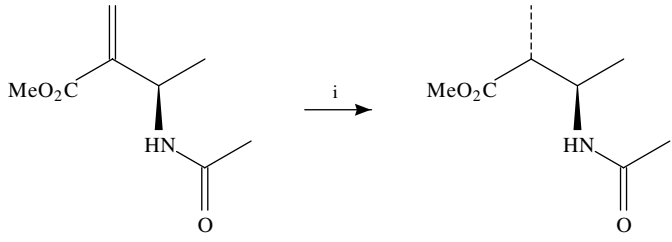
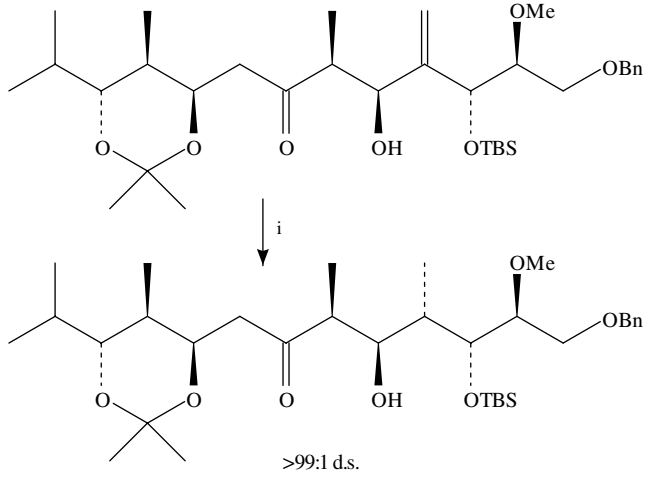


FIGURE 2. Directing effects in diastereoselective reductions



Reagents: (i) H_2, $[RhPh_2PCH_2CH_2PPh_2]^+$

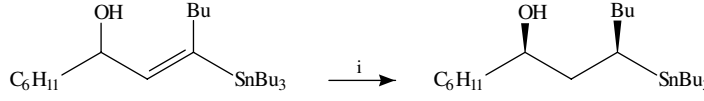
SCHEME 8



>99:1 d.s.

Reagents: (i) $[RhCl(PPh_3)_3]$, 15 bar H_2, 16 h

SCHEME 9

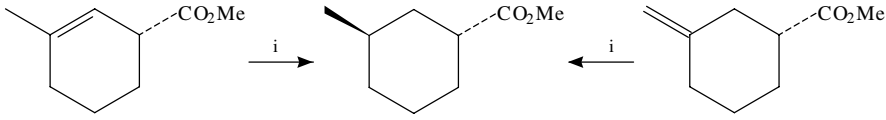


Reagents (i) $[Rh(NBD)(PPh_2CH_2CH_2PPh_2)]BF_4$, H_2

SCHEME 10

furnish synthetically valuable and highly diastereoisomerically enriched (60:1 to >500:1) stannanes (Scheme 10)[71]. Analogous transformations of trialkylsilyl substituted double bonds may also be achieved[71b]. Although the directing effect of an allylic alcohol is poor in this sense, a series of careful experiments have served to demonstrate that the sulphur chiral centre of vinylic sulphoxides can override its effect[72].

Amines can direct the reductions of proximal alkenes, as illustrated by a recent example of an enamine reduction to a diamine using the Crabtree iridium catalyst[73]. Esters and carboxylic acids, although less effective than alcohols, also direct stereoselective reduction reactions (Scheme 11)[6,74]. As in previous examples cationic rhodium and iridium complexes are favoured. Amides are also good directing groups, and actually slightly superior to esters due to better electron-donating qualities[75]. Directing effects of co-ordinating groups proximal to double bonds is critical to the success of asymmetric hydrogenations and several examples will feature in the next section.



Reagents: (i) $[Rh(NBD)(PPh_2CH_2CH_2PPh_2)]BF_4$, H_2 or $[Ir(COD)(PCy_3)py]PF_6$, 1 atm H_2

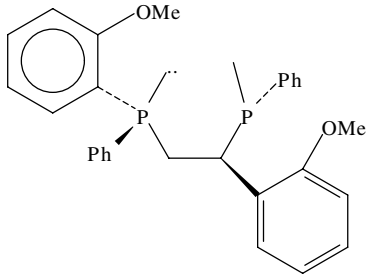
SCHEME 11

3. Enantioselective reductions

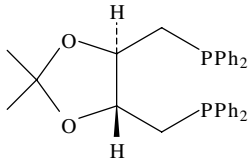
Recent years have witnessed an explosion in research into asymmetric homogeneous hydrogenations, and this will be reflected in the coverage featured in this section of this review. Several other excellent reviews have been published in this area[1,6,76]. Horner and Knowles were the first to report that the use of chiral phosphine complexes with rhodium(I) was effective at asymmetric hydrogenation reactions[77,78]. Later, several researchers found that chelating diphosphines were more convenient ligands and two of the earliest of these, DIPAMP **(P1)**[79] and DIOP **(P2)**[80], have proved to be as good in many respects as ligands reported at later dates. Each is designed with a different principal in mind; in the first the proximity of a chiral centre as close to the metal as possible and in the second the use of a chiral 'array' of phenyl groups to create a chiral environment. Many ligands have employed the same design characteristics since these were reported. Whilst it is impossible in a review of this type to be able to list all of the chiral phosphines which have been reported, a range of representative examples is given in Figure 3. Encyclopeadic surveys are available from other sources[1,76]. In addition to illustrating the great diversity of available ligands, the selection includes some very recently reported phosphines. Many of these will be referred to in the following discussion and will feature in future sections of this review.

The methods for the preparation of these ligands will not be discussed in detail in this review, however the introduction of the phosphine unit is most commonly achieved using a nucleophilic source of phosphine, e.g. Ph_2PLi etc. The synthesis of C2 symmetric ligands such as DiPAMP requires a key coupling reaction of two monophosphine precursors. As for most phosphines, oxidation by oxygen is a potential hazard. Whilst this can be avoided by careful handling, temporary protection of the phosphine as a borane complex has been very commonly employed during the synthesis of many of the chiral ligands shown below[104,105].

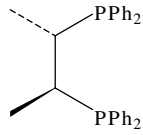
Although asymmetric hydrogenation has found many applications in synthesis, the most intensely investigated area is almost certainly the hydrogenation of α-*N*-acylaminoacrylates (Scheme 12)[1,6,76,106]. In most cases modest pressures (1 atm) of hydrogen are required, and low quantities (<1 mol%) of catalyst, which may frequently be conveniently formed *in situ* by the combination of a ligand with a non-chiral source of rhodium. Whilst rhodium is most commonly the metal of choice for catalysts, BINAP



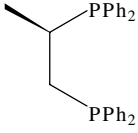
(P1) DiPAMP[79]



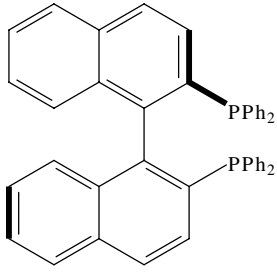
(P2) RR DIOP[80]



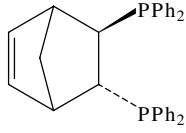
(P3) SS Chiraphos[81]



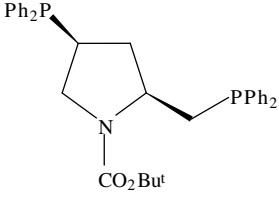
(P4) R Prophos[82]



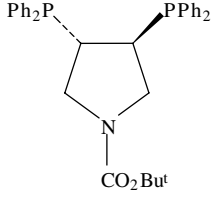
(P5) R-BINAP[83]



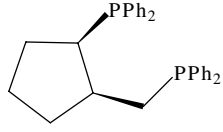
(P6) RR Norphos[84]



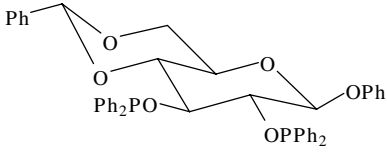
(P7) BPPM[85]



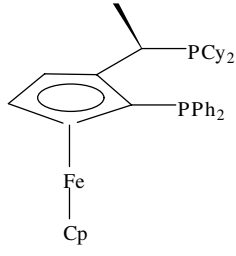
(P8) SS PYRPHOS[86]



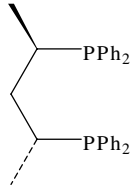
(P9) Skewphos[87]



(P10)[88]

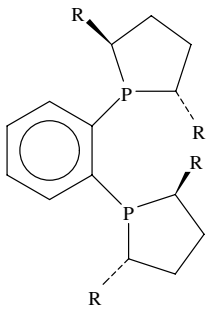


(P11) R-Josiphos[89]

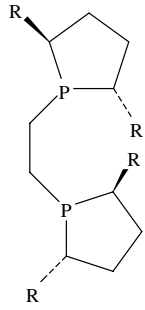


(P12)[90]

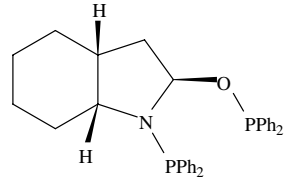
FIGURE 3. Representative chiral phosphine ligands



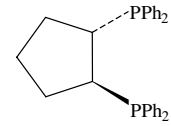
(P13) DuPhos
(R = Me, Et, i-Pr)[91]



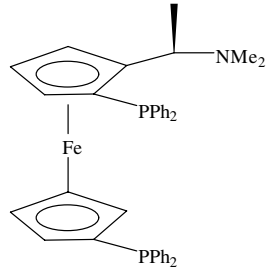
(P14) BPE
(R = Me, Et, i-Pr)[91]



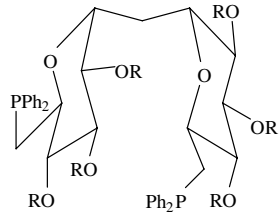
(P15)[92]



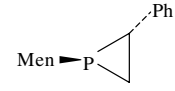
(P16)[93]



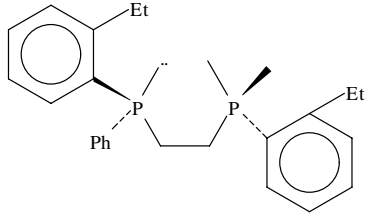
(P17)[94]



(P18)[95]



(P19)[96]



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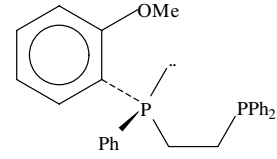

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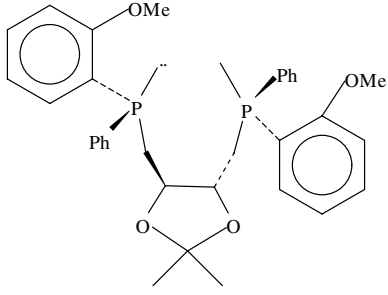
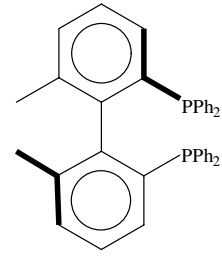
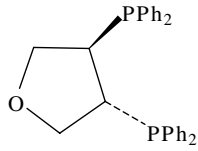


(P22)[99]

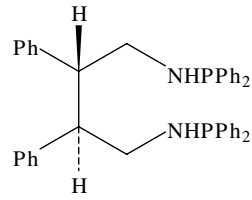


(P23) R-BICHEP[100]

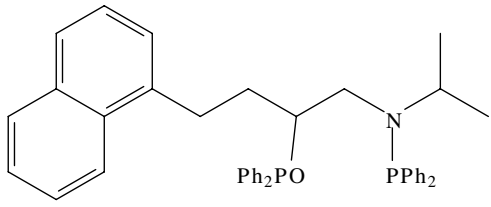
FIGURE 3. (*continued*)



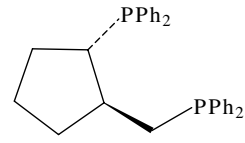
(P24)[86d]



(P25)[102]

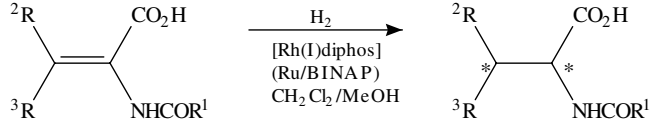


(P26)[103]



(P27)[87]

FIGURE 3. (*continued*)



SCHEME 12

is a notable exception and tends to be used in conjunction with ruthenium. This has been driven by their great synthetic importance as precursors of homochiral amino acids and their excellent compatibility with the hydrogenation process. The reduction of α-*N*-acylaminoacrylates, and in particular *Z*-acylaminocinnamic acids, has become a standard reaction for assessment of new phosphine ligands. The *E*-acylaminocinnamic acids and their derivatives tend to be less suitable as substrates although there are some exceptions[1,107]. Table 1 summarizes the results (optimised e.e.s only) for this standard hydrogenation process using the ligands shown in Figure 2, many of which are in the region of 99% e.e. Quantitative comparisons of relative rates are rather more difficult to find, due mainly to the variation in experimental conditions for each optimized process.

In terms of mechanisms many detailed investigations have been carried out on the DiPAMP–rhodium system, which have been reported in considerable detail elsewhere[1,79c,79d,107]. X-ray crystallographic structures have also been obtained to support the conclusions in this regard. It is now accepted that the substrate binds to the metal phosphine complex via both the double bond and the *N*-acylamino unit (Figure 4), the latter interaction being essential for control of stereochemistry in the process. Hydrogen is then added to the rhodium atom and transferred to the double bond in a *cis* fashion. An unexpected discovery in the early days of this work was that the major diastereomeric complex between catalyst and substrate is not the one that leads to the product. Instead it is the minor, and more reactive diastereoisomeric complex which enters the catalytic cycle. A rapid equilibrium between the two forms ensures full and rapid conversion to the product[1,107,108].

TABLE 1. Asymmetric hydrogenations of α-acylaminoacrylic acids and esters: % e.e. using ligand cited with Rh(I) unless otherwise indicated

Catalyst	Substrate: CO_2H, NHAc	CO_2H, Ph, NHAc	CO_2H, Ph, NHBz
DiPAMP (**P1**)	94	96	—
DIOP (**P2**)	73	81	—
Chiraphos (**P3**)	91	89	99
Prophos (**P4**)	90	91	93
BINAP/Ru (**P5**)	—	—	100
Norphos (**P6**)	90	96	89
BPPM (**P7**)	95	91	84
BPPFA (**P17**)	57	67	55
Pyrphos (**P8**)	—	99	—
Skewphos (**P9**)	—	96	—
P10	—	99	—
Josiphos (**P11**)	—	96 (Me ester)	—
P12	93	99	90
Duphos (**P13**)	—	99 (Me ester)	—
DPPE (**P14**)	—	99 (Me ester)	—
P15	—	57	62 (Me ester 72)
P16			—
P18	82 (Me ester)	—	—
P19	—	76	—
P20	—	93 (Me ester)	—
P22	—	70	—
P23	—	99	—
P24	—	97	—
P25	89	94	—
P26	—	—	95

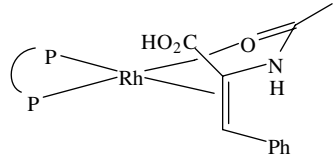
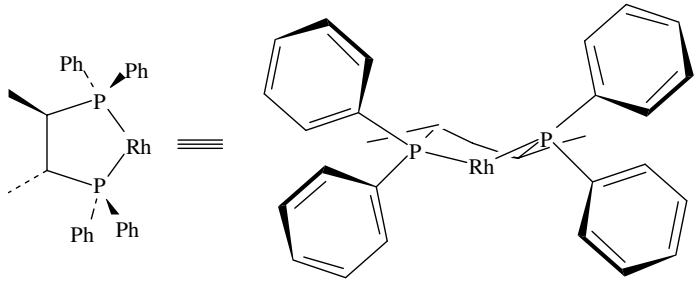


FIGURE 4

NMR studies on the rhodium complex formed between the modified ligand **P21** and methyl-*Z*-α-(acylamino)cinnamate revealed that a rapid exchange process takes place between the four possible pre-hydrogenation diastereoisomeric complexes. However, a single alkyl hydride complex is formed using hydrogen at $< -40\,^{\circ}C$[98]. The means by which asymmetric induction is achieved depends on the exact structure of the chiral environment created around the metal by the ligand, an environment which can vary dramatically with only small and subtle variations in the structure of the ligand. DiPAMP has been studied in most detail and some conclusions have been drawn about the important interactions which are involved[1]. The electron-donating properties of the methoxy group on DiPAMP appear not to be essential for asymmetric induction; the ethyl substituted analogue **P20** also gives very high e.e.s (Table 1)[97]. The presentation

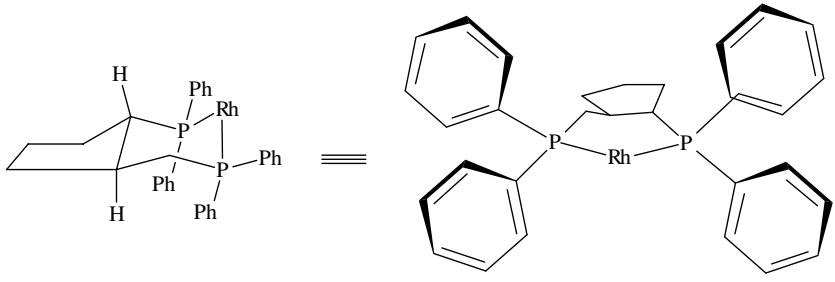
of a chiral array of phenyl rings (Figure 5)[107,109] to the metal is essential; whilst **P9** is an excellent ligand, the diastereoisomer **P27** fails to induce e.e.s higher than 20% because it can adopt a favoured pseudo-chair conformation which presents an achiral phenyl group array (Figure 6)[87]. Attempts have been made to combine the directing effects of ligands with chiral backbones with those containing chiral centres at the phosphorus centres, as in compound **P22** for example[86b,99]. Although this process is based on sound logic, the subtle effects so often found in asymmetric hydrogenations serve to confound most investigations into this area, and significant enhancements to e.e.s are rarely achieved.

Some of the most outstanding and remarkable results have been achieved using ligands which contain biaryl chirality, and in particular the ligand BINAP[110]. This highly rigid and versatile diphosphine forms very large and well defined chelate rings with a metal in a complex and presents a unique steric array of phenyl groups to the reactive centre. It is also unusual in that it is generally used with ruthenium(II), possibly because it is one of the few ligands which can form well defined complexes with a metal which is normally given to forming polymerization[111]. BINAP–Ru complexes have a remarkable substrate scope and reactivity, and will continue to feature in later sections of this report. Several reports have appeared describing new practical approaches to the synthesis of metal–BINAP complexes, such is the importance of this ligand[83f,112]. A very detailed and extensive



Chiral array of aromatic rings

FIGURE 5



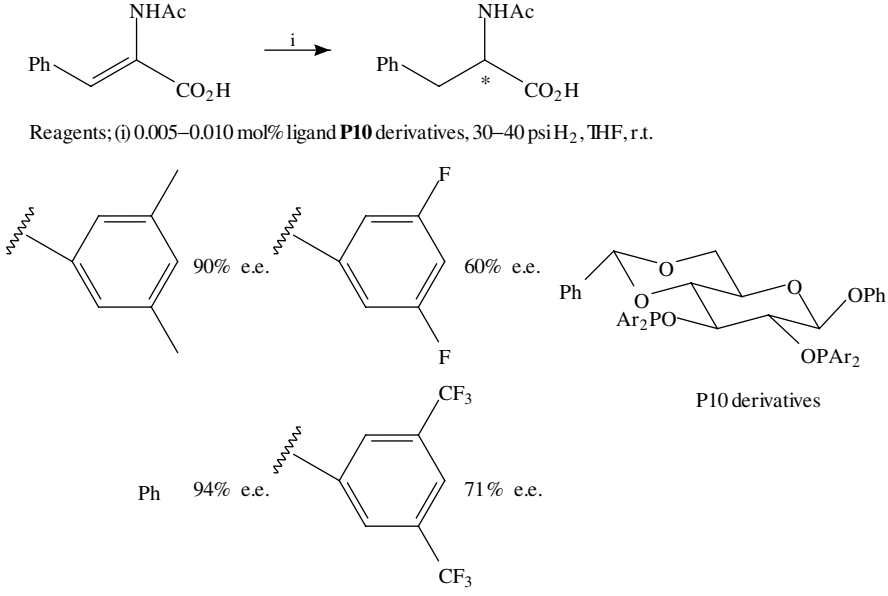
Achiral array of aromatic rings

FIGURE 6

series of studies have resulted in a new protocol for the practical preparation and use of diallyl ruthenium(II) complexes of a wide range of chiral diphosphines[113]. Many other ligands have been designed using the same principles as BINAP, most notably biaryl phosphines such as **P23** which give essentially identical levels of asymmetric induction in many cases[101].

The ligands **P13** (DuPHOS) and **P14**, which have been reported recently, are representative of the minority which do not rely on aromatic rings to create a chiral environment[91]. Some very impressive results have been achieved using these versatile ligands, which benefit from an elegant and ingenious double-C2 symmetric design concept. These ligands have notably been applied to the synthesis of unnatural amino acids. Enantiomeric excesses of up to 100% have been achieved using substrate/catalyst ratios commonly as high as 10,000, and often as high as 50,000. Like most chiral diphosphines rhodium(I) represents the metal ion of choice. Several X-ray crystallographic structures have been published which provide information about how chirality transfer is achieved in these compounds. A recent review summarizes these results[91i].

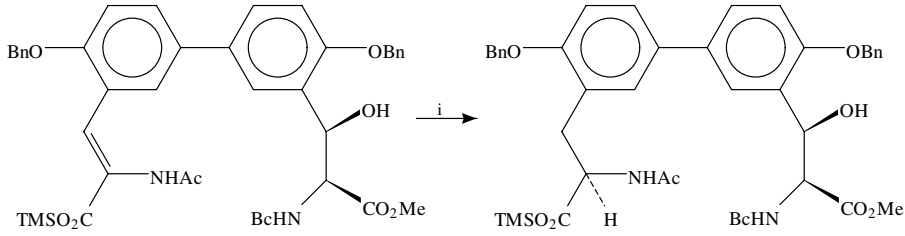
The electronic nature of ligands on the phosphine donors is often crucial. In a revealing experiment the variation of the aromatic ring in a series of ligands based on **P10** was clearly shown to give optimal results with reasonably electron-rich ligands (Scheme 13)[88c]. Electron-poor diphosphine ligands often require high pressures of hydrogen to promote reduction at reasonable rates[114]. In the case of ligand **P11** (R-Josiphos) the high e.e.s obtained depended critically on the incorporation of cyclohexyl groups on the benzylic phosphine. Inferior results were obtained using a diphenylphosphine group at this position[89a]. Diphosphinite ligands such as **P10** and related aminophosphine ligands[102] benefit from ease of preparation (usually, simply the reaction of Ph_2PCl with the amino or alcohol precursor) although few have given asymmetric inductions equal to those of other phosphines such as BINAP[103].



SCHEME 13

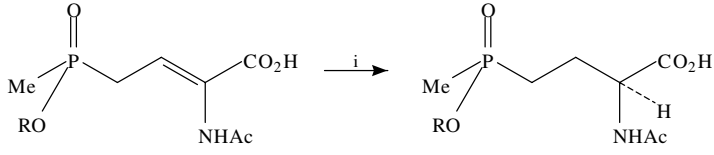
Dramatic steric effects can also operate. For example, the substitution of the phenyl rings in DIOP **P2** with *m*-methylphenyl groups results in a reversal of the enantioselectivity[115].

Provided the basic *Z*-acylaminocinnamic acid structure is preserved, a very wide range of substrates may be subjected to successful asymmetric hydrogenations. Scheme 14 shows a key step in the synthesis of Biphenomycin B, in which a highly selective reduction is achieved without interference from the other chiral centre[79f,h]. Transformations of acylaminoacrylates of this type, i.e. within peptides, have been reported in some detail[6,79g]. Chiraphos was the ligand of choice for the synthesis of L-phosphinothacin, a key component of an antibiotic tripeptide (Scheme 15)[89c], whilst in the case of the reduction shown in Scheme 16, (R)-Prophos was the favoured ligand[82e].



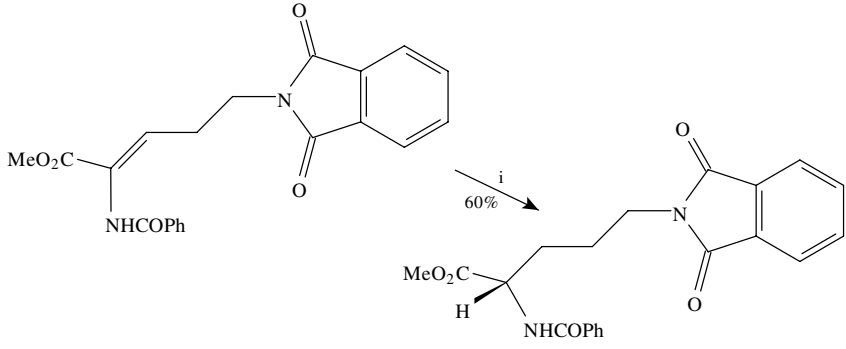
Reagents: (i) $[Rh(COD)(DiPAMP)]BF_4$, H_2, MeOH, 72 h, r.t.

SCHEME 14



Reagents: (i) [Rh. Chiraphos], H_2 91% e.e

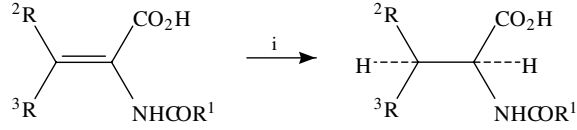
SCHEME 15



Reagents: (i) $[Rh.(R)Prophos]^+$, CH_2Cl_2, 30°C

SCHEME 16

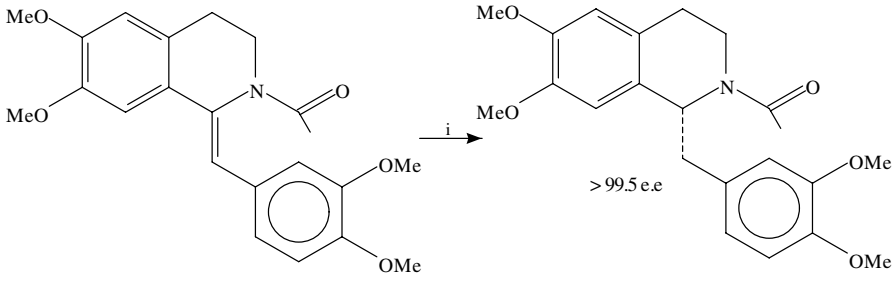
The asymmetric hydrogenation of β-disubstituted acrylates, which may potentially lead to the incorporation of an extra chiral centre, is a challenging objective. Some excellent results have been achieved using ligands **P13** (DuPHOS) and **P14** (SS-Me-BPE)[91h] which have furnished products with e.e.s in the region of 96.0 to 98.6% (Scheme 17).



Reagents: (i) [Rh(P13, R = Me)]. OTf or [Rh(P14, R = Me)]. OTf. 90 psi H_2

SCHEME 17

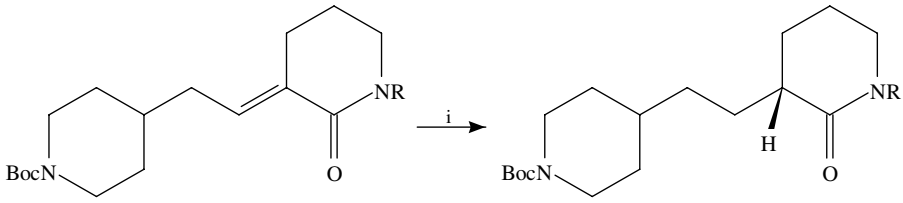
Reagents related to α-acylaminoacrylates. Given the key role played by an amide as a co-ordinating group in the hydrogenations of α-acylaminoacrylates, it would be expected that other reagents containing this group in an appropriate position would also be suitable asymmetric hydrogenation substrates. This has proved to be the case, although it should be noted that complexes of BINAP (and closely related reagents) with ruthenium have dominated this field. The acylamino group may also be incorporated at the β-position of acrylates, reductions of which thus lead to β-amino acids in high e.e.[116]. The presence of more than one acyamino group on an alkene can, however, lead to conflicting directing effects and low asymmetric indutions[117]. An early and notable application was in the asymmetric reductions of tetrahydroisoquinolines (Scheme 18), a process which leads directly to precursors of morphine and related alkaloids[118]. In this reduction process 0.5–1 mol% of the catalyst was employed and enantiomeric excesses of >99.5% were achieved. In many cases the minor diastereisomer was not observable by chiral HPLC methods.



Reagents: (i) 0.5-1 mol% [Ru(R-BINAP)$(OAc)_2$], 4 atm H_2, 5:1 EtOH:CH_2Cl_2, 48 h

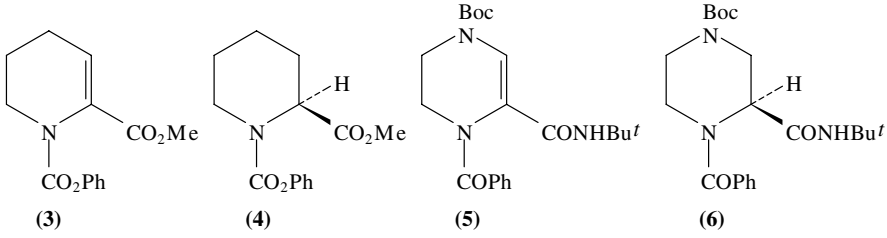
SCHEME 18

The reduction of lactam substrates containing proximal *exo* double bonds may be achieved in high e.e. as demonstrated by the reduction of 3-alkylidene-2-piperidones (Scheme 19)[119]. Cyclic amino acids may be prepared by, for example, asymmetric hydrogenation of **3** to **4** in up to 79% e.e.[120] and the reduction of **5** to **6** in 99% e.e.[121]. In the latter case a number of chiral diphosphines were screened, and the best results were obtained using BINAP as a ligand with rhodium metal. Several other diphosphines, notably DuPHOS and DIOP, also performed well. The research group which produced

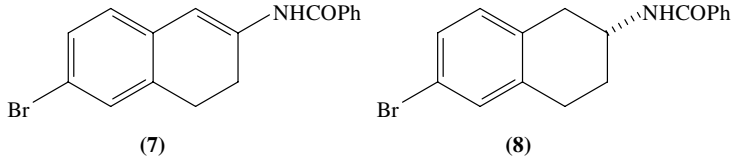


Reagents; (i) [Ru(S-BIBAP)Cl_2]. EtOH, 50 °C, 1500 psi H_2, 20 h

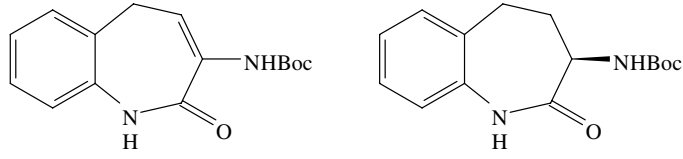
SCHEME 19



(3) **(4)** **(5)** **(6)**



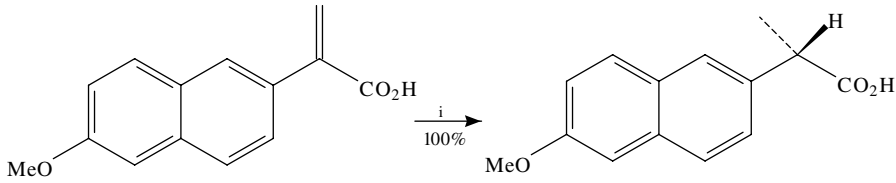
(7) **(8)**



(9) **(10)**

these results, based at Merck, have reported a number of other useful and highly selective reductions, for example the conversion of **7** to **8** (97% e.e.)[122] and **9** to **10** (82% e.e.)[123].

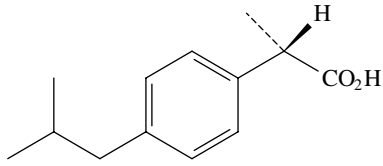
Acrylic acids may be reduced in high enantioselectivity using a number of asymmetric catalysts[124,125], although Ru/BINAP combinations have given some of the best results[126]. The reduction of tiglic acid has been studied in considerable depth, and the mechanism has been examined[127,128]. X-ray crystallographic structures have been obtained to support many of the proposals in this respect[129]. Reductions of this class of compound also have the advantage that they provide a direct access to a number of very important target molecules, for example the antiinflamatory Naproxen (Scheme 20)[127]. Another important reduction product achieved by an analogous route is ibuprofen **11**[125,130]. Using an appropriate catalyst, even trisubstituted acrylic acids may be reduced in high enantiomeric excesses[131].



97% ee

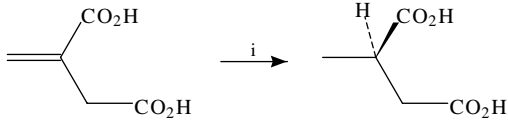
Reagents: (i) [Ru(S-BINAP)$(OAc)_2$], MeOH, 135 atm H_2, 12 h, s/c = 215

SCHEME 20



(11)

The asymmetric hydrogenation of itaconic acid (Scheme 21) and its derivatives[132] has become adopted as something of a standard by which catalysts are compared. A selection of results is given in Table 2 (e.e.s only)[133,76]. Further applications of related reductions include the synthesis of the Renin inhibitor subunit **12** by reduction of **13** in 95% e.e.[132] and the protease inhibitor **14** by reduction of **15** in this case in up to 84% e.e.[134]. For these processes the ligands of choice were either BINAP (in conjunction with Ru) or a derivative of BPPM (**P7**).



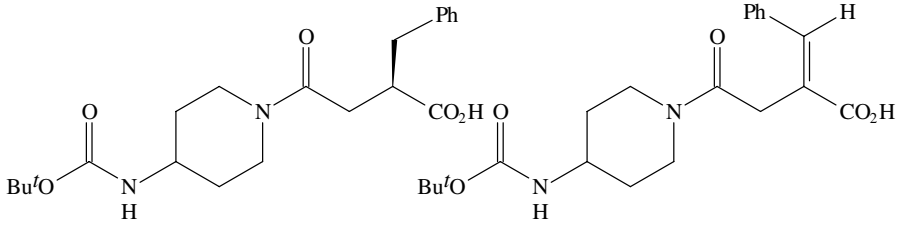
Reagents: (i) Chiral catalyst (see Table 2), H_2

SCHEME 21

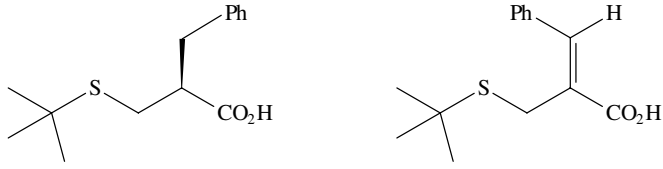
The reduction of unsaturated esters has, until recently, proved rather more difficult to reduce in high yield and selectivity, possibly due in part to their inferior donor properties

TABLE 2. Reductions of **itaconic** acid with representative Rh(I) or Ru(II)/chiral diphosphine complexes (Scheme 21)

Metal/ligand	% e.e.
Ru/BINAP **P5**	99
Rh/Josiphos **P11**	98–99
P12	47–54
BICHEP **P23**	>96
BPPM **P7**	>97



(12) **(13)**



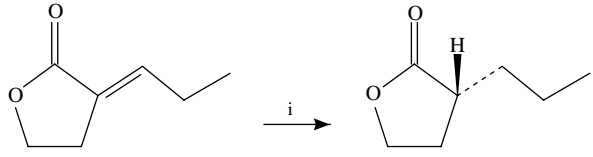
(14) **(15)**

(16) **(17)**

(18) **(19)**

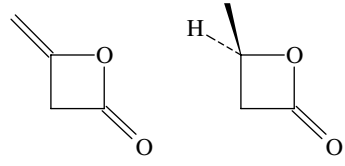
compared to acids and amides. Some excellent recent results have been reported however, driven mainly by developments in the use of BINAP/Ru complexes. BINAP has proved to be one of the best ligands for the reduction of **16** to **17** in up to 98% yield (DiPAMP/Rh also gave an excellent result)[135] whilst the related ligand BICHEMP (**P23**) was employed for the reduction of dimethylitaconate in 99% e.e.[101b]. In a further example a modified version of DIOP was used to mediate the reduction of **18** to **19** in e.e.s of 90–94%[136]. A trimeric version of the phosphine **P14** has been prepared and was reported to be capable of the reduction of dimethyl itaconate in up to 94% e.e.[91b]. In an interesting alternative approach to reduction of the same substrate, the combination of a *racemic* chiraphos/Rh complex with a second chiral phosphine — which acts as a 'chiral poison' — resulted in reduction up to 49% e.e. Although lower than the level using other methods, the need for an expensive diphosphine was avoided by this approach[137].

The reduction of *exo*-α,β-unsaturated lactones in high e.e.s has recently been reported to be achievable by the use of Ru/BINAP combinations (Scheme 22)[138]. Some extensive studies, reported in a detailed full paper by Noyori, have been carried out to identify which factors control the enantioselectivity of the reaction. That the carbonyl group is closely involved in directing the reaction is clearly demonstrated by the observation that



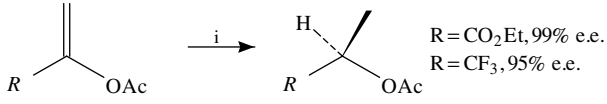
Reagents: (i)[Ru(BINAP)$(OAc)_2$], H_2

SCHEME 22



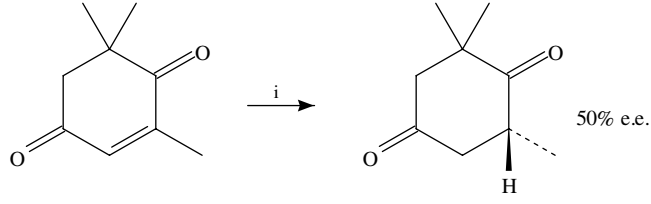
(20) **(21)**

unsaturated lactones containing *endo* double bonds are reduced in much lower e.e.[138b]. An unusual yet highly selective reduction is also observed in the conversion of butyrolactone **20** to **21** in 70% e.e. using Ru/BINAP[139]. The DuPHOS ligand **P13** and the related **P14** have proven to be ideal ligands for the asymmetric reduction of enol acetates when used in conjunction with rhodium(I) (Scheme 23)[91a]. Asymmetric hydrogenation of α,β-unsaturated aldehydes and ketones remains difficult[140], although some very interesting results have been reported, e.g. Scheme 24[140a].



Reagents: (i) Rh(I).PH, H_2

SCHEME 23

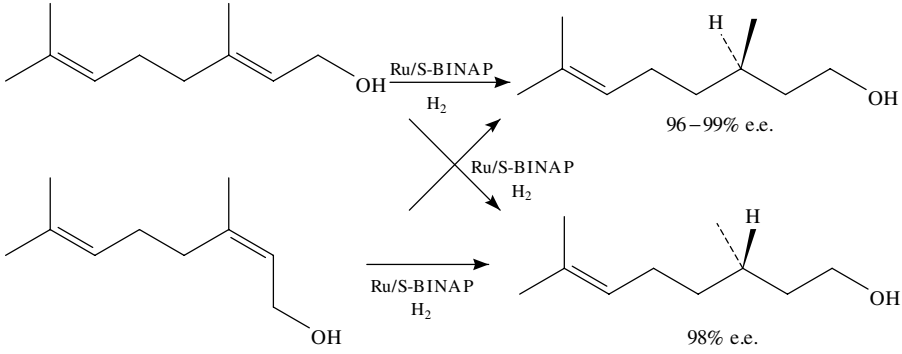


Reagents: (i) [Ru(BINAP)Cl.benzene].Cl, H_2, MeOH

SCHEME 24

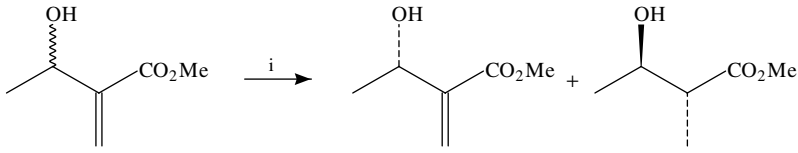
Alcohols may be employed to aid the direction of asymmetric reductions of proximal double bonds. Even polyenes are very selectively reduced at only the double bond closest

to the hydroxyl group. Many excellent result have been obtained, most notably in the reduction of allylic alcohols using Ru/BINAP combinations (Scheme 25) and in particular [Ru(BINAP)$(OAc)_2$][141]. The direction of the reduction is usually predictable and the selectivity high. A high pressure of hydrogen is not required however, and very low levels of catalyst (substrate/catalysts ratios as high as 50,000 are viable at 30 atm H_2) may be successfully employed. Detailed full papers on this work have been published[141b] and the use of closely related ligands has been reported[142].



SCHEME 25

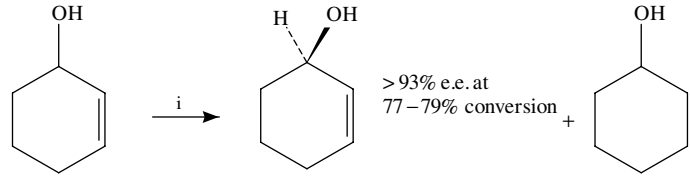
Kinetic resolutions may be achieved in asymmetric hydrogenations of racemic cyclic allylic alcohols, and in some cases impressive levels of discrimination have been achieved[143]. In the example given in Scheme 26, using a substrate/cat ratio of 200–1800, the starting material was recovered with an e.e. >99% at a conversion of 76%. Reduction of this recovered material with a non-chiral catalyst was then employed to give an enantiomeric product containing two chiral centres. In a variation on the 'chiral poisoning' approach, the combination of *racemic* BINAP/Rh complex with a (−)-1*R*,2*S*-ephedrine resulted in a good level of enantiodifferentiation in the reaction shown in Scheme 27[144]. At 77–79% conversion the unreacted starting material had an e.e. of >95%.



Reagents: (i) [Ru(S-BINAP)$(OAc)_2$], s/c 200-1800, 4 atm H_2, 25 °C, 11 h

SCHEME 26

Water solubility may be imparted upon chiral diphosphine ligands by the incorporation of polar groups. Whilst sulphonic acids have most commonly been employed[90a,145], amines have also been successfully used in this respect[90b,c]. Another approach is the use of surfactants or micelle-forming amphiphiles to permit neutral ligands to be used in an aqueous environment[85c,88b]. In all these cases the asymmetric inductions are similar to the level achieved by the original ligands and conditions.



Reagents: (i) Ru(±)BINAP cpx, (–)-(1R,S)-ephedrine

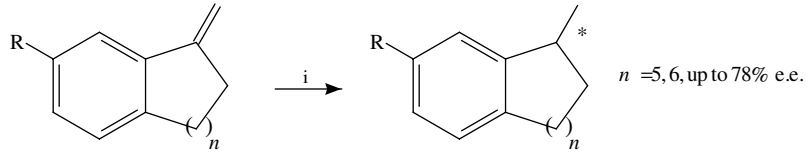
SCHEME 27

Immobilization of homogeneous catalysts has the advantage of practical simplicity in terms of use and environmental compatibility, since removal of the metal complex is facile[146]. Heterogeneous modification of a homogeneous system has been achieved by an unusual strategy in which a Ru(II)/sulphonated-BINAP catalyst is contained within a layer of ethylene glycol on the surface of small particles of glass suspended in an organic solvent. Using this system Naproxen can be prepared by the asymmetric hydrogenation of the precursor acrylic acid (Scheme 20) in up to 95.7% e.e.[127b,c]. Leakage of catalyst from the ethylene glycol is claimed to be minimal in this reagent, which can be recycled and reused without loss of activity.

Z-Acylaminocinnamic acids have been successfully hydrogenated in high enantiomeric excess using DuPHOS.Rh complexes in supercritical carbon dioxide[91g]. In some cases the e.e.s of the products exceed those achieved using methanol or hexane solvents.

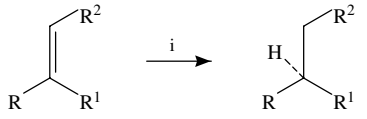
Modified ligands for asymmetric hydrogenation have been prepared by the incorporation of other function groups such as alcohols[147], or acceptors such as borane[148], in order to modify their properties and utility in unusual environments. Reports have appeared on the incorporation of chiral diphosphines within dendrimers[149] and appended to a peptide backbone[150]. The latter objective is the development of an optimized ligand by combinatorial modification of the peptide.

Reduction of simple alkenes. Few good methods exist for the asymmetric reduction of C=C bonds which contain no available groups for co-ordination to the chiral metal complex. One recent notable exception is the use of a Ru(II)/BINAP complex which is reported to be capable of the reduction of *exo* terminal alkenes in e.e.s of up to 78% (Scheme 28)[151]. Rather more success has been achieved using chiral titanocene catalysts and related organometallics[152]. Following some very promising early reports[153] a series of very valuable and versatile reagents has emerged. The complex **22** for example, catalyses the reduction process summarized in Scheme 29, for which substrates **23** to **26** are reduced with the e.e.s shown[154]. It should be noted that the actual active catalyst is formed by treatment of **22** with 2 equivalents of *n*-butyllithium and 2.5 equivalents of diphenylsilane prior to use. The related samarium complex **27** catalyses the reduction of simple alkenes



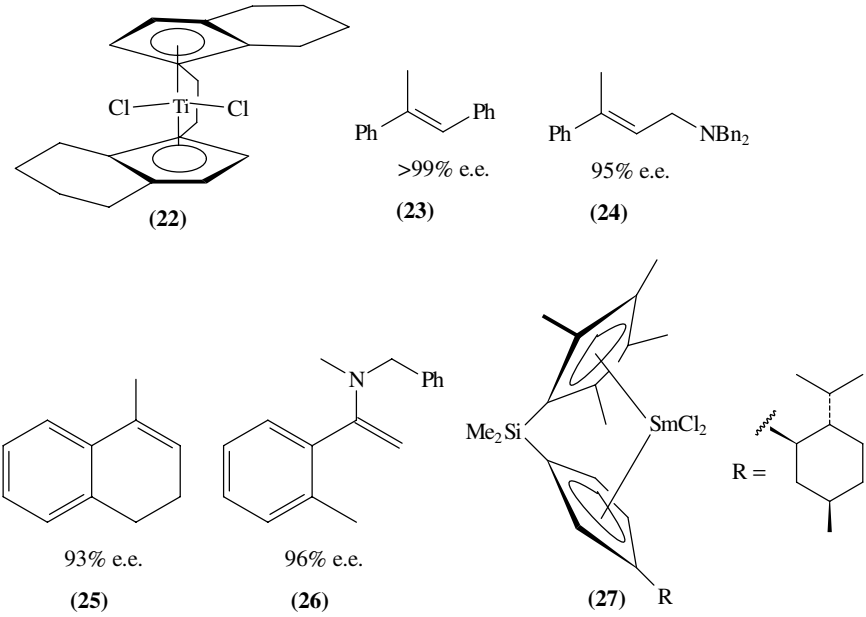
Reagents: (i) [Ru. (BINAP) $(OAc)_2$], H_2

SCHEME 28



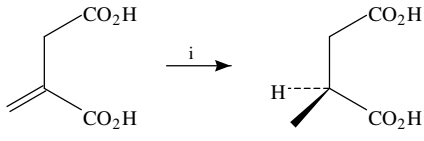
Reagents: (i) Catalyst from **22** + 2 eq. nBuLi + 2.5 eq. Ph_2SiH_2, 2000 psi H_2

SCHEME 29



in up to 96% e.e. after activation in the same way, but at lower temperature and hydrogen pressure[155].

An excellent review describing asymmetric transfer hydrogenation has been published[156]. Many excellent results have been achieved in recent studies of acrylic acid reductions employing the same catalysts of ruthenium or rhodium with a chiral diphosphine as were used in the hydrogen gas process[133f,157]. In this case, however, the most common hydrogen source is the combination of formic acid with an amine. The choice of amine is often critical; in the reduction shown in Scheme 30, the use



Amine	e.e.
S-α-methylbenzylamine	>97%
R-α-methylbenzylamine	81–87%
Benzylamine	87–89%

Reagents: (i) Rh(I).(S)-BPPM (**P7**), HCO_2H, R or S-α-methylbenzlamine

SCHEME 30

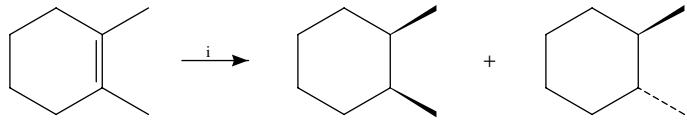
of S-α-methylbenzylamine gives product in >97% e.e. whilst use of the R-amine gives only 81–87% e.e.[133f]. In some cases an alcohol, often isopropanol, may be employed to provide the hydrogen in this class of reduction[157c].

B. Heterogeneous Methods

1. General comments

Heterogeneous hydrogenation of C=C bonds is a very well established synthetic process which is widely employed and has been extensively reviewed[158–160]. The most commonly used catalysts are finely dispersed metals such as palladium, rhodium, nickel or platinum supported on a neutral support such as alumina, silica or carbon (graphite). These reagents have the particular advantage associated with ease of use and recoverability and reusability. One disadvantage of the method is that facile double-bond isomerization can take place in certain cases. More dramatic rearrangements are observed in other cases, although homogeneous catalysts also suffer the same drawbacks on occasions[161]. The aim of this review will not be to extensively survey this area, or to discuss the kinetics and the transport phenomenon of the reactions, but to emphasize some of the more recent highlights of the literature.

Heterogeneous catalytic hydrogenation takes place on the surface of the catalyst, and in general *cis*-addition of hydrogen to alkenes is observed. A small amount of stereochemical control can be lost due to the problem of isomerization, although this can often be minimized by the correct selection of catalyst (Scheme 31/Table 3)[158]. The process of hydrogenation is very complex; a recent report described, for the first time, proof that ethylene on the Ni(III) surface was reduced by bulk hydrogen moving out of the metal to the surface, whilst the surface hydrogen had no effect[162]. Many efforts have been made to improve the definition of the surface of heterogeneous catalysts. Some of these have focussed on the preparation of carbon 'nanotubes' of defined shape and size designed to admit only substrate molecules or a specific size range, for example[163]. The same objective is shared by palladium catalysts suspended in hollow polymer fibres, some of which show improved selectivity for diene over monoene reduction[164]. Palladium catalysts supported in montmorillonite clays have been found to be capable of selective reductions of methyl acrylates over acrylates containing larger groups at the ester position[165].



Reagents: (i) Metal heterogeneous catalyst (see below), H_2

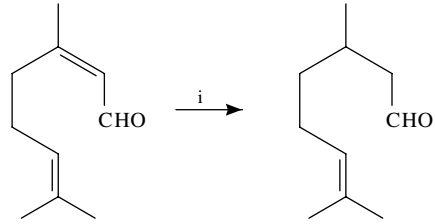
SCHEME 31

TABLE 3. Selectivity of reduction in Scheme 31

Metal	atm H_2	*cis*:*trans*
Pt	1	82 :18
Pt	300	96 :4
Os	1	98.4:1.6
Ir	1	98.9:1.1

A size-selective synthesis of nanostructured transition metal clusters (Pd, Ni) has been reported[166], as has the preparation of colloidal palladium in organic solvents[167], the latter of which is an active and stable catalyst for selective hydrogenation. The use of microwaves in the preparation of palladium catalysts on alumina and silica resulted in hydrogenation catalysts with improved crystallite size and activity[168].

The selective reduction of the C=C bond in enones is generally favoured over the reduction of isolated double bonds using a variety of catalysts (e.g. Scheme 32)[169]. The incorporation of a lanthanide(III) additive can increase the selectivity of C=C reduction over C=O in some cases[170]. New methods have been reported for the full reduction of aromatic rings[171], and for methods of reduction to the cyclohexene product[172]. The heterogeneous hydrogenation of C_{60} to $C_{60}H_2$ has been reported[173], and, conversely, the preparation and use of a hydrogenation catalyst based on C_{60} [$C_{60}Pd_n$ ($n = 4.61–5.15$)] for the reduction of alkenes and alkynes has been described[174].

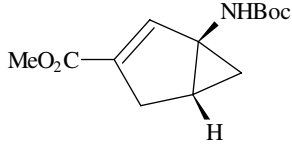


Reagents: (i) NH_4HCO_3, Pd/C, 25°C, 4h

SCHEME 32

2. Diastereoselective reductions

As was the case for homogeneous catalysts, certain reactive groups can mediate hydrogenation reactions through either a steric blocking effect or a co-ordinating, directing effect. Steric effects resulting in the blocking of a reaction on one face of an alkene are generally easy to identify and explain[158,175]. The selective reductions of **28** to **29**[176], of **30** to **31**[177] and of **32** to **33**[178] serve as typical examples. The latter example served as a key



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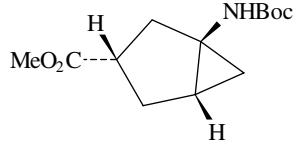

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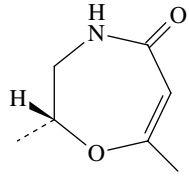

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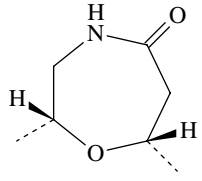

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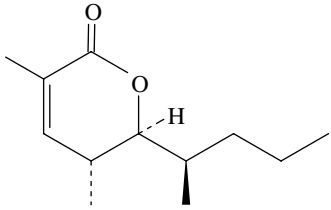

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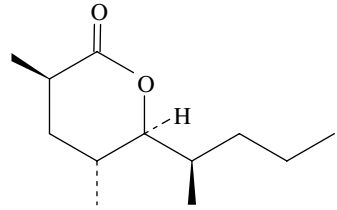
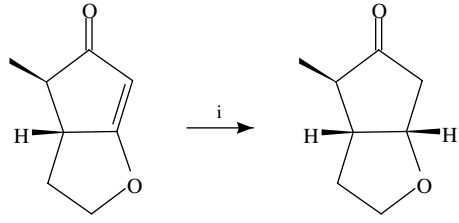


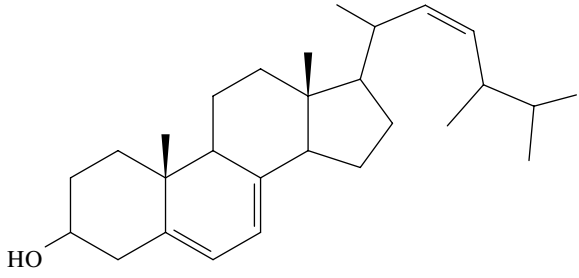
(33)

step in the synthesis of invictolide. Diastereoselective reductions of acylaminoacrylates attached to chiral auxiliaries have been employed as effective methods for the asymmetric synthesis of many amino acids[179]. A similar strategy has been employed for the asymmetric synthesis of 1,4-diesters and their derivatives[180]. The reduction of the C=C bond in enones is readily achieved using hetereogeneous catalysts (Scheme 33)[181], although this can on occasions be accompanied by the formation of acetals, assuming that an alcohol is employed as solvent[182]. Transfer hydrogenation methods may also be employed in heterogeneous hydrogenations, usually with the use of a formate salt to provide the hydrogen[183,184]. Dramatically different selectivities can be observed depending on which method is used; reduction of **34** with a copper or alumina catalyst and hydrogen gas in toluene solution gives **35** as the major product, whilst transfer hydrogenation conditions (cyclohexanol, 140 °C) furnish the diasteoisomeric product **36**[184].



Reagents: (i) 10% Pd/C, 60 psi H_2, THF, 60 h

SCHEME 33



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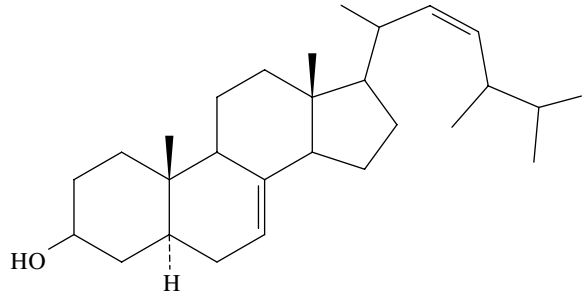

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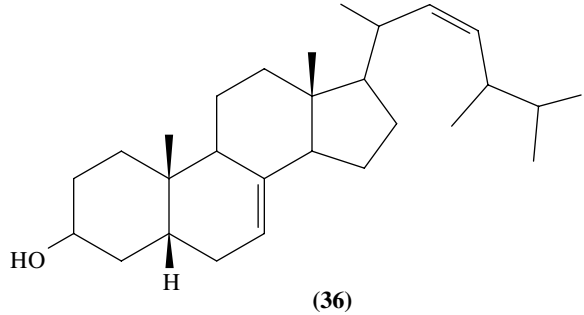
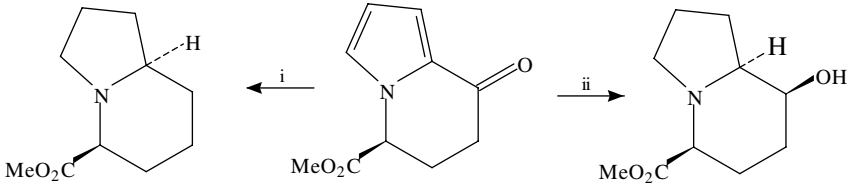


(36)

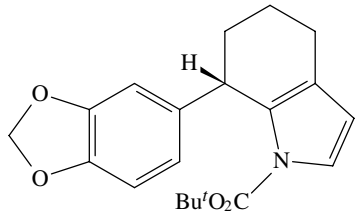
The reduction of heterocyclic compounds is a versatile process of great use in the synthesis of alkaloids[185]. The choice of catalyst is crucial however, as illustrated by the indolizidine alkaloid synthesis shown in Scheme 34[185a]. The reduction of **37** to **38** proceeds with a very high degree of stereocontrol which sets up the correct framework for intramolecular cyclization to complete a short synthesis of γ-lycorane **39**[186].



Regants. (i) H_2, Pd/C, H_2SO_4 or AcOH, (ii) Rh/Al_2O_3, H_2

SCHEME 34

The stereocontrol of reduction reactions by co-ordinating groups is far less prevalent than in the case of homogeneous catalysts, in which discrete molecular species are involved. There is evidence in some cases that this sort of effect might be operating through interactions of hydroxy and amino groups, although it is by no means a common phenomenon and is restricted only to certain metals. Examples are given in Schemes 35 and 36[187]. In the case of nickel an anchoring effect appears to be operating, whilst in other cases the functional group exerts only a steric effect. The reduction of citronellol using a



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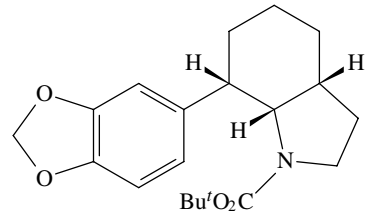

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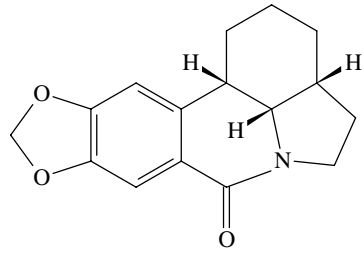

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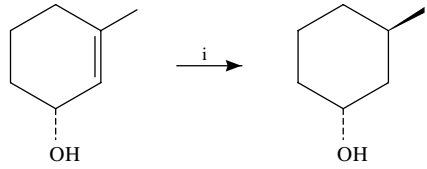
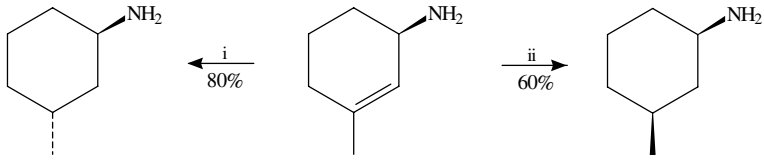


Reagents: (i) Ni catalyst, H_2

SCHEME 35



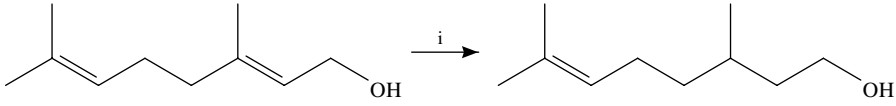
Reagents: (i) Ni or Pd, H_2, (ii) Pd/C, H_2

SCHEME 36

platinum/alumina catalyst modified with a carboxylic acid is selective for the double bond proximal to the alcohol, which is highly suggestive of a directing effect (Scheme 37)[188].

3. Enantioselective reductions

Unlike the reductions of C=O bonds, asymmetric methods of heterogeneous hydrogenation are relatively rare. In general, this area is difficult to study because of the difficulties



Reagents: (i) H_2, Pt/Al_2O_3 modified by RCO_2H

SCHEME 37

associated with the formation of a catalyst of a predictable and reproducible structure, which is an essential requirement. Enantiomeric excesses of 17% and 38% have been achieved through the use of a tartaric acid modified raney nickel[189] and a palladium black modified by (−)-dihydrovincolide alkoloid[190], respectively. Rather better results have been achieved in the reduction of *Z*-*α*-(acylamino)acrylates with a rhodium phosphine complex tethered to a zeolite support. In this example, where as little as 0.01 mol% catalyst is required, enantiomeric excesses of up to 97.9% have been achieved[191]. The large pore size of the zeolites selected for study is believed to be critical to the success of the catalyst.

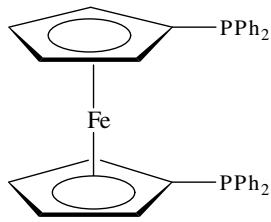
III. HYDROGENATION OF C=O BONDS

A. Homogeneous Methods

1. General comments

Unlike the heterogeneous variant, homogeneous hydrogenation of C=O bonds has not developed at the rate of the corresponding C=C reduction process. This is due mainly to the lack of early success in the use of the Wilkinson catalyst in this respect. In work that has been described elsewhere[192], the selection of the correct phosphine within a cationic complex was critical. Since these breakthroughs, progress in this area has been made at a tremendous pace, particularly in the area of asymmetric reductions, as will be described below.

New catalysts for the hydrogenation of C=O bonds continue to be reported. The ferrocene-based diphosphine **40**, in the form of a cationic rhodium complex [(COD)Rh(**40**)]OTf, is an excellent catalyst, promoting rapid hydrogenation, at the 0.2 mol% level, of ketones and aldehydes at room temperature at 60 psi hydrogen pressure[193]. New cationic ruthenium[194] catalysts containing bipyridyl ligands have also been reported, although even the neutral $[RuCl_2(PPh_3)_3]$ complex is an effective catalyst for C=O bond hydrogenation at the 0.1 mol% level, a result which demonstrates the improved compatibility of this metal compared to rhodium[195].



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Transfer hydrogenation of carbonyl groups is a popular method for reduction and may be mediated by a range of catalysts using an alcohol[196] or formic acid[197] as the hydride source. Microwaves have been shown to accelerate the reaction[197]. Iridium complexes have proved to be some of the most suitable for the reduction of enones to allylic alcohols[198]. Whilst several neutral complexes have been used, *o*-dimethylaminodiphenylphosphine appears to be a particularly suitable ligand which generates a very high degree of chemoselectivity in the reduction[198a].

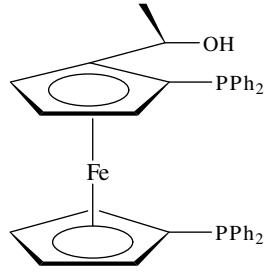
1,3,5-Triaza-7-phosphaadamantane **1**, which has been described in a previous section, imparts aqueous solubility on the hydrogenation complexes of ruthenium, of which it forms a part[199]. The complexes thus formed are highly selective for the reduction of the C=O bond of enones, as indeed are several cluster complexes of carboxyates with Co, Mo and Cu[200]. The use of sulphonic acid groups on phosphines can also impart aqueous solubility on transition metal complexes, however in one report the addition of such a ligand to an aldehyde, the reduction substrate, to give a stable salt, was observed[201]. This side reaction would of course be far less of a problem with non-polar C=C bonds.

Whilst the use of supercritical carbon dioxide as a solvent has recently been reported, it should be noted that it can also be a substrate; one ruthenium catalyst is reported to be capable of its conversion to formic acid at the rate of 1400 mol per mol of catalyst per hour[202].

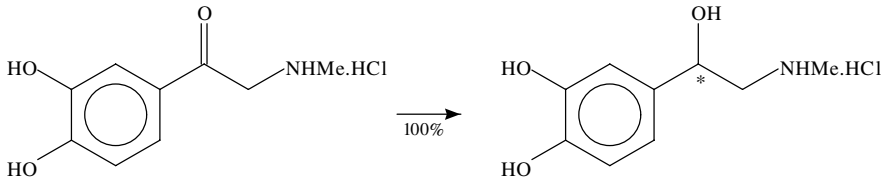
2. Diastereoselective and enantioselective reductions

There has been tremendous growth in this research area in recent years, and some remarkable breakthroughs have been achieved. This section of the review will focus on hydrogenation reactions using either hydrogen gas or transfer hydrogenation methods. Hydrosilylation will not be described in detail, although it should be noted that this process generates the same overall chemical transformation as hydrogenation.

As was the case for the reduction of C=C bonds, proximal co-ordinating groups were believed to be essential for the realization of high enantioselectivities, hence early investigations have concentrated on substituted substrates. α-Amino substituted ketones have proved to be ideal substrates for hydrogenation, early success being achieved with the use of the ligand **P28** (related to **P17** in Table 1)[203]. Scheme 38 summarizes the reduction of a typical substrate, which benefits not only from a high level of compatibility with the reaction conditions but also from the fact that it provides a means for the synthesis of a physiologically important class of target molecule. Rhodium complexes derived from other chiral phosphines, for example (*S*)-BPPM (**P7**), and related ligands, have also been employed to good effect in similar reductions[204]. One example is the reduction of **41** to

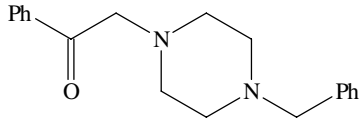


(P28) (*R*) (*S*)-BPPFOH



Reagents: (i) $[Rh(P28)(NBD)]ClO_4, H_2$ 95% e.e

SCHEME 38



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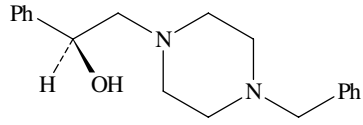

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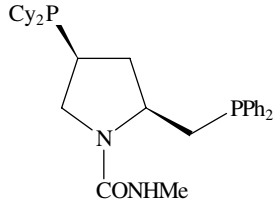

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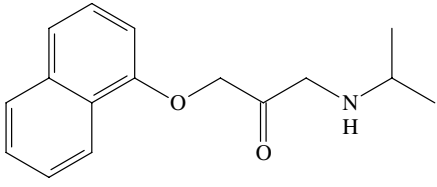

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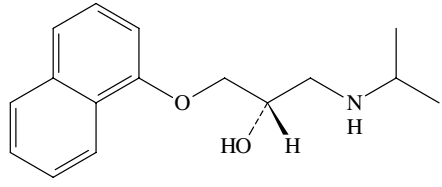

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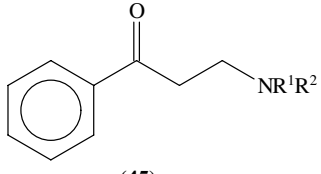

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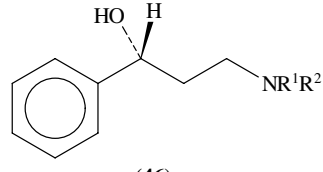
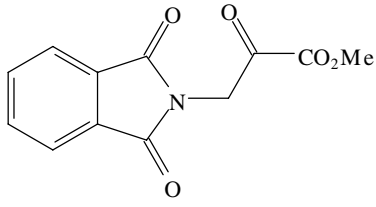


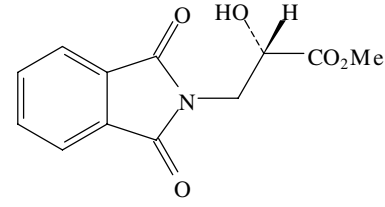
(46)

the amino alcohol **42** in *ca* 90% e.e. using a complex of **P29** with rhodium[204a]. Since the enantiomeric ligand is available, either product diastereisomer can be prepared. The same ligand has been used, in a complex with rhodium, to mediate the reduction of **43** to (*S*)-propronolol **44**, in this case in 90.8% e.e.[204b] and in the reduction of the β-amino ketone **45** to R-fluoxetine **46** in 91% e.e.[204c].

Notwithstanding the excellent results described above, the ligand/metal combination which has without a doubt made the biggest impression on this area is that of ruthenium and BINAP[205–207]. This combination will feature throughout the rest of this section of the review. As was the case for C=C reductions, either neutral (e.g. [Ru(BINAP)(OAc)$_2$]) or cationic complexes (e.g. [Ru(BINAP)Cl(arene)]X)[205] may be employed in asymmetric carbonyl reductions. Complexes may also be formed *in situ* by a ligand exchange between a complex such as [RuCl$_2$(benzene)$_2$] and BINAP[206], thus avoiding the need to prepare a sensitive organometallic complex prior to the reaction. Very high enantioselectivities are achieved using Ru/BINAP combinations for the reductions of unprotected α-amino ketones[205] although protection of the amino group electron-withdrawing functions can make the substrate less compatible; reduction of **47** to **48** using the cationic Ru/BINAP combination gave a product of only 81% e.e.[207]. Following the reaction the phthalimide group was removed to give a primary amine. In one of a number of related reports the use of a rhodium complex of a biaryl diphosphine ligand, closely related to BINAP, was shown to be capable of the reduction of the hydrochloride salt of α-amino acetophenone in 93% e.e.[133c].

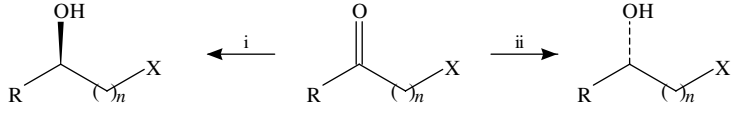


(47)



(48)

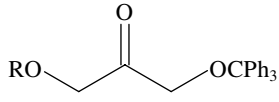
Several other classes of substituted ketones are suitable for reduction by Ru/BINAP complexes[208]. Scheme 39 and Table 4 summarize the range which is applicable. The sense of induction follows simply from the position of the available co-ordinating group in the substrate. In general, high ratios of substrate to catalyst may be employed and the enantiomeric inductions are consistently high. Diketones are reduced in correspondingly high e.e.s[208]. Several examples have been reported of the reductions of α,α'-dihydroxy ketones. A steric difference between the groups on the oxygen atoms is sufficient to produce an enantiodifferentiation in the reduction of **49** to give **50** in up to 96% e.e.[209]. The



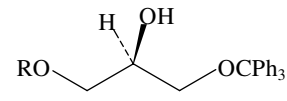
X = NR_2, CO_2R, Br, OH, etc., $n = 2$,

Reagents: (i) [Ru(R-BINAP)OAc)$_2$], H_2, (ii) [Ru(R-BINAP)(OAc)$_2$], H_2

SCHEME 39

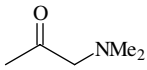
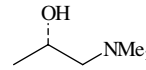
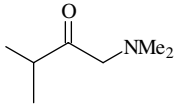
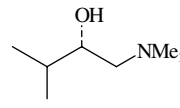
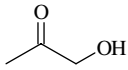
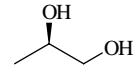
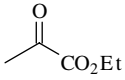
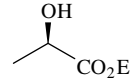
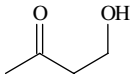
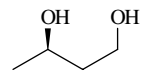
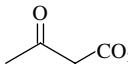
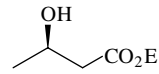
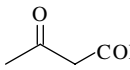
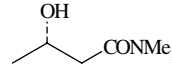
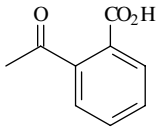
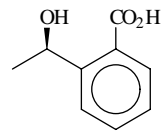
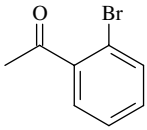
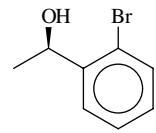
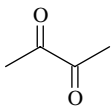
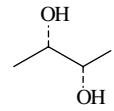
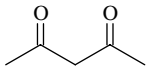
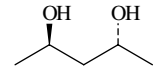


(49)



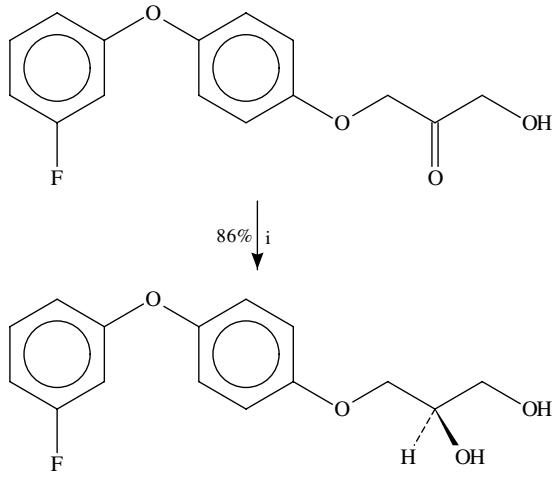
(50)

TABLE 4. Reductions of ketones of ruthenium/BINAP catalysts

Substrate	*R*/*S*-BINAP	Product	S/C	Yield (%)	e.e (%)
	*S*		780	72	96
	*S*		390	83	95
	*R*		230	100	92
	*R*		780	97	83
	*R*		900	100	98
	*R*		1260	100	>99
	*S*		680	100	96
	*R*		220	100	92
	*R*		1100	97	92
	*S*		680	100	100
	*R*		2000	100	100

presence of a trityl group as one of the protecting groups is essential for high inductions, however in the case where one hydroxyl is unprotected, the scope for substitution at the other position is rather broader (Scheme 40)[210].

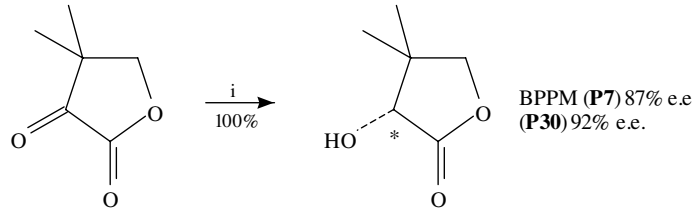
α-Keto esters and amides are excellent hydrogenation substrates. As early as 1978 the phosphine BPPM (**P7**) was used in a complex with rhodium for the reductions of ketopantolactone (Scheme 41) in high e.e. (87%)[211]. The same complex was used



95% e.e

Reagents: (i) $[Ru_2Cl_4(S\text{-}BINAP)(NEt_3)].H_2$, MeOH

SCHEME 40

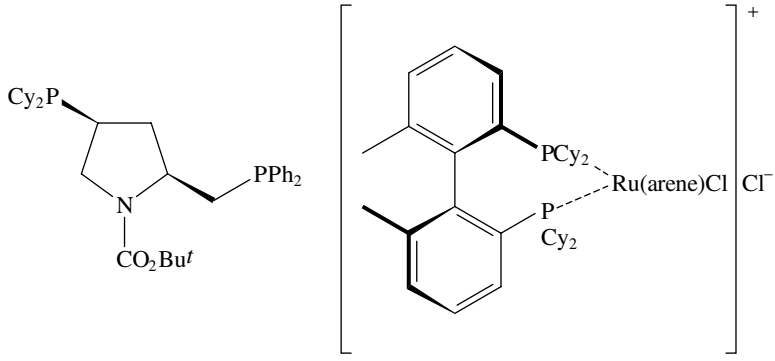


Reagents: (i) [Rh(BPPM-**P7**)] or [Rh(**P30**)], H_2, 30 °C, 48 h, benzene

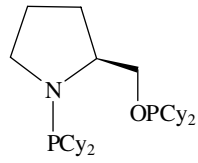
SCHEME 41

earlier for the reductions of α-keto esters[212]. A large number of ligands have since been screened, although perhaps the most interesting observation is the superiority in many cases of dialkylphosphine ligands over diphenylphosphines, which are otherwise commonly used[213,192]. An example is the use of BCPM, **P30**, a derivative of BPPM, in the reduction shown in Scheme 41, the e.e. of which is increased slightly, to 92%[214]. Using BICHEP (**P23**) and derivatives as ligands, cationic ruthenium complexes proved to be somewhat superior to the rhodium complexes[215,101a]. Again, however, the best ligands proved to be those containing fully hydrogenated rings on the phosphorus atom, such as **P31** (Scheme 42).

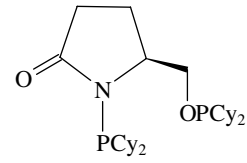
A series of reports have appeared describing the use of phosphines derived from amino acids and amides in combination with rhodium or ruthenium. Again, the best ligands proved to be those containing hydrogenated rings on the phosphines, for example **P32**[216] and **P33**[217]. Of these ligands, the latter appear to give slightly better results — up to 98.7% e.e. for the ketopantolactone reduction shown in Scheme 41 and 87% e.e. for reductions of α-keto amides. Silica-supported variants have also been reported[216d].



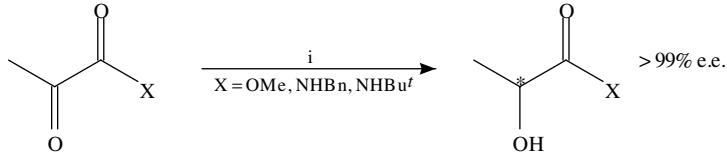
(P30)-BCPM **(P31)**



(P32)



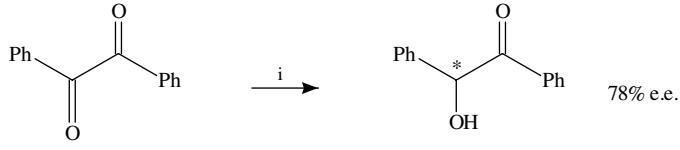
(P33)



Reagents: (i) **P31**, 5 atm H_2

SCHEME 42

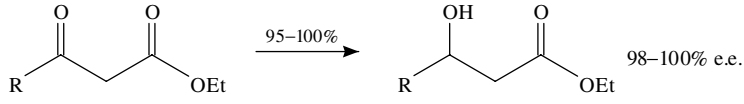
An interesting example of 1,2-diketone reduction using methods other than metal/phosphine catalysts is the use of a cobalt complex, in combination with quinine, for the reduction of benzil[218]. In this example the product was formed in 78% e.e. (Scheme 43).



Reagents: (i) $Co(dimethylglyoxime)_2$, quinine, benzylamine, –10° C

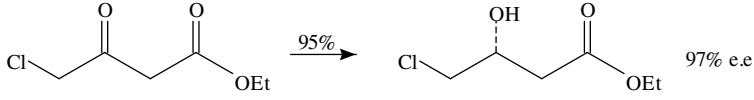
SCHEME 43

Ruthenium complexes of chiral diphosphines have proved to be some of the best reagents for the reduction of β-keto esters (Scheme 44). Both neutral and cationic complexes may be used. The sense of the asymmetric induction follows that obtained in the reduction of other substituted ketones assuming co-ordination of the metal by both ketone and ester groups. Since the initial reports of this and related reactions in 1987/8[208] the area has grown at a dramatic rate and reductions of this type are now widely used[219,126a]. Improved methods have been reported for the preparation and use of catalysts by the same team that first reported this methodology[205,220], and others[221]. Many important target molecules have been prepared using this as a key step, including building blocks for Vitamin D3[219d] and related HMG-CoA reductase inhibitors[219e]. The synthesis of carnitine, the carrier of acyl groups in fatty acid metabolism, provides an excellent example (Scheme 45)[208c]. In this reaction it was found that the use of high temperature (100 °C) for a short reaction time (5 minutes!) gave a superior result to the use of lower temperatures and longer reaction times. Only 0.05 mol% of the catalyst was employed in this reaction.



Reagents: (i) [Ru/BINAP(P5)], H_2, 100 atm

SCHEME 44

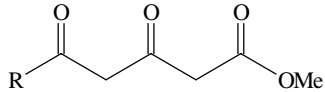


Reagents: (i) 0.05 mol % [Ru (S-BINAP (P5) $(OAc)_2$], 0 atm H_2, 100 °C, 5 min

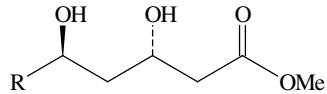
SCHEME 45

Some interesting experimental observations have been made. For example, the addition of 0.5 mol% triethylamine stops the hydrogenation (using 0.02–0.05% catalyst) and the addition of 1% HCl restarts the process[221c]. The use of hydrogen pressures of around 50 psi in a Parr shaker apparatus appears to be a satisfactory experimentally suitable procedure for most applications[221a–c]. Ruthenium allyl complexes containing BINAP have been reported to be suitable for atmospheric pressure reductions[221e].

The reductions of β,δ-diketoesters **51** with ruthenium/BINAP catalysts result in formation of the *trans*-diols **52** in high selectivity and e.e. Experiments have revealed that it is likely that the reduction takes place via the coordination of both ketones to the metal — the selectivity matches that obtained in the reduction of β-diketones[222]. Biaryl diphosphines closely related in structure to BINAP have also given excellent results[223]. Other excellent



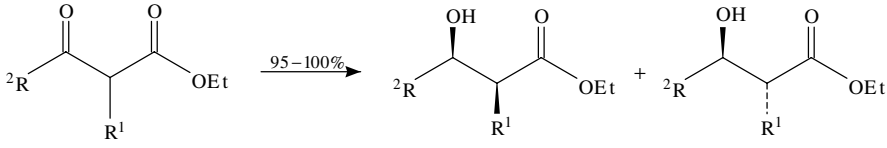
(51)



(52)

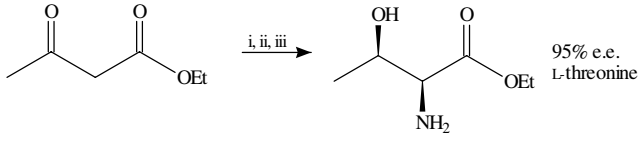
diphosphines which have recently been applied to this process include Josiphos (**P11**)[89a] and the doubly C2 symmetric ligand **P14** (BPE)[224]. In the latter case, using the isopropyl substituted derivative with ruthenium(II), a large number of reductions were achieved in over 98% e.e. and in some cases up to 99.4% e.e.[224].

An exciting variation on the β-diketone reduction process is the dynamic kinetic resolution of α-substituted substrates (Scheme 46). Since the racemization rate considerably outpaces that of the reduction, the result is the formation of one predominant product out of four possible products. Cyclic or acyclic substrates may be employed. In the acyclic case the *syn* product predominates. This reaction has been studied in some depth by Noyori and coworkers[225], who have also published a detailed mathematical treatment of the results[226]. Although BINAP is by far the most widely used ligand for this process, excellent results have also been obtained using BPE ligand **P14**[224] and modified, partially hydrogenated BINAP derivatives[227]. Applications of this type of methodology are extensive, being an excellent method of introducing two new valuable chiral centres in one step. α-Amino-β-keto esters can be reduced selectively to the α-amino-β-hydroxy ester products with high selectivity[225b,228], and a simple procedure has been developed for the synthesis of L-or D-threonine from 3-oxo-butyrate esters (Scheme 47)[228]. Reductions of α-chloro-β-keto esters[229] and α-aminomethyl-β-keto esters[230] with similar high selectivity have also been reported. The latter reduction leads to the formation of β-lactam precursors



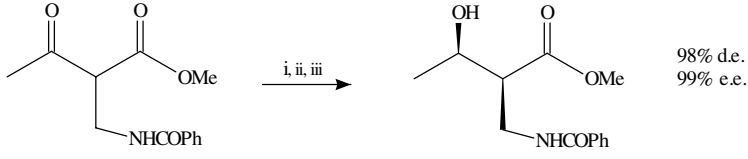
Reagents: (i) [Ru/S-BINAP (**P5**)], H_2, 100 atm

SCHEME 46



Reagents: (i) HNO_2, Pd/C, H_2, (ii) [Ru((+)-BINAP (**P5**), X_2], H_2, (iii) hydrolysis

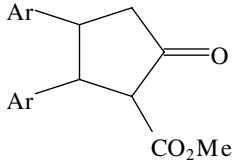
SCHEME 47



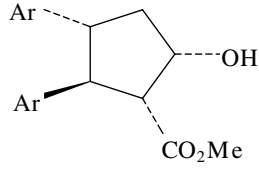
Reagents: (i) 0.1mol % [Ru(BINAP **P 5**] (arene)X]X, CH_2Cl_2, MeOH

SCHEME 48

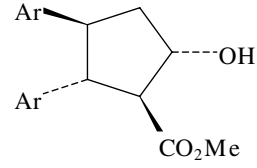
in up to 98% d.e. and 99% e.e. (Scheme 48). Highly active allylically substituted ruthenium complexes of BINAP have been used in this process to good effect[231]. In the reduction of racemic *trans*-**53**, each enantiomer was reduced to a different major diatereoisomer, **54** and **55** respectively, thereby allowing a method for the separation of the products[232]. Asymmetric dynamic hydrogenations of α-amino and α-bromo-β-keto phosphates have also been reported, the selectivities of which are at least as good as the carboxylic ester analogues[233].



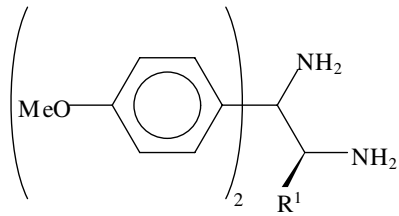
trans-(**53**)



trans-(**54**)

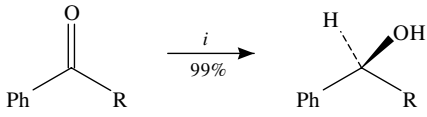


trans-(**55**)



(56) R^1 = Me, Pr^i, Bu^i

Asymmetric hydrogenations of simple ketones lack a suitable proximal co-ordinating group, however some dramatic recent developments have had a major impact on the field. Most significantly, Noyori has reported that the combination of a ruthenium complex with a suitable chiral diamine such as **56** results in formation of a complex which is capable of the reduction of simple ketones in e.e.s of up to 95% (Scheme 49)[234]. Remarkably, β-keto esters are inert under these conditions. The asymmetric reduction of deuterated aldehydes with chiral ruthenium/BINAP complexes has also been reported (up to 89% e.e.)[235]. The combination of iridium(I) with BINAP, together with the *addition* of an essential monophosphine such as **57**, also results in the formation of an excellent carbonyl reduction catalyst[236]. Aromatic/aliphatic ketones may be reduced in e.e.s of up to 84%[236a] using this combination, and cyclic ketones in up to 95% e.e. (Scheme 50)[236b]. The use of both phosphines is essential for the induction of high e.e.s, and it has been speculated that the monophosphine modifies the catalyst in a subtle manner by filling an otherwise vacant

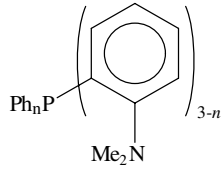


R	e.e.	R1 in 56
Me	87 (R)	Bu^i
Bu^n	90 (R)	Me
Pr^i	95 (R)	Pr^i

Reagents; (i) [Ru(S-BINAP)(**P5**)(56)], H_2, KOH

SCHEME 49

coordination site. Iridium hydrogenation complexes are notably selective for the reduction



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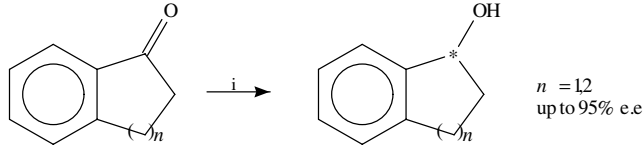
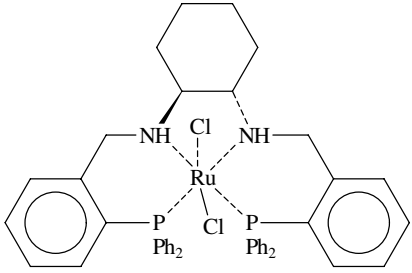


Reagents: (i) [Ir(BINAP)(COD)]BF_4, **E61**, 50 atm H_2, THF/MeOH

SCHEME 50

of the carbonyl groups of enones. Reports have appeared on the application of the above approach[236c] and a closely related system[237], to the synthesis of allylic alcohols, however the e.e.s do not yet match those of other ketones.

Another recent development which has implications for the asymmetric reductions of simple ketones is asymmetric transfer hydrogenation[238–240]. Some very recent studies have led to the development of several practical systems for achieving highly selective reductions in this manner, which benefit from the lack of a need for high-pressure hydrogenation equipment. Two examples serve to illustrate this exciting new area. In the first (Scheme 51) the ruthenium catalyst **58** is employed[239], and in the second (Scheme 52), use is made of the monoprotected diamine **59**, again in combination with a ruthenium(II) source[238]. The latter example is reported to work simply by mixing the reagents in an open vessel and in both cases the hydrogen is supplied by an alcohol, 2-hydroxypropane. Both reports have come from the Noyori group. The use of a samarium complex with a chiral, C2 symmetric amino diol in a related type of transformation has been reported to give excellent enantioselectivities in the reduction of aromatic ketones[240e].



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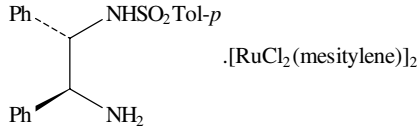
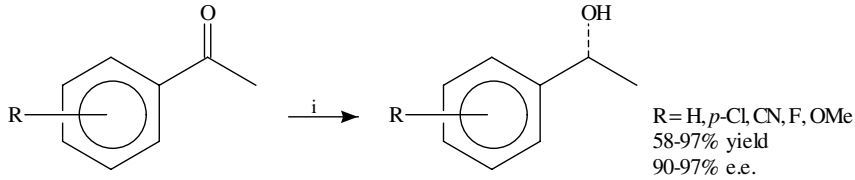
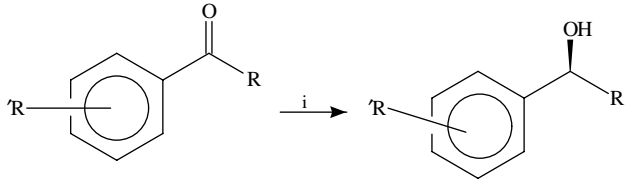


(59)(SS)-TSDPEN



Reagents: (i) **58**, Pr^i-OH, Pr^iOK

SCHEME 51

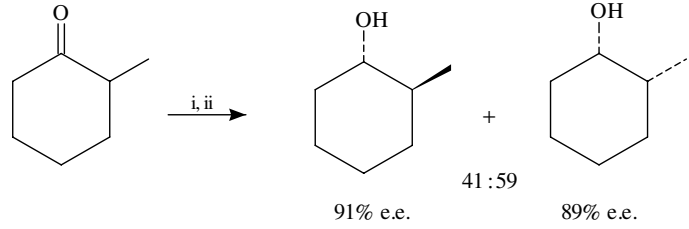


R	R′	e.e
Me	H	97%
Et	H	97%
Me	o-Me	53%
Me	p-Cl	95%
Me	p-OMe	53%

Reagents: (i) **59**, KOH, Pr^iOH

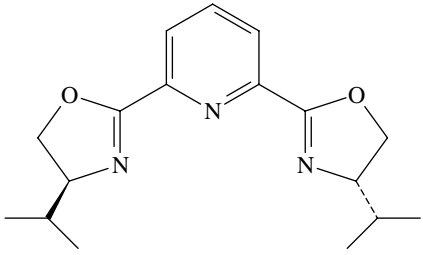
SCHEME 52

Hydrosilylation of C=O achieves the same objective as hydrogenation, following workup by treatment with aqueous acid. Some very interesting new methods have been reported in recent years. Oxazoline ligands in combination with rhodium(I)[241] have given some excellent results, and in particular the 'pybox' ligand **60** has been used to good effect. Using this ligand e.e.s of up to 76% have been achieved in the reduction of simple ketones[241a] and e.e.s of *ca* 90% for reduction of cyclic ketones (Scheme 53)[241b]. Titanium-centred C2 symmetric bis cyclo-pentadienyl catalysts have also given some excellent results in reductions of simple ketones, although they may lack the versatility and substrate scope of other methods[242]. Some excellent e.e.s have been obtained using phosphonites derived from 'TADDOL' diols as ligands in asymmetric hydrosilylation[243]. Asymmetric hydrosilylations of symmetrical diols have been achieved with very high e.e.s and diastereoselectivity using a combination of the diphosphine RR-SS-EtTRAP (**P34**) with rhodium(I)[244].

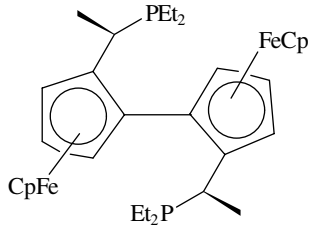


Reagents: (i) 1% [**60**.$RuCl_3$], 2% $AgBF_4$, Ph_2SiH_2, 0 °C (ii) H^+/H_2O

SCHEME 53



(60)



(P34)

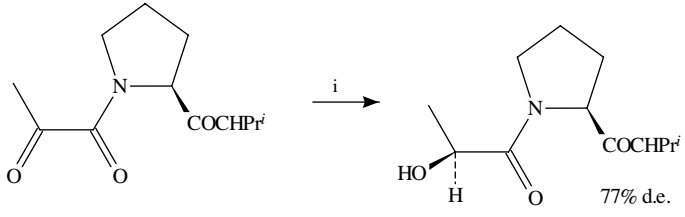
B. Heterogeneous Methods

1. General comments

Heterogeneous hydrogenations of C=O bonds have been described in detail in other places[192,245] and will not be covered in detail here. Many of the same comments as were made for the C=C reduction also apply here. Most common hydrogenation metals may be employed (Ni, Ru, Rh, Ir, Pt etc.) and the scope of the process is very broad. In the case of enones, a careful choice of catalyst must be made so that C=C reduction does not compete.

2. Diastereoselective reductions

As was the case with heterogeneous reduction of C=C bonds, the sense of diastereoselective reduction of C=O bonds is often very difficult to predict. A number of methods have been reported in which carbonyl groups attached to chiral auxiliary groups have been reduced by heterogeneous catalysts, however few give high d.e.s (Scheme 54)[245]. This is again mainly due to the lack of order and poor definition of the catalyst surface. The effects of small changes to the exact nature of the catalyst, to the solvent etc., can all have a dramatic effect on the sense and level of selectivity. Most of the dramatic and valuable developments in heterogeneous hydrogenation have been in the area of direct asymmetric hydrogenation using a chiral catalyst, and will be described in the next section.



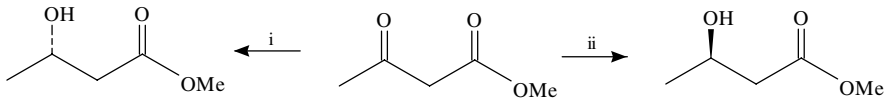
Reagents: (i) H_2, Pd/C

SCHEME 54

3. Enantioselective reductions

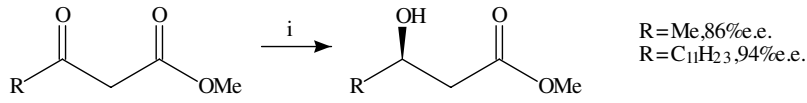
Two major areas of research have emerged from studies into asymmetric hydrogenations of carbonyl groups using modified heterogeneous catalysts. The first involves the

reductions of β-keto esters, a process for which Raney nickel modified by the incorporation of tartaric acid has emerged as the leading method[192,246]. The modified catalysts appear to be capable of giving reproducible sets of results for a range of substrates (Scheme 55). Although various metals have been examined, few are as successful as the Raney nickel reagent. In some cases, additives such as sodium salts and carboxylic acids may be incorporated into the catalysts and may result in higher e.e.s in some cases. The mechanism and kinetics of this reduction have been studied in considerable detail, and several recent reports have been published[247]. The process has been refined to a high degree and, using ultrasonicated Raney nickel and sodium chloride together with tartaric acid, leads to a catalyst which is capable of generating e.e.s of up to 94% (Scheme 56)[248]. Diastereoselective and enantioselective reductions using this class of catalyst are less satisfactory[249] Modified catalysts containing nickel supported on alumina also give inferior results[250], β-Diketones may be employed in this reaction to good effect, in which case reduction of both ketones is observed to give the *anti* product[248,251]. Using the ultrasonicated Raney nickel as described above some very highly selective reductions may be achieved (Scheme 57)[251a]. Asymmetric reduction of isolated ketones are less selective, although enantiomeric excesses of up to 80% have been reported[247c]. In one case the addition of pivalic acid was reported to improve the enantiomeric excess[252].



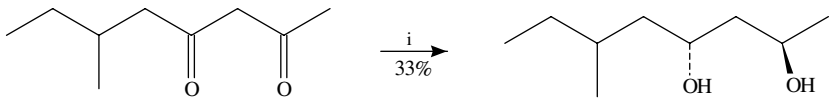
Reagents: (i) (SS)-Tartaric acid modified RaNi, H_2, (ii) (RR)-Tartaric acid modified RaNi, H_2

SCHEME 55



Reagents: (i)(RR)-Tartaric acid modified RaNi, NaBr, ultrasound, H_2

SCHEME 56

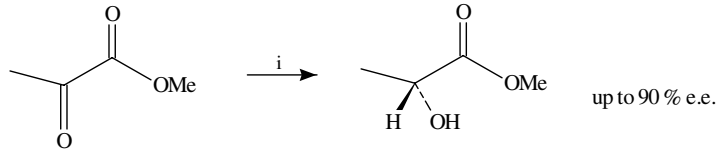


Reagents: (i) (RR)-Tartaric acid modified RaNi, NaBr, ultrasound, 100 atm H_2

SCHEME 57

The second, large area of research concerning asymmetric heterogeneous catalysis is the reductions of α-ketoesters such as methyl lactate. In contrast to the β-ketoester reductions, modified Raney Nickel catalysts, although effective, have proved not to be the best systems[253]. In contrast, the modification of platinum, on an inorganic support such as silica, with amino alcohols, have emerged as the most promising reagents. Of the many chiral groups examined, the alkaloid cinchonidine has given some of the best results, and

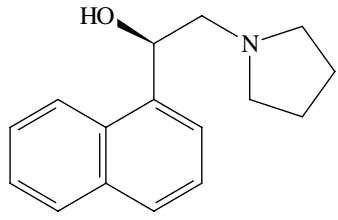
has therefore been the subject of intensive studies by a number of research groups[254]. One research group has found that the use of platinun on the silica-based support EUROPT-1 in combination with cinchonidine gives e.e.s of around 80% (Scheme 58)[255]. Other groups have achieved similar results with closely related systems[256]. Using this system, extremely low levels of chiral modifier and catalyst are required, which makes it a highly efficient and valuable process. The enantioselectivity of the reaction is extremely sensitive to changes in hydrogen pressure, temperature, method of catalyst preparation etc., and detailed studies have been published[255,256]. One report has described the reversal in enantioselectivity upon variation in the concentration of modifier employed[257]. A template model was forwarded in the early stages of development of this work[258]. However, further studies, which in particular suggest that high e.e.s are generated without the need for complex methods for catalyst preparation, suggest that the true mechanism is somewhat more complicated.



Reagents: (i) 6.3 %Pt/silica (EUROPT-1), cinchonidine, r.t., 10 bar H_2

SCHEME 58

In contrast to cinchonidine, the alkaloids codeine, dihydrocodeine, brucine and strychnine have been shown to give inferior results[259]. Simple amino acids such as **61** have been prepared and employed in this process[260]. However, although impressive catalytic effects were observed (using 0.3 mol% Pt catalyst and a ratio of modifier:reactant of 1:30,000 and 1 bar hydrogen pressure) even the best of these gave inferior asymmetric inductions to the cinchonidine example (best was around 75% e.e). In one report[260c] the simple amine 1-(1-naphthyl)ethylamine was reported to give e.e.s of up to 82%, however subsequent studies revealed that the true catalyst was the product of an *in situ* reductive amination of this amine with the ketoester substrate. Supported heterogeneous catalysts have been prepared using cinchona alkaloids tethered to crosslinked polystrenes and these have given results comparable with the original catalysts[261]. The use of iridium catalysts modified by cinchona alkaloids has been reported, but these are again less effective than the platinum analogues[262]. The reduction of α-diketones using this methodology has been reported, but the e.e.s, at around 33–38%, are lower than the ketoester reduction products[263].



(61)

IV. HYDROGENATION OF C=N BONDS

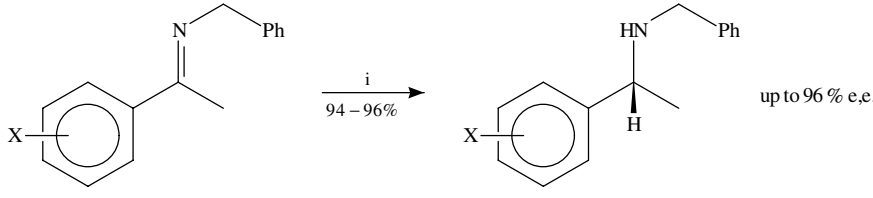
A. Homogeneous Methods

1. General comments

Many of the comments related to C=O reduction in this section also apply to the homogeneous reductions of C=N bonds, a process for which heterogeneous methods predominate[192]. This section will therefore concentrate on recent developments and, in particular, on asymmetric transformations. Transfer hydrogenations of C=N bonds by homogeneous catalysts have been reported[264].

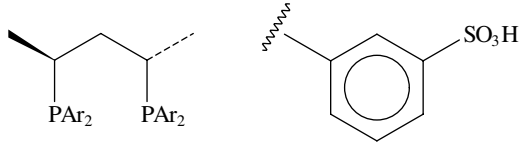
2. Diastereoselective and enantioselective reductions

Asymmetric hydrogenation of C=N bonds has proved more challenging than most other reductions. As in the case of carbonyl reduction, however, some excellent recent results in this area have been achieved. Using simple imines as substrates, some good asymmetric inductions have been achieved using rhodium[265] and ruthenium[266] catalysts. Of particular note is the use of the partially sulphonated ligands **P35**, as mediators in complexes with rhodium for asymmetric hydrogenations in aqueous solvents (Scheme 59). In the example shown mixtures of sulphonated ligands were used; a sulphonation extent of 1.41 corresponds to a mixture of 59% mono- and 41% di-substituted, for example. Enantiomeric excesses of up to 96% have been recorded in the products of reductions using this ligand system[265]. The degree of sulphonation, however, is essential, the best results being achieved with monosulphonated ligands. Good enantiomeric excesses can be achieved by matching the directing effect of a chiral group on the nitrogen atom with that of the ligand[267]. This latter method has actually been employed in a kinetic resolution of racemic amines via a reductive alkylation process.



Reagents (i) 1.41–1.65 eq. SO_3H sulfonated **P35**. $[Rh(COD)Cl_2]$, 70 bar H_2, H_2O. AcOEt

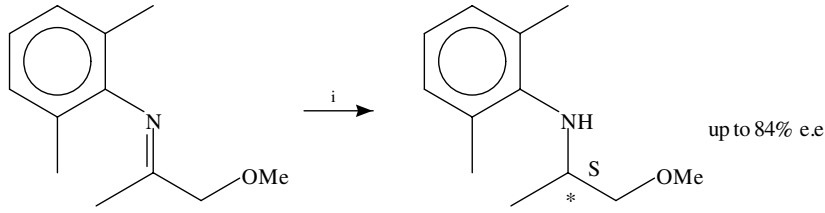
SCHEME 59



(P35) Ar = Ph or 1-4 sulphonated ligands

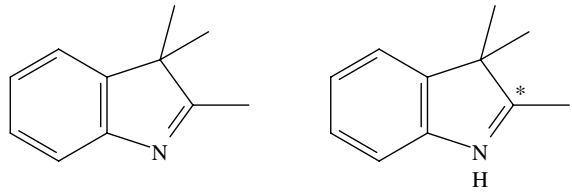
Iridium complexes appear to be more suited to the control of asymmetric reductions of simple imines than those of rhodium or ruthenium[268,269]. The use of ligand BDPP (**P12**)

in cationic complexes has emerged as one of the best combinations and has given some excellent results. As well as the example shown in Scheme 60, a large number of other substrates have been tested, including the cyclic imine **62** which is reduced to **63** in up to 80% e.e. using this catalyst. In a recent report a complex of iridium with BCPM (**P7**) ligand has been reported to give an e.e. of 91% with substrate **62**[270]. In the latter example the use of the additive bismuth triiodide appeared to be necessary for optimal results.



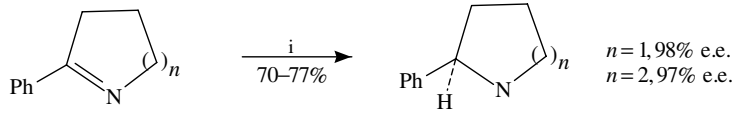
Reagents: (i) [Ir(COD)(2S,4S)-BDPP (**P12**)]BF_4, 40-55 bar H_2, r.t.

SCHEME 60



(62) **(63)**

Notwithstanding the promising results described above, perhaps one outstanding class of reagent which has made a dramatic impression on the area of simple imine reductions in recent years is that derived from chiral titanocene complexes[271,273]. The C2 symmetric complex **22**, which has already been described, may be activated using two equivalents of *n*-butyllithium and a slightly greater excess of a silane to give an active complex capable of directing imine hydrogenation with very high enantioselectivities (Scheme 61). Cyclic imines give some of the best results (e.e.s up to 99%) although acyclic imines also work well in this application. A model has been proposed to explain the sense and extent of the asymmetric induction (Figure 7). The model requires a well-defined stereochemistry between the imine substitutents, which may explain why acyclic substrates containing rapidly-interconverting isomers are less effectively reduced. The same problem is almost certainly responsible for the difficulties associated with the asymmetric reductions of oximes, for which the effect of the configuration has been studied[272].



Reagents: (i) Titanocene cat. **22** activated by $Bu^nLi + PhSiH_3$, 2000 psi H_2

SCHEME 61

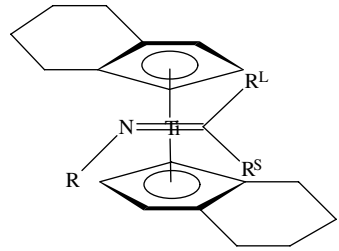
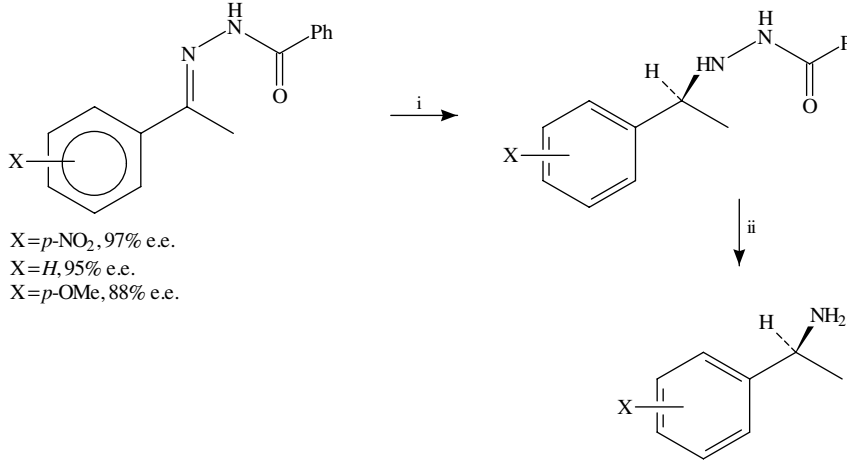


FIGURE 7

Appropriate functionalization of C=N bonds can greatly assist their asymmetic reduction. In particular, the reduction of N-acyl hydrazones with a rhodium complex of the ligand DuPHOS (**P13**) represents an outstanding example. In this process (Scheme 62) a product of up to 97% e.e. is obtained in high yield. After the reduction, samarium–iodide cleavage of the N–N bond gives the product amine[273,274].

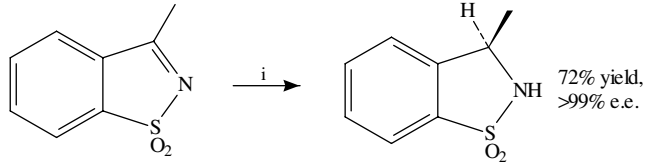


X=*p*-NO_2, 97% e.e.
X=*H*, 95% e.e.
X=*p*-OMe, 88% e.e.

Reagents: (i) 0.02 mol% [Rh(EtDuPHOS, **P13**)]OTf, 12 h, r.t., *i*-PrOH, 60 psi H_2, (ii) SmI_2

SCHEME 62

A remarkable high enantioselectivity was observed in the asymmetric hydrogenation of a cyclic sultam precursor using ruthenium/BINAP (Scheme 63)[275]. The factors which control this reaction are not fully understood, and it appears to be uniquely suited to



Reagents: (i) Ru_2Cl_4 [(R-BINAP)$_2$]Et_3N, 4 atm H_2, CH_2Cl_2, MeOH

SCHEME 63

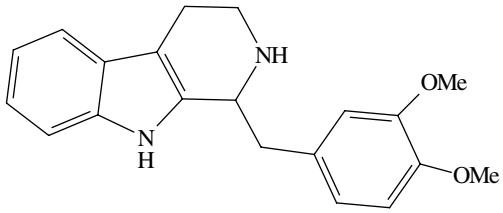
this class of reduction. Transfer hydrogenation of imines using a complex related to **59** (employed for carbonyl reduction) has very recently been reported to give excellent results when applied to the reduction of imines. Cyclic imines are especially good substrates which give, upon reduction, amines with enantiomeric excesses of up to 97%, depending on the exact catalyst used[238b].

B. Heterogeneous Methods

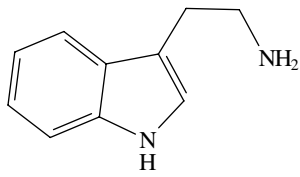
1. General comments

Heterogeneous hydrogenation of the C=N bond is a very widely used synthetic process with application to small and large-scale reactions. Many of the catalysts described in other sections may also be employed, for example those based on supported rhodium, palladium etc, and Raney Nickel. This area has been reviewed extensively recently[192]. Hydrogenation of oximes and hydrazones results in formation of amines. Milder conditions can be used for oxime reduction if the ethylaminocarbonyl derivative is prepared *in situ* prior to reduction[276].

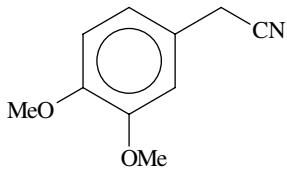
One of the most valuable and widely used applications of C=N bond hydrogenation is in the field of reductive alkylation, in which an aldehyde or ketone is condensed with an amine and reduced *in situ* with an appropriate catalyst to give a substituted product. This very valuable reaction has most notably been employed for the racemic synthesis of amino acids from α-ketoesters and acids. This type of reduction can be very powerful, as illustrated by the synthesis of tetrahydro-b-carbolines **64** (76% yield) by the reductive coupling of **65** and **66** under conditions of 1 atm of hydrogen and palladium on carbon catalyst[277].



(64)



(65)



(66)

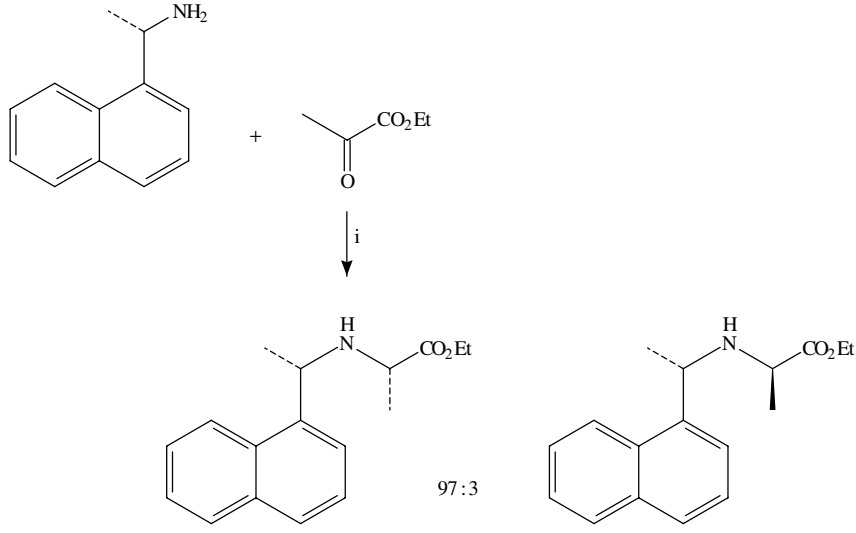
This section will deal with some recent developments in this area and concentrate mostly on stereoselective transformations.

2. Diastereoselective and enantioselective reductions

Many stereoselective reductions of C=N bonds have been reported, and in the case where the original chiral group is removable (i.e. a chiral auxiliary) this method may be

employed for the asymmetric synthesis of amines. The area has been quite extensively reviewed recently[278] and will be described only briefly here.

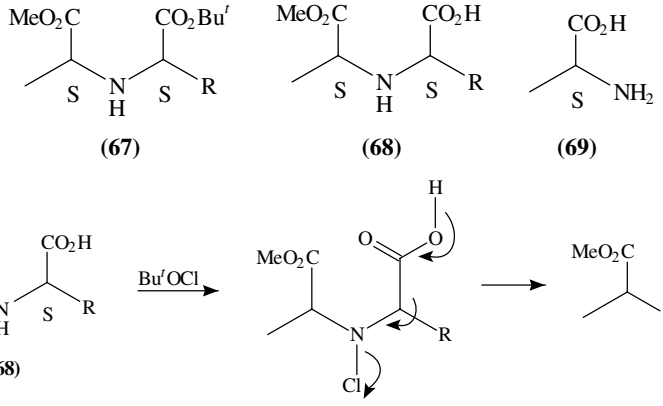
The formation and reduction of Schiff's bases by heterogeneous catalysts has been extensively used as the favoured method of approaching reductions of this type, for practical reasons. The condensation of α-keto acids with simple chiral benzylic amines provides an attractive approach to amino acid synthesis because the auxiliary group can be removed by further hydrogenation after the reduction. However, the e.e.s achieved using this method are rather low, with some notable exceptions[278,279]. The use of amines with extended π-systems gives the best results. In a recent report of the use of Pt-alumina modified by 1-(1-naphthyl)ethylamine for the reduction of ethyl pyruvate, a reductive alkylation of the amine occurred *in situ* with a selectivity of 97:3, one of the highest levels reported (Scheme 64)[260c]. This procedure led to a process for the synthesis of amino acids in >95% e.e. after hydrogenation of the chiral directing group. Efforts have been made to correlate the sense of induction with the conformation of the substrate and its interactions with the catalyst surface. However, as has been described in previous sections, the uncertainty of the structure of heterogeneous catalyst surfaces limits the reliability of this. The nature of the solvent and other reaction parameters has also been shown to have a dramatic effect on the selectivity of these reactions. Chiral benzylamines have recently been applied to the enantio- and diastereoselective reductions of imines derived from cyclic ketones[280].



Reagents: (i) Pt, Al_2O_3, AcOH, 25 °C, 25 bar H_2

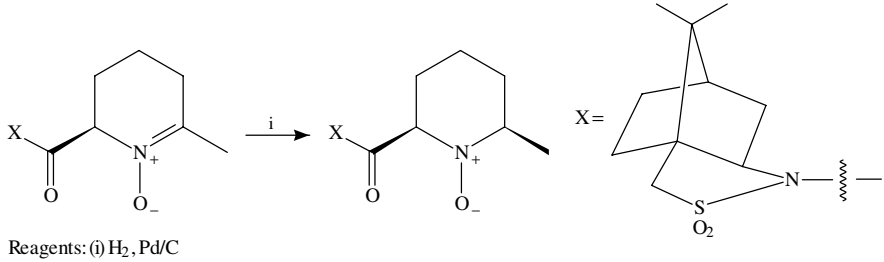
SCHEME 64

The reductive alkylation of methyl pyruvate with and the *t*-butyl esters of amino acids using Pd/C catalyst leads to the formation of iminodicarboxylic acids such as **67** in selectivities of 29–75% d.e. depending on the amino acid and solvent used (hexane gave the best results). Hydrolysis of the *t*-butyl ester to the acid **68** followed by hypochlorite-promoted decarboxylation and imine hydrolysis leads to the formation of (*S*)-alanine **69** in correspondingly high e.e.s[278,281]. The likely decarboxylation mechanism as far as the imine stage is shown in Scheme 65.



SCHEME 65

Although there is evidence to suggest that a chelation mechanism operates in the reductions of chiral imines bearing co-ordinating groups such as acids, esters and alcohols[278], excellent selectivities may also be achieved using sterically directed reductions. These processes work especially well in cyclic substrates, where the most reactive (i.e. unhindered) face can generally be predicted with a high degree of accuracy[282,283]. This has proved to be the basis of an excellent approach to chiral alkaloids[282]. The reduction of a cyclic nitrone attached to a sultam chiral auxiliary (Scheme 66) serves to illustrate this methodology[284].



Reagents: (i) H_2, Pd/C

SCHEME 66

V. CONCLUSIONS

This review has served to illustrate recent developments in the uses of hydrogenation reactions in synthesis. The emphasis on asymmetric applications serves to reflect the great growth in this area over recent years and the central position in asymmetric synthesis which this technique now occupies. New developments and trends have been identified for what is certain to be a continuing period of growth in the synthetic importance of hydrogenation.

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CHAPTER **16**

Heterogeneous catalytic hydrogenation

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I. ABBREVIATIONS

CPG	controlled pore glass
CVD	chemical vapor deposition
ee	enantiomeric excess
EPR	electron paramagnetic resonance
ESCA	electron spectroscopy for chemical analysis
EXAFS	extended X-ray absorption fine structure
fcc	face-centered cube
HTR	high temperature reduction
LTR	low temperature reduction
M	metal
MRNi	modified Raney Ni
PVP	poly(*N*-vinyl-2-pyrrolidone)
RDS	rate-determining step
SMSI	strong metal–support interaction
STO	single turnover
TA	tartaric acid
THF	tetrahydrofuran
TOF	turnover frequency
⋆	active center of metal surfaces
*	chiral atom

II. INTRODUCTION

This series of monographs reported on the hydrogenation of double-bonded functional groups in 1987[1]. A few years earlier a detailed treatment of the topic also appeared in a book, though with main emphasis on the stereochemistry[2]. The present review, consequently, covers the results of this field published during the last decade. In a few cases, however, earlier publications are also cited to give a more comprehensive treatment of certain topics. The literature coverage extends up to the middle of 1995, but relevant publications after this date have also been included.

As a usual practice of this series only the important developments are emphasized. Only the hydrogenation of compounds possessing carbon–carbon, carbon–oxygen and carbon–nitrogen double bonds or the combination of these is covered. Compounds with additional functional groups are not treated with the exception of a few examples of great significance. Results obtained with the use of heterogenized homogeneous catalysts are not included.

III. GENERAL CHARACTERISTICS

A. Catalysts

1. C=C bond

Platinum metals, first of all Pt, Pd and Rh, are the characteristic and most frequently used alkene hydrogenation catalysts which are highly active under ambient conditions[3–8]. In contrast, elevated temperatures and pressures are required when the much cheaper nickel is employed. Platinum is the catalyst of choice when isomerization is to be avoided. Palladium, in turn, has a tendency to bring about extensive isomerization (double bond migration). Metals used in catalytic hydrogenations are either prepared in situ by reducing their oxides or hydroxides (metal 'black' catalysts, e.g. Adams platinum[9]) or they are dispersed on a high surface area inert support (carbon, alumina, silica). Such supported metal catalysts are characterized by a large surface area per unit weight which is highly beneficial, since hydrogenation over heterogeneous catalysts is a surface reaction.

When one component of a bimetallic alloy is leached out, a finely divided metal powder of high surface area results. One of the oldest of these so-called skeletal metal catalysts is Raney nickel[10,11]. Nickel boride is a more recently developed hydrogenation catalyst prepared by the reduction of nickel salts with sodium borohydride[12–14]. Bimetallic catalysts are often used to achieve selective saturation of a double bond in bifunctional unsaturated systems, e.g. in dienes. Amorphous metal alloys, a newly developed class of metal catalysts[15,16], have also been applied in the hydrogenation of alkenes and dienes.

Certain oxides, first of all zinc oxide[17], as well as copper chromite[18] (a mixed copper–chromium oxide), are also active in the saturation of the C=C bond. Partial sulfur treatment under controlled conditions of metals or oxides can result in sulfided catalysts which exhibit specific activity and selectivity in hydrogenations[19–21].

2. C=O bond

Platinum, ruthenium and rhodium are the most often used metals in the hydrogenation of the C=O bond[8,22–26]. Slightly increased temperatures and pressures are usually required. Palladium is ineffective in the hydrogenation of aliphatic aldehydes and ketones but can be used to reduce aromatic carbonyl compounds. When aromatic aldehydes are hydrogenated, however, special care must be taken to avoid the hydrogenolysis of the resulting benzyl alcohol. This side-reaction can also occur during the hydrogenation of substituted aromatic carbonyl compounds even over platinum. Metal salts ($FeCl_3$ and $SnCl_2$) were found to promote the platinum-catalyzed hydrogenation of the aromatic carbonyl group.

Nickel, either as a Raney catalyst or in the form of nickel boride, is also effective in the reduction of the C=O bond. An increase in the catalytic activity can be brought about by metal promoters (chromium and molybdenum). Copper chromite may also be used.

3. C=N bond

Various classes of compounds possessing a C=N bond can yield different products depending on the hydrogenation conditions. Selectivity can be markedly affected by the catalyst. Pt, Pd and Raney nickel are used most often[27–31].

Examples on the use of these and other heterogeneous catalysts in the hydrogenation of double-bonded functional groups are found throughout this review.

B. Experimental Variables

1. Hydrogenation with the use of an external hydrogen source

The catalytic hydrogenation of the C=C bond with the most active platinum metal catalysts can usually be carried out at room temperature and atmospheric hydrogen pressure in the liquid phase. Elevated temperature and pressure must be used when less active catalysts are employed. Hydrogenation is most often carried out in a batch mode when all components of the reaction mixture (reactant, catalyst, solvent and additives) are placed in an appropriate reaction vessel[32,33]. Since this is a three-phase system (solid catalyst, gaseous hydrogen and reactant in the liquid phase) effective agitation is essential to overcome mass transport limitations and to achieve good and reproducible performance. Continuously operated systems[33] are of significance in both research (small-scale flow and pulse reactors and gas recirculatory reactors) and commercial hydrogenation processes.

2. Hydrogenation without external hydrogen

A convenient and useful alternative to conventional catalytic hydrogenation not requiring an external hydrogen source is transfer hydrogenation. The process, named by Braude and Linstead[34], involves hydrogen transfer from a suitable hydrogen donor molecule, in most cases an organic compound, to the molecule to be reduced. The method, carried out usually at reflux temperature in a simple apparatus, is particularly useful for the hydrogenation of the C=C bond.

Pd is the most active and most frequently used metal in transfer hydrogenations[35,36]. Cyclohexene, a cheap, readily available and reactive molecule, is the preferred donor compound which is successfully used in transfer hydrogenations in the gas phase[37–39]. Tetralin and monoterpenes, and, in general, hydroaromatic compounds are also used. Raney Ni, a cheap alternative to palladium, is usually applied with alcohols or amines as the donor.

Much experimental evidence indicates that Pd mediates the formation of a donor–acceptor complex followed by a direct hydrogen transfer[36]. This process, however, was disproved in the disproportionation of 1,4-cyclohexadiene (a special case of transfer hydrogenation) over colloidal nickel[40]. Another possibility is a consecutive dehydrogenation–hydrogenation process.

In addition to hydrogen transfer, other procedures also allow one to perform alkene hydrogenations without an external hydrogen source. Metal-assisted reductions with $NaBH_4$ can be considered as heterogeneous catalytic hydrogenation. Finely divided metal precipitated from its salt by $NaBH_4$ is believed to catalyze hydrogen addition with excess $NaBH_4$ serving as the hydrogen source[41–43].

A new procedure also carries out hydrogenation without added hydrogen. Triethoxysilane and 5 mol% of palladium acetate in a mixture of THF and water yields finely divided palladium dispersed on a polysiloxane matrix with concomitant hydrogen evolution[44]. Alkenes, present in this reaction mixture, are transformed to the corresponding saturated hydrocarbons in 100% yield at room temperature (equation 1).

$$\mathrm{RCH{=}CHR'} \xrightarrow[\substack{\mathrm{THF\text{-}H_2O\ (5:1),}\\ \mathrm{Me\ propionate,\ RT}}]{\mathrm{Pd(OAc)_2,\ (EtO)_3SiH}} \mathrm{RCH_2{-}CH_2R'} \qquad (1)$$

$\mathrm{R,R'} = \mathrm{H, Bu, C_8H_{17}}$

Though it is not a practical procedure, hydrogenation with spilt-over hydrogen is worth mentioning. Silica and alumina areogels can be activated in the presence of a supported metal catalyst (usually Pt or Ni) with hydrogen[45,46]. These spillover-activated oxides then promote hydrogenation of ethylene[46–48]. The mechanism is similar to that on metal oxides (see Section IV.A.6), since the molecular identity of the reacting hydrogen was found to be retained[47].

C. Solvent Effects

In liquid-phase hydrogenation catalyzed by heterogeneous catalysts, solvents are often necessary to dissolve the reactant and product molecules. Solvents, however, can affect the hydrogenation reaction itself in various ways[49,50]. In competitive hydrogenations, polar solvents facilitate the hydrogenation of nonpolar compounds. This is because a polar solvent solvates more effectively a polar compound, and, therefore, the less solvated nonpolar compound preferentially adsorbs on the catalyst surface. The reactivity of 1-hexene in the competitive hydrogenation in a mixture with 2-methyl-3-butene-1-ol in the presence of a 5% Pt–silica catalyst varied with the structure of solvent alcohols[51]. The rate of hydrogenation of 1-hexene increased with both increasing chain length and branching. The relative reactivities (the rate of hydrogenation of 1-hexene divided by that of 2-methyl-3-butene-1-ol measured at 293 K and 1 atm H_2) were 2.3, 11.1 and 7.7, respectively, in MeOH, 1-heptanol and *t*-BuOH.

The role of the support was also demonstrated in the competitive hydrogenation of cyclohexene and cyclohexanone in water–cyclohexane mixtures[52]. Cyclohexene was exclusively hydrogenated on a hydrophobic Rh—C, since this catalyst is covered by a cyclohexane layer, which preferentially dissolves cyclohexene. On a hydrophilic Rh–silica cyclohexanone, present mainly in the water phase covering the catalyst, was hydrogenated.

Solvent molecules can compete with the alkene being hydrogenated for the same adsorption site, thereby affecting the outcome of the hydrogenation reaction. This was demonstrated in the hydrogenation of methylenecyclohexane and 1-methylcyclohexene over palladium[53]. The two compounds were shown to undergo hydrogenation at comparable rates in ethanol. When methylenecyclohexane, in turn, was hydrogenated in ethanol–benzene, a large amount of 1-methylcyclohexene formed by isomerization was isolated. Apparently, the hydrogenation of the latter compound is severely retarded due to the competitive adsorption of benzene, whereas the adsorption of methylenecyclohexane is not affected.

Adsorbed solvent molecules can alter the characteristics of the active sites. A ^{3}M site possessing three coordinative unsaturations is assumed to catalyze hydrogen addition (see in detail in Section IV.A.7). When a solvent molecule, however, adsorbs at a ^{3}M site, this site is transformed into a ^{2}M site (a site with two coordinative unsaturations) which catalyzes only isomerization. The extent of hydrogen addition is, therefore, expected to decrease, whereas that of isomerization is expected to increase. This was indeed demonstrated in the liquid-phase hydrogenation of 4-methyl-1-cyclohexene over a 8.06% Pt–SiO_2 catalyst[54]. Surprisingly, however, the same phenomenon was observed in the gas-phase hydrogenation of 1-butene on Pt and Pd supported on controlled pore glass (CPG) when the catalysts were pretreated with solvents[55] (Table 1). The largest effects are observed in the presence of THF and methanol, whereas pentane has no effect indicating that it hardly interacts with the active sites. The changes are much smaller on Pd due to the strong isomerization activity of this metal.

Solvents can also affect selective hydrogenation of bifunctional compounds. As Table 2 shows, highly selective hydrogenation of the conjugated double bond of α-ionone was achieved in etheral solvents[56] (equation 2). This was attributed to the inhibition of

TABLE 1. Effect of solvents on the performance of catalysts in the hydrogenation of 1-butene (pulse experiments at ambient temperature with catalysts first treated with solvent then saturated with hydrogen)

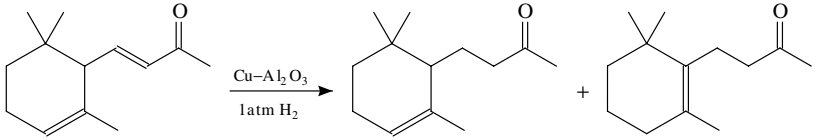
	4.9% Pt-CPG			1.8% Pd-CPG		
	butane[a]	2-butenes[b]	1-butene	butane[a]	2-butenes[b]	1-butene
None	41 + 20	2 + 2	27	22 + 12	18 + 45	4
Pentane	39 + 17	6 + 4	33	22 + 12	17 + 45	4
THF	20 + 12	9 + 9	50	19 + 9	21 + 45	6
Methanol	17 + 10	23 + 20	30	16 + 12	17 + 53	1

[a]Figures correspond to direct saturation and two-step saturation (see Section IV.A.7).
[b]*cis* + *trans*.

TABLE 2. Hydrogenation of α-ionone in various solvents (equation 2)

Solvent	Temp. (K)	Conversion (%)	Yield of products (%)	
			1	**2**
Dioxane	363	86	80	4
Toluene	383	86	12	50
Dibutyl ether	413	96	63	28
Decalin	433	96	17	61
Tetraglyme	453	81	88	0

isomerization by Cu^+ ions through the adsorption of nucleophilic solvent molecules.



(2)

(1) **(2)**

IV. HYDROGENATION OF C=C BONDS

Heterogeneous catalytic hydrogenation of alkenes discovered at the turn of the century[57] is one of the most studied catalytic reactions. It is a versatile and useful technique in organic synthesis frequently giving high yields. High chemo-, regio- or stereoselectivities can also be achieved provided the suitable experimental conditions are applied. Due to this great practical as well as theoretical significance, a large number of papers, books and review articles are available treating every aspect of the field[1,3–7,58–67].

A. Hydrogenation of Monoalkenes

1. Reactivity

The reactivity of C=C bonds depends on the number and nature of substituents attached to the sp^2 carbon atoms. Substituents affect the reactivity by affecting the rate constant of reaction and the adsorption properties.

Increasing substitution, in general, results in decreasing rate of hydrogenation, known as the Lebedev rule[49,68,69]. Terminal olefins, correspondingly, exhibit the highest reactivity, and the rate of hydrogenation decreases in the order $RCH{=}CH_2 > R_2C{=}CH_2 >$

RCH=CHR > R_2C=CHR > R_2C=CR_2. In the hydrogenation of 1-alkenes the rate decreases monotonously with the chain length[49]. The relative adsorptivity of terminal alkenes was shown to be the same, indicating that the chain length affects the rate constant. Since the polar effect of alkyl groups is identical, the difference in reactivity is caused by the steric hindrance of the alkyl chain. Of stereoisomeric compounds, *cis* isomers are hydrogenated in preference to the corresponding *trans* compounds[49,69]. The reactivity of cycloalkenes usually shows a maximum at cyclohexene[69]. Exceptions, however, are known. Cyclohexene, for example, exhibits extremely low reactivity on the P-2 Ni−B catalyst (relative reactivities are 1, 0.01, 0.26 and 0.20, respectively, for cyclopentene, cyclohexene, cycloheptene and cyclooctene)[70]. Other data indicate monotonous decrease in the reactivity of C_5–C_8 cycloalkenes over Rh[71] and Pt[69].

New observations of the relative reactivity of various alkenes in gas-phase hydrogenation on Pt[72] and Cu[73] have been reported. These data are in agreement with previous observations. The reactivity of terminal alkenes over Rh catalysts[74], in contrast, was shown to increase in the sequence 1-hexene < 1-heptene < 1-octene. An attempt was also made to quantify steric, polar and adsorption effects with the utilization of linear free energy relationships in the liquid-phase hydrogenation of alkenes[49].

Since the rate of hydrogenation is sensitive to operating conditions (temperature, pressure, catalyst quantity, solvent and agitation), relative rates determined in competitive hydrogenation of binary mixtures are considered to be more reliable than measuring individual rates[50]. Relative reactivities thus measured are determined by the ratio of rate and adsorption constants.

Supported metal catalysts with molecular sieving properties[75,76] are able to differentiate between alkenes with structures of differing steric demands in competitive hydrogenation. After an early report on the selective hydrogenation of propylene in the presence of isobutylene over a Pt-zeolite A catalyst[77] new examples have recently been published[78–84].

Shape-selective hydrogenation was demonstrated over an appropriately reduced Pt-ZSM-5 catalyst[81,82]. Neither Pt-ZSM-5 reduced in hydrogen nor Pt–Al_2O_3 displayed any selectivity (Table 3). Selective hydrogenation of various terminal alkenes was, however, achieved when Pt-ZSM-5 was reduced in the presence of a mixture of alkenes and hydrogen. The greatest selectivity was observed in the hydrogenation of a binary mixture of a straight-chain and a geminal dimethyl-substituted alkene[82] (Table 4). Shape selectivity was attributed to the large difference in diffusivities of the two types of compounds[82].

Significant shape selectivity was exhibited by Pt catalysts modified with organosilicon compounds using CVD[78–80]. The treatment of Pt supported on silica, titania and zirconia did not result in significant improvements relative to the parent samples in the competitive hydrogenation of 1-nonene and *trans*-4-nonene[78]. The relative rate on Pt–TiO_2, for example, was 2.62, which changed to 2.80 when the catalyst was treated with $(EtO)_4Si$. When zeolites were applied as supports, however, silane treatment afforded catalysts with excellent selectivity (Table 5)[78–80]. Catalysts treated with different silanes display

TABLE 3. Hydrogenation of alkene mixtures in the presence of Pt catalysts (548 K, flow reactor)

	% Hydrogenation	
	1-hexene	4,4-dimethyl-1-hexene
0.5% Pt–Al_2O_3	27	35
1% Pt-ZSM-5 reduced in H_2 (573 K, 1 h)	29	39
1% Pt-ZSM-5 reduced with alkenes + H_2 (673 K, 1 h)	90	1

TABLE 4. Shape-selective hydrogenation of alkene mixtures in the presence of 1% Pt-ZSM-5 catalyst reduced in a mixture of alkenes and H_2

Alkenes		Temperature	% Hydrogenation	
straight-chain	branched	(K)		
1-Pentene	4,4-Dimethyl-1-pentene	573	97	2
1-Heptene	4,4-Dimethyl-1-pentene	573	91	1
1-Hexene	6-Methyl-1-heptene	573	25	2
Styrene	2-Methylstyrene	698	50	2

TABLE 5. Selectivity in the competitive hydrogenation of 1-nonene and *trans*-4-nonene over Pt catalysts (150 mg of catalyst, 298 K, 1 atm H_2, hexane)

	Initial rate (10^{-5} mol h^{-1} g_{cat}^{-1})		Relative rate
	1-nonene (r_1)	*trans*-4-nonene (r_2)	r_1/r_2
Pt-zeolite A[a]	728	336	2.17
modified with $Me_2Si(EtO)_2$	192	30.6	6.3
modified with $(EtO)_4Si$	47.7	2.63	18.14
modified with $Ph_2Si(MeO)_2$	159	9.33	17.0
modified with $Ph_2Si(EtO)_2$	149	7.33	20.3
Pt-zeolite X[a]	647	173	3.73
Modified with $(EtO)_4Si$	10.7	0.4	26.75

[a] 30 mg of catalyst.

TABLE 6. Reactivities of isomeric octenes relative to 1-octene in competitive hydrogenation (for reaction conditions see Table 5)

	r_1/r_2[a]	
	Pt-zeolite A	Pt-zeolite A modified with $(EtO)_4Si$
cis-2-Octene	1.49	3.33
trans-2-Octene	1.61	2.94
trans-3-Octene	1.95	6.31
trans-4-Octene	1.61	14.90

[a] Initial rate of 1-octene/initial rate of the corresponding octene.

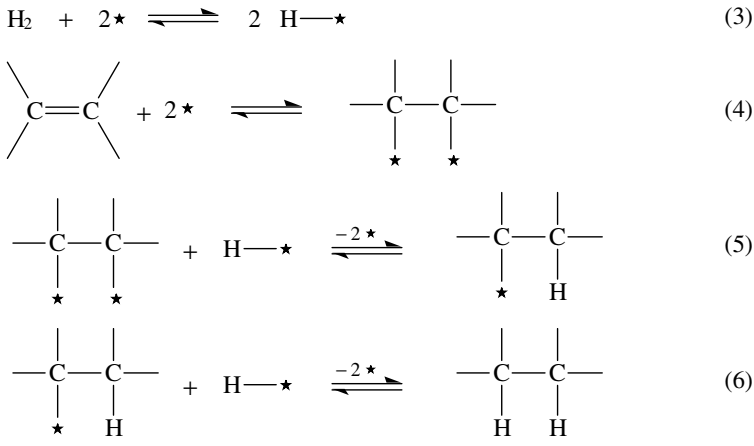
strongly varying shape selectivity (Table 5). A comparison of the rates in the competitive hydrogenation of isomeric octenes indicates that both the position of the double bond and the steric structure have a significant effect on selectivity[78,79] (Table 6).

XPS data suggest that the surface of the CVD catalysts is finely covered by a homogeneous silica layer except for Pt particles, where small holes are formed. Since hydrogenation exclusively occurs on Pt particles, selectivity is brought about by steric hindrance around the Pt site in the holes. Less hindered double bonds, consequently, are hydrogenated preferentially.

2. Mechanistic studies

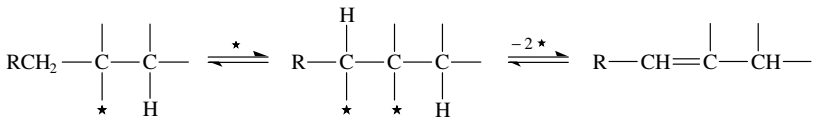
An early mechanism proposed by Horiuti and Polanyi in 1934 to interpret the hydrogenation of the C=C bond[85,86] over transition metals is still generally accepted and postulated in the majority of cases (equations 3–6). In its original form this mechanism

involves the dissociative adsorption of hydrogen molecule (equation 3) and the associative adsorption of alkene (equation 4). The 1,2-di-σ-adsorbed surface species thus formed reacts with adsorbed hydrogens in a stepwise manner, first forming an alkyl intermediate or half-hydrogenated state (equation 5), then the saturated product (equation 6). This corresponds to a reaction model in which the rate-determining surface reaction involves interaction between two adsorbed molecules or atoms (Langmuir–Hinshelwood mechanism[87]). An alternative but rare possibility is the reaction of an adsorbate with a gas-phase species (Eley–Rideal pathway[88,89]). In fact, this was only observed in the hydrogenation of cyclohexene over Cu(100)[90] (see Section IV.A.3) and ethylene over Cu(111)[91].



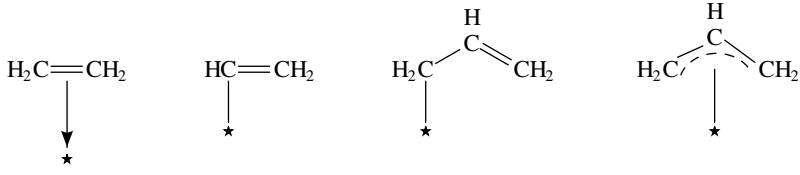
A similar mechanism is well-established for transition-metal complexes[92–94] including the observation of hydridoalkyl complexes[95]. Due to this close analogy between heterogeneous and homogeneous hydrogenation, step 3 may be viewed as migratory insertion of hydrogen and step 4 is the reductive elimination between hydrogen and the alkyl intermediate. Whereas this last step (equation 6) is virtually irreversible under hydrogenation conditions, both the formation and the reaction of the adsorbed alkene (equations 4 and 5) are reversible.

Various observations support the existence of this mechanism over heterogeneous metal catalysts. When the half-hydrogenated intermediate eliminates a hydrogen from another β-carbon it reverts to an isomeric olefin (equation 7). This transformation accounts for the isomerization (double bond migration and *cis–trans* isomerization) of alkenes occurring during hydrogenation[63,67]. When deuterium instead of hydrogen is used, the reversal of the half-hydrogenated intermediate results in deuterium exchange in alkenes[96–100]. It is also observed that deuterium addition does not result in a simple d_2 saturated hydrocarbon[6,67,101]. Instead, d_1, d_2 and d_3 products are usually formed in the ratio 1:2:1 independent of conversion[60,102]. This indicates that exchange and C–H activation must be involved in the hydrogenation reaction.



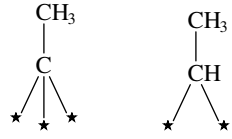
The stereochemistry of hydrogenation, the long recognized predominantly *cis* addition[103–105] (see Section IV.A.3) is also consistent with the stepwise addition of the two H atoms via the half-hydrogenated intermediate. H–D exchange reaction of alkanes is also interpreted with the involvement of the surface alkyl intermediate[106,107].

Further studies indicated that a considerable range of bonding configurations can be involved in hydrogenation. The π-adsorbed intermediate **3** and the dissociatively adsorbed σ-vinyl **(4)** and σ-allyl **(5)** species were suggested to exist on metal surfaces[67,108–112]. The unusual properties of Pd are believed to be related to its ability to generate the π-allyl (η^3-allyl) intermediate **(6)**. 1,1,2- and 1,1,3-tri-σ-adsorbed species were shown to be involved by means of infrared spectroscopy in the adsorption of linear butenes on Ni[113] and Co[114]. To underline the complexity of alkene hydrogenation recent papers have to be referred to where, in contrast with surface-bound hydrogen, bulk hydrogen was shown to be active in the hydrogenation of ethylene and cyclohexene on Ni catalysts[115–117].



(3) **(4)** **(5)** **(6)**

The most extensive mechanistic studies were carried out with ethylene over Pt(111) and Rh(111) single crystal faces under ultrahigh vacuum[112,118,119]. When exposed to ethylene the surface was shown to be instantly covered by an ethylidyne **(7)** overlayer[120–122]. Surface alkylidynes were also found to be present by means of IR spectroscopy upon adsorption of ethylene and terminal alkenes on supported metal catalysts[110,123–125]. Ethylidyne, however, is only a spectator, since its hydrogenation occurs at a rate six orders of magnitude lower than that of ethylene. The ethylidyne overlayer, in turn, can readily be compressed to open up new space for ethylene hydrogenation[122,126]. Reaction kinetics data were found to be consistent with the rapid equilibrium between molecularly adsorbed ethylene and surface ethyl species[127]. Strong evidence for the reversible formation of surface-bound ethyl groups on hydrogen-covered Fe(100) (migratory insertion of ethylene into a Fe–H bond and β-hydride elimination of ethyl group) was recently disclosed[128]. Similar results were found for C_3–C_6 alkenes[96].



(7) **(8)**

Another reaction model originally proposed by Thomson and Webb[129] assumes that H atoms are transferred from a strongly adsorbed hydrocarbon overlayer, represented as $M–C_xH_y$, to the alkene weakly adsorbed on top of the overlayer. This suggestion, among others, is based upon the observations that the form of metal (powder, foil, film or dispersed metal) does not influence reaction rates significantly and the activation energy of ethylene hydrogenation is the same for different metals within a narrow limit. It was

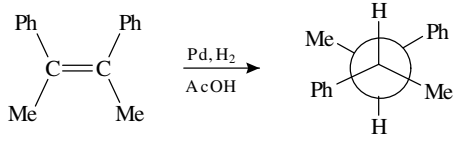
recently proposed[120,122,127] that H adds to the surface ethylidyne to form ethylidene (**8**). Two ethylidene species then react with gas-phase ethylene to yield ethane and regenerate ethylidyne. Ethyl radicals have recently been detected by EPR in conjunction with spin trapping on supported Pd catalysts[130].

The above interpretation is also consistent with ethylene self-hydrogenation. This occurs when transition metal surfaces are exposed to ethylene in the absence of hydrogen and requires the dissociative adsorption of ethylene to form ethane and hydrogen-deficient surface species[67,112]. In recent years, single crystal surfaces with different crystallographic orientation have been identified to promote this process. Although self-hydrogenation of ethylene is not always observed[98,100,128], it does occur on Pt(111)[99,127] and Ni(111)[131] at higher pressure. Self-hydrogenation of higher alkenes was also detected[67,101,132,133]. It is always noted, however, that alkane formation is greatly promoted by the presence of preadsorbed hydrogen[99,101,132,134].

A partially dehydrogenated hydrocarbon overlayer on metal surfaces under hydrogenation conditions is considered to be responsible for the structure insensitivity of alkene hydrogenation[135,136]. This means that turnover rates, i.e. the number of molecules reacting (or forming) per unit time per surface metal atom, are the same irrespective of support, metal loading or dispersion. In recent years, this phenomenon was observed in the hydrogenation on different metals of ethylene[120,137], propylene[138], cyclohexene[139] and styrene[140,141]. Another possible explanation of structure insensitivity is surface restructuring[142]. Structure insensitivity may also indicate that neither the dissociation of dihydrogen nor the adsorption of alkene requires multiple atoms but they take place on a single metal atom. The active sites, therefore, are not multinuclear in character and H addition occurs via the interconversions of various σ- and π-bonded intermediates as transient ligands of the same metal atom[143].

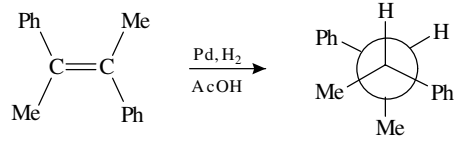
3. Stereochemistry

The basic principle of the stereochemistry of the hydrogenation of the C=C bond is *syn (cis)* addition. Established already in the early 1930s, it means that both hydrogen atoms add from the same face of the double bond. One of the highest selectivities was observed in the hydrogenation of isomeric 2,3-diphenyl-2-butenes[144]: the *meso* compound is formed from the *cis* isomer in 98% yield (equation 8), whereas the *trans* isomer gives the racemic compound in 99% yield (equation 9).



(8)

meso-2,3-diphenylbutane

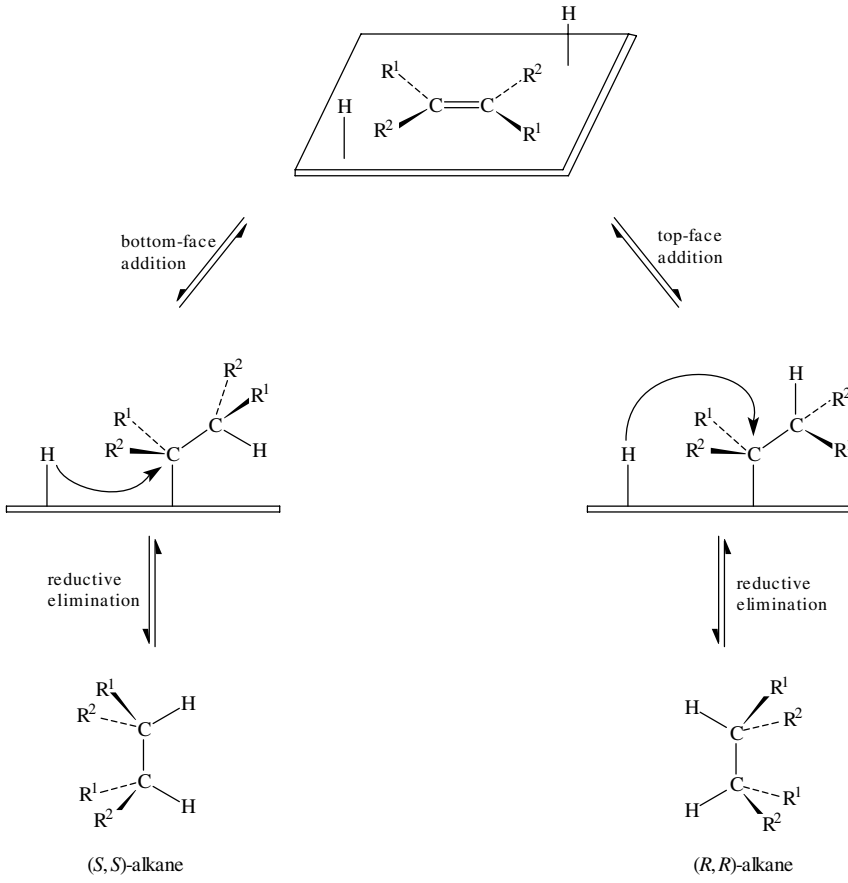


(9)

racemic-2,3-diphenylbutane

The *cis* stereochemistry is consistent with the Horiuti–Polanyi mechanism with the Langmuir–Hinshelwood pathway. The stepwise addition of the two hydrogen atoms from

the metal surface to the bottom face of adsorbed alkene via the half-hydrogenated intermediate ensures *syn* stereochemistry. It is important to emphasize that rotation about the C−C single bond does not affect the stereochemical outcome of addition. A new study demonstrated, however, that addition from the top side with identical stereochemistry is also possible[90]. The addition of hydrogen to cyclohexene on Cu(100) was shown to occur by the Eley–Rideal mechanism[88,89] (hydrogen from the gas phase adds to the adsorbed alkene). When a prochiral alkene is hydrogenated, the alkanes formed by bottom-face and top-face additions are mirror images of each other (Scheme 1. Group R^1 is more highly ranked according to the Cahn–Ingold–Prelog system than R^2).

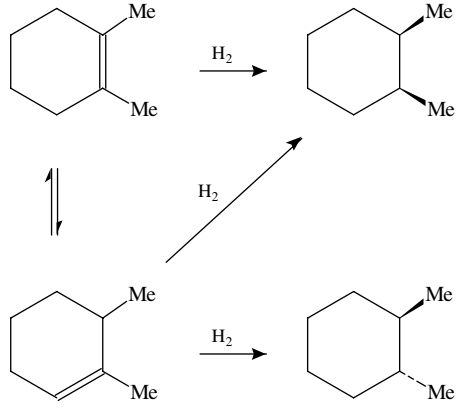


SCHEME 1

A further possibility to interpret *cis* addition is the so-called *cis*-concerted mechanism[74,145]. It assumes that the addition of the two hydrogen atoms takes place in a single step in a concerted fashion on a single ^{3}M site possessing three coordinative unsaturations. The transfer of the two hydrogens to the double bond through a concerted process, where the interaction with the catalyst removes the symmetry restrictions imposed by the Woodward–Hoffman rules, leads directly to alkane formation.

The transformation of substituted cycloalkenes provided further useful data on the stereochemistry. Most studies were performed in the 1960s. Further systematic studies were carried out and comprehensive interpretations were given by Augustine in the 1980s.

When 1,2-dimethylcyclohexene undergoes hydrogenation over Pt and Pd it always forms *cis*-1,2-dimethylcyclohexane as the dominant product expected from the *syn* addition of hydrogen[146–148]. Varying amounts of the *trans* isomer, however, are always formed. Detailed studies revealed that instead of *anti* (*trans*) addition, the *trans* isomer is formed through 1,6-dimethylcyclohexene, the product of double bond migration (Scheme 2). The latter can yield both *cis* and *trans* saturated products via *syn* addition. Iridium and osmium were shown to be the most selective metals forming the *cis* compound with almost 99% selectivity[148].



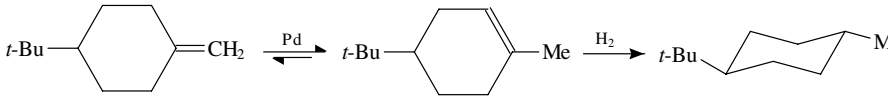
SCHEME 2

The effect of hydrogen pressure on the stereochemistry of addition is in accordance with this observation. It was established[62,67,149] that under conditions of high hydrogen availability (small catalyst quantity, high pressure and rapid agitation) the product-determining step is the adsorption of the alkene (step 2 in the Horiuti–Polanyi mechanism, equation 4). Desorption is negligible under these conditions and product stereochemistry is determined by the difference in steric constraints exerted by the two faces of the double bond with the catalyst surface. Under conditions of low hydrogen availability the product-determining step is the hydrogenation of the half-hydrogenated state (equation 6), since both the alkene adsorption and the formation of the half-hydrogenated state (equations 4 and 5, respectively) are reversible. Additional factors determining product distributions are the mode of adsorption affected by steric effects and the type of adsorbed intermediates formed on different metals.

In the transformation of 1,2-dimethylcyclohexene the fraction of the *cis* isomer was observed to increase with increasing hydrogen pressure. This is a clear indication that the hydrogen partial pressure affects step 3 (equation 5) in the Horiuti–Polanyi mechanism by shifting the equilibrium to the formation of the half-hydrogenated state, therefore suppressing isomerization and increasing selectivity.

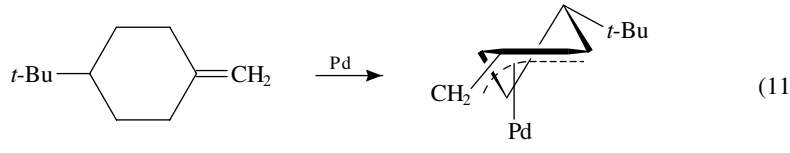
The effect of different metals on the stereochemistry was studied[149,150,151] in the hydrogenation of 4-*tert*-butylmethylenecyclohexane **(9)**. Whereas Pt, Rh, Ir and Ru yield predominantly the *cis* isomer, *trans*-1-*tert*-butyl-4-methylcyclohexane is the main product on Pd. The stereochemical behavior of **9** was very similar to that found for the hydrogenation of the isomeric 4-*tert*-butyl-1-methylcyclohexene **(10)** (increasing *cis* selectivity

with increasing hydrogen pressure). Since Pd exhibits the highest tendency to catalyze isomerization among platinum metals, it was always suggested that **9** first undergoes isomerization to **10**, which is then hydrogenated (equation 10).



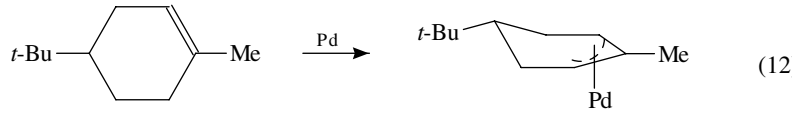
(9) **(10)** major product (10)

The amount of the *cis* isomer formed in the hydrogenation of **10** at various hydrogen pressures, however, is always considerably lower[150] than that formed in the hydrogenation of **9**. All these observations can be interpreted by invoking π-allyl-adsorbed species (**11** and **12**) instead of 1,2-σ-diadsorbed species as surface intermediates in the hydrogenation over Pd (equations 11 and 12)[150]. Of the two species, **12** formed from **10** (equation 12) is expected to result in a higher *trans* ratio.



(11)

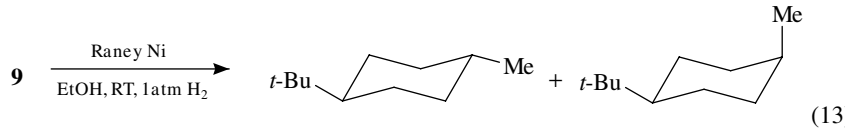
(9) **(11)**



(12)

(10) **(12)**

Interesting changes take place in the stereochemistry of the hydrogenation of **9** over Raney Ni. The *trans* compound is always the main product over a fresh catalyst, whereas high *cis* ratios are observed over aged samples (equation 13)[152]. This was interpreted to prove that the adsorption of the substrate becomes the product-controlling step over the aged catalysts.

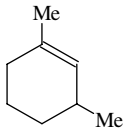
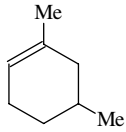
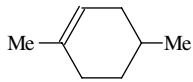
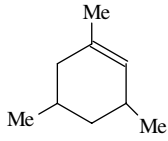


(13)

fresh catalyst	78	22
aged for 30 days	15	85
reflux in EtOH for 2 h	6	94
poisoned with CO	2	98

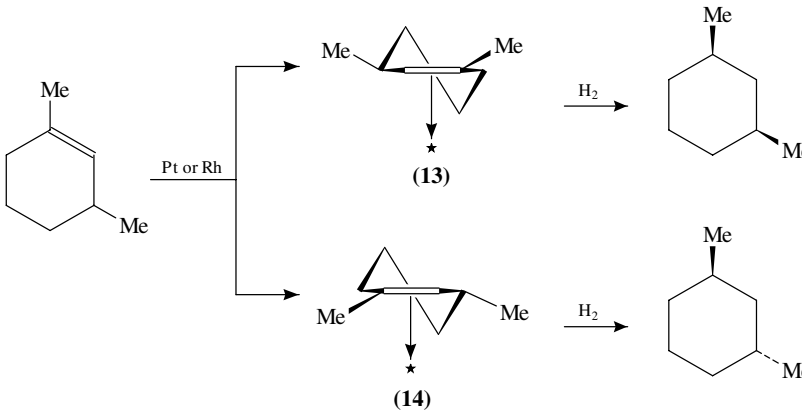
1,3-Dimethylcyclohexene and 1,5-dimethylcyclohexene yield an identical mixture of *cis*- and *trans*-1,3-dimethylcyclohexane on Pd[153] (Table 7). On Pt and Rh, in contrast, the two isomeric dimethylcyclohexenes lead to products of different composition (Table 7). The adsorption modes of 1,3-dimethylcyclohexene is illustrated by the π-adsorbed species **13** and **14** leading to *cis*- and *trans*-1,3-dimethylcyclohexane, respectively (equations 14 and 15)[155]. A comparison of **13** and **14** clearly indicates that the high *cis/trans* ratio

TABLE 7. Product distribution (*cis/trans* ratio) in the hydrogenation of substituted cyclohexenes (ambient temperature and pressure, ethanol)

Compound	Pt	Rh−C	Pd−C	Reference
	72/28	74/26	82/18	153
	59/41	49/51	81/19	153
	57/43 61/39	57/43 57/43	27/73 28/72[a]	153 154
	60/40[b]	54/46	73/27	155

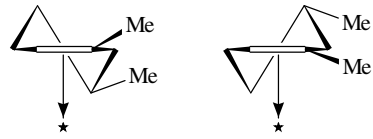
[a] Pd.
[b] Pt−C.

observed on Pt and Rh is a result of the steric interaction in **14** of the allylic methyl group with the catalyst surface.



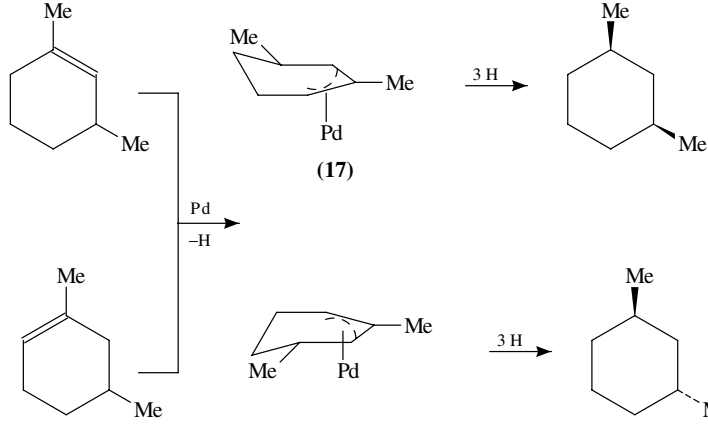
The π-adsorbed species of 1,5-dimethylcyclohexene are those depicted as **15** and **16**. The nearly equal amount of the isomeric products formed on Pt and Rh (Table 7) testifies to the almost equal degree of hindrance of the homoallylic methyl group with the catalyst surface in the alternate adsorption modes.

The identical product composition observed in the transformation of the two alkenes over Pd, however, is strong evidence of a common intermediate. This species is a π-allyl



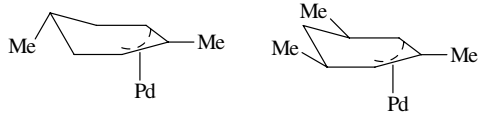
(15) **(16)**

intermediate adsorbed on the catalyst surface primarily in the less hindered *cis* mode **(17)** yielding *cis*-1,3-dimethylcyclohexane (equation 16).



(17) (16)

When 1,4-dimethylcyclohexene is hydrogenated on Pt and Rh, *cis*-1,4-dimethylcyclohexane is formed in slight excess (Table 7). These data, again, are consistent with the involvement of π-adsorbed species with an almost equal degree of hindrance in the alternate adsorption modes. The homoallylic substituent, consequently, does not exert any strong influence on stereochemistry. The *trans* compound, however, is the main product on Pd (Table 7) indicating a favored *trans* adsorption mode **(18)**.



(18) **(19)**

Hydrogenation of 1,3,5-trimethylcyclohexene over Pt and Rh gives essentially the same results (nearly the same amount of *cis* product) as obtained in the hydrogenation of 1,4- and 1,5-dimethylcyclohexene[155] (Table 7). This indicates that in this case the homoallylic methyl group is more influential in determining stereochemistry than the allylic methyl. The favored **19** π-allyl species is responsible for the high *cis/trans* ratio on Pd. The observations summarized above are supported by the results of the transformations of selectively deuterated substrates[156].

Further details on the stereochemistry of alkene hydrogenation can be found in earlier books and review papers[62,63,67]. They treat the effect of polar substituents

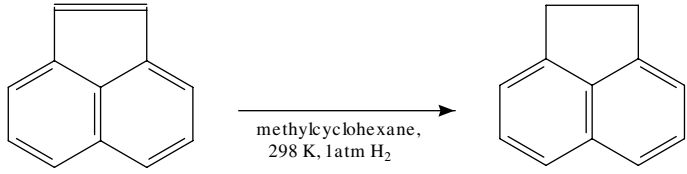
on stereochemistry, i.e. substrate-directed transformations are also discussed[157]. Such reactions are, however, outside the scope of the present review.

4. New catalysts for alkene hydrogenation

During the last 15 years many new catalyst preparations were introduced and their catalytic properties were very often tested in the hydrogenation of alkenes. Since heterogeneous catalytic hydrogenation is a surface reaction, the effectiveness of the process can be greatly increased by increasing the number of active sites available. This can be done by applying high surface area support materials and specific catalyst preparation techniques. These highly dispersed catalysts, i.e. catalysts with high active sites density, are expected to exhibit high specific activity. In this subchapter the most important examples of these new catalysts are discussed and their main characteristics in the hydrogenation of alkenes are demonstrated.

a. Metal atoms, clusters and colloidal particles. Free metal atoms, metal clusters and extremely small metal particles of diameters from one to some tens of nanometers exhibit profoundly different characteristics compared to metals in the bulk state. Various methods have been, therefore, developed to produce such metal agglomerates and test their catalytic behavior[158–160].

Solvated metal atoms can be dispersed in excess organic solvent at low temperature and used as a source of metal particles for the preparation of both unsupported metal powders and supported metal catalysts[158,161]. Alternatively, metal vapor is condensed into a cold solution of a stabilizing polymer to form crystallites of the order 2–5 nm in diameters[159]. Equation 17 illustrates the unique activity of a colloidal Pd catalyst in the partial hydrogenation of acenaphthene.



(17)

uptake of 1 equiv. H_2

Colloidal Pd	0.25 h
Pd black	5 h

Reduction methods can also be used to produce polymer-protected colloidal metal powder catalysts[160]. Ions of noble metals are readily reduced in solution in the presence of soluble protective polymers to form ultrafine metal particles. The protective polymers are physically adsorbed on the surface of the metal particles thereby preventing their aggregation by steric stabilization and dispersing them homogeneously in the liquid phase. Pt[162,163], Pd[164] and Rh particles[165] were covalently immobilized in this way. Such catalysts may exhibit much higher activity in the hydrogenation of alkenes than the corresponding supported catalysts (Table 8). Their activity, however, may be smaller than that of the nonprotected colloidal metal (Table 8).

Polymer-protected colloidal Pt could be deposited onto high-surface-area titania prepared by the sol-gel-aerogel method[166]. This catalyst exhibited much higher activity in the hydrogenation of *trans*-stilbene (306 K, isopropyl acetate, 1 atm H_2) than catalysts prepared by using commercial supports or Pt–titania made by the one-step aerogel technique[167].

TABLE 8. Catalytic activity of Rh and Pt catalysts in the hydrogenation of alkenes (303 K, 1 atm H_2, ethanol–water)[162,165]

	Initial hydrogenation rate (10^{-3} mol H_2 mol_{metal}^{-1} s^{-1})				
	ultrafine Rh particles	5% Rh–C	ultrafine Pt particles	colloidal Pt particles	50% Pt–C
Cyclopentene	230	44	n.a.[a]	n.a.[a]	n.a.[a]
Cyclohexene	150	7	36	240	2.1
1-Hexene	190	38	110	330	3.2

[a]n.a. denotes not available.

Various forms of nickel metal powders are prepared by the reduction of different nickel compounds with K–B alloy[168] or low-oxidation-potential metals (Na, Mg or Zn)[169]. The activity of the latter catalyst in the hydrogenation of alkenes (1-hexene and cyclohexene) is comparable with that of Raney nickel.

Graphimets, a special class of graphite intercalation compounds, contain metals between the layers of graphite either in atomic dispersion or as small clusters since the graphite layers prevent metal aggregation[170]. In addition, a considerable amount of the metal may be on the graphite surface. Alkene hydrogenation was used to study the characteristics of Pt[171–175], Pd[176], Ni[171,172,177] and Cu[172] graphimets. Interlayer metal particles do not participate in alkene hydrogenation since active sites located between the graphite layers are inaccessible for 1-butene[174] and cyclohexene[173,175] test molecules. As a result, hydrogenation occurs only on surface particles. Metal-graphimets, therefore, can be regarded as traditional supported metal catalysts in alkene hydrogenation[175].

b. Amorphous metal alloy powders. When certain metal salts are reduced by appropriate reagents, amorphous metal–metalloid alloys in the form of a finely divided black precipitate are formed, which exhibit excellent properties in hydrogenating many functional groups. Catalysts prepared from Ni and Co have been studied most[41].

The classical P-2 nickel boride catalyst is prepared by mixing a 95% ethanolic solution of nickel acetate with the ethanolic solution of sodium borohydride[14]. The resulting alloy powder is very sensitive to the alkene structure (cyclohexene is hydrogenated at a very low rate[70]) and shows an unusually low tendency for isomerization. With slight modifications of the original procedure Ni–B catalysts of different hydrogenation activities can be obtained. These catalyst preparations are usually more active and productive in alkene hydrogenations than Raney nickel[178–180]. Cobalt borides, in turn, are less active than nickel borides due to the lower activity of cobalt in alkene hydrogenation[181].

Catalytic activities were shown to strongly depend on the Ni concentration and the molar ratio of borohydride to nickel[179,180,182,183]. Ni–B powders showed maximum activity when the $NaBH_4$:$NiCl_2$ ratio was 1.5 (the rate of the hydrogenation of cycloheptene was 4.3×10^{-3} mol g-atom Ni^{-1} s^{-1}; 303 K, 1 atm H_2)[184]. When the synthesis, in contrast, was performed in the presence of PVP serving as a protective polymer, a threefold excess of $NaBH_4$ was required to achieve maximum activity (191×10^{-3} mol g-atom Ni^{-1} s^{-1})[184]. The polymer-protected sample proved to be especially effective in the hydrogenation of compounds with isopropenyl group (2-methyl-1-hexene and α-methylstyrene).

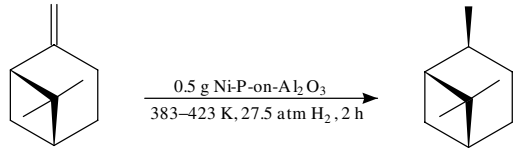
The activity of three $Ni_{67}B_{33}$ catalyst samples was compared in the hydrogenation of ethylene[185]. The parent amorphous powder made by reducing Ni^{2+} ions with $KaBH_4$ in an aqueous solution was heat-treated to produce partially amorphous and crystalline catalysts.

TABLE 9. Surface and catalytic properties of $Ni_{67}B_{33}$ alloy catalysts in the hydrogenation of ethylene (423 K, 1 atm, H_2/ethylene = 1)

Catalysts	Surface area ($m^2\ g_{cat}^{-1}$)	Conversion (%)	H_2 uptake (10^{-6} mol g_{cat}^{-1})	Relative turnover frequency
Amorphous	19	50	23	1.00
Partially amorphous (heat treatment at 573 K)	15	88	41	0.99
Crystalline (heat treatment at 773 K)	8	24	11	1.00

Though the relative rates were very similar, the partially amorphous catalyst exhibited the most rapid hydrogen uptake when expressed in gram of catalyst used (Table 9).

Nickel–phosphorous amorphous alloy powders are produced by the reaction of an aqueous solution of $NiCl_2$ and NaH_2PO_2. A $Ni_{85}P_{15}$ sample prepared in this way showed stable activity in the hydrogenation of styrene when compared to an amorphous $Ni_{87}P_{13}$ ribbon prepared by the rapid quenching method[186]. Amorphous Ni–P deposited on silica by electroless plating is superior to polycrystalline Ni–silica and a $Ni_{90}P_{10}$ ribbon in the hydrogenation of styrene (453–573 K, atmospheric pressure, cyclohexane, flow reactor)[187]. Ni–P deposited on various alumina supports showed high activity and selectivity in the hydrogenation of α-pinene to *cis*-pinane[188] (equation 18), comparable to those of polycrystalline nickel catalysts[189].



31–69% conversion
87–95% selectivity

(18)

c. Rapidly quenched amorphous metal alloys. In the early 1960s a new technique was developed to produce bi- or multicomponent amorphous metal alloys, also called metallic glasses. This method, the rapid quenching from the melt[190,191], made amorphous alloys easily available in large quantities in the form of thin ribbons or flakes. During the last 15 years numerous studies have been performed to explore the catalytic properties of these unique materials[15,16]. Due to their low surface area they usually require activation and in many instances they exhibit better activities and selectivities than their crystalline counterparts.

In the liquid-phase hydrogenation of *cis*-cyclododecene the ratio of isomerization to hydrogen addition was higher on amorphous $Pd_{80}Si_{20}$ and $Pd_{77}Ge_{23}$ than on the crystalline alloys, i.e. the amorphous catalysts produced more *trans* isomer[192,193]. In the hydrogenation of (+)-apopinene (6,6-dimethyl-1*R*,5*R*-bicyclo[3.1.1]hept-2-ene) the two amorphous alloys resulted in exceptionally low isomerization relative to addition[194–196]. On the basis of these observations a method to characterize palladium catalysts using (+)-apopinene as probe molecule was developed (see Section IV.A.7).

Many amorphous alloys were tested in the hydrogenation of ethylene. It was shown that the thermal pretreatment of a $Cu_{70}Zr_{30}$ amorphous precursor in hydrogen leads to structural modification and the resulting catalysts exhibit extremely high activities in ethylene hydrogenation[197] (Table 10).

TABLE 10. Catalytic activity of hydrogen-treated (473 K, 16 h) $Cu_{70}Zr_{30}$ catalysts in the hydrogenation of ethylene (1.6 atm total pressure, ethylene/hydrogen = 1)

Catalysts	BET surface area[a] ($m^2\ g^{-1}$)	Initial rate (10^6 mol $m_{cat}^{-2}\ s^{-1}$)		
		358 K	423 K	453 K
Completely amorphous precursor	0.56	3.7	29.9	34.9
Partially amorphous precursor	0.03	117	455	579
Crystalline precursor	n.a.[b]	n.a.[b]	18.1	21.0
Cu powder	n.a.[b]	n.a.[b]	11.5	15.3

[a] Surface area determined by krypton physisorption calculated by the Brunauer–Emmett–Teller equation.
[b] n.a. denotes not available.

TABLE 11. Effect of pretreatment of amorphous and crystalline $Cu_{62}Zr_{38}$ alloys on the surface characteristics and catalytic activity in the hydrogenation of ethylene (473 K)[a]

Catalysts and pretreatments	Cu concentration ($I_{Cu}/I_{Cu} + I_{Zr}$)	BET surface area ($m^2\ g_{cat}^{-1}$)	Initial rate (10^5 mol $min^{-1}\ g_{cat}^{-1}$)
A (hydrogen, 473 K, 2 h)	0.30	2.12	13
A (1 M HF, 5 min + hydrogen at 473 K, 2 h)	0.95	7.52	410
A (1 M HNO_3, 5 min + hydrogen at 473 K, 2 h)	0.10	1.13	1
A (1 M HNO_3, 5 min + oxygen at 473 K, 1 h + hydrogen at 473 K, 2 h)	0.38	2.85	10
C (hydrogen, 473 K, 2 h)	0.41	2.32	2
C (1 M HF, 5 min+hydrogen at 473 K, 2 h)	0.89	4.96	8

[a] A denotes amorphous, C denotes crystalline; I_{Cu} and I_{Zr} are peak intensities of Cu and Zr, respectively, in the ESCA spectra.

Dissolution of Zr from bimetallic amorphous alloys proved to be a very effective way of activation[198,199]. A pulverized amorphous $Cu_{62}Zr_{38}$ alloy treated with hydrogen fluoride (1 M solution, 5 min) gave a Raney-type copper catalyst exhibiting much higher activity in the hydrogenation of ethylene than the catalyst made from the crystalline alloy[198] (Table 11). The high activity was attributed to the increase in both the surface area and the surface concentration of copper. Similar conclusions were arrived at when the same HF dissolution was applied for amorphous and crystalline $Ni_{36}Zr_{64}$ ribbons[199].

$Ni_{81}P_{19}$ and $Ni_{62}B_{38}$ glassy alloys were studied in the hydrogenation of simple alkenes (ethylene, propylene and butenes) and dienes (1,3-butadiene and isoprene, see Section IV.B.1). Successive treatments of the virgin alloy ribbons with HNO_3, oxygen and hydrogen brought about high catalytic activity for both hydrogenation and isomerization of C=C bonds[200]. Activation of $Ni_{62}B_{38}$ was also achieved by heat treatment below 623 K resulting in specimens in the precrystallization state[201,202] and by the pulverization in a vibratory rod mill[203]. In all these cases, electronic interactions between nickel, oxygen and the metalloid were invoked to account for favorable changes in hydrogenation activity.

Numerous alloy ribbons in both amorphous and crystalline forms were tested in the hydrogenation of 1-hexene[204–206]. Selectivities were found to be independent on crystallinity. Ni-containing alloys (Ni–Zr, Fe–Ni–B, Fe–Ni–P) and Cu–Zr were

TABLE 12. Catalytic activity and selectivity of amorphous and crystalline alloys in the hydrogenation of 1-hexene (0.4 g alloy, 5 ml 1-hexene, 5 ml 1,4-dioxane, 323 K)

Catalysts	Activity[a]		Selectivity[b]	Hydrogen pressure
	A	C		(10^5 Pa)
$Ni_{30}Zr_{70}$	0.33	—[c]	57	7
$Fe_{20}Ni_{60}B_{20}$	0.31	—[c]	85	12
$Fe_{20}Ni_{60}P_{20}$	0.34	—[c]	93	12.5
$Fe_{18}Ni_{54}B_{16}Pd_{12}$	0.77	0.56	58	12
$Cu_{30}Zr_{70}$	0.42	0.34	55	15
$Pd_{80}Si_{20}$	1.7	1.2	54	14
$Pd_{35}Zr_{65}$	1.0	0.48	49	7
Ni foil	0.38	—[c]	65	14
Pd foil	1.1	—[c]	57	14

[a]Reciprocal log time (min) required for 10% conversion. A denotes amorphous, C denotes crystalline.
[b]Percentage of *n*-hexane at 10% conversion.
[c]Too low for accurate comparisons.

considerably less active than Pd-based alloys (Pd–Si, Pd–Zr) and slightly less active than Ni foil (Table 12). Ni alloys, however, exhibited better selectivities. Two alloys, $Fe_{20}Ni_{60}P_{20}$ and $Fe_{20}Ni_{60}B_{20}$, showed very high selectivity for hydrogenation. Addition of Pd to the latter catalyst increased the activity but resulted in a considerable drop in selectivity.

A highly dispersed Pd on ZrO_2 catalyst was prepared by activating an amorphous $Pd_{35}Zr_{65}$ alloy by oxidation at 543 K. Almost complete conversion in the hydrogenation of cyclohexene (523 K, hydrogen/cyclohexene = 9) was achieved with the catalyst prepared by a 10-h oxidation[207]. The conversion with the as-received sample was only about 5%.

5. Surface modification

Adsorption and/or transformation of appropriately selected molecules can alter the surface characteristics of metal catalysts thereby affecting both activities and selectivities.

The poisoning of the hydrogenation of propylene and cyclohexene was caused by decomposing Et_3SiH on silica-supported Ni, Rh, Pd, Pt and Cu catalysts[208]. Different silanes (Et_3SiH, Pr_2SiH_2 and $PenSiH_3$) were shown to exhibit increasing poisoning activity with increasing number of Si−H bonds in the molecules in the hydrogenation and isomerization of 1-pentene[209]. The sensitivity of the metals to poisoning increased in the sequence Rh < Cu < Pt. Decomposition of Et_3SiH resulted in a gradual loss of activity in the hydrogenation of cyclohexene over supported Pd and Pt catalysts[210]. Upon oxidation, however, the poisoned catalysts regained their activities after hydrogen treatment. Moreover, in some cases, activities greater than the original level were detected. These changes in activity were attributed to the formation of a new, different surface.

Sulfur poisoning affects both hydrogenation and isomerization of alkenes[21]. The decrease in activity of hydrogenation of 1-butene over Pd pretreated with thiophene is, however, much more pronounced than the decrease in isomerization[211]. Isomerization, for example, still takes place on a catalyst which is inactive in hydrogenation. Since isomerization does not consume hydrogen, this was interpreted to demonstrate that sulfur affects essentially hydrogen activation.

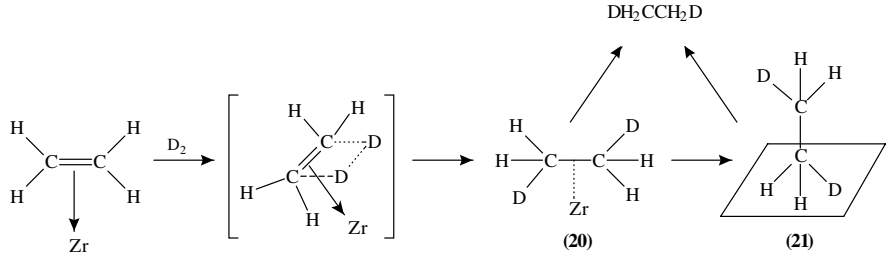
The effect of quinoline and CCl_4 on the activity of silica-supported transition metal catalysts in the hydrogenation of 1-hexene and cyclohexene was studied[212].

6. Hydrogenation of alkenes over metal oxides

Much less information is available on the mechanism of the hydrogenation of alkenes on oxides. Among these oxides ZnO and ZrO_2 have been the most intensively studied.

Hydrogenation of alkenes on ZnO was studied by means of IR spectroscopy[17]. The interaction of π-adsorbed ethylene and ZnH species was concluded to yield adsorbed ethyl, which reacts with ZnOH to form the product ethane. Higher alkenes adsorb as allylic species. Active sites for hydrogenation and those for exchange and isomerization are independent of ZnO. As a result, the main product in the deuteration of alkenes is the d_2 isotopomer.

Different features of the hydrogenation of ethylene on ZrO_2 were revealed in recent studies[213]. Over this oxide preadsorbed hydrogen species (ZrH and OH) are not reactive in hydrogenation but replaced by π-bonded ethylene[214]. Hydrogen without dissociative adsorption, in turn, is believed to participate in hydrogenation. The H_2 molecule is activated on (or in the vicinity of) the site where ethylene is already adsorbed. Both H atoms are instantaneously involved in the product without the participation of the ethyl species to form side-on adsorbed **(20)** and end-on adsorbed ethane **(21)** (Scheme 3).



SCHEME 3

The reaction of propylene on ZrO_2 exhibits the same characteristics as on other oxides. Propane-d_2, for example, is selectively formed in the deuteration process, with no hydrogen exchange in propylene[215]. New features appear, however, when zirconia is dispersed on other oxides (alumina, silica, titania)[215,216]. A considerable rate increase is observed and exchange in propylene proceeds simultaneously with addition via the associative mechanism through the common intermediate *n*-propyl and *s*-propyl species.

The activity of $Mo-Al_2O_3$ in alkene hydrogenation has been recently correlated with the oxidation state of Mo[217]. A sharp increase in activity of propylene hydrogenation (347 K, flow microreactor) was observed and an increased abundance of Mo^{3+} species was detected when the catalyst was reduced at temperatures higher than 573 K. Reduction at even higher temperatures (at and above 973 K), in turn, resulted in the formation of significant amounts of Mo metal and hydrogenolysis became the predominant reaction.

Perovskite oxides, though they characteristically promote hydrogenolysis, were demonstrated to exhibit activity in the hydrogenation of simple alkenes[218]. Exclusive hydrogen addition to ethylene occurs over $LaCoO_3$ below 420 K[219]. Increasing temperature, however, brings about sharply increasing activity of hydrogenolysis of the product saturated hydrocarbons.

Photocatalytic decomposition of water over various metal oxides to H_2 and O_2 is of current interest, representing an approach to the utilization of solar energy. This catalytic system catalyzes C−C bond fission and, to a lesser extent, the hydrogenation of multiple bonds. Titania[220,221] and its binary oxides[222] have been studied most in the hydrogenation of simple alkenes (ethylene, propylene and butenes). This photohydrogenation activity is,

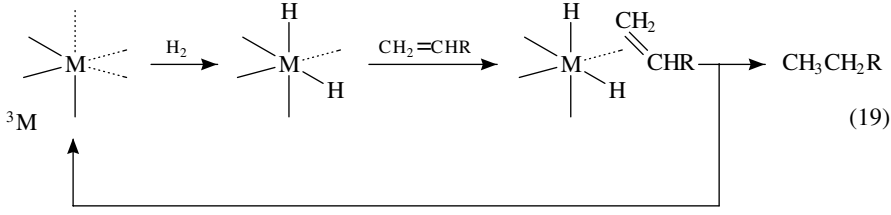
however, enhanced significantly by the addition of small amounts of metals (Pt, Pd, Ni and Cu)[223,224]. The highest activity and selectivity were achieved by loading Pt and Cu in an optimum ratio into titania[224]. Increasing partial pressure of water led to further increase in the yield of ethane in the photohydrogenation of ethylene[223].

7. Alkene hydrogenation as probe reaction

Practical heterogeneous metal catalysts (metals dispersed on inert supports) possess different types of surface atoms exhibiting different adsorption and reaction characteristics. These atoms (sites) are thought to catalyze various processes (exchange reaction, isomerizations, both double bond migration and *cis–trans* isomerization, hydrogen shift and hydrogen addition). Different sites may also catalyze the same reaction with different activation energies, i.e. different reaction rates are expected. Attempts have been made to find correlation between the various surface sites (atoms) and the reactions they catalyze by studying the transformation of appropriately selected probe molecules under carefully controlled reaction conditions. This approach can provide direct information on the selectivity of various surface sites and has the significance to establish product–site correlations.

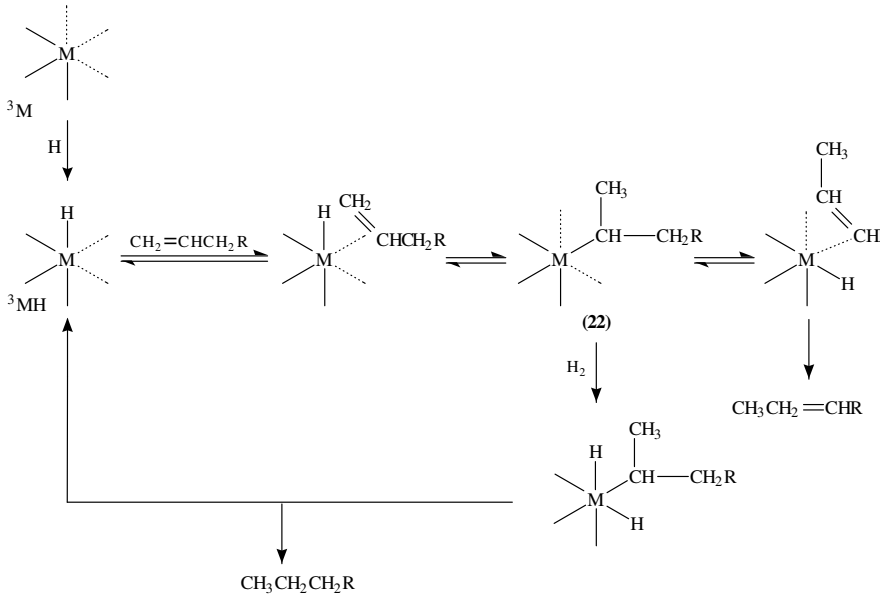
Metal surfaces contain three principal types of sites. First Ledoux[225] correlated the reactions taking place with possible surface sites. Then Siegel[226] suggested to relate these sites to organometallic coordination sites with different degrees of coordinative unsaturation. ^{3}M sites with three coordinative unsaturations are analogous to corner (kink) atoms of metal surfaces. ^{2}M sites (two coordinative unsaturations) and ^{1}M sites (one coordinative unsaturation), in turn, correspond to edge (step) and face (terrace) atoms, respectively.

Augustine developed a technique to determine the relative number of these various active sites present on supported metal catalysts. The method has been applied to characterize Pt[174,227–229], Rh[230] and Pd[151,230] catalysts. During an STO olefin hydrogenation process each site reacts only once per turnover sequence. The product composition, therefore, could be related directly to the densities of the various types of sites present. In an STO sequence measurement, the catalyst is first exposed to hydrogen to achieve complete coverage followed by the injection of 1-butene. Product composition (alkane, initial and isomerized alkenes) is determined and then a portion of the alkene which remained on the catalyst is removed by a second hydrogen pulse as alkane. The amount of alkane formed originally is related to the number of ^{3}M sites present[229] catalyzing hydrogen addition according to equation 19. These sites later were directly correlated with corner atoms[231].



(19)

The amount of alkane formed from the second hydrogen pulse determines the number of ^{3}MH sites[228,229,231]. Since these sites catalyze hydrogen addition in a two-step process (Scheme 4) involving a metalalkyl intermediate **(22)**, they are also called two-step hydrogenation sites or metalalkyl sites. From the degree of isomerization the number of ^{2}M sites (edge atoms) present on the catalyst surface can be calculated, although isomerization can

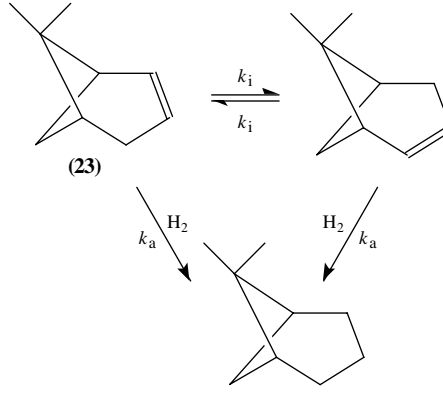


SCHEME 4

also occur on ^{3}MH sites (Scheme 4). Surface sites of supported Pd catalysts characterized by the same technique were shown to exhibit different reactivities than those of Pt[151].

The STO method was used to characterize Pt-CPG catalysts with different metal loadings and reduction temperatures to determine the most useful preparation conditions for maximum hydrogenation activity[232] and explore the effects of various heat treatments for the reactivation of deactivated samples[233].

Another approach in surface characterization of metal catalysts by alkene transformations is the use of (+)-apopinene **(23)** as the probe molecule[194,196]. Due to its peculiar geometry this molecule can expose only one face of its double bond to a catalyst surface.



SCHEME 5

Therefore, double bond migration leads to its enantiomer, which has reactivities identical to the starting enantiomer for a symmetrical surface (Scheme 5).

This technique was used to characterize supported Pt[234] and Pd[235] catalysts by measuring the extent of isomerization (by determining the change in optical rotation during hydrogenation) and the degree of saturation. These data allow one to calculate the ratio of isomerization to addition, k_i/k_a, which was found to go through a maximum at about 60% dispersion (percentage exposed metal atoms). This maximum occurs approximately at the maximum in the number of edge sites on fcc octahedral crystallites. These sites are identified as ^{2}M sites catalyzing isomerization, whereas ^{3}M sites can catalyze both addition and isomerization.

Alkene hydrogenation was also suggested to test for mass transfer effects during liquid-phase hydrogenations[236,237]. The method is based on the linear poisoning of hydrogen addition to alkenes (cyclohexene and apopinene) by CS_2. When the active sites of Pd or Pt catalysts are titrated with CS_2 the decrease in rate is linear unless mass transfer limitations occur.

B. Hydrogenation of Dienes and Polyenes

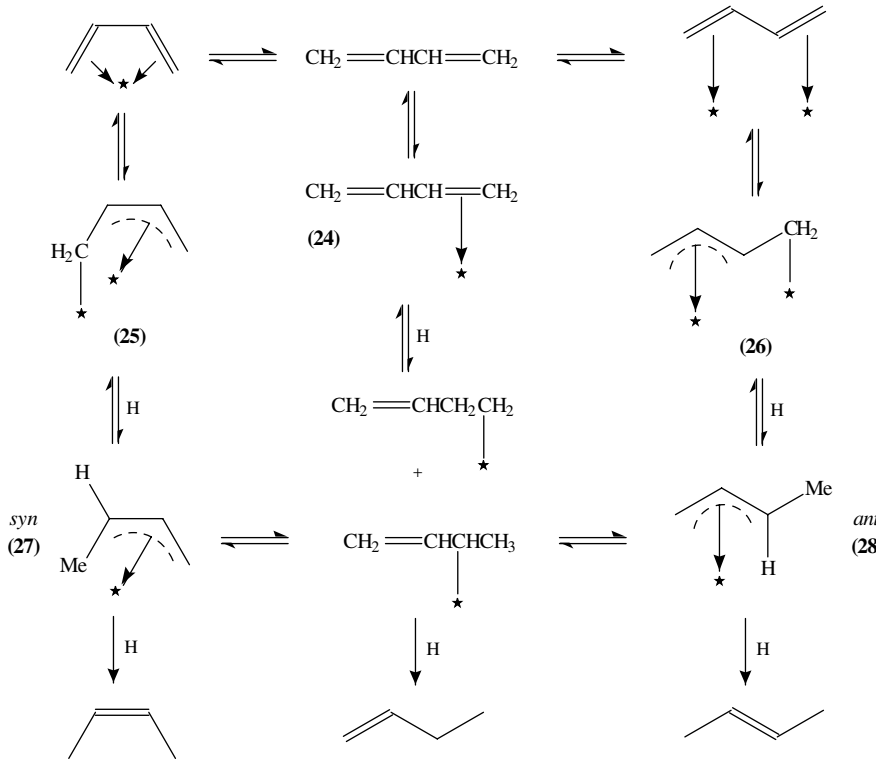
Selective hydrogenation of a diene means the saturation of one of the double bonds to form a monoene. Such regioselective saturation, called semihydrogenation, is essentially governed by the same effects that determine the relative reactivities of monoalkenes during competitive hydrogenation in binary mixtures: a terminal double bond exhibits higher reactivity than other, more substituted double bonds and, therefore, it is saturated preferentially (see Section IV.A.1). A different kind of selectivity also arises when a diene is hydrogenated, since the newly formed monoene and the unreacted diene compete for the same active site.

1. Conjugated dienes

The reactivity of conjugated dienes, in general, exceeds that of monoenes and even nonconjugated dienes. This is attributed to the fact that in these compounds the entire π system is involved in adsorption through di-π-coordination which is more favored than the di-σ mode of adsorption of a single double bond[238]. Due to its practical importance (see Section IV.C) and theoretical significance the semihydrogenation of 1,3-butadiene has been studied extensively and data are also available for isoprene and 1,3-pentadienes.

a. Open-chain dienes. Monohydrogenation of 1,3-butadiene can take place by either 1,2 or 1,4 addition to produce 1-butene or 2-butenes, respectively. It was established that on palladium 1-butene and *trans*-2-butene are the main products with only a small amount of *cis*-2-butene[239]. Other Group VIII metals[240,241], and Cu[240] and Au[242], catalyze mainly 1-butene formation and the isomeric 2-butenes are formed in roughly equal amounts. These metals are classified as Type A catalysts (dominant 1-butene formation, near-unity *trans*:*cis* ratio), whereas Pd (as well as Fe) is a Type B metal (1-butene and *trans*-2-butene are the main products). Rare-earth metal clusters (Sm and Yb) studied recently yield 2-butenes in high amounts[161]. Catalyst pretreatment and the form of catalyst (supported or bulk metal), however, can markedly affect selectivity[240].

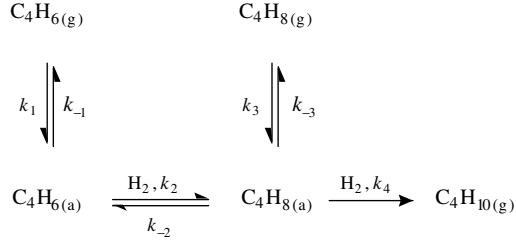
The two types of addition were proposed to occur through different surface absorbed forms[240,243] (Scheme 6). The **24** π-adsorbed intermediate is suggested to result in 1,2 addition (Type A metals). The **25** and **26** π-allyl species, in contrast, ensure 1,4 addition. The selectivity of the formation of stereoisomeric 2-butenes, in turn, depends on the interconversion of the possible half hydrogenated *syn* and *anti* surface π-allyl complexes



SCHEME 6

(**27** and **28**)[243]. Since the s-*trans* conformer of 1,3-butadiene is much more stable than the s-*cis* conformer, the high *trans/cis* ratio over Pd indicates that the interconversion of the adsorbed π-allyl complexes is not significant.

A general scheme of hydrogenation of 1,3-butadiene, the 'rake' mechanism, is given in Scheme 7. Two kinds of selectivity for the intermediate butenes can be defined. Selective formation of butenes can be expected if $k_2 > k_4$ (mechanistic selectivity). On the other hand, if $k_1/k_{-1} > k_3/k^*_{-3}$, adsorption of the diene prevents the readsorption of butenes and hence the consecutive hydrogen addition cannot take place (thermodynamic



SCHEME 7

selectivity). All experimental observations indicate that Pd exhibits the highest selectivity for semihydrogenation. Over Pd the rates of saturation of the first double bond and the consecutive hydrogenation of the product butenes have the same order of magnitude. Selectivity, therefore, is attributed to the stronger adsorption of the diene compared to that of the monoene formed[97,238,244,245].

Hydrogenation of 1,3-butadiene exhibits antipathetic structure sensitivity, i.e. turnover numbers decrease with increasing dispersion[246]. This was observed on Pd[247,248], Pt[249] and Rh[250], and suggested not to be an intrinsic property of these metals[251]. Overcomplexation (autoinhibition), i.e. too strong interaction of the diene with the catalytic site at high dispersion, was invoked to explain this behavior. Electron-donating additives like piperidine are able to increase the activity by modifying the adsorption properties through electron donation[251–253]. Mechanistic selectivity was assumed to be dependent on the ability of metals to form carbene species[251]. Since carbenes are directly transformed to butane, carbene-forming metals (Pt and Rh) are characterized by low selectivity for semihydrogenation.

Under practical hydrogenation conditions the selectivity of semihydrogenation decreases with increasing conversion even on Pd. Catalyst modification, however, was found to result in significant improvements. Bimetallic Pd catalysts containing Cu[254], Ag[255,256], Sn[257], Pb[257,258], Sb[257], Cr[259], Co[260] and Ni[261] as the second metal, proved to be especially selective. The general observation is that addition of the second metal leads to a decreased activity but the selectivity increases. The improved selectivity is suggested to be due to the modification of the electronic structure of Pd[257,259,261,262]. This, in turn, results in a change in the relative adsorption strength of the diene and intermediate alkene. When added to Pd–Al_2O_3, a similar effect was attributed to ceria[262]. The beneficial role of Cu is, however, accounted for in a different way. In this case, the concentration of available surface hydrogen decreases due to the poor ability of Cu to adsorb or absorb hydrogen[254]. The further hydrogenation of monoenes, therefore, is severely retarded.

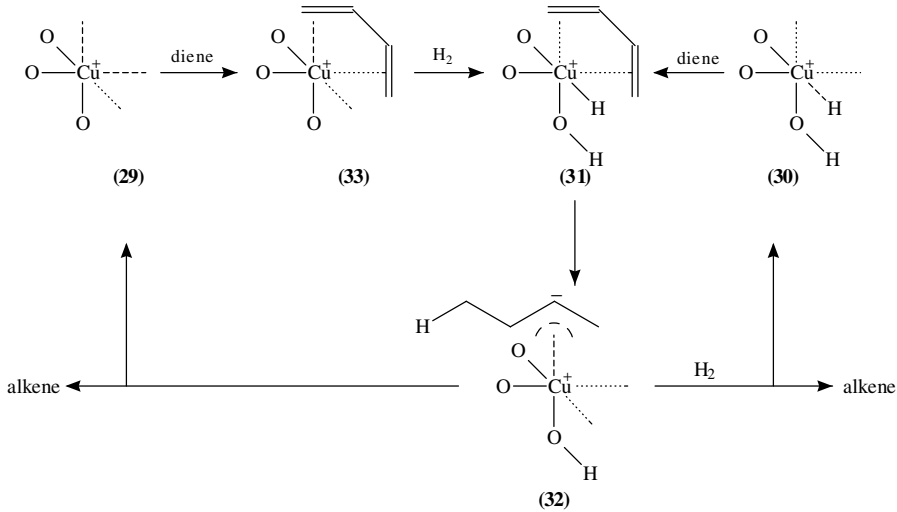
Bicomponent amorphous alloys also exhibit high selectivity[15,16]. A rapidly quenched $Cu_{70}Zr_{30}$ alloy after activation (annealed in hydrogen at 473 K for 16 h) showed an activity one order of magnitude higher than that of copper foil and 100% selectivity during the first stage of reaction[263,264]. The product distribution resembled that of Type A catalysts. This catalyst exhibited excellent characteristics to remove 1,3-butadiene from industrial olefin feedstocks[265]. At 348 K, for example, a mixture of butenes containing 3% 1,3-butadiene could be converted to a diene-free product with only 1.63% butane. It also hydrogenates 1,3-butadiene in ethylene with a selectivity of 95% with no hydrogenation of ethylene. The Raney-type catalyst prepared by HF treatment of a pulverized $Cu_{62}Zr_{38}$ glassy alloy showed the same activity enhancement in the hydrogenation of isoprene as in ethylene hydrogenation[198]. In contrast with the above observation, a $Ni_{63.7}Zr_{36.3}$ alloy is far less active in the amorphous state than in the crystalline form, but it exhibits much higher selectivity to butenes (97% vs 79% at 80% conversion)[266].

Rapidly quenched $Ni_{81}P_{19}$ and $Ni_{62}B_{38}$ alloys[200,201,267] and a $Pd_2Ni_{50}Nb_{48}$ ribbon[268] are also selective catalysts in the hydrogenation of conjugated dienes (1,3-butadiene and isoprene). They show the usual activity enhancement after appropriate pretreatments (dilute HNO_3, then oxidation and reduction, see Section IV.A.4.c) attributed to electron-deficient Ni species.

Detailed studies have been carried out with metal–boron (Ni–B, Pd–B, Pt–B) and metal–phosphorous (Ni–P, Pd–P) films prepared by radiofrequency sputtering[269–272]. Pt hardly interacts with boron and shows the low selectivity of the pure metal[269]. Interaction between Ni or Pd and the metalloids results in a change in the electron density of

Ni and Pd, which, in turn, brings about a change in the selectivity of the hydrogenation of dienes. The best selectivities are around 98–99%. Further enhancement could be achieved by the heat treatment of Pd–B and Pd–P with high metalloid content[271,272]. This was attributed to the formation of new, highly selective phases, for example Pd_3B and Pd_5P_2.

Conjugated dienes are hydrogenated on copper chromite[273–276] and copper aluminate[273]. Once activated by hydrogen they are able to hydrogenate dienes even in the absence of gaseous hydrogen, i.e. they behave like a reversible hydrogen reservoir. The catalytic site involves cuprous ions in an octahedral environment and occluded hydrogen species (hydride ions) located in anionic vacancies. According to the mechanism assumed by studying isomeric C_5 dienes[273,276] (Scheme 8) the allyl carbanion **32** is the major surface species. The catalytic cycle is **30–31–32–29** over the prereduced catalyst when occluded hydrogen is present. When gaseous hydrogen is used, in turn, the **29–33–31–32–30** route is operative.



SCHEME 8

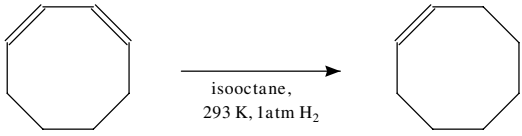
Metal oxides (CaO, MgO, CeO_2, ZrO_2 and La_2O_3) are active and selective in the hydrogenation of conjugated dienes at ambient temperature[277]. The rate is about 1 or 2 orders of magnitude higher when the reaction is carried out by hydrogen transfer relative to the hydrogenation with gaseous hydrogen. In addition, the hydrogen transfer process exclusively yields monoalkenes. *trans*-2-Butene is formed in very high yield (90–95%) over CeO_2. Exclusive 1,4 addition was proved by the transformation of 1,3-butadiene-d_6.

b. Cyclic dienes. Hydrogenation of simple, nonsubstituted cyclic conjugated dienes (cyclopentadiene and 1,3-cyclooctadiene) is less complicated, since only a single cycloalkene is formed. Cyclopentene is produced in excellent yield by the selective hydrogenation of cyclopentadiene over $Cu–Al_2O_3$ aerogel in the gas phase (453–493 K, 100% selectivity at 92% conversion)[278]. The Eley–Rideal mechanism[88,89] was shown to be operative with the RDS between adsorbed cyclopentadiene and gas-phase hydrogen.

Similar high selectivity values were reported when the reaction was carried out in the presence of colloidal Pd[279,280].

The characteristics of the selective hydrogenation of cyclopentadiene over Pd–P and Pd–B alloys were very similar to those observed for 1,3-butadiene[271,272]. The selectivity increased with increasing P and B content and by the heat treatment of the alloys with higher metalloid content. Over catalysts containing more than 20% P the selectivity was 100%. Amorphous Ni–B and Ni–P catalysts prepared by chemical reduction proved to be more active than Raney nickel[281,282]. Activity was increased by the addition of Pd whereas hydrogenation in the presence of pyridine resulted in increased selectivity[281].

Pd is the preferred metal for the partial hydrogenation of 1,3-cyclooctadiene. Pd–$CaCO_3$, Pd–C and Pd–γ-Al_2O_3 exhibit high selectivity[283] (equation 20)[256]. Addition of Ag to Pd decreased the activity, without affecting selectivity[256].



(20)

Pd–C: 99% selectivity at 99.8% conversion
Pd–γ-Al_2O_3: 99.2% selectivity at 100% conversion

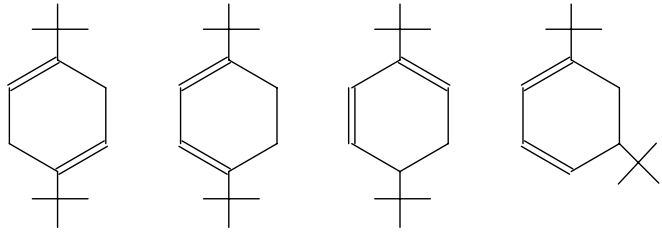
Pumice-supported Pd showed similar selectivity (100% up to complete conversion) which is due to the very low hydrogenation rate of the intermediate cyclooctene[284]. The activity was invariant up to 35% dispersion, then decreased slowly, which is explained by the increasing electron density of Pd brought about by Na^+ and K^+ ions present in the support. The decrease in both activity and selectivity is anticipated when Pd is alloyed with Pt, a nonselective metal[285]. The substantial decrease in activity of Pd–Pt–pumice catalysts (TOF values are 90 s^{-1} for Pd–pumice and 12 s^{-1} for Pd–Pt–pumice) was attributed to the reduced amount of Pd_4 units necessary for the surface reaction and the very strong Pt–diene bond.

High selectivity was also observed on a silica-supported Fe–Cu catalyst prepared by coprecipitation (333 K, 10 atm H_2, ethanol)[286] and over polymer-protected colloidal Pd–Pt cluster catalysts (303 K, 1 atm H_2, ethanol)[287,288]. In contrast with the above observation, the activity of the bimetallic alloy was 1.4–3 times higher than that of the monometallic Pd cluster reaching the maximum activity at a composition of Pd/Pt = 4:1.

Rapid uptake of one equivalent of hydrogen was observed when 1,3-cyclooctadiene was hydrogenated over colloidal Pd supported on PVP[289]. The yield of cyclooctene was 99.9% (303 K, 1 atm H_2). Alcohols, particularly methanol, were found to be good solvents. The activity of PVP-protected colloidal Cu–Pd alloys[290] reached the activity of pure Pd at a molar composition of 1:1. Both the presence of the protective polymer and the Cu/Pd ratio affect selectivity. It is assumed that PVP works as a position-blocking ligand whereas Cu acts by releasing electrons. These actions weaken the coordination of monoene to Pd but do not alter significantly the strength of diene–catalyst complexation.

Siegel carried out detailed studies with di-*tert*-butyl-substituted cyclohexadienes with the aim of clarifying their role as intermediates in the hydrogenation of di-*tert*-butylbenzenes on a 5% Rh–alumina catalyst[291]. The three isomeric dienes (**34**, **35**, **36**)

isolated in the hydrogenation of 1,4-di-*tert*-butylbenzene were shown to exhibit increasing reactivity (1:3:30) and increasing ability to exclude intermediate alkenes from the catalyst. Of the five isomeric dienes formed from 1,3-di-*tert*-butylbenzene the 1,5-di-*tert*-butyl-1,3-cyclohexadiene **(37)** interacts most strongly with the catalytic site[292].



(34) **(35)** **(36)** **(37)**

c. Sulfur poisoning. Much attention has been paid to the effect of sulfur poisoning on the hydrogenation of conjugated dienes, since pyrolytic gasoline streams, undergoing catalytic hydrorefining to selectively hydrogenate diolefins, always contain various sulfur compounds.

Sulfur is known to increase the selectivity of the semihydrogenation of dienes[21]. Improved 1,4 addition observed on Ni presulfided with H_2S in the hydrogenation of 1,3-butadiene was attributed to a change in the electron density of nickel[293]. A similar improvement was observed on presulfided Pd[211]. The yield of cyclopentene was markedly increased when cyclopentadiene was hydrogenated on a Pd–C catalyst partially poisoned by sulfur (97% vs 75%)[294]. Improved selectivity, in turn, was not always manifested on various crystallographic Pt faces[295–297].

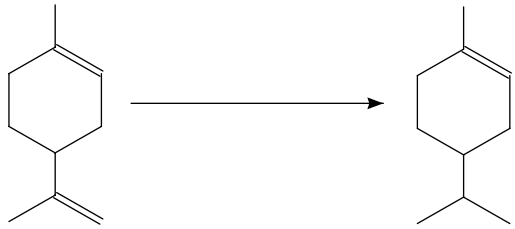
The way sulfur treatment is applied gives rise to pronounced differences in selectivities[21]. A decrease in the overall alkene yield was observed when 1,3-butadiene was hydrogenated on presulfided Pd. In contrast, much improvement in selective alkene formation from isoprene was achieved when sulfur was present in the feed. In the latter case adsorption competition was suggested to account for the favorable effect of sulfur.

2. Nonconjugated dienes

The problem of selective hydrogenation of one double bond of a nonconjugated diene is essentially the same as that of competitive hydrogenation of alkene mixtures (see Section IV.A.1). The less substituted double bond of the diene, consequently, can preferentially be hydrogenated under appropriate reaction conditions. The use of nonisomerizing catalysts, in general, is recommended to achieve such regioselective reaction.

Industrial processes were developed for the selective partial hydrogenation of 4-vinylcyclohexene with Ni catalysts exhibiting minimized isomerization activity in the presence of additives[298,299]. For example, supported nickel arsenides prepared by reducing nickel arsenate with $NaBH_4$ display high selectivity in the formation of 4-ethylcyclohexene (96% selectivity at 96% conversion on Ni–As–Al_2O_3, 398 K, 25 atm H_2, acetone additive).

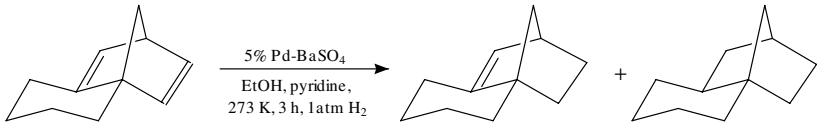
Metal-assisted reductions with $NaBH_4$ can be used to hydrogenate various functional groups[41,42]. The Co^{2+}–$NaBH_4$ system selectively reduces limonene at the less substituted double bond[300] though W-4 Raney Ni proved to be more effective[301] (equation 21).



(21)

$NaBH_4$, $CoCl_2.6H_2O$, EtOH, 273 K, 12.5 h 79% yield
W-4 Raney Ni, RT, 1 atm H_2 96% yield

The hydrogenation of norbornadiene possessing two double bonds of identical reactivity, in contrast, yields the saturated product[300]. Regioselective semihydrogenation of a similar molecule with two different double bonds, however, can be achieved with a supported Pd catalyst[302] (equation 22).



40 1 (22)

Since differences in the hydrogenation rates of variously substituted monoalkenes were found over Pt–zeolite catalysts modified by CVD (see Section IV.A.1) these catalysts were anticipated to exhibit regioselectivities in the hydrogenation of dienes. Selective saturation of the less substituted double bonds of linear and cyclic dienes was indeed achieved over Pt–zeolite A and Rh–zeolite A catalysts treated with tetraethoxysilane[78] or diethoxydiphenylsilane[79,80] (Table 13).

Nonconjugated dienes, as mentioned, react less readily than conjugated dienes. The reactivity of 1,5-cyclooctadiene over an $Fe–Cu–SiO_2$ catalyst, for example, was almost two orders of magnitude lower than that of 1,3-cyclooctadiene[286]. Isomerization (double-bond migration) of nonconjugated molecules to the more reactive conjugated dienes,

TABLE 13. Regioselective semihydrogenation of dienes over CVD-modified Pt and Rh catalysts[a] (298 K, hexane, 1 atm H_2)[78,80]

	1,5-Undeca-diene	1,5-Trideca-diene	1,11-Octadeca-diene	Limonene	8-Cyclohexyl-1,5-octadiene
Pt–zeolite A[b]	5.0	20.8	20.0	59.3	2.4
CVD–Pt(Et)[c]	34.8	65.2	n.a.	87.8	58.9
CVD–Pt(Ph)[d]	74.8	78.7	91.5	n.a.	47.1
CVD–Rh(Ph)[d]	n.a.	n.a.	64.9	91.5	n.a.

[a]CVD–Pt(Et): Pt–zeolite A modified with $(EtO)_4Si$, CVD–Pt(Ph): Pt–zeolite A modified with $Ph_2Si(OEt)_2$, CVD–Rh(Ph): Rh–zeolite A modified with $Ph_2Si(OEt)_2$.
n.a. denotes not available.
Values indicate maximum yield of the corresponding monoalkene with internal double bond.
[b]Catalyst quantity = 60 mg.
[c]Catalyst quantity = 30 mg except for limonene (600 mg).
[d]Catalyst quantity = 250 mg.

therefore, may be beneficial. Isomeric dienes were indeed detected in the hydrogenation of 1,5-cyclooctadiene over Pd catalysts[283,289,303]. The hydrogenation of 1,5-cyclooctadiene is usually less selective[256,283] than that of 1,3-cyclooctadiene, except on colloidal Pd[289]. Phenylacetaldehyde, however, was shown to increase the selective formation of cyclooctene (97.4% and 97.6% selectivity over Pd black and Pd–$CaCO_3$, respectively)[303]. The decrease in selectivity observed on a Pd–Ag–C catalyst relative to monometallic Pd–C (87.6% vs 92.4%) is interpreted in terms of a decrease in the rate of the 1,5- to 1,3-cyclooctadiene isomerization caused by silver[256].

3. Polyenes

There are very few new data on the hydrogenation of polyenes[97,304]. The process is practiced in the partial hydrogenation of glycerides.

C. Industrial Applications

Catalytic hydrogenation of the C=C bond plays an important role in large-scale industrial processes. These are called catalytic hydrorefining and used in the purification of cracker streams[305,306]. Cracking processes produce gasoline and basic raw materials in large quantities for the petrochemical industry. These are ethylene, propylene, butenes and butadiene. Before their further use, however, selective hydrogenation is needed to remove impurities (alkynes and dienes) present. Palladium on alumina is the most selective and widely used catalyst to carry out such purifications. This catalyst transforms diene (and alkyne) contaminants to the corresponding alkenes. The additional advantage of palladium is that it is less sensitive to sulfur poisoning than nickel-based catalysts. Bimetallic Pd catalysts[307,308] and Cu–silica[309] were recently shown to be highly active and selective in such applications.

In C_3 hydrorefining the selective conversion of propadiene (and methylacetylene) present in propylene streams is necessary. Liquid-phase or gas-phase processes are practiced.

C_4 raw cuts of stream crackers typically contain butanes (4–6%), butenes (40–65%) and 1,3-butadiene (30–50%), as well as some vinylacetylene, 1-butyne, propadiene and methylacetylene. First, acetylenes are selectively hydrogenated and the 1,3-butadiene is extracted resulting in butene cut (or raffinate I). Isobutylene is next removed to produce raffinate II which contains linear butenes and some residual 1,3-butadiene. The latter needs to be removed to achieve maximum butene yields. The methods and catalysts for this process are chosen according to the final use of butenes. The demand for polymer-grade 1-butene, for example, has increased recently. Hydrogenation of residual 1,3-butadiene, therefore, must be carried out under conditions to avoid isomerization of 1-butene to 2-butenes[305]. Butenes are also of considerable importance in alkylation. The removal of 1,3-butadiene decreases the acid consumption of the alkylation step and thus improves operating conditions and product quality. In this case, however, hydroisomerization of 1-butene to 2-butene is a desirable reaction, since it upgrades the alkylation feed resulting in better alkylates[310–312]. Oxygenates (alcohols and ethers) have recently gained significance as additives to increase the octane number of reformulated gasoline. Purification of isoamylenes[313] and higher alkenes[314] by removing 1,3-butadiene under conditions of hydroisomerization has the advantage of forming branched (trisubstituted) alkenes which are transformed to tertiary alkyl methyl ethers.

Gasoline hydrorefining is applied to remove polymerizable by-products (isoprene, cyclopentadiene, styrene and indene) from stream-cracked gasoline to prevent gum formation. Partial hydrogenation of dienes to monoalkenes and the hydrogenation of

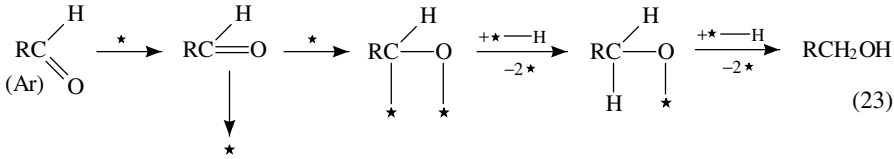
the alkene double bond in arylalkenes without the saturation of the aromatic ring are achieved by Pd, Ni or Ni–W sulfides at elevated temperature (313–373 K) and pressure (25–30 atm)[305].

V. HYDROGENATION OF C=O BONDS

Catalytic hydrogenation of carbon–oxygen double bonds to the corresponding alcohols proceeds readily in the presence of various metal catalysts, usually under ambient conditions. Two reviews were published[1,315] in 1987 and 1991, respectively, since our monograph appeared in 1985[2]. In the latter book this field is summarized in detail with reference to earlier monographs. The present review shortly summarizes the results published recently and discusses the basic conclusions arrived at on the hydrogenation of oxo compounds.

A. Hydrogenation of Aldehydes

Aldehydes are readily hydrogenated to primary alcohols under low pressure conditions (equation 23).



(23)

Pt, Rh, Ru and Ni catalysts are often used, and Cu has also found application, but Pd is much less active in the hydrogenation of aliphatic aldehydes.

The main conclusions of earlier observations in the field of hydrogenation of aldehydes are as follows:

the hydrogenolysis of the product alcohols formed in the hydrogenation of aliphatic aldehydes leading to alkanes is usually not a major side-reaction,

in the hydrogenation of aromatic aldehydes, however, the hydrogenolysis may become significant, mainly in the presence of Pd under acidic conditions and also on other catalysts,

Raney Ni and copper chromite are selective in forming benzylic alcohols from these compounds,

hydrogenolysis can be avoided by carrying out the hydrogenation under mild conditions and in the presence of small amounts of organic or inorganic bases,

CO formed through the decarbonylation of aldehydes may poison noble metal catalysts,

the deactivated catalysts can be activated by the effect of air followed by hydrogen treatment,

hydrogenation of glucose to sorbitol over Ni is an important example of industrial aldehyde hydrogenation.

Recent research activities resulted in the following additional information.

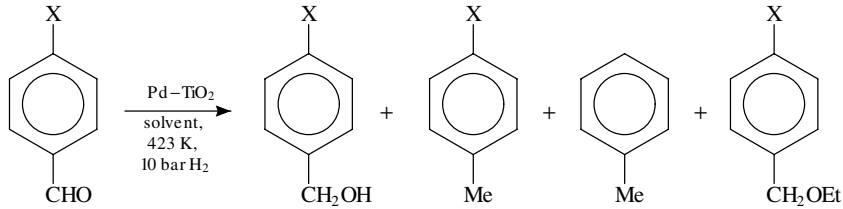
Most data deal with the hydrogenation of aliphatic aldehydes[316–321], mainly that of butyraldehydes[318–321], to the corresponding primary alcohols, and the industrial application of this process. In the majority of cases Ni-based catalysts are used, but new results were disclosed using Cu-containing catalysts[321–324]. The results concerning the active sites of Cu catalysts[322] are especially important. Both Cu^0 and copper ions were shown to participate in the hydrogenation reaction. Catalyst supports play an important role in forming and stabilizing these active sites.

The kinetics of the hydrogenation of propionaldehyde was investigated on different transition metals[325]. The catalytic activity of the metals studied changes in the sequence Pt > Ir > Rh > Ni > Cu > Co.

Kinetic measurements and adsorption studies[325] allowed one to determine the mechanism of the hydrogenation.

A detailed investigation was carried out to study the deactivation of a Ru–alumina industrial catalyst[326] used in the hydrogenation of glucose. This and numerous other patent applications[327–332] testify to the importance of industrial applications of the hydrogenation of aliphatic aldehydes.

Of the aromatic aldehydes the hydrogenation of *para*-substituted benzaldehydes was studied on supported Pd, Pt and Rh catalysts prepared with different types of TiO_2 (equation 24)[333,334].



(24)

X =				
COOH	>90%	max.55%	min.	min.
Me	max.64%	max.77%	max.6%	99%
Cl	0%	max.30%	max.62%	100%

Most experimental data are reported on the use of Pd–TiO_2 catalysts in the hydrogenation. As equation 24 shows, product distribution is considerably affected by the *para* substituent. The formation of benzyl alcohols is favorable on nonacidic supports while acidic supports promote hydrogenolysis. Hydrogenolysis can also be avoided under strongly acidic conditions in the presence of ethanol. In this case, the product benzyl alcohol readily undergoes dehydration to form benzyl ethyl ether.

Transfer hydrogenation of aldehydes with 2-propanol without the formation of side-products is described on a silica-supported Zr catalyst[335].

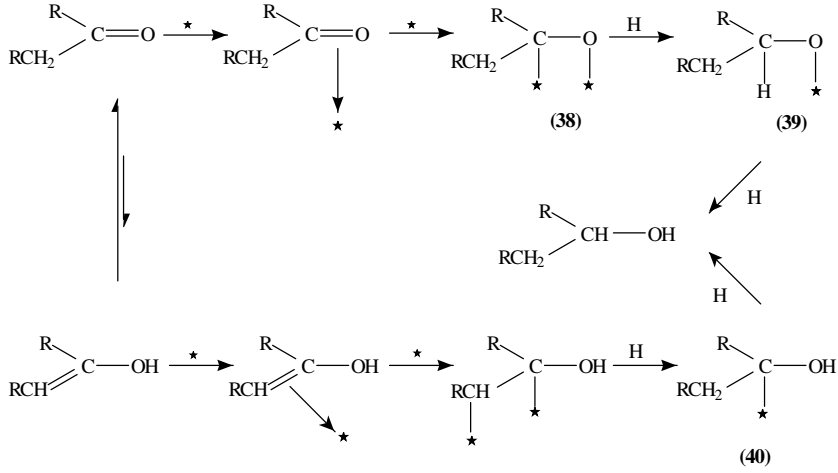
B. Hydrogenation of Ketones

1. Reactivity and mechanistic studies

Selective synthesis of secondary alcohols through the hydrogenation of ketones has long been one of the important reactions of preparative organic chemistry. Numerous reviews were published. An earlier review[2] summarizes the following important conclusions:

The majority of group VIII metals and Cu-containing catalysts can be used. Pt, Ni and Cu catalysts are applied most frequently. Pd exhibits negligible activity in the hydrogenation of aliphatic ketones. It can be used, however, in the hydrogenation of phenyl ketones, since the reactant is able to adsorb on the catalyst surface through the aromatic ring. The rate of hydrogenation of ketones is generally lower than that of the corresponding aldehydes.

The hydrogenation of the carbonyl group can, in principle, proceed in two ways (Scheme 9): by the addition of adsorbed hydrogen to the C=O bond (ketonic mechanism), or by the addition of adsorbed hydrogen to the C=C bond of the enol form (enolic mechanism). Deuteration appears to be a good method to distinguish the two mechanisms: the ketonic mechanism would give rise to a C(1)–D bond, whereas the enolic mechanism



SCHEME 9

leads to a product with C(1)−D and C(2)−D bonds. It has been found that the ketonic mechanism predominates at lower temperatures, while the enolic mechanism does so at higher temperatures (423–523 K)[2].

When cyclic ketones undergo deuterium addition on a fused iron catalyst in the temperature range of 323–483 K, the deuteriogenation proceeds via both the ketonic and enolic mechanisms[336].

Numerous mechanistic investigations have been carried out (see an earlier summary[2] and new publications, e.g. References 325, 337–339). The reaction of **38** or **39** is regarded as the RDS (Scheme 9). Of the two half-hydrogenated states (**39** and **40**), **39**, in principle, is the more stable, since the oxygen–metal bond is stronger than the carbon–metal bond.

In recent years special attention has been paid to the study of support effects. The role of the SMSI was mainly examined concerning its effect on the hydrogenation rate[337,340–347]. The main conclusions of these investigations can be summarized as follows:

TiO_2-supported noble metals exhibit high activity in the hydrogenation of molecules containing carbonyl bonds,

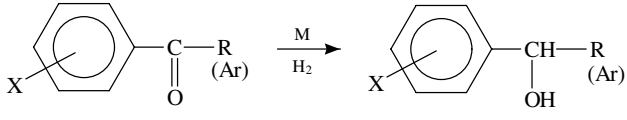
the sites at the metal–support interface are responsible for this high activity,

new sites of high activity appear to reside at the oxide–metal adlineation,

the effects of titania on these reactions are attributed to an interaction between C=O bonds and Ti^{3+} ions located at the perimeter of titania islands.

Table 14 gives characteristic data demonstrating the role of SMSI[342].

Numerous publications have appeared recently disclosing observations on the hydrogenation of aryl or diaryl ketones to yield aromatic carbinols (equation 25)[39,338,343–345,348].



(25)

The hydrogenolysis of the carbinol C−O bond and the perhydrogenation of the aryl groups may be side-reactions. In most cases, hydrogenolysis is undesirable, but selective hydrogenolysis[349] may be the aim of certain synthetic processes. Practical

TABLE 14. Hydrogenation of acetone to isopropyl alcohol (*i*-PrA) over Pt (303 K, $P_{total} = 0.1$ MPa, H_2/acetone = 3.06)[342]

Catalyst	Activity (10^{-6} mol *i*-PrA s^{-1} g_{Pt}^{-1})	Turnover frequency (10^2 s^{-1})	E_{act} (kcal mol^{-1})
Pt powder	0.041	0.74	16.6
5.0% Pt–SiO_2	19.7	1.24	16.3
0.7% Pt–SiO_2	15.7	0.52	15.3
2.1% Pt–η-Al_2O_3	35.7	2.39	18.6
1.9% Pt–TiO_2 (LTR)	106	2.75	14.1
1.9% Pt–TiO_2 (HTR)	238	565	16.3
66% Pt powder + TiO_2 (physical mixture)	0.36	0.66	17.8

applications[350–354] were disclosed in new patents. Pt[345], Pd[39,350–352], Co[348] and Ni[338,343,344] catalysts were applied and disclosed in new patents. Pt[345], Pd[39,350–352], Co[348] and Ni[338] catalysts were applied in different ways (various supports, additives, mainly bases, bimetallic catalysts, solvents). In most cases, carbinol selectivities over 90% can be obtained in the liquid phase, at elevated hydrogen pressure, with 100% or nearly 100% conversions.

2. Stereochemistry

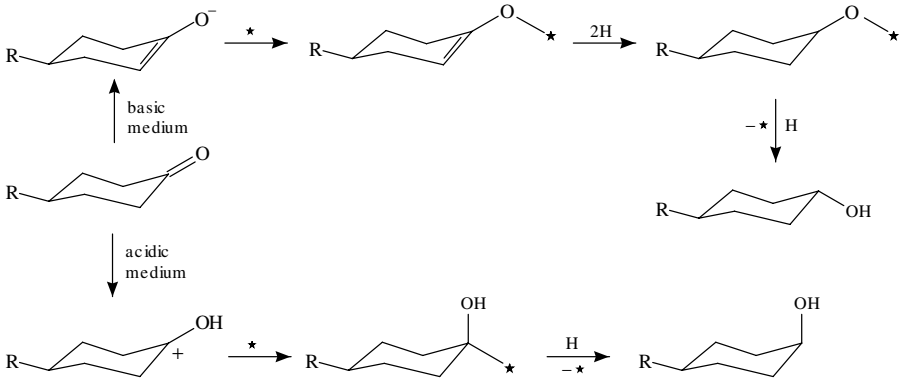
Alicyclic ketones, in general, are the appropriate compounds to study the stereochemistry of addition reactions and, in particular, the stereochemistry of hydrogenation. The stereochemical characteristics of the hydrogenation of the carbonyl group have been studied for 70 years. Numerous observations have been made allowing to formulate certain rules, which, however, are suitable for predicting the stereochemistry of hydrogenation only in certain cases. According to the Auwers–Skita[355,356] rule, reduction with a Pt catalyst in acidic medium leads to a product mixture rich in the *cis* isomer, whereas reduction with a Raney Ni catalyst under neutral or alkaline conditions yields predominantly the *trans* isomer. Later, Skita and then others[2] established that the isomer ratio is affected not only by the pH of the medium, but also by the rate of hydrogenation (fast and slow hydrogenations favoring the formation of the *cis* and the *trans* isomer, respectively), the temperature, the pressure and the catalyst activity.

Barton[357] studied steroid ketones and modified the empirical rule. Catalytic hydrogenation of both hindered and nonhindered ketones in strongly acidic medium (fast hydrogenation) results in an axial OH group, while in neutral medium (slow hydrogenation) an equatorial OH group is formed from nonhindered ketones, and an axial OH group from hindered ketones.

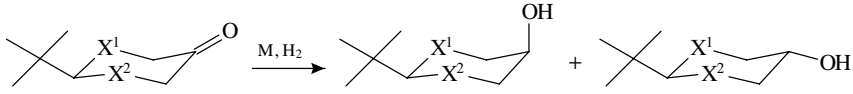
One of the numerous schemes published in the literature with respect to the stereochemistry of hydrogenation reaction is given in Scheme 10.

In spite of the large number of investigations, the characteristic conclusion with respect to the stereochemistry of catalytic hydrogenation of cyclic ketones is that it depends on many factors, namely on the structure of the substrate, the nature of the catalyst and the reaction conditions (solvent, reaction temperature, hydrogen pressure, additives).

An earlier review[2] gives detailed information about the stereochemistry of the hydrogenation of the C=O group. Some recent investigations[358,359] allowed one to demonstrate the decisive role of the structure of the substrate in determining the stereochemistry. Characteristic results shown in equation 26 were achieved by studying alkylcyclohexanones and their corresponding O-containing[358] and N-containing[359] heterocyclic analogues.



SCHEME 10



$X^1 = X^2 = CH_2$	32–77%	23–68%
$X^1 = O, X^2 = CH_2$	70–96%	4–30%
$X^1 = X^2 = O$	90–100%	0–10%

M = Co, Ni, Ru, Rh, Pd, Pt, Ir

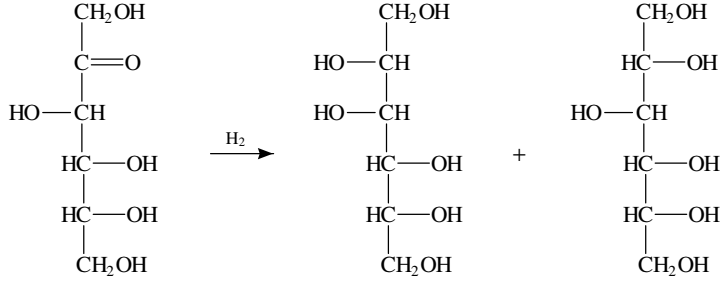
(26)

A high *cis* selectivity is observed in the hydrogenation of oxa- and dioxacyclohexanones. A similar tendency also predominates when the corresponding N-containing analogues are reduced. These results were explained in terms of intramolecular $n_O - \pi_{CO}$ and $n_N - \pi_{CO}$ interactions.

During the hydrogenation of methylcyclohexane-1,4-dione on Pt and Pd catalysts the less hindered 4-carbonyl group is selectively hydrogenolyzed[360].

3. Industrial applications

The study of the hydrogenation of D-fructose is of both practical importance and theoretical significance since it allows one to investigate stereochemical regularities (equation 27).



D-fructose D-mannitol D-sorbitol

(27)

The aim of the investigations is to perform the stereoselective hydrogenation of D-fructose to D-mannitol which is widely used as a sweetening agent and finds also different applications in the food industry. D-Sorbitol, the other isomer, is an important starting material in the preparation of Vitamin C and can easily be prepared from D-glucose. Detailed studies were carried out[362–364] for the stereoselective preparation of D-mannitol. Based on the information of an earlier patent[361] many different Cu catalysts were prepared and tested. With the best catalysts after suitable modification and under appropriate reaction conditions, selectivities of 85–95% at high conversions can nowadays be obtained.

C. Hydrogenation of Unsaturated Carbonyl Compounds

The hydrogenation of unsaturated carbonyl compounds has recently become a research field studied in great detail. The reason is the practical importance of the selective hydrogenation of two different functional groups of these easily accessible compounds. Of the possible products, saturated oxo compounds and unsaturated alcohols are useful synthons in preparative organic chemistry. The increased interest in this field is verified by the appearance of comprehensive works in recent years[1,365–367].

From a thermodynamic point of view, the hydrogenation of the C=C bond is more favorable than that of the C=O group. Since there are numerous other important processes to synthesize saturated aldehydes and ketones, the main objective of recent research efforts is to increase the selectivity of hydrogenation of unsaturated oxo compounds into unsaturated alcohols. The results summarized below clearly indicate the significant success achieved in the selective hydrogenation of unsaturated aldehydes. The hydrogenation of unsaturated ketones, in turn, cannot be accomplished yet with similar selectivities.

1. Hydrogenation of unsaturated aldehydes

a. Reactivity and selectivity. The hydrogenation of α,β-unsaturated aldehydes was mostly studied. The reaction can be carried out according to Scheme 11. The products of hydrogenation are the saturated aldehyde and the α,β-unsaturated alcohol being formed through competitive reactions as well as the saturated alcohol from consecutive hydrogenation of the intermediate compounds.

The hydrogenation of α,β-unsaturated aldehydes to saturated aldehydes is readily achieved over most platinum metal catalysts under mild conditions. The selective synthesis of unsaturated alcohols is, however, much more difficult to perform and several attempts have been made to develop a suitable catalytic system.

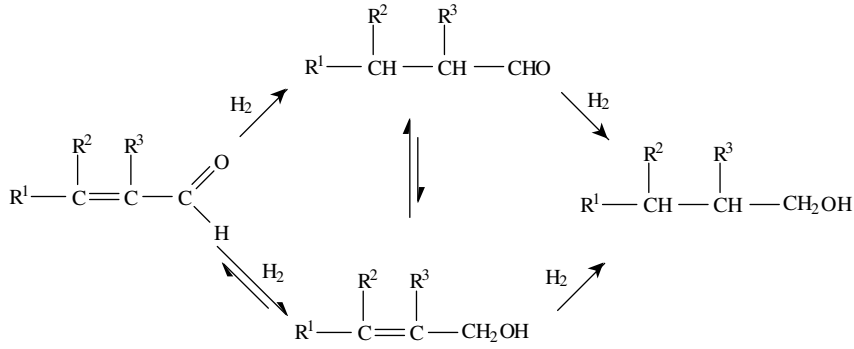
The characteristic results are given in Tables 15–19 arranged according to the substrates investigated. The corresponding reactions are given in equations 28–31 and Scheme 12.

According to the data listed in the tables, most of the investigations were carried out on Ru[370,375,377,379,382,383,386,390,392–403] and Pt[372–375,378–381,387–389,404–416] catalysts. Numerous studies were also carried out with Co[375,384,404,417], Ni[368,375,385,418,419], Rh[371,376,377,379,391,420–422], and Cu[369,371]. Investigations were also performed on Pd[377,416,423], Os[376], Ir[375,376], Ag[424,425] and Re[426]. The fundamental aim is to explore the effect of the catalysts, their modification and the different experimental conditions on the rate of hydrogenation, i.e. to establish the activity and selectivity of the catalysts.

In order to achieve this purpose, investigations were carried out to study the following:

the effect of the preparation and pretreatment of catalysts[372,373,376,384–389,391,395,399,407,409,412,414,417,419,421],

the effect of modification of catalysts by bases[379,382,383,397,398,400,426],



$R^1 = R^2 = R^3 = H$ acrolein

$R^1 = Me, R^2 = R^3 = H$ crotonaldehyde

$R^1 = R^2 = Me, R^3 = H$ 3-Me-crotonaldehyde

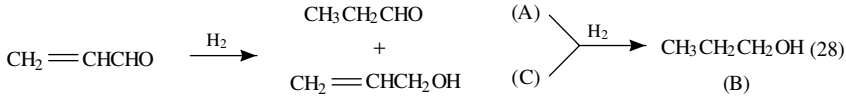
$R^1 = R^3 = Me, R^2 = H$ 2-Me-crotonaldehyde

$R^1 = R^2 = H, R^3 = Me$ methacrolein

$R^1 = Ph, R^2 = R^3 = H$ cinnamaldehyde

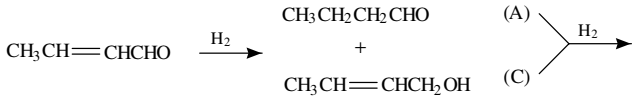
SCHEME 11

TABLE 15. Characteristic data on the hydrogenation of acrolein



Catalyst	Temp. (K)	Conversion (%)	Selectivity (%)			Reference
			A	B	C	
Ni–glass	373				major	368
$Cu–Al_2O_3$	423	67	75	4	7	369
$Cu–Al_2O_3$ + thiophene	423	17	68		29	369
$Ru–Al_2O_3$	363	low	24		45	370
$Ru–Sn–Al_2O_3$	363	low	35	6	53	370
$Ru–Fe–Al_2O_3$	363	low	43		57	370
$Ru–Ge–Al_2O_3$	363	low	71	9	17	370
$Ru–Zn–Al_2O_3$	363	low	76	4	7	370
$Rh–Sn–SiO_2$	353		80		18	371
$Pt–Nb_2O_5$ (LTR)	373		58	24	18	372
$Pt–Nb_2O_5$ (HTR)	373		30	0	70	372
$Pt–SiO_2$	353	low	93	2	2	373
$Pt–Sn–SiO_2$	348	15	70	10	20	374
$Pt–Fe–SiO_2$	353	low	85	7	7	373
Co, Ni, Ru, Ir or Pt on Al_2O_3, SiO_2 or ZrO_2					major	375

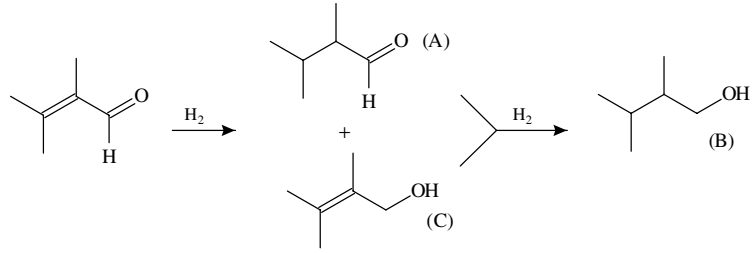
TABLE 16. Characteristic data on the hydrogenation of crotonaldehyde



(29)

Catalyst	Temp. (K)	Conversion (%)	Selectivity (%)			Reference
			A	B	C	
$Cu-Al_2O_3$	423	100	1	98	1	369
$Cu-Al_2O_3$ + thiophene	423	26	59	3	29	369
$Ru-TiO_2$ (LTR)	373	79	51	30	min.	376
$Ru-TiO_2$ (HTR)	373	40	43	38	13	376
$Rh-TiO_2$ (LTR)	373	100	71	17		376
$Rh-TiO_2$ (HTR)	373	41	76	15	min.	376
$Rh-SiO_2$		99	100			377
$Rh-Sn-SiO_2$		51	65	7	28	377
$Ir-TiO_2$ (LTR)	373	73	18	44	15	376
$Ir-TiO_2$ (HTR)	373	29	17	28	48	376
$Pt-SiO_2$	353	<10	98	2		378
$Pt-Ni-SiO_2$	353	<10	92	6	2	378
$Pt-Ga-SiO_2$	353	<10	37	6	56	378
$Pt-Sn-SiO_2$	353	<10	63	6	31	378
$Pt-SiO_2$	353	low	50	34	13	373
$Pt-Fe-SiO_2$	353	low	50	26	28	373
$Pt-Sn-SiO_2$	353	low	50	19	30	373

TABLE 17. Characteristic data on the hydrogenation of other unsaturated aldehydes[a]

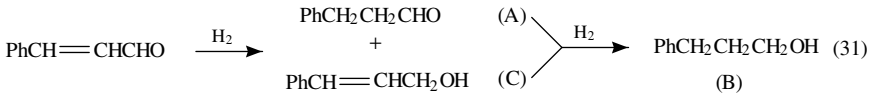


(30)

Catalyst	Substrate	Temp. (K)	Conversion (%)	Selectivity (%)			Reference
				A	B	C	
$Cu-Al_2O_3$	2-Me-crotonaldehyde	423	100	min.	96		369
$Cu-Al_2O_3$ + thiophene	2-Me-crotonaldehyde	423	45	43	38	15	369
Rh–NaY	3-Me-crotonaldehyde	373	25	84	10	6	379
Rh–KY	3-Me-crotonaldehyde	373	25	80	10	10	379
Pt–NaY	3-Me-crotonaldehyde	343	25	48	10	42	379
Pt–KY	3-Me-crotonaldehyde	343	25	42	2	56	379
Pt(110)	3-Me-crotonaldehyde	353	10	35	30	25	380
Pt(111)	3-Me-crotonaldehyde	358	10	8	20	70	381
$Pt-SiO_2$	3-Me-crotonaldehyde	353	low	17	55	21	373
$Pt-Fe-SiO_2$	3-Me-crotonaldehyde	353	low	5	14	80	373
$Pt-Sn-SiO_2$	3-Me-crotonaldehyde	353	low	8	15	78	373
$Pt-Sn-SiO_2$	Methacrolein	353	low	61	11	26	373
$Ru-SiO_2$	3-Me-crotonaldehyde	313	2.1	100			382
$Ru-K^+-SiO_2$	3-Me-crotonaldehyde	313	2.6	27	3	70	383

[a] A: saturated aldehyde, B: saturated alcohol, C: unsaturated alcohol.

TABLE 18. Characteristic data on the hydrogenation of cinnamaldehyde[a]

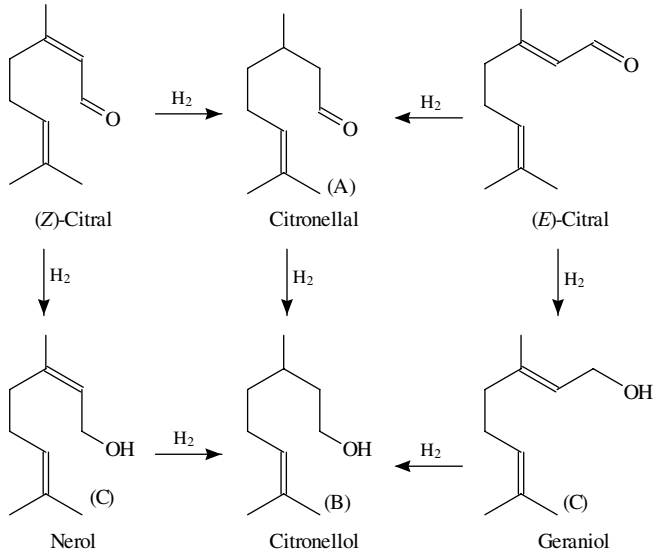


(31)

Catalyst	Temp. (K)	Conversion (%)	Selectivity (%)			Reference
			A	B	C	
$Co-SiO_2$	303	50			93	384
Ni_2B	298	100	99			385
Ru–KY	373	25	16	17	67	379
Ru–C	333	40	30	10	60	386
Ru–Sn–C	333				90	386
Rh–KY	373	25	47	20	33	379
Pt–C	333	70	80	5	10	387
Pt–Nylon	333	95	15	5	80	387
Pt–Nylon + $GeCl_4$	333				94	388
Pt–C + $FeCl_2$	333	75			86	389

[a] A: 3-phenylpropionaldehyde, B: 3-phenyl-1-propanol, C: cinnamyl alcohol (3-phenyl-2-propen-1-ol).

TABLE 19. Characteristic data on the hydrogenation of citral



SCHEME 12

Catalyst	Temp. (K)	Conversion (%)	Selectivity (%)			Reference
			A	B	C	
Cu–Cr–oxide	413	50	70	15	15	304
Ru–C	333	90	30	35	35	386
$Ru-Al_2O_3$	333	50	50	35	15	390
Ru–Sn–C	333	30	15	5	80	386
$Rh-SiO_2$	340		90			391
$Rh-Ge-SiO_2$	340		20		70	391
$Rh-Sn-SiO_2$	340		min.		95	391

the modification of catalysts with metal cations[373,388,389,416,417],

the role of the bimetallic catalysts[370,371,377,378,386,390,391,394,395,404,405,408,410,419,421,422,424,425],

the effect of the modification of catalysts with sulfides and in other ways[369,371,374,384,407,416],

the effect of the supports[369,375,378,379,384,394,396–400,408,410,415,417,425] including the role of SMSI[372,376,378,384,396,406,408,409,415],

the role of the dispersion (particle size) of supported metal catalysts[375,380,381,386,392–395,413,414,417,420,423],

the role of the experimental parameters of the hydrogenation reaction (temperature, pressure, ratio of reactants, effect of solvents, etc.)[369,374,376,388,400,402,403,409,411,416],

effect of the structure of the substrate[369–371,373,374,379,385,413,417],

the mechanism of the hydrogenation reaction[369,372,373,380–382,392,400,406,415,422].

These studies led to the following conclusions:

all metal catalysts which are active in the hydrogenation of alkenes and carbonyl compounds are also active in the hydrogenation of α,β-unsaturated aldehydes,

due to thermodynamic reasons the reactivity of the unsubstituted C=C group in hydrogenation with unpromoted metals is generally higher than the reactivity of the aldehyde group,

saturated alcohols, formed in consecutive hydrogenation, are produced at high conversion,

the activity and the selectivity depend on the preparation conditions and the pretreatment of the catalyst, and the conditions of the hydrogenation (temperature, substrate–H_2 ratio, pressure, solvent, etc.),

metal particle size and morphology also affect selectivity,

the selectivity is strongly dependent on the nature of the metal and the crystal face,

the adsorption through the C=O bond are preferred on metals which have a much larger d-band width and a less filled d-band (Os, Ir),

the selectivity of the formation of α,β-unsaturated alcohols can considerably be increased with various promoters (the highest selectivity could be achieved with nontransition elements),

the promoter can exert its activity only when it is on the metal surface; in the majority of cases, ionic species are responsible for the promoter effect,

the relative accessibility of the groups being hydrogenated and the binding strength to the catalyst of the C=C and C=O groups are important in determining selectivity,

the adsorption through the carbonyl group becomes more significant with increasing steric hindrance of the C=C group,

the trends in activity and selectivity of different catalysts indicate that the substituent effect are mainly steric in origin,

the enhancement in the selectivity of hydrogenation of unsaturated aldehydes on modified Cu catalysts is attributed to both geometric and electronic effects and the relative importance of these effects was found to depend on the nature of the organic substrate.

On the basis of the above conclusions, the selective hydrogenation of α,β-unsaturated aldehydes to unsaturated alcohols can be achieved by taking into account the following considerations and factors:

modification of the metal catalysts with different additives to improve the adsorption and the reactivity of the C=O bond compared to those of the C=C bond,

promotion effects in the hydrogenation of unsaturated aldehydes depend on the way in which cations of the promoter activate the C=O bond and bind the C=C bond,

it appears that the key factor governing the selectivity of the formation of unsaturated alcohols is the tilting of the alkyl chain far from the surface,

factors promoting the formation of α,β-unsaturated alcohols:

the number and the steric demand of alkyl substituents (geometric effects),

modification of supported metal catalysts with the addition of a second metal (bimetallic catalysts) or ions (Lewis acids),

generation of SMSI on supported metals,

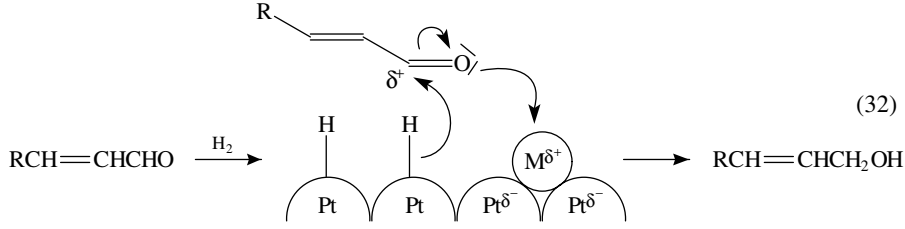
decrease in dispersion (increase in particle size) when supported metal catalysts are used,

when metal–zeolite catalysts are applied, the increased basicity of the zeolite results in increased selectivity,

increase in the partial pressure of substrate.

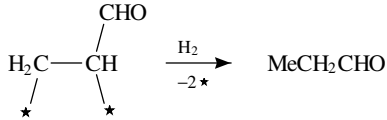
b. Mechanistic studies. It was shown[378] that promotion of Pt by non-noble metals like Ni, Sn, Ga and Ti increased significantly the rate of hydrogenation of the carbonyl group of crotonaldehyde. The presence of Pt and of a metal with a fractional positive charge or a metal cation acting as electron pair acceptor site was shown to be indispensable for hydrogenation of the C=O group. Based on the decrease in the catalytic activity, it was concluded that two types of such a Pt–promoter combination exist in the catalysts studied: the bimetallic phases of Pt–Ni and Pt–Sn, and the interface between Pt and nonstoichiometric titanium and gallium oxide particles. The enhancement of the rate of C=O group hydrogenation is believed to be caused by electron pair donor–acceptor interactions between the positively charged sites and the carbonyl oxygen.

In the case of Pt–Fe, the two metals were suggested[389,421] to be in the metallic state forming an alloy. EXAFS studies indicated an electron transfer from Fe to Pt, which allowed the conclusion that the aldehyde double bond is more easily adsorbed on the 'induced sites'. In the case of Pt–Sn and Pt–Ge, the authors suggested that Sn^{n+} or Ge^{n+} ions (Lewis acids) activate the carbonyl group by enhancing the positive charge of the carbonyl carbon (equation 32).

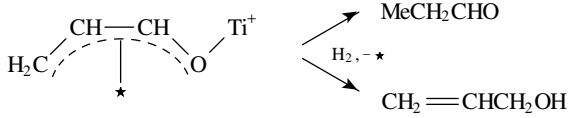


(32)

The use of TiO_2 as support significantly increases the rate of hydrogenation of the carbonyl group of crotonaldehyde to crotyl alcohol as compared to SiO_2[408,415]. Pt–TiO_2 exhibited the highest activity for this reaction. In comparison to silica-supported catalysts it was shown that mainly the rate of C=O bond hydrogenation is enhanced, while differences in the specific activities of C=C bond hydrogenation were significantly smaller. The Pt–Ti interface was suggested to be active for C=O group hydrogenation. The polarity of the active site is suggested to be responsible for the activation of the carbonyl group (equations 33 and 34).

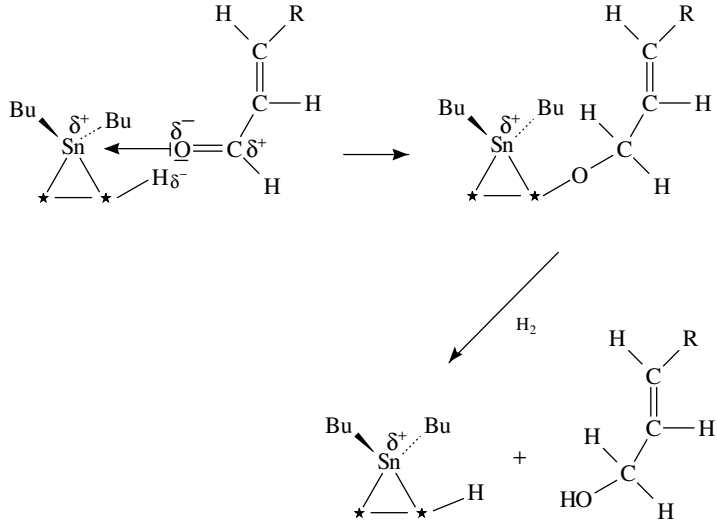


(33)



(34)

In the hydrogenation of cinnamaldehyde[390], a higher selectivity to cinnamyl alcohol was observed on larger Ru particles. This was attributed to a steric effect of the aromatic ring which facilitates the adsorption of cinnamaldehyde through the C=O group on the larger metal particles. In the hydrogenation of citral, a compound without aromatic ring, such a steric effect does not exist. The effect of tin using modified catalysts is twofold[390,421]. One is to poison the Ru or Rh surface sites causing a decrease in the overall rate of reaction. The other effect is to activate the C=O group by facilitating the hydrogen transfer from adjacent Ru or Rh sites. The activating effect can be ascribed to the presence of tin ions which polarize the carbonyl group (equation 35).

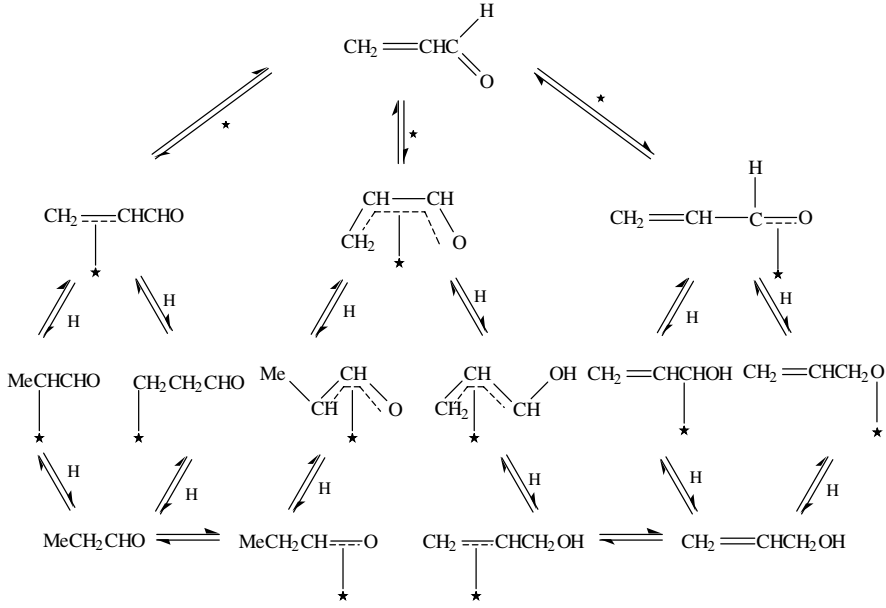


(35)

The pore structure of the zeolites[379] led to higher selectivity toward the unsaturated alcohol in the case of cinnamaldehyde, where steric constraints of the reactant prevented adsorption at the C=C bond on metal sites within the pores. 3-Methylcrotonaldehyde, in contrast, underwent less selective hydrogenation, since the mobility and orientation of this molecule was not inhibited by the zeolite pores. The selectivity of the formation of the unsaturated alcohol could be increased, however, by replacing Na^+ compensating cations in the zeolite with K^+ cations. This modification brought about a decrease in C=C hydrogenation attributed to enhanced metal electron density combined with an increase in C=O hydrogenation due to an interaction between the carbonyl function and the more basic zeolite cation.

The various experimental results with respect to the hydrogenation mechanism of α,β-unsaturated aldehydes led to the proposal of the mechanism depicted in Scheme 13 with acrolein as a model compound[372,427].

The nature of surface species, and consequently the reaction mechanism and thereby the selectivity, are determined by the substrate, the nature of the metal, the type of exposed crystal face and promoters as basic factors. The η^2(C−C), η^2(C−O) and η^4(C−C−C−O)



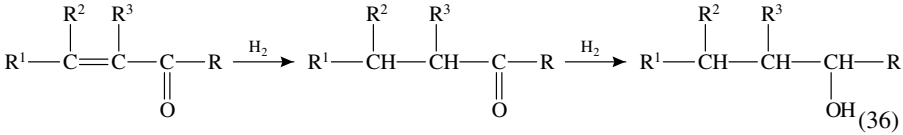
SCHEME 13

surface species were also detected by different spectroscopic methods (See, e.g., References 420, 423).

2. Hydrogenation of unsaturated ketones

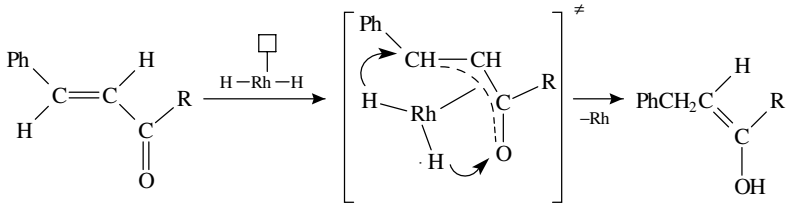
The number of papers on the hydrogenation of unsaturated ketones is significantly fewer than those on α,β-unsaturated aldehydes. A possible reason is that the secondary alcohols formed by the hydrogenation of ketones are less important than the primary alcohols. In addition, the preparation of unsaturated secondary alcohols proved to be less successful although their significance as synthons in preparative organic chemistry is indisputable. The primary products of the catalytic hydrogenation of unsaturated ketones were shown to be the corresponding saturated ketones. Though these are important compounds their preparation by other well-known procedures is more economical.

α,β-Unsaturated compounds, the most extensively studied unsaturated ketones, are easily hydrogenated in both the liquid and the gas phase, even under mild experimental conditions (equation 36),

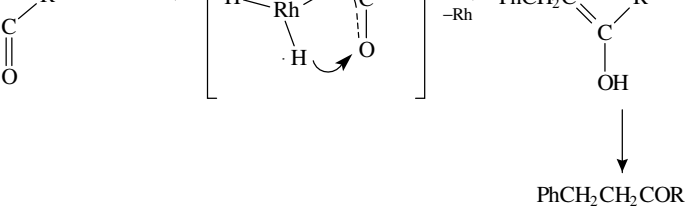


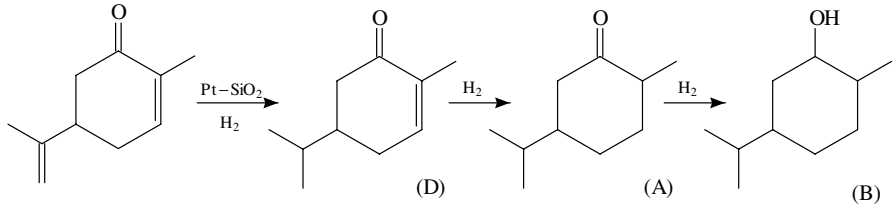
(36)

The catalysts used are Ni, Ru, Rh, Pd, Ir, Pt and Cu. The characteristic experimental results disclosed in recent publications are summarized in Tables 20 and 21. The majority of hydrogenations were carried out in the presence of Rh, Pt and Cu catalysts. Characteristic examples can be seen in equations 37–41, which also illustrate some exceptional behaviors.



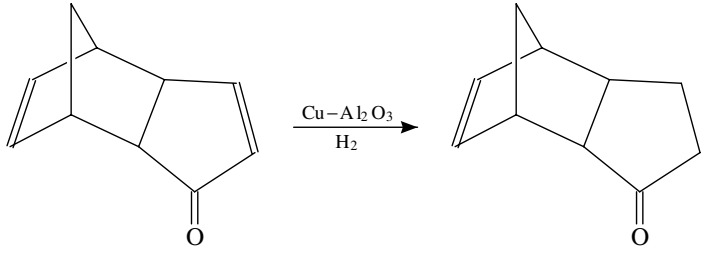
(37)[432]



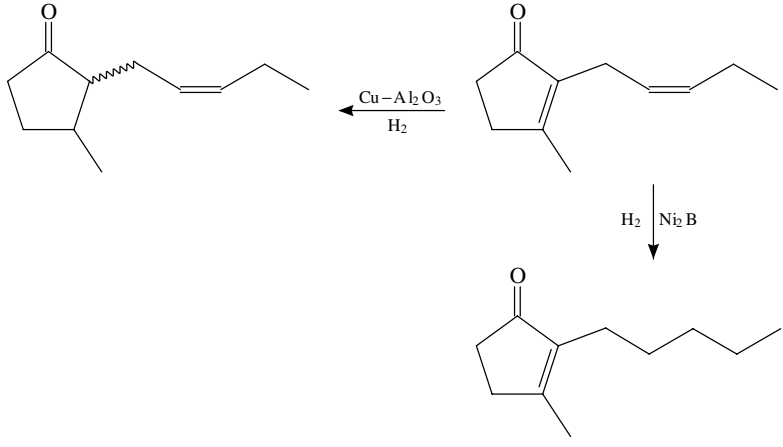


Carvone Carvotanacetone Carvomenthone Carvomenthol

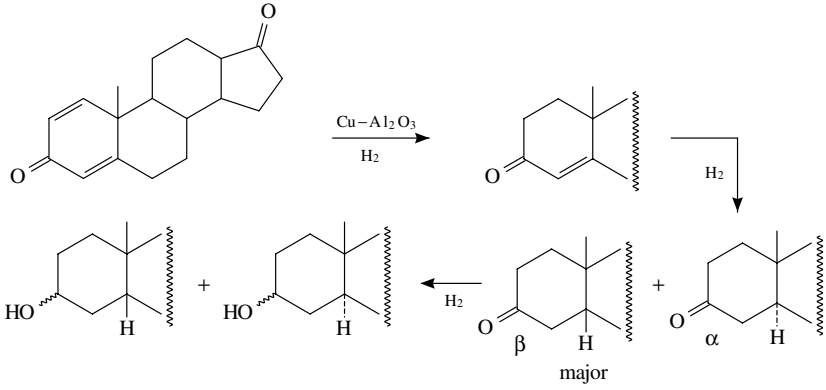
(38)[431]



(39)[56]



(40)[56,385]



(41)

The investigation of hydrogenation reactions included the study of the following variables and problems:

preparation and pretreatment of catalysts[304,369,373,385,431,433–435],

use of bimetallic catalysts[373,428,431],

the role of the support effect[429,430,434], including SMSI[206],

dispersion of the supported metal catalysts[431,434],

TABLE 20. Characteristic data on the hydrogenation of unsaturated ketones[a]

Catalyst	Substrate	Temp. (K)	Conversion (%)	Selectivity (%)				Reference
				A	B	C	D	
$Cu-Al_2O_3$	Mesityl oxide	323	100	8	88		4	369
$Cu-Al_2O_3$ + thiophene	Mesityl oxide	323	48	36	12	3	10	369
$Rh-SiO_2$	Methyl vinyl ketone	298	100	82	16			428
$Rh-Sn-SiO_2$	Methyl vinyl ketone	298	100	98	2			428
$Ir-TiO_2$ (LTR)	5-Hexen-2-one	323	100	20	80			376
$Ir-TiO_2$ (HTR)	5-Hexen-2-one	323	17	82	6		12	376
$Pt-Al_2O_3$	Methyl vinyl ketone	298	50	80	20			428
$Pt-Zr-Al_2O_3$	Methyl vinyl ketone	298	20	100				428
$Pt-SiO_2$	Methyl vinyl ketone	353	low	97	3	min.		373
$Pt-Fe-SiO_2$	Methyl vinyl ketone	353	low	84	16	min.		373
$Pt-Sn-SiO_2$	Methyl vinyl ketone	353	low	96	4	min.		373

[a] A: saturated ketone, B: saturated alcohol, C: unsaturated alcohol, D: other products.

TABLE 21. Characteristic data on the hydrogenation of cycloalkenones[a]

Catalyst	Substrate	Temp. (K)	Conversion (%)	Selectivity (%)				Reference
				A	B	C	D	
Ni	Verbenone	373	100	100				429
Ni–B	Verbenone	398	100	5	95			429
Ni_2B	Carvone	298	100	>99				385
Cu–Cr–oxide	2-Cyclohexen-1-one	413	50	100				304
Cu on various supports	α-Ionone	363	>90	90				430
$Cu-Al_2O_3$	2-Cyclohexen-1-one	353	100	<1	99	<1	0	369
$Cu-Al_2O_3$ + thiophene	2-Cyclohexen-1-one	353	13	44	20	17	19	369
$Pt-SiO_2$	Carvone	373		>50			<50	431
$Pt-Au-SiO_2$	Carvone	373		<50			>50	431

[a] A: saturated ketone, B: saturated alcohol, C: unsaturated alcohol, D: other products.

the hydrogenation conditions (method, temperature, pressure, solvent, additives, etc.)[56,369,373,429,435–437],

the decisive role of the substrate[56,369,385,432,438],

the stereochemistry of hydrogenation[430,432,434,435,438,439],

the mechanism of hydrogenation[432,434].

The most essential conclusions of the investigations are summarized below. Note that all considerations discussed in connection with the hydrogenation of α,β-unsaturated aldehydes are also relevant to the hydrogenation of unsaturated ketones:

the hydrogenation activity of the metals investigated changes in the order Pt $\sim$ Pd $\sim$ Rh $\gg$ Ru $>$ Ni $>$ Cu[436],

on all catalysts, with the exception of Pd, saturated ketones are first formed through the selective hydrogenation of the olefinic double bond, then further hydrogenated to secondary alcohols,

the role of geometric-stereochemical factors in determining the selectivity of hydrogenation is even greater than in the hydrogenation of unsaturated aldehydes, if the hydrogenation of the C=O group is hindered by two bulky groups,

the only example describing the formation of an α,β-unsaturated alcohol was the hydrogenation of 2-cyclohexen-1-one (*ca* 17% selectivity) over a thiophene-modified $Cu-Al_2O_3$ catalyst[369],

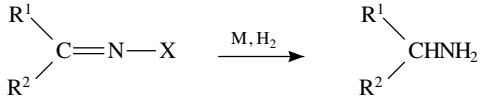
in the transformation of α,β-unsaturated carbonyl compounds containing an additional isolated olefinic bond (carvone, α- and β-ionone etc.) generally only the conjugated olefinic bond is hydrogenated,

a *cis*-concerted mechanism was assumed for the hydrogenation of (*E*)-benzylidene ketones over Rh–sepiolite catalysts[432] (equation 37),

highly selective formation of the α,β-unsaturated alcohol occurs on MgO through transfer hydrogenation[440].

VI. HYDROGENATION OF C=N BONDS

The C=N bonds of imines, oximes and hydrazones can be hydrogenated to form the corresponding amines even under ambient conditions on Pt, Pd, Rh and Raney Ni catalysts in acidic, neutral or basic media (equation 42). The imines, furthermore, are intermediates in the hydrogenation of nitro compounds, nitriles and oximes, and likewise play a key role as intermediates in the reductive amination of carbonyl compounds.



(42)

R^1 = alkyl, cycloalkyl, aryl

R^2 = H, alkyl, cycloalkyl, aryl

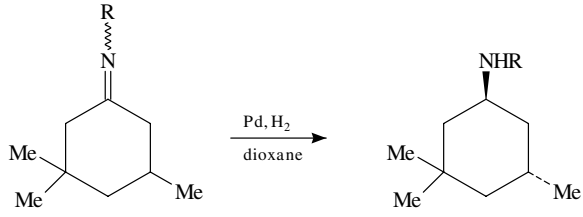
X = H, OH, OR, OAc, NH_2, NHR

The general characteristics of the hydrogenation of compounds possessing C=N bonds were already described in the 1940s and the reaction has been applied in preparative organic chemistry. The results were summarized in monographs[315,441–446]. In recent years mainly the asymmetric hydrogenation of the C=N bond has been studied.

The use of an acidic medium, in general, is favorable for the hydrogenation with any of the above catalysts. This is presumably connected with the elimination of the inhibitory effect of the amines formed during the hydrogenation. In imine hydrogenation reactions on Rh, five- to eightfold rate increases are observed when tartaric, phthalic, mandelic, salicylic or formic acids are added to the alcoholic reaction mixture (in a 95:5 mixture of EtOH–MeOH)[447].

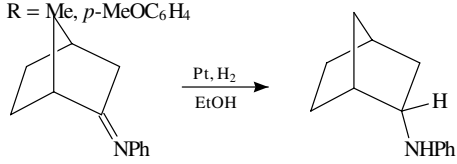
Aldimines are generally more easily hydrogenated than ketimines, due to the steric hindrance arising with the latter compounds[444]. The rate of hydrogenation of imines and the product composition are determined by the structure of the imine[448].

The stereochemistry of the hydrogenation strongly depends on the catalyst and the reaction conditions. Some examples illustrating the stereochemistry of the hydrogenation of imines are given in equations 43–47.

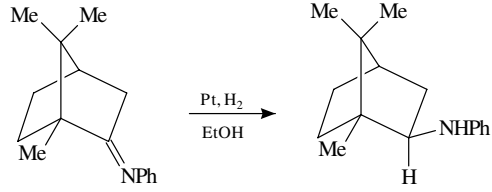


(43)[449]

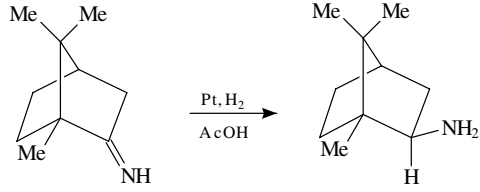
R = Me, *p*-MeOC$_6$H$_4$



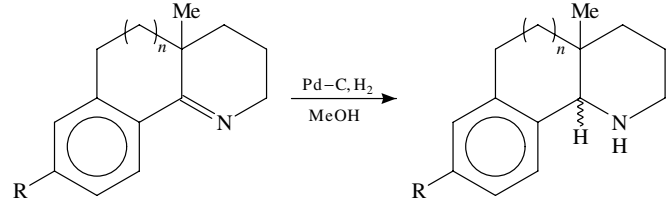
(44)[450]



(45)[450]



(46)[451]



(47)[452,453]

R = H, MeO

trans/cis = 89–100/11–0

The high stereoselectivity results from the attack of hydrogen from the sterically less hindered side during *cis* addition.

The heat of hydrogenation of 1-azacyclopentene was determined by measuring the heat of hydrogenation of its trimer. The data give information on the heats of formation and strain energies of a number of cyclic and acyclic imines[454].

There has been no new information on the hydrogenation of oximes in recent years. A detailed summary of this field was published in 1985[446].

VII. ASYMMETRIC HYDROGENATIONS

The asymmetric hydrogenation of double-bonded functional groups has recently become of great practical importance.

Heterogeneous metal catalysts can be modified for chiral synthesis in two general ways. Either supported metals are treated with chiral modifiers or metal catalysts are prepared by using chiral supports. Two systems have been developed into highly asymmetric heterogeneous hydrogenation catalysts. Systematic studies on the chiral heterogeneous catalytic hydrogenation were carried out using Raney Ni modified with various chiral reagents. (2*R*,3*R*)-(+)-Tartaric acid was found to be the best chiral modifying reagent in the presence of NaBr co-modifier. The other system is the cinchona alkaloid modified Pt catalyst.

The heterogeneous catalytic hydrogenation of carbonyl compounds using chirally modified metal catalysts has been reviewed in recent years[315,455–459]. The conclusions can be summarized as follows:

not only Ni and Pt but several other metals (Co, Fe, Ru, Pd, Rh, Cu) have been investigated,

the substrates used were mainly α- and β-keto esters, as well as 1,2- and 1,3-diketones,

on the TA–NaBr–MRNi catalysts the ee values on hydrogenation of β-keto esters are 88–92%,

the cinchona alkaloid modified Pt catalysts used for the chiral hydrogenation of α-keto esters giving α-hydroxy esters with ee values up to 95%,

the optical purity of the product is dependent not only on the preparation method of the catalyst (quantity and type of modifier, impregnation methods, support, catalyst dispersion, metal source etc.) but also on the reaction conditions (H_2 pressure, solvent, reaction temperature, substrate concentration and others),

catalysts with the largest metal particle sizes gave the highest enantioselectivity,

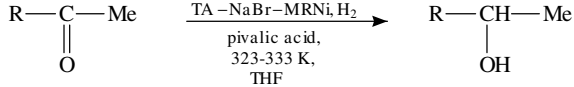
the solvent has a large effect on the reaction (aprotic solvents like THF and various esters are the best),

additives (inorganic salts, water, organic acids) enhance the ee values,

despite the large amount of published data there is still no agreement on the nature of the chiral hydrogenation site and the origin of the observed enantio-differentiation.

The majority of recent publications still deal with the chiral hydrogenation of ketones containing other functional groups as well. The general characteristics of these reactions are illustrated by the asymmetric hydrogenation of α,β-unsaturated ketones. In addition, the purpose of the present review is to summarize the latest results of the chiral hydrogenation of ketones which do not contain other functional groups (dialkyl ketones and alkyl aryl ketones).

The chiral hydrogenation of dialkyl ketones with high ee (80%) was performed on the TA–NaBr–MRNi catalyst in the presence of pivalic acid as co-modifier[460–465]. The first substrates examined were 2-alkanones (equation 48).



(48)

R = Et, Bu, Pen, Hex, octyl, undecyl

The preparation of the catalyst and the effect on the ee of hydrogenation conditions (temperature, solvent, the ratio of substrate to solvent, concentration of co-modifier) were

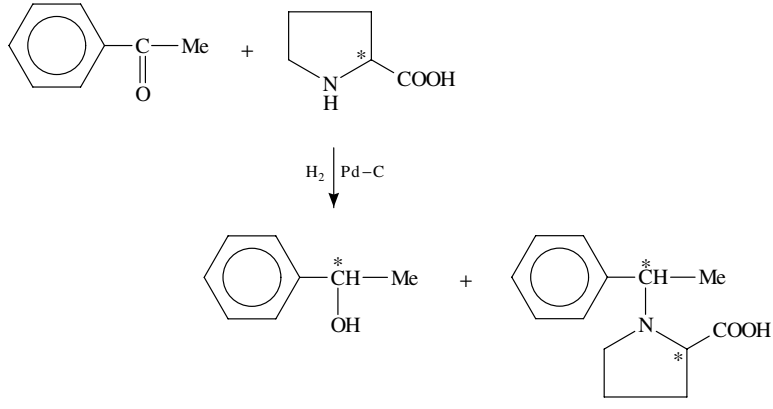
described in detail[461]. Lower ee (63%) was observed in the case of the hydrogenation of 2-butanone[460]. 2-Butanol of 72% optical purity was, however, obtained[466] by optimizing the reaction variables (solvent, carboxylic acid as co-modifier, reaction temperature, amount of TA–NaBr–MRNi, pivalic acid/2-butanone ratio) and modification variables (NaBr/TA ratio, pH, amount of modifying solution). The degree of the intrinsic enantio-differentiating ability of the adsorbed TA for 2-butanone was supposed to be similar to the ability of TA for higher 2-alkanones.

The enantio-differentiating hydrogenation of 3-octanone[467] carried out with TA–NaBr–MNi catalyst was compared with that of 2-alkanones. Significant differences were observed. For example, the hydrogenation of 3-octanone on a TA–NaBr-modified fine nickel powder resulted in a better optical yield (30%) than over a similarly modified Raney nickel. In addition, the hydrogenation at a lower temperature resulted in a lower optical yield in the hydrogenation of 3-octanone, whereas the optical yield was higher in the hydrogenation of 2-alkanones.

The differentiation between methyl and other alkyl groups takes place as follows[467]. First TA forms an associative complex on the catalyst surface with pivalic acid added to the reaction system[462]. The substrate is adsorbed to the catalyst surface through TA. The TA–pivalic acid complex recognizes the structure of the substrate through an interaction between the alkyl group of pivalic acid and that of 2-alkanones. Finally, hydrogen adds to the substrate from the catalyst surface. This enantio-differentiating model for the hydrogenation of 2-alkanones is given in Figure 1[468].

According to this model, the carboxylic acid added to the reaction system is the key factor for achieving the enantio-differentiating hydrogenation of 2-alkanones. Therefore, more detailed comparative studies of the enantio-differentiating hydrogenation of 2- and 3-alkanones, including the structure of the carboxylic acid added to the reaction system, would lead to the development of highly efficient heterogeneous catalysts for the enantio-differentiating hydrogenation of 3-alkanones. In addition, factors necessary to differentiate between various alkyl groups can be recognized.

Enantioselective heterogeneous catalytic hydrogenation of acetophenone[469–471] to (*R*)-(+)-1-phenylethanol (ee 20%) in the presence of (*S*)-proline (the chiral auxiliary) was investigated. The effect of various catalytically active metals (Pt, Rh, Raney Ni, Pd), the reaction temperature and the amount of catalyst on the optical purity was studied. The correlation between the optical yield and the conversion, the concentration of the reactants, different pretreatment methods and additives was also investigated[469] (equation 49).



(49)

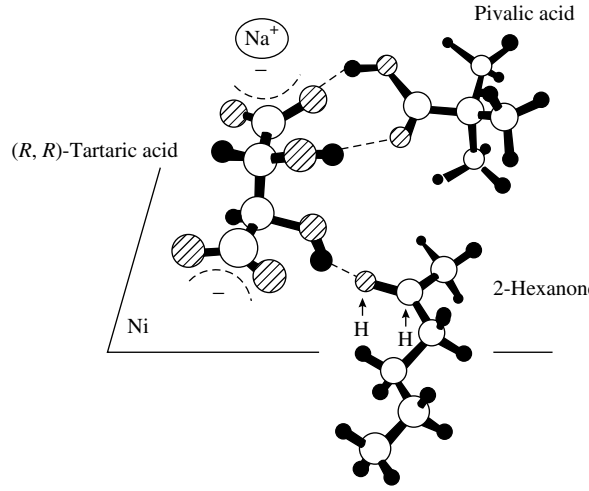
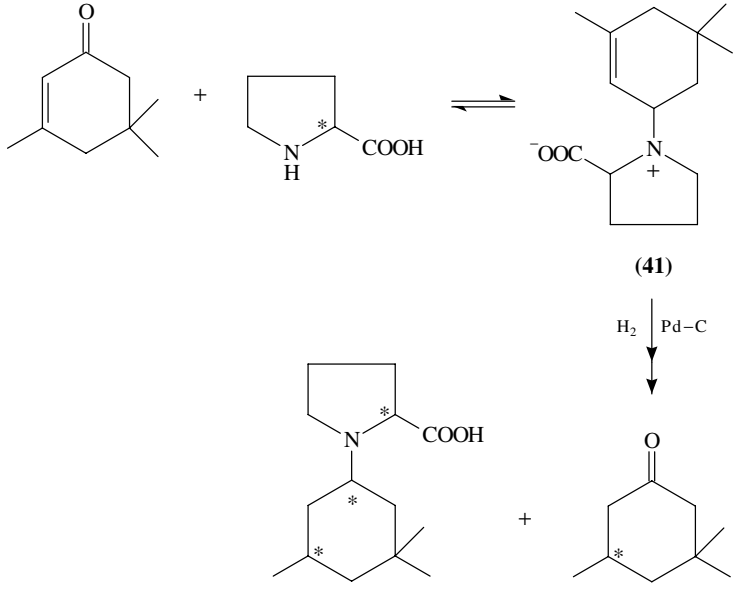


FIGURE 1. Model of asymmetric hydrogenation of 2-alkanones (C, ●●● O, ● H)

Of the α,β-unsaturated ketones only the chiral hydrogenation of isophorone (3,3,5-trimethyl-2-cyclohexen-1-one) was investigated[470–473]. The effects of catalyst, pH, hydrogen pressure and intensity of agitation on the enantioselective hydrogenation of isophorone were discussed. The changes in chemical and optical yields of the saturated ketone as a function of conversion and the water content of the solvent were also investigated. An iminium salt intermediate **(41)** undergoing hydrogenation was indentified[472] (equation 50). The reaction product was (*S*)-3,3,5-trimethylcyclohexanone (ee 60%), and an alkylated proline side product was also formed.



(50)

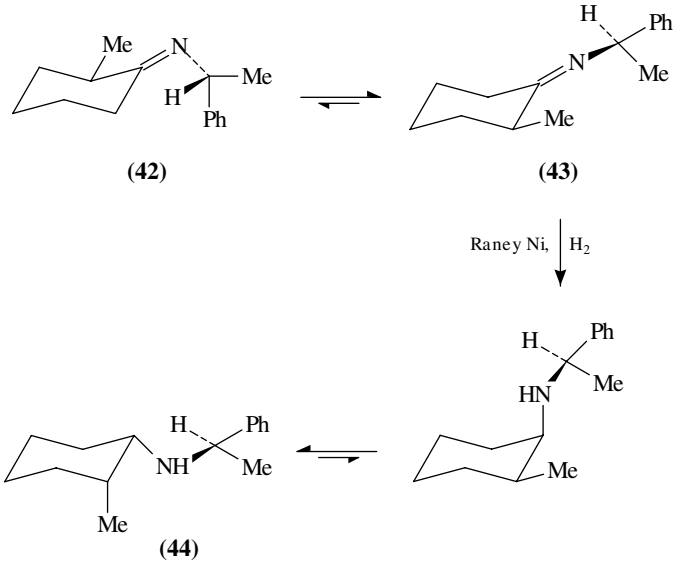
Note that there are virtually no data for the asymmetric hydrogenation of the C=C bond over heterogeneous catalysts. The first example[474] described the chiral hydrogenation of α-phenylcinnamic acid with 15% ee.

The hydrogenation of isophorone and acetophenone in the presence of (*S*)-proline shows some similarities. The effect of Pd–C–(*S*)-proline system is based on the addition reaction of the reactants and (*S*)-proline in solution and on the chemoselectivity of Pd. Both hydrogenations should be termed diastereoselective rather than enantioselective, since the asymmetric induction takes place in the adduct molecules.

A relatively small number of examples have appeared on the asymmetric hydrogenation of imines, oximes and hydrazones without any other functionality, though the resulting optically active amines are synthetically important compounds. In contrast, many more publications deal with the asymmetric hydrogenation of compounds with C=N bond containing other functional groups. This is mainly due to the importance of α-amino acids. On the other hand, the prochiral substrate must be a bifunctional compound possessing a hydrogenation site and a binding site in order to get high enantioselectivity.

There are detailed summaries treating the asymmetric hydrogenation of such bifunctional compounds[315,455,475]. The present review, consequently, deals only with the asymmetric hydrogenation of compounds in which the C=N bond is the sole functional group.

The chiral hydrogenation of ketimines can be performed either by the hydrogenation of compounds containing a chiral auxiliary group on achiral catalysts, or by hydrogenating achiral ketimines on chiral catalysts. Some examples for diastereoselective hydrogenation of ketimines can be seen in equations 51–53.



(42) **(43)**

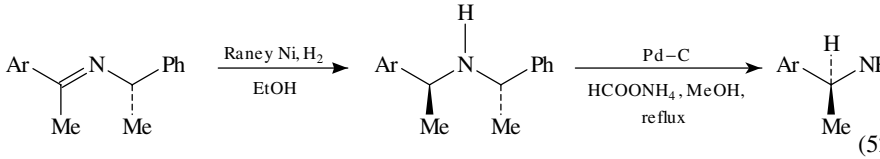
(51)

(44)

The formation of chiral, enantio-enriched imines by the utilization of optically active amines, and the subsequent hydrogenation of the diastereotopic imine faces provides a powerful method for the introduction of new stereogenic centers, often with high diastereomeric excesses. New, optically active amines are then obtained by the removal of the chiral auxiliary group[475]. Thus, the condensation of 2-alkylcyclohexanones with optically active 1-phenylethylamine yielded the mixture of imines **42** and **43** which were hydrogenated over Raney Ni to give essentially only one optically active, diastereomerically

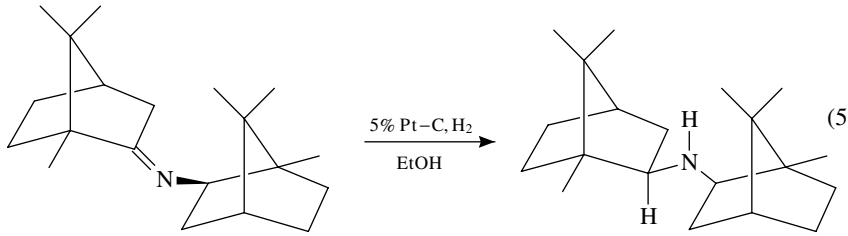
enriched *cis* secondary amine **44** in good yield[476]. These results require that an asymmetric interconversion of the diastereomeric imines (**42**, **43**) occurs prior to hydrogenation and that either the diastereomer **43** is greatly favored at equilibrium or that the reduction rate of **43** (or its conformational isomer) is much faster than that of **42**. The same method was applied in the transformation of 2-alkylcyclopentanones[477].

An efficient method has been reported[478,479] for the asymmetric synthesis of chiral 1-arylethylamines. The method is the reductive amination with optically active 1-phenylethylamine of substituted acetophenones via the corresponding imines (equation 52).



(52)

Diastereoselective hydrogenation of *N*-isobornylcamphor imine has also been utilized to prepare the useful optically active diisobornylamine (equation 53)[480].



(53)

No new literature data are available for the asymmetric hydrogenation of ketimines without any other functionality.

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CHAPTER **17**

Syntheses and uses of isotopically labelled compounds containing C=C, C=O or C=N groups

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I. INTRODUCTION

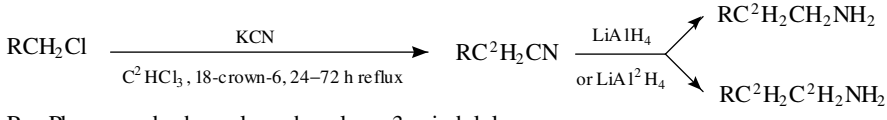
As in the past, the majority of the sometimes very laborious syntheses of isotopically substituted or isotopically labelled compounds has been carried out to provide the biologically active substances useful as analytical, diagnostic or therapeutic agents. The first six parts of this chapter are devoted to a brief description of the methods used in the preparation of compounds isotopically labelled with stable and radioactive isotopes, including the short-lived positron emitters carbon-11 and fluorine-18 widely applied in nuclear medicine. This time, we give also in Section VII of the chapter a rather extensive presentation of isotopic studies aimed at a better understanding of the mechanisms of chemical processes proceeding in vitro and in vivo, including chemical catalytic and enzymatic biochemical reactions cited in Volumes 119, 120 and 121 of *Chemical Abstracts*. The growing number of isotope effect papers with each year reflects the existence of numerous questions which should be given immediate answers on the chemical, atomic and molecular levels, to develop a coordinated interdisciplinary strategy linking the life sciences and technology trends to meet both human and economic concerns of contemporary society.

II. SYNTHESES AND USES OF COMPOUNDS CONTAINING C=C, C=O OR C=N GROUPS LABELLED WITH STABLE ISOTOPES

A. Compounds Labelled with Deuterium

1. Synthesis of deuterium-labelled benzyl cyanides

In the substitution of alkyl halides by cyanide ion in aprotic organic solvents in the presence of crown ethers[1,2] some α,α-$^2H_2$ benzyl chlorides lose deuterium when the reaction is carried out in acetonitrile. This has been used[3] for the synthesis of deuteriated benzyl cyanides by refluxing with cyanide ion and crown ether in deuteriosolvents (C^2HCl_3, C^2HCl_3/CH_3O^2H, C^2H_3CN, and less efficient $C^2H_2Cl_2$ and $C_6{}^2H_6$) as shown in equation 1.

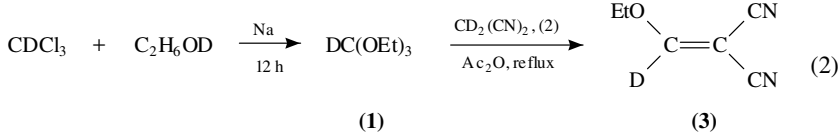


R = Ph-, m- and *p*-benzyloxyphenyl-, or 3-*n*-indolyl (1)

Deuteriochloroform was the solvent of choice. The β,β-$^2H_2$ and $\alpha,\alpha,\beta,\beta$-$^2H_4$ phenylethylamine, *m*- and *p*-tyramine and tryptamine obtained[3,4] have been used as tracers in metabolic studies and as internal standards in quantitative mass spectrometry[3–5].

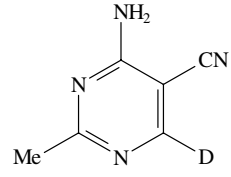
*2. Synthesis of triethoxy-[^{2}H]methane **1**, and ethoxy-[^{2}H]methylene malononitrile, **3***

1 has been prepared[5] in 31% yield by reacting deuteriochloroform with monodeuteriated ethanol in the presence of sodium during 12 hours and subsequent work-up and separation of deuterioorthoester using a short Vigreux column. **1**, reacted with deuteriomalononitrile, **2**, in acetic anhydride provided **3** in 86% yield deuteriated in 96–97% (equation 2). Ring closure of **3** with acetamidine, $CH_3C(NH)NH_2$, in ethanol leads to 4-amino-5-cyano-2-methyl-6^{2}H-pyrimidine, **4**, without loss of deuterium. **3** was synthesized[6] in the course of studies on the mechanism of the cleavage of thiamine, **5**, which, treated with sulphite, decomposed to sulphonic acid betaine, **6** (equation 3)[7].

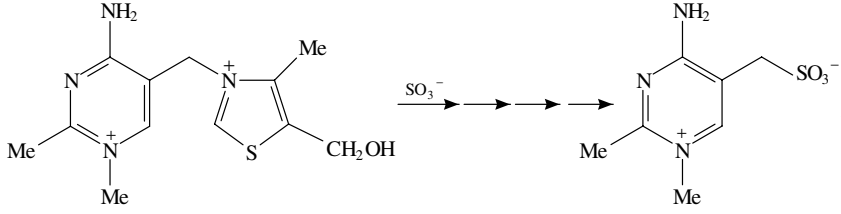


(2)

(1) **(3)**



(4)



(3)

(5) **(6)**

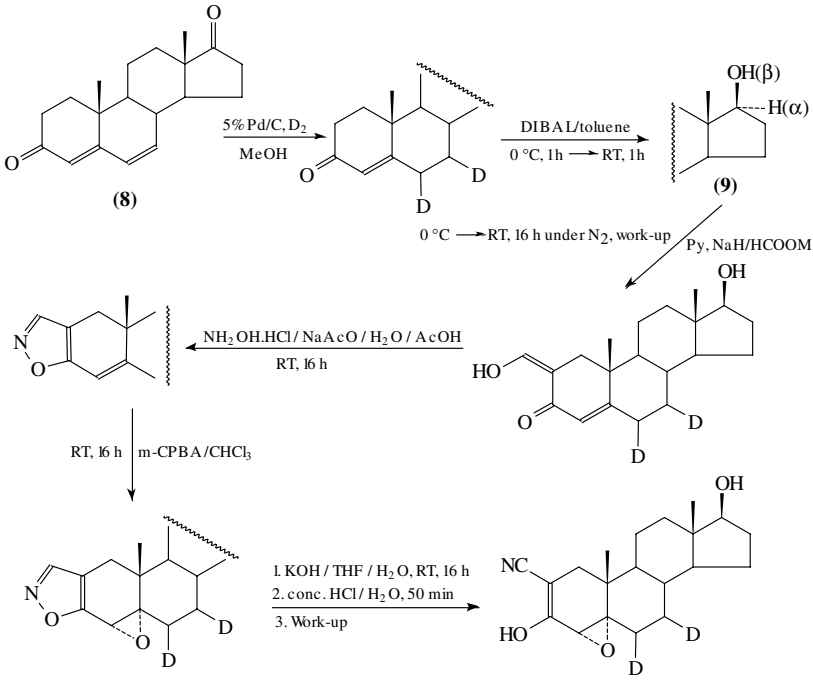
3. Synthesis of [6,7-$^2H_2$]trilostane

The title compound, (4α, 5α, 17β)-4, 5-epoxy-[6,7-$^2H_2$]-3, 17-dihydroxyandrost-2-ene-2-carbonitrile, **7**[8,9], has been found to be of benefit in the treatment of some forms of breast cancer[9]. It has been synthesized[10] in 6 steps as shown in equation 4. The label has been introduced into **7** in the first reaction step by catalytic deuteriation of androsta-4,6-dien-3,17-dione, **8**. Similarly, [4-^{14}C]trilostane (sp. act. 95 µCi/g, r.p. >98%, 57% overall yield) has been prepared[10,11] in four steps from [4-^{14}C]testosterone, **9**.

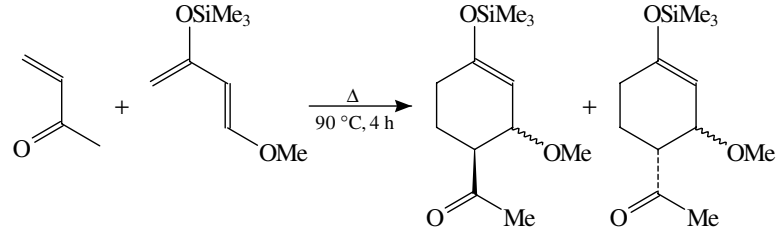
*4. Synthesis of (±)-1-(1,3-dithiane-2-yl)-4-(1-hydroxy-1-[$^2H_3$]-methylethyl)-cyclohex-2-en-1-ol, **10**, and [$^2H_{10}$]-Δ^1-THC-7-oic acid, **11***

10 has been synthesized as shown in equation 5 and used for the preparation[12] of **11**, by condensation of **10** with [$^2H_7$]-olivetol, **12**, Δ^1-THC-7-oic acid, the major psychoactive

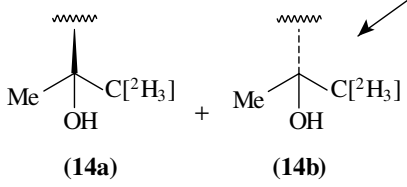
constituent of *Cannabis*, is the major urinary metabolite of Δ^1-tetrahydrocannabinol (Δ^1-THC) in man[13,14]. The carbon-14 labelled terpene synthon has been obtained[12] by using carbon-14 labelled methyl iodide in the conversion of the keto function in **13** to the tertiary alcohol in compound **14**. Compound **11** is suitable as internal standard for MS assays.

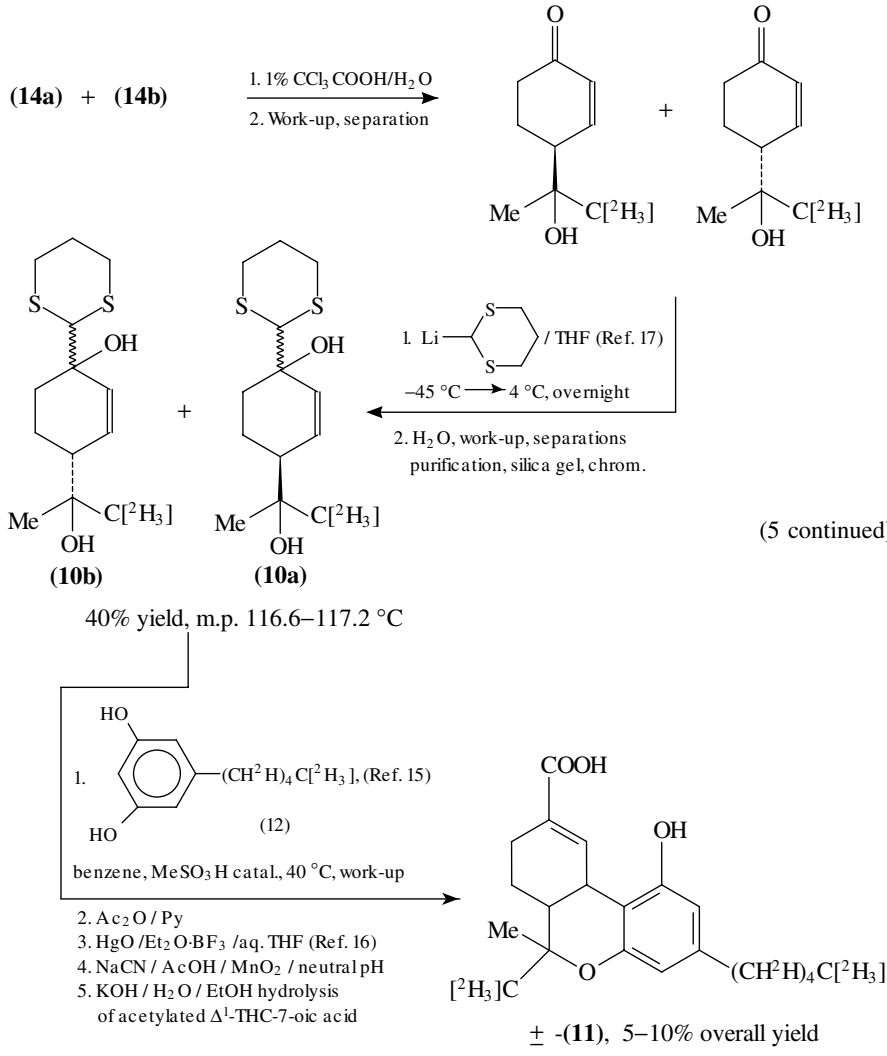


(4)



(5)

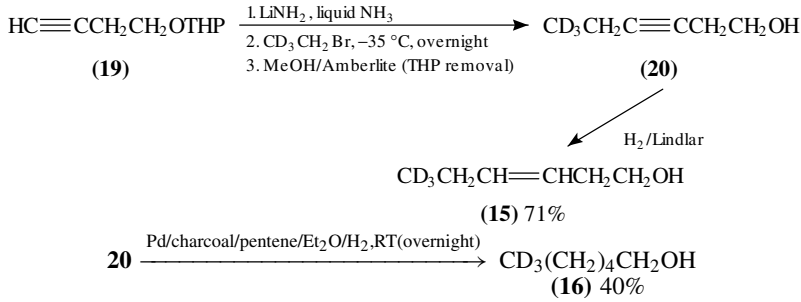




5. Synthesis of deuterium-labelled hexenols

Hexenols are important flavour components of fruit and vegetables. Syntheses of *cis*-3-hexen-1-ol-6,6,6-$^{2}H_3$, **15**, hexan-1-ol-6,6,6-$^{2}H_3$, **16**, *cis*-2-hexen-1-ol-6,6,6-$^{2}H_3$ **17**, and *trans*-2-hexen-1-ol-6,6,6-$^{2}H_3$, **18**, have been accomplished[18] in order to incorporate these precursors into the biochemical system of living fruit tissue (to study the complex multi-enzyme systems of their production and metabolism). Deuteriated *cis*-hexenol **15** and hexanol **16** have been obtained[18–20] by alkylation of (THF)ether of 3-butyn-1-ol, **19**, with 1-bromoethane-2,2,2-$^{2}H_3$ followed by partial hydrogenation of alkynol **20** leading to **15**, or by hydrogenation of **20** using 5% palladium on charcoal giving product **16**

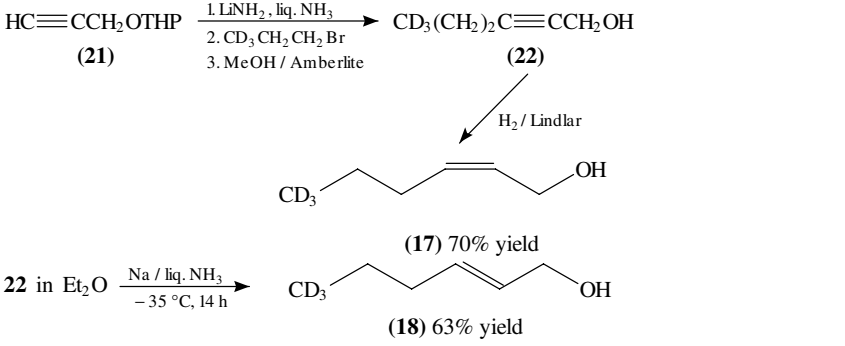
(equations 6a and 6b).



(6a)

(6b)

Cis-**17** and *trans*-**18** hexenols have been prepared in similar fashion from the acetylenic alcohol **21** (equations 7a and 7b),

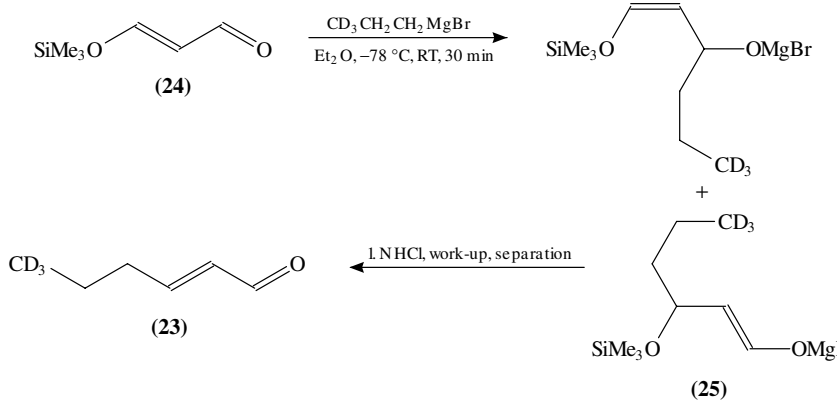


(7a)

(7b)

6. Synthesis of 6,6,6-$^2H_3$-2E-hexanal ***(23)***

23, 'leaf-aldehyde', product of the enzymatic and oxidative degradation of unsaturated fatty acids in processed foods, important aroma constituent in a number of fruit, vegetables, and leaves[21,22], has been synthesized[23] in 45% yield and 99.3% G.C. purity in a one-pot procedure (equation 8) of 3,3,3-$^2H_3$-*n*-propyl magnesium bromide with an



(8)

ethereal solution of 3-trimethylsiloxy-2-propenal, **24**, prepared *in situ* (equation 9). The side products, RCH=CHCH(OH)R and RCH=CHCHR($OSiMe_3$), R = *n*-Pr, Ph, isolated in test experiments, are consistent with the 1,4-addition of Grignard reagent to **24** and formation of the intermediate **25** prior to hydrolysis. **24** has been obtained by silylation of potassium malondialdehyde[24] with Me_3SiCl in the presence of catalytic amounts of *N*, *N*-dimethylaminopyridine (equation 9).

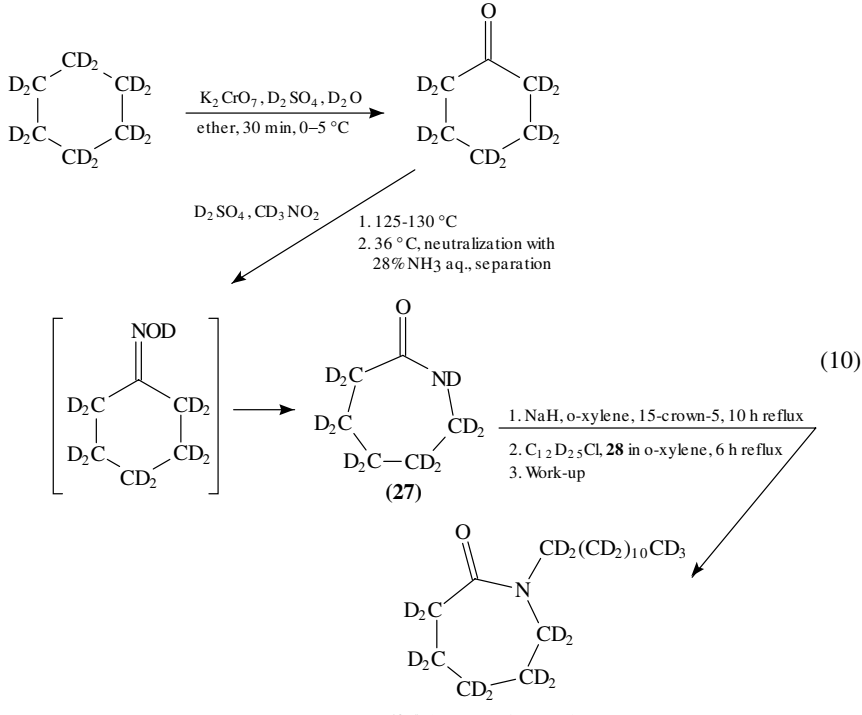
$$(RO)_2CHCH_2CH(OR)_2 \xrightarrow[\text{2. 5 N KOH}]{\text{1. 2 N HCl, 50 °C}} \underset{\textbf{(25)}}{[SiMe_3OCH(R)CH{=}CHOMgBr]} \xrightarrow[\text{DMAP (cat.), } Et_2O\text{, RT}]{\text{TMSCl, } Et_3N\text{ (0.1 eq)}} \textbf{24} \quad (9)$$

R = Me (68% yield)

R = Et (75% yield)

*7. Synthesis of D_{35}-1-dodecylhexahydro-2H-azepin-2-one **(26)***

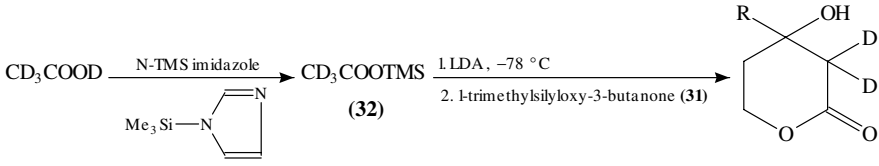
The title compound, perdeuterioazone, **26**, a dermal penetration enhancer[25] increasing the passage of the wide range of molecules through the skin, has been synthesized[26] in 45% yield by the base-catalyzed coupling of D_{11}-hexahydro-2*H*-azepin-2-one, **27**, with D_{25}-1-chlorododecane, **28** (equation 10), in one step. Comparison of the mass spectra of **27** and **26** and use of the mass calculation program showed that **26** contains more than 98% atom% D. **26** will be applied to further investigate the mechanism of action of azone by use of Fourier transform IR spectroscopy[27] and neutron reflectometry[28].



(10)

*8. Synthesis of (±)[2-$^2H_2$]mevalonolactone **(29)** and (±)[2-$^2H_2$]homomevalonolacetone **(30)***

(a) **29** has been prepared[29,30] in 77% yield by condensation of lithiotrimethylsilyl [2-$^2H_2$]acetate generated by action of LDA with 1-trimethylsilyloxy-3-butanone, **31** (equation 11). The regiospecificity of the labelling retention of ^2H in **29** was more than 95%.

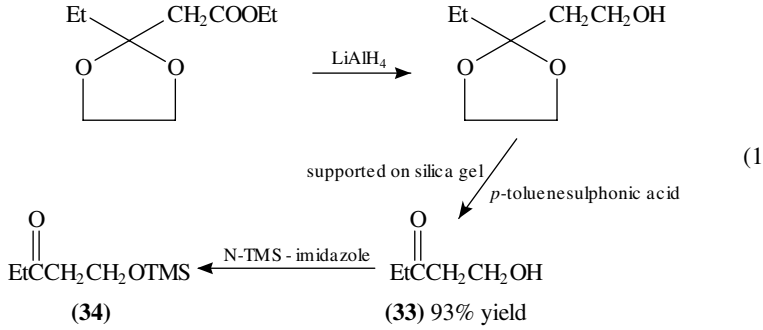


(29) R = Me, **(30)** HMVA; R = Et

LDA = Lithium diisopropylamide

(11)

(b) Synthesis of **30** has been carried out[29] in 70% yield by condensation of 1-trimethylsilyloxy-3-pentanone **34** with **32**. The intermediate **33** was prepared in high yield as shown in equation 12.



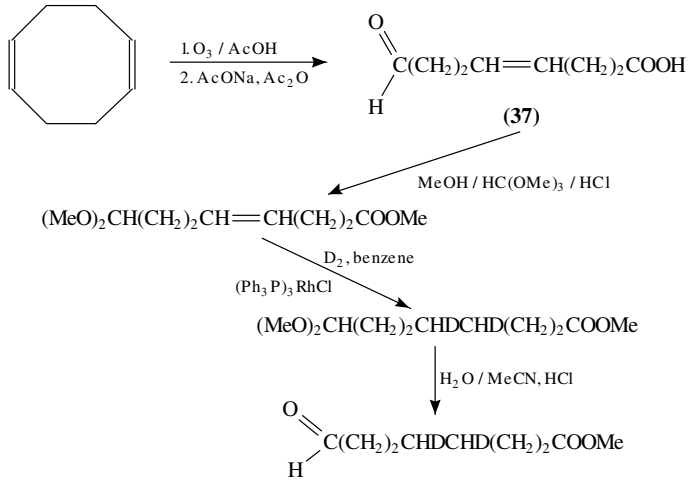
(12)

No signals for protons at $C_{(2)}$ have been found in the ^1H NMR spectrum of **30**. This indicates complete deuteriation at this position and that no significant deuterium exchange took place under the conditions of the synthesis. Compounds labelled with stable isotopes are finding increasing applications in biosynthetic studies[31]. Labelled HMVA are required for metabolic studies in insects[29].

9. Synthesis of 8- and 12-carbon deuterium-labelled aldehydic esters

Methyl 8-oxooctanoate-4,5-D_2, **35**, and methyl 12-oxododecarbate-4,5,8,9-D_4, **36**, have been synthesized[32] as shown in equations 13 and 14 by monoozonization and sodium acetate cleavage of 1,5-cyclooctadiene and 1,5,9-cyclododecatriene, respectively. The resultant unsaturated aldehydic acids **37** and **38** have been converted to the corresponding acetal esters, which have been deuteriated with Wilkinson's catalyst[33] and hydrolysed to the deuterium-labelled aldehydic esters **35** and **36** in 47% and 49% overall yields and

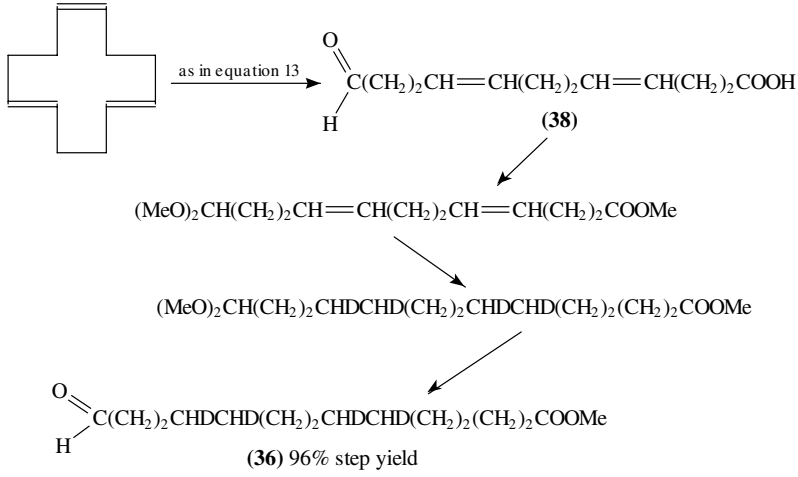
isotopic purities of 97% and 89%, respectively.



(13)

(35) 95% step yield, b.p. 91–94 °C

The acetal ester does not trimerize and can be stored for years before hydrolysis and use[34]. The deuterium-labelled fats have been needed in multigram quantities for studies of the metabolism of configurational and positional fatty acid isomers in humans.



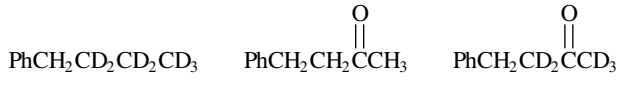
(14)

(36) 96% step yield

*10. Synthesis of [β, β, γ, γ, δ, δ, δ-$^2H_7$]-n-butylbenzene **(39)***

39, required in substantial amount as a starting material for preparation of mass spectrometric standards, has been synthesized in a two-step procedure[35]. In the first step the *β*, *β*- and *δ*, *δ*, *δ*-hydrogens of 4-phenyl-2-butanone **40** have been replaced with deuterium atoms by base-catalyzed isotopic exchange of the five labile *β*- and *δ*-hydrogens of **40** with excess of D_2O–MeOD containing a solution of NaOD in D_2O under reflux. In the

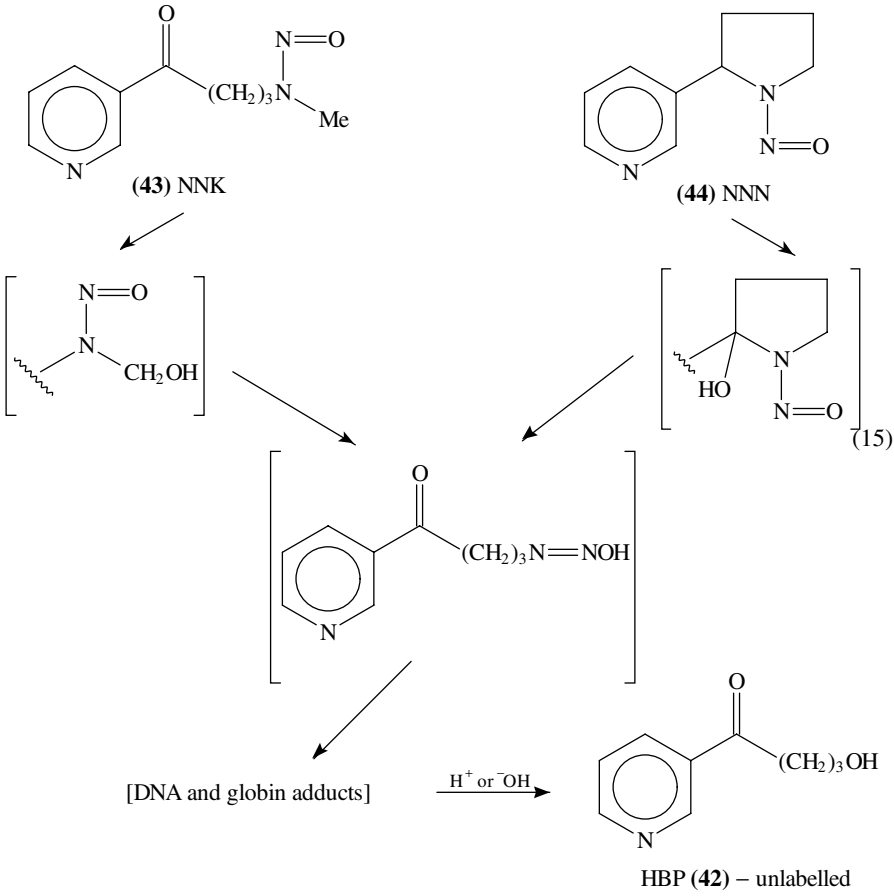
second step the carbonyl group of the isolated intermediate product **41** has been reduced in THF with zinc dust, and the required amount of DCl was generated *in situ* by reaction of D_2O with trimethylsilyl chloride[36].

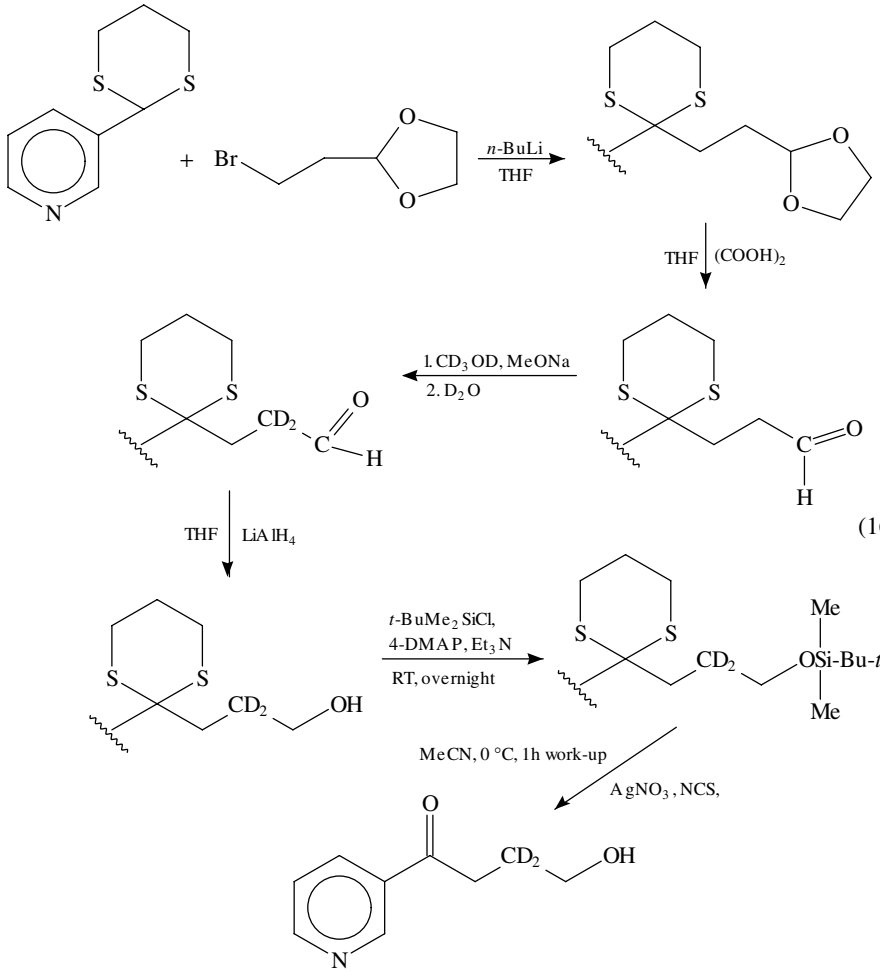


(39) **(40)** **(41)**

*11. Synthesis of [3,3,-D_2]-4-hydroxy-1-(3-pyridyl)-1-butanone, [3,3,-D_2]HPB **(42)***

42 was needed as internal standard for quantification of HPB[37] released upon hydrolysis of DNA and globin adducts with metabolically activated (α-hydroxylated) 'NNK', **43**, and 'NNN', **44**, playing an important role in causing cancers of the lung, oral cavity, esophagus and pancreas in people who use tobacco[38,39] products (equation 15). Recently, **42** has been produced[40] in good yield as shown in equation 16, more efficiently than in the previous low-yield procedure used for production of [4,4-D_2]HPB[41].





(16)

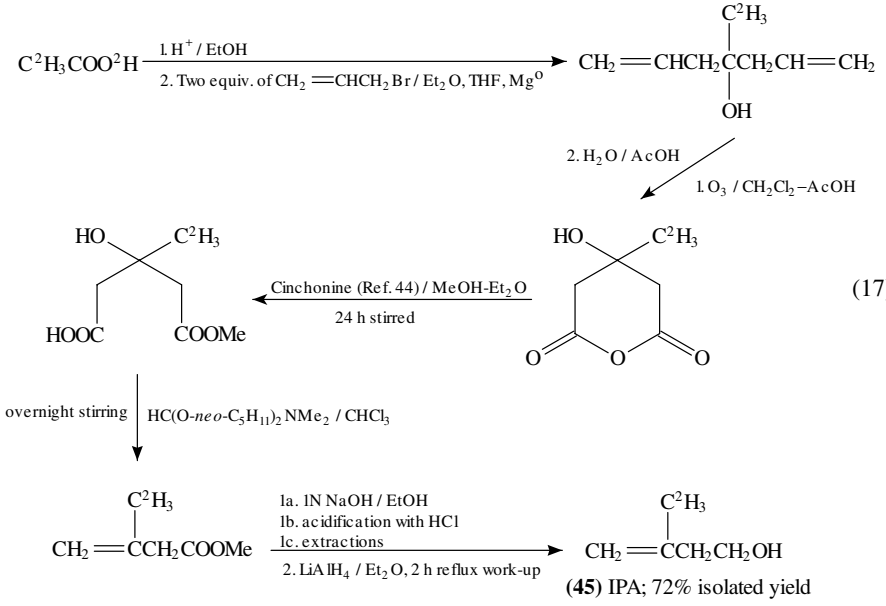
(42) [3,3-D_2]HPB, 100% D_2 by NMR
4-DMPA = 4-dimethylaminopyridine

The NICI–MS (negative ion chemical ionization–mass spectrometry) of the pentafluoro-benzoate derivative of **42** has been identical to the corresponding derivative of [4,4-D_2]HPB. The levels of HPB released from hemoglobin of NNK-treated rats, determined using [3,3-D_2]- and [4,4-D_2]-HPB standards, were the same[40].

*12. Synthesis of 3-[$^2H_3$methyl-3-buten-1-ol **(45)***

The use of stable isotopes in biosynthetic studies has increased greatly in recent years[42]. The title compound, the Δ^3-isopentyl alcohol, IPA, **45**, needed for the preparation of the corresponding Δ^3-isopentyl pyrophosphate[42], IPP, has been obtained according to equation 17, using perdeuterioacetic acid as the starting material[43,44]. The product **45**

consisted predominantly (95%) of [$^2H_3$] species.

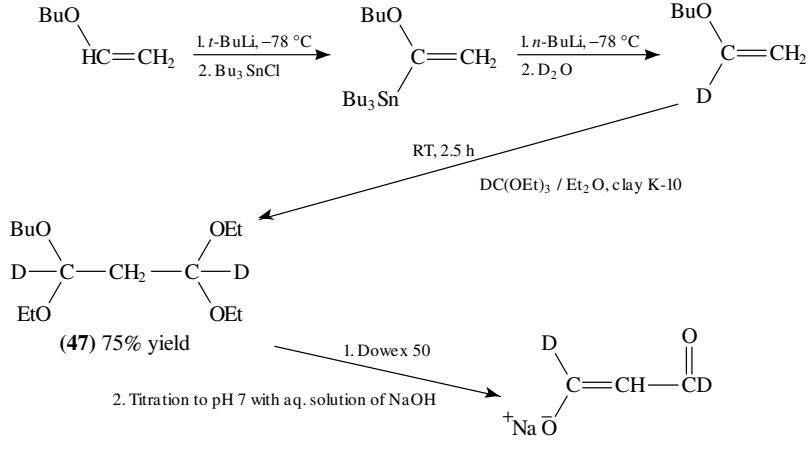


(17)

(45) IPA; 72% isolated yield

*13. Synthesis of 3-hydroxy[1,3-$^2H_2$]-2-propenal **(46)***

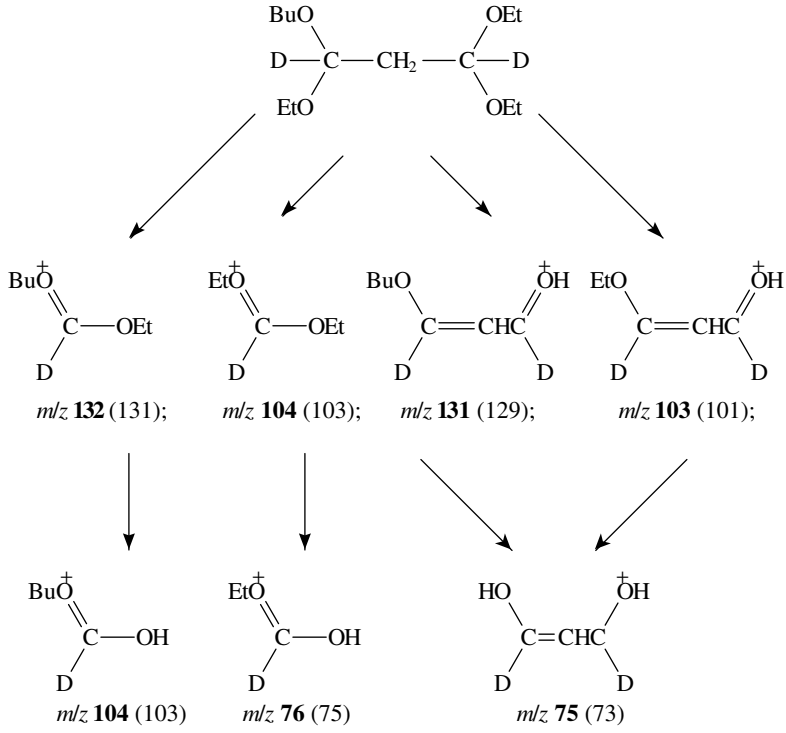
The title compound, 1,3-dideuteriated malondialdehyde, MDA-**46**, formed in a lipid peroxidation process involved in the pathogenesis of many human diseases[45,46], has been needed for quantitative determination of MDA in human blood or urine by isotope dilution mass spectrometry. It has been synthesized[47] by condensation of deuteriated butyl vinyl ether with deuteriated triethyl orthoformate in the presence of montmorillonite clay K-10 (equation 18).



(18)

(46) dihydrate sodium salt of malondialdehyde

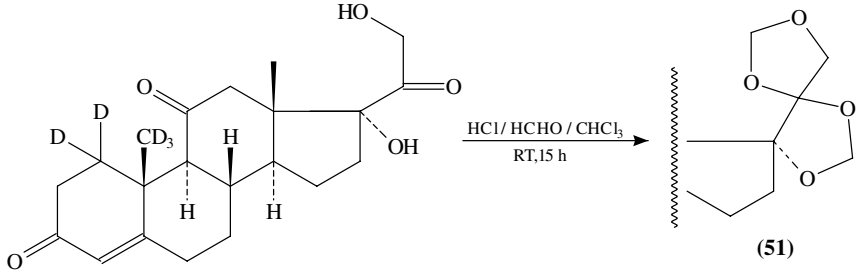
A comparison of the mass spectra of the deuteriated diacetal **47** and the non-deuteriated analogue (given in parentheses) led to the complete assignment of the observed fragmentation peaks presented in equation 19.



(19)

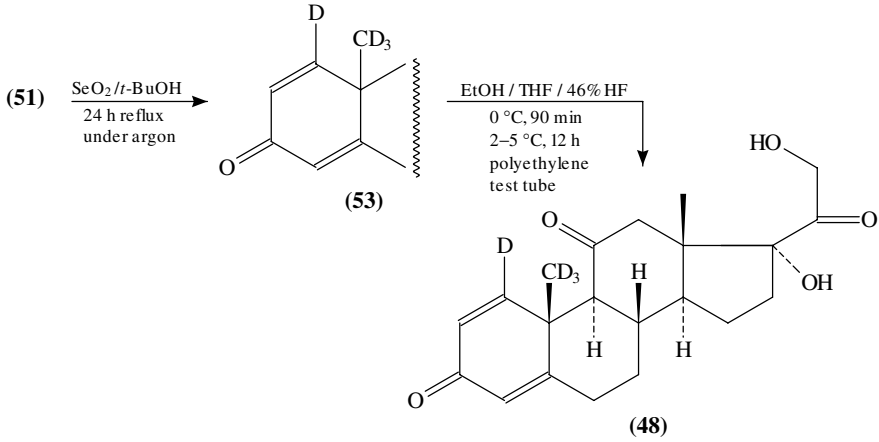
14. Synthesis of multiply deuterium-labelled prednisone and prednisolone

[1,19,19,19-$^2H_4$]Prednisone, **48**, and [1,19,19,19-$^2H_4$]prednisolone, **49**, containing four deuterium atoms at chemically stable sites, have been synthesized[48] starting from [1,1,19,19,19-$^2H_5$]cortisone, **50** (equations 20a, 20b and 20c). No loss of deuterium from the $C_{(19)}$ and $C_{(1)}$ positions has been observed in the course of synthetic sequence, which involved the oxidation of the intermediates **51** and **52** with selenium dioxide in *t*-butanol.

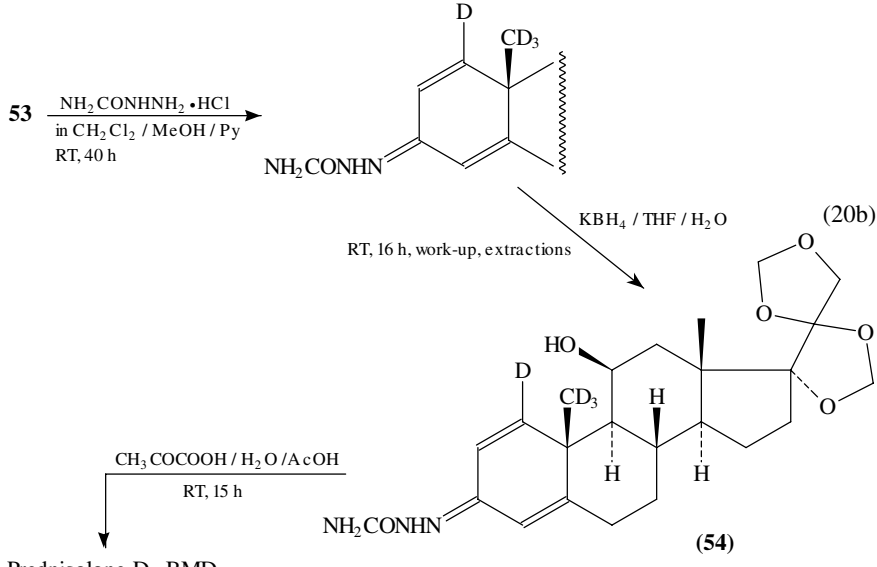


(50) cortisone –D_5 **(51)**

(20a)

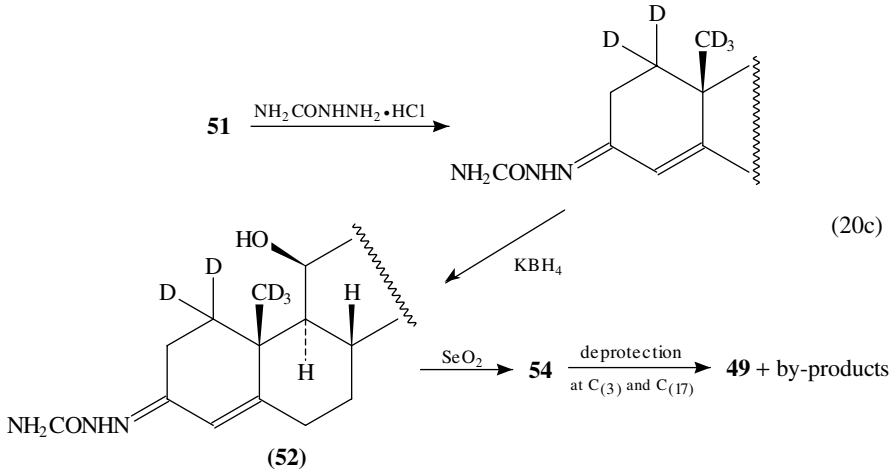


[1,19,19-$^2H_4$]-17α, 21-Dihydroxypregna-1,4-diene-3,11,20-trione (prednisone-D_4)



(49) 55% yield

The route 20c has been less satisfactory because of the formation of by-products, especially in the oxidation of **52**.



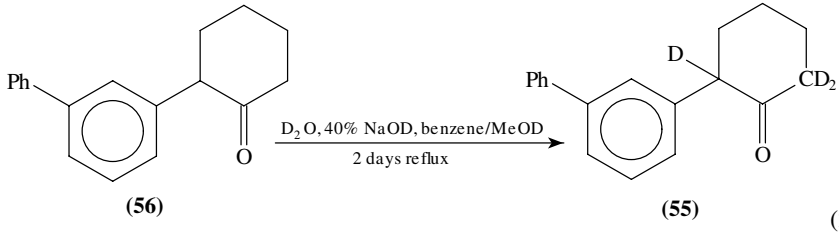
(20c)

48 and **49** with ^{2}H-label in chemically and biologically stable $C_{(19)}$ and $C_{(1)}$ positions are suitable for use in stable isotope methodology (coupled with GC-MS[49,50]) of investigations on steroid hormones in humans[51].

15. Synthesis of deuterium- and tritium-labelled (3-xenyl)cyclohexane

The use of PCBs (polychlorinated biphenyls), organic heating medium causing skin affliction in humans[52] and producing non-metastasizing neoplastic liver nodules in rats and mice[52], is prohibited[53] in Japan. Hydrogenated terphenyls (HTPS) are used as a substitute. (3-Xenyl)cyclohexane, known to be a major component of the HTPs, has been tritium and deuterium labelled[54] to study its metabolic fate in living organisms by Clemmensen reduction of 2-(3-xenyl)cyclohexanone, **55**, and by Wolf–Kishner reduction of **55**.

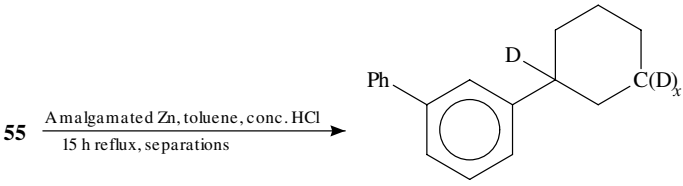
(a) 2-(3-xenyl)cyclohexanone-2,6,6-[$^3H_3$], **55**, has been prepared by deuterium exchange catalysed by 40% NaOD in dry benzene and MeOD (equation 21).



(21)

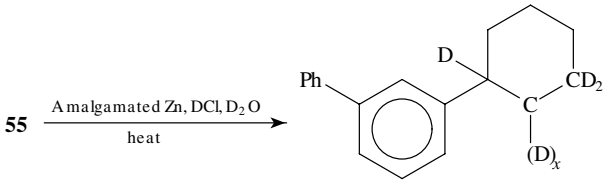
(b) The deuteriated product **57** has been obtained by Clemmensen reduction of **55** (equation 22).

The deuteriated product **58** has been prepared as shown in equation 23 using concentrated DCl in D_2O.



(22)

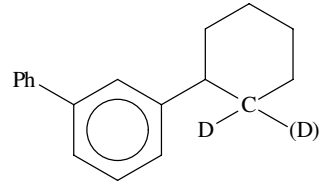
(57)



(23)

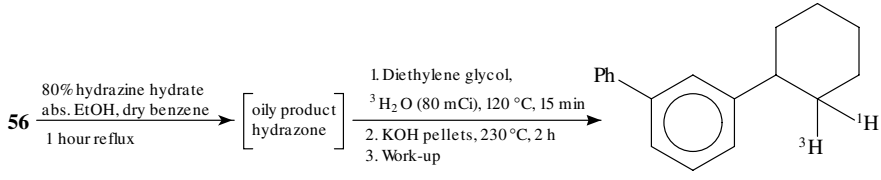
(58)

The deuterium labelling has been achieved also by Wolf–Kishner reduction of 2-(3-xenyl)cyclohexanone. The hydrazone of **56** dissolved in diethylene glycol containing D_2O was heated first at 120 °C for 15 min and, after addition of KOH, heated at 230 °C for an additional two hours. The product **59** has been identified by the mass spectrum as the predominant constituent.



(59)

The tritium-labelled 1-(3-xenyl)cyclohexane-2-[^{3}H], **60**, has been obtained similarly (in 84.3% chemical yield and 0.89% radiochemical yield based on the total radioactivity of ^3H_2O used); see equation 24.



(60)

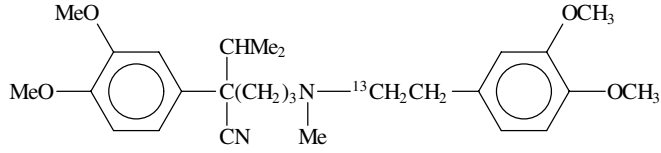
(24)

The Clemmensen reduction was accompanied by D/H exchange via acid-catalysed enolization of the carbonyl group, resulting in the production of deuteriated compounds **57** and **58** with various numbers of deuterium atoms. The mixture of the compound **59** obtained by the Wolf–Kishner reduction was predominantly labelled at position 2. This has been proved by the ^{13}C-NMR spectrum. Isotope shift and loss intensivity on substituted $C_{(2)}$ carbon signals have been observed[54,55].

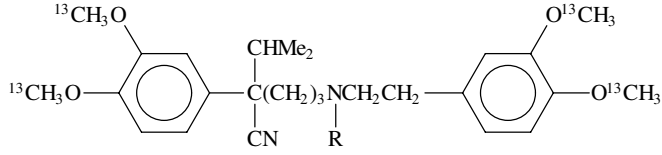
B. Compounds Labelled with Carbon-13

1. Synthesis of ^{13}C-labelled verapamil compounds

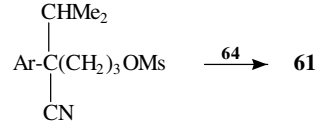
Verapamil, a slow calcium channel antagonist used in treatment of angina, hypertension and superventricular tachycardia[56,57], labelled with ^{13}C in the 1-position of the phenethyl side chain, **61**, and with ^{13}C-labels in all four *O*-methyl groups, **62**, and also containing 50% of ^{13}C in the *N*-methyl group, **62**, has been prepared[58] in multistep syntheses which involved, in the case of the synthesis of **61**, the displacement of mesylate **63** with *N*-methyl-2-(3,4-dimethoxyphenyl)-1-[^{13}C]-ethyl amine, **64** (equation 25).



(61)

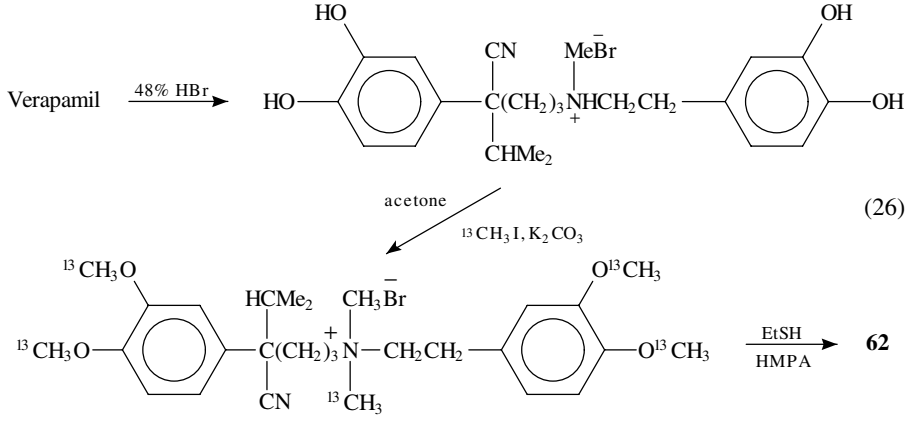


(62) R = $^{12}CH_3$ and $^{13}CH_3$



(63) (25)

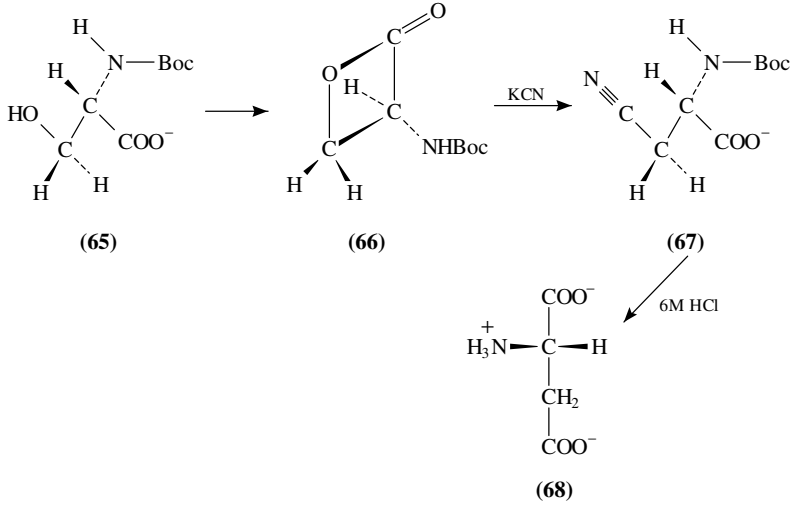
Synthesis of **62** commenced from verapamil hydrochloride, which has been O-demethylated by heating in aqueous 48% HBr (equation 26).



(26)

2. Synthesis of L-[4-^{13}C] and L-[3,4-$^{13}C_2$]aspartic acid

Biosynthetically prepared, isotopically labelled serine has been N-protected by conversion to the L-N-(*t*-Boc)-[3-^{13}C]serine, **65**, which has been cyclized by treatment with Ph_3P and dimethyl azodicarboxylate (DMAD) at −78 °C to yield the β-lacton, **66**, The solution of **66** and dialkyl azodicarboxylate in DMSO added to a solution of $Na^{13}CN$ in DMSO gave L-β-[cyano, 3-$^{13}C_2$]cyanoalanine, **67**. Acid hydrolysis of **67**, provided L-[3,4-$^{13}C_2$]aspartic acid, **68** (equation 27), in 96% enantiomeric excess and 13.3% overall yield based on **65**. Similarly, L-[4-^{13}C]aspartic acid has been prepared from L-serine and $K^{13}CN$. L-Configuration of the labelled amino acid has been required for studies of amino acid metabolism and for studies of peptide and protein structure and dynamics[58,59].

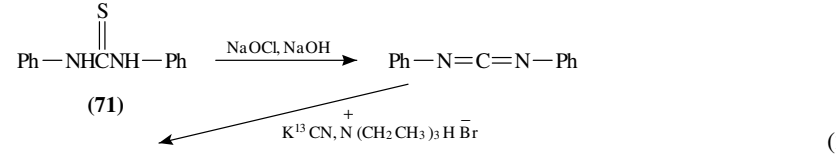


(65) **(66)** **(67)** (27)

(68)

3. Synthesis of α-^{13}C-glycine ***(69)***

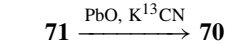
Gram quantities of **69** have been prepared[60] from $K^{13}CN$ as shown in equation 28 and its incorporation into thioredoxin studied by heteronuclear NMR[60].



(71) (28)

(70) **(69)**

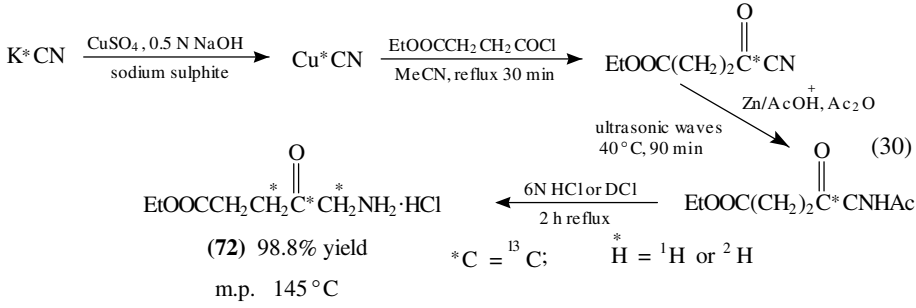
69 had been synthesized previously[61] from the intermediate **70** (equation 29).



(29)

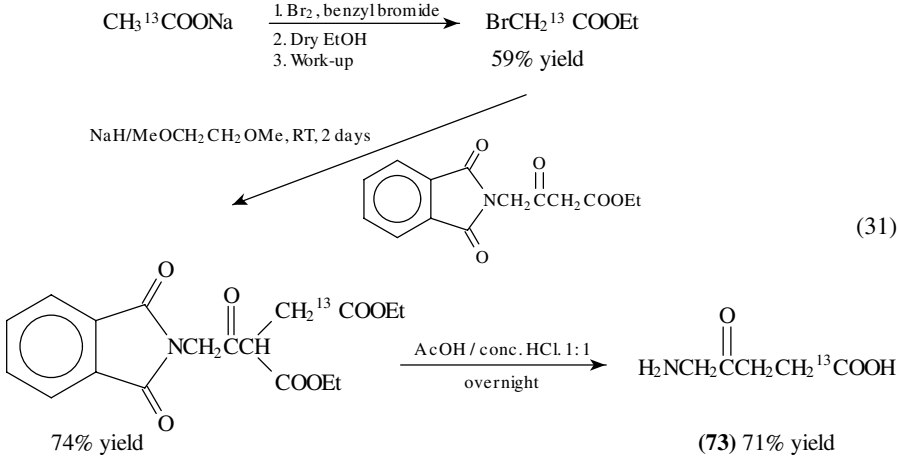
4. Synthesis of δ-aminolevulinic acid (ALA) labelled with ^{13}C

(a) Synthesis of [5-^{13}C]ALA, **72**, has been carried out[62] as shown in equation 30.

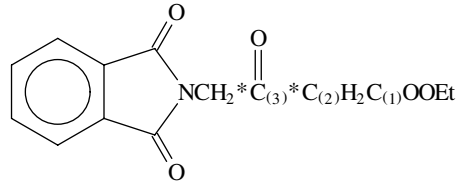


(30)

(b) [1-^{13}C]ALA, **73**, has been synthesized[62] as indicated in equation 31. [2-^{13}C]ALA, **74**, has been synthesized similarly starting with [2-^{13}C]sodium acetate. [3-^{13}C]ALA, **75** and [4-^{13}C]ALA, **76**, have been synthesized also according to equation 31 but using [2-^{13}C]ethyl phthalimidoacetoacetate, **77**, and [3-^{13}C]ethyl phthalimidoacetatoacetate, **78**, as reactants.



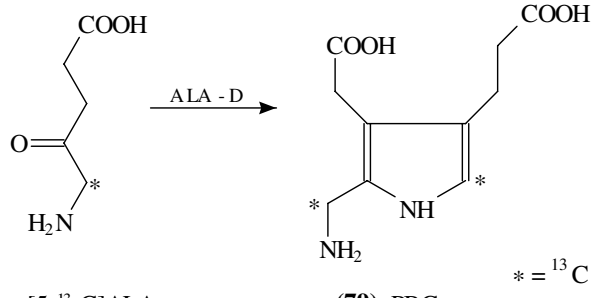
(31)



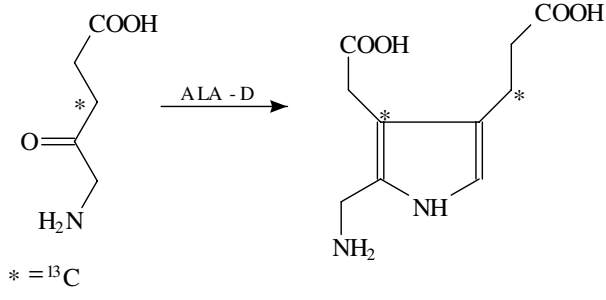
(77) $^{*}C_{(3)} = {}^{13}C_{(3)}$

(78) $^{*}C_{(2)} = {}^{13}C_{(2)}$

(c) The enzymatic transformation of the obtained ^{13}C-labelled ALA to ^{13}C-porphobilinogen (PBG), **79**, has been investigated[62] by direct observation of ^{13}C-NMR of the ^{13}C-labelled PBG (the intermediate in biosynthesis of heme) without chemical degradation. Formation of PBG *in vivo* from two molecules of ALA is catalysed by ALA dehydratase, obtained from human erythrocytes or rat liver[63] (equations 32a and 32b).



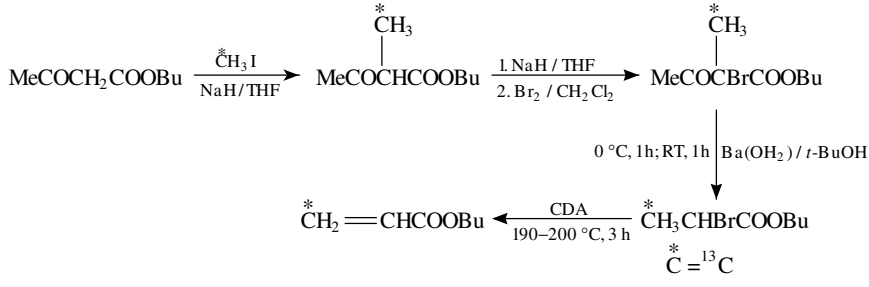
[5-^{13}C]ALA **(79)** PBG (32a)



[3-^{13}C]ALA **(79)** PBG (32b)

*5. Synthesis of n-butyl [3-^{13}C]acrylate **(80)***

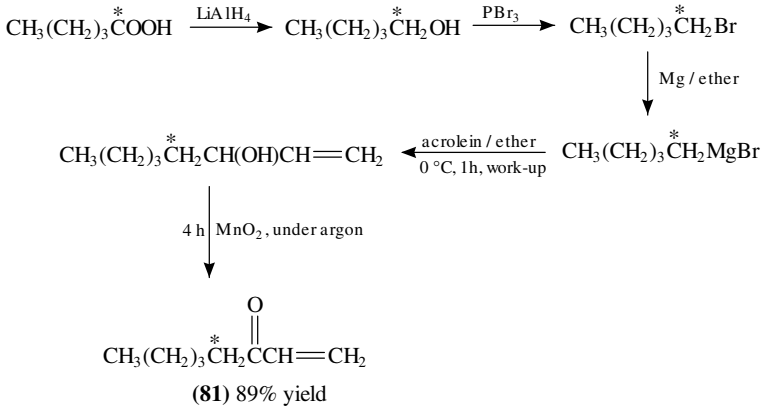
80 has been obtained[64,65] by methylation of butyl acetoacetate, subsequent bromination, alkaline cleavage and dehydrobromination with cyclohexyldimethylamine (CDA), (equation 33). **80** has been required for studies of its metabolism in small animals.



(80) 98% purity,
75.6% ^{13}C enriched by MS (33)

6. Synthesis of the [4-^{13}C]oct-1-en-3-one (81)

The ^{13}C label has been introduced[66] into **81** by the sequence in equation 34. The compound **81** was needed to explain the MS mechanism of the fragmentation of the 2-hydroxy-1,3-butadiene.

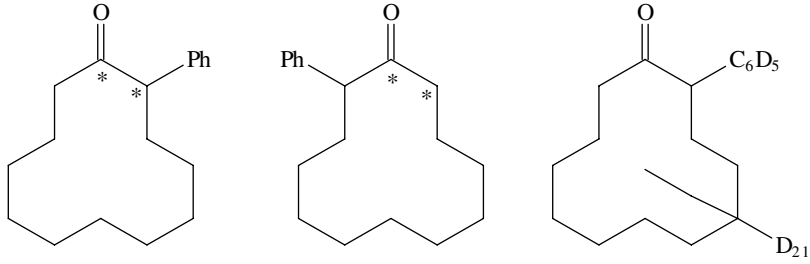


(34)

(81) 89% yield

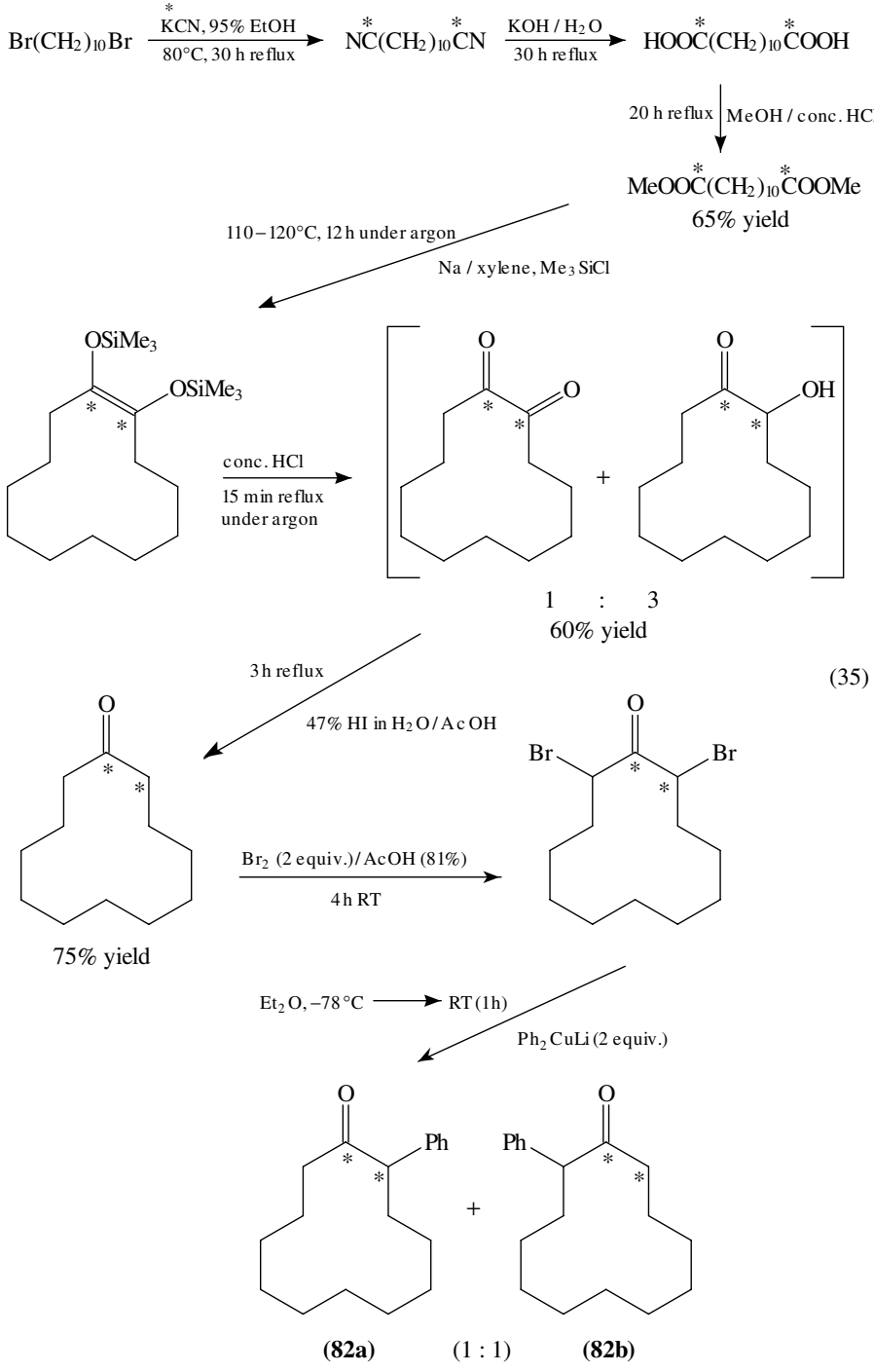
7. Synthesis of ^{13}C- and ^{2}H- labelled 2-phenylcyclododecanones

The commercially unavailable 2-phenylcyclododecanone-$^{13}C_2$ (**82a** and **82b**) and perdeuterio-2-phenylcyclododecanone **(83)** have been synthesized[67–69] to study the effects of magnetic isotopic substitution at the radical centres on the dynamics of flexible biradicals[70,71]. The compounds **82a** and **82b** have been synthesized in 8 steps as shown in equation 35. The ^{13}C has been incorporated by treating 1,10-dibromodecane with two equivalents of K^{13}CN (99% ^{13}C).

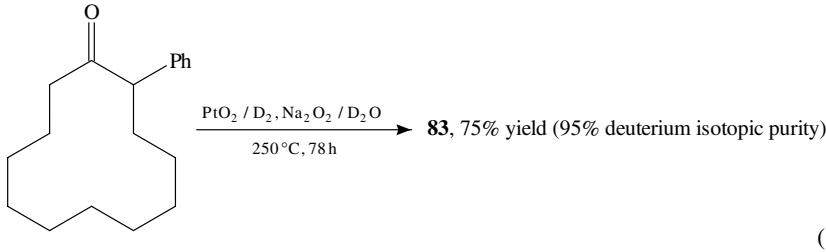


(82a) **(82b)** **(83)**

Perdeuterio-2-phenylcyclododecanone, **83**, has been prepared[67] by H/D exchange between unlabelled 2-phenylcyclododecanone and excess of D_2O, catalysed by D_2-reduced PtO_2 in the presence of alkaline catalyst (D_2O_2 and NaOD) prepared by adding 30 mg of Na_2O_2 to 20 ml of D_2O at 0 °C over 1 hour. The exchange reaction proceeded at 240–250 °C in autoclave for 78 hours under 1000 psi of nitrogen (equation 36). Photochemical studies using ^{13}C-labelled **82** and perdeuteriated derivatives of 2-phenylcyclododecanones **83** are in progress.


Br(CH2)10Br
KCN, 95% EtOH
80°C, 30 h reflux
NC(CH2)10CN
KOH / H2O
30 h reflux
HOOC(CH2)10COOH
20 h reflux
MeOH / conc. HCl
MeOOC(CH2)10COOMe
65% yield
110–120°C, 12 h under argon
Na / xylene, Me3SiCl
OSiMe3
OSiMe3
conc. HCl
15 min reflux
under argon
O
O
O
OH
1 : 3
60% yield
3 h reflux
47% HI in H2O / AcOH
O
75% yield
Br2 (2 equiv.) / AcOH (81%)
4 h RT
Br
Br
Et2O, –78 °C
RT (1h)
Ph2CuLi (2 equiv.)
Ph
Ph
(82a)
(1 : 1)
(82b)

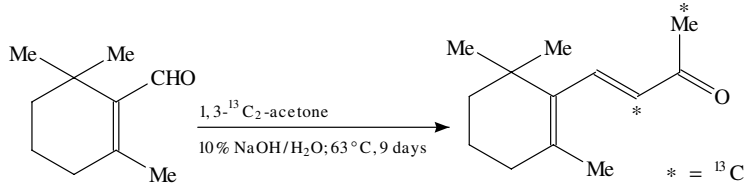
(35)



(36)

8. Synthesis of [1,3-$^{13}C_2$]-4-(2,6,6-trimethylcyclohexen-1-yl)buten-2-one (β-ionone) (84)

84, a simplified retinoid, a useful tool to probe by NMR the conformation of protein-bound retinoids used to treat skin diseases and as cancer chemopreventive agents[72,73], has been synthesized by aldol condensation of [1,3-$^{13}C_2$]acetone with β-cyclocitral, **85**, catalysed by aqueous sodium hydroxide[74] (equation 37).



(37)

(85) **(84)** 73% yield, yellow oil

*9. Synthesis of 1,3,4-thiadiazol-2-ylcyanamide-[5-^{14}C], sodium {LY217896-[5-^{14}C]Na} **86**-[5-^{14}C], and 1,3,4-thiadiazol-2-ylcyanamide-[UL-$^{13}C_3$] sodium {LY217896-[UL-$^{13}C_3$] Na}, **86**-[UL-^{13}C]*

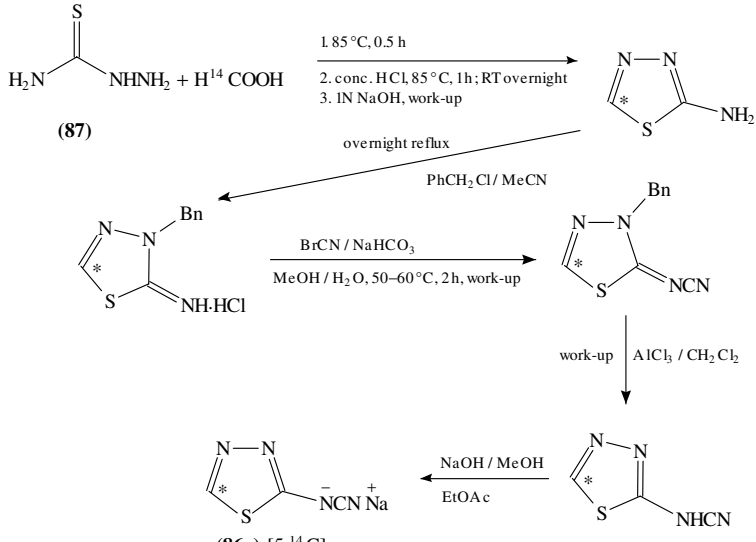
The new anti-influenza agent, LY217896, **86,** active against both A and B strains of influenza[75], has been ^{14}C and ^{13}C labelled[76] to support the pre-clinical as well as clinical drug **86** metabolism and disposition studies and to facilitate the identification of metabolism of **86** *in vivo*.

(a) LY217896-[5-^{14}C], **86a**, has been obtained in five steps which involve the formylation of thiosemicarbazide **87** with formic[^{14}C] acid in the absent of solvent as the first reaction step (equation 38).

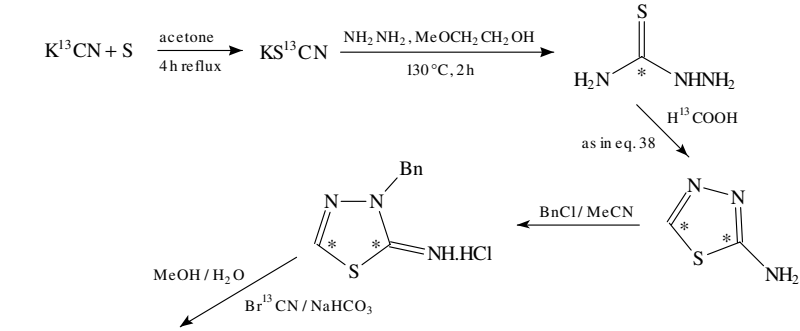
(b) The uniformly labelled LY217896[^{13}C], **86b**-[UL-^{13}C], has been synthesized[76] for metabolite identification utilizing potassium cyanide, cyanogen bromide and formic acid more than 99.5 isotopically enriched with ^{13}C (equation 39).

10. Synthesis of 2,3-disubstituted [3-^{13}C]naphthalenes and [9a-^{13}C]naphthol[2,3-d]-1,2,3-oxadiazole

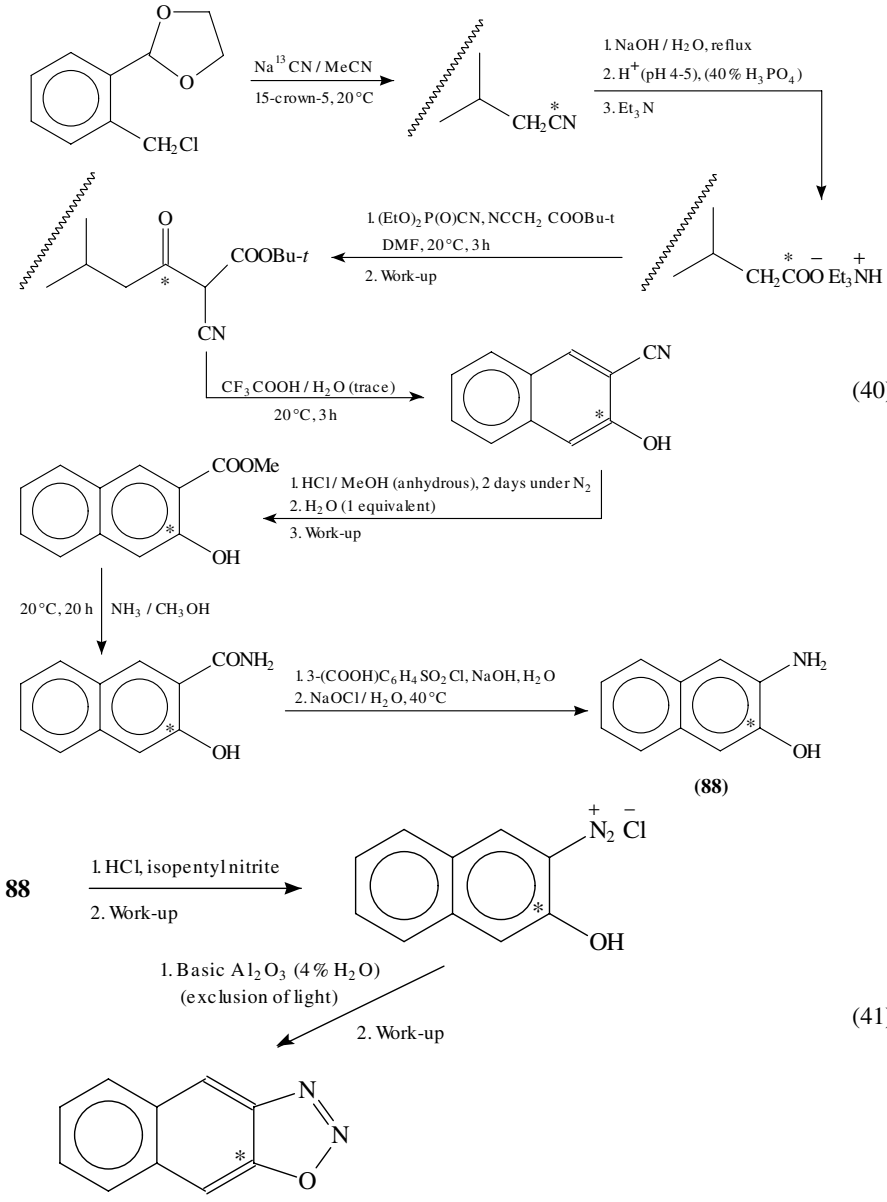
2-Amino-3-hydroxy[3-^{13}C]naphthalene, **88**, has been obtained[77] in seven steps starting with 2-(1,3-dioxolan-2-yl)-benzyl chloride and Na^{13}CN (equation 40). The diazotation of the labelled amino compounds **88** followed by deprotonation provided [9a-^{13}C]naphthol [2,3-d]-1,2,3-oxadiazole, **89** (equation 41).


1. 85 °C, 0.5 h
2. conc. HCl, 85 °C, 1h; RT overnight
3. 1N NaOH, work-up
(87)
overnight reflux
PhCH2Cl / MeCN
BrCN / NaHCO3
MeOH / H2O, 50–60 °C, 2h, work-up
work-up
AlCl3 / CH2Cl2
NaOH / MeOH
EtOAc
(86a)-[5-14C]
LY217896-[5-14C]Na, 24.8% yield
r.purity ≥ 99.2%
sp. act. 34.75 μCi / mg (5.14 mCi / mmol)
* = 14C label

(38)


K13CN + S
acetone
4h reflux
KS13CN
NH2NH2, MeOCH2CH2OH
130 °C, 2h
H13COOH
as in eq. 38
BnCl / MeCN
MeOH / H2O
Br13CN / NaHCO3
as in eq. 38
* = 13C, Bn = PhCH2 —
(86b) - [13C]
NaOH / MeOH
EtOAc
(86) - as sodium salt
LY217896[UL-13C]Na, 26.7% yield

(39)



(40)

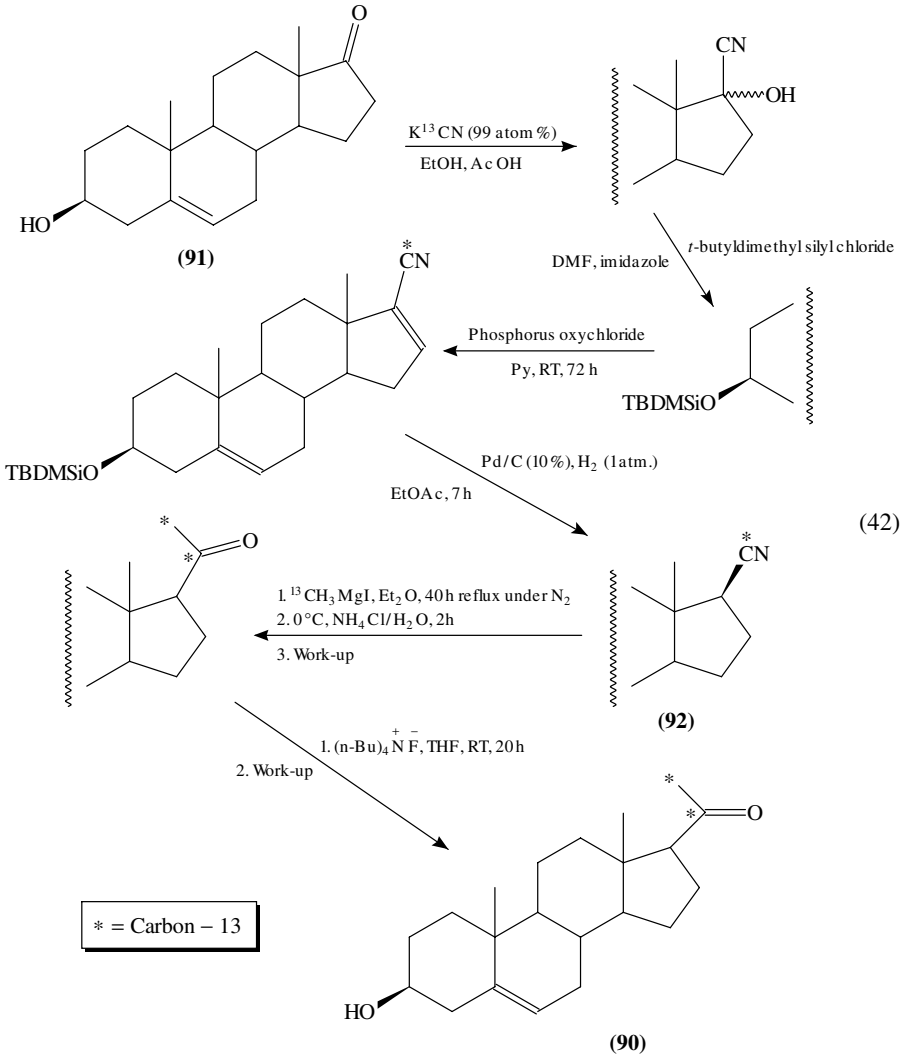
(41)

(89) 16.6% yield, m.p. + 77°C (decomp.), storage at −20°C

The β-^{13}C-labelled naphthalenes obtained have been characterized by their ^{13}C-NMR chemical shifts and $^{13}C-^{13}C$ coupling constants determined in CD_3OD.

*11. Synthesis of [20,21-$^{13}C_2$]-pregnenolone **(90)***

90 labelled with ^{13}C at $C_{(20)}$ and $C_{(21)}$ has been obtained[78] by condensation of androst-5-en-3β-ol-17-one, **91**, with $K^{13}CN$ and by Grignard reaction of nitrile derivative **92** with $^{13}CH_3MgI$ (equation 42). The location of carbon-13 was confirmed by ^{13}C-NMR spectroscopy.

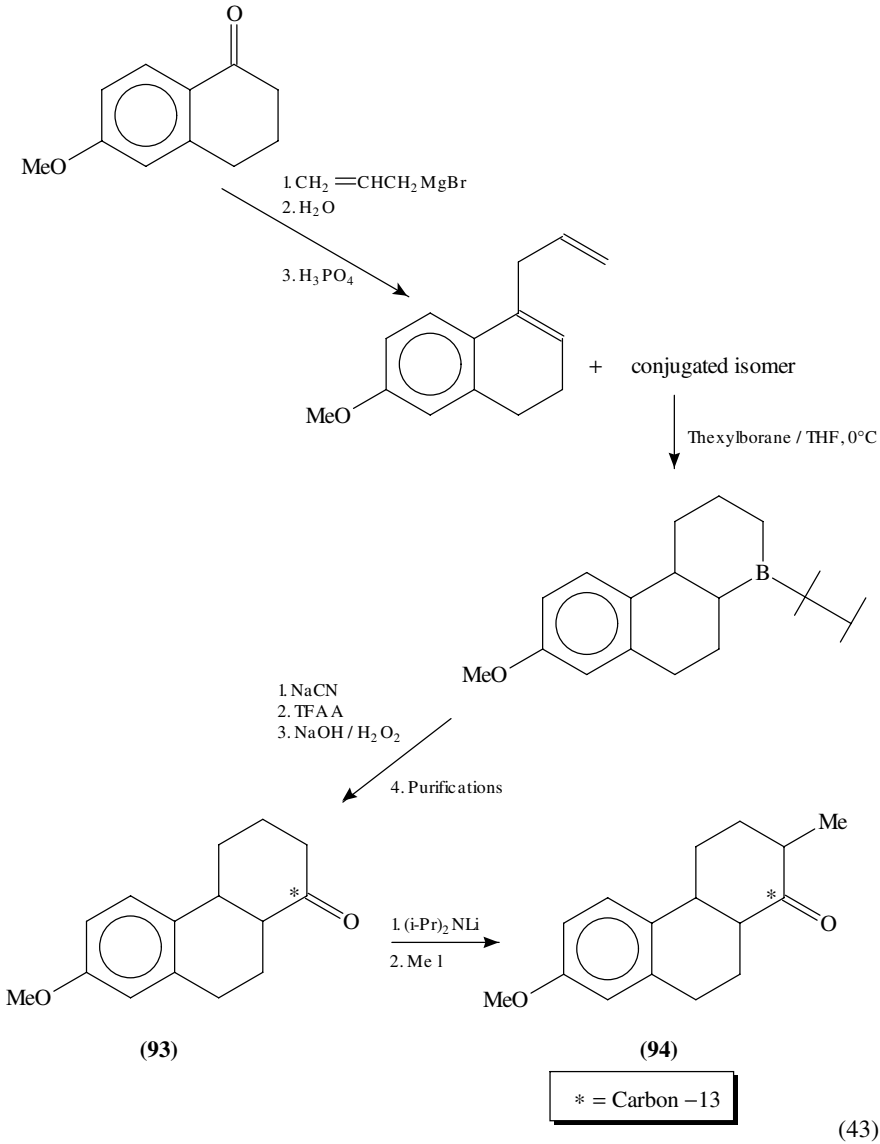


(42)

12. Synthesis of carbon-13 labelled 1-keto-7-methoxyoctahydrophenanthrene

The syntheses of carbon-13 labelled *trans*-tricyclic ketones **93** and **94** have been carried out[79] via the cyanidation reaction of organoborane (equation 43). The isomerically pure *trans*-tricyclic ketones **93** and **94** were needed in connection with the undertaken synthesis

of carbon-11-labelled 17β-estradiol and related hormones[80,81].

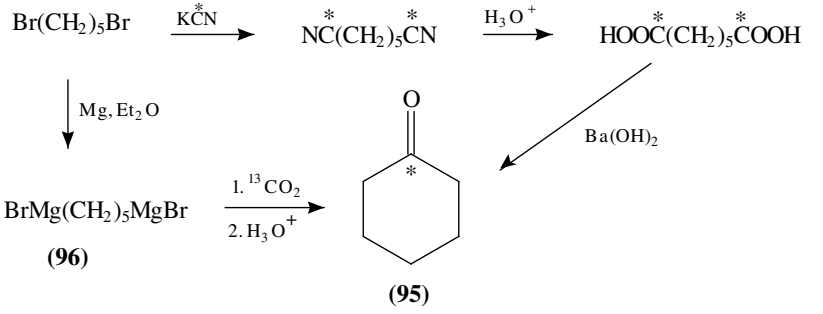


(43)

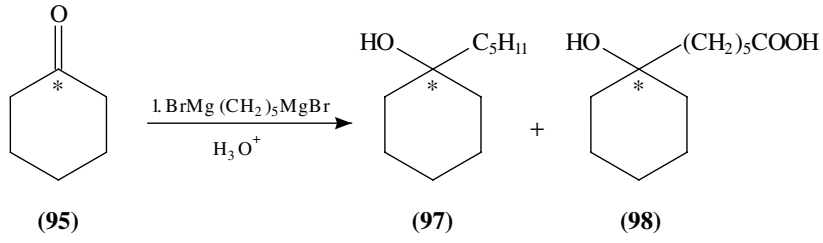
13. Synthesis of 1,2,3,4,-tetrahydrocarbazole-9a-^{13}C and carbazole-9a-^{13}C

The title ^{13}C-labelled heterocyclic compounds have been synthesized[82] to understand better the coal liquification process[83], Cyclohexanone-1-^{13}C, **95**, has been prepared through the sequence of reactions shown in equation 44. The carbonation of **96** at −78 °C gave **95** in 24–38% yield. At −8°C, the condensation of **95** with excess of Grignard

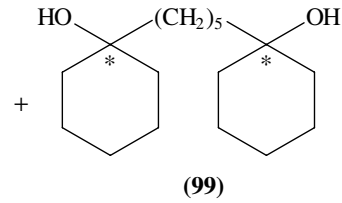
reagent provided the alcohols **97, 98** and **99** and no **95** (equation 45). **100** and **101** have been prepared in 77% and 85% yields, respectively (equation 46), starting with **95**. Several ^{13}C-labelled compounds **100** have been synthesized also to study the effectiveness of hydrogen transfer solvents in coal liquification process[84].

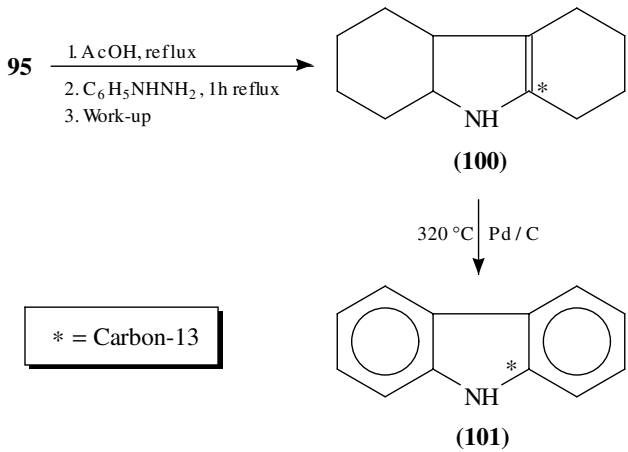


(44)



(45)

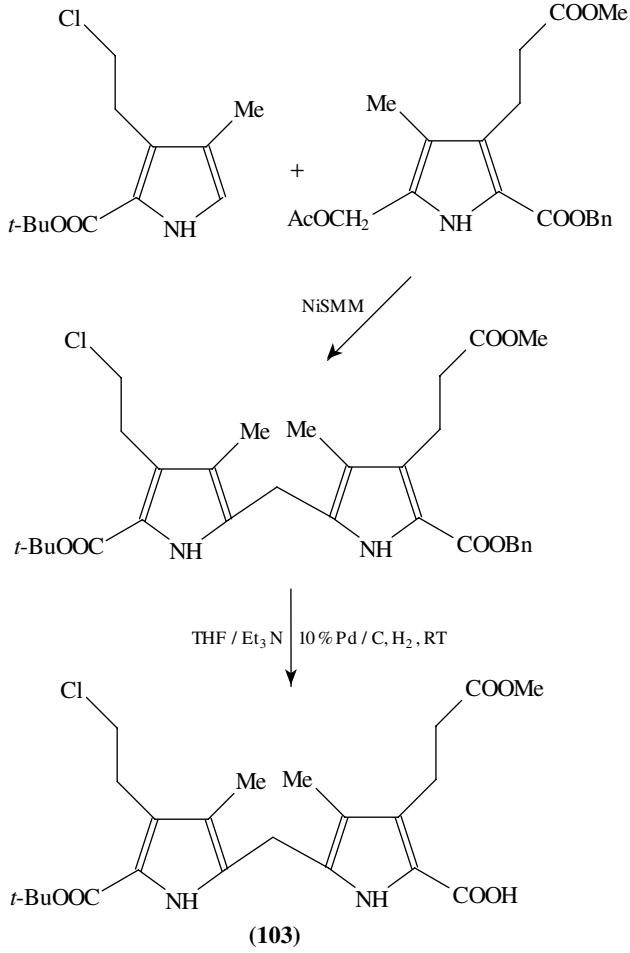




(46)

14. Synthesis of [10-^{13}C]bilirubin IXα ***(102)***

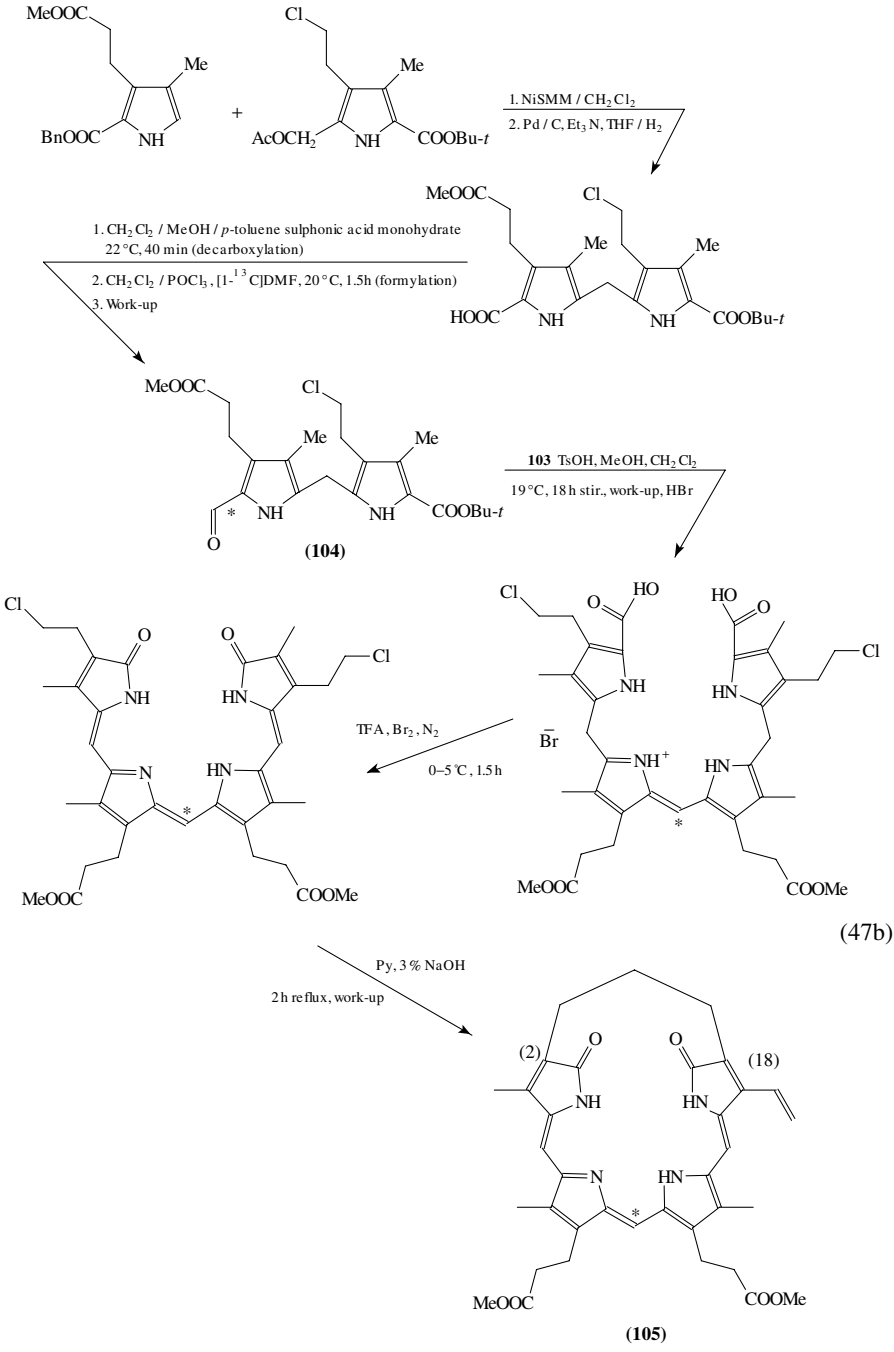
102, the major product of haem degradation, is poorly excreted in the newborn. Its accumulation leads to damage of the central nervous system. The tracer kinetic studies *in vivo* with the use of radiolabelled bilirubin have, because of ethical reasons, not involved neonates. [10-^{13}C]bilirubin has therefore been synthesized[85,86] in overall 6% yields to elucidate the pathophysiological mechanism of bilirubin metabolism in humans. The total synthesis of **102** presented by equation 47 involves the Vilsmeier formylation of one of the dipyrrolic fragments using [1-^{13}C]dimethyl amide. The penultimate dehydrohalogenation reaction has been complicated by side elimination reaction leading to 2,18 bridged with propane ether biliverolin derivative[87], **105**. For these reasons the route shown in equations 47a, b, c seems not to be the most propitious approach and the use of phenylselenylethyl groups as protected vinyl substituents[88] has been suggested.

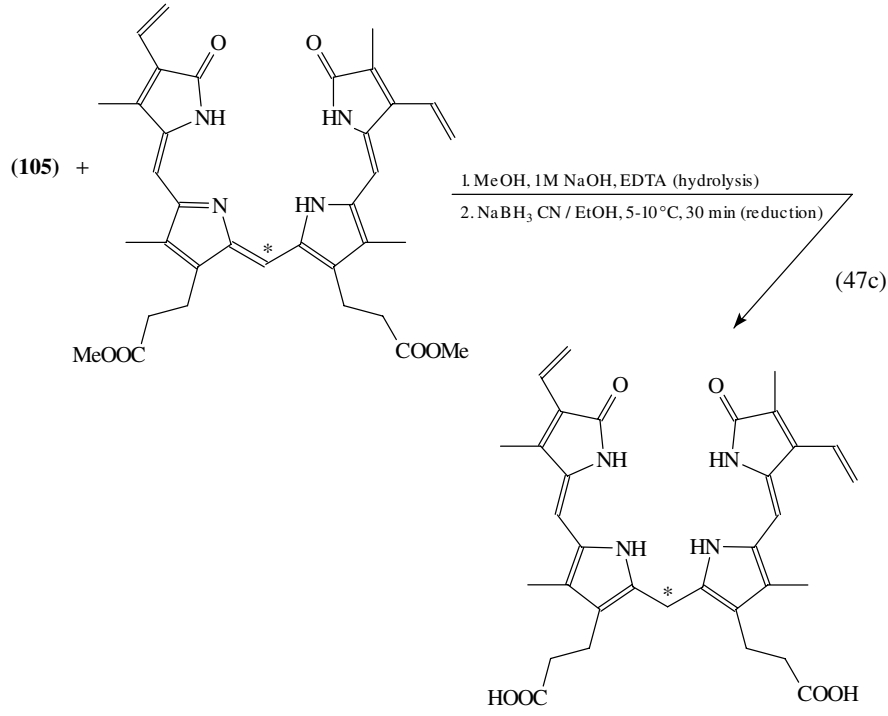


(47a)

(103)

NiSMM = Synthetic Mica Montmorillonite with Incorporated Nickel


MeOOC
Me
BnOOC
NH
+
Cl
Me
AcOCH2
NH
COOBu-t
1. NiSMM / CH2Cl2
2. Pd / C, Et3N, THF / H2
MeOOC
Cl
Me
Me
HOOC
NH
NH
COOBu-t
1. CH2Cl2 / MeOH / p-toluene sulphonic acid monohydrate
22 °C, 40 min (decarboxylation)
2. CH2Cl2 / POCl3, [1-13C]DMF, 20 °C, 1.5h (formylation)
3. Work-up
MeOOC
Cl
Me
Me
*
NH
NH
COOBu-t
O
(104)
103 TsOH, MeOH, CH2Cl2
19 °C, 18 h stir., work-up, HBr
Cl
O
NH
O
HN
Cl
N
HN
*
MeOOC
COOMe
TFA, Br2, N2
0–5 °C, 1.5 h
Cl
O
HO
NH
HO
O
HN
Cl
Br
NH+
HN
*
MeOOC
COOMe
(47b)
Py, 3 % NaOH
2 h reflux, work-up
(2)
O
NH
O
HN
(18)
N
HN
*
MeOOC
COOMe
(105)



(102)

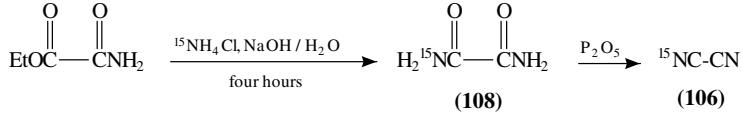
IXα-Bilirubin, m.p. 235 °C (decomp.)
EDTA = Ethylenediaminotetraacetic acid

C. Compounds Labelled with Nitrogen-15

*1. Synthesis of mono-^{15}N-cyanogen **(106)** and mono-^{13}C-cyanogen **(107)***

106 and **107** have been obtained[89] in procedures respectively involving dehydration of mono-^{15}N, **108**, and mono-^{13}C-oxamide, **109**, with phosphorus pentoxide (equations 48 and 49).

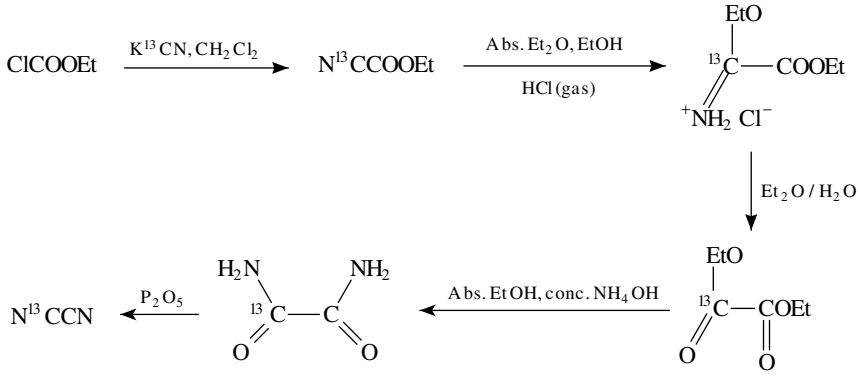
The two symmetrically labelled isotopomers of cyanogen, $^{15}NCC^{15}N$ and $N^{13}C^{13}CN$, have been prepared[89] by thermolysis of ^{15}N and ^{13}C-silver cyanide, respectively. **106** and **107** have been needed for infrared spectral investigations. The cyanogen, NCCN, was detected in the atmosphere of the Saturn moon Titan[90] and the chemical spectroscopic and theoretical studies of the C_2N_2 isomers have been reviewed[91–93].



(108) **(106)**

23.5% yield

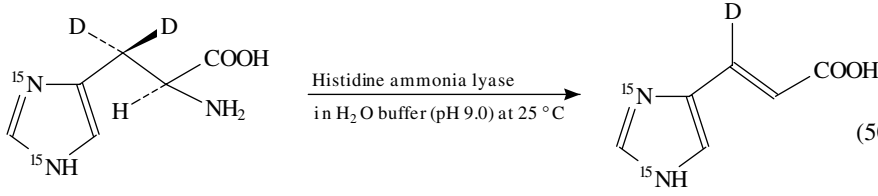
(48)



(107) 21.2% yield **(109)** (49)

2. Synthesis of urocanic acids multilabelled with ^{2}H, ^{13}C and ^{15}N

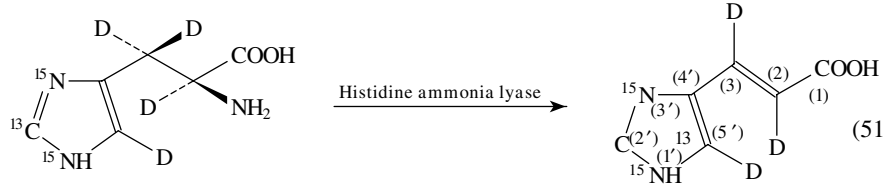
(a) [3-^{2}H, 1′,3′-$^{15}N_2$]urocanic acid, **110**, and [2, 3, 5′-$^{2}H_3$, 2′-^{13}C, 1′,3′,-$^{15}N_2$]urocanic acid, **111**, have been synthesized[94] by the enzymatic reaction of DL-[3,3-$^{2}H_2$, 1′,3′-$^{15}N_2$]histidine, **112** (equation 50) and DL-[2,3,3,5′-$^{2}H_4$, 2′-^{13}C, 1′,3′-$^{15}N_2$]histidine, **113** (equation 51), respectively. Reaction 51 has been carried out in a D_2O buffer system to avoid the enzyme-catalysed hydrogen exchange at $C_{(5')}$ of the imidazole ring[95].



(50)

(112) **(110)** 85% yield

(from L-isomer in labelled racemic histidine)



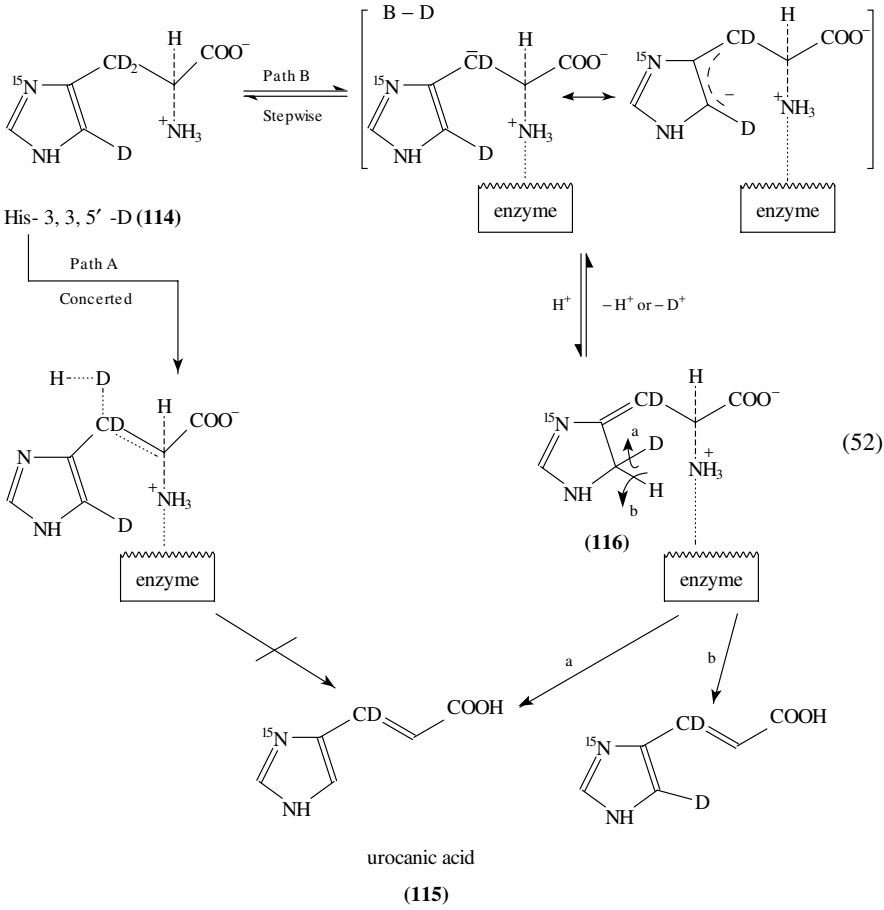
(51)

(113) **(111)**

75% yield from L-isomer in labelled racemic histidine

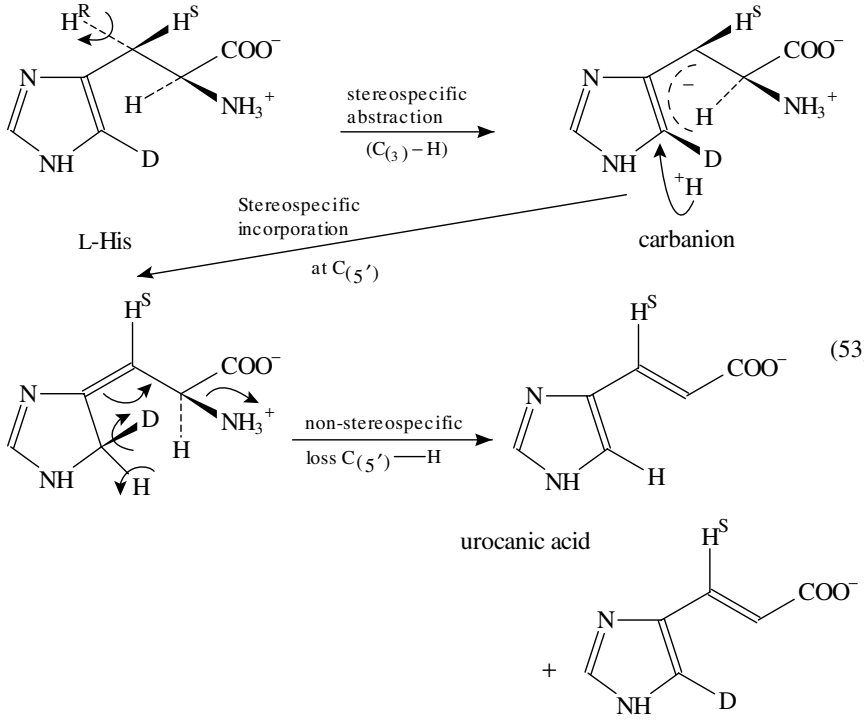
110 and **111** have been obtained to investigate the pharmacokinetics of L-histidine in humans. **112** and **113** have been synthesized previously[96,97] to detect the heterozygote state[98] of histidinemia, a hereditary metabolic disorder, caused by deficiency of the liver enzyme, histidine ammonia lyase[99], characterized by mental and/or speech retardations.

(b) The mechanism of the enzymatic elimination of ammonia from L-histidine, catalysed by histidine ammonia lyase (EC4.3.1.3), has been reinvestigated[95] by carrying out the synthesis of L-[3,3,5′-$^2H_3$, 3′-^{15}N]histidine, **114**, starting from [3,3,5,5-$^2H_4$]-2,5-diamino-4-oxo-pentanoic acid[96]. The isolated urocanic acid product (UA-3,5′-D_2), **115**, was found to contain protons at the $C_{(5')}$ position of the imidazole ring, and its NMR spectrum indicated 44% loss of deuterium at $C_{(5')}$. Practically the same value (45.3%) of deuterium loss was obtained from the GC-MS selected ion monitoring data. Without the use of the enzyme the deuterium at $C_{(5')}$ of histidine **114** was found to be retained completely. When DL-[2,5′-$^2H_2$]histidine has been used, 42% deuterium loss was observed. No deuterium loss at $C_{(2)}$ was found. These losses of deuterium at $C_{(5')}$ during the enzymatic reaction have therefore been interpreted as the result of the enzyme-catalysed hydrogen exchange, The incubation of the unlabelled L-histidine with histidine ammonia lyase under the D_2O-buffer conditions (pD 9.0) led to *ca* 20% incorporation of deuterium at $C_{(5')}$ of urocanic acid (by ^{1}H NMR). The above D/H and H/D exchange data have been taken as excluding the possibility of a concerted mechanism of elimination of ammonia from L-histidine, illustrated by path A in equation 52, and as favoring the stepwise mechanism via a carbanion intermediate illustrated by path B.



(52)

Neglecting the possibility of occurrence of intramolecular hydrogen/deuterium kinetic isotope effect in the competitive rupture of the $C_{(5')}-H$ versus $C_{(5')}-D$ bonds in the unstable intermediate **116** and taking into account[99,100] the stereospecific abstraction of $C_{(3)}$ hydrogen (*pro-3R*) followed by delocalization of the 3-carbanion to $C_{(5')}$, Furuta and coworkers[95] proposed the reaction scheme (equation 53) explaining the *ca* 45% deuterium exchange at $C_{(5')}$. According to this scheme the stereospecific hydrogen incorporation at $C_{(5')}$ from the solvent is followed by subsequent non-stereospecific loss of a proton at $C_{(5')}$ and formation of urocanic acid retaining 50% deuterium (equation 53). The elimination mechanism of ammonia is a subject of controversy[101,102]. After the preliminary deuterium and tritium exchange and T/H, D/H, T/D kinetic isotope effect studies, the microscopic mechanisms of the non-enzymic elimination reactions are usually investigated by the heavy-atom isotope effect[103] method involving the successive isotope labelling techniques using ^{13}C, ^{14}C and ^{15}N. KIE determinations of ^{14}C and ^{15}N permit one to distinguish between the carbonium ion E_1 mechanism, the concerted E_2 mechanism and carbanion E_1cb mechanism and to establish the relative degrees of the $C_{(3)}-H$ and $C_{(2)}-N$ bond ruptures in the activated complex which is not indicated explicitly in the reaction schemes shown in equations 52 and 53.

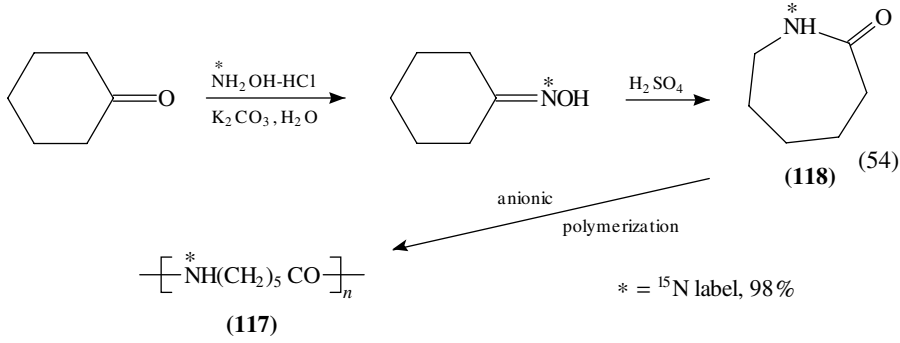


(53)

*3. Synthesis of ^{15}N-labelled nylon 6 **(117)***

117 has been synthesized[104] by anionic polymerization of ε-caprolactam, **118** (equation 54), for investigations of the morphology of this commercially important

polymer by solid-state ^{15}N NMR, IR and Raman spectroscopies.



(118) (54)

(117)

4. Synthesis of [^{15}N]labelled acetamide and acetonitrile

^{15}N-labelled acetonitrile has been usually synthesized[105–107] as in equations 55–58.

$$MeI + KC\overset{*}{N}/NaC\overset{*}{N} \longrightarrow MeC\overset{*}{N} \quad (88\text{–}95\%\ \text{yield}) \tag{55}$$

$$Me_2SO_4 + KC\overset{*}{N} \longrightarrow MeC\overset{*}{N} \quad (67\%\ \text{yield}) \tag{56}$$

$$Ac_2O + \overset{*}{N}H_3 \longrightarrow Ac\overset{*}{N}H_2 \tag{57}$$

$$Ac\overset{*}{N}H_2 \xrightarrow{P_2O_5} Me\overset{*}{C}N \quad (34\text{–}47\%\ \text{yield}) \tag{58}$$

The first two methods[105,106] require the use of the rather expensive $KC^{15}N$ or $NaC^{15}N$. In the third approach[107] the relatively inexpensive $^{15}NH_3$ or $^{15}NH_4Cl$ are the starting isotope compounds. The rather low yield in two-step reactions 57 and 58 has been improved[108] by employing 2,2,2-trifluoroethyl acetate for the reaction with $^{15}NH_4OH$ (equations 59 and 60).

$$AcOCH_2CF_3 + {}^{15}NH_4OH \longrightarrow Ac^{15}NH_2 + CF_3CH_2OH + H_2O \quad (85\%\ \text{yield})\ \text{m.p. } 81.5\text{–}82\,^{\circ}C \tag{59}$$

$$Ac^{15}NH_2 + P_2O_5 \longrightarrow MeC^{15}N \quad 75\%\ \text{step yield, } 64\%\ \text{overall yield} \tag{60}$$

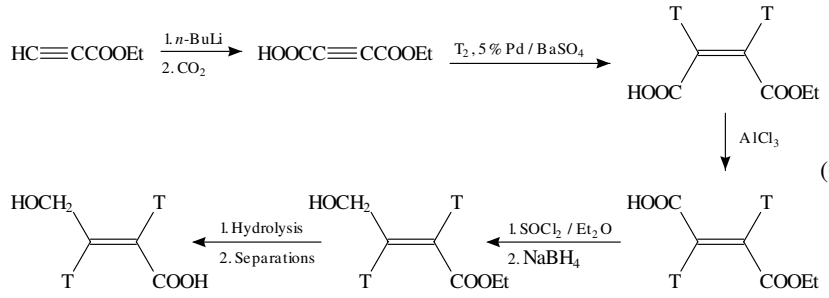
III. SYNTHESIS AND USES OF COMPOUNDS CONTAINING C=C, C=O OR CN GROUPS LABELLED WITH TRITIUM

A. Compounds Labelled with Tritium

*1. Synthesis of [^{3}H]-labelled trans-4-hydroxycrotonic acid (THCA-[2,3-^{3}H]) **(119)***

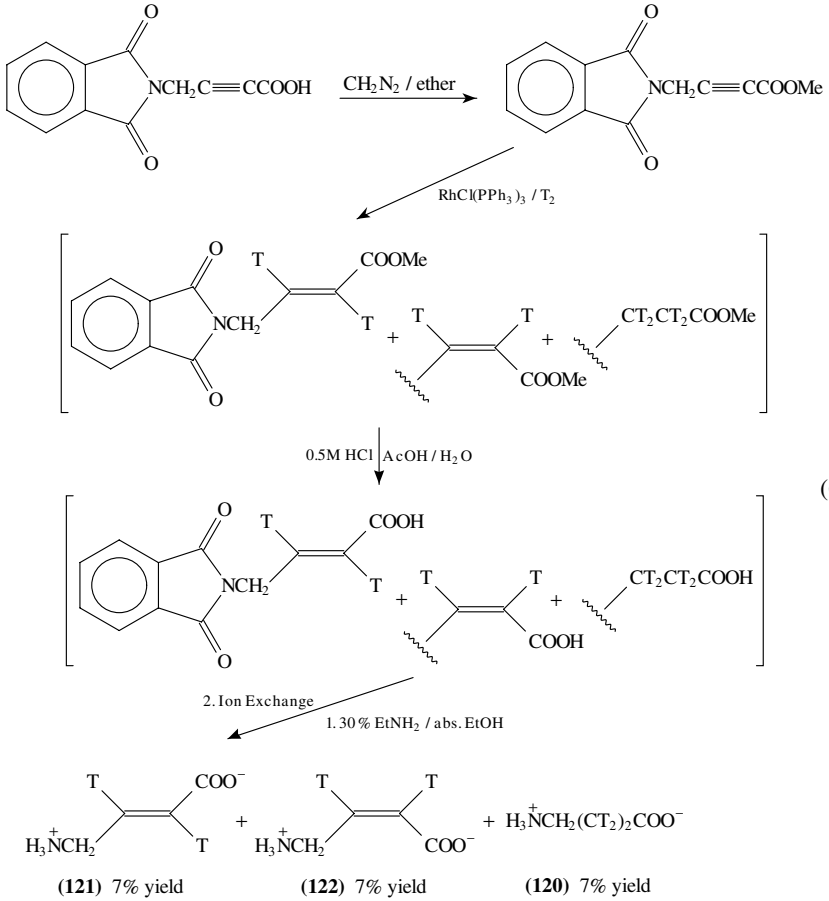
119, identified in the central nervous system of mammalians[109], and interacting with the specific GHB (4-hydroxybutyrate) biological targets[110], has been tritium labelled[111]

at the 2,3-positions as shown in equation 61.



(61)

(119) sp. activity 45 Ci/mmole, rad. purity 97%



(62)

(121) 7% yield
sp. act. 52.6 Ci / mmol
r. purity 91% (TLC)

(122) 7% yield
sp. act. 55.8 Ci / mmol
r.purity 88% (TLC)
+ impurities (14% yield)

(120) 7% yield
sp. act. 83.3 Ci / mmol
r.purity 48% (TLC)

2. Synthesis of tritiated E- and Z-4-aminobut-2-enoic acids

The title unsaturated 4-aminobut-2-enoic acids, **121** and **122**, usually referred to as TACA (*trans*-aminocrotonic acid) and as CACA (*cis*-aminocrotonic acid), exhibiting significant pharmacological activities with respect to GABA, **120**, A and B receptors[112,113], have been synthesized[114] from methyl 4-*N*-phthalimidobut-2-ynoate by catalytic hydrogeneration with tritium gas in the presence of *tris* (triphenylphosphine)rhodium(I) chloride (equation 62). The HPLC separation of [^{3}H]-*E*- and [^{3}H]-*Z*-isomers as well as of tritiated 4-aminobutanoic acid (GABA) have been described[114].

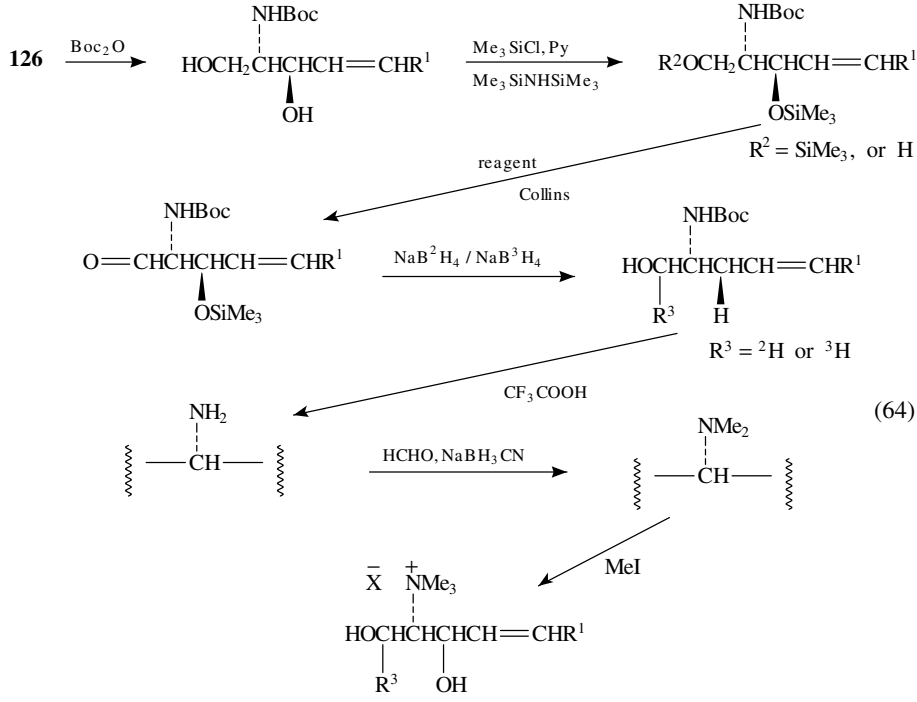
3. Synthesis of sphingosines tritium labelled at the 3-position

C_{18}-Sphingosine [(2*S*,3*R*,4*E*)-2-amino-4-octadecen-1,3-diol], a constituent of the plasma membrane of vertebrates[115], has been tritium labelled at the 3-position for the investigation of its biological function[116] (equation 63). Reduction of the keto derivatives **123** with [^{3}H]$NaBH_4$ and subsequent conversion of the azido group into the amino group by a Staudinger reaction provided stereoselectively the tritiated D-*erythro*- and L-*threo*-sphingosines **124A**, **124B** and **125A**, **125B** respectively.

(63)

4. Synthesis of (2S,3R,4E)-2-amino-4-octadecene-1,3-diol-1-^3H

It has been suggested[117–119] that the sphingosine, **126**, *N*,*N*-dimethylsphingosine, **127**, and *N*,*N*,*N*-trimethylsphingosine, **128** might have a pharmacological use for the prevention of tumor growth and other pathological processes, since they have been shown to be the potent modulators of protein kinase C (PK-C)[119,120]. Tritium has therefore been introduced[119] into their 1-position with complete retention of the original stereochemistry, employing regiospecific oxidation of the primary hydroxy group followed by reduction with NaB^3H_4 (equation 64).

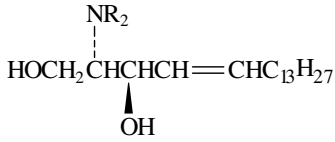


(64)

$R^3 = {}^3H$, sp. act. 97 mCi / mmol, r. purity 97%

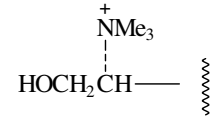
$R^1 = -C_{13}H_{27}$; Boc = —COOCMe$_3$

X = I or Cl



(126) R = H, sphingosine

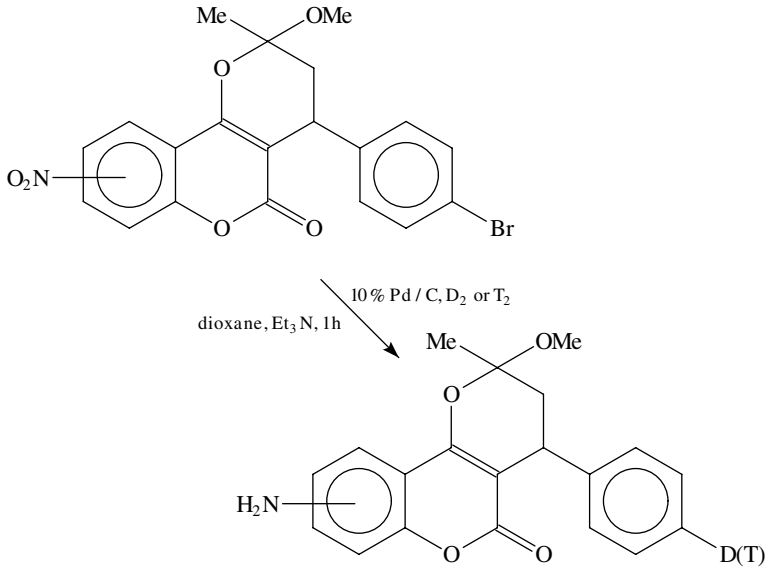
(127) R = Me, *N*,*N*-dimethylsphingosine



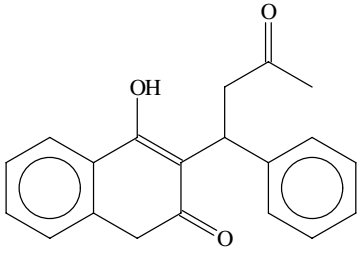
(128) *N*,*N*,*N*-trimethylsphingosine

5. Synthesis of tritium-labelled aminowarfarin methyl ketal regioisomers

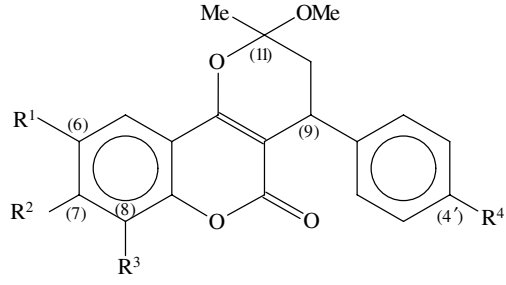
The anticoagulant drug, warfarin [4-hydroxy-3-(3-oxo-1-phenylbutyl)-2*H*-1-benzopyran-2-one], **129**, a useful tool for the study of the cytochrome P450 superfamily of enzymes[121], has been tritium labelled[122] for defining the nature of the substrate-binding sites of the enzymes. 6-Bromo-4′-nitro-, **130**, 4′-bromo-6-nitro-, **131**, 4′-bromo-7-nitro-, **132** and 4′-bromo-8-nitrowarfarin, **133**, have been subjected to catalytic tritiation to produce the tritium-labelled aminowarfarin methyl ketals (equation 65). Tritiation of 5 mg of an equal mixture of **130, 131, 132** and **133** gave a product containing 200 mCi of tritium after removal of labile tritium. These compounds can be directly converted to the tritium-labelled ring-opened azidowarfarins via diazotization and azide substitution. All four azido compounds inactivate P4501A1, when photoactivated in its presence[122].



(65)



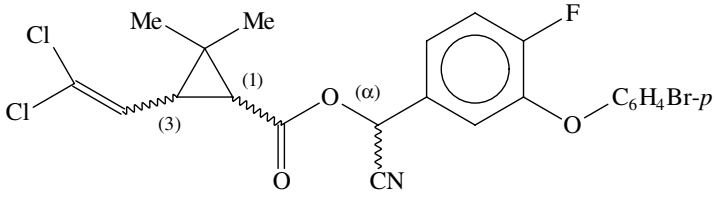
(129)



(130) $R^1 = Br$, $R^4 = NO_2$, $R^2 = R^3 = H$
(131) $R^4 = Br$, $R^1 = NO_2$, $R^2 = R^3 = H$
(132) $R^4 = Br$, $R^2 = NO_2$, $R^1 = R^3 = H$
(133) $R^4 = Br$, $R^3 = NO_2$, $R^1 = R^3 = H$

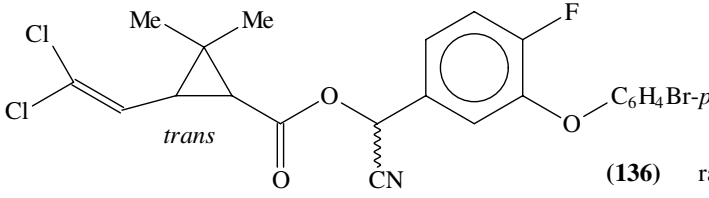
6. Synthesis of [^{3}H]cyfluthrin

Cyfluthrin, **134**, a synthetic insecticide[123] possessing three chiral C-atoms (1,3 and α), has been synthesized[124] starting with bromocyfluthrin, **135**, as shown in equation 66. For distribution and biotransformation studies in tse-tse files, **134** was diluted to a specific activity of 1.0 mCi/ml.



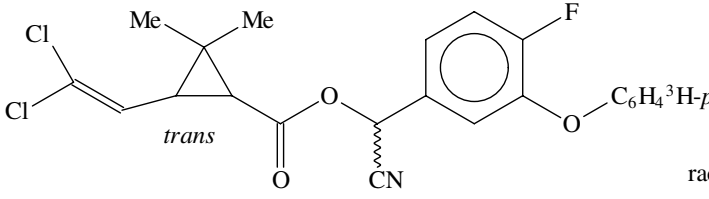
(135) (racemates I, II, III and IV)

Column separation of racemates



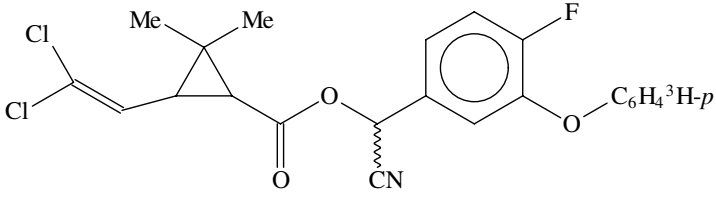
(136) racemate IV

$^3H_2$ / Pd / $CaCO_3$, Et_3N (66)



racemate IV

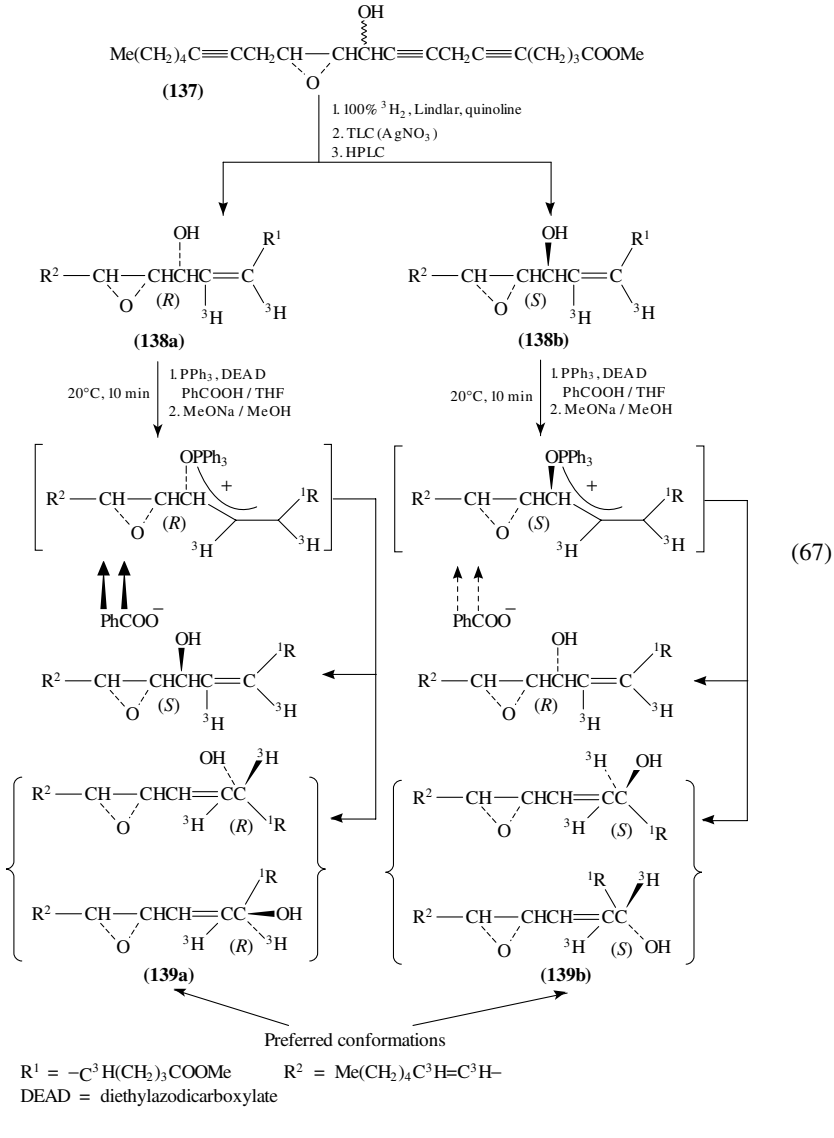
epimerization in EtOH in position α



(134) mixture of racemates III and IV

*7. Synthesis of methyl [5,6,8,9,14,15-$^3H_6$]-hepoxilin B_3 (**138a** and **138b**) and methyl [5,6,8,9,14,15-$^3H_6$]-hepoxilin A_3 (**139a** and **139b**)*

The biologically active hepoxilins HxA_3, **139a, 139b** and HxB_3, **138a, 138b**, stimulating insulin secretion, enhancing Ca^{2+} transport across membranes, potentiating hormone-induced vascular permeability and contraction, etc.[125–127], have been tritium labelled[128] to investigate their metabolism both *in vitro* and *in vivo*, by selective tritiation of the triacetylenic analog of the HxB_3 i.e. 10(*R*/*S*)-hydroxy-11(*R*),12(*S*)-epoxyeicosa-5,8,14-triynoate, **137**, using larger amounts of Lindlar catalyst (equation 67) to form **138a** and **138b**. The ratio of two [$^3H_6$]-HxB_3 epimers 138**a** : 138**b** was 65 : 35.

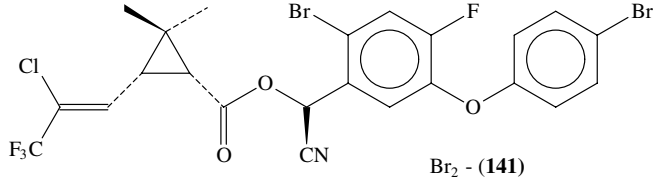


(67)

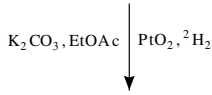
138a and **138b** have been subsequently transformed into $[^3H_6]$-HxA_3 methyl esters **(139ab)** in almost equal ratio by allylic rearrangement[129] via the corresponding $[^3H_6]$-HxA_3 benzoates (equation 67) followed by mild treatment with MeONa in MeOH to hydrolyse the benzoates.

*8. Synthesis of (αS,Z,1R,3R)-[4′,4″-^{3}H]cyhalothrin, **140a**, and -[4″,6′-^{3}H]-4′-fluorcyhalothrin, **140b***

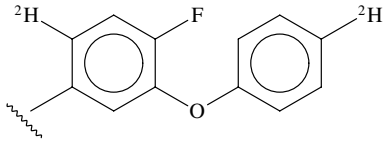
These highly potent insectides, **141** and **140**, have been synthesized[130] (equations 68 and 69) for identifying and for the studies of the mechanism of pyrethroid-sodium channel interaction[131,132]. The ^{3}H incorporation was detected by ^{1}H NMR of $[^3H]$-**140** and by proton coupled and decoupled ^{3}H-NMR determinations of **140, 140a** and **140b**. These are suitable radioligands for binding studies with neuronal membranes on the molecular level.



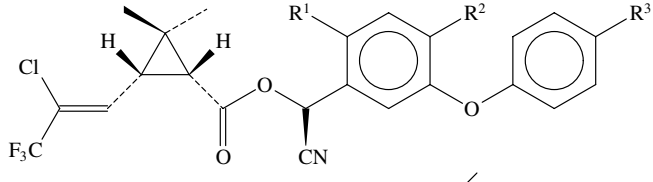
Br_2 - (**141**)

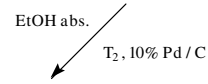


(68)

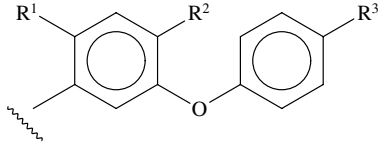


[^{2}H] - (**141**)





(69)

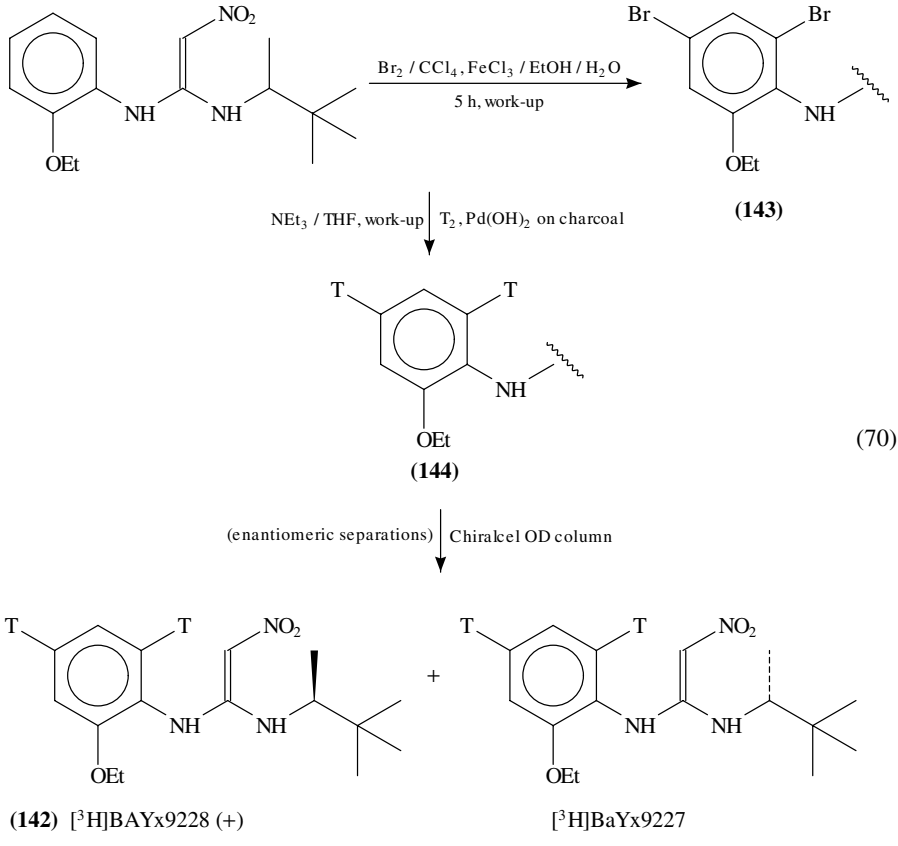


(140a) $R^1 = H, R^2 = R^3 = I$ $[^3H]$- **(140a)** $R^1 = H, R^2 = R^3 = {}^3H$

(140b) $R^1 = R^3 = I, R^2 = F$ $[^3H]$- **(140b)** $R^1 = R^3 = {}^3H, R^2 = F$

9. Synthesis of (+)-N-(6-ethoxy[2,4-^{3}H]phenyl)-N-(1,2,2-trimethylpropyl)-2-nitroethene-1,1-diamine ([^{3}H]BaYx9228), ***142***

The novel potassium channel opener, **142**, hyperpolarizing the cellular membrane and increasing the efflux of K^+ (or Rb^+) from tissues[133] has been tritium labelled[134] by dehalogenization of the dibrominated racemic precursor, **143**, with Pearlman's catalyst[135] which dehalogenated **143** more rapidly (within two minutes) than it reduced the nitro group (equation 70). BAYx9227 has no potassium channel activity. The tritiated **142** was needed for the search for specific binding sites in different cell types, since the potassium channel openers are considered as the new drugs for hypertension, angina pectoris, asthma and other treatments.



(70)

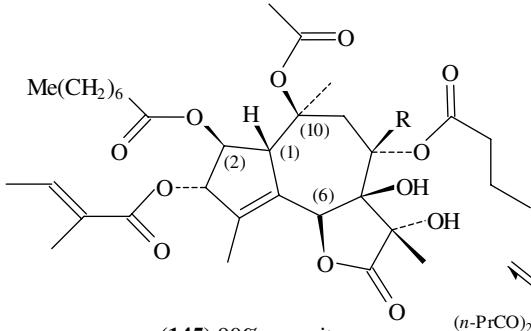
(142) [^{3}H]BAYx9228 (+) [^{3}H]BaYx9227

sp. activity 47.9 Ci / mmol, enantiomeric purity = 98.3%

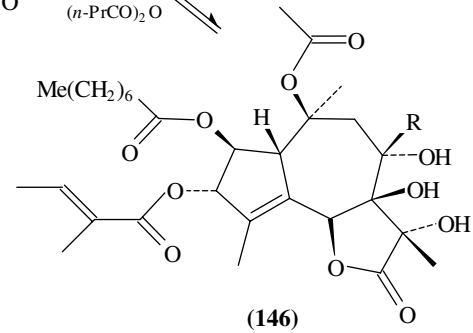
10. Synthesis of tritium-labelled thapsigargin ***(145)***

The tumor-promoting **145**, activating a broad number of cells by inhibition of endoplasmic calcium ATPase[136,137], has been tritium labelled[138] (equation 71) by butanoylation of debutanoylthapsigargin, **146**, prepared by stereoselective reduction of ketene **147** with sodium boro[^{3}H]hydride. The fluorescent derivative **148** of **145** has also been synthesized

by treating **146** with *N*-dansyl-β-alanine followed by acetylation, for studies on the distribution of the molecule in the cell[138].



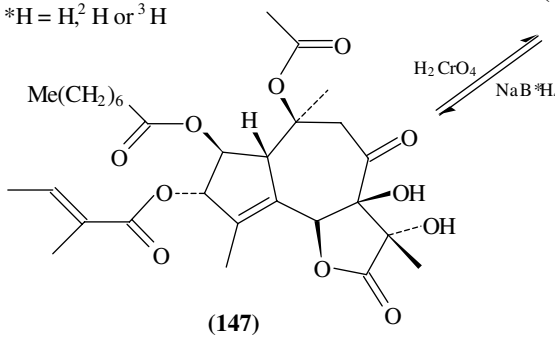
(145) 90% r. purity



(146)

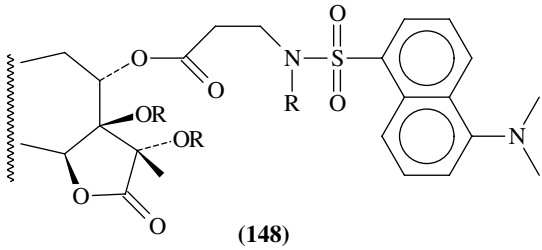
R = H^2, H or ^{3}H

*H = H, ^{2}H or ^{3}H



(147)

(71)

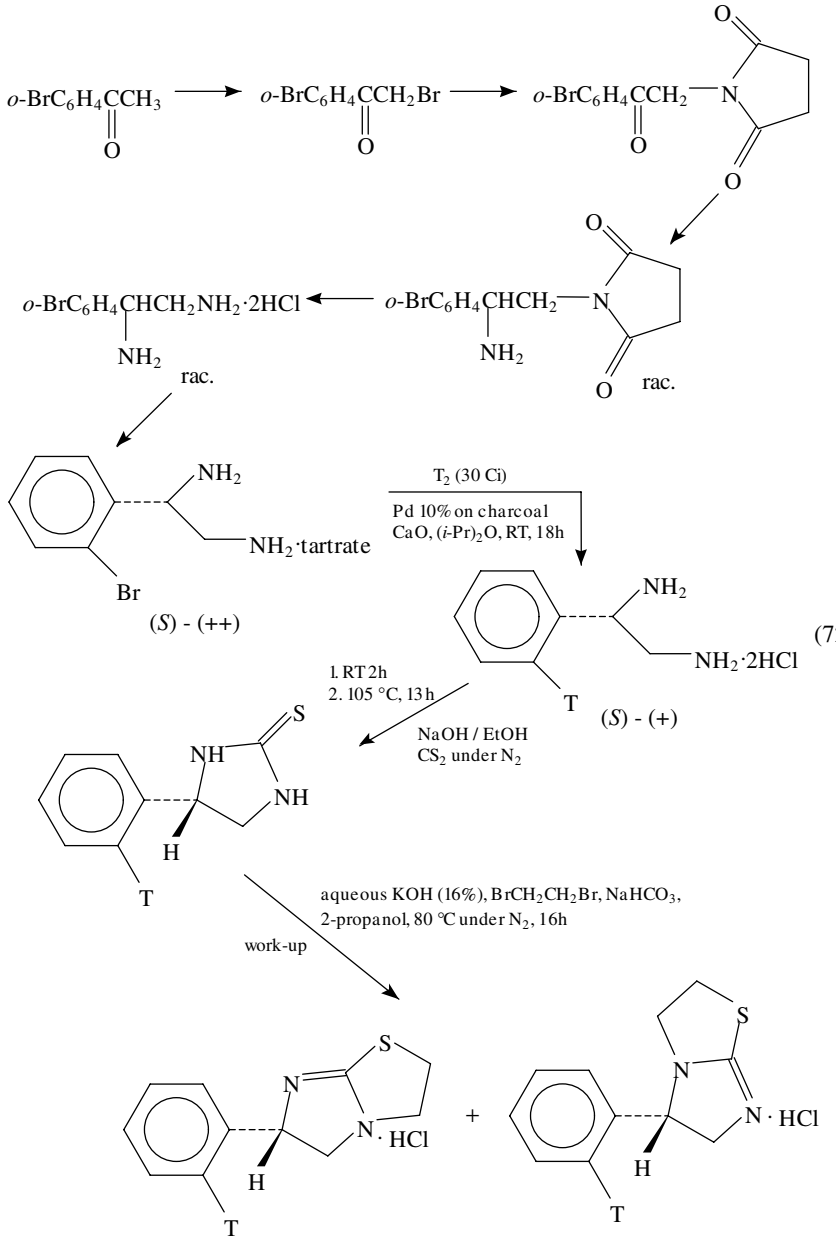


(148)

R = Ac

*11. Synthesis of ^{3}H-labelled levamisole **(149)***

149, of high specific activity, a potent anthelmintic also showing immunotropic properties, has been synthesized[139,140] (equation 72).

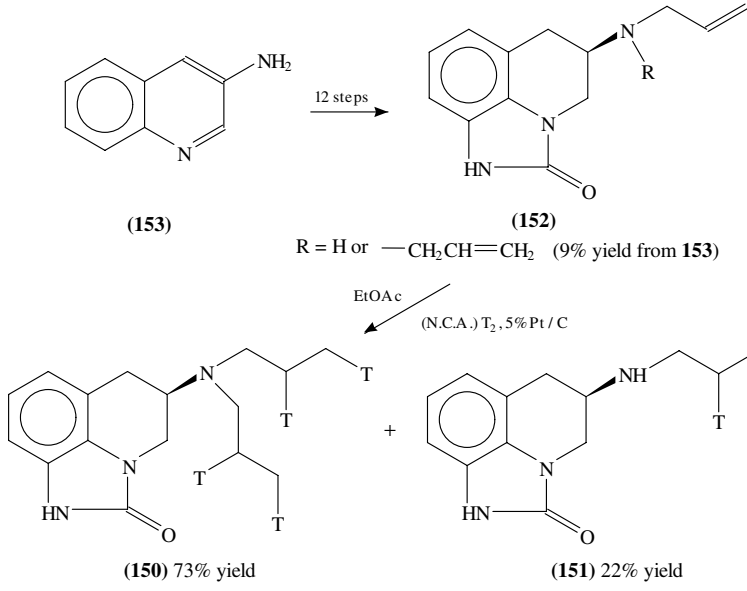


(72)

(*S*) - (-) **(149)** 51% of radioactivity (*S*) 47% of radioactivity

12. Synthesis of [^{3}H]U-86170, **150**, *and [^{3}H]U-91356,* ***151***

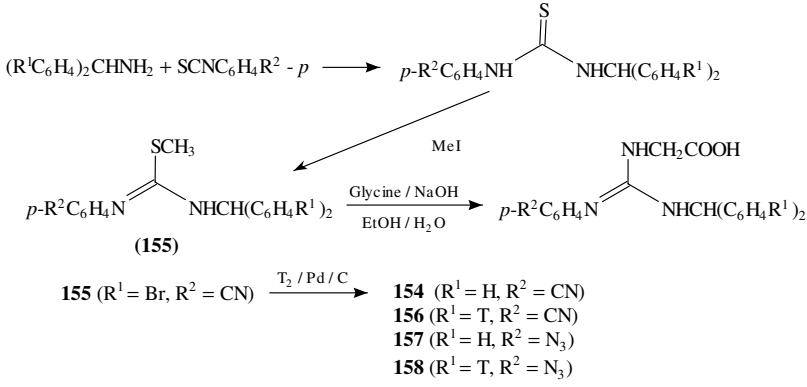
The title compound **150** and a significant by-product **151** a potent dopamine D_2 agonist and radioligand, were used in receptor binding studies[141] and have been tritium labelled[142] (equation 73). **150** has shown good stability. Its radiochemical purity, when stored in MeOH (1 and 10 mCi/ml) at −70 °C for 18 months, declined from 99% to 83%. Partially degraded samples of **150** have been purified by HPLC[142].



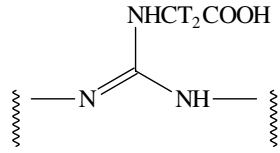
(73)

13. Synthesis of tritium-labelled guanidineacetic acids ***(156)*** *and tritiated photoaffinity labelling reagent*

156 sweeteners, binding to the receptor molecules on the surface of the tongue[143] with potencies in excess of 10^5 times that of sucrose[144], have been synthesized[144] from isothiourea **155** (equation 74). Ditritioglycine has been used for the synthesis of radioglycine **156a**.



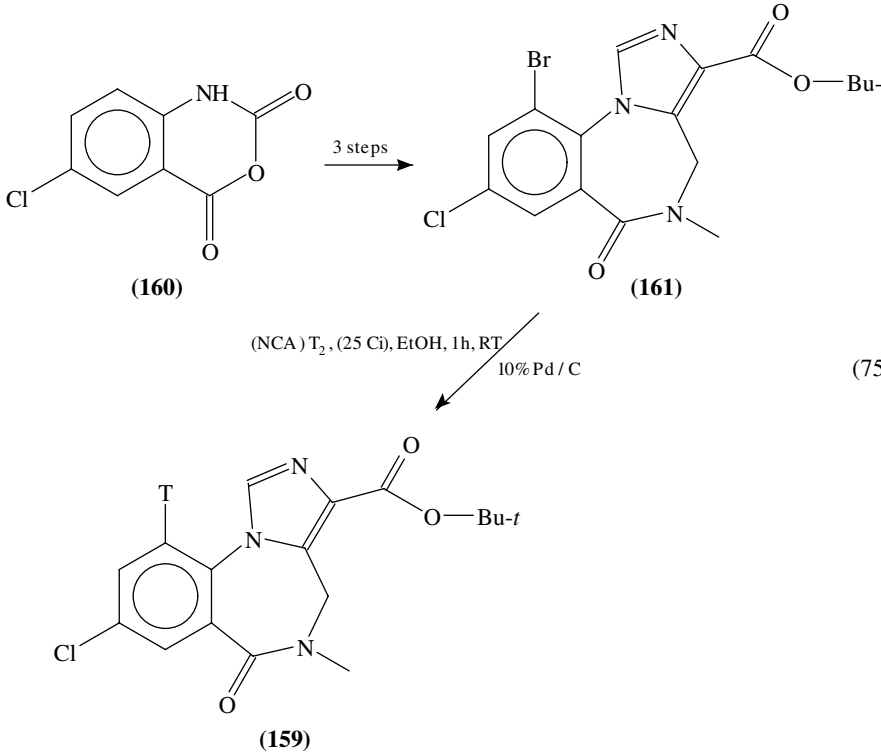
(74)



(156a)

*14. Synthesis of [^{3}H]t-butyl 8-chloro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine 3-carboxylate **(159)***

159, [^{3}H]TCIB, has been obtained[145] starting with 5-chloroisatoic anhydride **160** and catalytic tritiolysis of **161** (equation 75). **159** is considered a valuable tool to study the structure, function and pharmacological role of DI receptors ('diazepine insensitive' subtype of benzoadepine receptor[146], BZR).



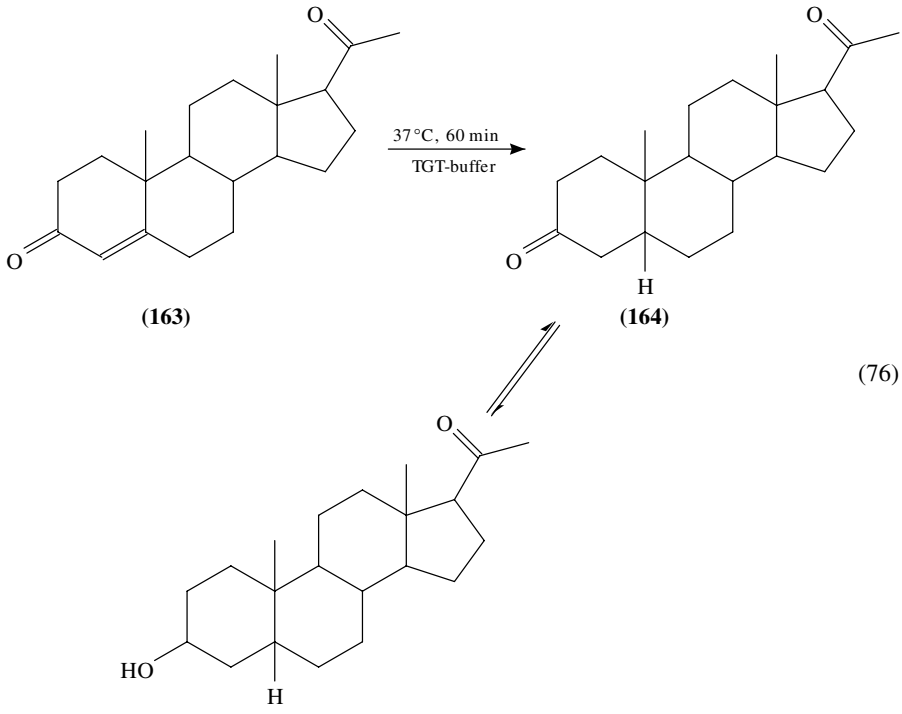
(160) **(161)** **(159)**

(75)

*15. Biosynthesis of tritium-labelled 3α-hydroxy-5α-pregnan-20-one **(162)***

The title compound, 3α-hydrohy-5α-[1,2,6,7-^{3}H]-pregnan-20-one (^{3}H-HPO), **162**, has been prepared[147] from [1,2,6,7-^{3}H]-progesterone, **163**, via 5α-pregnanedione, **164**, using a microsomal preparation from rat liver and NADPH, containing two metabolizing enzymes, 5α-reductase and 3α-hydroxysteroidoxidoreductase[147] (equation 76). **162** was used to

study the allosteric binding site for HPO *in vitro*[147].

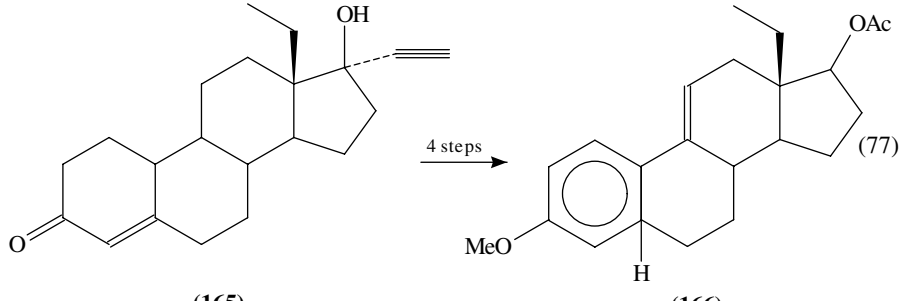


(163) **(164)** (76)

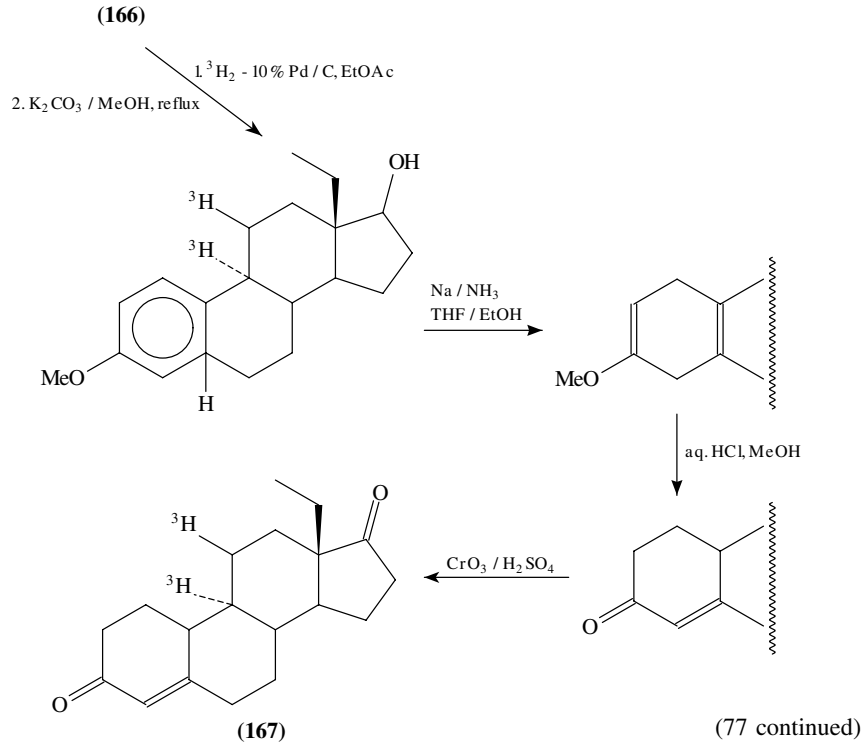
(162) 60% yield, purity > 98%

16. Microscale synthesis of norgestrel-[9,11-^{3}H] ***(165)***

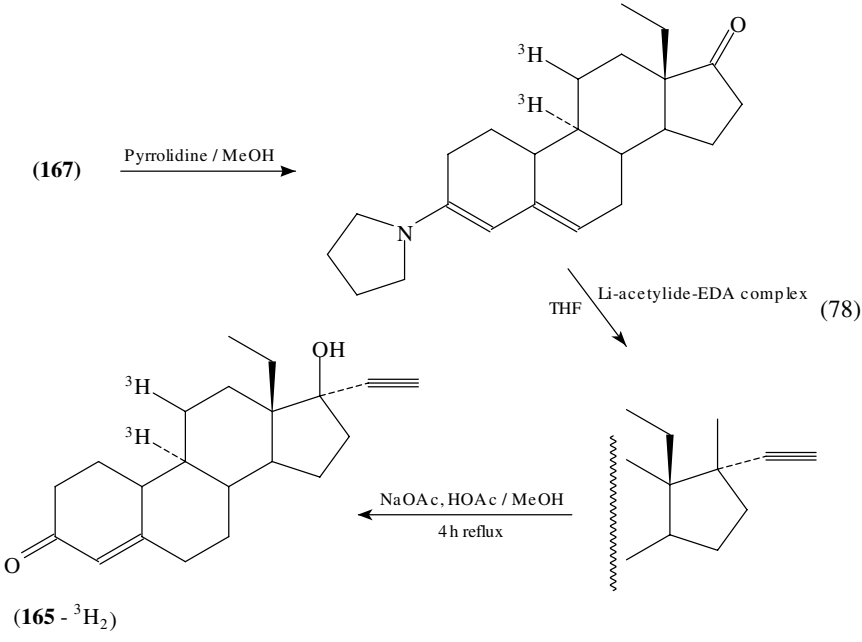
165, has been prepared[148] from **166** (from norgestrel itself (equation 77)) used for the preparation of 18-methyl-4-estren-[9,11-^{3}H]-3,17-dione **(167)**, which was transformed subsequently into **165** $^3H_2$ following equation 78. **165** is an orally active progestational agent[149] and **165**-$^3H_2$ will be applied in highly sensitive radioimmunoassay (RIA) methodologies connected with the development of enhanced formulations[148].



(165) **(166)** (77)

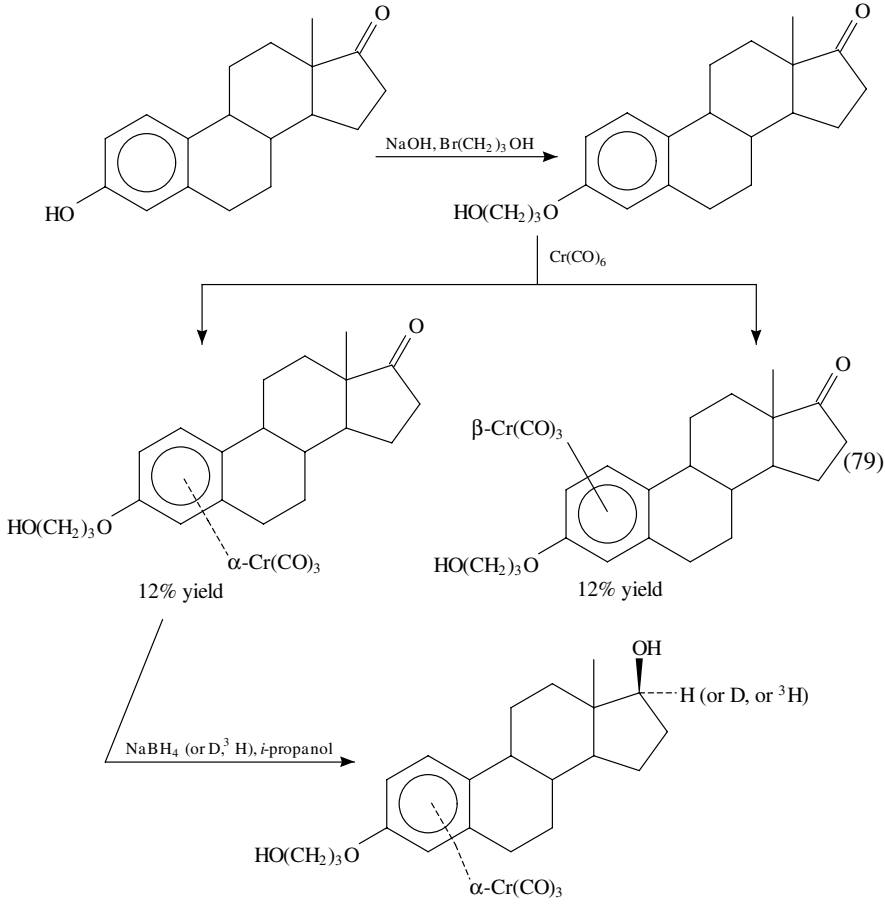


(77 continued)



17. Synthesis of tritium-labelled [3-O-(3-hydroxypropyl)]-17α-estradiol chromium tricarbonyl ***(168)***

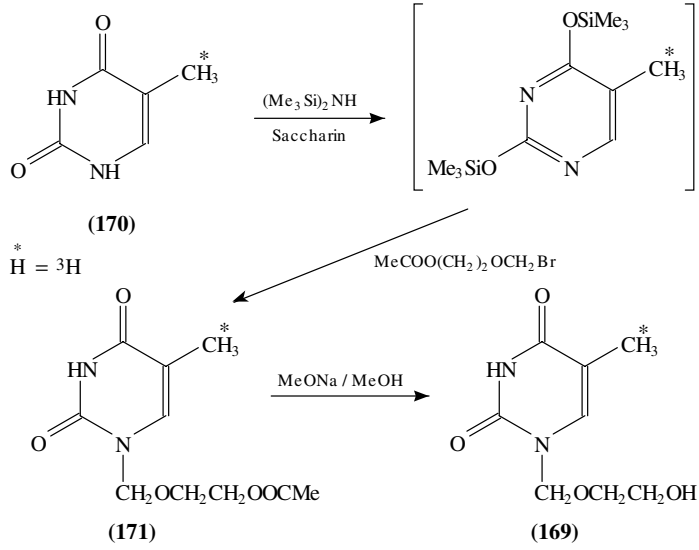
168 has been deuterium or tritium labelled[150] by reduction of the corresponding estrone by $NaBD_4$ or $NaB[^3H]_4$ (equation 79). The specific activity of **168** (4.1 Ci/mmol) is sufficiently high for hormone receptor binding studies.



(168) 94% step yield

18. Synthesis and tissue distribution of N-[2-(hydroxyethoxy)methyl]-5-[³H]methyl-uracil, ^{3}*H-****169***

^{3}H-**169** has been synthesized[151] for evaluation as tumor diagnostic agent, by converting 5-[^{3}H]-methyluracll, ^{3}H-**170**, to the 2,4-bis-trimethylsilyl intermediate[152], and further to ^{3}H-**171** and then to ^{3}H-**169** (equation 80). The tissue distribution of ^{3}H-**169** has been examined in mice bearing Lewis Lung (LL) carcinomas. The title compound was found to be an unsatisfactory diagnostic agent for LL carcinoma because of low tumor uptake and rapid urinary elimination of injected radioactivity from the body.

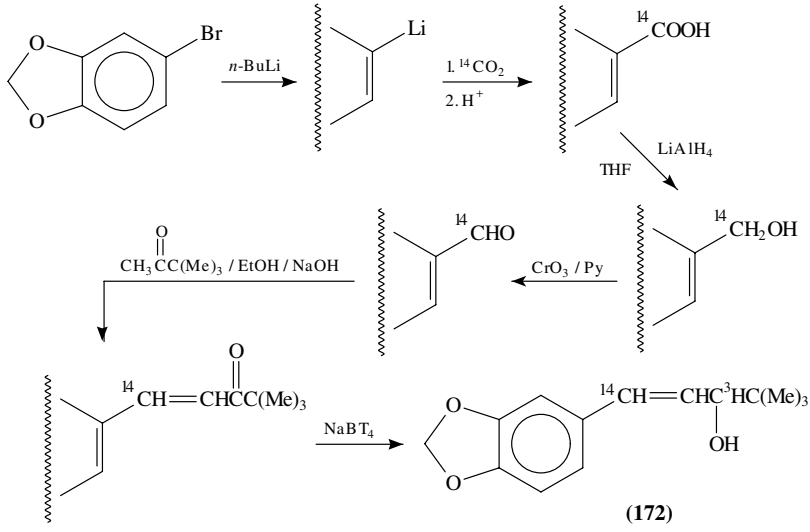


(80)

B. Double-labelled Compounds

1. Synthesis of 4,4-dimethyl-(3,4-methylenedioxyphenyl)-1-pentene-3-ol labelled with ^{14}C and ^{3}H

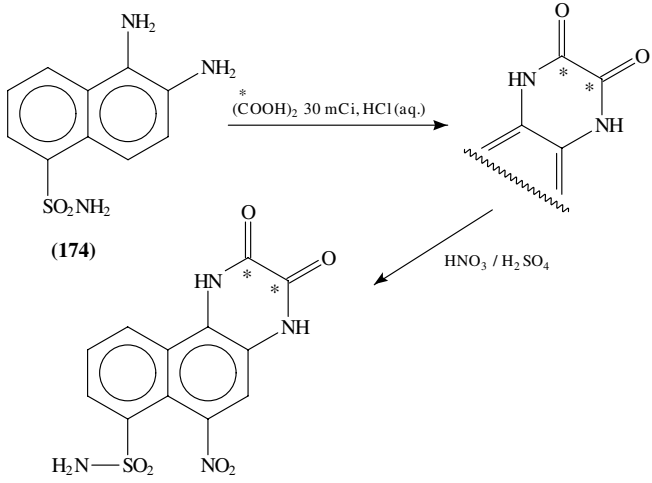
Carbon-14 has been introduced at the $C_{(1)}$ position of the pentene group of drug **172**[153,154] starting with $Ba^{14}CO_3$ in 28% yield and tritium has been introduced into the position at $C_{(3)}$ of the chain in the final reaction step by reduction of the ketone group with $NaBT_4$[155] (equation 81). The double-labelled compound **172** is applied in pharmacokinetic studies in animals[155].



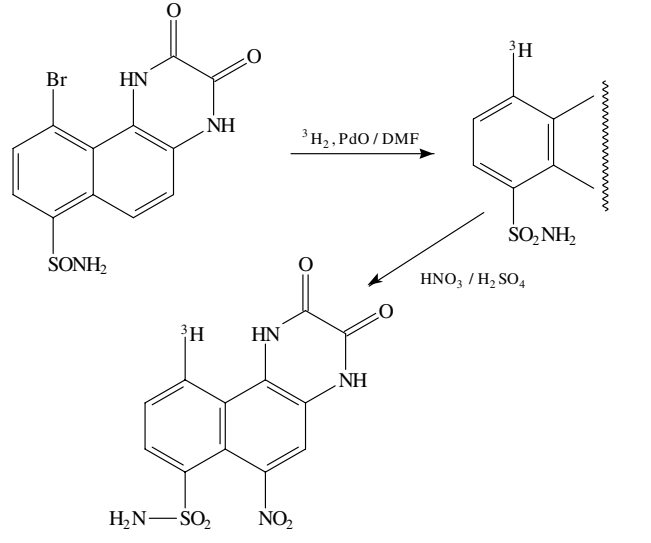
(81)

*2. Synthesis of ^{14}C- and ^{3}H-labelled 6-nitro-7-sulphamoylbenzo[F]quinoxalin-2,3-dione **(173)***

The ^{14}C-labelled **173**, effective as a neuroprotectant for cerebral ischemia[156], has been synthesized[157] from 1,2-diamino-5-sulphamoylnaphthalene **174** and ^{14}C-oxalic acid (equation 82). The tritiated analogue of **173**, **173b**, has been synthesized as shown in equation 83. **173** shows potent antiparkinsonian effects in primates and rats.



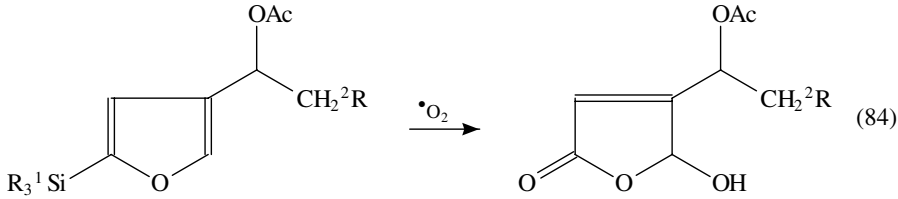
(82)



(83)

3. Synthesis of carbon-14 and tritium labelled analogues of manoalide

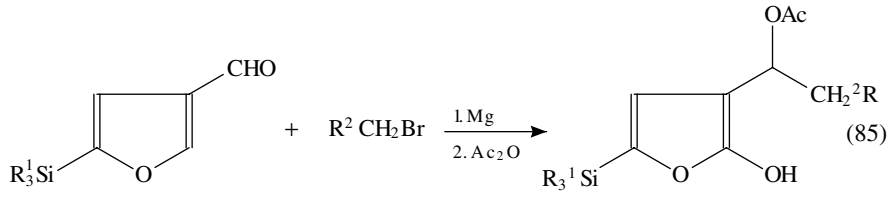
Several analogues of manoalide, isolated[159] from *Luffariella variabilis*, which inhibits phospholipase A_2 and possesses topical anti-inflammatory activity[159], have been carbon-14 and tritium labelled by modification of the non-isotopic syntheses[160]. Manoalide analogues 4-(1-acetyloxyalkyl)-5-hydroxy-2(5*H*)-furanones, **175**, bearing ^{14}C or ^{3}H in the acetyl molety of the side chain, have been obtained by singlet oxygenation of 2-trialkylsilyl-4-alkylfurans[160], **176** (equation 84).



(84)

(176) **(175)**

The substrates **176** have been prepared by Grignard reaction of the carbon-14 labelled alkyl bromides with 2-trialkylsilyl-4-furancarboxaldehyde **177** (equation 85).

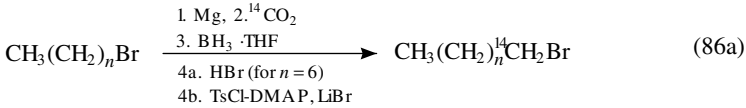


(85)

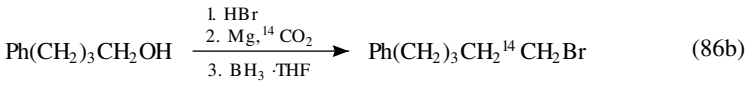
(177)

R^1 = Me or Et R^2 = $-(CH_2)_6CH_3$, $-(CH_2)_{10}CH_3$, $-(CH_2)_4Ph$

The required carbon-14 labelled alkyl halides have been prepared by standard Grignard reaction-based methods[161,162] shown in equations 86a and 86b.



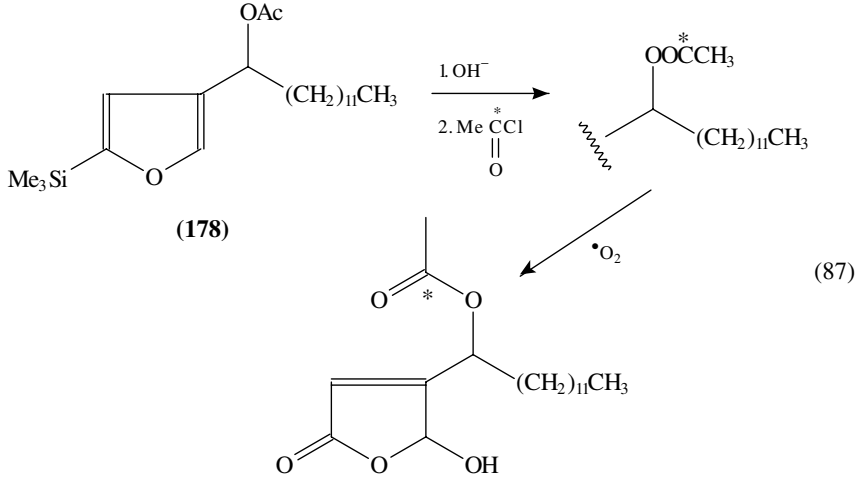
(86a)



(86b)

The compound **175a**, labelled with carbon-14 in the acetyl moiety, has been obtained as indicated in equation 87 by basic hydrolysis of 4-(1-acetoxytridecyl)-2-trimethylsilylfuran, **178**, and reacetylation of the resulting alcohol with acetyl-1-^{14}C-chloride, followed by

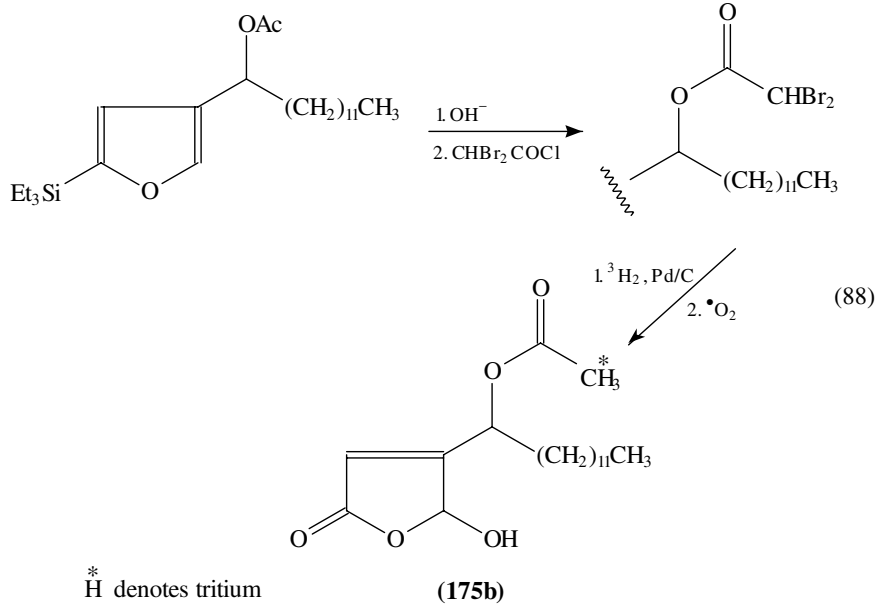
singlet oxygenation (equation 87).



(178) **(175a)** (87)

* denotes carbon-14

Tritium in the acetyl moiety **175b** has been obtained using, in a similar sequence of reactions, dibromoacetic acid and subsequent catalytic halogen–tritium exchange (equation 88).



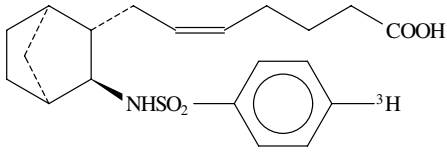
(88)

$^{*}_{H}$ denotes tritium **(175b)**

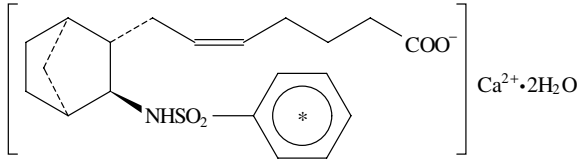
The ^{14}C- and ^{3}H-labelled compounds **175** are used in biological studies.

*4. Synthesis of [^{14}C]- and [^{3}H]-labelled (+)-{1R-[1α,2α(Z) 3β,4α]}-7-{3-[(phenylsulphonyl)amino]bicyclo[2.2.1]hept-2-yl}-5-heptenoic acid ((+)-S-145, **179**) and its Ca salt (S-1452, **180**)*

S-145, **179** thromboxane A_2 (TXA_2)-receptor antagonist which efficiently suppresses platelet aggregation and vascular, respiratory smooth muscle constriction[163,164], and its chemically stable calcium salt, **180**, have been labelled with ^{3}H and ^{14}C for metabolic studies and for characterization of the receptor binding[165] as well as for use in the chemotherapy of various TXA_2- and PGH_2-mediated circulatory disorders like angina pectoris, asthma and myocardial infraction.



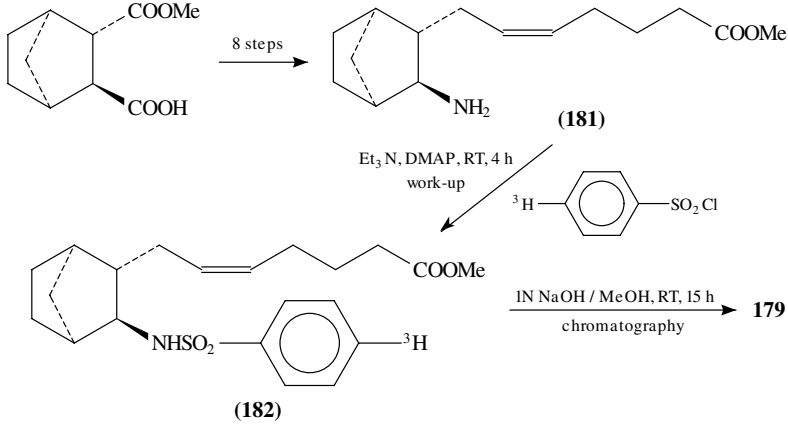
[^{3}H]-(+)- *S*-145 **(179)**



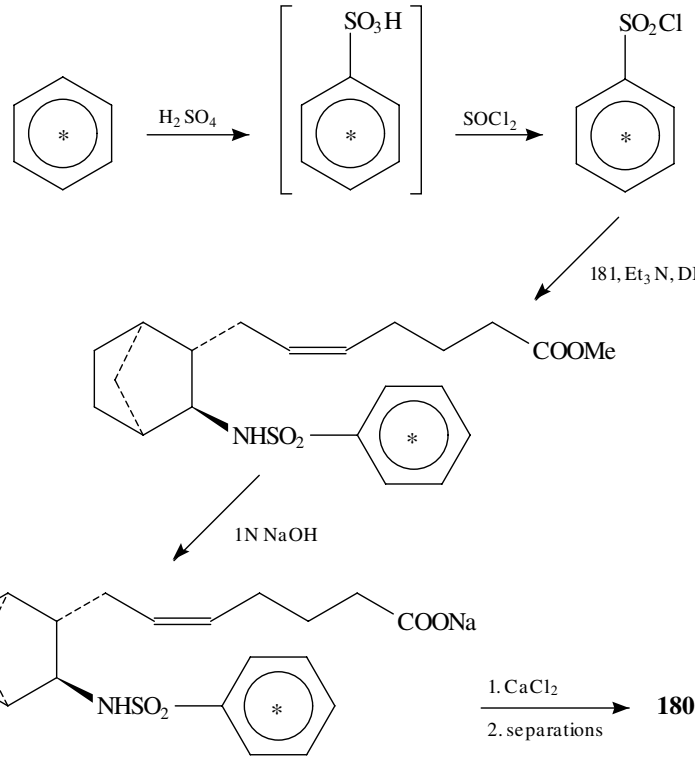
[^{14}C]- *S*-1452 **(180)**

= [U-^{14}C]benzene

The amine **181** reacting with solution of [4-^{3}H]benzenesulphonyl chloride in benzene gave the methyl ester **182**, which after treatment with sodium hydroxide in MeOH and chromatography provided the sodium salt of **179** (equation 89). **180** have been prepared similarly using [U-^{14}C]benzenesulphonyl chloride synthesized from [U-^{14}C]benzene (equation 90).



(89)



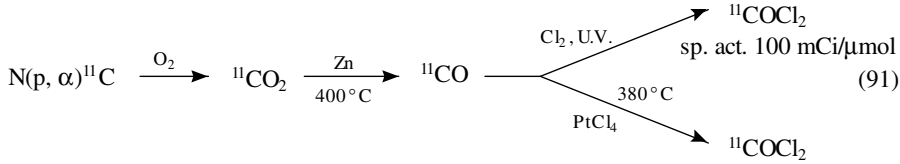
(90)

IV. SYNTHESES AND USES OF COMPOUNDS CONTAINING C=C, C=O OR CN GROUPS LABELLED WITH RADIOACTIVE CARBON

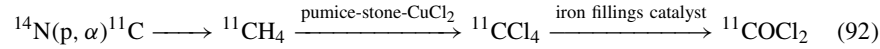
A. Compounds Labelled with Carbon-11

1. New synthesis of ^{11}C-labelled phosgene

[^{11}C]Phosgene, allowing the insertion of ^{11}C-labelled carbonyl function between two stereochemically close amino functions, has been usually synthesized from [$^{11}CO_2$] either by photochemical reaction[166] or by reaction on platinum chloride[167] (equation 91). To obtain [^{11}C]phosgene for receptor studies by PET, [^{11}C]methane has been chosen as the precursor[168], using chlorination of [^{11}C]CH_4 to carbon tetrachloride followed by catalytic oxidation to [^{11}C]phosgene (equation 92).



(91)



(92)

2. Synthesis of 9-[^{11}C]heptadecan-9-one (183)

183 has been synthesized[169] from di-*n*-octylthexylborane with K^{11}CN followed by rearrangement and alkaline oxidation (equation 93). During rearrangement using TFAA the octyl groups migrated from the boron to carbon atom. Equation 93 is applicable to the synthesis of various ^{11}C-labelled dialkyl ketones, e.g. of 10-[^{11}C]nonadecan-10-one with di-*n*-nonylthexyl borane[169]. Synthesis of ^{11}C-labelled hexestrone, 17β-estradiol and related hormones with the use of organoboranes are under investigation[169,170].

$$2\{CH_3(CH_2)_5C{=}CH_2\} + Me_2C{=}CMe_2 + BH_3{\cdot}THF \xrightarrow{THF} [CH_3(CH_2)_7]_2BCMe_2CHMe_2$$

$$(n\text{-}C_8H_{17})_2B(^{*}CN)(CMe_2CHMe_2) \xrightarrow[2.\ 3M\ NaOH\ /\ 50\%\ H_2O_2,\ 0\ ^\circ C]{1.\ (CF_3)_2O,\ ice\ bath,\ RT,\ 5\ min\ stir.} (n\text{-}C_8H_{17})_2{}^{*}C{=}O \qquad (93)$$

3. Seperations, HPLC

(183) 95% r. purity

$^{*}C = {}^{11}C$

3. Synthesis of high specific activity [^{11}C]urea

[^{11}C]urea, used in production of NCA radiopharmaceuticals, has been produced[171] from NCA $^{11}CN^{-}$[172] by quantitative oxidation of the $^{11}CN^{-}$ to O $^{11}CN^{-}$ with $KMnO_4$ at pH = 13.5, decomposing the excess of $KMnO_4$ with H_2O_2 and decomposition of KO^{11}CN to $NH_4O^{11}CN$ followed by thermal transformation of $NH_4O^{11}CN$ in ethanol medium into [^{11}C]urea (equation 94). The oxidation of CN^{-} into OCN^{-} is also quantitative in the presence of copper hydroxide[173] as a catalyst (equation 95), but its use presents several disadvantages[171] and additional purification of the ^{11}C-labelled compound is required. The conversion of $NH_4O^{11}CN$ to [^{11}C]urea is pseudo-first-order in the presence of the excess of ammonium ions and has been studied[173–175].

$$^{11}CN^{-} \xrightarrow{KMnO_4,\ aqueous\ KOH,\ H_2O_2} O^{11}CN^{-} \xrightarrow{(NH_4)_2SO_4,\ EtOH} (NH_2)_2{}^{11}CO \qquad (94)$$

$$3K^{11}CN + 2KMnO_4 + H_2O \xrightarrow{Cu(OH)_2} 3KO^{11}CN + 2MnO_2 + 2KOH \qquad (95)$$

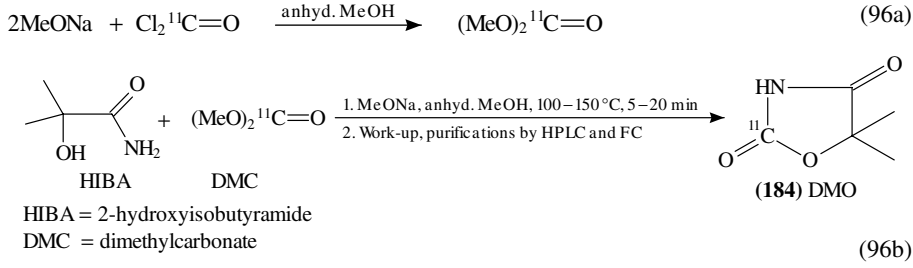
4. Synthesis of [2-^{11}C]5,5-dimethyl-2,4-oxazolidinedione (184)

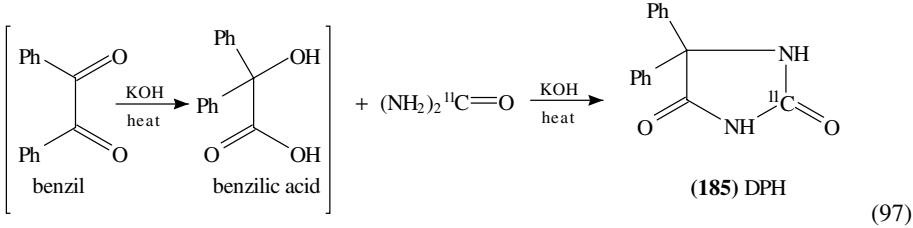
[2-^{11}C]DMO, **184**, is used to measure routinely regional cerebral tissue pH *in vivo* in man by PET, and is helpful in establishing treatment regimens for patients with primary and/or metastatic brain tumors and their focal pathology[176]. It has been synthesized[177] utilizing [^{11}C]phosgene[178], DMC and HIBA as shown in equations 96a and 96b). The amount injected into a human is no more than 1 mg of DMO, far below the value 900 mg stated in the protocols[179].

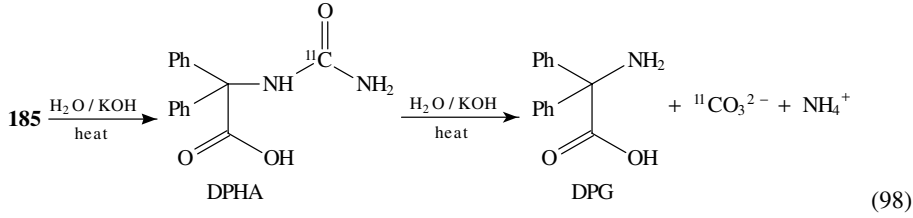
5. Synthesis of 2-[^{11}C]-5,5-diphenylhydantoin (185)

DPH, **185**, widely used in treatment of epileptic seizures[180], has been labelled with ^{11}C and isolated in high specific activity in reaction of [^{11}C]urea with benzil[181] (equation 97). The effect of reaction time, of reaction temperature and of KOH molarity on the yield

of [^{11}C]DPH has been investigated to optimize the reaction conditions. The effect of various reactant concentrations (ammonium sulphate, hydrogen peroxide) has also been studied. The instability of **185** under the experimental conditions has been assigned to its dissociation to diphenylhydantoic acid (DPHA), which decomposes in turn to α,α-diphenylglycine (DPG) and carbonate (equation 98).







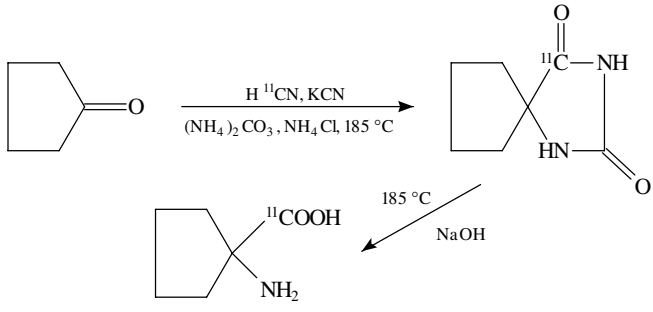
6. Routine production of [^{11}C]-1-aminocyclopentanecarboxylic acid ***(186)***

([^{11}C]-ACPC), **186**, used to study the metabolism of tumors by PET, has been synthesized routinely[182] as shown in equation 99, for medical use, and since 1982 in yield higher than reported previously[183,184]. Optimal conditions for H^{11}CN production have been established[182]. The product **186** has been suitable for injection.

7. Automated radiosynthesis of NCA-S-[^{11}C]CGP 12177 ***(187)***

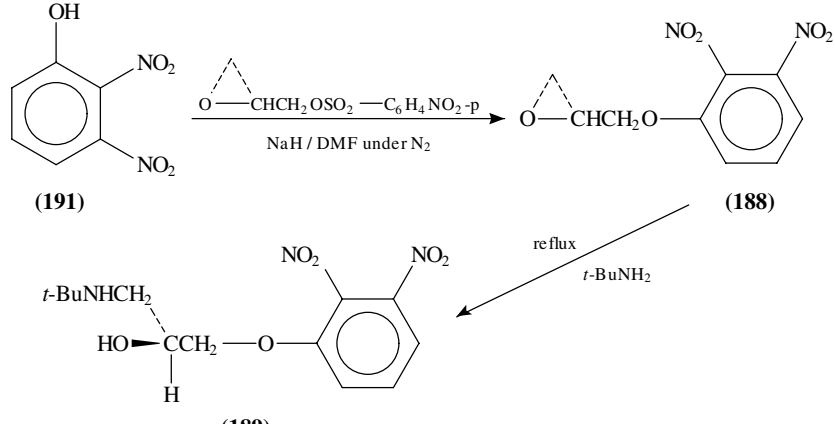
S-(3′-*t*-Butylamino-2′-hydoxypropoxy)-benzoimidazol-2-[^{11}C]one, **187**, has been synthesized[185] in >95% *S*-(−)-enantiomeric excess (after HPLC) in three steps from 2,3-dinitrophenol and the chiral auxiliary, *S*-glycidyl-3-nitrobenzenesulphonate, to provide the precursor **188** for the amine **189** and asymmetrical diamine, **190**, which in reaction with [^{11}C]phosgene[186] gave **187** (equation 100). The *S*-enantiomer of [^{11}C]CPG, **187** is being applied to study β-receptors in heart and in lung with PET and in biological experiments[186], since previous studies with *S*-, *R*- and *R,S*-[^{3}H]CPG 12177 showed

that the *S*-enantiomer has greater affinity than the *R*-enantiomer for *β*-adrenergic receptors[187,188].



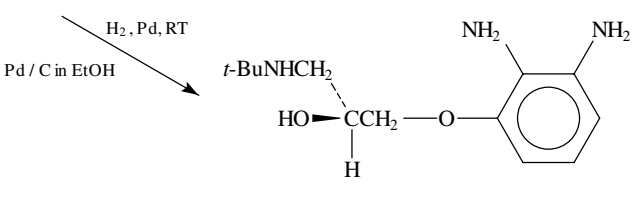
(99)

(186) 60 ± 3% yield

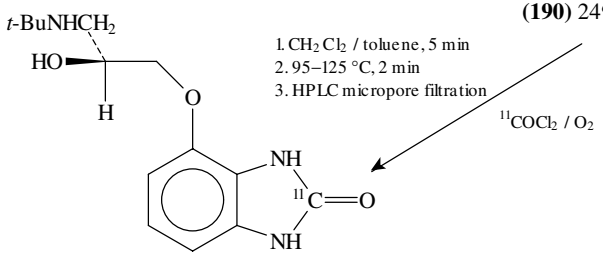


(191) **(188)**

(189)



(190) 24% from **191**



(187) 3.7–5.9 GBq ready for clinical use

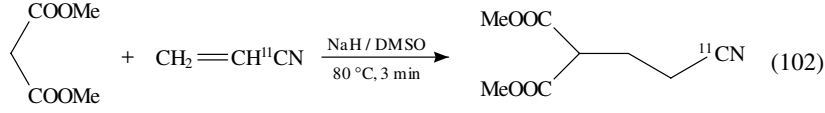
(100)

8. Synthesis of ^{11}C-labelled α,β-unsaturated nitriles

The synthetically useful α,β-unsaturated [^{11}C]-labelled precursors, [^{11}C]acrylonitrile **(192)** and [^{11}C]cinnamonitrile **(193)**, have been prepared[189–191] with potassium [^{11}C]cyanide (equation 101). The substitution reactions have been performed in MeCN, benzene, 1,2-dichlorobenzene, DMSO and THF solvents, but the highest radiochemical yields were obtained in acetonitrile. **192** was used in a model reaction (equation 102) to synthesize 2-cyano[^{11}C]ethyldimethyl malonate **194** from sodium hydride/dimethyl malonate.

$$\mathrm{RHC{=}CHBr + K[^{11}C]N \xrightarrow[40\,^{\circ}C\ (\text{compd. }\mathbf{192})\ \text{or}\ 100\,^{\circ}C\ (\text{compd. }\mathbf{193})]{Pd^{0}\ [P(Ph)_3]_4,\ 18\text{-crown-6, acetonitrile}} RHC{=}CH^{11}CN} \quad (101)$$

(192) R = H
(193) R = Ph

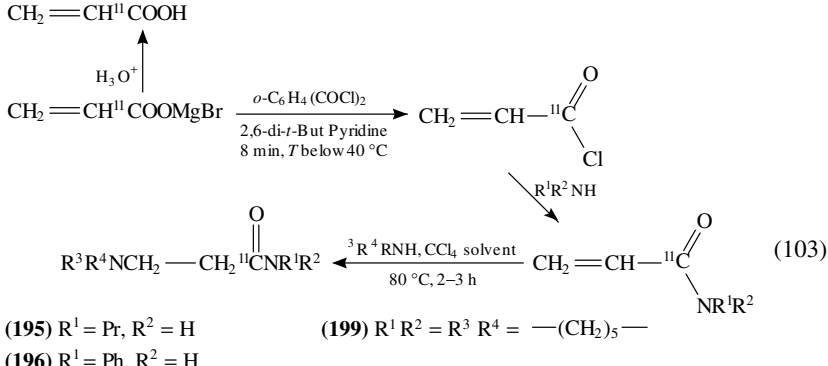


(102)

(194)

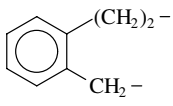
9. Synthesis of [^{11}C]propenoic acid, [1-^{11}C]propenoyl chloride and N-[^{11}C]-substituted propenamides

[^{11}C]Acrylic acid has been obtained[191] by ^{11}C carbonation of ethenylmagnesium bromide in THF and separation of the [^{11}C]propenoic acid on reverse-phase column. [1-^{11}C]acryloyl chloride and [1-^{11}C]propenamides have been prepared as outlined in equation 103. Besides *N*-propyl[^{11}C]propenamide, **195**, *N*-phenylpropenamide, **196**, 1-piperidylpropenone, **197** and 1-(1,2,3,4-tetrahydroisoquinolin-3-yl)-propenone, **198**, the Michael adducts 1,3-bis-piperidylpropanone **(199)** and 1,3-bis(1,2,3,4-tetrahydroisoquinolin-3-yl)propanone **(200)** have been prepared also[191].



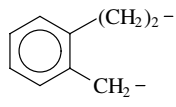
(103)

(195) R^1 = Pr, R^2 = H
(196) R^1 = Ph, R^2 = H
(197) R^1R^2 = —$(CH_2)_5$—
(198) R^1R^2 =



(199) $R^1R^2 = R^3R^4$ = —$(CH_2)_5$—

(200) $R^1R^2 = R^3R^4$ =



*10. New synthesis of [^{11}C]propyl ketene **(201)** and its reactivity with alcohols*

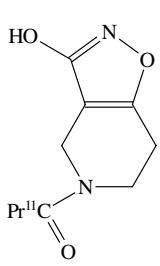
The total yield of **201** was increased and the synthesis time reduced by extracting [^{11}C]butyric acid from its lithium salt by dry 0.1% HCl/He gas mixture and carrying out its pyrolysis at 530 °C over glass beads (equation 104). The relative reactivity of **201** to primary, secondary and tertiary alcohols (equation 105a, b, c) has been found to be as 1:0.4:0.1, respectively. Several bioactive compounds have been labelled with [^{11}C]propyl ketene, such as carbohydrate compounds[193] and *N*-butyl compounds, for instance *N*-[^{11}C]butyryl THPO, **202**, and some phorbol esters[192], **203**, **204** and **205**.

$$^{11}CO_2 \xrightarrow{PrLi} Pr^{11}COOLi \xrightarrow{HCl/He} Pr^{11}COOH \xrightarrow[530\,^\circ C]{Pyrolysis} EtCH{=}{=}{}^{11}C{=}{=}O \quad \textbf{(201)} \qquad (104)$$

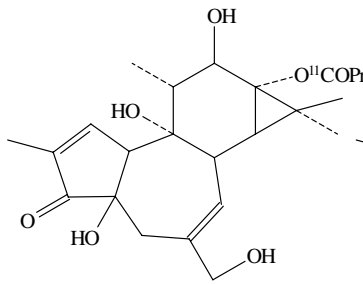
$$PhCH_2CH_2OH \xrightarrow{\textbf{201}} PhCH_2CH_2O^{11}CPr \quad (105a)$$

(105b)

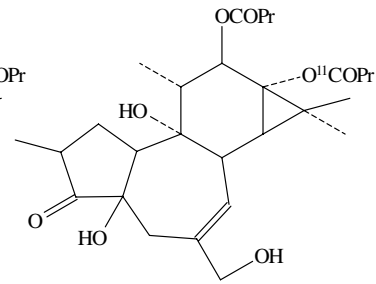
$$PhCH_2C(Me_2)OH \xrightarrow{\textbf{201}} PhCH_2C(Me_2)O^{11}CPr \quad (105c)$$



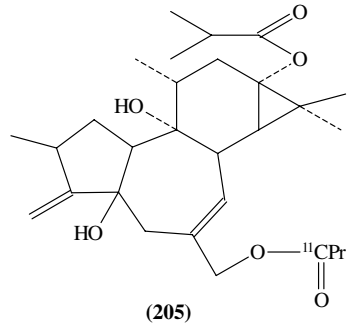
(202)



(203)



(204)



(205)

*11. Synthesis of [α-^{11}C]amphetamine, **206**, and [α-^{11}C]phenethylamine, **207***

206 and **207**, increasing the synaptic levels of major neurotransmitters in the mammalians brain, noradrenaline or dopamine via stimulation of their release, have been synthesized[194] (equations 106 and 107).

$$CH_3{}^{11}CH_2NO_2 + PhCHO \xrightarrow[104\,^\circ C,\ 10\ min,\ separations]{AcOH,\ AcONH_4} PhCH{=}{}^{11}C(Me)NO_2 \xrightarrow{LiAlH_4} PhCH_2{}^{11}C(Me)NH_2 \quad \textbf{(206)} \qquad (106)$$

$$^{11}CH_3NO_2 + PhCHO \xrightarrow[2.\ HCl]{1.\ NaOH} PhCH{=}{}^{11}CHNO_2 \xrightarrow{LiAlH_4} PhCH_2{}^{11}CH_2NH_2 \quad \textbf{(207)} \qquad (107)$$

*12. Synthesis of [^{11}C]methylenetriphenylphosphorane and [β-^{11}C]styrene **(208)***

The original Wittig synthesis[195,196] of **208**, shown in equation 108 involving synthesis of [^{11}C]methyltriphenylphosphonium iodide, [^{11}C]methylenetriphenylphosphorane and the ^{11}C-Wittig type reaction used for preparation of the ^{11}C-labelled methylene group, has been largely improved[196] [^{11}C]methyl iodide and benzaldehyde have been easily converted in high yield to **208** as shown in equation 109.

$$^{11}CH_3I + Ph_3P \xrightarrow[90\,^\circ C,\ 6\ min]{THF} \overset{-}{I} + Ph_3\overset{+}{P}{}^{11}CH_3 \xrightarrow[BuLi]{THF} Ph_3P{=}{}^{11}CH_2 \xrightarrow{PhCH=O} PhCH{=}{}^{11}CH_2 \quad \textbf{(208)} \qquad (108)$$

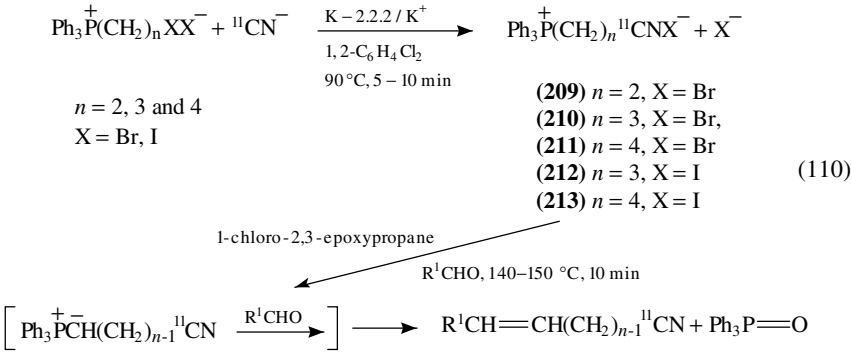
$$Ph_3\overset{+}{P}{}^{11}CH_3 + PhCH{=}O \xrightarrow[1,2\text{-dibromobenzene}]{epichlorhydrin} PhCH{=}{}^{11}CH_2 \qquad (109)$$

80 – 90% r. yield

13. Synthesis of [^{11}C]cyanoalkyltriphenylphosphoranes

The ^{11}C-labelled bifunctional precursors 3-[^{11}C]cyanoethyltriphenylphosphonium bromide, **209**, 4-[^{11}C]cyanopropyltriphenylphosphonium bromide, **210**, 5-[^{11}C]cyanobutyltriphenylphosphonium bromide, **211**, 4-[^{11}C]cyanopropyltriphenylphosphonium iodide, **212** and 5-[^{11}C]cyanobutyltriphenylphosphonium iodide, **213** have been obtained[197]. The intermediates **209–213** were treated in one-pot reactions with epichlorhydrin (generating the base *in situ*[196,198]) and aldehyde (Wittig reaction) providing the ^{11}C-labelled olefins (equation 110). The aromatic olefins have been obtained from **209–213** in 85–96% radiochemical yield; the aliphatic olefins have been obtained in 60–78% radiochemical yield from **212** and **213**. No change in the stereochemical outcome (*Z*/*E* ratios) was

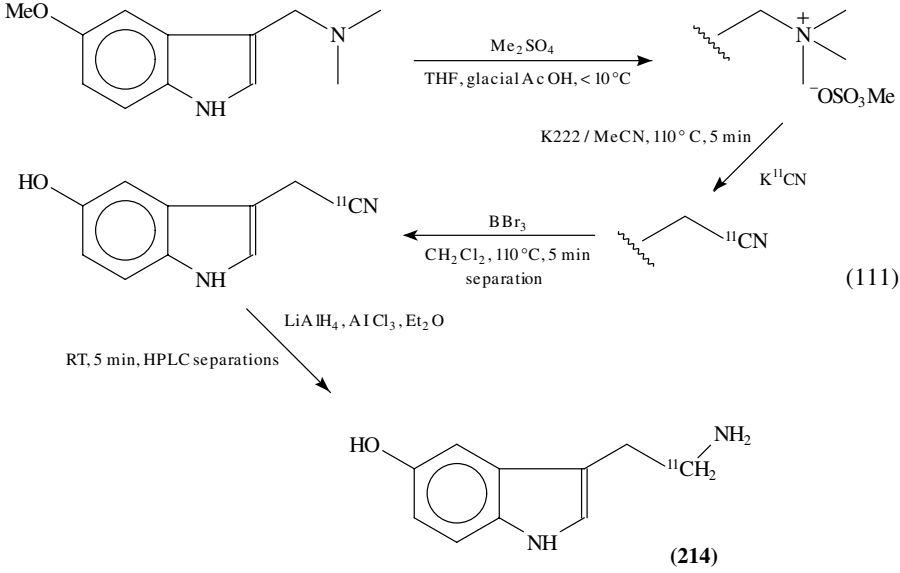
observed when using the bromide or iodide salt.



(110)

*14. Synthesis of ^{11}C-labelled 5-hydroxytryptamine, [^{11}C]5-HT **(214)***

[^{11}C]serotonin **(214)** has been sythesized[199] as outlined in equation 111 and was ready for injection to study the transport of [^{11}C]5-HT across the pulmonary endothelial cell membrane and to make external non-invasive measurements of uptake of amines by the lung with standard nuclear medicine imaging equipment[199]. [^{14}C]5-HT has been used before as a marker of lung damage[200].

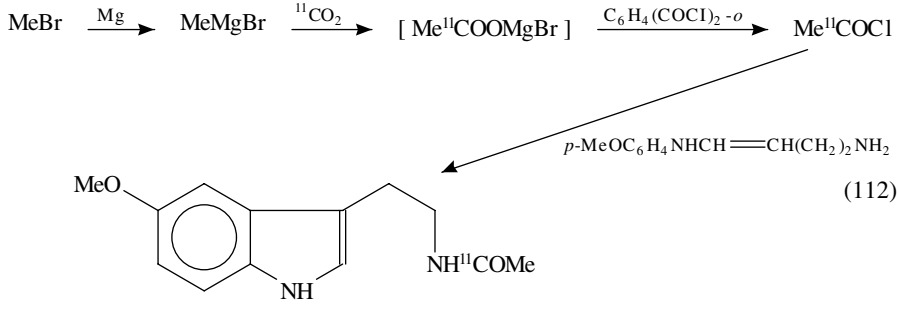


(111)

*15. Synthesis of [^{11}C]melatonin **(215)***

This hormone of the pineal gland, **215**, has been labelled[201] with carbon-11 to study its role in health, depressive illness and internal clock disorders (cyclic events of life in mammals). The new labelling reagent [^{11}C]acetyl chloride has been used as shown

in equation 112. Using ^{13}C-enriched CO_2, ^{13}C-melatonin has been synthesized also and examined by ^{13}C-NMR spectroscopy and mass spectrometry. The melatonin had ^{13}C-enriched carboxamido carbon[202].

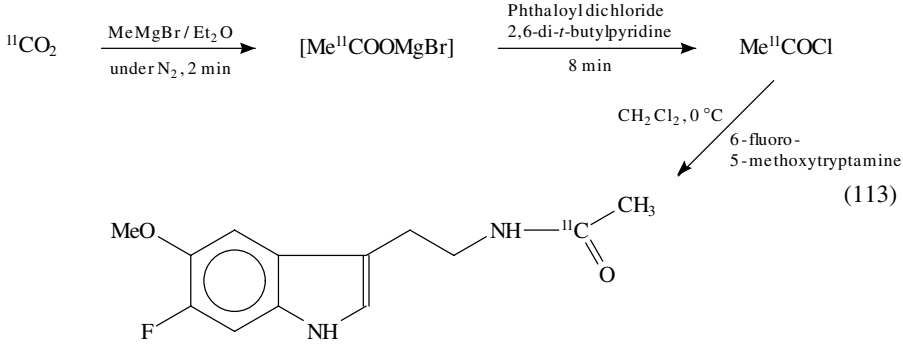


(112)

(**215**) 13% r. yield

16. Synthesis of [carbonyl-^{11}C]6-fluoromelatonin ***(216)***

This indoleamine-type neurohormone[201], **216** secreted by the pineal gland[203], has been prepared[204] as shown in equation 113 with a 200-fold greater specific activity than the 6-[^{18}F]fluoromelatonin synthesized by Chirakal and coworkers[205]. **216** permits one to study low populations of high-affinity binding sites or receptors of melatonine with PET[206,207].

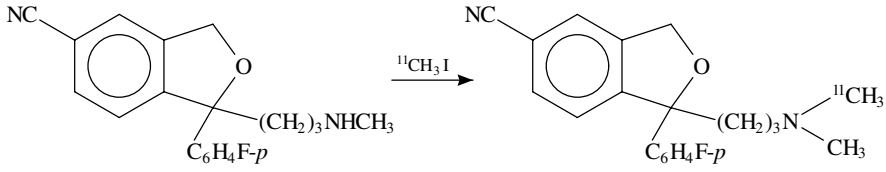


(113)

(**216**) 35% r. yield from cyclotron produced [^{11}C]CO_2

17. Synthesis of ^{11}C-labelled citalopram ***(217)***

This prototype drug[208], **217**, has been ^{11}C-labelled[209] for assessment of serotonin uptake sites in depressed patients by reaction of [^{11}C]iodomethane with desmethylcitalopram, **218**, in 18–66% radiochemical yield (equation 114). **217** has been obtained also by Dannals and coworkers[210] by reacting freshly prepared desmethylcitalopram dissolved in DMF with [^{11}C]methyl iodide. The radiochemical yield based on [^{11}C]CH_3I was about 20%; the overall radiochemical yield was about 9% based on the initial activity of [^{11}C]CO_2 produced by 16 MeV proton irradiation of nitrogen gas in biomedical cyclotron.

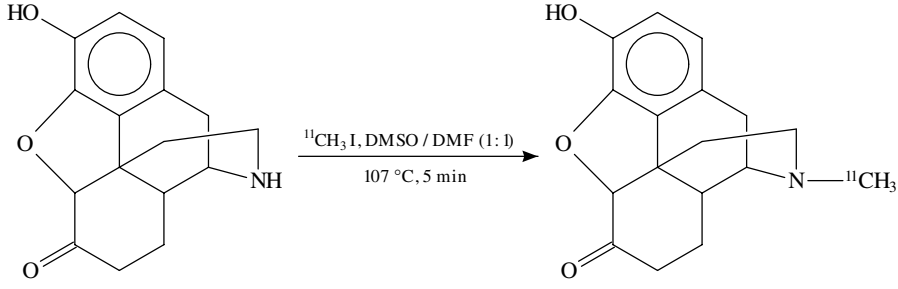


(218)

(217) r. purity > 95%,
sp. act. $(2.52 - 16.06) \cdot 10^3$ GBq / mmol
(68 – 434) Ci / mmol at the end of synthesis (114)

18. Synthesis of N-[methyl-^{11}C]hydromorphone ***(219)***

219 has been obtained[211] in the direct alkylation of desmethyl hydromorphone, **220**, with $^{11}CH_3I$ using a remote-controlled synthetic system[212] (equation 115). Compound **219**, an opiate receptor ligand, has been used[211] to study the distribution and kinetics in brain of macaque monkeys[213] by PET. The ^{11}C-labelled alkaloids such as morphine, heroin, codeine, nicotine and bromocryptine have also been prepared by N-alkylation of the corresponding desmethyl compounds with $^{11}CH_3I$ in DMF or in acetonitrile[214].



(220)

(219) r. purity > 99.5%
after semipreparative HPLC (115)

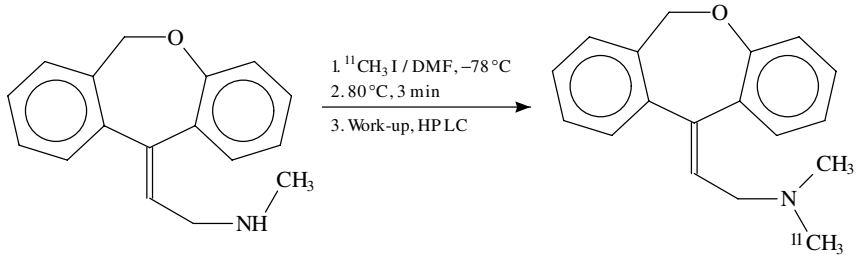
19. Synthesis of (N-[^{11}C]methyl)doxepin **(221)**

Doxepin, **221**, a tricyclic antidepressant, one of the most potent histamine H_1 antagonists[215], has been labelled[216] with carbon-11 by N-alkylation of normethyldoxepin (equation 116).

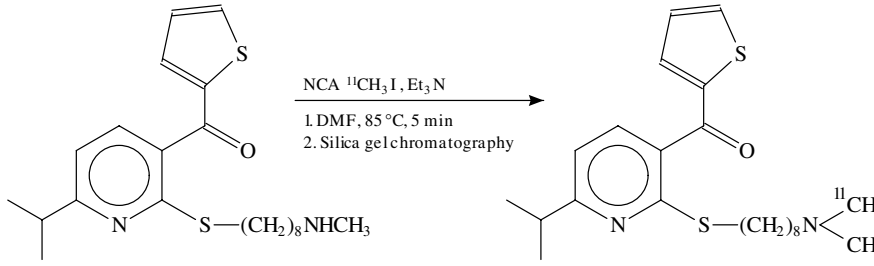
20. Synthesis of (N-[^{11}C]methyl)Y-29794 ***(222)***

The title compound, 2-(8-dimethylaminooctylthio)-6-isopropyl-3-pirydyl-2-thienyl ketone (**222**), a potent competitive reversible inhibitor of the enzyme PEP (prolyl endopeptidase which cleaves a variety of oligopeptides in brain and peripheral tissues[217]), has been synthesized[218] by [^{11}C]alkylation of the *N*-desmethyl precursor **223** (equation 117). **222** crosses the BBB and inhibits brain PEP in rodents[219]. It is used in the study of biodistribution and activity of brain proteases by PET to evaluate the roles

of peptides and protein degradative processes in normal and diseased human brain[218].



(221) sp. ct. 1.63 Ci / μmol (EOS)
15% r. yield based on $^{11}CH_3I$ (116)



(223) **(222)** 10 – 17% (EOB) (117)

*21. Synthesis of D-[1-^{11}C]glucopyranose **(224)** and D-[1-^{11}C]galactopyranose **(225)** using diborane*

224 and **225** have been obtained[220] from D-arabinopyranose (**226**) and D-lyxopyranose, (**227**) respectively (equation 118). In the previous synthesis of **224** from D-gluconolactone the reaction time at room temperature was 3.5 hours for optimal yield[221].

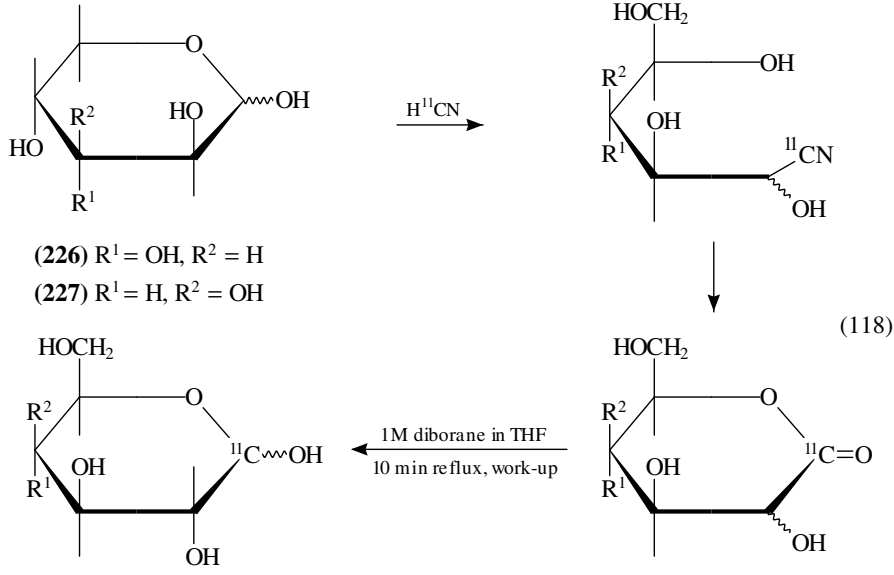
*22. Synthesis of DL-[1-^{11}C]alanine **(228)** from [^{11}C]HCN*

228 has been synthesized[222] in high radiochemical yield and purity (equation 119) by introducing [^{11}C]HCN into a solution of sodium 1-hydroxyethanesulphite in 8% ammonium hydroxide and subsequent hydrolysis of [1-^{11}C]2-aminopropanenitrile to DL-[1-^{11}C]alanine. The above reaction conditions have been selected from extensive investigation of the effects of [^{11}C]HCN trapping temperature, reaction temperatures, volume and concentration of precursor. [1-^{11}C]Pyruvic acid ready for use in PET studies has been prepared subsequently from crude **228** in an enzymatic synthesis[222–224].

23. Synthesis of [^{11}C]dexetimide and [^{11}C]levetimide

In vitro[225] and *in vivo*[226] studies with [^{3}H]dexetimide and [^{3}H]levetimide showed that dexetimide, **229**, binds to m-AChR ('muscarinic cholinergic receptors') while levetimide,

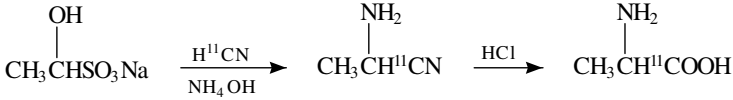
230, is a pharmacologically inactive enantiomer and did not show preferential uptake in regions of human brain known to have high concentration of m-AChR. **229** and **230** have therefore been ^{11}C-labelled for non-invasive *in vivo* investigation of m-AChR by PET, by alkylation of the appropriate norbenzylamine substrate, **231**, with [α-^{11}C]benzyl iodide (equation 120)[227].



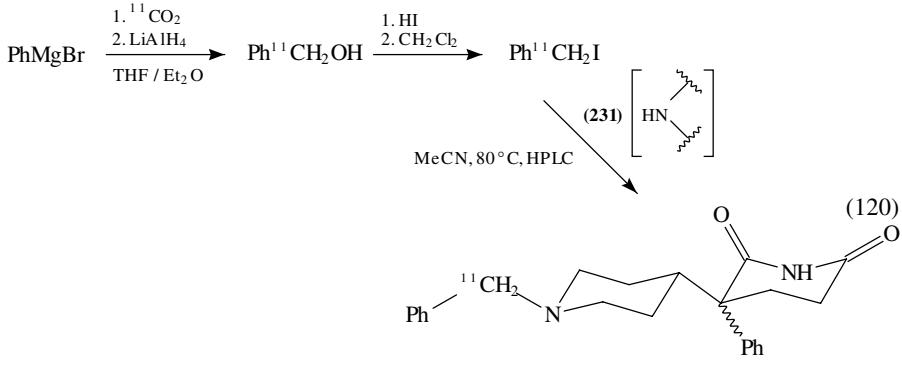
(226) R^1 = OH, R^2 = H
(227) R^1 = H, R^2 = OH

(118)

(224) R^1 = OH, R^2 = H
(225) R^1 = H, R^2 = OH

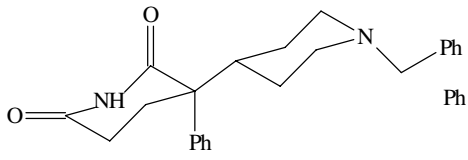


(228) (119)

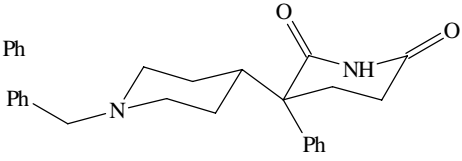


(120)

[^{11}C]dexetimide / levetimide
sp. act. 905 mCi/μmol



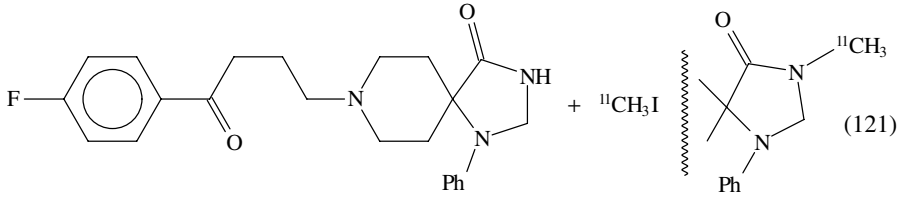
(229)
Dexetimide



(230)
Levetimide

*24. Synthesis of 3-N-[^{11}C]methylspiperone, ^{11}CNMS **(232)** with high specific activity*

232 has been produced automatically[228] with high specific activity at EOB by reaction of [^{11}C]CH_3I with spiperone (equation 121), for measurement of dopamine D_2 receptors in the human brain with a positron camera.



(121)

(232) 85–95% labelling yield from $^{11}CH_3I$

The yield of **232** decreased[228,229] to <50% at higher reaction temperatures and longer reaction time. The observed fast self-radiolysis of ^{11}C-NMS has been suppressed remarkably by addition of hydroxyl radical scavengers[230] such as potassium iodide (rate constant 1.0×10^{10} $M^{-1}\,s^{-1}$ at pH 7) and accelerated slightly by hydrated electron scavengers such as sodium nitrate (1.1×10^{10} $M^{-1}\,s^{-1}$ at pH 10 in aqueous solutions). The carrier methylspiperone (NMS) decomposed on ^{60}Co irradiation gave the same compound with a molecular weight of 425 as the ^{11}C-NMS gave upon self-radiolysis. The *G*-value of NMS decomposition by ^{60}Co irradiation was about two in aqueous solution. Polysolvate-80 (emulsifier, with three alcoholic OH groups in one molecule) and EtOH have been used[228] as *i.v.* injectable additives to protect ^{11}C-NMs against decomposition.

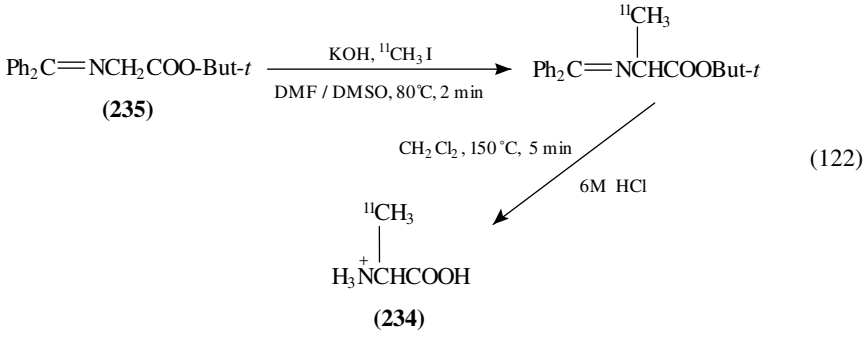
*25. The synthesis of [3-^{11}C]pyruvic acid **(233)***

233, a normal metabolite in the myocardium, applied in *in vivo* metabolic studies, has been obtained[233] from racemic DL-[3-^{11}C]alanine, **234**, in turn obtained from *N*-(diphenylmethylene)glycine *t*-butyl ester, **235**, as shown in equation 122, and subsequent enzymatic synthesis[232,233] of **233** using D-amino acid oxydase (D-AAO)/catalase and glutamic-pyruvic transaminase (GPT) in a coupled, one-pot reaction presented in equations 123a and 123b.

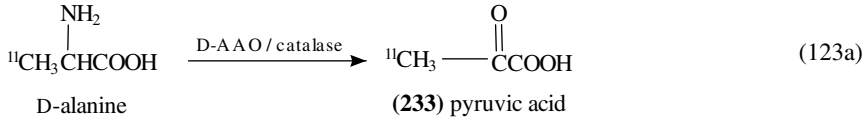
26. Microwave method of radiolabelling with [^{11}C]cyanide

The use of the microwave cavity in the typical syntheses involving NCA and carrier added [^{11}C]cyanide[234], such as cyano-de-halogenation with subsequent hydrolysis

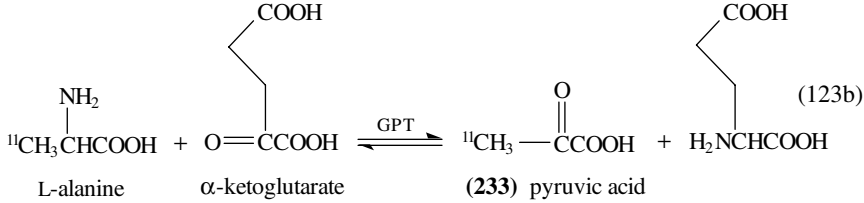
of the nitrile (equation 124), or Bucher–Strecker synthesis of aromatic amino acids[235] (equation 125) instead of



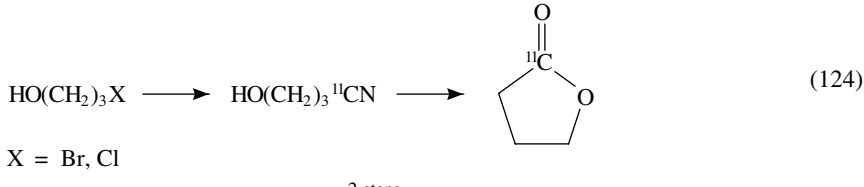
(122)



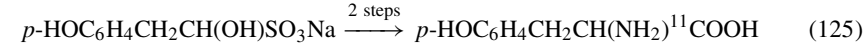
(123a)



(123b)



(124)



(125)

thermal treatment reduces the reaction time in the case of short-lived radionuclide, ^{11}C, by about one half-life of the radionuclide and provides nearly 100% more radioactive product (at EOS). Thus less starting radioactivity is required to produce the given amount of radiotracer and the previously rejected radiolabelling routes because a small half-life of radioisotope may now be possible.

27. Synthesis and uses of [^{11}C]thiocyanate

[^{11}C]Thiocyanate has been obtained[236] in 94% radiochemical yield under anhydrous conditions[237] and used for preparation of ethyl- *i*-propyl- and benzyl[^{11}C]thiocyanates in 78%, 71% and 88% radiochemical yields within 27 min, 28 min and 25 min synthesis time, respectively (equation 126). The organic [^{11}C]thiocyanates will be converted to [^{11}C]thiocarbamates[236]. They might be potentially useful also in the study of the tubular

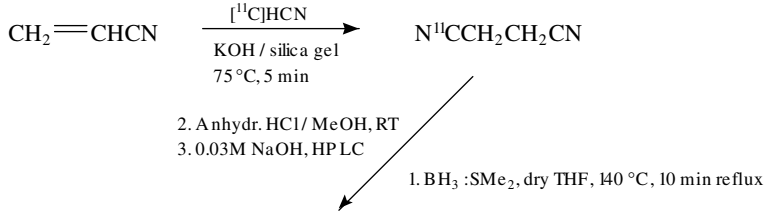
transport of anions in the kidneys.

$$^{11}CNBr + Na_2S \xrightarrow[DMSO,\ 80\,^{\circ}C,\ 1\ min]{K[2.2.2]} S^{11}CN^{-} \xrightarrow[\substack{80-120\,^{\circ}C,\ 2-5\ min\\ separations}]{RX,\ DMSO} RS^{11}CN \qquad (126)$$

R = ethyl-, 2-propyl-, benzyl-

28. Synthesis of [1-^{11}C]putrescine (236)

The radiosynthesis of **236** has been significantly improved[238] by near-quantitative trapping of the [^{11}C]HCN in anhydrous silica gel coated with potassium hydroxide, Michael addition reaction to acrylonitrile under anhydrous conditions on the same solid support medium and reduction of the [1-^{11}C]succinonitrile obtained in anhydrous form with BMS (borane methyl sulphide complex) (equation 127). The absence of water during the addition reaction eliminated the formation of by-products and decreased the total synthesis time. The biochemical tumor masker[239–241] **236** has been obtained also previously[242,243] but with lower radiochemical yields using $BrCH_2CH_2CN/Na^{11}CN/NaOH$ reagent[242] or $CH_2{=}CHCN/Na^{11}CN/NaOH$[243].



(127)

$^{11}CH_2(NH_2)CH_2CH_2CH_2NH_2$

(236) [1-^{11}C]-1, 4-diaminobutane.

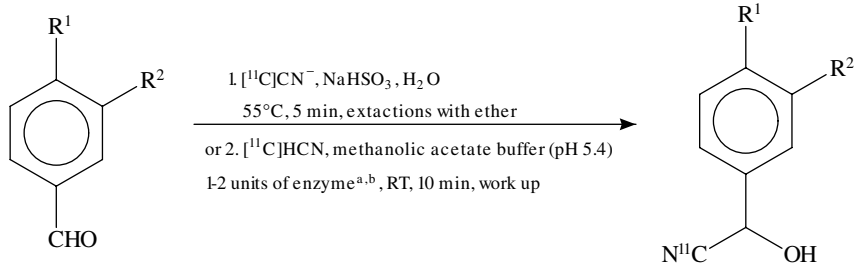
29. Synthesis of [^{11}C]octopamine (237a,b)

[^{11}C]-*p*- and *m*-Octopamine, **237a,b**, have been synthesized[244] from [^{11}C]HCN through the [^{11}C]cyanohydrin intermediates **238** (equation 128). The radiochemical yield of **237** at the end of 40–60 min synthesis time was 0.7–2.3%; the (*S*)-enantiometric purity of the [^{11}C]octopamine obtained through the enzymatic process was 92%, the (*R*)-enantiomatic purity of [^{11}C]-*m*-octopamine was 42%[244,245]. Studies with [^{3}H]-*p*- and *m*-octopamine[246] suggested its role in emotional and neurovegatative responses to stress[247]. The ^{11}C-labelled compounds **237** in enantiomeric pure or enriched forms were needed to study the activities of the stereoisomers of *p*- and *m*-octopamine on α-adrenoceptors[248].

30. One-line synthesis of [^{11}C]cyanide from cyclotron-produced [^{11}C]carbon dioxide

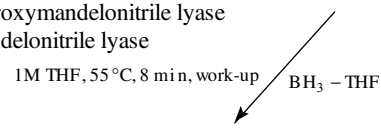
(a) H[^{11}C]CN, **240**, was recently produced[249] in essentially quantitative yield by passing an [^{11}C]CH_4–ammonia mixture over a platinum catalyst in a furnace held at 1000 °C. The yield of **240** obtainable by this method highly depends on the proton energy and current impinging on the target and the compact cyclotrons providing 9.4 MeV proton

beams of only 10–15 μA cannot be used in the above procedure. The [^{11}C]cyanide can also be prepared[250] in high yield in a simple on-line gas-flow system using a low-energy cyclotron by producing [^{11}C]CO_2 by irradiation of N_2 gas, combining it in line with H_2, drying, mixing on line the $^{11}CO_2/H_2$ with NH_3 (desiccated over solid KOH) and finally passing the [^{11}C]CO_2–H_2–NH_3 mixture through a quartz tube, containing platinum wire, installed in a furnace held at 950 °C. The [^{11}C]cyanide is extracted from the outflow from the quartz tube in a glass column packed with quartz wool impregnated with NaOH. The trapped radioactivity has been eluted with water. The radioactivity of the starting [^{11}C]CO_2 was comparable to the radioactivity of the produced [^{11}C]CN^-.

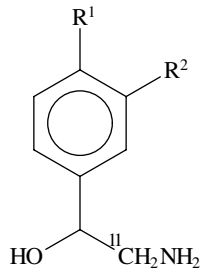


(239a) R^1 = OH, R^2 = H
(239b) R^1 = H. R^2 = OH
(a) enzym for **239a**: hydroxymandelonitrile lyase
(b) enzym for **239b:** mandelonitrile lyase

(238)



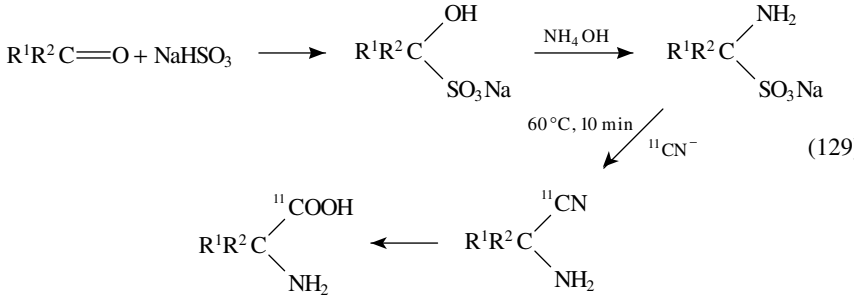
(128)



(237a) R^1 = OH, R^2 = H
(237b) R^1 = H, R^2 = OH

(b) Optimization of earlier methods of **240** production from [^{11}C]CO_2 for routine synthesis of [1-^{11}C]amino acids has been investigated by Iwata and coworkers[251]. More than 95% radiochemical yields of **240** have been obtained at 5 vol% of NH_3. 99% yield of **240** was achieved when metallic sodium coated on quartz wool was used to adsorb traces of O_2 which interfere with the catalytic reaction of [^{11}C]CH_4 with NH_3 on Pt. Higher NH_3 concentration prevents the oxidation of [^{11}C]CH_4. Higher flow rates and shorter contact time gave higher conversion yield of [^{11}C]CH_4 to **240**. High yield of **240** was obtained over the temperature interval 850 to 950 °C. Above 950 °C a slight decrease in yield of **240** was observed due to its decomposition. The effect of the Pt amount on the yield of **240** was also studied.

(c) As regards synthesis of NCA [^{11}C]amino acids from **240**, the optimal conditions for the synthesis of NCA[1-^{11}C]amino acids according to the procedure shown in equation 129 have been chosen[251]. The best reaction temperature, time and HCl concentration for acid hydrolysis of aminonitriles were found to be 160 °C, 15 min and 6N, respectively. The replacement of the bisulphite group by [^{11}C]cyanide proceeded quantitatively. The following [1-^{11}C]amino acids have been prepared according to the above procedure within about 1 h: phenylglycine, α-methylphenylglycine, cyclohexylglycine, phenylalanine, aminocyclohexanecarboxylic acid, aminocyclopentanecarboxylic acid, valine, leucine and norleucine in about 50% radiochemical yield. The method of equation 129 is suitable for automation of [1-^{11}C]amino acid production.

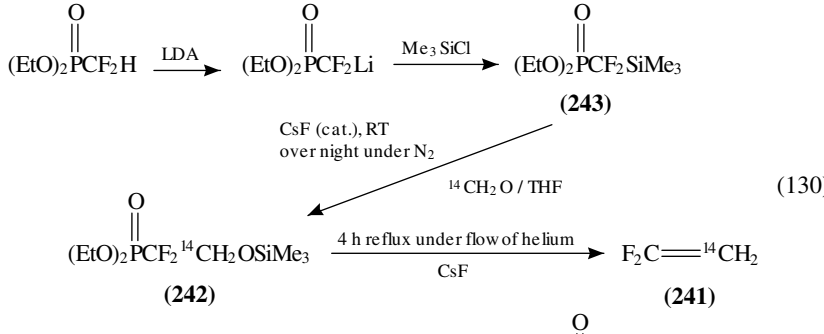


(129)

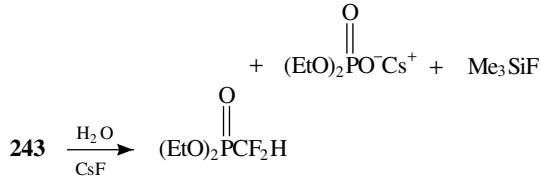
B. Compounds Labelled with Carbon-14

1. Synthesis of [1-^{14}C]-2-2-difluoroethene ***(241)***

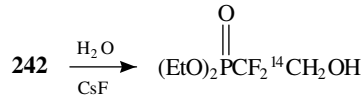
1,1-Difluoroethene (DFE) is a volatile industrial monomer widely used in the production of a variety of polymers. DFE-induced hepatotoxicity and acetonemia have been detected in the rats[252–254]. **241** has been therefore synthesized[255] to expedite study of the metabolic fate of the carbon fragment of **241** (equation 130). **241** has been obtained in low yields of 10–15%, caused by trace amounts of water which destroy the intermediates **243** and **242** (equations 131 and 132).



(130)



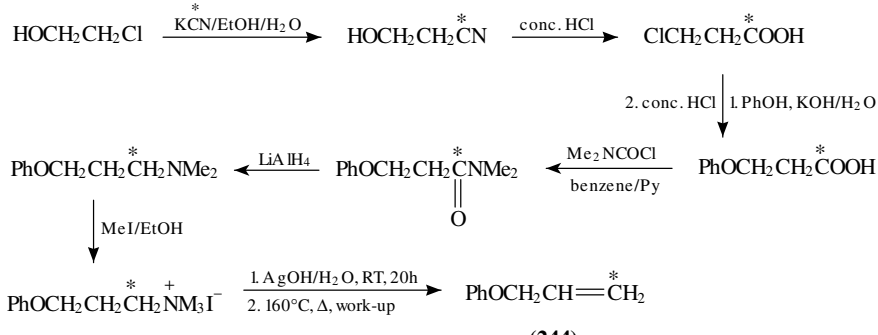
(131)



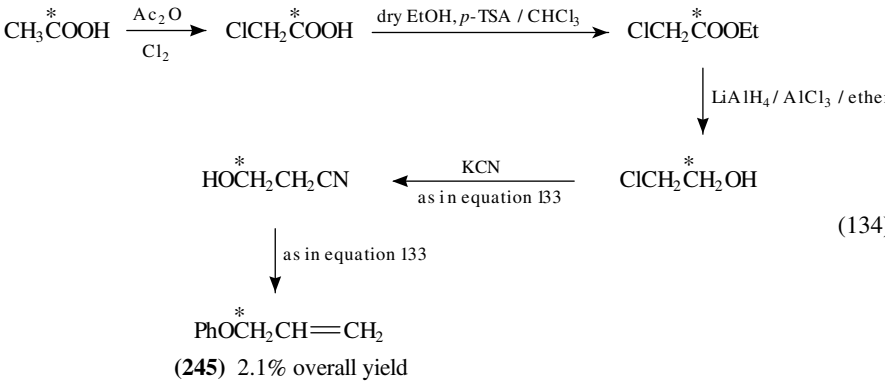
(132)

2. Synthesis of 3-phenoxy[1-^{14}C]- and 3-phenoxy[3-^{14}C]propene (**244** and **245**)

244 and **245** have been synthesized[258] (equations 133 and 134) for ^{14}C KIE studies in the Claisen rearrangement.



(133)



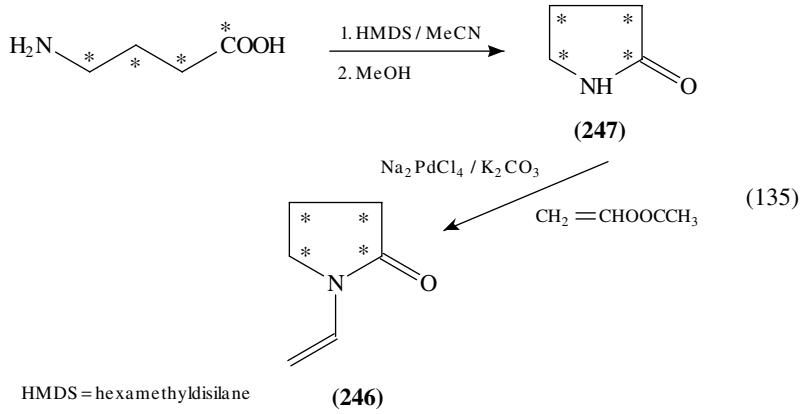
(134)

* = ^{14}C label

3. Synthesis of [2,3,4,5-^{14}C]-1-vinylpyrrolidinone (**246**)

NVP, **246**, is the intermediate in the production of PVP (polyvinylpyrrolidinone)[257] widely employed in the pharmaceutical, medicinal, food and beverage industries, and the small quantities (0.2% or less) of NVP contained as impurity in PVP might present a certain risk for the general population. Studies on the *in vivo* disposition of NVP have therefore been undertaken and **246** has been synthesized[258] (equation 135). [3,4-^{3}H]-NVP and [4-^{3}H]-NVP have been prepared previously in low yields[259] because the volatility of NVP itself and of the vinyl acetate had not been controlled properly in the synthetic and

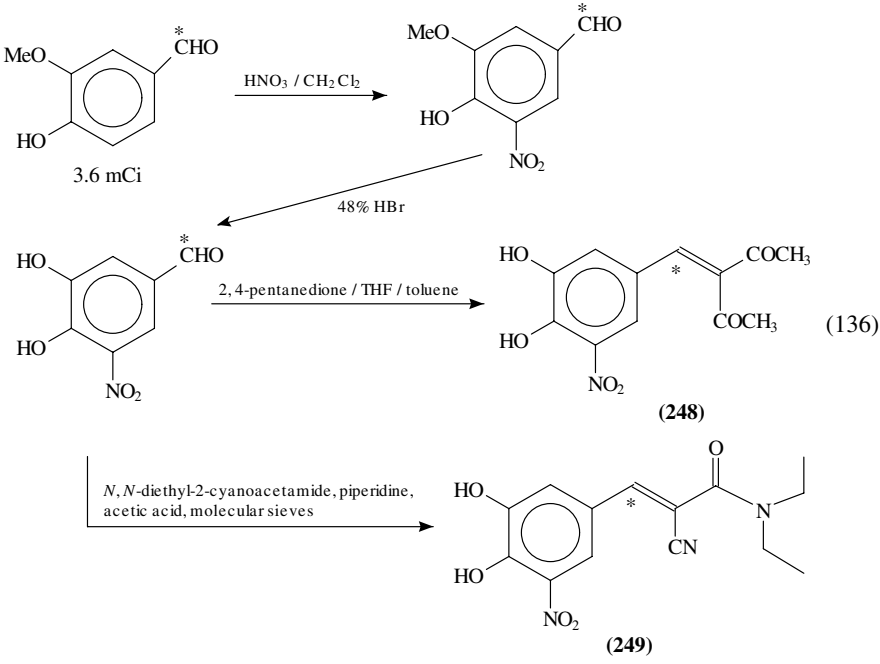
separation procedures.



(135)

4. Synthesis of ^{14}C-labelled catechol-O-methyltransferase inhibitors

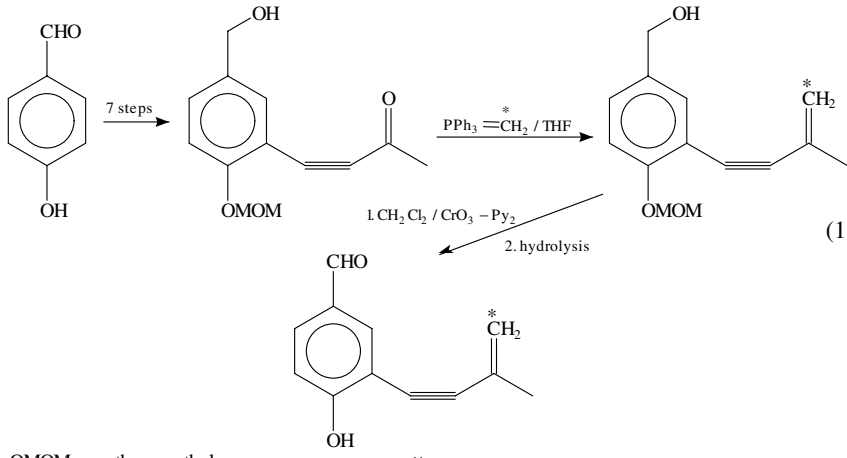
The two title COMT enzymes (inhibitors), which may open new possibilities for the treatment of Parkinson's disease[260,261], namely 3-(3,4-dihydroxy-5-nitropenylmethylidene)-2,4-pentadione **(248)** and *E*-*N*,*N*-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acryloamide **(249)**, have been labelled[262] with carbon-14 using [carbonyl-^{14}C]vanillin as the starting compound (equation 136). [^{14}C-]-**248** and- **249** are necessary in studies of the mechanism and pharmacokinetic properties of these drugs.



(136)

5. Synthesis of [^{14}C]-labelled eutypine **(250)**

The 4-hydroxy-3-(3-methyl-3-buten-1-ynyl)benzaldehyde, **250**, a phytotoxic compound responsible for vineyard die-back, has been [^{14}C]-labelled[263] via Wittig reaction using [^{14}C]CH_3I as precursor (equation 137).



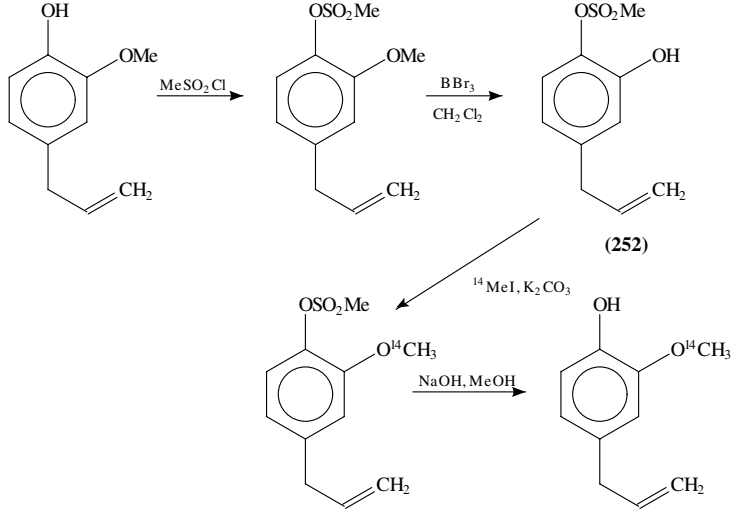
(137)

OMOM = methoxymethyloxy

(250) [^{14}C] Eutypine

6. Synthesis of [methoxy-^{14}C]eugenol **(251)**

251 has been synthesized[264] in reaction of mesylate **252** with $^{14}CH_3I$ (equation 138). **251** has been needed to evaluate the transfer and fate of eugenol during the smoking of clove cigarettes, to determine its deposition in various organs of rodents exposed to clove cigarette smoke and to investigate the related health effects[265].

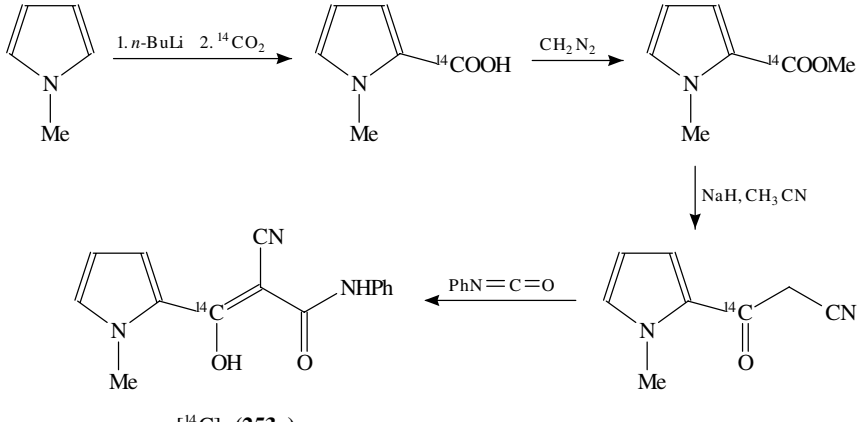


(138)

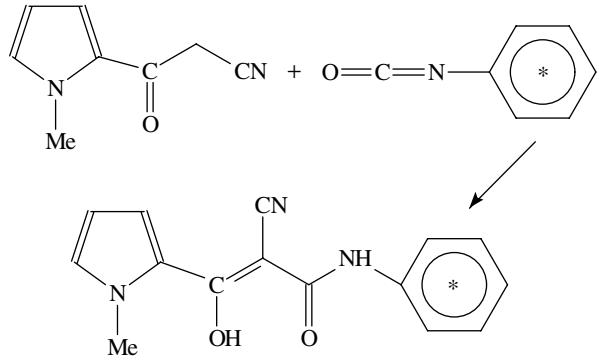
(251) 95% yield

7. Synthesis of ^{14}C-labelled prinomide (253)

Prinomide, **253**, a potential aspirin-like NSAID[266] (non-steroic anti-inflammatory drug) and its metabolite **254** have been synthesized[267] following as in equations 139–141. **253a**, **253b** and **254** are used in pharmacokinetic and metabolism studies[267,268].



[^{14}C]-(**253a**) (139)



[U-^{14}C]-(**253b**) (140)

* = uniformly ^{14}C ring labelled

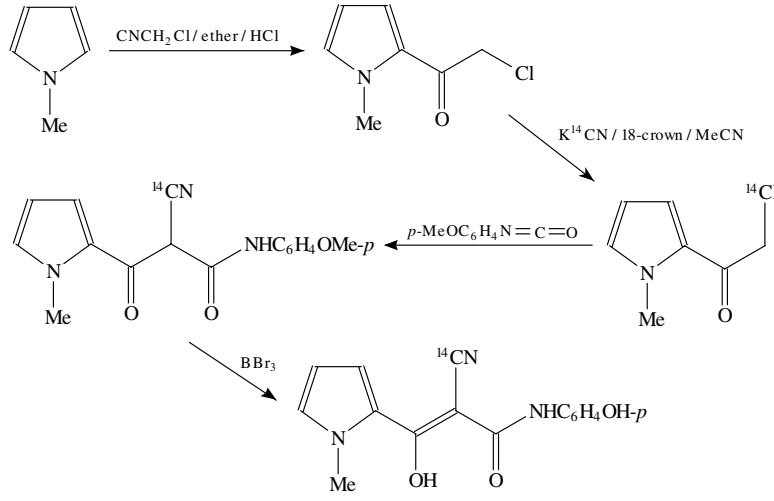
8. Synthesis of [3-^{14}C]acetocetate (255)

255 and other labelled β-keto esters have been obtained in quantitative yield for the synthesis of many types of pharmaceuticals[269] by heating of magnesium ethyl malonate with labelled 1-[^{14}C]acetylimidazole followed by acid hydrolysis and decarboxylation (equation 142).

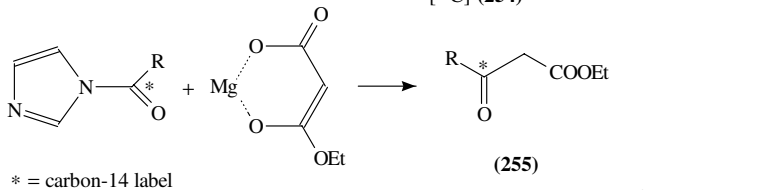
9. Syntheses of [^{14}C]labelled ketones

Numerous [^{14}C]labelled ketones have been synthesized[270] by the acylation of trimethylsilyl-2-lithiomalonates and trimethylsilyl-2-lithioalkane carboxylates with

[1-^{14}C]acyl halides (equation 143) and applied for the synthesis of different [^{14}C]labelled compounds, mainly biochemicals. A whole variety of labelled acyl halides, prepared from corresponding [^{14}COOH]acids, synthesized directly from $^{14}CO_2$ or via the [^{14}C]cyanide route, have been utilized in reaction 143. ^{14}C-Labelled biochemicals such as chlorophacinone, amphetamine, olivetol, heptadecane, indole, pyridazine derivatives, 5-aminolevulinic acid, noradrenaline, showdomycine, myosmine, nornicotine, nicotine, cotinine, norcotinine, coniine, palmitic or stearic acid, and other compounds, have been prepared by the method outlined in equation 143 by Pichat[270].



[^{14}C]-(**254**) (141)



(**255**) (142)

* = carbon-14 label

$$R^1COX + R^2CLi(COOTMS)_2 \longrightarrow R^1COCR^2(COOTMS)_2 \xrightarrow{H^+} R^1CCH_2R^2 \quad (143)$$

R^2 = H, Me, Et, Pr, Bu, $-CH_2COOTMs$, $-CHMeCOOTMS$, $-NHAc$, $-CH_2CN$, $-CH_2CH_2CN$, $(EtO)_2CH_2CH_2^-$, $-(CH_2)_mCOOTMS$

10. Synthesis of [phenyl-^{14}C]benzazepine derivative SK and F 103829-J

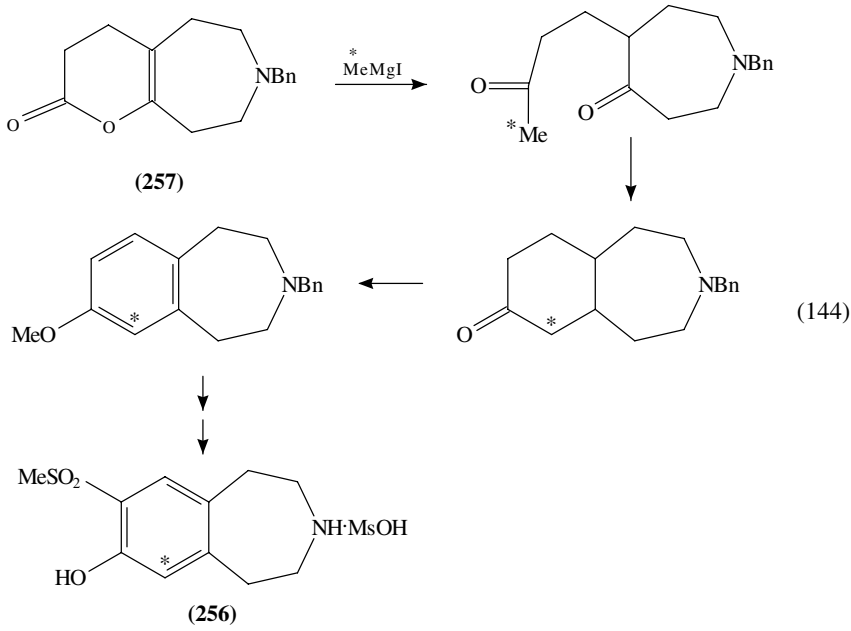
99% pure [6-^{14}C]SK and F 103829-J, **256**, has been prepared[271] in 10% overall radiochemical yield from $^{14}CH_3I$ and the key substrate, enol lactone, **257** (equation 144).

*11. Synthesis of methyl 3-oxo-4,4-dimethylpentanoate-1,3-^{14}C (**258**)*

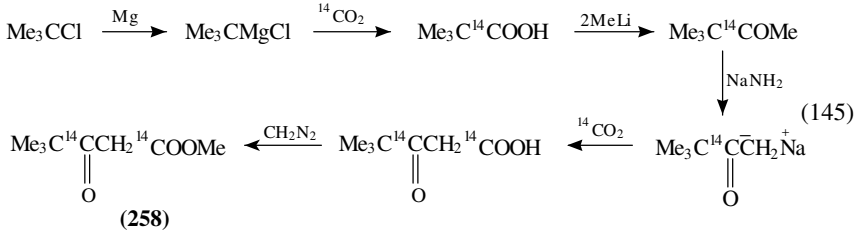
258 has been synthesized[272] as shown in equation 145.

12. Synthesis of [^{14}C]-fentanyl ***(259)***

259, a potent opioid analgesic with a faster onset and shorter duration than morphine[273,274], has been ^{14}C-labelled[275] in the anilidopiperidine substructure, resistant to metabolic extraction of the ^{14}C-label, using [UL-^{14}C]aniline as a source of carbon-14 (equation 146).



(144)



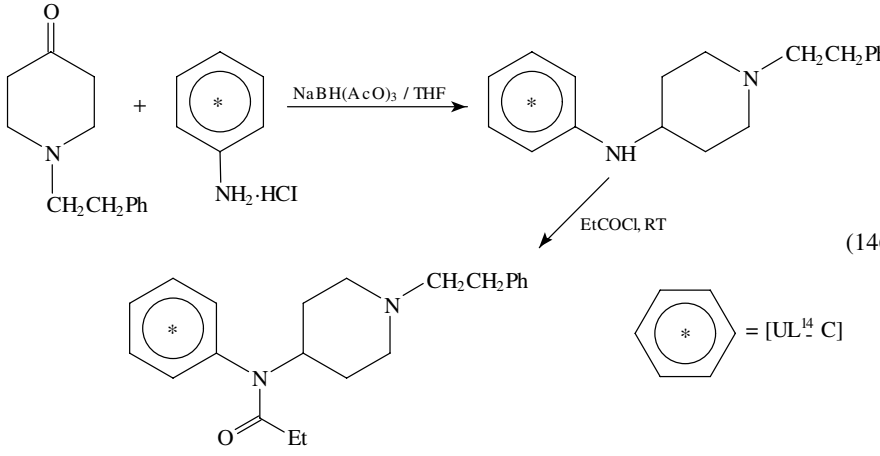
(145)

13. Synthesis of the cardiotonic agent ^{14}C-loprinone ***(260)***

260 presently under development[276] for the treatment of congestive heart failure, has been ^{14}C-labelled for pharmacokinetic profile studies[277]. **260** (^{14}C-loprinone hydrochloride) has been synthesized using **262** (equation 147).

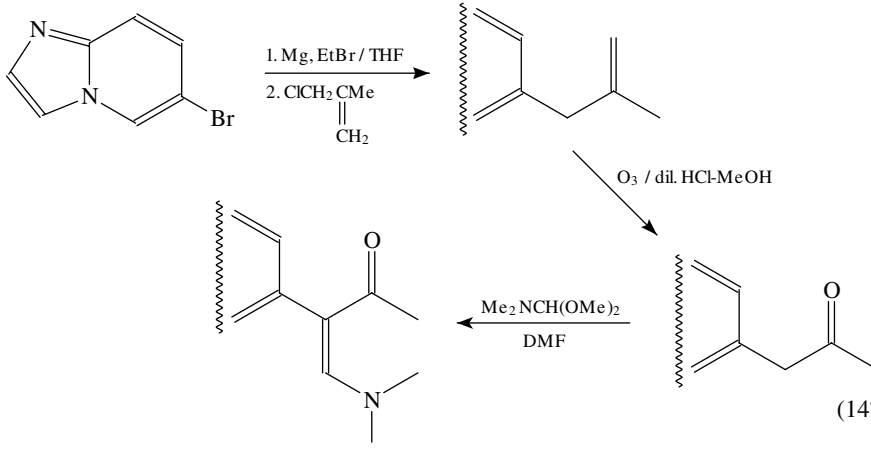
14. Synthesis of [^{14}C]-labelled perlrinone ***(263)***

263, a potent inotropic agent (AY-28, 768 hydrochloride), selected for clinical development[278], has been ^{14}C-labelled in four steps (equation 148) for metabolic studies[279].



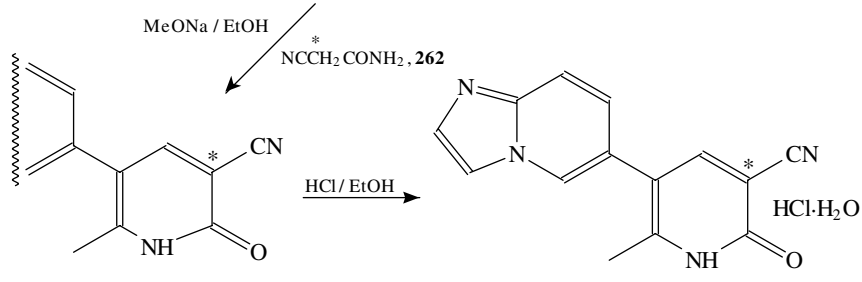
(146)

(259) 18% overall r. yield, r. purity > 99%, sp. act. 2.4 mCi/mmol

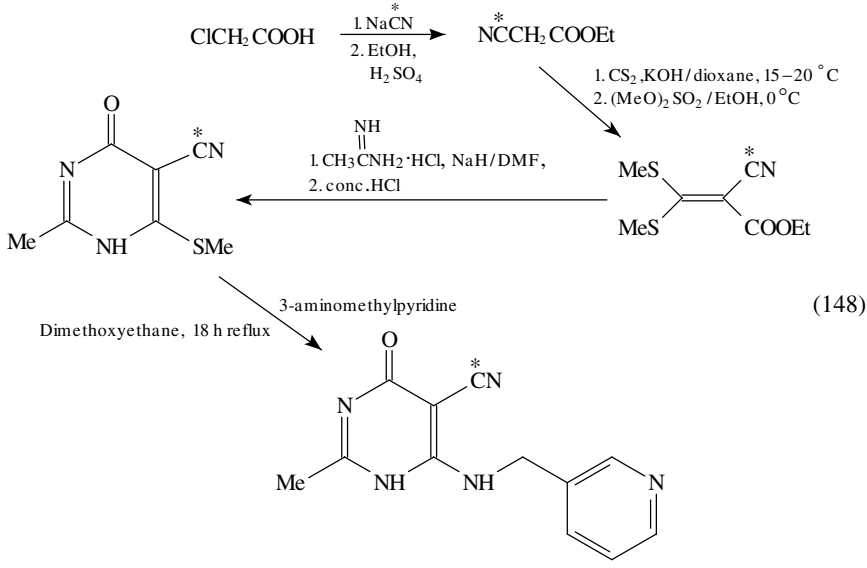


(147)

(261)

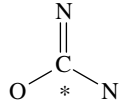
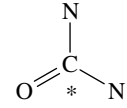


(260)



(148)

*15. Synthesis of [2-^{14}C]-labelled 2,2′-anhydrouridine **(264)** 2′-deoxyuridine derivatives **(265)** and 5-ethynyl- and 5-ethyl-2′-deoxyuridine **(266)***

The title compounds **264–266**, possessing significant activity against the Herpes simplex viruses[280,281], have been synthesized[282] according to equation 149. The higher specific activity of **266b** than that of **264** is caused probably not by the ^{14}C KIE in the transformation of  bond system in **264** into  bond system in **267** but by the smaller LSC counting efficiency of not well dried [2-^{14}C]**264** sample.

16. Synthesis of ^{14}C-labelled azasteroids

The azasteroids **268** and **269** of potential clinical utility for the treatment of acne, hirsutism or prostatic hypertrophy, have been ^{14}C-labelled in ring A and the *t*-butyl portion of carboxamide for metabolism and bioavailability studies[283].

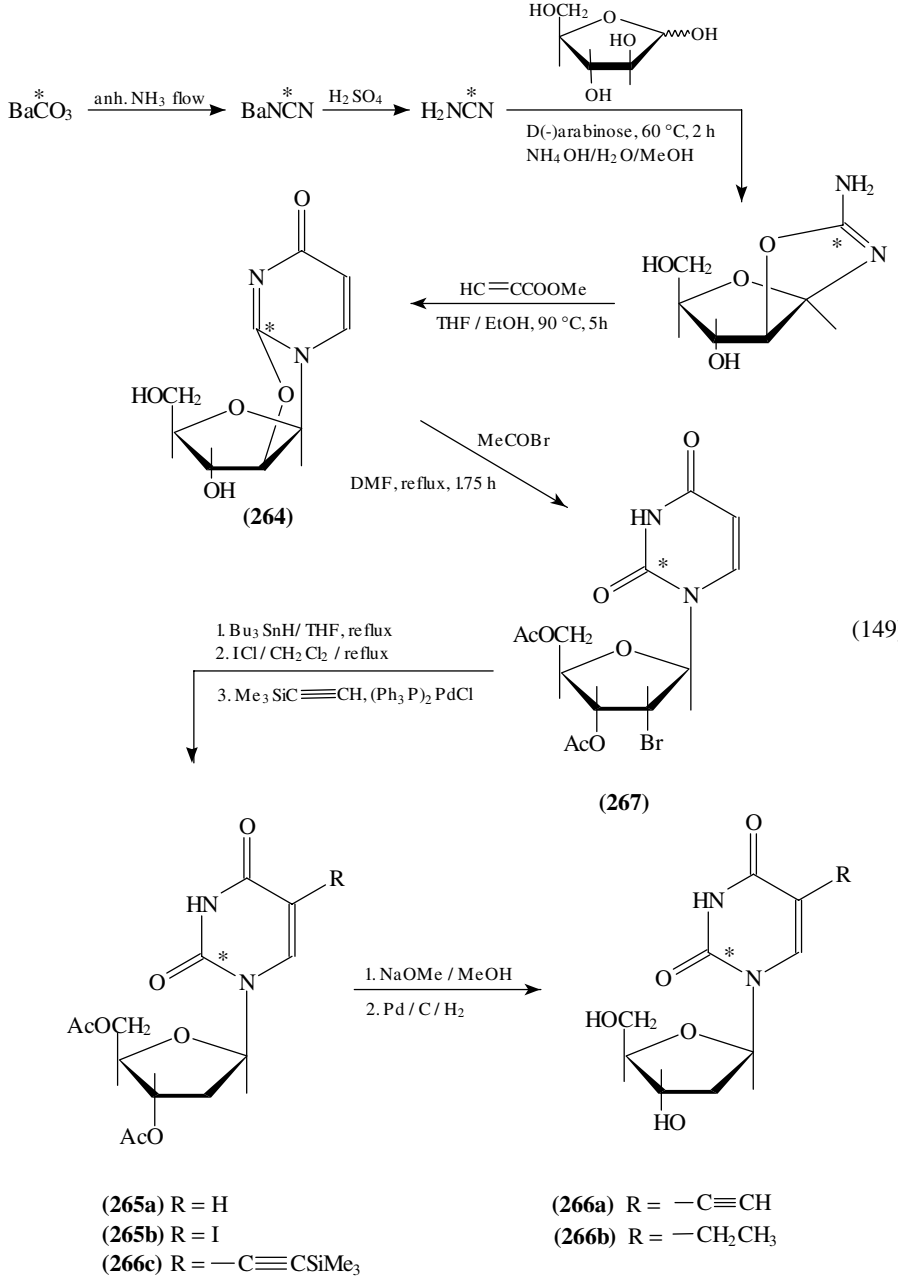
*17. Synthesis of [phenyl-U-^{14} C]tefluthrin **(270)***

270, a synthetic insecticide active against soil pests, has been ^{14}C-labelled[284] for metabolism and residues studies (equation 150).

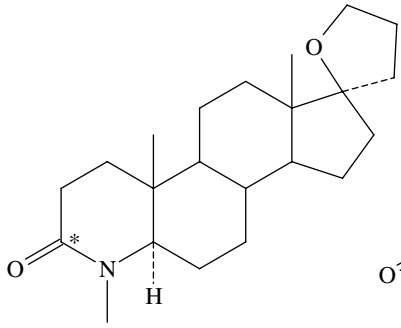
*18. Disposition of [^{14}C]prinomide **(271)** in normal subjects*

The disposition of this new ^{14}C-labelled anti-inflammatory drug, **271**, and its metabolite, **272**, in 4 volunteers has been studied[285]. The elimination half-life of **271** was about

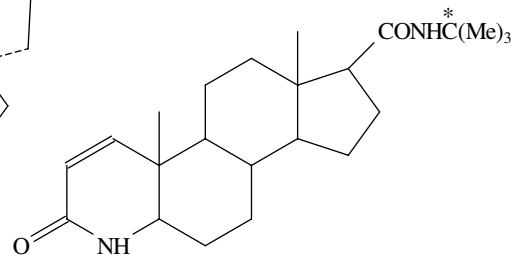
16.1 ± 2.9 h. 66.8–93.2% of radioactive dose was recovered in urine and 5.8–7.0% in feces over 13 days after dosing. The drug was extensively metabolized by structural alterations at the phenyl ring, pyrrol ring and the nitrile group.



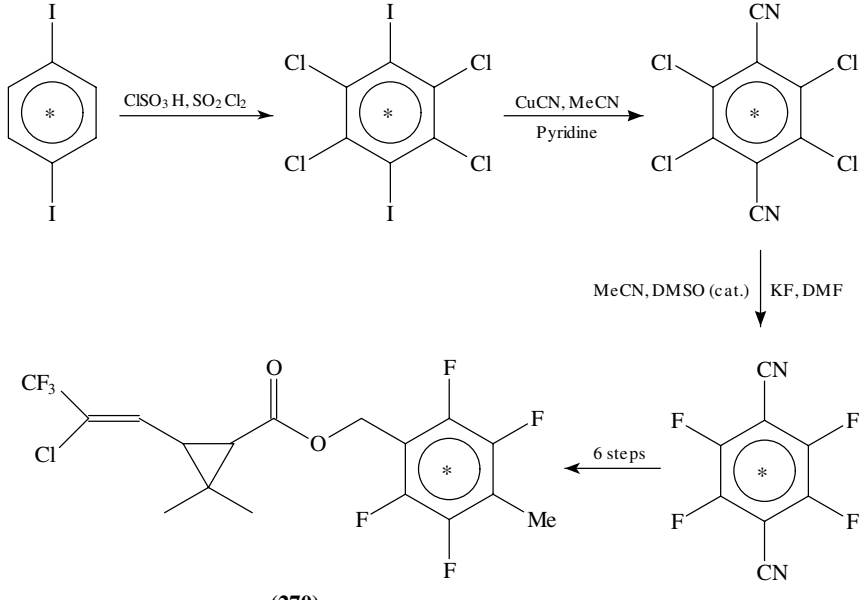
(149)



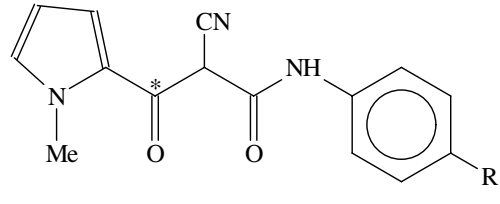
(268)



(269)



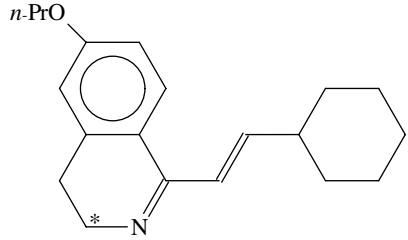
(150)



(271) R = H
(272) R = OH

19. Synthesis of ^{14}C-labelled BW A871 (273)

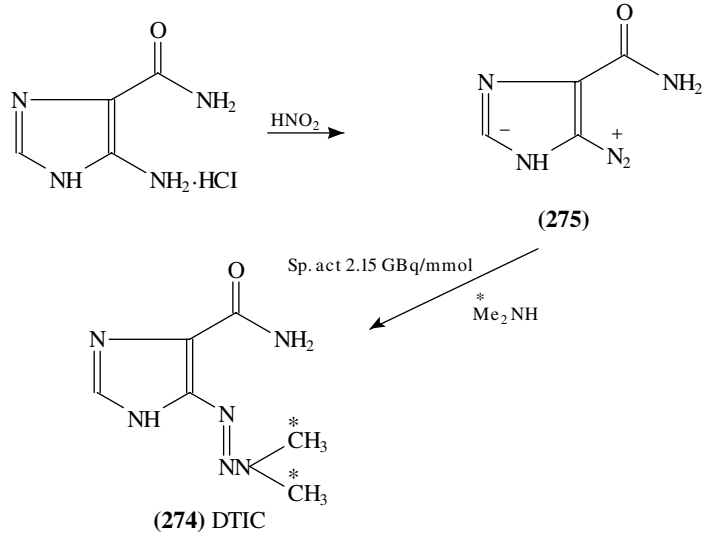
273 has been synthesized and ^{14}C-labelled for topical treatment[286] of *Trichomonas vaginalis* and *Candida albicans*. The ^{14}C label has been introduced into the 3 position of the isoquinoline ring by treating the 3-propyloxybenzyl chloride with $K^{14}CN$, followed by reduction of the nitrile to the amine which, treated with cyclohexyl acryloyl chloride, gave the amide. Cyclization of the amide provided **273**.



(273)

20. Synthesis of ^{14}C-labelled DTIC (274)

274, an anti-tumor drug[287], has been synthesized[288] from **275** with di[^{14}C]methylamine (equation 151).



(151)

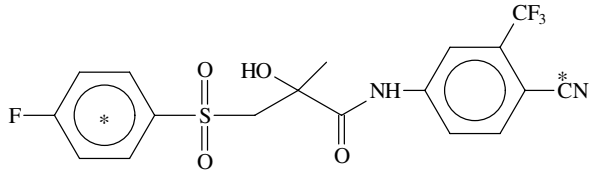
(274) DTIC

70.9% radiochemical yield

21. Synthesis of ^{14}C- and ^{3}H-labelled ICI-176,334 (276)

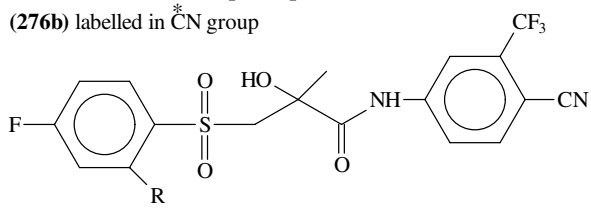
276, intended for use in the clinical treatment particularly of cancer of the prostate, has been uniformly ^{14}C-labelled in the 4-flourophenyl group[289] and in the cyano group. Thus **276a** and **276b** have been obtained from potassium [^{14}C]cyanide in multi-stage processes,

while **277a** has been prepared by catalytic dehalogenation of the corresponding brominated precursor, **277b**.



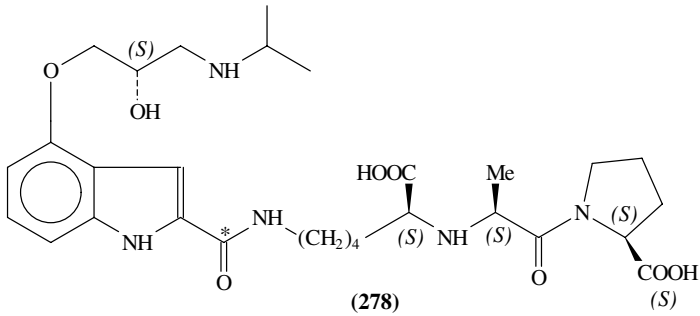
(276a) labelled in ring 

(276b) labelled in $^{*}CN$ group

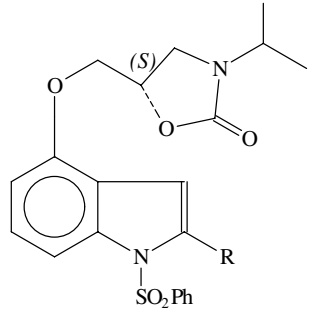


(277a) R = ^{3}H, sp. act 13.8 Ci/mmol, r.purity 98%

(277b) R = Br



(278)



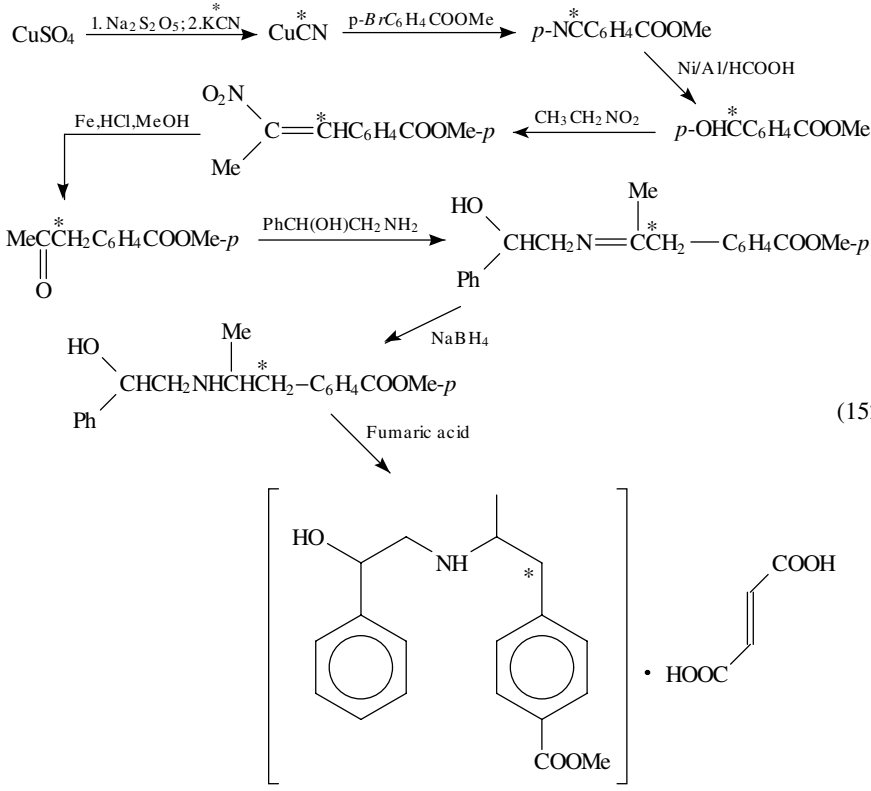
(279)

*22. Synthesis of ^{14}C-labelled BW B385C **(278)***

The antihypertensive agent **278** has been ^{14}C-labelled by carbonation of the 2-lithiated indole, **279** (R = Li), with $^{14}CO_2$ and subsequent combination with a preformed peptide side chain. In **279** (R = H) the indole nitrogen has been converted into its benzenesulphonyl derivative to direct properly the lithiation while the 2-hydroxy-3-isopropylaminopropoxy side chain has been protected as oxazolidin-2-one[290].

*23. Synthesis of [^{14}C]BRL 26830A **(280)***

280, a novel β-adrenoceptor agonist[291] which may find clinical utility in the treatment of both obesity and type II diabetes[291], has been synthesized[292] from K^{14}CN in 9 steps (equation 152).



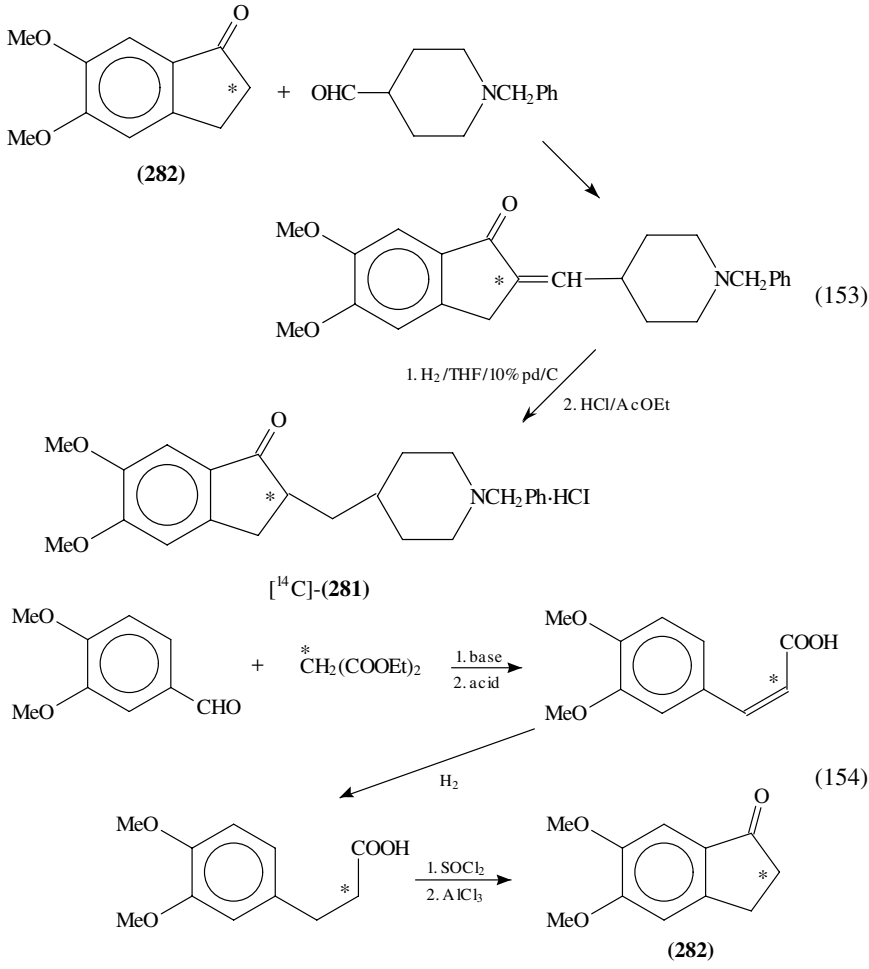
(152)

(280)[^{14}C]BRL 26830A

*24. Synthesis of 1-benzyl-4-{(5,6-dimethoxy[2-^{14}C]-1-indanon)-2-yl}-methylpiperidine hydrochloride, E2020-^{14}C **(281)***

281, one of the most potent AChE (acetylcholineesterase inhibitors[293]), a candidate for drug treatment of patients with Alzheimer's disease, has been synthesized[294] using

5,6-dimethoxy[2-^{14}C]-1-indanone, **282**, as the starting labelled material (equation 153). **282** has been prepared as shown in equation 154. [^{14}C]-**281** is applied for pharmacokinetic profile studies.



(153)

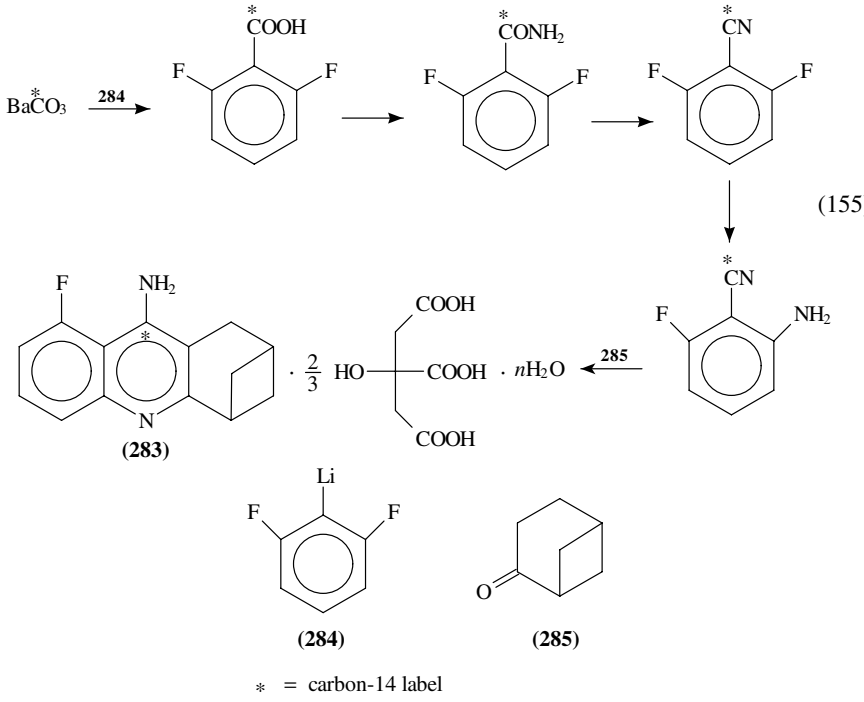
(154)

*25. Synthesis of ^{14}C-labelled tetrahydroacridine **(283)***

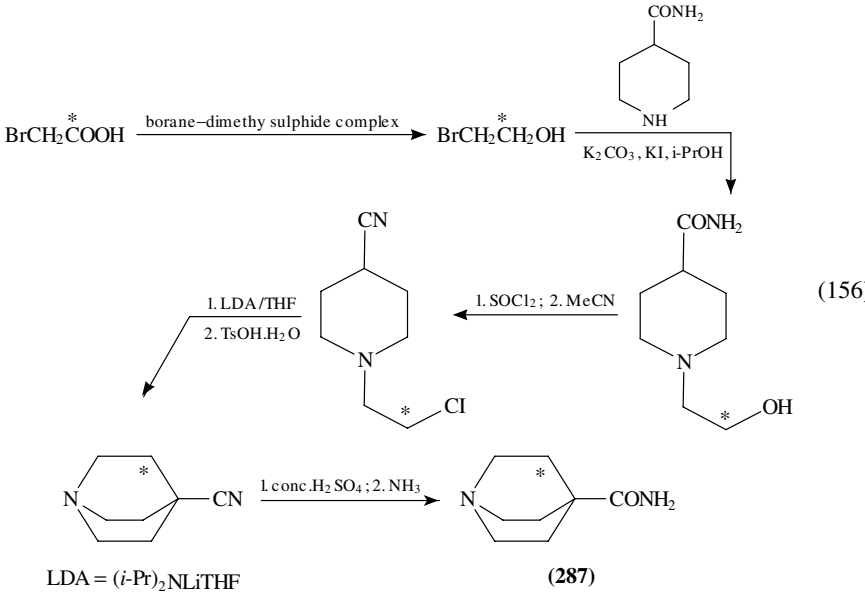
The 9-amino-8-fluoro-2,4-methano-1,2,3,4-tetrahydro[9-^{14}C]acridine citrate, SM-10888, **283**, has been synthesized[295] in five steps (equation 155) for cholinergic treatment in Alzheimer disease[296–300].

*26. Synthesis of ^{14}C-labelled Cefclidin **(286)***

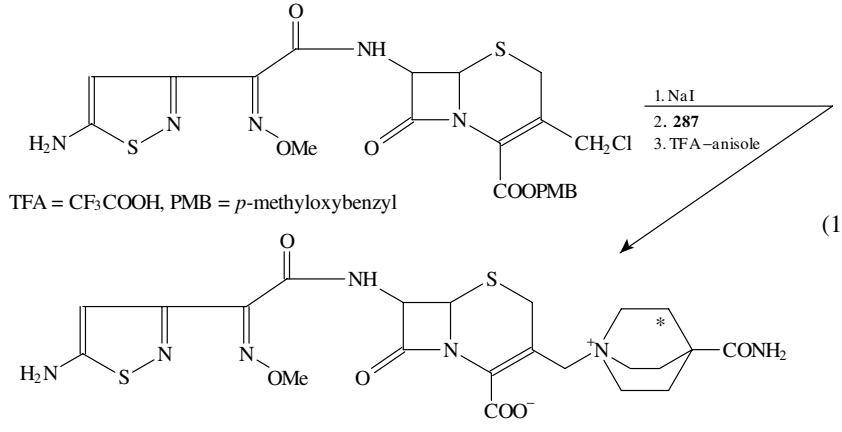
286, a new injectable cephalosporin with potent antipseudomonal activity[301,302], has been prepared[303] from **287**, as shown in equations 156 and 157.


*BaCO3
284
*COOH
F
F
*CONH2
*CN
NH2
285
COOH
HO
COOH
· nH2O
· 2/3
N
(283)
Li
(284)
O
(285)
* = carbon-14 label

(155)


BrCH2COOH
borane–dimethy sulphide complex
BrCH2CH2OH
CONH2
NH
K2CO3, KI, i-PrOH
CN
CONH2
1. LDA/THF
2. TsOH.H2O
1. SOCl2; 2. MeCN
N
CI
OH
N
CN
1. conc.H2SO4; 2. NH3
CONH2
LDA = (i-Pr)2NLiTHF
(287)

(156)

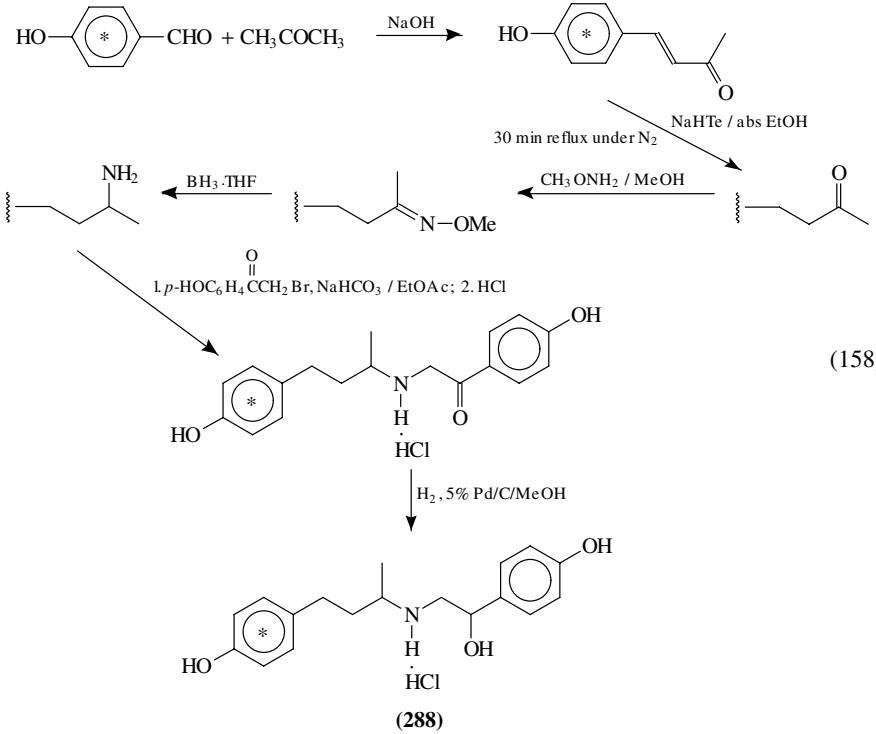


(157)

(286)

*27. Synthesis of [Ph-UL-^{14}C]ractopamine hydrochloride **(288)***

(EL-737), **288**, promoting growth and carcass leanness when fed to swine[304], has been uniformly labelled[305] with carbon-14 in one of the two phenyl rings in six-step synthesis in 14% yield (equation 158).

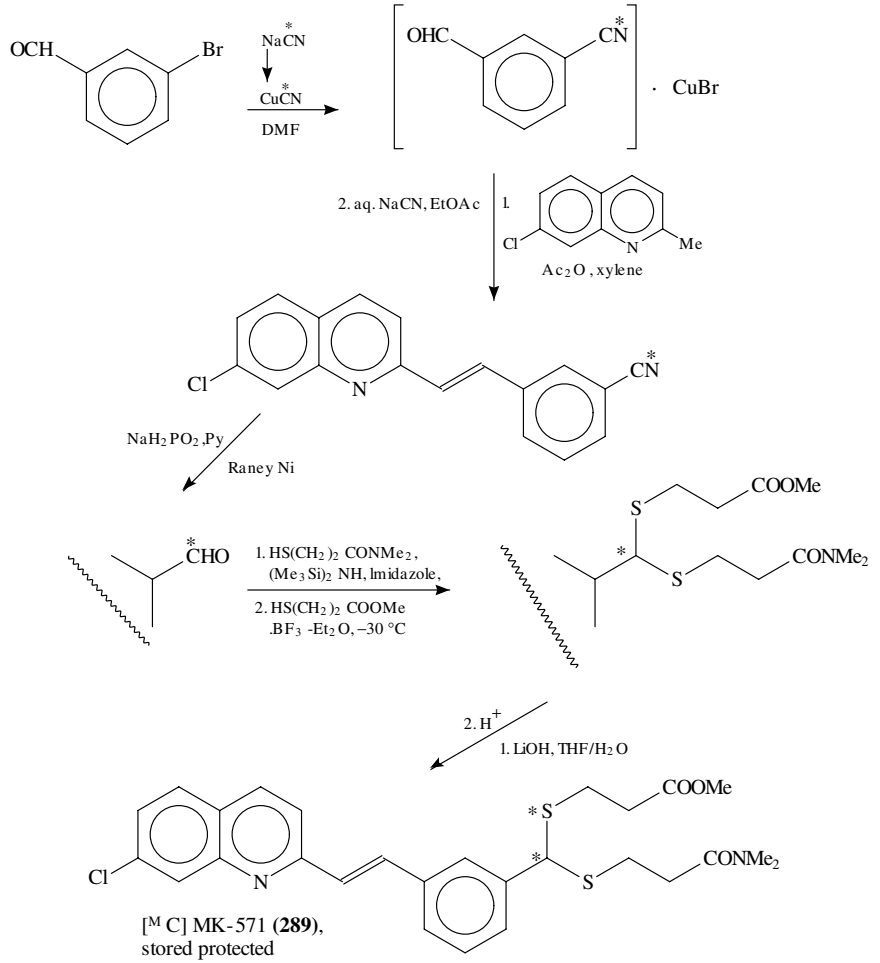


(158)

(288)

*28. Synthesis of carbon-14 labelled LTD_4 antagonist MK-571 **(289)***

The title compound, [^{14}C]MK-571, **289**, a promising antiasthmatic agent[306,307], has been synthesized[308] from Na^{14}CN via the sequence shown in equation 159.



(159)

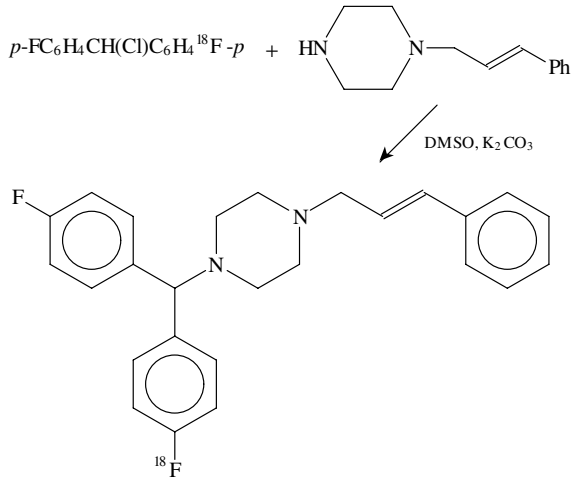
V. SYNTHESES AND USES OF COMPOUNDS CONTAINING C=C, C=O OR CN GROUPS LABELLED WITH RADIOACTIVE HALOGEN

A. Compounds Labelled with Fluorine-18

*1. Synthesis of [^{18}F]flunarizine **(290)***

290, a clinically used calcium channel blocker of the piperazine class[309] recently used for treatment of neurological disorders such as epilepsy and migrene[309], has been prepared

(equation 160) for *in vivo* biodistribution studies[310].

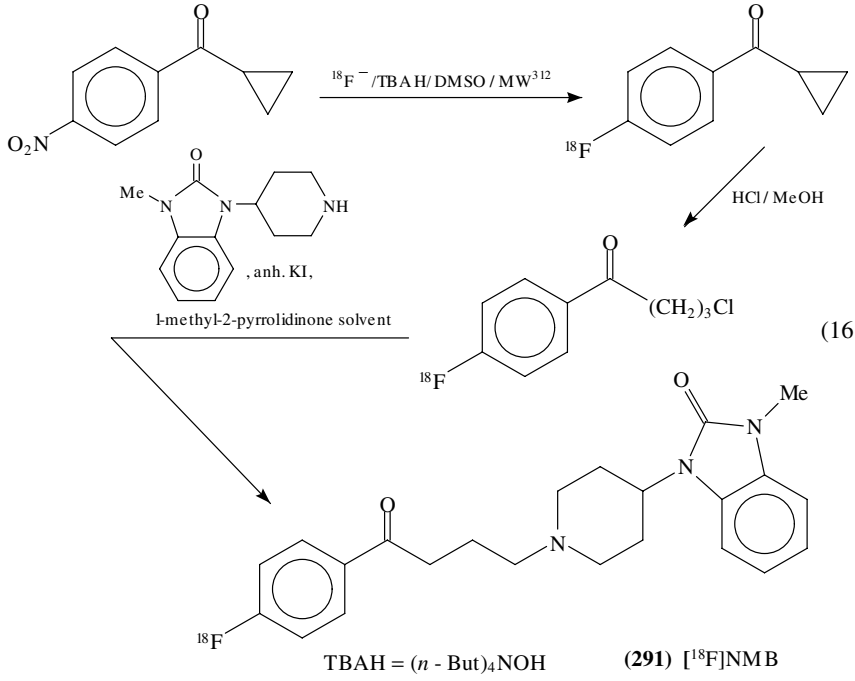


(160)

(290)

*2. Synthesis of [^{18}F](3-N-methyl)benperidol (NMB, **291**)*

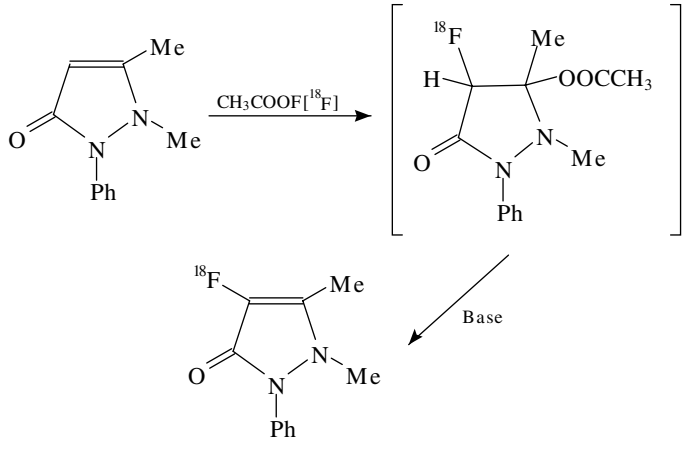
291 has been synthesized as shown in equation 161[311].



(161)

3. Synthesis of [^{18}F]4-fluoroantipyrine (292)

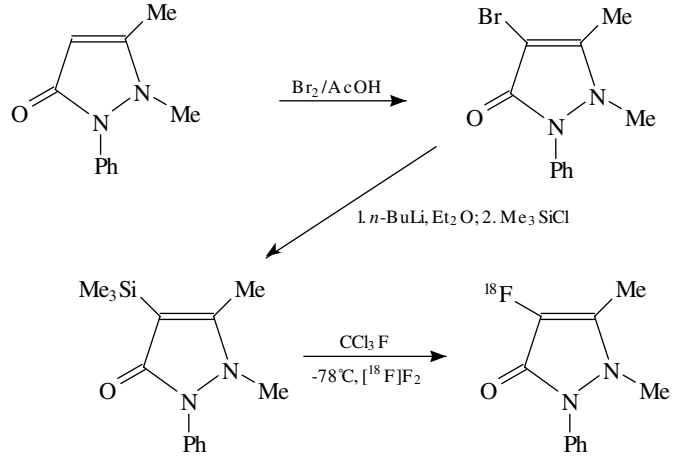
(a) **292**, an important blood flow tracer especially useful in multitracer radiography[313], has been synthesized[314] as shown in equation 162. The simplicity of the methods allows a remotely operated synthesis for day-to-day operation[315].



(162)

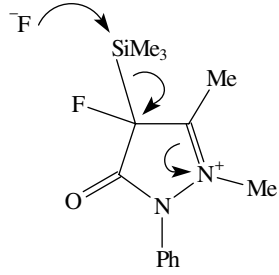
(292)

(b) **292** has been synthesized also[315] by direct fluorination of the corresponding silane (equation 163). As to the mechanisms of reactions 162 and 163, it has been suggested[315] that reaction 163 proceeds through the intermediate **293**. The initial electrophilic addition by fluorine at $C_{(4)}$ is followed by elimination of trimethylsilane probably by F^- and electron shift. A ^{14}C KIE study of the last reaction step in equation 163 should clarify the above mechanistic suggestions concerning timing of bonding changes in TS.



(163)

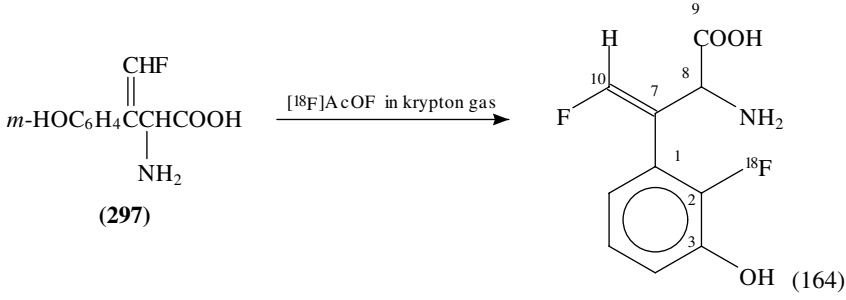
(292)



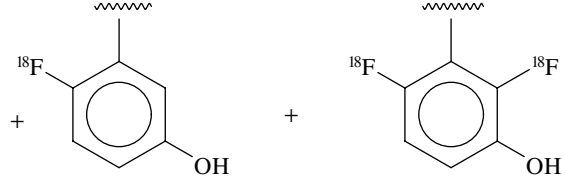
(293)

*4. Synthesis of ^{18}F-labelled (E)-β-fluoromethylene-DL-m-tyrosine (FMMT, **294**)*

2-Fluoro-FMMT, **294**, 6-fluoro-FMMT, **295**, and 2,6-difluoro-FMMT, **296**, labelled with ^{18}F, have been obtained[316] in the direct reaction[317] of **297** with $AcO^{18}F$[38] (equation 164). The specific activity at the end of 60 min preparation time was about 200 mCi/mmol. The HPLC purification yields a radiotracer which can be directly injected after sterilization for the assessment of presynaptic CNS dopamine nerve terminals using PET[319].



(297) **(294)** (164)



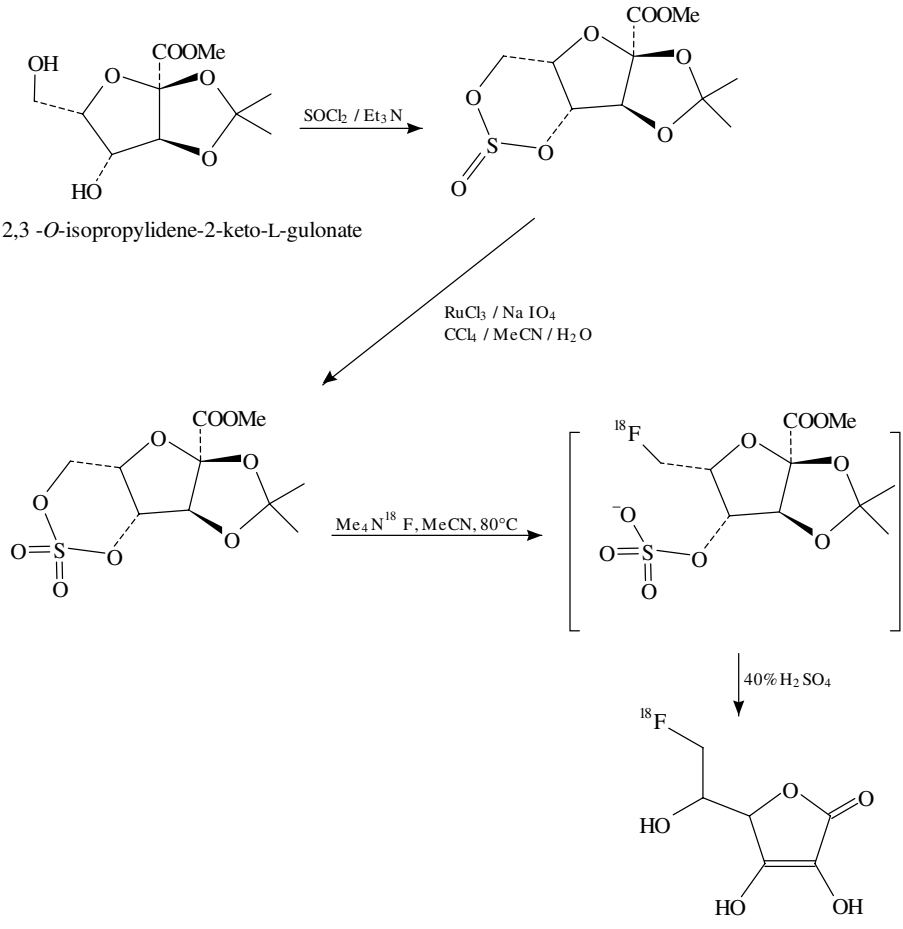
(295) **(296)**

The structures of **294–296** have been resolved unambiguously by fast atom bombardment mass spectrometry and ^{1}H-, ^{13}C- and ^{19}F- NMR spectroscopic studies[316].

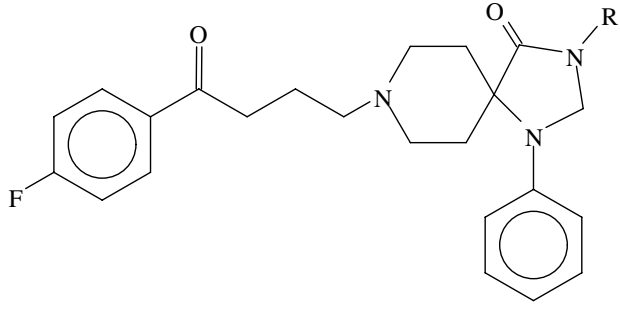
*5. Synthesis of 6-deoxy-6-[^{18}F]fluoro-L-ascorbic acid (^{18}F-DFA, **298**)*

298, needed for imaging *in vivo* the biochemical functions of antioxidants in humans, has been obtained[320] in one-pot synthesis via nucleophilic displacement of cyclic sulphate

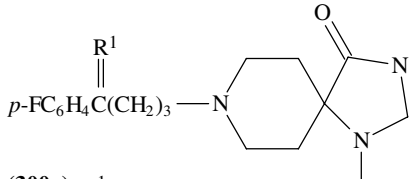
with no-carrier-added [^{18}F]fluoride ion (equation 165).



(165)



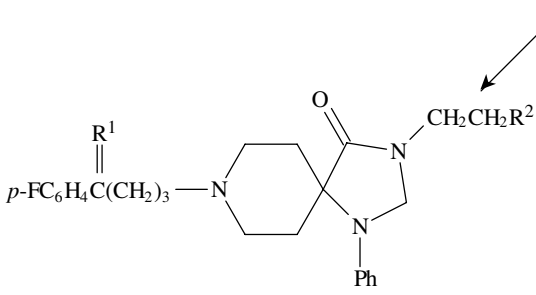
(299a) R = $CH_2CH_2{}^{18}F$, **(299b)** R = $CH_2CH_2{}^{19}F$, **(299c)** R = H



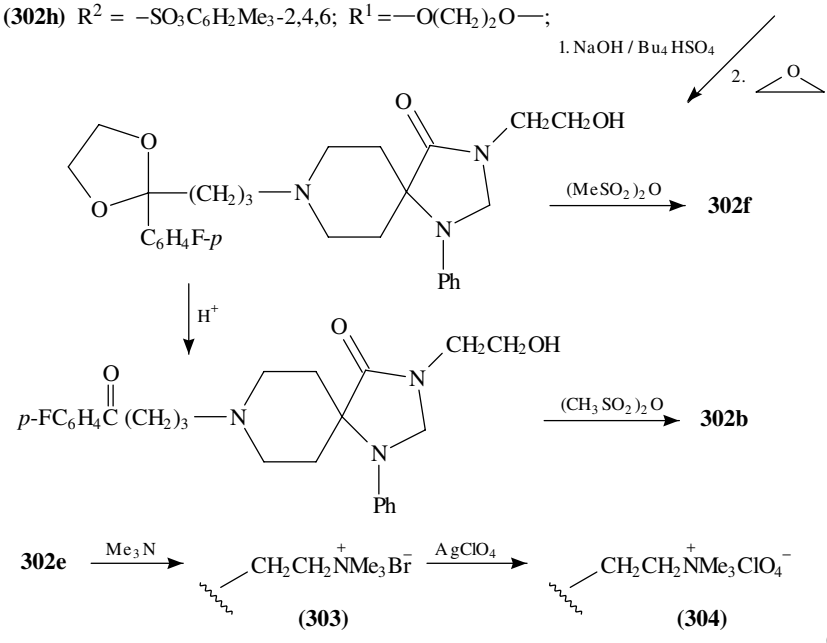
+ $R^2CH_2CH_2R^2$

(300a) R^1 = O,
(300b) R^1 = $O(CH_2)_2O$

(301a) R^2 = Br, **(301b)** R^2 = —SO_3Me
(301c) R^2 = —$SO_3C_6H_4Me$
(301d) R^2 = —$SO_3C_6H_2Me_3$ –2,4,6



(302a) R^2 = Br, R^1 = O; **(302b)** R^2 = —SO_3Me, R^1 = O;
(302c) R^2 = —$SO_3C_6H_4Me$-*p*, R^1 = O; **(302d)** R^2 = —$SO_3C_6H_2Me_3$-2, 4, 6; R^1 = O;
(302e) R^2 = Br, R^1 = —$O(CH_2)_2O$—; **(302f)** R^2 = —SO_3Me, R^1 = —$O(CH_2)_2O$—;
(302g) R^2 = –$SO_3C_6H_4Me$-p, R^1 = —$O(CH_2)_2O$—;
(302h) R^2 = –$SO_3C_6H_2Me_3$-2,4,6; R^1 = —$O(CH_2)_2O$—;



(166)

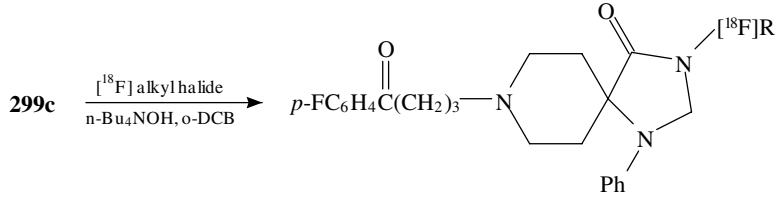
The biodistribution study of ^{18}F-DFA in normal rats has shown high uptake of radioactivity in the adrenals, kidneys, liver and small intestine organs, possessing high concentration of L-ascorbic acid in cells[320,321]. A certain uptake of radioactivity of the brain has been observed also between 10 and 120 min after *in vivo* injection[322]. **298** is able to accumulate in the tumor of mice bearing 3-methylcholanthrene induced fibrosacroma[320]. It has been suggested[320,323] that ascorbic acid may have some roles in the prevention or treatment of cancer[323].

*6. Synthesis of 3-(2′-[^{18}F]fluoroethyl)spiperone) **(299a)***

299a, useful for imaging the brain dopamine receptor system *in vivo* by PET, has been synthesized[324] from **300a** and **301**, ketalization of **302** and treatment of the products **302f–h** (equation 166) with NCA K^{18}F/Kryptofix in MeCN at 100 °C for 15 min. The tomographic behaviour of **299** in human brain tissue was found to be consistent with the labelling of dopamine D-2 receptors[325–327]. X-ray analysis using **299b** unequivocally established that the flouroethyl group resides on the amide nitrogen. The compound **299b** was given also a detailed IR, NMR and MS investigation[324].

*6. Synthesis of NCA N-([^{18}F]fluoroalkyl)spiperone derivatives (**305** and **306**)*

3-*N*-([^{18}F]fluoroalkyl)spiperone derivatives **305** and **306** have been prepared[328] by N-alkylation of spiperone **299c** with fluoroalkyl halides (equation 167).

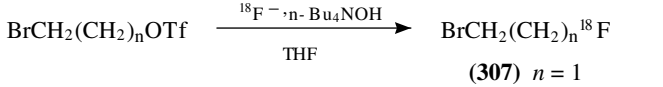


(167)

(305a) R = —$CH_2CH_2{}^{18}F$, **(306a)** R = —$CH_2CH(^{18}F)Me$
(305b) R = —$(CH_2)_3{}^{18}F$, **(306b)** R = —$CH_2CH(^{18}F)Et$
(305c) R = —$(CH_2)_4{}^{18}F$, **(306c)** R = —$CH_2CH(^{18}F)Pr$-*n*
(306d) R = —$CH_2CH(^{18}F)But$-*n*

o-DCB = 1,2-dicyanobenzene

The fluoroalkylating agents **307–309** have been prepared from the corresponding trifluoromethanesulphonates by [^{18}F]fluoride (equation 168).



(307) *n* = 1
(308) *n* = 2
(309) *n* = 3

(168)

Synthesis of 2-[^{18}F]fluoroalkyl (Et, Pr, But, pentyl and hexyl) spiperone derivatives, **306a–d**, involved iodo[^{18}F]fluorination of terminal olefins (equation 169) followed by

N-alkylation of spiperone[329].

$$CH_2{=}CHR \xrightarrow[\text{N-iodosuccinimide, } CH_2Cl_2 \text{ solvent}]{^{18}F^-,\ H_2SO_4} ICH_2CH(^{18}F)R \quad (169)$$
$$R = Me, Et, Pr, But, Pen$$

The brain uptake efficiency and distribution of the above compounds as well as D_2 receptor affinities of derivatives of spiperone containing aliphatic halogens have been studied also[330].

The synthesis of fluorine-18-labelled receptor-based radiopharmaceuticals carried out before 1986 have been reviewed[331] and the methods applied for the synthesis of ^{18}F-butyrophenone neuroleptics such as spiroperidol (spiperone), haloperidol have been critically evaluated. The synthesis for preparing *N*-(2-[^{18}F]fluoroethyl)spiperone[330] involving the [^{18}F]fluoride ion displacement of a suitable leaving group on the ethyl side chain was found to be particularly good (>50% yield).

Synthesis of ^{18}F-opiates and ^{18}F-steroids have been briefly reviewed also[331]. Biological studies of the above ^{18}F-labelled receptor ligands in animals have been discussed briefly[331,332].

The synthesis of 21-[^{18}F]fluoro-16α-methyl-19-norprogesterone, 21-[^{18}F]fluoro-16α-ethyl-19-norprogestrone, 21-[^{18}F]fluoro-16α-methylprogestrone and 21-[^{18}F]fluoro-16α-ethylprogestrone[333] of high specific activity has already been reviewed in this series[334].

B. Compounds Labelled with Heavier Radiohalogens

*1. Synthesis of 1-(2′-fluoro-2′-deoxy-β-D-ribofuranosyl)uracil **(311)** and 1-(2′-chloro-2′-deoxy-β-D-ribofuranosyl)uracil **(312)** radiolabelled with ^{18}F, ^{34m}Cl, ^{38}Cl, ^{14}C and ^{3}H*

Pyrimidine nucleosides labelled with radiohalogens have been studied for diagnostic[335] and therapeutic[336] applications in oncology. They may serve as indicators of tissue proliferation suitable for non-invasive tumor localization. **311** and **312** have been radiolabelled for evaluation as diagnostic radiopharmaceuticals[337].

6-[^{3}H]-2′-FUdR and 2-[^{14}C]-2′-FUdR have been prepared by reaction of anhydrous hydrogen fluoride (AHF) with 6-[^{3}H]- or 2-[^{14}C]-labelled 2,2′-anhydro-1-β-D-arabinofuranosyl-uracil, **310** (2,2′-AUR) (equation 170a), 6-[^{3}H]-2′-ClUdR has been prepared by reaction of $CaCl_2$ with 6-[^{3}H]-2,2′-AUR (equation 170b). Reaction of [^{18}F]-AHF with 2,2′-AUR, **310**, provided 2′-[^{18}F]-2′-FUdR, **311**, while the reaction of 2,2′-AUR, **310**, with [^{36}Cl]NaCl and TFA gave 2′-[^{36}Cl]-2′-ClUdR, **312** 2′-[^{34m}Cl]-2′-ClUdR has been similarly prepared using [^{35m}Cl]$MgCl_2$ or [^{34m}Cl] labelled Dowex 21-K anion exchange resin.

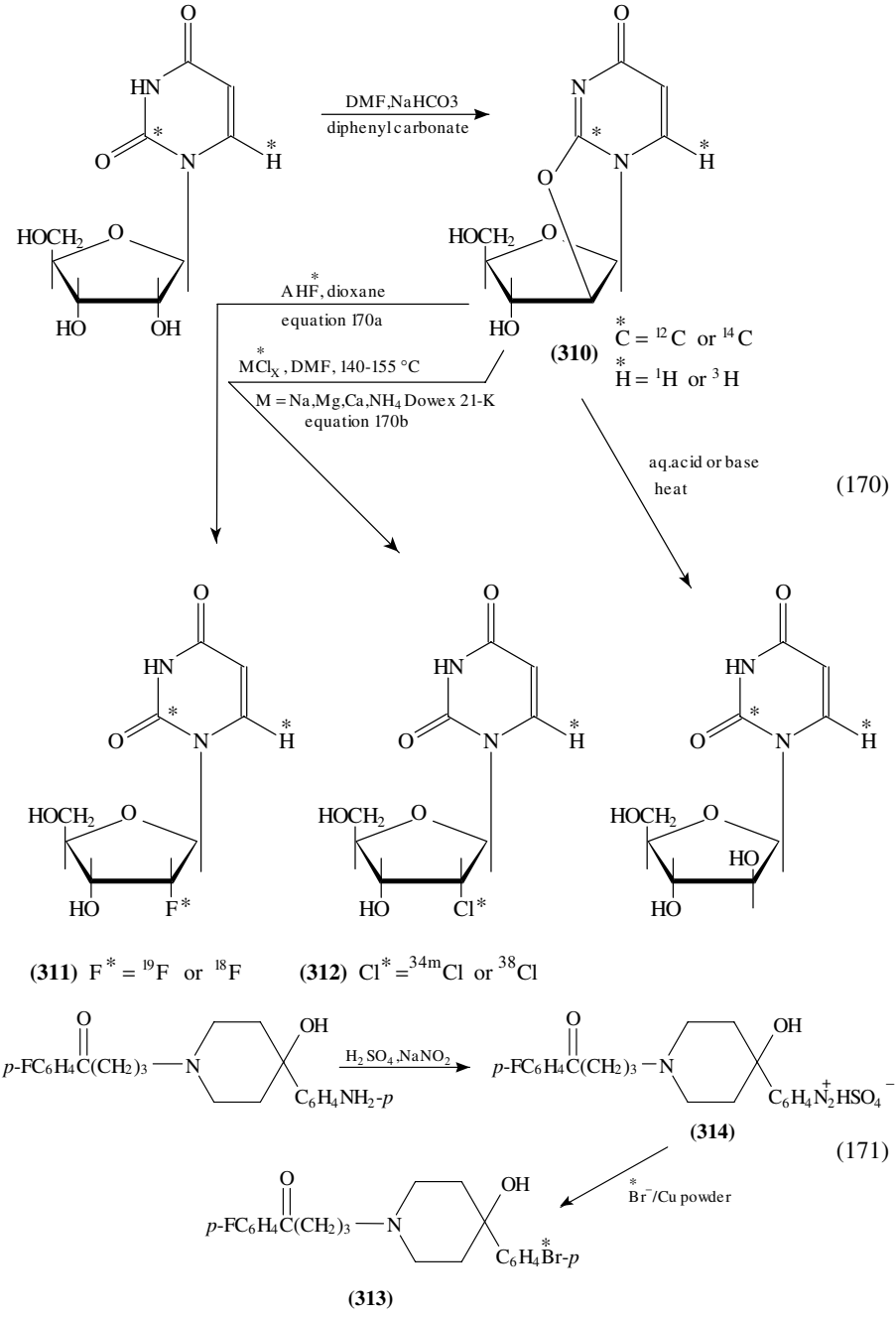
*2. Synthesis of bromperidol **(313)** labelled with ^{75}Br and ^{77}Br*

313, proved to be effective for the treatment of schizophrenia and to have high affinity to dopamine receptors[338–340], has been synthesized[341] from the diazotized precursor **314**, with NCA $^{75}Br^-$ or $^{77}Br^-$ (equation 171).

*3. Synthesis of radiobrominated spiroperidol **(315)***

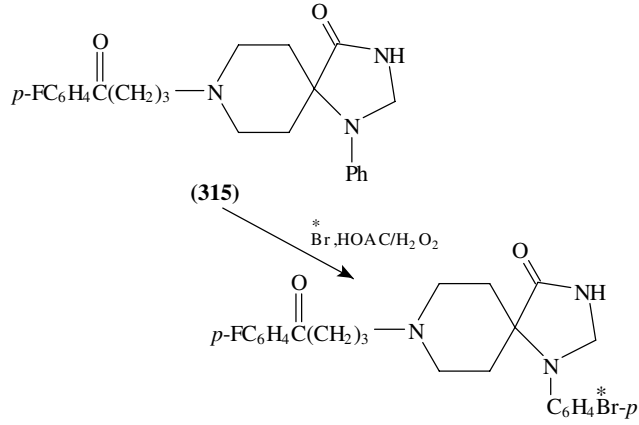
315, directed to DAD_2 receptors related to some neuropsychiatric disorders[342], has been labelled[343] with ^{75}Br, ^{76}Br and ^{77}Br in 80–90% radiochemical yields as shown[344]

in equation 172.



(170)

(171)

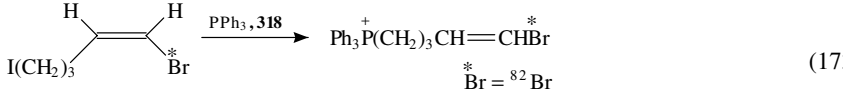


(172)

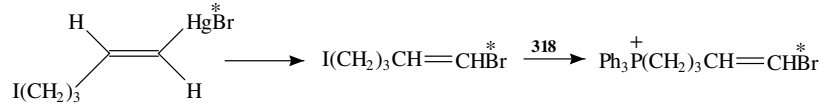
[^{76}Br]-*p*-bromospiroperidol (B*SP) and [^{77}Br]-*p*-bromospiroperidols have been used to determine non-invasively the time course of the uptake and the time course of the binding of *p*-bromospiroperidol in striatum and cerebellum of a rhesus monkey by PET and in rat striatum, frontal cortex and cerebellum, and the striatum to cerebellum uptake ratio[345].

4. Synthesis of {(Z) and (Z,E)-(1-[^{82}Br]bromo-1-penten-5-yl)}triphenylphosphonium cations ***(316)***

316-*Z* has been obtained[346] from **317**-*Z*[347], and phenylphosphine, **318** (equation 173). Similarly, condensation of **319** synthesized by bromodemercuration of **320**[348] with **318** provided **321** (equation 174).



(317) - *Z* (316) - *Z* (173)

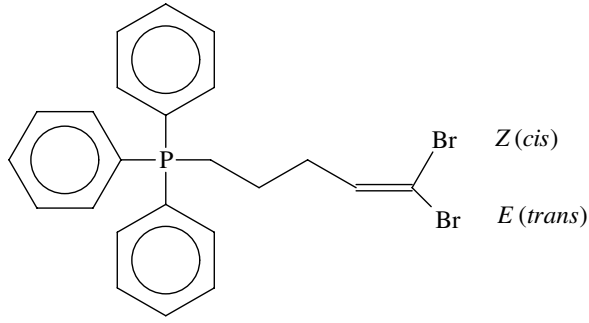


(320) (319) (321) - *Z* / *E* (174)

The structure of the **321**-*Z*/*E* mixture was confirmed by single-crystal X-ray analysis[349]. Both the *cis* isomer[^{82}Br], **316**, and the *cis/trans* mixture [^{82}Br]-**321**-*Z*/*E* showed high myocardial extraction[350] due to the *trans* membrane potential gradient and high heart/blood ratios[346]. This suggests that the corresponding ^{75}Br (half-life = 101 min) and ^{76}Br (half-life = 15.9 h) labelled agents could be good candidates for myocardial imaging by PET.

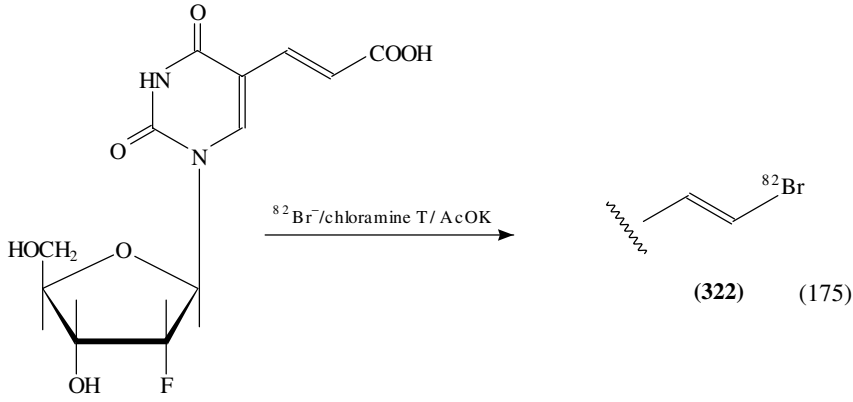
5. Synthesis of (E)-5-(2-[^{82}Br]bromovinyl)-1-(2-deoxy-2-fluoro-β-D-ribofuranosyl) uracil ***(322)***

[^{82}Br]BVFRU, **322**, has been synthesized[351] from CVFRU, **323** (equation 175).



(321) - *Z* / *E*

The antiviral activity of **322**, determined[351] using primary rabbit kidney cells injected with HSV-1 (*Herpes Simplex Virus* type 1), showed that BVFRU has antiviral potency and transport characteristics suitable for *in vivo* diagnosis of HSE (*Herpes Simplex Encephalities*) because of greater stability of bromine–carbon bonds than iodine–carbon bond present in [^{131}I]IVDU[352], [(*E*)-5-(2-iodovinyl)-1-(2-deoxy-β-D-ribofuranosyl)uracil].



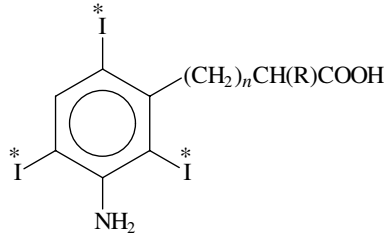
(323) **(322)** (175)

6. Synthesis of organic acids labelled with ^{125}I in pivalic acid melt

Radioiodination by isotope exchange with Na^{125}I in a melt of pivalic acid, Me_3CCOOH, has been applied[353] for the synthesis of a wide variety of compounds labelled with ^{125}I and with ^{123}I, currently the iodine nuclide of choice for scintigraphic imaging. The exchange reactions, proceeding rather by electrophilic than by nucleophilic mechanisms, were completed within 1–3 hours at 155 °C.

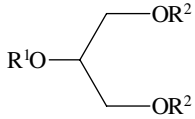
ω-(3-Amino-2,4,6-triiodophenyl)alkanoic aids **324** have been radioiodinated in 59–99% yields.

Esterification of glycerol with acids **324a–324e** provided a series of *mono*-, *di*- and *trisubstituted* triacylglycerols **(325)** in 70–99% radiochemical yields labelled with ^{125}I, Cholesteryl-ω-(3-amino-2,4,6-triiodophenyl)alkanoates have been ^{125}I-labelled in pivalic acid, also in high 94–98% yields.

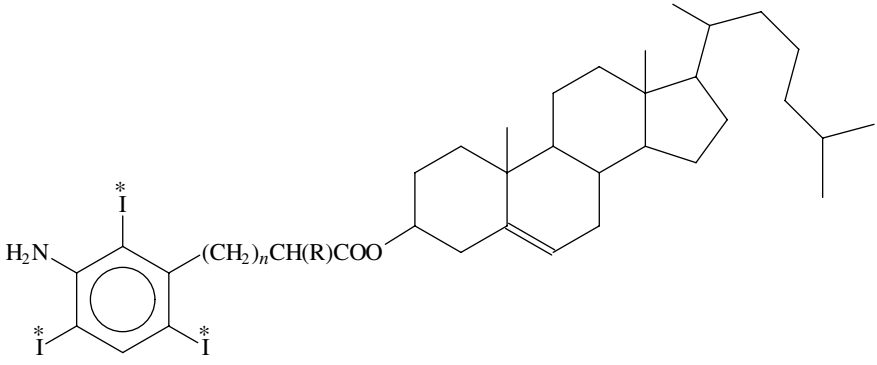


(324) **(a)** $n = 0$, R = H, exchange time = 2 h, yield = 59%
(b) $n = 1$, R = H, $t = 1$ h , yield = 99%
(c) $n = 1$, R = Et, $t = 1$ h , yield = 98%
(d) $n = 10$, R = H, $t = 1$ h , yield = 99%
(e) $n = 15$, R = H, $t = 3$ h , yield = 59%

(plus 31% side products)



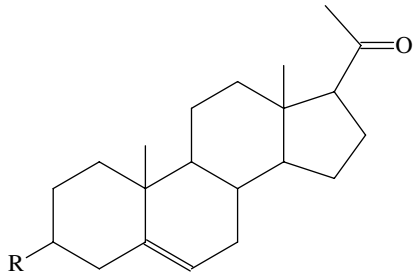
(325a) R^1 corresponds to acyl groups listed under **324** and R^2 to palmitate
(325b) or R^1 palmitate, R^2 = acyl groups listed under **324**
(325c) $R^1 = R^2$ = **324b** (92% yield after 2 h)
324c (70% yield after 6 h)
324d (93% yield after 1.5 h)
324e (80% yield after 2 h)



$\overset{*}{I} = {}^{125}I$

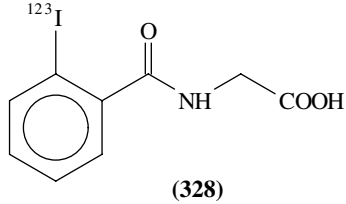
(326a) $n = 1$, R = H, 94% yield after 1 h
(326b) $n = 1$, R = Et, 98% yield after 1 h
(326c) $n = 10$, R = H, 95% yield after 3 h

Radioiodinated pregnenolone mono- and polyiodinated benzoate esters **327a–f** and carbonate **327g** have been obtained in pivalic acid with slightly lower yields.



(327a) R = 2,3,5-triiodobenzoate, 95% yield after 1 h
(327b) R = 3,4,5-triiodobenzoate, 99% yield after 1 h
(327c) R = 2,5-diiodobenzoate, 81% yield after 1 h
(327d) R = 2,-iodobenzoate, 82% yield after 1 h
(327e) R = 4-iodobenzoate, 81% yield after 1 h
(327f) R = 2,6-dimethyi-3-iodobenzoate, 63.5% yield after 1 h
(327g) R = 4-(4-iodophenyl)butyryl-carbonate, 68% yield after 1 h

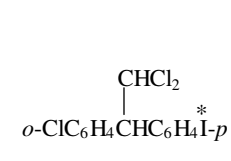
o-Iodohippuric acid (hippuran, **328**), a scintigraphic agent for assessing kidney function, has been radioiodinated in pivalic acid [353]similarly as had been done earlier[354].



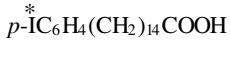
(328)

Other medically important compounds, such as the adrenal chemotherapeutic agent 5-iodotubercidin **(329)**, the adenosine kinase inhibitor, **330**, and the myocardial imaging agent 15-(4-iodophenyl)-pentadecanoic acid **(331)**, have been radioiodinated in pivalic acid[353] or in a melt of benzoic acid[355], also in high yields. 3-Iodobenzoic acid and 3-bromobenzoic acid were radioiodinated by interhalogen exchange in low yield[353] due to deactivation by the electron-withdrawing carbonyl group[256]. [U-^{125}I]iodoundecanoic acid has been synthesized[253] in 99% yield by ^{125}I for Br exchange[357] to give carrier-free iodoalkanoic acids.

The time and temperature dependencies of the radiochemical yield (%) have been investigated in the case of iopanoic acid **(324c)**[353]. The effect of medium (acetoamide, benzoic acid, pivalic acid) on the radioiodide exchange between Na^{125}I and cyclohexyl iopanoate has been studied at 155 °C for 1 h. The yields were decreasing in the following order: 78% (in pivalic acid) >65% (in benzoic acid) >9% (in acetamide). By increasing the amount of Na^{125}I and decreasing the amount of iopanoic acid, [^{125}I]iopanoic acid with a specific activity of over 700 Ci/mmol in 60% radiochemical yield has been achieved[353].

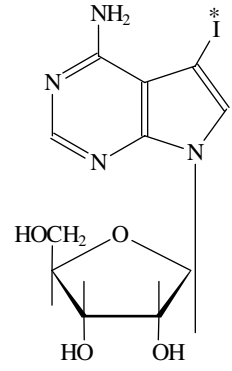


(329)



(331)

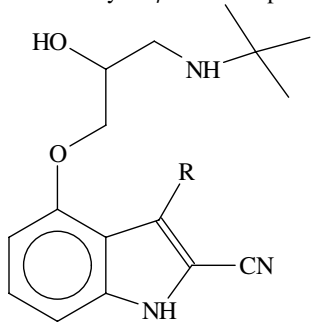
$^{*}I = {}^{123}I, {}^{125}I$



(330)

7. Synthesis of NCA(−)-[^{123}I]iodocyanopindolol ***(332)***

332, a high-affinity β-adrenergic antagonist, has been synthesized[358] for SPECT evaluation of cardiac adrenergic receptor density by a modified chloramine-T radioiodination of (−)cyanopindolol, **333**, with Na[^{123}I]iodide followed by a novel reversed-phase HPLC purification, in 59% radiochemical yield (16 mCi). The radiosynthetic procedure will be automated to minimize radiation exposure. The commercially available (−)-[^{125}I]iodocyanopindolol (specific activity 2175 Ci/mmol) has been used previously for intensive study of β-adrenoceptors[359,360].

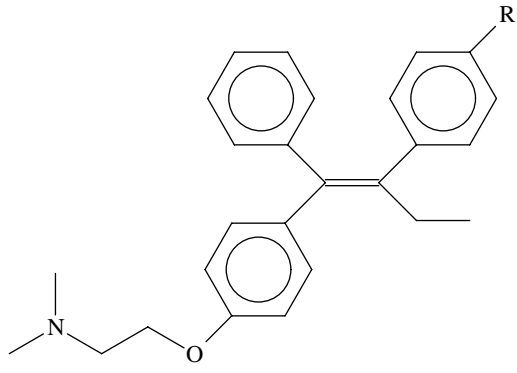


(332) R = ^{123}I
(333) R = H

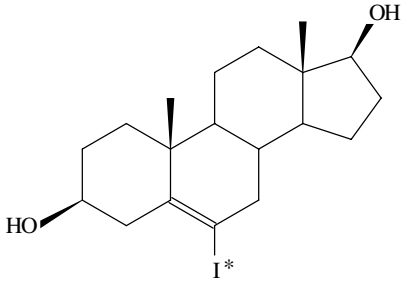
8. Synthesis of [^{131}I]iodotamoxifen ***(336)***

Tamoxifen, **334**, employed for treatment of breast tumors which are estrogen receptor positive[361], has been labelled[362] with NCA ^{131}I via an aryl diazonium salt intermediate, **335** (equation 176), for detection of breast tumors[362].

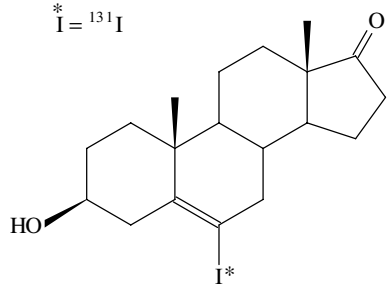
$$\textbf{335}\cdot \text{ hexafluorophosphate } (PF_6^-) \xrightarrow[\text{MeCN, } 82^{\circ}\text{C, 1 min}]{Na^{131}I} \textbf{336} \qquad (176)$$



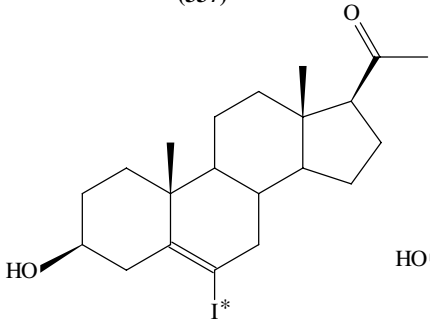
(334) R = H; **(335)** R = N_2^+; **(336)** R = ^{131}I



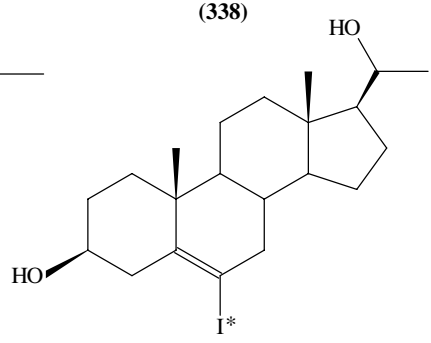
(337)



(338)



(339)

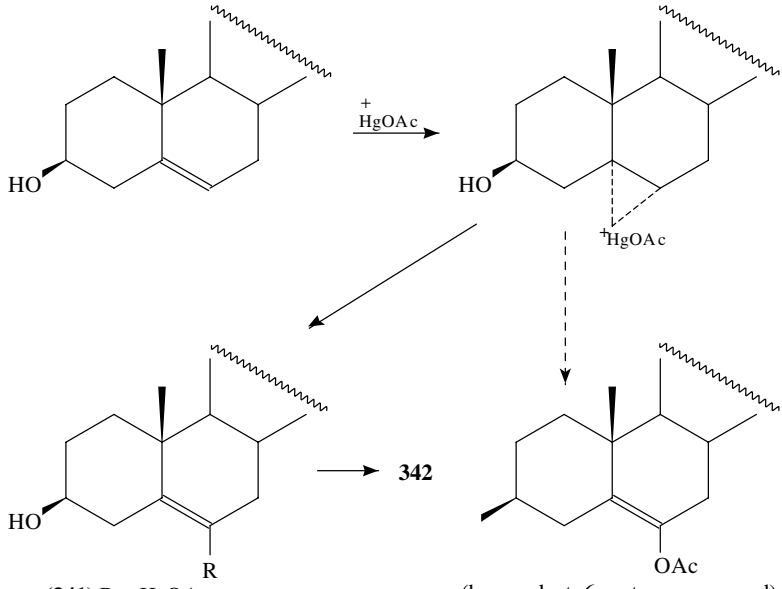


(340)

9. Synthesis of [^{131}I]-6-iodo-androsten-5-enes and [^{131}I]-6-iodo-pregnen-5-enes

The 6-iodo-steroids, [^{131}I]-6-iodoandrost-5-en-3β,17β-diol, **337**, [^{131}I]-6-iodoandrost-5-en-3β-ol, 17-one, **338**, [^{131}I]-6-iodo-preg-5-en-3β-ol-20-one, **339** and [^{131}I]-6-iodopregn-5-en-3β,20-diol, **340**, have been synthesized[363–366] by direct mercuration of the parent Δ-5 steroids with mercuric acetate followed by conversion of the 6-acetoxymercury compound **341** into **342** by exchange with sodium chloride, and subsequent treatment of **342** with [^{131}I]sodium iodide in the presence of chloramine-T in 20% H_2O in EtOH

(equation 177).



(177)

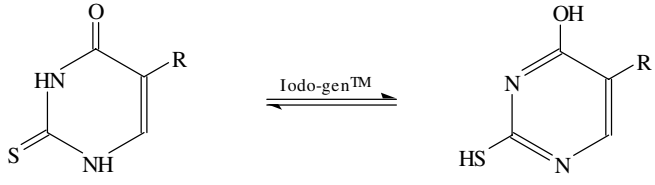
(341) R = HgOAc
(342) R = HgCl

(by-product, 6-acetoxy compound)

The tissue distribution study of these NCA[^{131}I]-6-iodo-steroids in liver, spleen, adrenal, stomach, tyroid and lung showed a very rapid adrenal uptake with a peak value (in rats) at 15 min post-injection or at even shorter time periods[363].

*10. Synthesis of 5-iodo-2-thiouracil (ITU) **(343)** labelled with ^{123}I, ^{125}I and ^{131}I*

ITU, **343**, able to bind specifically to the pigment melanin during melanogenesis, is of potential value in the diagnosis and treatment of malignant melanoma[367,368]. ITU labelled with radioiodine has been synthesized[369] for melanoma therapy experiments directly from 2-thiouracil using commercially available Iodo-Gen™ in 0.05M phosphate buffer pH 7.0 (equation 178). Iodo-Gen™ (1,3,4,6-tetrachloro-3α,6α-diphenylglycoluril generates the reactive electrophilic I^+ species).



(178)

2-thiouracil, R = H (TU),

(343) 5-iodo-2-thiouracil, R = I* (I*TU)

I* = ^{123}I, ^{125}I, ^{131}I

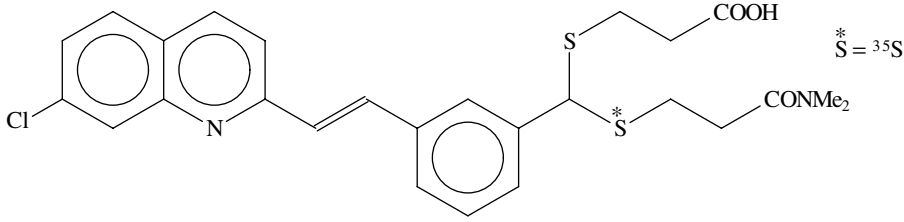
[^{125}I]ITU has been applied in clinical trials for distribution and clearance studies, [^{123}I]ITU for the whole body imaging studies and [^{131}I]ITU to successfully treat the Harding–Passey melanoma carried in Balb/c mice[369].

In previous methods of electrophilic radioiodination the sulphur has been protected by a methoxymethyl group[370] or a benzyl group[371] which had to be removed.

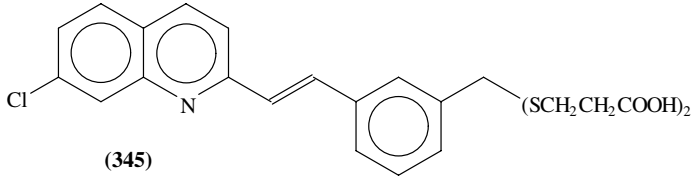
VI. SYNTHESIS AND USES OF COMPOUNDS CONTAINING C=C, C=O, OR CN GROUPS LABELLED WITH RADIOACTIVE SULPHUR

*1. Synthesis of 5{3-[2-(7-chloroquinolin-2-yl)ethenyl]phenyl}-8-dimethylcarbamyl-4,6-[6-^{35}S]dithiooctanoic acid **(344)***

MK-0571, **344**, potent antagonist of LTD_4[306], has been synthesized[307] to evaluate the role of leucotriene D_4 in human disease states. **344** has been obtained by exchange between diacid **345** and 3-[^{35}S]mercaptopropanoic acid in trifluoroacetic acid (equation 179). **346** has been generated from **348** prepared as shown in equations 180 and 181.



(344)



(345)

(179)

CF_3COOH, 1h

$H^{35}SCH_2CH_2CONMe_2$ **(346)**

344 (45% yield) + **345** + $\overset{*}{(SCH_2CH_2CONM_2)_2}$

(347)

$Ph_3COH \xrightarrow{H_2{}^{35}S,CF_3COOH} Ph_3C^{35}SH \xrightarrow[MeCN, DBU]{CH_2=CHCONMe_2} Ph_3C^{35}SCH_2CH_2CONMe_2$

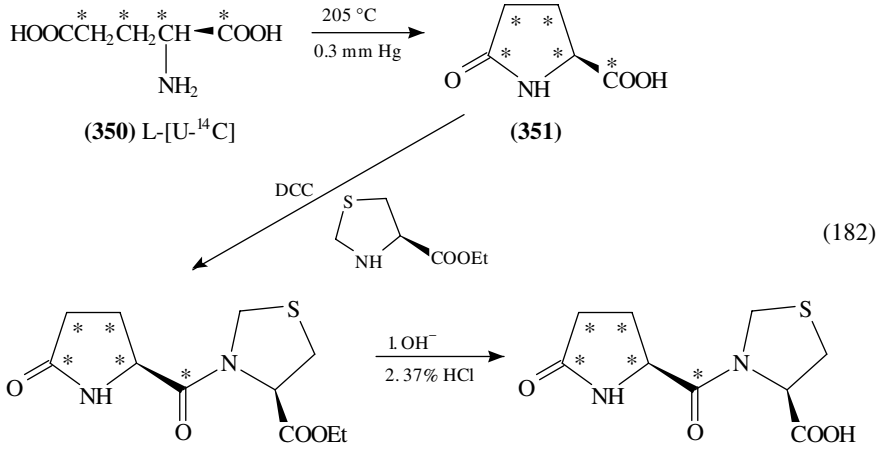
(348) (180)

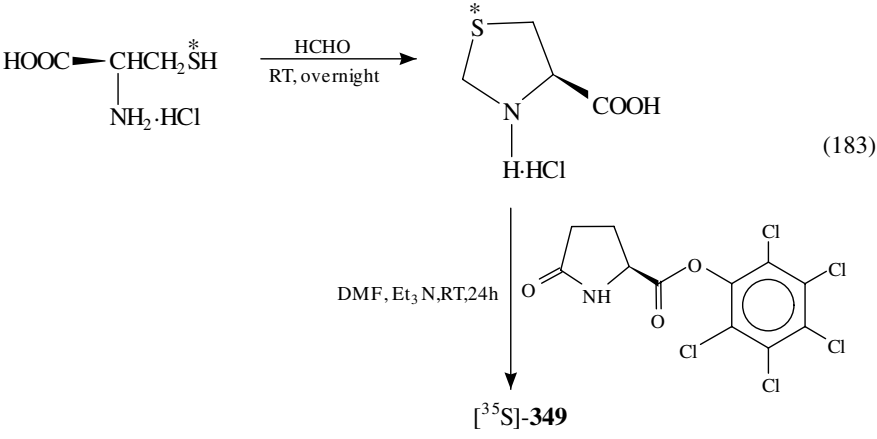
$Ph_3CH \xrightarrow[3.\ n\text{-}Bu_3P\ 4.\ CF_3COOH]{1.\ n\text{-}BuLi,\ THF\ 2.\ [^{35}S]sulphur} Ph_3C^{35}SH \longrightarrow Ph_3C^{35}SCH_2CH_2CONMe_2$ (181)

(348)

*2. Synthesis of pidotimod **(349)** labelled with ^{14}C- and ^{35}S-isotopes*

The ^{14}C-labelled **349**, the new immunostimulating agent with a peptide-like structure, has been synthesized[372] from **350** (equation 182). [^{35}S]-Pidotimod-**349** has been prepared[372,373,374a] as shown in equation 183, [^{14}C]- and [^{35}S]-**349** have been needed to study the pharmacokinetics and metabolism of **349** in immunodeficiencies. **349** increases cell-immediate immune response by stimulation of IL-**351** production[374b,374c].





(183)

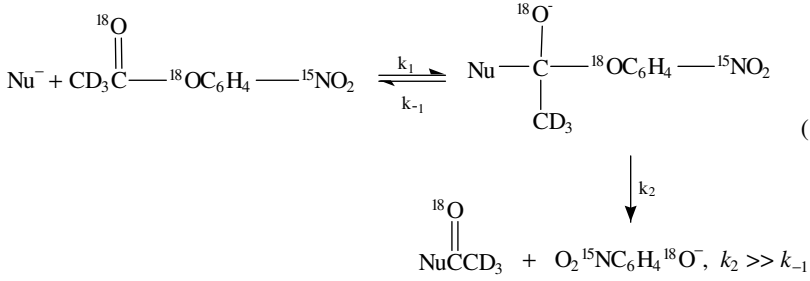
VII. ISOTOPE EFFECT STUDIES

A. Isotope Effect Studies of Chemical Reactions

1. Oxygen-18, nitrogen-15 and β-deuterium isotope effects in the transfer reactions of p-nitrophenyl acetate (PNPA) with various nucleophiles

The ^{18}O, ^{15}N and $\beta-^{2}H$ isotope effects in the acyl transfer reactions of PNPA (equation 184) have been studied[375], and the conclusion has been reached that these

transfers are concerted with no stable tetrahedral intermediate of a significant lifetime.



(184)

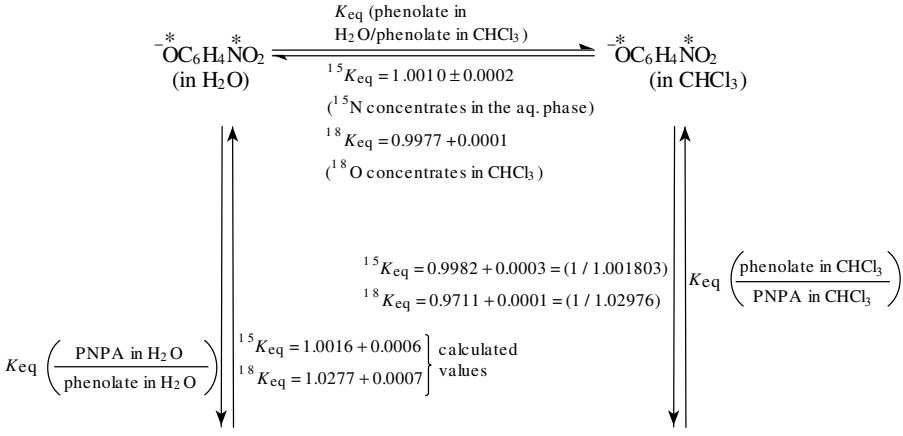
where:

Nu^- = hydroxide	^{15}k: 1.0002 ± 0.0001
(pK = 15.7)	$^{18}k_{lg}$: 1.0135 ± 0.0007
(room temperature)	$^{18}k_{carbonyl}$: 1.0039 ± 0.0003
(pH of 9.5)	D_k (for 3 deuterium atoms, CD_3): 0.9562 ± 0.0008
Phenolate (pK = 9.9)	^{15}k: 1.0010 ± 0.0002
(ice bath temperature)	$^{18}k_{lg}$: 1.0199 ± 0.0009
pH of 9.7)	$^{18}k_{carbonyl}$: 1.0043 ± 0.0008
	$D_k(D_3)$: 0.9583 ± 0.0010
$(CF_3)_2CHO^-$	^{15}k: 1.0010 ± 0.0002
(pK of 9.3)	$^{18}k_{lg}$: 1.0210 ± 0.0010
(RT, pH 9)	$^{18}k_{carbonyl}$: 1.0058 ± 0.0006
	$D_k(D_3)$: 0.9481 ± 0.0030
mercaptoethanol	^{15}k: 1.0001 ± 0.0003
(pK = 9.5)	$^{18}k_{lg}$: 1.0219 ± 0.0009
(RT, pH 9)	$^{18}k_{carbonyl}$: 1.0119 ± 0.0003
	$D_k(D_3)$: 0.9780 ± 0.0008
anion of $HSCH_2CH_2COOMe$	^{15}k: 1.0003 ± 0.0001
(pK = 9.3)	$^{18}k_{lg}$: 1.0172 ± 0.0004
(RT, pH 9)	$^{18}k_{carbonyl}$: 1.0117 ± 0.0004
	$D_k(D_3)$: 0.9765 ± 0.0006
methoxyethylamine	^{15}k: 1.0011 ± 0.0001
(RT, pH 9)	$^{18}k_{lg}$: 1.0330 ± 0.0007
	$^{18}k_{carbonyl}$: 1.0064 ± 0.0003
	$D_k(D_3)$: 0.9682 ± 0.0010

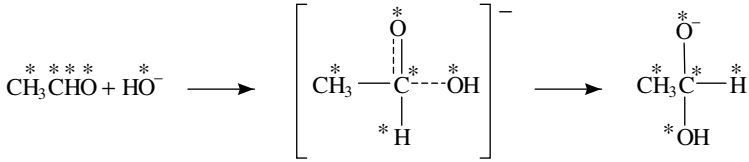
The RT (at pH 9) equilibrium isotope effect determinations are presented in the upper, lower and right-hand side of equation 185. They have been used to calculate the isotope effect for the equilibrium between *p*-nitrophenolate and PNPA in water since the PNPA undergoes hydrolysis during the equilibrium. The $^{18}K_{eq}$ isotope effect for deprotonation was found to be 1.01533. The earlier reported value[376] was 1.018 ± 0.002.

The computed $^{18}K_{carbonyl}$ oxygen isotope effects for the conversion of the carbonyl double bond of the reactant to the nearly single bond of a tetrahedral intermediate are about 1.025 for the very late transition state[377–379]. The computed D_k values have been estimated to be 0.89 (inverse, also for a very late TS of the formation of tetrahedral intermediate). In the concerted mechanism (equation 186) the carbonyl π-bond may not be

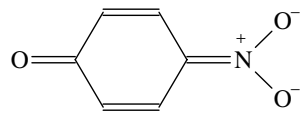
altered. In this study the $^{18}k_{carbonyl}$ is in the range 1.0039–1.0058 for oxyanion reactions, indicating some tetrahedral character in the TS only. The magnitudes of the isotope effect for the *p*-nitrophenyl leaving group are lower than those expected for an alkyl leaving group due to the contribution of the resonance structure which compensates to some extent the loss of the bond order to the carbonyl carbon in the TS. In the reaction with both phenolate nucleophiles the nitrogen-15, ^{15}k, effects are nearly unity. The magnitudes of $^{18}k_{carbonyl}$ effects in reactions with thiolates are twice those of the oxyanion reactions, indicating greater loss of carbonyl π-bond and the TS structure shown below.

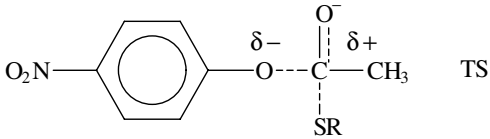


(185)



(186)



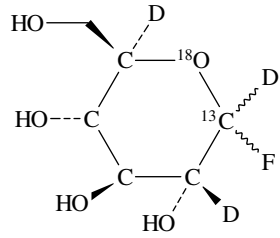


TS

The differences between hydrosulphide and hydroxide have been investigated theoretically in the case of carbonyl addition reactions to formaldehyde and formamide[380]. The data for the reaction of PNPA with methoxyethylamine indicate that the bond cleavage to the leaving group takes place in the rate-limiting step of this last reaction to a higher degree than in the case of other nucleophiles, and/or smaller charge delocalization which reduced the $^{18}K_{lg}$ values in the previous reactions more than one-half. The maximum ^{18}O KIE (value of reduced partition function = 1.0408) for ^{12}C-$^{16}O/^{12}C$-^{18}O bond rupture equals 1.0665 at 25 °C. No temperature dependence of the above KIEs have been studied. The $^{1}H/^{2}H$, $^{12}C/^{13}C$, and $^{16}O/^{18}O$ KIE and equilibrium IE have been computed[378].

2. Deuterium, carbon-13 and oxygen-18 KIE in the hydrolyses of α- and β-glucopyranosyl fluorides

The kinetic isotope effects k_{light}/k_{heavy}, for the hydrolysis at pH 6.0 of α-glucosyl fluoride at 80 °C and β-glucosyl fluoride at 50 °C, isotopically substituted as shown in structure **352**, have been found[381] to be as follows:



(352)

for α-D ($C_{(1)}$) site: 1.142 ± 0.0075 and 1.086 ± 0.0012,
for β-D ($C_{(2)}$) site: 1.067 ± 0.0077 and 1.030 ± 0.0083,
for γ-D ($C_{(5)}$) site: 0.979 ± 0.0032,
for anomeric [1-^{13}C]: 1.032 ± 0.0032 and 1.017 ± 0.0022,
for ring ^{18}O: 0.984 ± 0.0049 and 0.985 ± 0.0049,

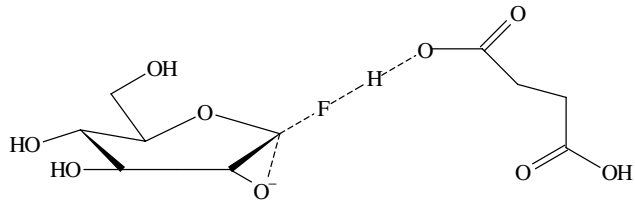
In the reaction of the α-glucosyl fluoride with azide ion, the α-D effect increased modestly to 1.169 ± 0.0082 while the [1-^{13}C] effect increased to 1.085 ± 0.0082.

In the hydrolysis of glucosyl fluoride in 0.3 M sodium succinate buffer (pH 6.0, I = 1.0 M $NaClO_4$) at 50 °C, the KIEs are as follows:

for α-D: 1.105 ± 0.0053,
for β-D: 1.059 ± 0.0010,
for (5-D): 0.981 ± 0.0074,
for anomeric [1-^{13}C]: 1.064 ± 0.0070,
for ring [5-^{18}O]: 0.988 ± 0.0036.

BEBOVIB-IV-TS structure for α-glucosyl fluoride hydrolysis involving the ring in a flattened $^{4}C_{1}$ chair conformation and water and fluoride ion about the anomeric centre has been presented[381,382]. The conformations based on this structure reproduced well the α-D, β-D, 5-D and [5-^{18}O] experimental KIE, but not the [1-^{13}C] KIE (theor. KIE = 1.023 compared with 1.032 for exp. KIE).

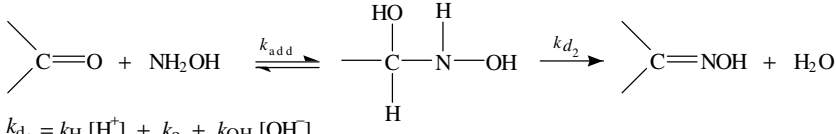
The qualitative TS structure for succinate-catalyzed hydrolysis of β-glucosyl fluoride, shown as **353**, has been proposed[381].



(353)

3. Deuterium IE study of oxime formation

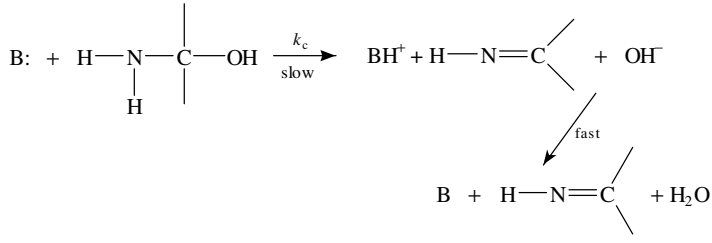
The rate-determining step of the oxime formation from carbonyl compounds (equation 187) changes with increasing pH from formation of the addition intermediate to its dehydration to the products.



$$k_{d_2} = k_H [H^+] + k_o + k_{OH} [OH^-] \qquad (187)$$

At pD 6.9 (calculated from the relation pD = pH+0.4) the solvent DIE in the oxime formation from hydroxyamine with cyclohexanone and bicyclic ketones equals[383] $(k_H/k_D) = 1.50 \pm 0.05$ and the reaction occurs via a rate-limiting dehydration of the addition intermediate being in equilibrium with the ketone and hydroxyamine. The TS of the acid catalyzed reaction (pH 4 to *ca* 8) is characterized by a moderate cleavage of the C−O bond[384] with the carbon atom nearer to sp^3 than to sp^2. In the pH-independent region (pH 8 to *ca* 10) the TS with more extensive C−O cleavage and with the carbon atom nearer to sp^2 than to sp^3 has been assumed. The deuterium solvent IE of 1.50 in neutral solution also indicates that not the N−D bond rupture but the C−OD bond rupture is rate-determining.

Two mechanisms shown in equations 188 and 189 have been proposed[385] (pH 10 to *ca* 13).

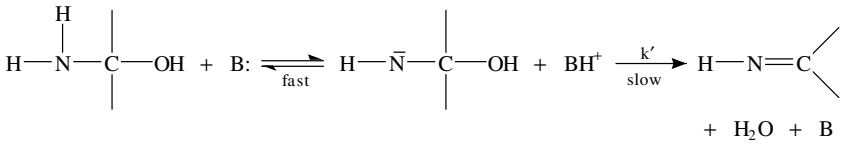


(188)

In the base-catalysed dehydration for oxime formation a significant development of the carbon−nitrogen double bond in the TS is assumed.

4. Deuterium IE studies with malonamide

In the course of mechanistic studies of the nitrosation (equation 190), bromination and iodination of malonamide (MA), proceeding according to the mechanism involving



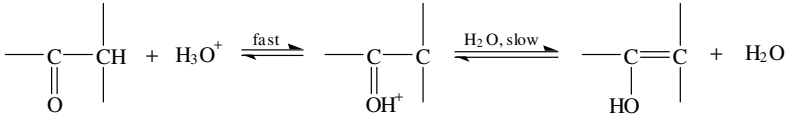
$k' = K_c K_w / K_a$ (K_w = dissociation constant of water, K_a = dissociation constant of α-aminoalcohol as acid) (189)

the reaction of the electrophile with an intermediate, suggested to be the enol tautomer (equation 191–193), the substrate kinetic isotope effect $(k_e)_H/(k_e)_D$ of 2.30 and 2.20 for $CD_2(COND_2)_2$ and values of the solvent isotope effect $(k_e)H_2O/(k_e)D_2O$ of 1.09 and 1.05 have been observed[386] for iodination under zero-order conditions, when enolisation is rate-limiting. In the absence of mineral acid the disappearance of resonance of the methylene proton NMR at δ 5.7 was 80% complete in one day. In the presence of D_2SO_4 the H/D exchange was 89% complete in 5 min and 96% complete in 12 min (at 25 °C). The KIE of 2.2–2.3 found in enolization of MA, when methylene protons were replaced by deuterium, is significantly smaller than the value $k_H/k_D = 6.7$ found for acetone enolization[387]. Maximum isotope effects are expected to occur when $\Delta pK \equiv 0$, and are smaller for both the 'early' and the 'late' TS. The greater acidity of the protons in MA than in acetone should be responsible for the observed difference in KIE. Kinetic solvent isotope effects[387–389], k_{H_2O}/k_{D_2O}, are usually around 0.5.

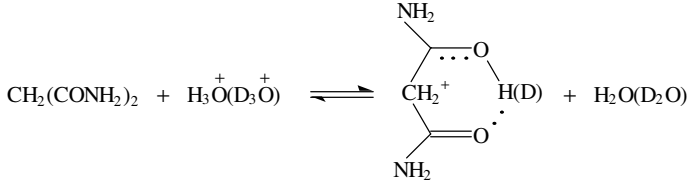
$$CH_2(CONH_2)_2 + HNO_2 \xrightarrow{H^+} HON{=}C(CONH_2)_2 + H_2O \tag{190}$$

$$MA \overset{k_e[H^+]}{\rightleftharpoons} Enol \tag{191}$$

$$Enol + I_2 \xrightarrow{k} Product \tag{192}$$



The near-unity values of 1.09 and 1.05 for enolisation of MA in $(H_2SO_4–H_2O)/(D_2SO_4–D_2O)$ and DMA (deuteriated malonamide, $CD_2(COND_2)_2$) in $(H_2SO_4–H_2O)/(D_2SO_4–D_2O)$ are explained by assuming that the normal (i.e. about 0.5) IE is offset by the isotope effect in intramolecular hydrogen-bonding shown in equation 194.



5. Aqueous diazene and its dismutation in fully deuteriated medium

Aqueous 1,2-diazene, N_2H_2, the optically detected intermediate in the acid-assisted hydrolysis of azodiformate (equation 195), believed to be also an intermediate in certain

oxidations of hydrazine[390,391], undergoes a second-order concerted dismutation on a time scale longer than that of its generation when the hydrolysis is conducted[392] at pH ≈ 4 (equation 196). The overall DKIE, $k_{1(H)}/k_{1(D)}$, when the dismutation reaction (equation 196) has been conducted in fully deuteriated medium, was 3.3 ± 0.5. This value (sum of the primary, secondary and solvent IEs) is consistent with a significant degree of hydrogen atom transfer in the TS. A two-step mechanism of decay of aqueous diazene has been proposed (equation 197 and 198).

$$(NCO_2)^{2-} + 2H^+ \xrightarrow{\text{fast}} N_2H_2 + 2CO_2 \tag{195}$$

$$2N_2H_2 \xrightarrow{k_1} N_2 + N_2H_4 \tag{196}$$

$$trans - N_2H_2 \rightleftharpoons cis - N_2H_2 \; k_{(trans-cis)} \tag{197}$$

$$cis - N_2H_2 + trans - N_2H_2 \xrightarrow{k_{(2H)}} N_2 + N_2H_4 \tag{198}$$

In the rapid pre-equilibrium the high-energy *cis*-isomer is formed, and double hydrogen atom transfer takes place in the last step. It is likely that the value KIE = 3.3 will be typical of other hydrogenations by diazene[392].

6. Deuterium isotope effects in the reactions of 2-nitroso-2-methyl propane with formaldehyde, glyoxylate, glyoxylic acid, pyruvic and phenylglyoxylic acid

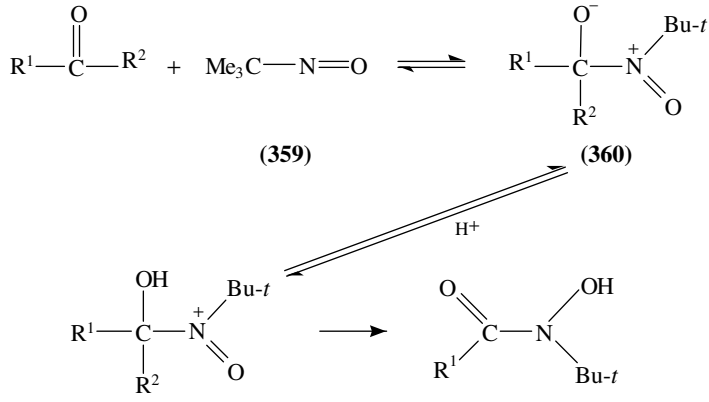
All the title reactions, involving the dipolar addition intermediates (equation 199), yield the corresponding *N-t*-butyl hydroxamic acids[393]. The aliphatic C-nitroso group acts as nucleophile in the reaction steps leading to the formation of these intermediates. The inverse solvent deuterium isotope effect (k_{D_2O}/k_{H_2O}) of 2.02 observed in the reaction of **359** with formaldehyde, **354**, producing *N-t*-butyl formohydroxamic acid, is interpreted as arising in the reversible equilibrium proton transfer to the intermediate **360**. The primary kinetic isotope effect (k_H/k_D) of 4.52 for HCHO and DCDO used in reaction 199 is consistent[394] with a rate-controlling proton transfer from carbon of the nitrosocarbinolic intermediate **361** leading to hydroxamic acid **362**.

The solvent deuterium isotope effect in the reaction of **359** with glyoxylate decreases from (k_{H_2O}/k_{D_2O}) of 1.66 to (k_{H_2O}/k_{D_2O}) of 1.17 with increasing pH from 1.25 to 6.43, respectively. **361** probably decarboxylates via a cyclic transition state. Transfer of the carboxylic proton takes place simultaneously with heavy-atom reorganization as indicated by small solvent DIE in the acid-catalysed reaction. The solvent DIE k_{H_2O}/k_{D_2O} of 1.20 at 1. M H^+, observed in the reaction of **359** with pyruvic acid, is similar to the reaction of pyruvic acid with nitrosobenzene for which nucleophilic attack of nitroso nitrogen has been proposed[395].

7. Deuterium KIE in the metalation of imines by lithium diisopropylamide

The deuteriated (97%) imines **363** and **365**, and the hydrazone **364** have been prepared[396–399] by treating 2,6,6-trideuterio-2-methylcyclohexanone and 2,2,6,6-tetradeuteriocyclohexanone with the corresponding deuteriated ammonium salts (RND_3Cl) and used in the KIE studies of the metalation of the above 'C=N' compounds with lithium diisopropylamide (LDA) in THF, in *N*, *N*, *N′*, *N′*-tetramethyl ethylenediamine (TMEDA) and in dimethylethylamine (DMEA) solvents (equation 200). The rates, d[imine]/d*t* of that of imines **363** and **364** metalation are zero order with respect to [THF], [TMEDA]

and [DMEA] concentrations in hexane, 1/2 order with respect to [LDA] and first order with respect to [imine] (equation 201).



(359) **(360)**

(199)

(361) **(362)**

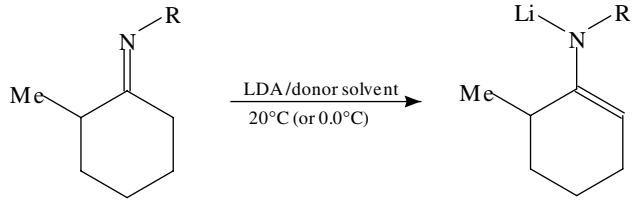
(354) $R^1 = R^2 = H$

(355) $R^1 = H$, $R^2 = COO^-$

(356) $R^1 = H$, $R^2 = COOH$

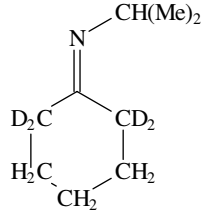
(357) $R^1 = Me$, $R^2 = COOH$

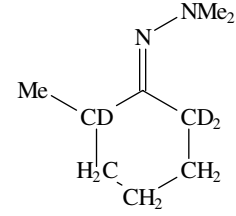
(358) $R^1 = Ph$, $R^2 = COOH$



(200)

$$d[imine]/dt = k'[imine]\ [LDA]^{1/2}[TMEDA]^0 \quad (201)$$





(363) k_H / k_D (temp. °C, solvent)

11.2 ± 2.0 (20°C, THF / hexane)

6.2 ± 1.2 (20°C, TMEDA / hexane)

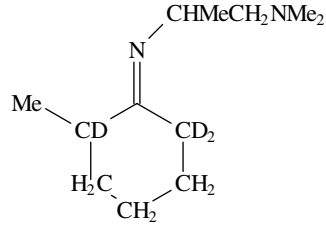
7.7 ± 1.0 (20°C, DMEA / hexane)

(364) k_H / k_D (temp. °C, solvent)

6.4 ± 0.6 (0.0°C, THF / hexane)

8.3 ± 1.2 (0.0°C, TMEDA)

6.9 ± 1.8 (0.0°C, DMEA)
(rapid metallation at 20°C)



(365) k_H / k_D (temp. °C, solvent)

>5 (0.0°C,THF/hexane), very slow reaction

2.0 ± 0.1(0.0°C, TMEDA)

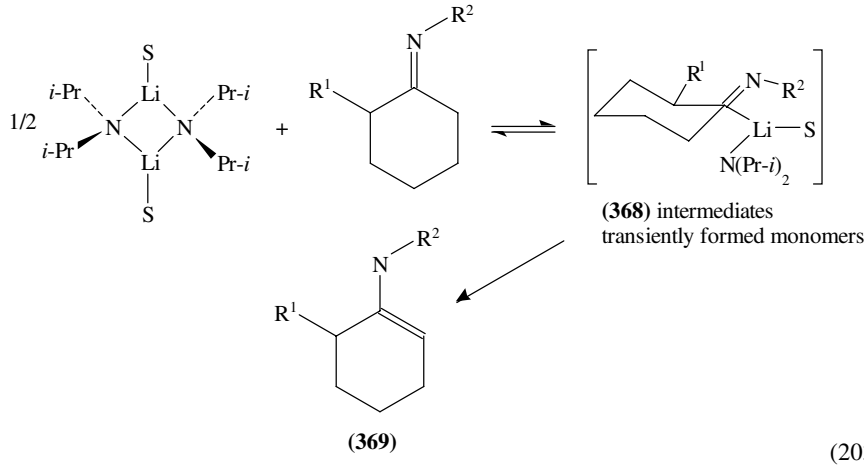
2.3 ± 0.1(0.0°C, DMEA)

Metallation rates determined by monitoring the loss of the C=N stretch of the starting imine (1656 – 1660 cm^{-1}) were comparable (±10%) with rates determined by monitoring product formation (1590 – 1600 cm^{-1})

In the case of imine **365**, an inverse second-order dependence on [TMEDA] and [DMEA] has been observed (equation 202).

$$d[\text{imine}]/dt = k''[\text{imine}]\ [\text{LDA}]\ [\text{TMEDA}]^{-2} \tag{202}$$

A suggestion has been made[397] that **364** and **363** are metallated by monomer-based mechanisms shown in equation 203.



(368) intermediates transiently formed monomers

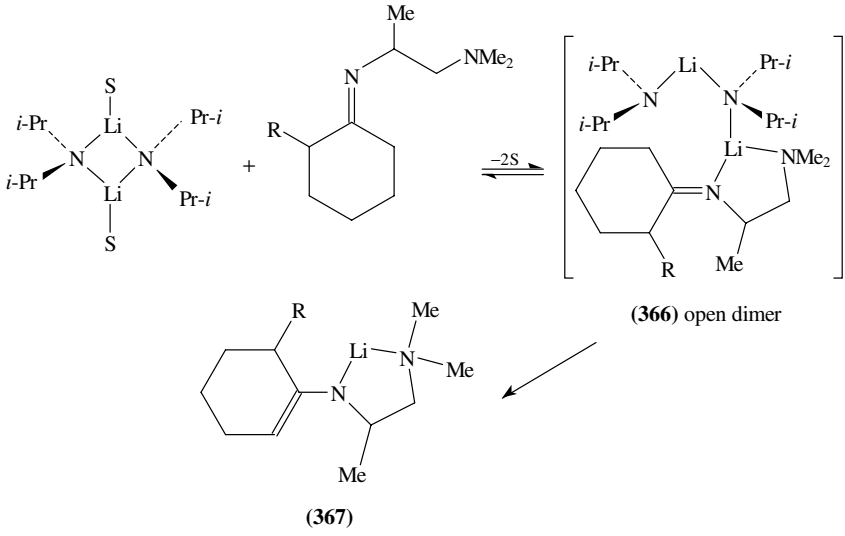
(369)

(203)

Metallation of **365** in THF/hexane mixtures is also described by rate equation 201, but that of **365** ('bearing pendant Me_2N moieties') in TMEDA and DMEA, described by rate equation 202, suggests a mechanism involving rate-limiting metallation via dimeric LDA dimer stripped free of donor solvents, shown in equation 204.

These problems have been discussed extensively, reviewed and a conclusion has been reached that the proton abstraction in intermediate **366** leading to **367** proceeds through the 'optimal' eight-membered transition structure ring size[397]. The values of deuterium

KIEs shown under structures **363**, **364** and **365** clearly indicate that the rupture of the $C_{(6)}-D$ bonds are involved in the metallation of **363** and of **364** in the rate-determining step and the TS structure shown in equation 203 is a symmetric one. The (k_H/k_D) value of 11.2 ± 2.0 observed at 20 °C in the metallation of **363** in THF/hexane mixture suggests that the transfer of proton from the $C_{(6)}-H$ bond to nitrogen of the solvated lithium diisopropylamide in **368** is accompanied by tunneling. The (k_H/k_D) values of 2.0 observed at 0.0 °C in TMEDA/hexane and in DMEA/hexane solvents (2.3 at 0.0 °C) in the lithiation of **365** with solvent-free LDA dimer are characteristic for asymmetric TS in hydrogen abstraction-transfer processes. The detailed timing of bond changes in **366** leading to **367** is a KIE computational problem as well as an experimental one to be solved and completed.



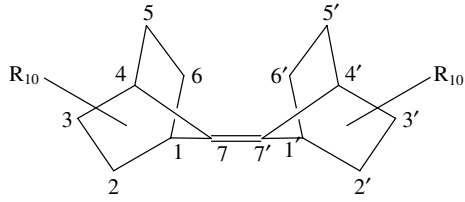
(204)

*8. Inverse deuterium KIEs in the bromination of perdeuteriated 7-norbornylidene-7′-norborane **370***

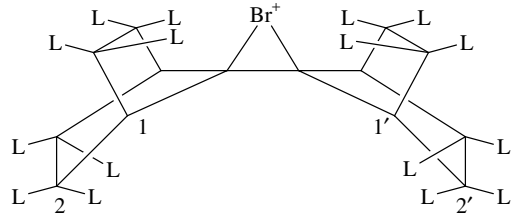
Large inverse DKIE have been observed[400] in the reaction[402] of **370** and **371** with Br_2 in AcOH and MeOH at 25 °C in the presence of LiBr, and explained by a pronounced steric DKIE[401,403] on the partitioning of a reversibly formed bromonium ion **372**. There is less compression of the *endo* C-L groups in the rate-limiting TS for electrophilic addition to **371** (D_{20} species) than to **370** (H_{20} species).

In AcOH, the DKIE increase from 1.53 (at M = 0.1 $LiClO_4$) at zero added $[Br^-]$ to 2.75 at $[Br^-] = 0.05$ M. In MeOH, the inverse DKIE is practically independent of the added $[Br^-]$ and equal to 1.85 ± 0.15. In AcOH, the amount of dibromide product increases up to 82.6 5 with increasing $[Br^-]$ to 0.05 M. In MeOH, the methoxy bromide is the prominent product[400] even at the highest $[Br^-]$.

The inductive effect of the donating C−D bonds to the observed large inverse secondary deuterium isotope effect has not been given proper consideration but treated as a rather minor component superimposed on the important steric component caused by larger amplitudes of vibrations of C−H bonds than those of the C−D bonds. ^{14}C KIE have not been studied in this reaction. The C_2, C_2‘, C_3‘, C_3, *endo* hydrogens are separated only by 2.11 Å, substantially less than van der Waals radii (2×1.2 Å)[404].



(370) R = H, **(371)** R = D



(372)

9. Secondary β-tritium IEs in elimination reactions

The secondary tritium, H/T and D/T IEs in E2 reactions of $RNMe_3{}^+Br^-$, where R = *p*-$CF_3PhCLTCH_2$, **373**, L = H or D; R = $PhCHCL_2T$, **374**, L = H or D; R = *p*-ClPhCLTCHPh, **375**, L = H or D, defined in the case of **373** by equations 205, 206 and 207, have been determined[405] in the temperature interval 29.60–74.00 °C.

$$ArCL_2CH_2X + RO^- \xrightarrow{2k_1} ArCL{=}CH_2 + ROL + X^- \quad (205)$$

$$ArCLTCH_2\,X + RO^- \xrightarrow{k_2} ArCL{=}CH_2 + ROT + X^- \quad (206)$$

$$ArCLTCH_2\,X + RO^- \xrightarrow{k_3} ArCT{=}CH_2 + ROL + X^- \quad (207)$$

When L=H, $(k_1/k_3) = {}^Hk_H/{}^Tk_H$, and when L = D, $(k_1/k_3) = {}^Dk_D/{}^Tk_D$, the subscript represents the transferred atom, the superscript represents the atom remaining behind. The (k_1/k_3) values have been determined by comparing the activity of the product olefin at the beginning of the reaction, $R_s{}^0$, with the activity of the quaternary ammonium salt, R_0. Equation 208 has been used for calculating the IE in the reaction of **373** and equation 209 in the case of compound **374**, which has three reactive hydrogens.

$$(k_1/k_3) = 0.5R_0/R_s^0 \quad (208)$$

$$(k_1/k_3) = 2R_0/3R_s^0 \quad (209)$$

In the reaction of **373** with EtO^-/EtOH as the base/solvent system, the ratios ${}^Hk_H/{}^Tk_H$ have been found to equal (at temperatures given in parentheses): 1.332 ± 0.009 (at 29.60 °C), 1.293 ± 0.008 (at 40.00 °C), 1.266 ± 0.013 (at 50.20 °C), 1.25 ± 0.006 (at 60.00 °C) and 1.209±0.003 (at 69.80 °C). In the case of elimination reaction of **374** with *t*-BuO^-/*t*-BuOH, the ${}^Hk_H/{}^Tk_H$ values are equal to 1.252±0.004 (at 35.50 °C), 1.238±0.004 (at 44.95 °C), 1.224 ± 0.005 (at 54 °C), 1.223 ± 0.004 (at 54.80 °C), 1.217 ± 0.004 (at 65.05 °C) and 1.206 ± 0.006 (at 74.00 °C).

In the reaction of **375** with EtO^-/EtOH the corresponding $({}^{H}k_H/{}^{T}k_H)$ values are: 1.271 ± 0.006 (at 29.9 °C), 1.258 ± 0.003 (at 40.35°), 1.238 ± 0.004 (at 50.00 °C), 1.228 ± 0.003 (at 60.40 °C) and 1.206 ± 0.008 (at 70.20 °C).

The equilibrium isotope effect, ${}^{H}K_H/{}^{T}K_H$, for complete sp^3 to sp^2 rehybridization at the isotopically substituted position has been assessed[406,407] to be 1.17 at 50 °C.

The secondary ${}^{H}k_H/{}^{T}k_H$ KIE in the eliminations of **373**, **374** and **375** presented above which are higher than this maximum possible secondary IE value, are taken as strongly implicating tunnelling. This conclusion has been supported also by intercomparison of secondary H/T and D/T isotope effects in E2 reactions of $RNM_3{}^+Br^-$ at 50 °C. The secondary IE is depressed markedly when deuterium rather than proton is transferred, which also implicates tunnelling:

$$\left.\begin{aligned}({}^{L}k_L/{}^{T}k_L) &= 1.267 \pm 0.012 \text{ (for L = H)}\\ &= 1.032 \pm 0.003 \text{ (for L = D)}\end{aligned}\right\} \text{ in reaction of } \mathbf{373} \text{ with } EtO^-/EtOH$$

$$\left.\begin{aligned}&= 1.224 \pm 0.005 \text{ (for L = H)}\\ &= 1.029 \pm 0.003 \text{ (for L = D)}\end{aligned}\right\} \text{ in reaction of } \mathbf{374} \text{ with } t\text{-}BuO^-/t\text{-}BuOH$$

$$\left.\begin{aligned}&= 1.238 \pm 0.004 \text{ (for L = H)}\\ &= 1.031 \pm 0.003 \text{ (for L = D)}\end{aligned}\right\} \text{ in reaction of } \mathbf{375} \text{ with } EtO^-/EtOH$$

In the absence of tunnelling the value of the exponent R in relation[408] 210 equals 3.26:

$$(k_H/k_T) = (k_D/k_T)^R \tag{210}$$

In this study[405], ${}^{H}k_H/{}^{T}k_H > ({}^{D}k_D/{}^{T}k_D)^{3.26}$ and the value of relation 210 is satisfied for the exponent R of $(7.0\text{–}7.5) \pm 0.1$ in accord with significant tunnelling. The low values of the Arrhenius parameters $(A_{aH}/A_{aT}) = 0.602 \pm 0.026$ and $(E_{ArhT} - E_{ArhH}) = 0.478 \pm 0.028$ kcal mol^{-1} found in reaction with **373** also support the above conclusion[409]. The carbanion-like TS in the E2 reaction of **373** favours tunnelling greatly.

10. Carbon-14 C and deuterium KIE in the reductions of benzophenone with $NaBH_4$, $LiAlH_4$ and $LiBH_4$

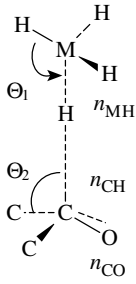
Carbon-14 and deuterium KIE in the reduction with benzophenone, determined at 25 °C, are listed in Table 1. The ^{14}C KIEs are greater for SBH reduction than for LAH; the deuterium KIEs are normal for LAH and inverse for SBH. These results suggest a product like TS, **376**, for the SBH reduction. In the course of the reductions the configuration at

TABLE 1. KIE in the reduction of benzophenone at 25.0 ± 0.1 C.

Reagent/solvent	k_{12}/k_{14} (av.)	k_{H4}/k_{D4}
$LiAlH_4/Et_2O$	1.024 ± 0.003	1.10 ± 0.01^a
$LiBH_4/Et_2O$	1.043 ± 0.007	1.09 ± 0.03^b
$NaBH_4$/l-PrOH	1.066 ± 0.004	0.72 ± 0.03^a
		0.77 ± 0.001^c

[a]Determined by GC/MS, [b]Determined by NMR. [c]The ratio of the second-order rate constants for the protio and deuterio runs are $k_H = (2.23 \pm 0.05) \times 10^{-3}$ dm^3 mol^{-1} s^{-1} ($NaBH_4$), $k_D = (2.90 \pm 0.05) \times 10^{-3}$ dm^3 mol^{-1} s^{-1} ($NaBD_4$).

the metallation site changes from tetrahedral to planar, while the configuration at the carbonyl carbon changes from planar to tetrahedral when the bond order, n_{CH}, of the newly formed C−H bond increases from 0 to 1. The detailed calculation of ^{14}C and D KIEs, neglecting the interaction of ROH solvent molecules in the TS with carbonyl oxygen and with boron atom, respectively, have been carried out[410,411] for the model and its geometrical parameters shown in structure **376**. In the reduction of benzophenone with LAH the simultaneous matching of calculated D_4 and ^{14}C KIEs with the experimental values was achieved when $n_{CH} = 0.35$, that is for a reactant-like TS. Similar matching was achieved for the SBH reduction when $n_{CH} = 0.75$ (product-like TS). The extent of hydride transfer from B to carbonyl carbon in the LBH reduction was determined as $0.55n_{CH}$.



(376)

$n_{MH} = 1.0 - n_{CH}$, $n_{CO} = 2.0 - n_{CH}$,
$n_{CC} = 1 - 0.1n_{CH}$, $\Theta_1 = 120.0 - 10.5n_{CH}$,
$\Theta_2 = 90.0 + 19.5n_{CH}$, M = Al or B

11. Carbonyl-^{14}C KIE in the reactions of ketones with organolithium reagents

The following carbon-14 kinetic isotope effects have been observed in the reactions of labelled ketones with MeLi and Me_2CuLi providing the corresponding tertiary alcohols[412] (equations 211–213):

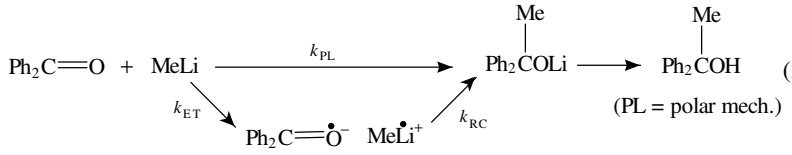
$$Ph_2{}^{14}C{=}O + MeLi : (k_{12}/k_{14}) = \begin{array}{r} 1.000 \pm 0.0002 \\ \rho = 0.27 \pm 0.07 \end{array} \quad (211)$$

$$Ph_{12}{}^{14}C{=}O + Me_2CuLi : (k_{12}/k_{14}) = \begin{array}{r} 1.029 \pm 0.005 \\ \rho = 1.96 \pm 0.12 \end{array} \quad (212)$$

$$2,4,6\text{-}Me_3C_6H_2{}^{14}COPh + MeLi : (k_{12}/k_{14}) = 1.023 \pm 0.004 \quad (213)$$

The above data have been rationalized in terms of the mechanisms shown in equation 214, and taken as indicating that reaction 211 proceeds via rate-determining electron transfer (ET), while in reactions 212 and 213 the rate-determining step shifts to recombination (RC) because in reaction 213 the RC-step becomes slower for the more hindered ketone. The small $\rho = 0.27$ value in reaction 211 also means that the extent of the geometrical changes is negligible in the TS of this reaction. These qualitative interpretations of the ^{14}C KIE have not been supported by model calculations as has been done similarly in the reactions of ketones with SBH and LAH. The $^{14}CH_3Li$-carbon-14 KIE have not been studied in reactions 211–213. The inverse ^{14}C KIE is expected in

$^{14}CH_3$-KIE governed by transformation of the weak covalent $^{14}C-Li$ bond into a more covalent $^{14}C-^{12}C$ bond in the TS leading to tertiary alcohols.



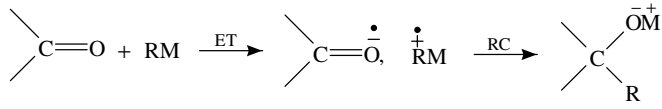
(214)

It has been found[412–414] that there are no carbon-14 KIE in the reaction of benzophenone with MeLi, while there is a large KIE (of 1.056) in the addition reaction of MeMgI, and that the reaction of benzophenone with alkyl magnesium bromide proceeds with a carbonyl ^{14}C KIE of unity. The very small (close to unity) carbonyl-^{14}C KIEs have been determined at 0.0 °C in additions of PhLi and allylithium to benzophenone and benzaldehyde[415] (equation 215–217) and a general conclusion has been reached that all the reactions of aromatic carbonyl compounds with RLi studied proceed via the same mechanism, in which the rate-determining step is the initial ET step, followed by a subsequent fast step (equation 218). In no case are there any bonding changes at the carbonyl carbon in the rate-determining TS of these reactions[415].

$$Ph_2CO + PhLi \text{ (in } c\text{-hexane/}Et_2O,\ 7/3),\ (k_{12}/k_{14}) = 1.003 \pm 0.001 \tag{215}$$

$$Ph_2CO + CH_2{=}CHCH_2Li(\text{in } Et_2O),\ (k_{12}/k_{14}) = 0.994 \pm 0.003 \tag{216}$$

$$PhCHO + PhLi \text{ (in } c\text{-hexane/}Et_2O,\ 7/3),\ (k_{12}/k_{14}) = 0.998 \pm 0.003 \tag{217}$$



(218)

12. Carbonyl-^{14}C KIE in the reactions of bezophenone-7-^{14}C with various Grignard reagents

The mechanism of the Grignard reaction has been studied for many years[416–418] and the sequence shown in equation 219 has been proposed[417]. The ^{14}C KIEs in the reactions of benzophenone with various Grignard reagents, listed in Table 2, have been determined[419] to identify the rate-determining step. The large ^{14}C KIEs found in reactions with MeMgX, ArMgBr, and $PhCH_2MgBr$ have been interpreted as an indication of C–C bond formation in the rate-determining step; the ^{14}C KIE of unity (and a near-zero ρ value, and no steric retardation) observed for allylic reagents has been taken as evidence of the initial SET rate-determining step (equation 219). Small ^{14}C KIE, large ρ value and no steric rate retardation observed in the Grignard reaction with *t*-BuMgCl are reported as indication of another route in which the isomerization of the radical ion-pair intermediate is the rate-determining step.

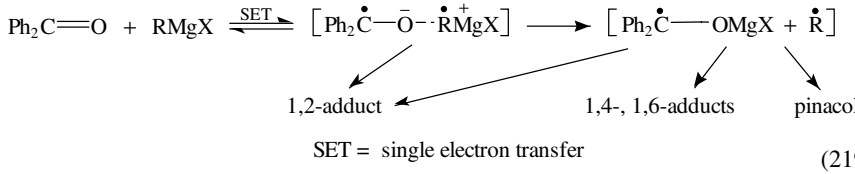


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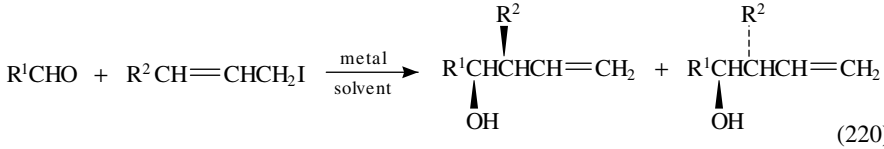
TABLE 2. Carbon-14 KIEs in the reaction of Ph_2CO with various Grignard reagents

Reagent/solvent	k_{12}/k_{14}	ρ Value
$MeMgI/Et_2O$	1.056 ± 0.002	0.54 ± 0.16
$MeMgBr/Et_2O$	1.050 ± 0.011	
MeMgBr/THF	1.056 ± 0.004	0.90 ± 0.11
$PhMgBr/Et_2O$	1.056 ± 0.004	0.59 ± 1.10
$o\text{-}MeC_6H_4MgBr/Et_2O$	1.060 ± 0.014	
$PhCH_2MgBr/Et_2O$	1.024 ± 0.007	
$CH_2{=}CHCH_2MgBr/Et_2O$	0.999 ± 0.002	-0.02 ± 0.09
$MeCH{=}CHCH_2MgBr/Et_2O$	0.999 ± 0.002	0.01 ± 0.03
$t\text{-}BuMgCl/Et_2O$	1.010 ± 0.007	3.0[e]
$t\text{-}BuMgCl/Et_2O$[a]	1.004 ± 0.004	
$MeMgI + FeCl_3/Et_2O$[b]	1.063 ± 0.003[c]	
	0.997 ± 0.019[d]	

[a]Different batches of ketone and solvent were used.
[b]5 mol% $FeCl_3$ added.
[c]For 1,2-adduct formation.
[d]For pinacol formation.
[e]Taken from reference 420

13. Carbonyl-^{14}C KIE in Zn-promoted Barbier-type reactions

Two possible reaction pathways have been proposed[421] for the Barbler-type carbonyl addition (equation 220): the polar (PL) route and the electron transfer–radical coupling (ET–RC) sequences with rate-determining ET or rate-determining RC (equation 221).



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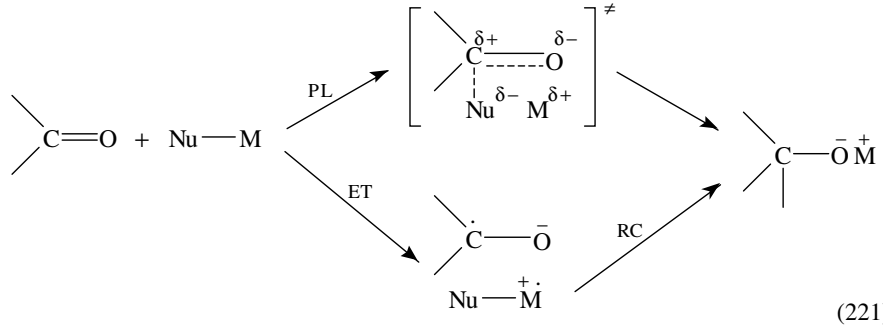
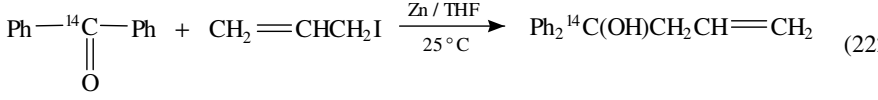


(221)

The reactions of allyllithium and allylmagnesium bromide proceed through the ET–RC pathway[415,419] with rate-determining ET, while the reactions of allyltin and allyllead proceed via the PL route[422,423]. ^{14}C KIE in the Zn-promoted Barbier-type reaction of allyl iodide, occurring in solution and not on the metal surface with benzophenone, (equation 222) was found[421] to equal 1.041 ± 0.006 ($\rho = 0.70 \pm 0.06$), indicating that the binding to carbonyl carbon is changing in the rate-determining TS. This value of ^{14}C

KIE is consistent with a polar, PL, mechanism, and with an ET–RC-mechanism with partial rate-determining RC. The supplementary experiments led the authors[421] to the conclusion that the reaction 222 is realized through the polar nucleophilic mechanism. No supplementary evidence was obtained for electron transfer during the reaction. The small but positive ^{14}C KIE ($k_{12}/k_{14} = 1.012 \pm 0.006$, $\rho = 0.16 \pm 0.06$) was observed in the reaction with benzaldehyde (equation 223) and interpreted also proceeding likely through the polar mechanism. An early and six-membered TS has been proposed for reaction 223 with benzaldehyde, occurring for steric reasons 9 times faster than the reaction 222 with benzophenone.



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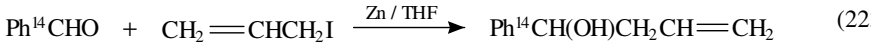

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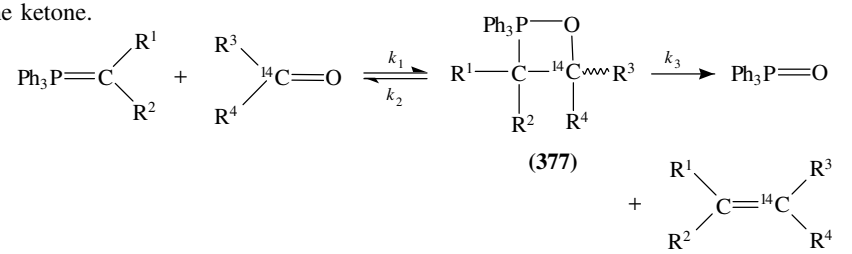
14. ^{14}C KIE in the Wittig reaction of benzophenone(carbonyl-^{14}C) with isopropy/idenetriphenylphosphorane

According to ^{31}P-NMR studies[424,425] the Wittig reaction[426] proceeds as shown in equation 224 in which the cyclohexanone and ethylidenetriphenylphosphorane give rapid formation of oxaphosphetane followed by its slow decomposition into phosphine oxide and alkene. The ^{14}C KIE in the title reaction has been found to be equal to 1.053 ± 0.002. This value clearly indicates that the bonding at the carbonyl carbon is changing in the rate-determining step (RDS) of the reaction and is consistent with a mechanism in which the RDS is the direct formation of oxaphosphetane, although the decomposition of the latter may also be rate-limiting[425]. The authors[425] admit that the formation and decomposition of oxaphosphetane may have similar TS characteristics and both steps may give similar KIE. To clarify this point further studies have been considered. A statement has been also made that the ET is the RDS in reaction with benzaldehyde, while C–C formation (because of steric hindrance) and oxaphosphetane formation become the slower RDS for the ketone.



(377)

(224)

In view of the ambiguity involved in the detailed model calculations and lack of data concerning temperature dependences of the ^{14}C KIEs presented in this part of the chapter, the numerical values of ^{14}C KIEs collected in Table 2 and 3 should be given also the alternative simple interpretation which could be verified by determination of the ^{14}C KIE for ^{14}C-labelled, ylides and by ^{14}C KIE temperature-dependence study.

In the course of formation of the relatively stable or fast decomposing **377** (equation 224) the [^{14}C]-carbonyl double bond is transformed into a single [^{14}C]-carbon–oxygen bond, if the P–O bond formation in TS is much more advanced than

TABLE 3. Carbonyl- ^{14}C KIE in the Wittig reactions in THF solvent

Substrate	Ylide	exp. conditions (0 °C)	k_{12}/k_{14}
PhCHO	$Ph_3P{=}CMe_2$	Li salt free (0 °C)	1.003 ± 0.002
		Li salt present (0 °C)	0.971 ± 0.004
	$Ph_3P{=}CHPr$	Li salt free (0 °C)	0.998 ± 0.002
		Li salt present (0 °C)	0.995 ± 0.003
		Li salt free (−78 °C)	0.993 ± 0.003
$Ph_2C{=}O$	$Ph_3P{=}CMe_2$	Li salt free (0 °C)[a]	1.053 ± 0.002
		Li salt present (0 °C)[a]	1.041 ± 0.010
PhCHO	$Ph_3P{=}CHPh$	Li salt free (0 °C)	1.060 ± 0.003
		Li salt present (0 °C)	1.015 ± 0.004

[a] In Et_2O.

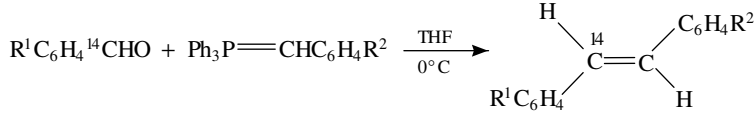
$^{12}C-^{14}C$ bond formation, or into two single bonds, $^{14}C-O$ and $^{12}C-^{14}C$, in the case of four-centered oxaphosphetane-like TS. Neglecting the contribution from rotation of both reactants and TS in the liquid phase and considering only carbonyl bond vibration in the substrates [$\omega(^{12}C{=}^{16}O) = 1750\ cm^{-1}$, $\omega(^{14}C{=}^{16}O) = 1676.96\ cm^{-1}$] and taking values $\omega(^{12}C-^{16}O) = 1093\ cm^{-1}$, $\omega(^{14}C-^{16}O) = 1047.4\ cm^{-1}$, $\omega(^{12}C-^{12}C) = 900\ cm^{-1}$ and $\omega(^{14}C-^{12}C) = 867.22\ cm^{-1}$ for vibration of the single C−O and C−C isotopic bonds in TS, we obtain in the 'sinh' approximation[427–429] the (k_{12}/k_{14}) values for the oxaphosphetane-formation step equal to 1.067 (at 25 °C) and 1.074 (at 0 °C) for TS with far more advanced P−O bond formation, and values of (k_{12}/k_{14}) equal to 0.9838 (at 25 °C) and 0.9835 (at 0 °C) for four-centered oxaphoshetane-like TS. The above brief calculations indicate that in the reactions of benzaldehyde with non-stabilized ylides, the formation of **377** *determines* in general the observed ^{14}C kinetic fractionation in the overall Wittig reaction. The very instructive ^{14}C KIE in the first-order decomposition of the oxaphosphetane derived from $Ph^{14}CHO$ and $Ph_3P{=}CMe_2$ have not been listed by Yamataka and coworkers[425]. The ^{14}C KIEs observed in sterically hindered reactants (benzophenone, semistabilized and stabilized ylides) are reproduced by advanced P−O bond formation TS. Full solution of the TS structure requires the ^{14}C-ylide and ^{18}O-carbonyl KIE determinations in Wittig reactions. The ^{14}C KIEs in the Wittig reactions described adequately by equation 224 should depend on the k_3/k_2 ratio and on the degree of $^{14}C-^{18}O$ bond rupture and on the degree of $^{14}C{=}^{12}C$ double-bond formation in the TS of the overall reaction. The full vibrational analysis of oxaphosphetanes is required. The small ρ value suggests that the TS is non-polar in the oxaphosphetane decomposition step.

15. Carbonyl KIE in the Wittig reaction of benzaldehydes with benzylidenetriphenylphosphoranes

The carbonyl- ^{14}C KIEs in the title reaction system (equation 225), which gives a nearly 50 : 50 mixture of *cis–trans* isomers, depends very much on the ylide used[430], and indicate that the reactions proceed via cycloaddition TS of considerable nucleophilic character, inferred also from the substituent effects studied. Positive ρ values indicate that the Wittig reaction is nucleophilic in nature. Assuming as before the four-centered TS, the authors[430] conclude that the C−C bond formation is much advanced of the P−O bond formation in the TS and that 'the carbonyl-carbon KIE are expected to be larger for later TS' salt-free reaction[410] (more reactant-like for Li salt present in reaction).

16. Carbonyl-^{14}C KIE in the Wittig reaction of non-stabilized ylides with benzaldehyde and benzophenone

The carbonyl ^{14}C KIEs in the reaction of benzaldehyde with non-stabilized ylides have been found to be very small[432] in contrast to the reactions of benzophenone, and taken as an indication of mechanistic differences between aldehydes and ketones. The numerical values of the ^{14}C KIE collected in Table 3 have been interpreted within the reaction scheme shown in equation 224 and 226. The authors final conclusion[432], influenced also by previous model calculation[433], was that the non-stabilized ylide has enough ability to transfer an electron to benzaldehyde and benzophenone, and the Wittig reaction proceeds via initial electron transfer from ylide to carbonyl compounds. The electron transfer is the RDS for benzaldehyde while the radical coupling, RC, following the electron transfer step, is rate-determining[432] for benzophenone. The reactions of semi-stabilized ylides proceed through the polar nucleophilic addition mechanism.



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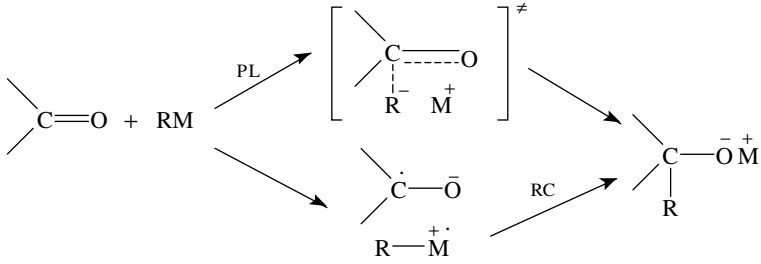

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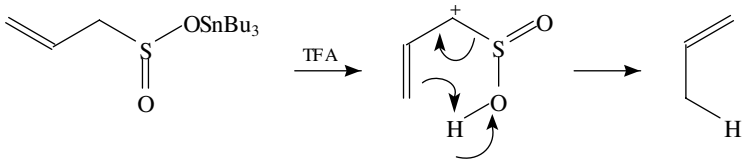
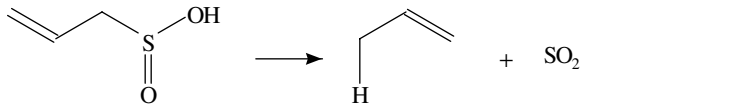
17. Brief review of KIEs in chemical reactions

Deuterium KIE in the reaction of 3-metyl-1-butene, **378**, with CF_3COOH-D (TFA-D), providing 3-methyl and 2-methylbutyl trifluoroacetate, **389**, in about 53:47 ratio both in TFA-H and in TFA-D, was 6.8 (at 26.5 °C)[434]. In the similar reaction with 2-methyl-1-butene **379**, and 2-methyl-2-butene, **380**, with TFA-D, the D KIEs have been found[434] to be 5 (**379**, −18 °C). and 3.9 (**380**, −18 °C). **378** reacts by carbocationic mechanism and undergoes a Me shift. Extensive H/D exchange between the solvent and the ester **381** took place.

The deuterium KIE of 2.5 ± 0.1, observed at 297 K in the cleavage of tributyltin allylsulphinate with [^{2}H]TFA in toluene[435] (equation 227) has been interpreted as suggesting a rigid compact and 'reactant-like' early TS, and as confirming the concerted retro-ene mechanism of thermal desulphination of allylsulphinic acid (equation 228). The mechanism of hydroxyl radical-induced decarboxylation of 2-(alkylthio)ethanoic acid

derivatives has been investigated[436] in H_2O and D_2O.





Deuterium KIEs in the oxidation of C_6H_6/C_6D_6, C_6H_5Me/C_6D_5Me, $C_6H_5Me/C_6H_5CD_3$, $1,3\text{-}Me_2C_6H_4/1,3\text{-}(CD_3)_2C_6D_4$, $1,4\text{-}Me_2C_6H_4/1,4\text{-}(CD_3)_2C_6D_4$ with permanganate in aqueous solution[437] have been found to be 1.0, 1.0, 13.6, 11.3, 16.8, respectively, at 70 °C. In the case of the $C_6H_5Me/C_6D_5CD_3$ system, D KIE decreased from 16.4 at 50 °C to 10.8 at 90 °C. D KIE in the oxidation of alkylbenzenes with $HMnO_4$ has been studied also. KIE $k_0^H/k_0^D = 1.45 \pm 0.09$, corresponding to oxidation with $HMnO_4$, has been observed in the oxidation of toluene/toluene-D_8 in $KMnO_4-H_2O$ solutions under conditions of varying acidity[438].

D KIEs proved[439] that in the oxidation of formaldehyde on a polycrystalline platinum electrode modified with Pb atoms and on pure platinum electrode, the cleavage of both OH and CH bonds and the abstraction of the hydrogen atom from an OH bond in hydrated formaldehyde are rate-determining on the Pt/Pb and on the Pt electrode, respectively. The k_H/k_D for the oxidation of formaldehyde at copper electrode (at pH 13, at 25 °C) depends on the electrode potential and reaches the highest value of 7 at low potentials and drops to about 2.5 at higher positive potentials[440].

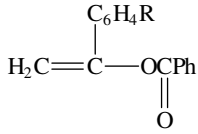
The KIE in the oxidation of selectively deuteriated aliphatic alcohols (2-propanol, 1,2-butanediol, 1,4-butanediol and 2,3-butanediol) at a polycrystalline gold electrode in alkaline solutions with cyclic voltametry have been determined and discussed[441]. Isotope effects in the electrochemical reduction of deuteriated oxalic and benzoic acids at Pb cathodes in deuteriated media have been determined[442]. DOOCCOOD in D_2O provided deuteriated glyoxylic acid but the large isotope effect of 5.3 found in this reaction leads to significant depletion of D in the aldehyde group. D KIE of 2.4 has been found in reduction of PhCOOD to $PhCD_2OD$. The unlabelled $PhCH_2OH$ has been obtained in CD_3OH/dil. H_2SO_4 medium. No incorporation of D into the aromatic nucleus has been observed.

D KIE of 6.35 has been observed in the oxidation of α-deuteriomandelic acid by pyridinium bromochromate to the corresponding oxo acid. The analysis of the D KIE indicated that the reaction involves a symmetric transition state[443]. The oxidations of phosphinic and phosphorous acids by pyridinium bromochromate exhibits a substantial primary deuterium KIE[444]. The hydroxyacids, glycolic, lactic, mandelic and malic acids are oxidized by pyridinium hydrobromide perbromide in acetic acid–water mixtures to oxo acids[445]. The primary KIE in the oxidation of α-deuteriomandelic acid is $k_H/k_D = 5.07$, and it does not exhibit a solvent isotope effect. A mechanism involving hydride ion transfer to the oxidant has been proposed[445].

The oxidation of primary aliphatic alcohols by *bis*(2,2′-bipyridyl)copper(ll) permanganate (BBCP) in aqueous acetic acid leads to the formation of the corresponding aldehydes[446]. The oxidation of $[1,1\text{-}^2H_2]$ethanol exhibited[446] a k_H/k_D of 4.50. The formation constants for BBCP–alcohol complexes and the rates of their decomposition have been evaluated. Aliphatic aldehydes are oxidized by pyridinium hydrobromide

perbromide to carboxylic acid[447]. Michaelis–Menton type kinetics with respect to aldehydes are observed; $\rho^* = -1.85$ at 298 K points to an electron-deficient carbon centre in the TS and hydride ion transfer. A substantial D KIE indicates that the aldehydic C−H bond is cleaved in the rate-determining step[447]. The kinetics of oxidation of 2-propanol, 2-butanol and 2-pentanol by pyridinium fluorochromate has been studied. The D isotope effect of 3.2 observed with 2-propanol indicated that the C−H bond is broken in the RDS[448]. The oxidation of benzaldehydes by pyridinium fluorochromate has been studied also and a mechanism involving a complex between hydrated aldehyde and protonated oxidant has been suggested[449].

A DIE of $k_{H_2O}/k_{D_2O} = 3.2$ has been found in the hydrolysis of α-benzoyloxystyrenes, **382**, in concentrated perchloric acid solution[450]. The rate of hydrolysis was found to be linear with the acidity function, H_0. A small inverse deuterium KIE, $k_H/k_D = 0.78$, at the α-carbon has been found in the oxidation of cinnamic and crotonic acids[451] by quinolinium dichromate. The reaction involves electrophilic attack on the double bond and a carbonium-ion intermediate ($\rho = -4.0$). A small inverse D KIE [$(k_H/k_D) = 0.80$, $\rho = -4.0$] has been also observed[452] in the acid cleavage of substituted styrenes by quinolinium dichromate in DMF in the presence of acid[452].

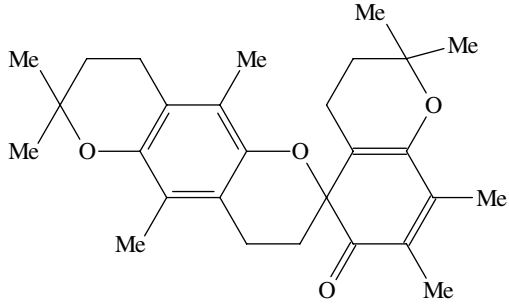


(382) R = Me, H, Cl, NO_2, substituent effect $\rho = -1.60$

Values of $k_H/k_D = 3.87$ and $k_{H_2O}/k_{D_2O} = 0.912$ have been observed[453] in the alkaline oxidation of allyl, crotyl and propargyl alcohols by monoperiodate complex of trivalent copper[453]. Deuteriation of the vitamin E model compound 2,2,5,7,8-pentamethylchroman-6-ol **383** at C_{5a}[454] inhibits its oxidation and favors the formation of **384**. The products of α-tocopherol **385** oxidation in biological membranes have been identified[454]. TS structures and KIEs for the Claisen rearrangement of chorismic acid, **386**, have been computed and compared with the experimental measurements[455].

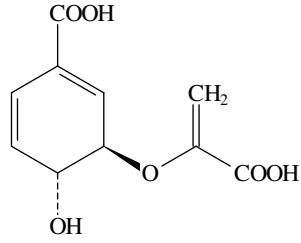
Inverse secondary KIEs, $k_H/k_D < 1.0$, have been observed in the reaction of Y-benzoyl, Y-benzenesulphonyl and Y-benzyl halides with deuteriated X-anilines in acetonitrile[456], and their variations with substituents X and Y investigated. The smallest inverse solvent kinetic isotope effects (SKIEs) have has been found in the reaction of deuteriated aniline nucleophiles with benzoyl fluoride, reflecting the tight TS for this compound. The large SKIE of 2.1–2.9 have been found[457] in a reaction of a series of 19 ring-substituted benzyl aldehydes with propylamine in CH_3OD. A mechanism involving α-amino alcohol formation in the fast pre-equilibrium followed by the rate-limiting OH^- detachment providing iminium ions has been proposed[457]. Deuterium solvent isotope effects in the acid-catalyzed hydrolysis of *N*-phenyl-4-substituted benzohydroxamic acids, $4\text{-}XC_6H_4CON(OH)Ph$(X = H, Me, OMe, NO_2, Cl, F), in sulphuric acid solutions, have been found[458] to be compatible with a changeover from an A-2 mechanism at low acidities to a A-1 mechanism at high acidity.

Improved yields of products have been achieved from oxidative free-radical cyclization of deuteriated substrates[459], The reaction of $CH_2{=}CMeCH_2CH_2COCD(COOMe)CH_2CH{=}CH_2$ **(387)** with $Mn(OAc)_3$ afforded 65% **388** (R^1R^2 = H, Me) whereas **387** of natural isotopic composition provided only 22% of **388** under the same conditions. Large



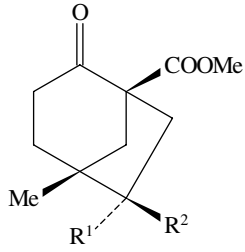
α-tocopherol, $C_{29}H_{50}O_2$ **(385)**

(384)



(386)

KIEs change the nature of the termination step and prevent the formation of acyclic radical $CH_2{=}CMeCH_2CH_2C\dot{O}(COOMe)CH_2CH{=}CH_2$ **(389)** by internal hydrogen transfer.



(388)

The primary kinetic H/D isotope effects in the *syn* elimination of HX from CH_3CH_2X (where X = H, BH_2, Me, NH_2, NH_3^+, OH, OH_2^+, F, Cl and Br) producing C_2H_4-HX complexes have been examined theoretically[460] Four-centered TS structures are found for all but X = H, BH_2 and Me (for H and Me three-centered TS are predicted). The primary KIE increases systematically as the central atom of X varies from left to right along a row or down a column of the periodic table and as X−H−C angle in the TS increases. The tunnelings in these elimination reactions have been discussed[460].

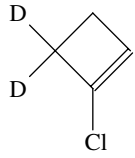
DIEs in the ion−molecule reaction $OH^- + H_2CO \longrightarrow H_3O^- + CO$ have been studied[461]. The rate constants for thermal dissociation of H_3O^+ and D_3O^+ in helium have been found to be 1.6×10^{-12} $cm^3\ s^{-1}$ and 1.1×10^{-12} $cm^3\ s^{-1}$ $((k_H/k_D) = 1.455)$[461].

The α-deuterium secondary KIE (k_H/k_D) for the rearrangements of (2,2-dideuteriocyclo-propyl)chlorocarbene to chlorocyclobutenes **390** and **391** have been

found to be equal 1.20 at 21 °C[462]. The corresponding theoretical value was calculated by *ab initio* methods[462] and was interpreted as originating in hybridization changes at the migrating carbon atom. Deuterium has been applied[463] in the study of the intramolecular reactivity of arylcarbenes, 2-(alkoxymethyl)phenylcarbenes, 2-$ROCH_2C_6H_4C(H)$:, eventually giving rise to benzylcyclobutenes as side product. The reaction of Ar_2CHCF_3 (Ar = $O_2NC_6H_{4-}$) with various bases occur according to the E1cB mechanism[464] (equation 229). The additions and E1cB eliminations by salts (equation 230) have been studied[465] and D KIE values of 1.28 ± 0.02 and 1.87 ± 0.04 have been observed for the reactions of Ar_2CDF_3 and $Ar_2CDCOOEt$, respectively. Such low values of k_H/k_D for the reaction between C-acids and bases are observed when the TS is product-like or when D/H exchange with the solvent interferes with D KIE determinations. Supplementary test experiments suggested that the former is responsible for the low k_H/k_D values observed[465].

$$Ar_2CHCF_3 + B \xrightarrow[-HF]{\text{slow}} Ar_2C{=}CF_2 \xrightarrow[-F]{\text{very fast}} Ar_2C{=}CB_2 \tag{229}$$

$$Ar_2C{=}CR_2 + X^- \underset{k_2}{\overset{k_2}{\rightleftharpoons}} Ar\overset{-}{C}{-}R_2X \underset{k_2(-HX)}{\overset{k_1(+HX)}{\rightleftharpoons}} Ar_2CHCR_2X + X^- \tag{230}$$



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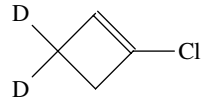


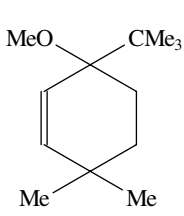
(391)

Stable isotope effect studies carried out during 1972–1992 concerning correlation of IEs with molecular forces and molecular structures, correlation of zero-point energy and its IEs with molecular forces and molecular structure, vapour pressure isotope effects and fractionation of stable isotopes have been reviewed[466].

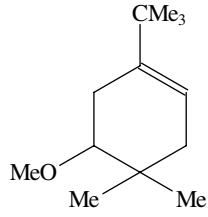
Nuclear tunnelling in the aqueous iron (2+)-iron (3+) electron transfer has been investigated[467] and the rate enhancement for H_2O has been assessed to be 65 times the classical rate, and that for D_2O 25 times the classical rate, yielding a H/D isotope effect of 2.6. The occurrence of the general base catalysis and sizable primary D KIEs indicated that the isomerization of 1*H*-indene-1-carboxylic acid to 1*H*-indene-3-carboxylic acid in aqueous solution takes place through an enolization–reketonization sequence[468]. Kinetic HH/HD/DD isotope and solvent effects have been used in a dynamic NMR study[469] of the tautomerization of ^{15}N-and ^{2}H -labelled bicyclic oxalamidines.

The stereoselectivity of the gas-phase 1,2-eliminations of deuterium-labelled **392** and of **393** with several bases have been studied[470]. The SDIE has been used[471] to study the mechanism of hydrolysis of the enol ether, $2\text{-}MeOC{=}CHC_6H_4COOH$, which yields the acylal, **394**, rather than the formal product of hydrolysis.

The acidic properties of (methoxymethylcarbene)pentacarbonylchromium, **395**, have been known for many years[472]. A rapid conversion of **395** CH_3 into **395**-CD_3 has been observed in dilute $NaOCH_3/CH_3OD$ solution[473]. Recently[474] DKIEs [$k_H/k_D = k_1{}^{OH}$ (**395**-CH_3)/$k_1{}^{OH}$ (**395**-CD_3) of the order of 2.5–3.0 for the deprotonation of **395**-CD_3 by OH^- in various MeCN–water mixtures and $k_H/k_D = k_1{}^{OH}$ (**395**-CH_2Ph)/$k_1{}^{OH}$ (**395**-CD_2Ph) of



(392)



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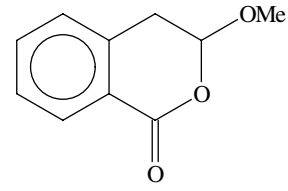
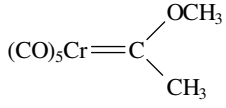
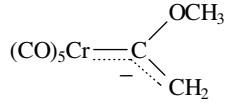


(394)

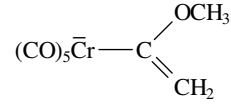
2.53 ± 0.10 in the deprotonation of benzylmethoxycarbenepentacarbonylchromium, **395**-CH_2Ph, also by OH^-, as well as D KIE of 5.51 ± 0.35 in the deprotonation of **395**-CH_2Ph by piperidine have been measured[474]. The lower values of D KIE observed in this study than in the deprotonation of other C−H acids have been explained by assuming that, apart from compressing the C−C bond and stretching the M−C (carbene) bond, the M−C(CO) and C−O bonds are also affected. A substantial coupling of proton transfer to heavy-atom motion involving bond changes in the CO ligands is observed (in THF, where **395**-CH_2^- is stable). The CO stretching frequency shifts from 1941 cm^{-1} in **395**-CH_3 to 1898 cm^{-1} in **395**-CH_2^- due to charge delocalization into the carbonyl ligands[475,476].



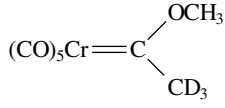
(395) - CH_3



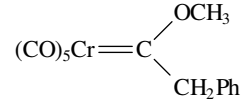
(395) - CH_2^-



(395) - resonance structure



(395) - CD_3



(395) - CH_2Ph

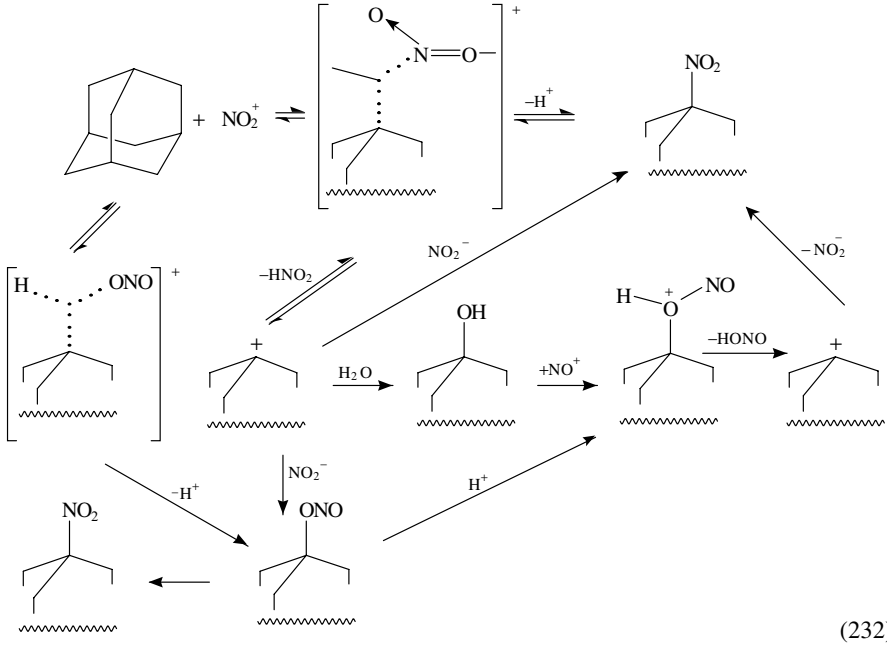
Primary D KIEs in the hydrogen abstractions at 130 °C from PhOH vs PhOD by *t*-butoxy radical have been found[477] to equal 1.33 ± 0.029 (in CCl_4), 1.40 ± 0.19 (C_6H_6), 2.79 ± 0.03 (MeCN). In the analogous reaction (equation 231) with PhSH vs PhSD the k_H/k_D values are in the range 1.02, 1.05 and 1.07 in CCl_4 C_6H_6 and MeCN, respectively (asymmetrical TS). In the reactions of $PhCH_3/PhCD_3$, the k_H/k_D IEs are 6.76 (CCl_4), 4.40 (C_6H_6) and 5.38 (MeCN), respectively. H/D isotope effects for radical abstraction reactions are discussed by Denisov[478].

$$\text{PhXH(D)} + t\text{-BuO}^{\bullet} \xrightarrow{k_{H(D)}} \text{PhX}^{\bullet} + t\text{-BuOH(D)} \qquad (231)$$

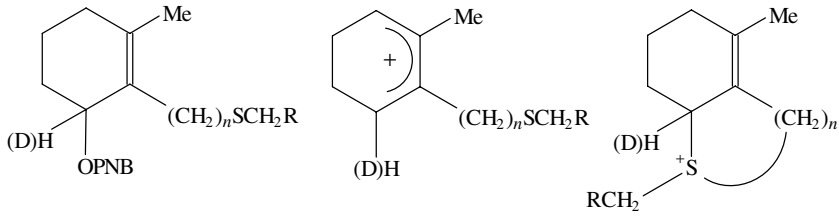
$$\text{X} = \text{S or O}$$

The solvent deuterium IEs for the acid-catalysed hydrolysis of benzaldehyde diaryl thioacetals[479], $PhCH(SC_6H_4R)_2$ (where R = H, R = NO_2, *m*-Cl, *p*-Cl, *p*-OMe), are 1.46.

Small hydrogen KIEs of $k_H/k_D = 1.2–1.3$ have been observed[480] in the reaction of an equimolar mixture of adamantane and 1,3,5,7-tetradeuterio-adamantane ($k_H/k_D = 1.30 \pm 0.05–1.31 \pm 0.05$) with nitronium tetrafluoroborate, and in nitration of 1-deuterioadamantane with pure nitronium tetrafluoroborate in nitroethane solvent ($k_H/k_D = 1.20 \pm 0.05$) and interpreted as indicating a non-linear highly unsymmetrical TS in the RDS of the reaction 232.



(232)



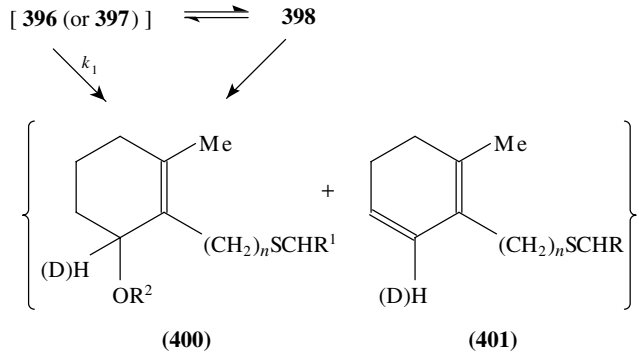
(396) R = H, n = 2, 3, 6
(397) R = Ph, n = 2, 3, 6

(398)

(399)

α-Deuterium IE of 1.18–1.20 at 50 °C has been observed[481] in the stepwise solvolysis (path k_1 in equation 233) of 2-(ω-methylthioalkyl)- and (ω-benzylthioalkyl)-3-methyl-2-cyclohexenyl *p*-nitrobenzoates **396** and **397** in 80 vol% ethanol, which involves an allylic cation **398** as a reaction intermediate and (k_H^α/k_D^α) = 1.01–1.03 in the solvolysis involving neighboring sulphur participation (k_2 path in equation 234) and formation of an intermediate cyclic sulphonium cation **399**. Compounds **400** and **401** are produced in the path (k_1), compounds **402** and **403** in the reaction path (k_2). The rate of oxidation of acetylacetone by chloramine-T and bromamine-T in the presence of hydrochloric acid

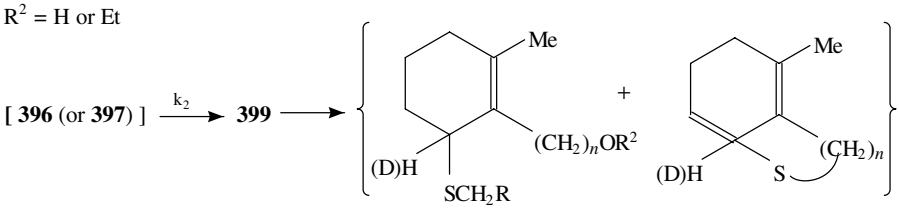
increased in D_2O medium[482].



(233)

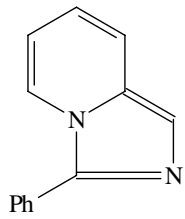
(400) **(401)**

R^2 = H or Et

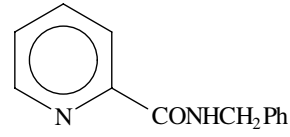


(402) **(403)** (234)

In neutral medium the deuterium solvent isotope effect, (k_{H_2O}/k_{D_2O}), in the hydrolysis of diaryldiacyloxyspirosulphuranes[483], **404–407** has been found to be 1.66. In acidic medium the ratio of catalytic rate constants has been found to be 0.56. Heterocondensed imidazoles **408**, are produced in the reaction of N-benzylamides, **409**, of nitrogen heterocyclic carboxylic acids with phosphorus pentachloride. Deuterium labelling experiments have been carried out to understand the mechanism of this reaction involving a nitrile ylide species[484].



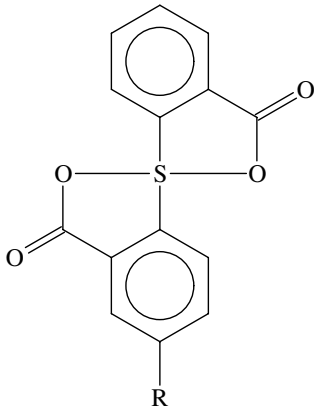
(408)



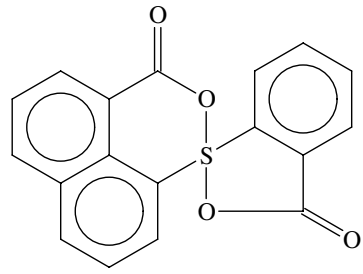
(409)

The reactions between OH or OD radicals and CO at temperatures down to 80 K have been studied[485a].

Isotope effect studies of the mechanism of hydration of alkynes with formic acid as water donor[485b,485c] leading to ketones (equation 234a) have been undertaken recently[485d] by observing the kinetic isotope fractionation of ^{13}C in the course of carbon monoxide



(404)



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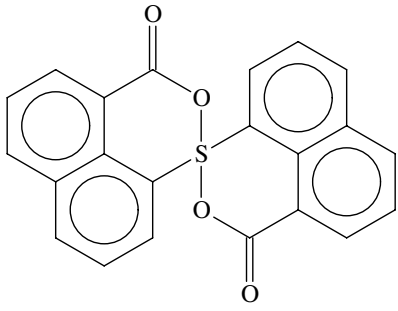
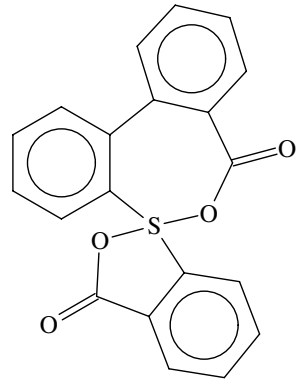


(406)



(407)

evolution in this reaction under variable experimental conditions.

$$R^1C{\equiv}CR^2 + H\overset{*}{C}OOH \longrightarrow R^1COCH_2R^2 + \overset{*}{C}O \qquad (234a)$$
$$\overset{*}{C} = {}^{13}C \text{ or } {}^{14}C$$

B. Isotope Studies of Chemical Catalytic Reactions

1. The gas-phase reactions of benzene and benzene-D_6 with group VIB metal pentacarbonyls and tetracarbonyls

Weak inverse KIEs have been observed in the gas-phase reactions of C_6H_6 and C_6D_6 with $M(CO)_5$ (M = Cr and W) and $W(CO)_4$ studied by time-resolved IR spectroscopy[486] (equation 235–245).

$$W(CO)_5 + C_6H_6 \xrightarrow{k_1} (\eta^2 - C_6H_6)W(CO)_5 \qquad (235)$$
(411)

$$W(CO)_5 + C_6D_6 \xrightarrow{k_2} (\eta^2 - C_6D_6)W(CO)_5 \quad (236)$$

$k_2/k_1 = 1.25$ (at 293 K) **(412)**

$$W(CO)_5 + CO \xrightarrow{k_3} W(CO)_6 \quad (237)$$

$$Cr(CO)_5 + C_6H_6 \xrightarrow{k_4} (\eta^2 - C_6H_6)Cr(CO)_5 \quad (238)$$

$k_5/k_4 = 1.10$ **(410)**

$$Cr(CO)_5 + C_6D_6 \xrightarrow{k_5} (\eta^2 - C_6D_6)Cr(CO)_5 \quad (239)$$

$$Cr(CO)_5 + CO \xrightarrow{k_6} Cr(CO)_6 \quad (240)$$

$$W(CO)_4 + C_6H_6 \xrightarrow{k_7} (\eta^2 - C_6H_6)W(CO)_4 \quad (241)$$

$$W(CO)_4 + C_6D_6 \xrightarrow{k_8} (\eta^2 - C_6D_6)W(CO)_4 \quad (242)$$

$k_8/k_7 = 1.17$

$$W(CO)_4 + CO \xrightarrow{k_9} W(CO)_5 \quad (243)$$

$$(\eta^2 - C_6H_6)W(CO)_4 + CO \xrightarrow{k_{10}} (\eta^2 - C_6H_6)W(CO)_5 \quad (244)$$

$k_{10}/k_{11} = 1.0805$

$$(\eta^2 - C_6D_6)W(CO)_4 + CO \xrightarrow{k_{11}} (\eta^2 - C_6H_6)W(CO)_5 \quad (245)$$

The gas-phase reaction of *nascent* $M(CO)_5$ species produced by 355-nm UV laser photolysis of the parent $M(CO)_6$,

$$M(CO)_6 \xrightarrow{h\nu} M(CO)_5 + CO$$

with C_6H_6 and C_6D_6, leads to formation of the benzene/$M(CO)_5$ complex in which benzene coordinates to M via an 'isolated double bond'. The unsaturated species is stable in the millisecond time scale. η^2-Coordinated arenes play a central role[487] as intermediates in C−H bond activation of arene systems.

2. The acid behaviour of zeolites

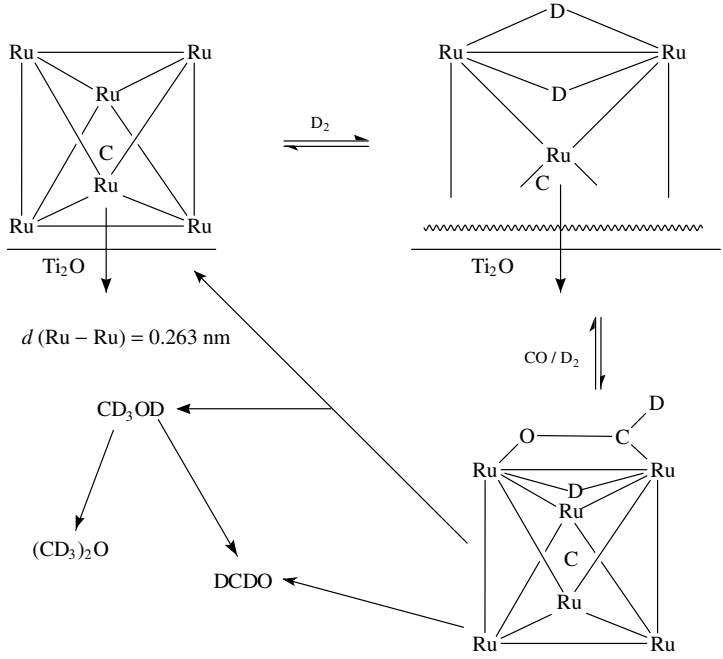
The catalysis by protonated zeolites, used in industrial cracking, isomerization and alkylation of hydrocarbons, involves proton transfer and formation of carbenium or carbonium ions as reactive intermediates[488,489]. To understand the function of the zeolite, the reactions between CD_4 and acidic hydrogens of OH groups of two zeolite samples have been studied recently[490].

3. Deuterium isotope effects in the oxygenate synthesis from CO/H_2 on supported [Ru_6C]clusters

The syntheses of MeOH, Me_2O and HCHO take place in the CO/H_2 reaction on the supported carbido-clusters in contrast to the preferential formation of methane and

hydrocarbons on the conventional Ru catalyst and the supported non-carbido clusters[491]. CO breathing-induced structural changes upon incorporation or release of carbon monoxide from the [Ru_6C] framework has been observed. The large uptake of carbon monoxide (8–11 CO per cluster) on [Ru_6C]/MgO and La_2O_3 prevent the dissociation of CO and increases the selectivity of oxygenate synthesis. Reverse D KIEs (k_D/k_H in the range 1.4–2.0, average value of $\cong$1.7) have been found in the formation of methanol, dimethyl ether and formaldehyde in CO/H_2 reactions on [Ru_6C]/TiO_2, [Ru_6C]/La_2O_3 and [Ru_6C]/MgO clusters, respectively. The H_2/D_2 isotope exchange reaction on [Ru_6C]/oxides in CO has been more than 3000 times faster than the steady-state oxygenate synthesis. Therefore, it has been assumed that step (246) is rate-determining in the syntheses of all three oxygenated compounds shown in equation 247. Dimethyl ether is formed by dehydration of methanol on oxide support[492]. The above conclusion is supported also by calculations[491,493–495] of the equilibrium constant for the step shown in equation 246, found to equal $(K_D/K_H) = 1.9$, which coincides with the observed value of 1.7 ± 0.3. Inverse D KIEs have been reported[493,494] also for reactions on Ru/SiO_2 and on Ru/Al_2O_3.

$$CO(a) + H(a) \longrightarrow CHO(a) \tag{246}$$



(247)

Negligible D KIEs in the formation of hydrocarbons (CH_4, C_2H_4, C_3H_6) which is favoured on contracted [Ru_6C]/TiO_2 and Al_2O_3 indicate that the dissociation of CO on the clusters is the RDS. Deuterium isotope shifts in the IR spectra of transient intermediates have been observed in the 1700–1200 cm^{-1} region. The weak peak at 1576 cm^{-1} in the CO/H_2 reaction corresponding to a formyl species (equation 247) is shifted to 1551 cm^{-1} after the switch of ambient gas from $CO + H_2$ to $CO + D_2$ at 532 K. The similar deuterium peak shifts from 1587 cm^{-1} to 1545 cm^{-1} (on Rh/SiO_2) and from 1584 cm^{-1} to 1575 cm^{-1} (on $RuCo_3/SiO_2$) have been observed previously[496,497a]. The observed deuterium shifts (given in parentheses) in the $CO + D_2$ reaction have been assigned: 3020

(2260) cm^{-1} for methane in the gas phase, 2965 (2221) cm^{-1}, 2877 (2186), 1441 (1427) and 1346 (1332) cm^{-1} to methyl, and peaks at 2929 (2203) and at 2856 (2137) cm^{-1} to ν_{CH} of the methylene species. The peak around 1954 cm^{-1} corresponding to terminal hydride in H_2 atmosphere (without CO) at 290 K for $[Ru_6C]/TiO_2]$ shifted to 1430 cm^{-1} in D_2. The RDS in olein hydroformylation with CO/H_2 and CO/D_2 has been studied by Yuan and coworkers[497b].

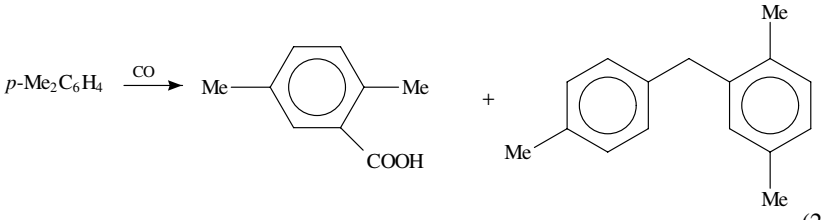
4. Deuterium isotope effect in the Pd–Cu catalysed carboxylation of alkynes with carbon monoxide

The effect of metal additives [Fe, $FeCl_2$, $FeCl_3$, $Co(OAc)_2$] to palladium(II) catalysing carboxylation of cyclohexane, propane and *p*-xylene with carbon monoxide have been investigated[498] and the highest yields of the corresponding carboxylic acids have been obtained with excess of the mixed catalyst $Pd(OAc)_2/Cu(OAc)_2$ (equation 248–250). It has been suggested that the reaction with mixed catalyst proceeds via an electrophilic mechanism similar to that with Pd, but different from the radical mechanism operating in the catalysis by Cu(II) alone and in $K_2S_2O_8$ system (equation 251).

$$C_6H_{12} \xrightarrow{CO} C_6H_{11}COOH \quad (248)$$

(413)

$$C_3H_8 \longrightarrow Me_2CHCOOH + n\text{-Pr-COOH} \quad (249)$$



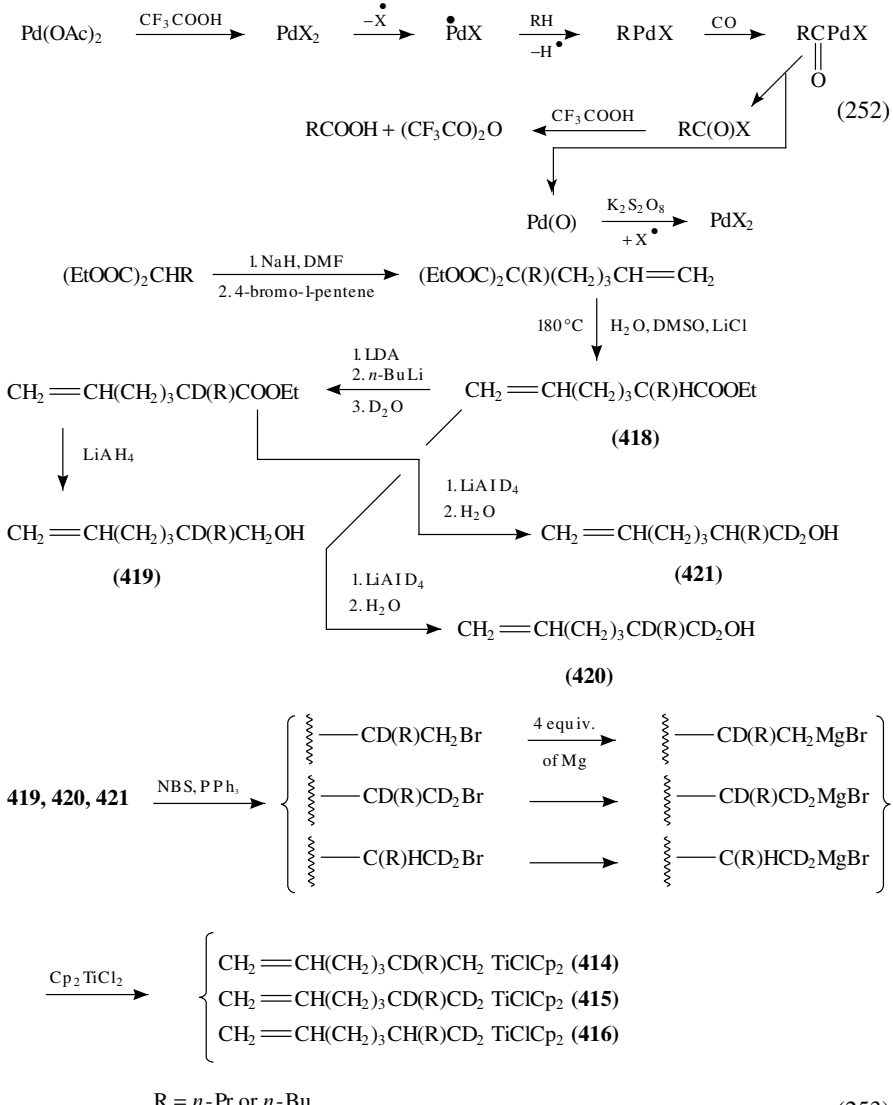
(250)

$$RH + CO + K_2S_2O_8 + 2CF_3COOH \longrightarrow RCOOH + 2KHSO_4 + (CF_3CO)_2) \quad (251)$$

This view has been supported by deuterium KIE determinations. Equimolar amounts of cyclohexane and cyclohexane-D_{12} treated with a Pd(II)–Cu(II) mixed catalyst under CO provided **413** and $C_6D_{11}\overset{*}{C}OOH$ in 3.2:1.0 ratio. In a similar reaction catalysed by Pd(II), the ratio was the same. In the reaction catalysed by Cu(II) the above two acids were obtained in equal yields. This indicates that in the carboxylations catalysed by Pd(II) the C–H bond cleavage proceeds in the RDS, unlike in the reaction with C(II). In the Pd(II)/Cu(II) system the C–H bond is cleaved by palladium. The R–PdX (X = CF_3COO) σ-complex reacts fast with CO, palladium(O) is reoxidized with $K_2S_2O_8$ and the catalytic cycle is completed (equation 252). In the reaction with Cu(II) the radical reaction is predominant. The decomposition of $K_2S_2O_8$ followed by hydrogen abstraction affords an alkyl radical which, with CO, provides the alkanecarboxylic acid via an acyl radical[499,500].

5. Alpha- and beta-deuterium isotope effects in the MgX_2 and methylaluminoxane promoted intramolecular olefin insertion of Cp_2TiClR complexes

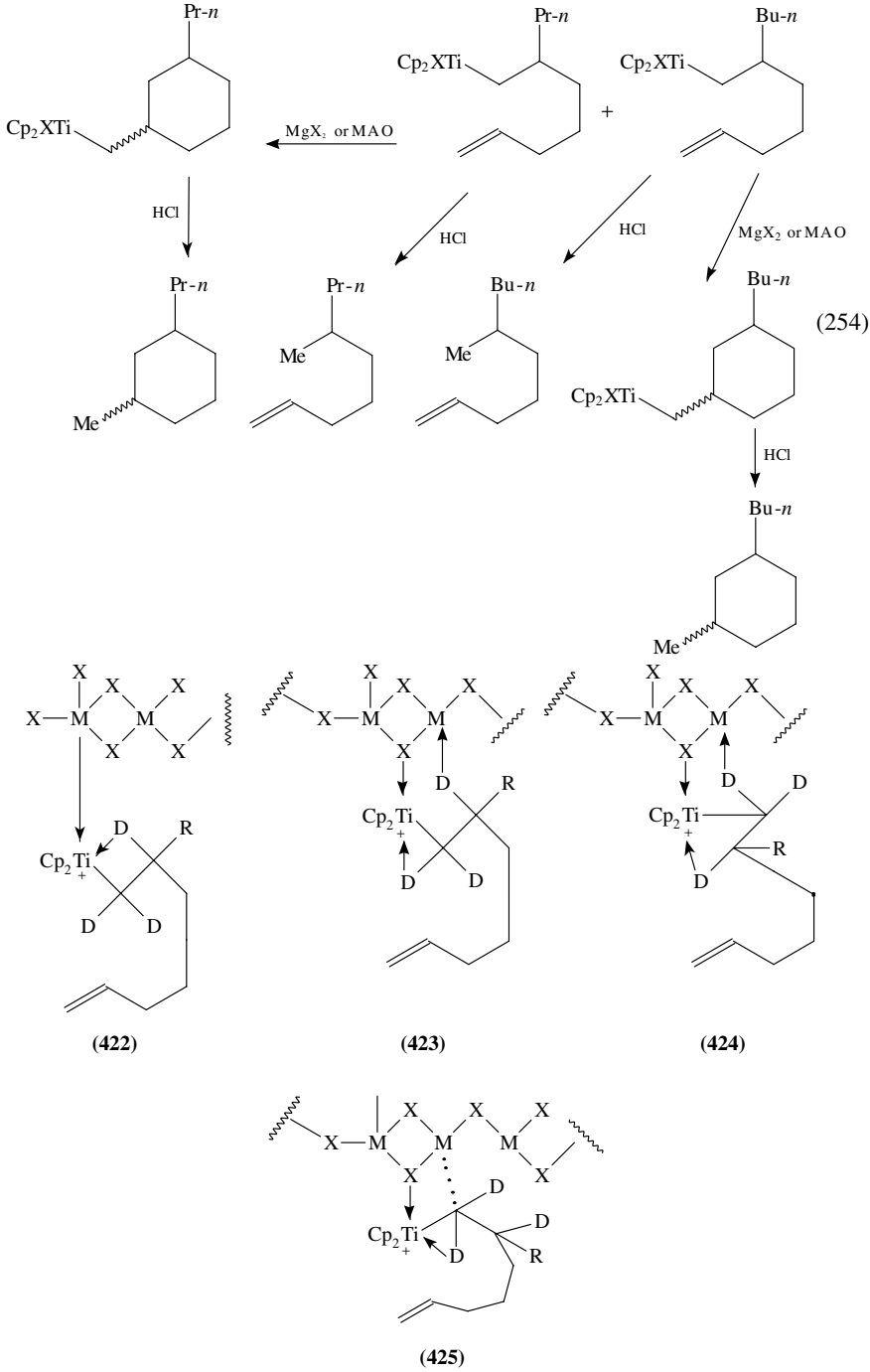
2-Alkyl-6-hepten-1-yl ligands, **414**, **415** and **416**, deuterium labelled in the α- and β-positions, have been synthesized by the method outlined in equation 253 and applied to



(252)

(253)

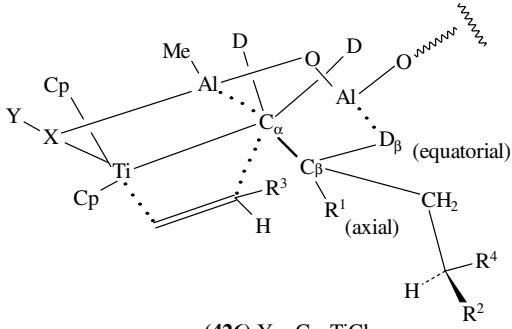
study the participation of α- and β-hydrogens in the intramolecular insertion of an α-olefin into a titanium–carbon bond by determining the isotope competitive cyclization rates[501]. In the MgX_2 (X = Cl, Br) promoted cyclization (equation 254) the k_H/k_D values for the α- positions, **416**, have been found to be 1.22 ± 0.03 and 1.28 ± 0.03 for R = *n*-Pr and *n*-Bu substrates, respectively. The k_H/k_D values for the β-position, **414**, were 1.09 ± 0.02 and 1.10 ± 0.02 for these substrates. Cooperative α- and β-deuterium isotope effects, **415**, for intramolecular olefin insertion, have been 1.36 ± 0.03. In the case of insertion


Pr-n
Cp2XTi
MgX2 or MAO
Pr-n
Cp2XTi
Bu-n
Cp2XTi
+
HCl
HCl
HCl
MgX2 or MAO
Pr-n
Me
Pr-n
Me
Bu-n
Me
Bu-n
Cp2XTi
HCl
Bu-n
Me
X
M
D
R
Cp2Ti
(422)
(423)
(424)
(425)

(254)

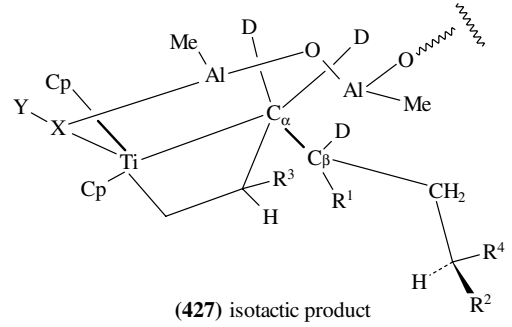
promoted by methylaluminoxane (MAO) an inverse D KIE has been observed for α-hydrogen ($k_H/k_D = 0.88 \pm 0.09$) for the *n*-propyl and $k_H/k_D = 0.95 \pm 0.04$ for the *n*-butyl substrates, respectively), but the k_H/k_D value of 1.06 ± 0.04 has been observed for β-hydrogen participation for each substrate **(414)**.

The above findings are evidence for the α-H participation and slight β-H participation in the RDS of α-olefin insertion for titanium-based Ziegler–Natta systems and for any system which models a propagating α-olefin polymer chain. Smaller values of β-D KIE than of α-D KIE are observed because coordination of the hydridic β-H in an agostic interaction does not require the same degree of geometric change at the β-C as is necessary in the case of agostic interaction of the α-carbon (structures **422**, **423**, **424** and **425** in equation 255).



(426) Y = Cp_2TiCl

(255)



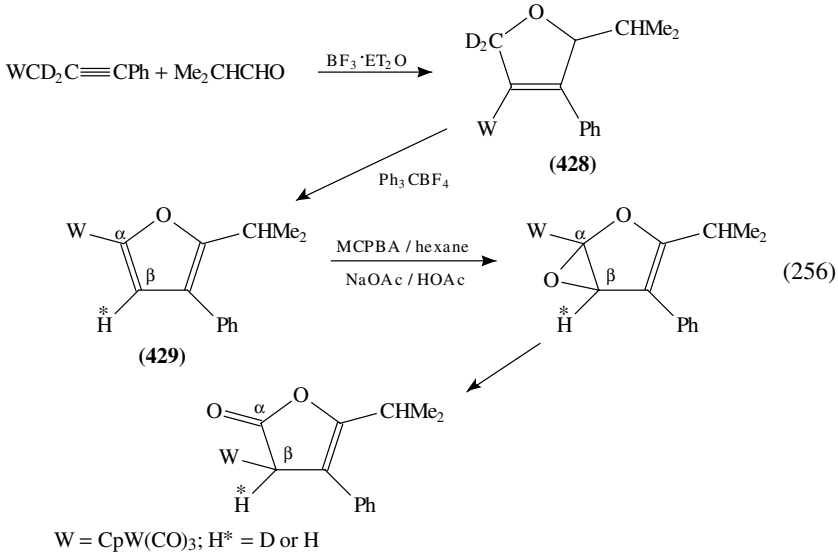
(427) isotactic product

The temperature-dependent stereoregular MAO-promoted polymerization of α-olefins[502] has been explained by β-hydrogen interactions in the olefin insertion and formation of a six-membered $-C_\alpha-C_\beta-D_\beta-Al-O-Al$ ring TS. The stereoselective isotactic product formation occurs as a result of the substituent orientation at the β-carbon (R^1 vs $CH_2CHR^2R^4$ in the conformationally restricted **426**; equation 255).

6. Deuterium study of the mechanism of oxidation of tungsten η^1-2,5-dihydrofur-3-yl compounds to η^1-Δ^3-butenolide derivatives

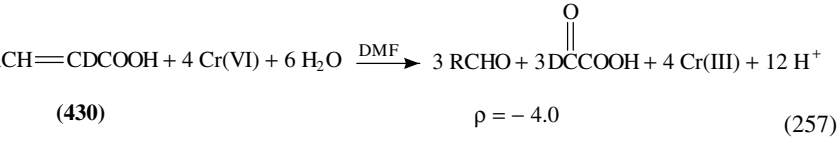
The deuterium-labelled **428** has been synthesized[503] via $PhC{\equiv}CCD_2OH$ to confirm the source of the $C_\beta-H$ hydrogen in **429**. The ^{1}H-NMR spectra of the furan, derived from

428, confirmed a 1,2-hydrogen shift (equation 256).



7. Deuterium isotope effects in the oxidative cleavage of unsaturated acids by quinolinium dichromate

A small inverse KIE, $k_H/k_D = 0.78$, has been observed[504] in the oxidation of cinnamic-α-d acid, **430** with quinolinium dichromate (QDC) (equation 257). In the case of the oxidation of β-d-cinnamic acid, $(k_H/k_D) = 0.987$ at 40 °C.

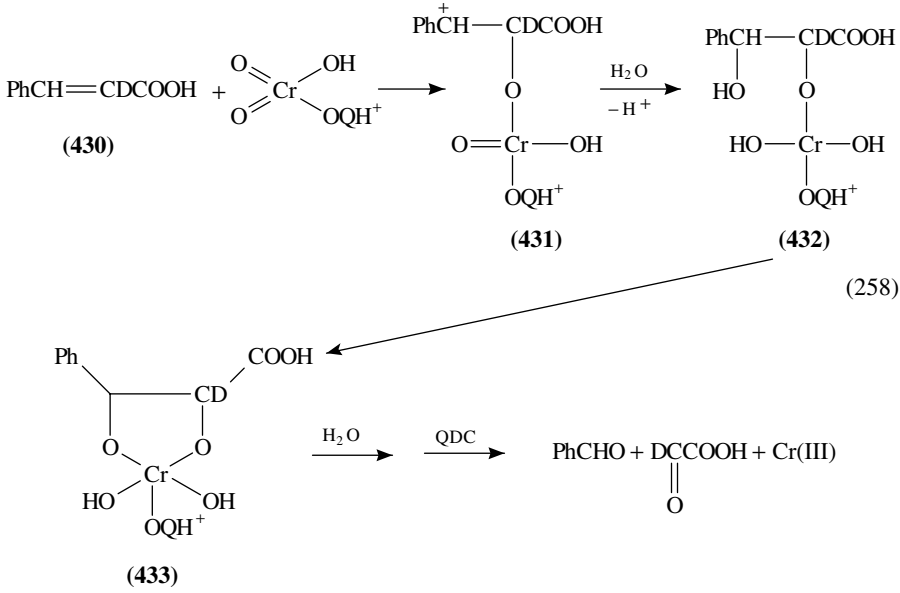


The above values of α- and β-D KIEs indicate a change in the state of hybridization from sp^2 to sp^3 of the α-carbon atom and no sp^2 character of hybridization change at β-C in the RDS of the oxidation of **430** by QDC. A substantial $C_\alpha-O$ bond formation and negligible $C_\beta-O$ bond formation take place in TS after QDC attack. The mechanism of reaction 257 involves electrophilic attack of the protonated oxidant on the double bond of the substrate **430**, formation of the carbonium ion, **431**, its reaction with water to form the intermediate **432**, conversion of **432** to the chromate ester **433** and its cleavage to products (equation 258). The positive value ($\Delta H^{\#} = 82$ kJ mol^{-1}) of enthalpy and negative value of entropy ($\Delta S^{\#} = -57$ kJ^{-1} mol^{-1}) of the reaction indicate that the TS of reaction is highly solvated and considerably rigid.

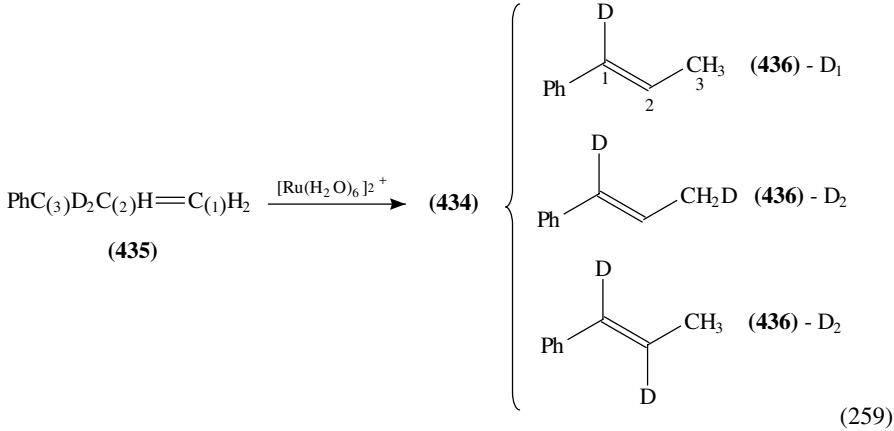
8. The rearrangement of 3-phenyl propene-3,3-D_2 **435** *catalysed by $[Ru(H_2O)_6]^{2+}$*

The rearrangement of **435** by $[Ru(H_2O)_6]^{2+}$, **434**, in C_2D_5OD, $(CD_3)_2$ CO, THF-D_8, and Et_2O provided[505] a mixture of *trans*-phenylpropene with deuterium content in

all carbons of the propyl chain, i.e. **436**-D_1 and **436**-D_2 (equation 259). The ratio of **436**-D_1 to **436**-D_2 is insensitive to solvent. The three IR signals in the region of the C−D stretching vibration (2236, 2195 and 2160 cm^{-1}) agree with deuterium on all three carbons of the propene chain. The rearrangement of **435** to **436** was irreversible. 79% of **436**. $PCH^*{=}CH^*CH_3{}^*$, contained 1 deuterium atom and 19% of **436** contained two deuterium atoms (determined by ^1H NMR and ^{13}C NMR) (equation 260).



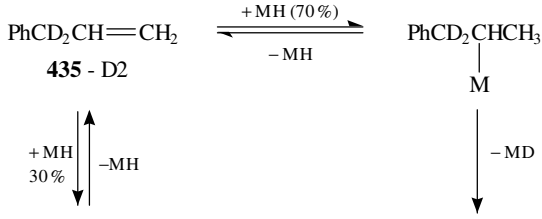
(258)



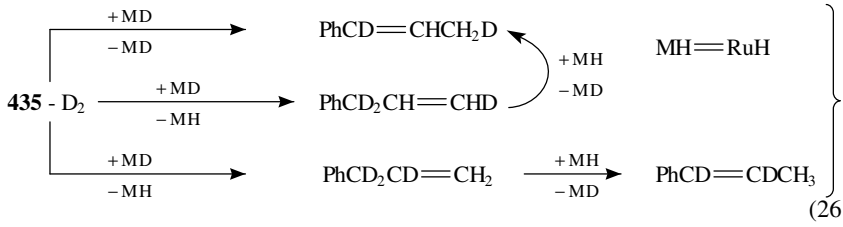
(259)

The above results are consistent with a steric specific *syn* 1,2-addition–elimination of metal hydride intermediate which is formed fast in a pre-equilibrium {[MH] ≫ [MD]} and adds to the olefinic substrate to form the metal alkyl intermediate (equation 261). The β-hydride elimination of the most stable rotamer (equation 262) is the RDS in the rearrangement, leading to a metal hydride–product complex, which starts a new cycle faster than uncoordinated metal hydride. The protonated catalyst, **434**, produces a precursor

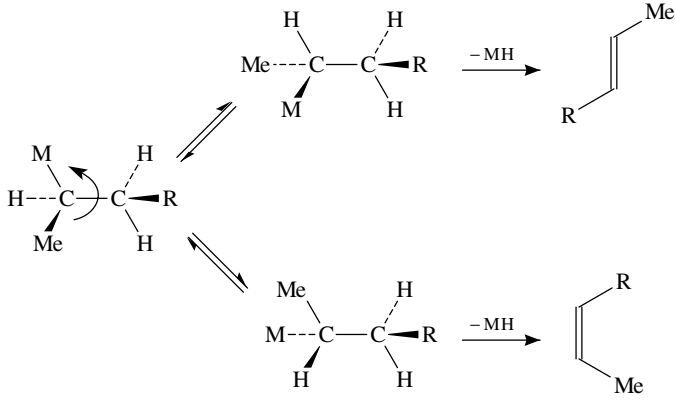
of the type $[(H_2O)_5Ru(\eta^2\text{-olefin})]^{2+}$ which rapidly yields the ruthenium alkyl complex. The deuterium exchange between metal hydride and solvent has been found to be slow compared to rearrangement.



(260)

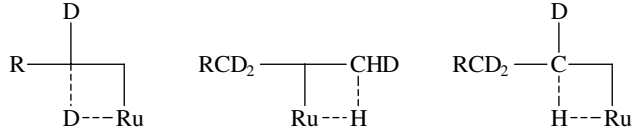


(261)

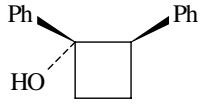


(262)

At 302 K, the **435**-D_2 (after an induction period of 5 min) rearranges 2.3 times lower than undeuteriated **435**. This DKIE has not been interpreted in terms of TS structures **437–434** probably due to the lack of data concerning the rearrangement of $PhCD_2CD{=}CD_2$, $PhCD_2CD{=}CH_2$ and $PhCH_2CH{=}CD_2$ isotopomers[506].

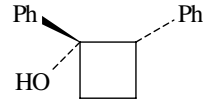


(437) **(438)** **(439)**



(440) - *cis*

440 - *cis* (pH 11.6)

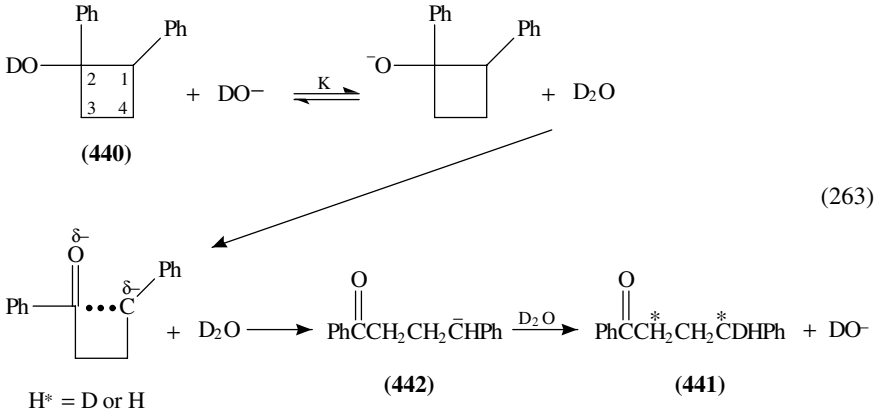


(440) - *trans*

440 - *trans* (pH 12.01 / D_2O)
$k_{H_2O} / k_{D_2O} = 0.68$

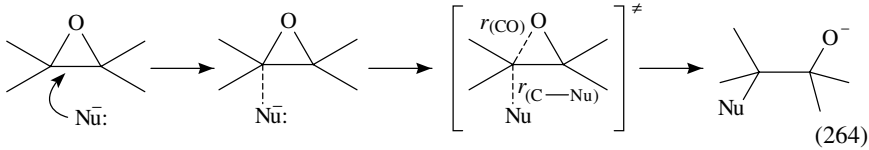
*9. Deuterium isotope effect in ring opening of 1,2-diphenylcyclobutanols **(440)***

Cis- and *trans*-**440** with base yield 1,4-diphenylbutan-1-one, **441**. In D_2O the product incorporates one deuteron at $C_{(4)}$ and varying amounts of deuterium at the enolizable 2-position[507] (equation 263). The inverse solvent deuterium isotope effect (k_{H_2O}/k_{D_2O} = 0.68) and the discrimination isotope effect ($k_H/k_D = 0.99 \pm 0.05$)[508] support a reaction scheme, in which the alkoxide reacts in the RDS to yield a benzylic anion **442**, which in turn yields the deuteriated product **441** (equation 263).



(263)

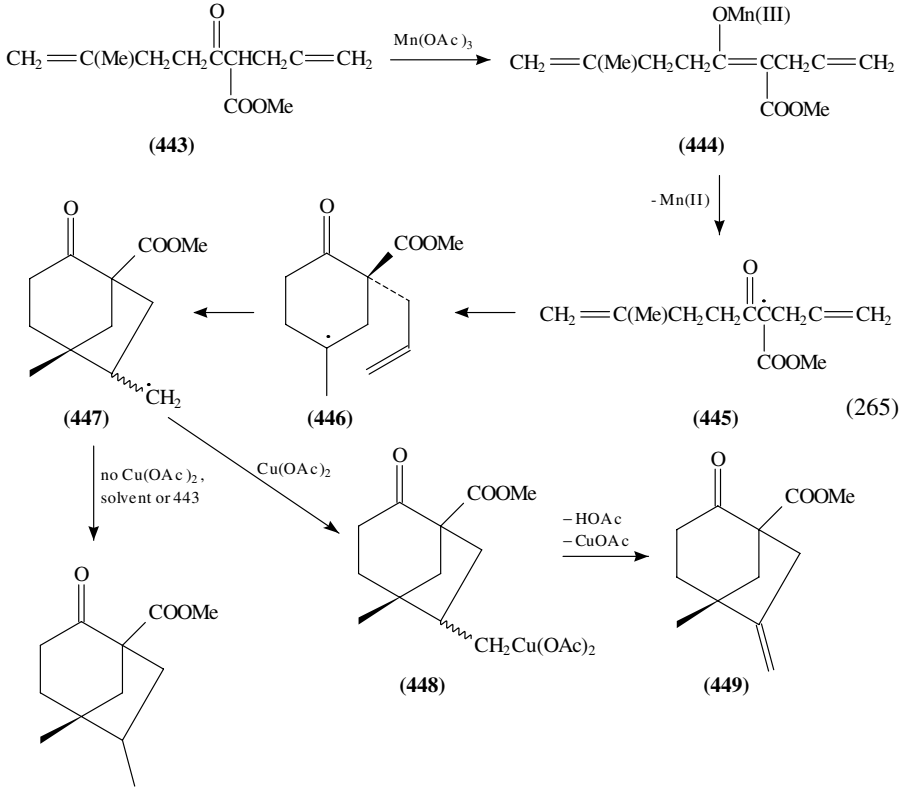
In the reaction of benzylic anion with H_2O controlled by H−O/D−O bond ruptures the discrimination (k_H/k_D) isotope effect should be observed. An *ab initio* study of the deuterium α-secondary KIEs and of the corresponding transition structures in the ring opening of ethylene oxide by different nucleophiles, like NH_3, F^-, OH^-, NH_2^-, H^-, Cl^-, SH^- (equation 264), has been carried out[509], and the conclusion has been reached that the KIE decreases as the TS becomes more product-like, i.e. tighter. An almost linear correlation between TS geometry and secondary KIE has been found. This correlation is primarily due to bending vibrations, but the absolute value of the secondary KIEs is governed mainly by stretching vibrations and cannot be explained by considering the C_α−H(D) out-of-plane bending vibration only.



(264)

10. Deuterium tracer and isotope effect study of Mn(III)-based oxidative free-radical cyclizations

The unsaturated β-keto ester **443** is converted to methylenecyclo[3.2.1]octane, **449**, with 2 equiv. of $Mn(OAC)_3$ and 1 equiv. of $Cu(OAc)_2$[510] (equation 265). Oxidation of **443** with 2 equiv. of $Mn(OAc)_3$ in AcOH without $Cu(OAc)_2$ provides alkene **449** in 14% only and alkanes **450a** and **450b** in 7% and 17% yields, respectively[510]. Oxidation of **443** with 2 equiv. of $Mn(pic)_3$ and 1 equiv. of $Cu(OAc)_2$ in AcOH provides none of alkene **449**, 15% of alkane **450** and 69% of oligomeric material. To understand the above observations deuterium tracer and KIE studies have been undertaken[511].

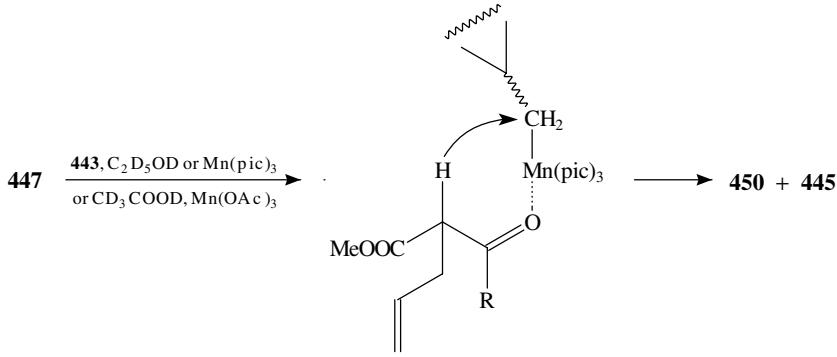


(450a) α-Me, **(450b)** β-Me

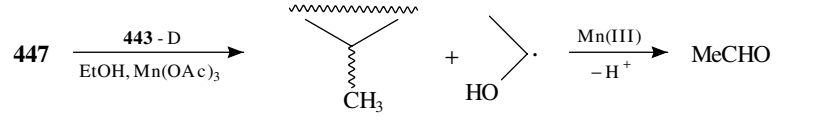
(a) *The source of hydrogen atom* transferred to **447** has been established by carrying out the oxidative cyclization of **443** in AcOD, CD_3COOD, C_2H_5OD and C_2D_5OD. No deuterium incorporation in the product has been found, showing that radical **447** abstracts in this case the α-hydrogen from **443** to afford alkane **450** and the acyclic radical **445** (equation 266).

(b) The reaction of the β-keto ester **443**-D with 2 equiv. of $Mn(OAc)_3$ and $Cu(OAc)_2$ provided **450** in 65% yield, while β-keto ester **443**-H provides only 2% of **450** under the same conditions. Similarly, oxidation of **443**-D with 2 equiv. of $Mn(pic)_3$ and 1 equiv. of $Cu(OAc)_2$ in EtOH (proceeding at a slower rate than oxidation of **443**-H) increased the yield of **450** from 22% with **443** to 67% with **443**-D. In AcOH, the yields of **450**

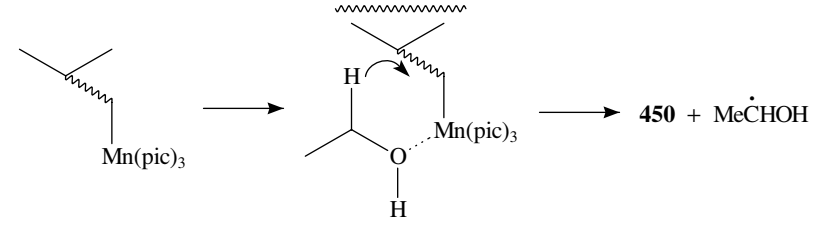
with both $Mn(pic)_3$ and $Mn(OAc)_3$ oxidants increased to about 60%. No evidence for incorporation of deuterium in alkane **450** has been noted. The suggestion has therefore been made[511] that these oxidations proceed according to equation 267: **447** abstracts the α-hydrogen from EtOH in these experimental condition and Mn(III) is being consumed in reaction 267. The (k_H/k_D) of 8.57 has been assessed at RT for the conversion of β-keto ester **443** to manganese enolate **444**, which is the RDS in the formation of alkene **449**. This value is higher than DKIE caused by zero-point energy effect only. Due to the large deuterium KIE, no D incorporation in **450** has been observed with either **443**-D or perdeuteriated solvents. In the cyclization of **443**-D, the alkylmanganese picolinate **451** is converted to alkane **450** nearly exclusively via complex **452** because the deuterium transfer from **443**-D is slow (equation 267a). **451** is converted to **450** almost exclusively via complex **453** if deuteriated solvent is used, owing to the large DKIE.



(453) (266)



(452) (267)

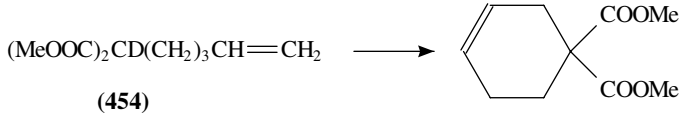


(451) **(452)** (267a)

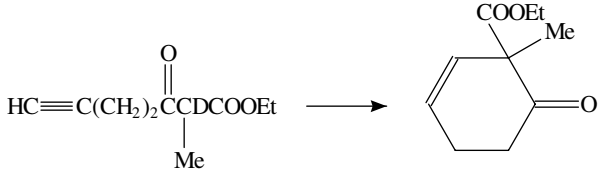
Both of the above reaction pathways are suppressed if **443**-D and perdeuteriated solvents are used simultaneously in cyclization reaction 265. Mainly oligomer and less than 5% of alkane **450** were then produced. This has been explained by different reactivities of radical **445** formed directly from **444** or formed by abstraction of hydrogen atom from **443** through complex **453**. The more energetic radicals formed by hydrogen atom transfer from **443**, add intermolecularly to an alkene and initiate preferentially oligomerization[512], while

the less energetic radicals **445** formed from manganese enolate **444** cyclize preferentially to give the cyclic radical **447**.

The deuteriated dimethyl 4-pentenylmalonate (99% D at C_α), **454**, and deuteriated acetylenic β-keto ester **455** have been synthesized and applied in oxidation studies[511] with the one-electron oxidants $Mn(OAc)_3$ and $Cu(OAc)_2$ in EtOH and AcOH (equations 268a and b).



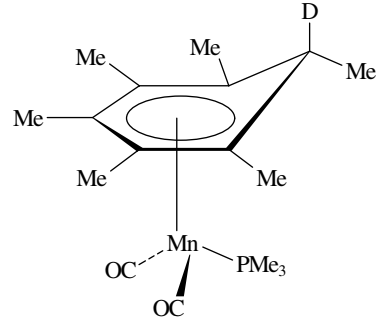
(454) (268a)



(455) (268b)

11. Deuterium isotope effect in the hydride ion transfer from carbon–hydrogen bonds to CS_2

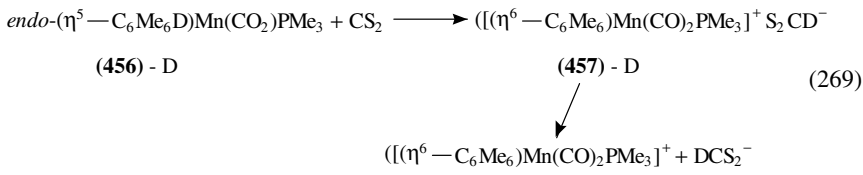
The manganese complexes, *endo*-(η^5-$C_6Me_nH_{7-n}$) Mn(CO)LL′ (n = 0, 3, 6; L,L′ = CO, PR_3), transfer hydride ion to CS_2 or to COS in THF providing HCS_2^- and $H(O)S^-$, respectively, and the cation [(η^6-$C_6Me_nH_{6-n}$) Mn(CO)LL′]$^+$. The deuteriated cyclohexadienyl complex, *endo*- (η^5-C_6Me_6D) $Mn(CO)_2PMe_3$ derivative, **456**, prepared by reducing [(η^6-arene) $Mn(CO)_2PMe_3$]PF_6 cation with $NaBD_4$ in THF, has been used[513,514] to study the mechanism of this reaction (equation 269).



(456)

The D KIE (k_H/k_D) in reaction 269 has been found to be 3.2 at 28 °C. Small primary DKIEs are usually associated with unsymmetrical TS in hydrogen transfer and non-linear atomic arrays. The above value of k_H/k_D observed in this study suggests that C–H bond polarization is occurring. No radical species have been found in reaction of **456** with CS_2 by ESR study[514]. Therefore it was suggested that the reduction does not proceed by initial SET from manganese species followed by hydrogen atom transfer but directly by a concerted one-step hydride ion transfer. The course of reaction 269 between **456**-H

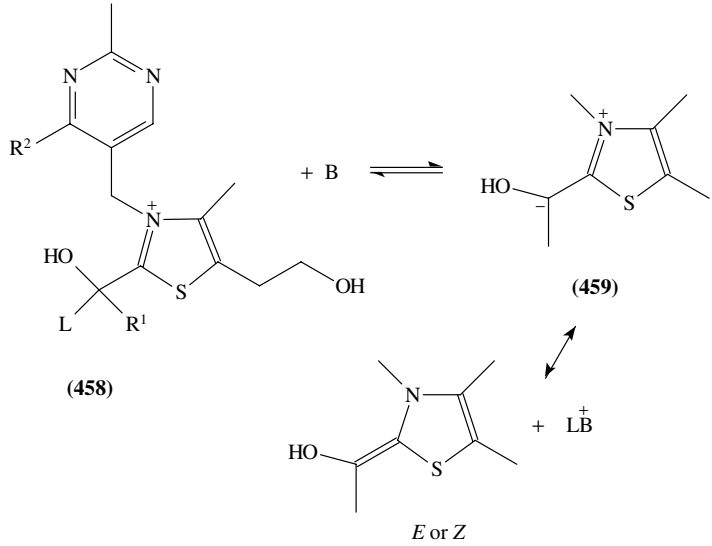
and CS_2 has been followed by IR. The derivative **457** has been formed quantitatively (by IR and ^1H NMR). The cationic complexes **457** display spectra similar to the original complexes $[(\eta^6\text{-}C_6Me_6)\ Mn(CO)_2PMe_3]\ PF_6$ except for the presence of dithioformate (HCS_2^-) as the counterion. The values of k_{obs} have been determined.



(269)

*12. Deuterium and tritium isotope effects in the base-catalysed C_α–hydron transfer from 2-(1-hydroxylbenzyl)oxythiamin (HBOT; **458**)*

The primary T and D KIEs for cacodylate-catalysed C_α–hydron transfer from racemic **458** (equation 270), $k_H/k_T = 1.8 \pm 0.1$, obey the Swain–Schaad relation[515] and are consistent with incomplete proton transfer in the rate-limiting TS[516,517].



(270)

R^1 = Ph, R^2 = OH, B = $(CH_3)_2As(O)OK$

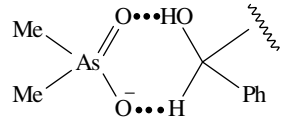
pH range: 4:5 – 10, *I*(ionic strength) = 1.0 M (KNO_3)

The above KIE determinations have been taken as providing evidence against the rate-limiting TS involving diffusion-controlled separation of the buffer acid from the $C_{(\alpha)}$–carbanion/enamine **459** resonance-stabilized conjugated base[515,518].

The TS of the C_α–hydrogen transfer reaction from **458** is probably preceded by the formation of the hydrogen-bonded structure[519] **460**.

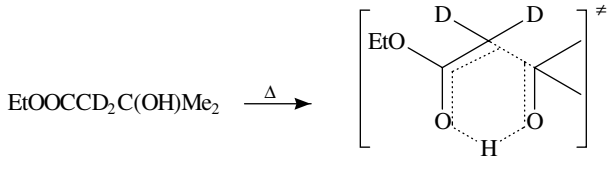
13. Deuterium isotope effects in the thermolysis of β-hydoxy esters

It has been proposed[520–522] that the β-hydroxy esters undergo thermal decomposition into aldehydes, ketones or esters through a cyclic six-membered TS (equation 271). The



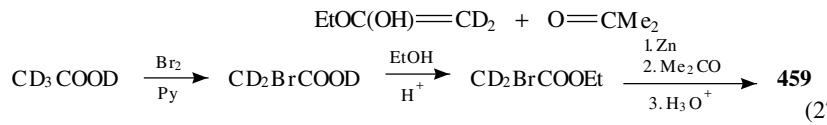
(460)

small value of the primary DIE suggested[522] a non-linear and either early or late TS. The secondary DIE k_{H_2}/k_{D_2}, of 1.26 ± 0.06 observed[523] in the pyrolysis of **459** is in agreement with the structure **460** of TS shown in equation 271, and compatible with the change of hybridization of $C_{(2)}$ from sp^3 to sp^2 in the course of the decomposition. According to Streitwelser[524] the alpha deuterium IE is caused by the change of a tetrahedral C−H bending vibration to an 'out of plane' deformation in the TS. The experimental value of 1.26 is consistent with the theoretical calculations[525,526] and suggests a late TS, but the ^{13}C and ^{14}C KIE in the rupture of the $C_\alpha - C_\beta$ bond have not been determined. A D KIE value of 1.22 has been obtained in the sigmatropic rearrangement[527] of 3,3,4,4-tetradeuterio-1,5-hexadiene at 200 °C.



(271)

(459) **(460)**



(272)

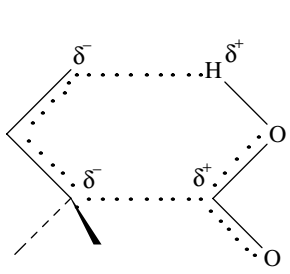
*14. Deuterium and carbon-14 KIE in the thermal decarboxylation of but-3-enoic acid **(461)** and its derivatives*

461 decomposes to propene and carbon dioxide (equation 273):

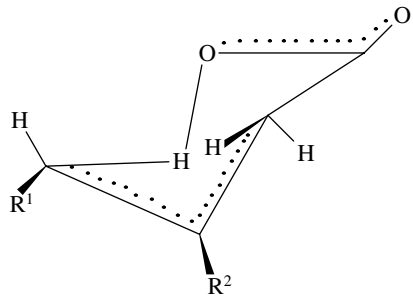
$$CH_2{=}CHCH_2COOH \longrightarrow CH_3CH{=}CH_2 + CO_2 \tag{273}$$

A Sizable primary KIE's have been observed in the gas-phase thermal decomposition of 2,2-dimethyl-4-phenyl but-3-enoic acid[528,529], consistent with a synchronous mechanism via a six-membered cyclic ideal TS, **462**. Recently[531] the mechanism of thermal decarboxylation of **461** and its derivatives $HR^1C{=}CR^2CH_2COOH$ (R^1 and R^2 = H, F, Me, Et and Cl) has been studied again[530,531] from the theoretical point of view by *ab initio* MO calculations and a 'twisted chair' six-membered cyclic TS **(463)** has been constructed.

The best estimate of 156.8 kJ mol^{-1} for the activation energy is in reasonable agreement with the experimental value of 164 ± 7 kJ mol^{-1} for the unsubstituted case. The Mulliken charges are consistent with the expected charge distribution shown in structure **462**. The

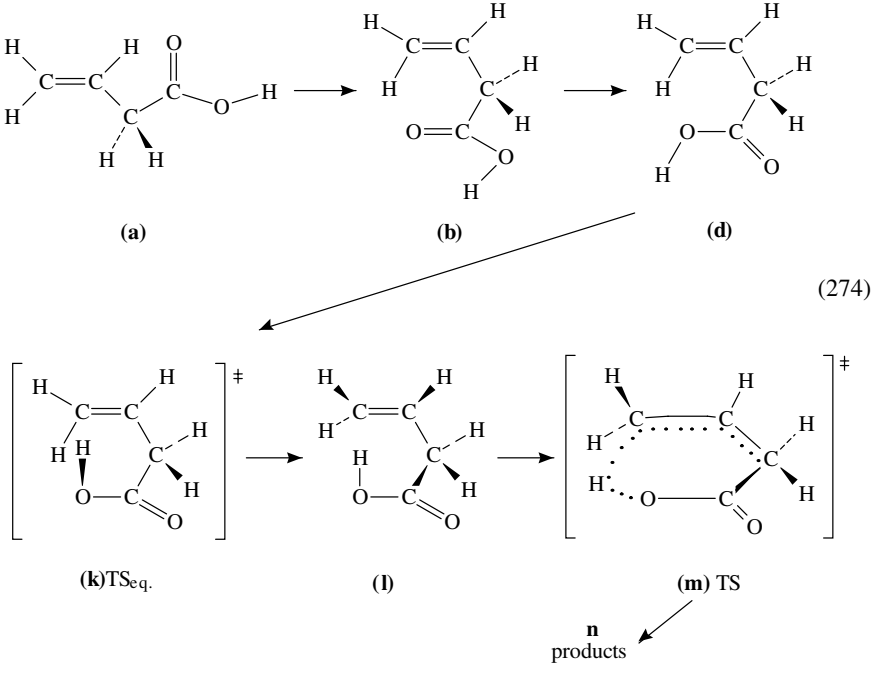


(462)



(463)

normal-mode vibration frequencies for **461** have been calculated and the zero-point energy (ZPE) corrections and primary k_{12}/k_{14} values computed using a modified version of the BEBOVIB program[532]. The values of $(k_H/k_D) = 2.45$ (using Wigner's equation) and 2.86 (using Bell's equation) have been computed at 650 °C. The k_{12}/k_{14} values equal to 1.02 (with Wigner's correction) and 1.03 (with Bell's correction) have been calculated[529] also, and compared with $(k_{12}/k_{14})_{exp} = 1.035 \pm 0.010$ determined[528] for PhCH=CHCMe$_2$COOH at 550 °C. The energy profile for the decarboxylation has been constructed[528]. The series of transformations of subsequent conformers, preceding the TS formation shown in equation 274, has been presented but the equilibrium thermodynamic isotope effect fractionation related with these transformations from the lowest energy conformation **(a)** to the reacting conformer (**k**, **l**), which is followed by the RDS of reaction **(m)**, have not been calculated.



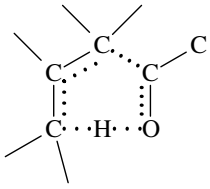
(a) **(b)** **(d)**

(274)

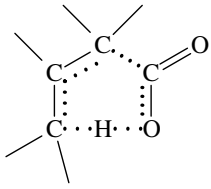
(k)$TS_{eq.}$ **(l)** **(m)** TS

n
products

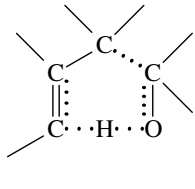
The conformational change **d** to **l** has the highest rotational barrier (of 40.6 kJ mol^{-1}) but is much lower than the activation energy of 215.0 kJ mol^{-1} (in the HF/3-21 G′ approximation). It is interesting to note that in the earlier studies[529] of D KIE in the thermolysis of β-hydroxy olefins, 4-penten-2-ol, 3-butenoic acid and 3-butyn-1-ol as a function of temperature over a large temperature range, the experimental values of k_H/k_D, corresponding to the transfer of hydrogen between the carbon and oxygen termini in the sigmatropic hydrogen migrations (TS, **464**, **465**, **466**), and the theoretical k_H/k_D values, corresponding to a fully symmetrical transition state, computed assuming that the zero-point energy difference of OH and OD stretching vibrations alone determines the k_H/k_D values, are nearly coincident in the relatively high temperature region (500 °C–390 °C) investigated.



(464)



(465)



(466)

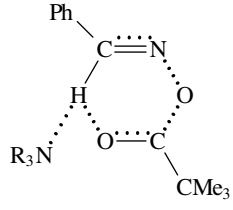
15. Deuterium KIE in the nitrile-forming elimination (E)-O-pivaloylbenzaldoxime ***(467)***

The deuterium KIE in the nitrile-forming elimination of **467** (equation 275), promoted by Et_3N–MeCN, *t*-BuOK–*t*-BuOH–and *t*-BuOK–DMSO, has been found[533] to be dependent on the base–solvent variation from *t*-Bu-OH to DMSO.

$$\underset{(\mathbf{467})X = H(D)}{PhC(X){=}NOOCCMe_3} + base \xrightarrow{\text{solvent}} PhCN + {}^{-}OOCCMe_3 \qquad (275)$$

At 25.0 ± 0.1 °C the values of k_H/k_D increase in the order 3.67 ± 0.31 (Et_3N–MeCN), 4.15 ± 0.36 (*t*-BUOK–*t*-BuOH), 5.06 ± 0.01 (*t*-BuOK–DMSO).

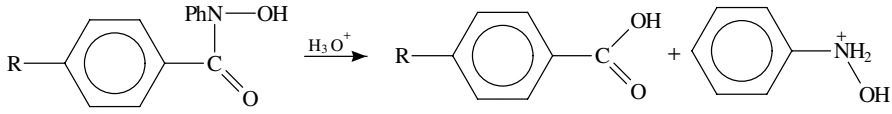
Reaction 275, producing benzonitrile quantitatively, has been classified as proceeding according to the E2 mechanism with the cyclic transition state **468**. The structure of the TS has not been corroborated by ^{14}C, ^{15}N and ^{18}O KIE studies so far. The change in (k_H/k_D) value from 4.2 to 5.1 for solvent variation from *t*-BuOH to DMSO has been interpreted[534,535] as arising from the slight shift of the TS from a partly asymmetric product-like one to a more symmetrical one in DMSO, which is a poorer anion-solvating solvent that *t*-BuOH.



(468)

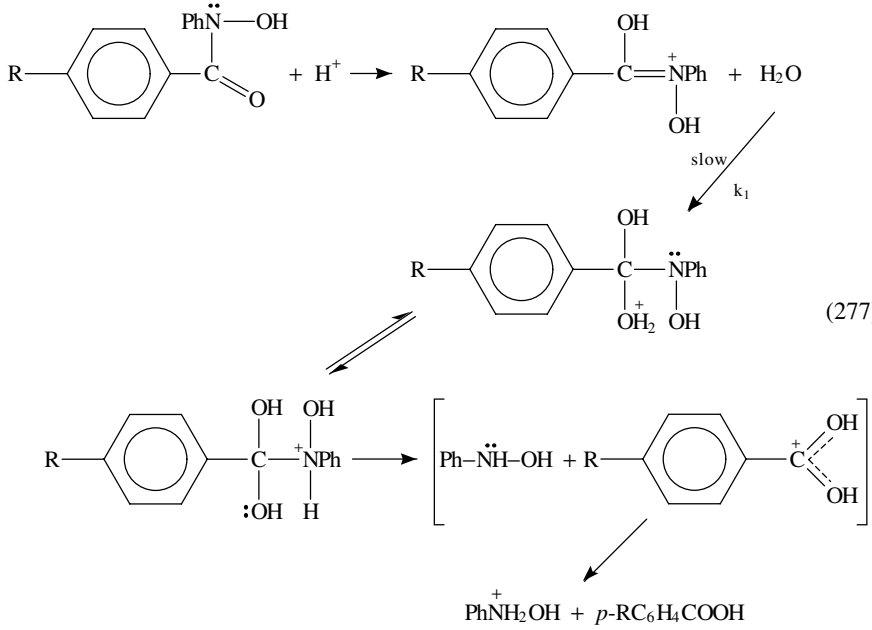
16. Solvent D KIEs in the acid-catalysed hydrolysis of benzohydroxamic acids

Solvent D KIE in the acid-catalysed hydrolysis of some *N*-phenyl-4-substituted-benzohydroxamic acids (equation 276), using either H_2SO_4 or D_2SO_4 in 20/80 dioxane–water medium, have been observed to be equal (Table 4)[536].



(469) (276)

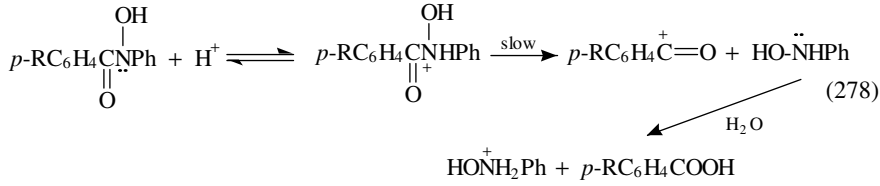
It has been suggested that reaction 276 proceeds according to the A-2 mechanism shown in equation 277 at low acidities and according to the A-1 unimolecular mechanism at high acidities (equation 278). The protonation behaviour of **469** and the problem whether the hydrolysis proceeds via N- or O-protonated conjugate acid is currently being studied[536–541].



(277)

TABLE 4. Solvent D KIEs (k_H/k_D) in the hydrolysis of **469**

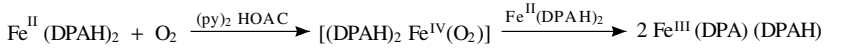
Phenyl x substituent (R)	With 2.9 M D_2SO_4	With 10.4 M D_2SO_4
H	0.59	1.066
OMe	0.80	1.11
Me	0.65	—
NO_2	0.68	1.17
Cl	0.93	1.03
F	0.76	1.05



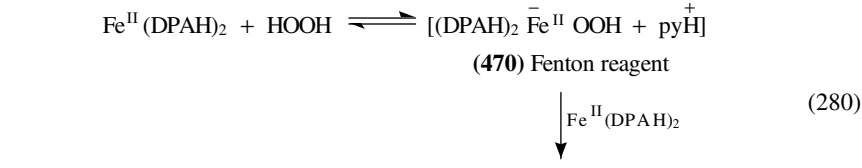
(278)

17. D KIE determinations in the ketonizations of methylenic carbons with dioxygen (O_2) catalysed by $Fe^{II}(DPAH)_2$ complex

D KIEs have been determined[542] in the course of studying the mechanism of ketonization of c-C_6H_{12} with Fe^{II} $(DPAH)_2$ ($DPAH_2$ = 2,6-dicarboxypyridine) and $^{18}O_2$ in $(py_2)_2 \cdot HOAc$[543,544]. HOOH is the primary product from combination of $Fe^{II}(DPAH)_2$ and O_2 in $(py)_2$ HOAc. Also, the $Fe^{III}Cl_3$/HOOH, $^{18}O_2$/c-C_6H_{12}/$(py)_4$ HOAc system produced[545] c-$C_6H_{12}(^{18}O)$ and $C_6H_{11}{}^{18}OH$. $Fe^{II}(DPAH)_2$ provides the hydrogen atoms for the formation of H_2O_2. Addition of O_2 to $Fe^{II}(DPAH)_2$ results in rapid autooxidation and production of HOOH, which in turn reacts very fast with $Fe^{II}(DPAH)_2$ (equation 279 and 280).



(279)



(280)

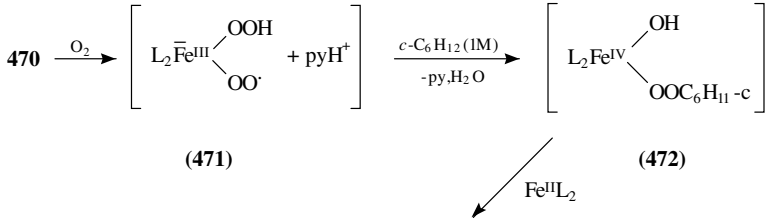
In the presence of c-C_6H_{12}/c-C_6D_{12} and PhSeSePh, c-C_6H_{11}SePh and c-C_6D_{11}SePh are produced (equation 281). The H_2O_2 generated from $Fe^{II}(DPAH)_2$ and O_2 is activated by excess $Fe^{II}(DPAH)_2$ and generates these products.

$$Fe^{II}(DPAH)_2 + HOOH + c-C_5H_{12}\{c-C_6H_{12}\} + 1/2PhSeSePh \longrightarrow$$
$$Fe^{III}(DPA)(DPAH) + c-C_5H_{11}SePh\{c-C_6D_{11}SePh\} + 2H_2O \qquad (281)$$

In the $Fe^{II}(DPAH)_2$/O_2/c-C_6H_{12} (or/and c-C_6D_{12}) system the intermediate **470**, produced via nucleophilic addition of HOOH to $Fe^{II}(DPAH)_2$, combines with O_2 to form the adduct **471** which, reacting with c-C_6H_{12} (and/or c-C_6D_{12})[542,544], provides c-C_6H_{10}(O)/[and/or c-C_6D_{10}(O)] with a KIE of 2.0 (equation 281a). In the case of large HOOH/$Fe^{II}(PA)_2$ or $(DPAH)_2$ ratio **472** reacts with another RH molecule (equation 282).

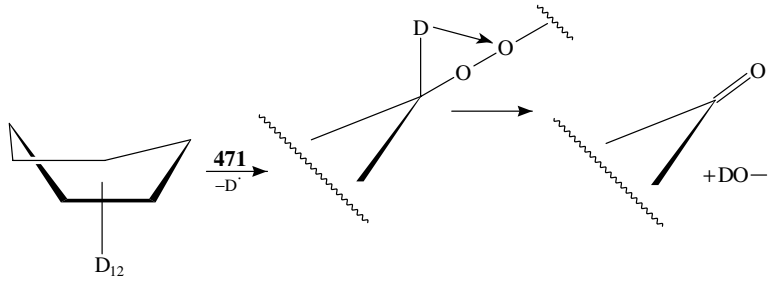
The D KIE in the above reactions of the Fenton reagent have been determined using 1 : 1 cyclohexane/cyclohexane-D_{12} mixture as a substrate, and calculated from the product ratios c-C_6H_{10}(O)/c-C_6D_{10}(O), (c-C_6H_{11})py/(c-C_6D_{11})py) and c-C_6H_{11}SePh c-C_6D_{11}SePh. In the presence of the carbon radical trap PhSeSePh, the $k_H/k_D = k_{c-C_6H_{12}}/k_{c-C_6D_{12}}$ ratios were in the range 2.2–2.4. In the absence of PhSeSePh the k_H/k_D ratios were in the range 2.0–2.1. The production of (c-C_6D_{11})py in Fe^{II}(DPAH)/HOOH/Ar

in the $(py)_2$ HOAc system proceed with a D KIE of 1.7–1.8. No TS structures have been assigned to the above D KIEs determined from the product ratios. According to the reaction pathways[542] outlined in equation 281a the C−D bond rupture takes place in the course of interaction of **471** with the saturated hydrocarbon C_6D_{12} to produce the carbon radical C_6D_{11} that is trapped by the bound dioxygen to give **472**-C_6D_{11}, which in turn rapidly transfers the second D atom to the nearest oxygen and stabilizes as ketone $C_6D_{10}(O)$ (equation 283).



(281a)

$$\mathbf{472} + R^1H \longrightarrow \underset{c\text{-}C_6H_{10}(O)}{R^2(O)} + R^1OH + H_2O + \underset{2Fe^{III}(DPA)(DPAH)}{Fe^{II}(PA)_2 \text{ or } Fe^{II}(DPAH)_2} + 2H_2O \qquad (282)$$



(283)

D KIEs in the free radical splitting of the C−H/C−D bonds in the RDS caused by the energy difference of C−H/C−D bonds should have (at 25 °C) the value of 7. Cyclohexane-D_{12} contained 99.5 atom % D at the beginning of reaction, but the yields of the products have been of 2–8 mM only, although the initial concentration of substrates was 0.5 M c-C_6H_{12}/0.5 M c-C_6D_{12}. In the initial periods of reaction at degrees of oxidation less than 0.5% the deuteriated ketone might be formed by free radical splitting of the residual C−H bonds in a not completely deuteriated $C_6D_{11}H$ compound. The interpretation of the k_H/k_D of 2 in terms of specific interaction of **471** with c-C_6D_{12} at very low degrees of conversion of substrate should thus be postponed.

18. Brief review of isotope effect studies in catalytic reactions

Substantial KIEs have been observed in the direct dissociative chemisorption of CD_4/CH_4 and C_2D_6/C_2H_6 on the Ir (110) surface[546] associated with the asymmetric CD and CH stretching modes.

Oxidative coupling of CH_4/CD_4 mixtures over natural Mn mineral catalysts was found to be comparable with that carried out over a synthetic Mn oxide catalyst[547]. Theoretical predictions of secondary D IEs for ring opening in the reactions *cis*, *cis*, *cis*-1,3,5-cyclooctatriene has been made using *ab initio* MO theory[540]. A secondary DIE of 1.3 at 99.5 °C has been observed in the extrusion of ethylene-D_4 from rhenium(V)

diolates, (η-$C_5(Me)_5$)Re(O)(OCHRCHRO), and the kinetics of oxidation of norbornene, norbornadiene and *trans*-cyclooctene by (η-$C_5(Me)_5$)ReO_3 has been determined[549]. The isomerization and metathesis of 1-butene over molybdenum-aluminia catalyst has been studied[550] with the use of 1-butene-D_8.

The noticeable inverse DIEs in formation of hydrocarbons and of oxygenates (including MeOH, EtOH, MeCHO) have been observed by performing $CO-H_2$ and $CO-D_2$ reactions over Rh catalyst promoted with vanadium[551]. The inverse DIE for the ethene formation through a late TS has been observed[552] in ethanol dehydration over Nb dimers on a SiO_2 surface. The dimers have an oxygen-bridged dimeric structure [Nb–O (surface) = 0.193 nm, Nb–Si = 0.328 nm, Nb–Nb = 0.303 nm] by EXAFS. The Nb monomers possess the dehydrogenation ability. The shift of the catalyst from dehydrogenation (basic property) to dehydration (acidic property) has been activated by the nucleation of one atom to two Nb atoms in active structures. The mechanism of catalytic dehydrogenation of alcohols by the 2,2-bipyridine-copper(I) chloride–dioxygen system in acetonitrile has been studied with the use of deuterium isotope effect determinations[553]. Deuterium IE study of the dehydrogenation of cyclooctane with $IrCl(CO)(PR_3)_2$ indicated the substantial H–H bonding in the TS of this reaction[554]. The decomposition of $(Me_2CD)_2$ Te in helium in the presence or absence of mercury and/or Me_2Cd showed that the all-hydrogen abstraction reactions occur from the Me groups since D_1-propene and D_1-propane are the only observable products[555]. Deuterium isotopic labelling showed that catalytic hydrogenation of α-methylstyrene by 9,10-dihydroantracene proceeds via a stepwise radical mechanism induced by bimolecular formation of radicals[556]. The inductive formation of H_2, HD and D_2 has been observed in the oxidation of ascorbic acid by nitrosylpentacyanoferrate(II) promoted by illumination with visible light and the use of excess oxidant[557]. The non-statistical distribution of deuterium has been interpreted as the indication of KIE. The mechanism of oxidation of H/D cyclohexane, toluene, adamantane, propane and ethane in the presence of *t*-Bu hydroperoxide and oxygen gas with methane monooxyenase (MMO) structural model, iron complex {FeO(OAC)[tris-((1-methylimidazol-2-yl)methyl)amine]$_2$}$^{3+}$, has been investigated[558]. The deuterium isotope effect, k_H/k_D of 2.1 ± 0.3, has been found for the oxidation of cyclohexane in the system MeCN/Zn/HOAc/O_2/2-methyl-imidazole/Fe porphyrin/Me viologen (methyl viologen = 1,1′-dimethyl-4,4′-bipyridinium dichloride)[559].

A substantial inverse solvent isotope effect (k_{H_2O}/k_{D_2O}) = 0.18 ± 0.02 has been observed[560] in the stepwise solvolysis of *trans*-[Ru^{VI}(tpy)$(O)_2$ (MeCN)]$^{2+}$ by PPh_3, $Ph_2PCH_2CH_2PPh_2$ or by $Ph_2PCH_2PPh_2$ to give the free diphoshine dioxides and [Ru^{II}(tpy)$(MeCN)_3$]$^{2+}$ (tpy = 2,2′,6′,2″-terpyridine). An appreciable inverse deuterium isotope effect for the aldehyde formation has been observed[561] in the hydroformylation of liquid olephins (1-hexene, 1-heptene, 1-octene and Me-10-undecenoate) by CO/D_2 versus CO/H_2, catalysed by SiO_2-supported sulphonated-triphenylphosphine–rhodium complexes. The H_2/D_2 coordination and hydrogenolysis of formyl species in the last step are considered as responsible[561] for the overall inverse IE. Low values of DIEs have been observed in the reaction of $R^1R^2CN_2$ with $(MeO)_2P(O)D$ catalysed with $Cu(OAc)_2(CuL_2)$ complex and interpreted as consistent with rate-limiting attack of LCu:CR^1R^2 on the phosphoryl-group O, while the high value of the DIE observed in $Cu(OTf)_2$ catalysed reaction of diazafluorene has been interpreted as consistent with intermediacy of a carbene–CuOTf complex[562] and rate-limiting D transfer. Solvent IEs in the oxidation of chloracetic acids by sodium-*N*-bromo-*p*-toluenesulphonamide (BAT, bromamine-T) catalysed by Ru(III) ion has been studied in D_2O[563]. The primary DIE of 1.62 ± 0.13 observed in the addition of catecholborane to the CpRu(PPh_3)Me complex leading to formation of the corresponding ruthenium hydride and methylcatecholborane[564] and other

factors have been taken as indicating that the mechanism involves a four-centered TS with partial cleavage of the B−D bond during formation of the B−C bond. The mechanism of the synthesis of indoles from *o*-tolyl isocyanides catalysed by $Ru(dmpe)_2$ (H) (naphthyl) and $Ru(dmpe)_2(H)_2$ has been studied[565] using 4-*t*-butyl-2,6-xylyl-α,α,α-D_3 isocyanide. The observed D KIE in this case showed that the C−H activation is faster than the C−D activation in an intramolecular competition. No DIE was noted in a competitive isotope experiment in which the selection of the bond was intermolecular[565].

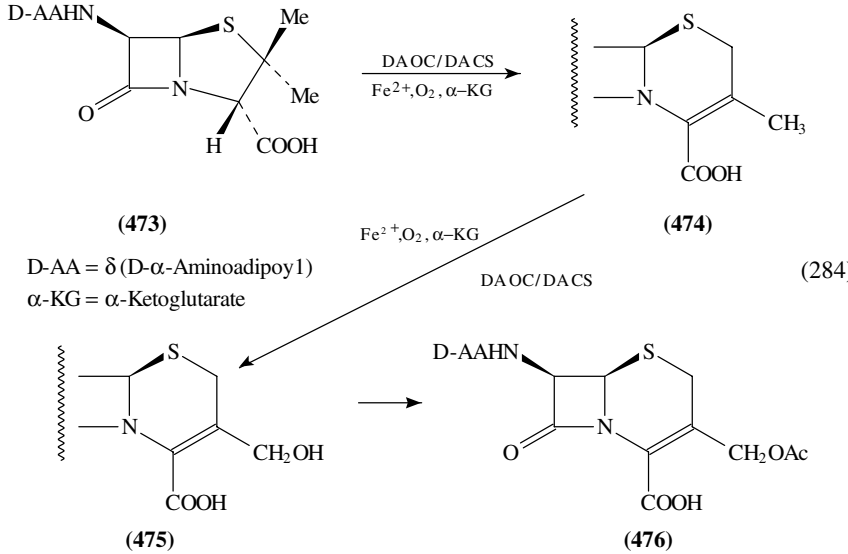
The ^{13}C-labelling experiments allowed one to determine the relative contributions of cyclic and of bond-shift mechanisms in the isomerization and cracking reactions of 2-methylpentane and hydrogenolysis of methylcyclopentane over Pt TiO_2 catalysts prepared by different methods[566].

Deuterium isotope effects in the photocatalytic and thermal dark dehydrogenation of 2-propanol-2-D (at 82.4 °C) with $\{[Ru(SnCl_3)_6]^{3-} \longrightarrow [RuCl(SnCl_3)_5]^{4-}\}$ complexes have been found to be 2.53 and 2.10, respectively, and interpreted as caused by C−H bond splitting in the RDS[566b].

C. Isotope Studies of Enzymatic Biochemical Reactions

1. Deuterium tracer and KIE studies with Cephalosporins

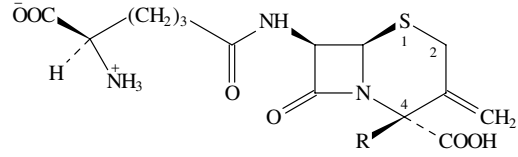
Deacetoxy/deacetylcephalosporin C synthase (DAOC/DACS), the enzyme isolated from *Cephalosporium acremonium* catalysing[587] the ring expansion of penicillin N, **473**, to deacetoxycephalosporin (DAOC), **474**, and the hydroxylation of **474** to deacetylcephalosporin C(DAC), **475**, which *in vivo* is acetylated by a different enzyme to give cephalosporin C, **476** (equation 284), converts also the unnatural substrate exomethylene cephalosporin C, **477a**, directly to DAC, **475** (equation 285).



(284)

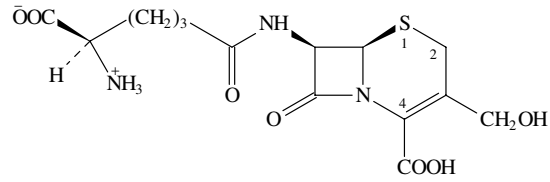
The mechanism of reaction 285 proposed previously[568] has been reinvestigated[567] by synthesizing the [4-^{2}H]exomethylene cephalesporin C, **477b**, by electrolysis of **476** in a deuteriated buffer. Incubation of **477b** with DAOC/DACS provided **475**, and also the spiro-epoxide cepham **478**. The ratio of **475** to **478** varied with the overall degree of

enzymic conversion from 1 : 0.4 (at approximately 25% conversion) to 1 : 0 (at 100% conversion of **477b**). A conclusion from this and other isotopic experiments has been reached that **478** is a shunt metabolite formed through the operation of a DIE on an enzyme-bound intermediate. Aldehyde **479** was isolated from the post incubation mixture when **478** was treated by DAOC/DACS and cofactor (equation 286).



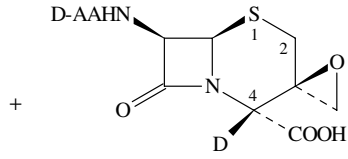
(477a) R = H

(477b) R = D

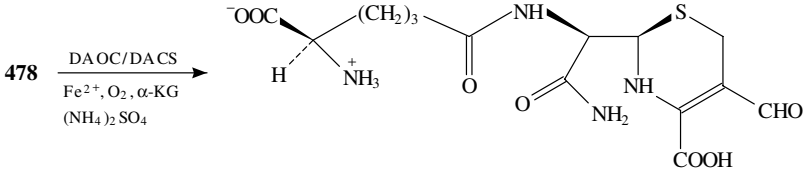


(285)

(475)



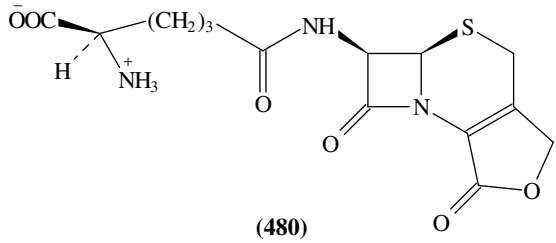
(478)



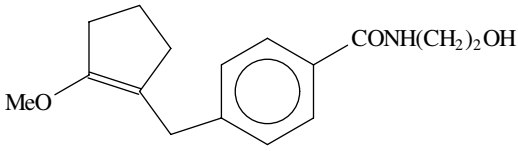
(479) (286)

Two competitive KIE experiments have been carried out subsequently in which a mixture of **477a** and **477b** have been incubated with DAOC/DACS. Samples of varying degrees of enzymic conversion were removed at different reaction times and the ratio **477a/477b** determined by MS. No isotopic enrichment was detected during conversion. This indicates that the $C_{(4)}-D$ bond is not involved in steps up to and including the first irreversible one[569,570].

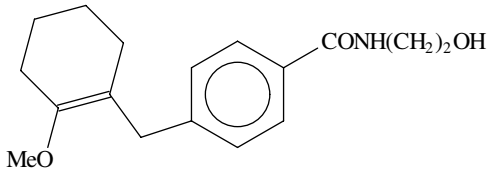
Formic acid treatment of a mixture of epoxide **478** with **475** provided the cephalosporin C lactone **480** together with **478**. The detailed mechanism involving the addition of iron(IV)-oxene to the double bond shown in equation 285 has been proposed[567].



(480)



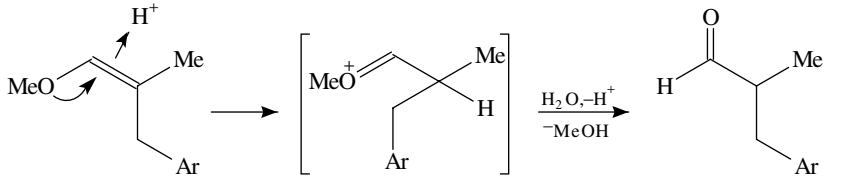
(483)



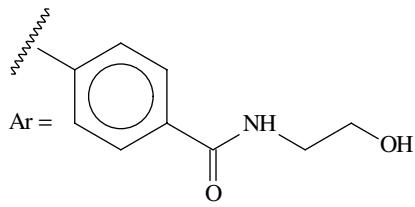
(484)

2. Deuterium solvent IE in the antibody catalysed hydrolysis of enol ethers

The enantioselective hydrolysis of alkyl enol ether **481** to the corresponding carbonyl compound **482**, catalysed by the antibody 14D9 proceeding[571] with very high enantioselectivity of protonation at the β-carbon atom (equation 287), has been studied[572] in both H_2O and D_2O. The solvent KIE was $(k_H/k_D)_{cat} = 1.75$ for the antibody catalysed reaction and 1.92 for the reaction of **481** with hydronium ion. The reduction of the isotope effect in the antibody catalysed reaction is consistent with the side chain operating as a general acid in the rate-determining proton transfer to the β-carbon of the enol/ether. The catalysis increases by a factor of 34 from the six-membered ring enol ether **484** to its five-membered ring analog **483**.

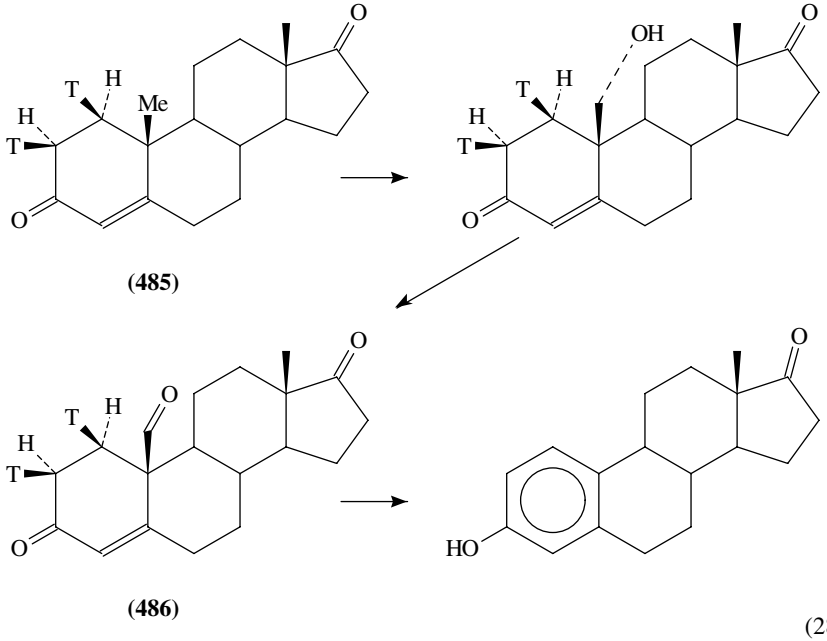


(481) **(482)** (287)



*3. Mechanistic study of aromatase (cytochrome P450 CYP19) in rat ovary and human placenta with the use of [1α,2α-^{3}H]androstenedione and [1β,2β-^{3}H]androstenedione **485***

High estrogen levels are associated with a number of diseases including breast cancer and endometriosis, and those/these have been treated successfully by decreasing estrogen levels through inhibition of the CYP19 enzyme[573]. The three consecutive steps in aromatase oxidation of **485**, requiring 3 equiv. of NADPH and molecular oxygen leading to aromatization of the steroid A-ring and loss of formic acids[574,575], are shown in equation 288.



(288)

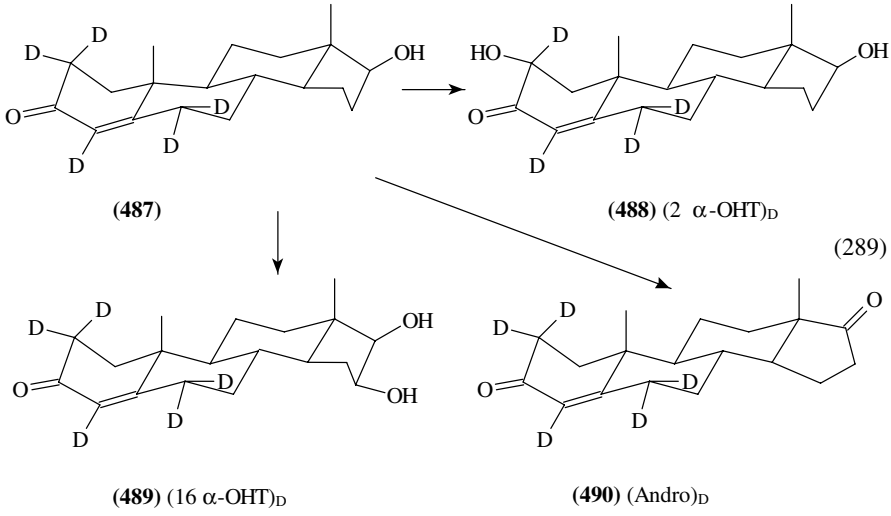
The tritium KIEs in estrogen formation by aromatase determined by comparing the rate constants associated with 7-[^{3}H]androstanedione with those tritiated specifically at $C_{(1)}$ and $C_{(2)}$, have been found to be insignificant[576] and were interpreted as indicating that there exists an enzymatic step between the 19-al-androstenedione intermediate **486** and hydrogen abstraction or enolization[575,577]. No tritium KIEs have been detected[576], in oxidations of **485**, and the [1α,2α-$^3H_2$] and [1β-^{3}H] androstenediones by rat ovary microsomes (ROM). The distribution of tritium in the products in these oxidations showed that tritium is lost stereoselectively from the β-face upon incubation with HPM (equation 288) and retained on the α-face following incubation. The aromatase located in ROM differs from aromatase in HPM by an inability to remove the 2β-tritium from androstenodione. Aromatization of the steroid A-ring requires, besides the oxidative removal of the 1β-hydrogen atom and deformylation, also the enolization of the $C_{(3)}$ carbonyl.

The retention of tritium at $C_{(2)}$ in the conversion of testosterone to estradiol is interpreted as the result of triitium IE associated with enolization of 4-dien-3-one intermediate. The enolization follows after the deformylation and 1β-hydrogen abstraction steps and is

assisted by the enzyme. Differences in accumulation of intermediates between aromatase in rat ovary and in human placenta suggest that these enzymes are structurally different[576].

4. Deuterium isotope effect study of the metabolism of testosterone by CYP2C11

Cytochrome P450 system, CYP2C11, converts[578] testesterone to 2α-hydroxytestosterone, **488**, and to 16α-hydroxytestosterone, **489** and androstenedione, **490**. Pathways of the testosterone-2,2,4,6,6-2H_5 **(487)** metabolism by CYP2C11 are shown in equation 289. Deuteriated **488** is formed by the deuterium abstraction pathway via the active oxygen intermediate **491** (EOS_w). The D-ring metabolites **489** and **490** are formed by non-deuterium abstraction pathways from the active oxygen intermediates **492** (EOS_x). In competitive experiments the CYP2C11, incubated with mixtures of D_0–T and D_5–T catalyzed the formation of metabolites in the ratio $(2\alpha - OHT)_H/(2\alpha - OHT)_D = 5.10 \pm 0.09$, $(16\alpha - OHT)_H/(16\alpha - OHT)_D = 1.12 \pm 0.06$ and $(Andro)_H/(Andro)_D = 1.23$. The non-competitive experiments, combined with steady-state rate equations derived for multimetabolite formation, indicated[579] that testosterone is able to dissociate from the (EOS) complexes and then reassociate in the same or in different orientation. Thus the single title enzyme is able to hydroxylate opposite ends of substrate **487** providing metabolites **488**, **489** and **491**.



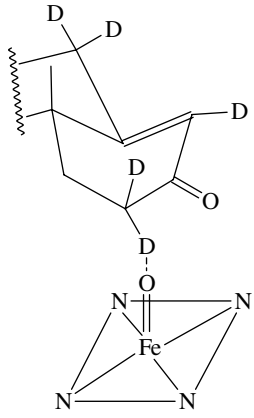
(487) **(488)** $(2\ \alpha\text{-OHT})_D$

(289)

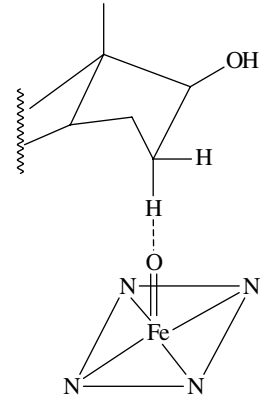
(489) $(16\ \alpha\text{-OHT})_D$ **(490)** $(Andro)_D$

5. Deuterium solvent IE in the androstenedione formation from progesterone

The pL (L = H or D) dependence of the solvent DIEs associated with progesterone **493** oxidation to 17α-hydroxyprogesterone **494** and 17-*O*-acetyltestosterone **495** and 17α-hydroxyprogesterone oxidation to androstenedione **496** has been determined in microcosms from pig testes[580] (equation 290). The initial rate of oxidation of **493** to **494** has been associated with the pL-independent inverse solvent isotope effect (SIE) ($k_H/k_D = 0.75 - 0.95$ in 30% DOD) while the oxidation of **495** has been associated with the pL-independent positive SIE in 30% DOD (k_H/k_D of about 2), DOD inhibited the formation of **496** from **444** in noncompetitive in pL-dependent manner. Androgens are synthesized from progesterone in a two-step reaction involving the 17α-hydroxylation

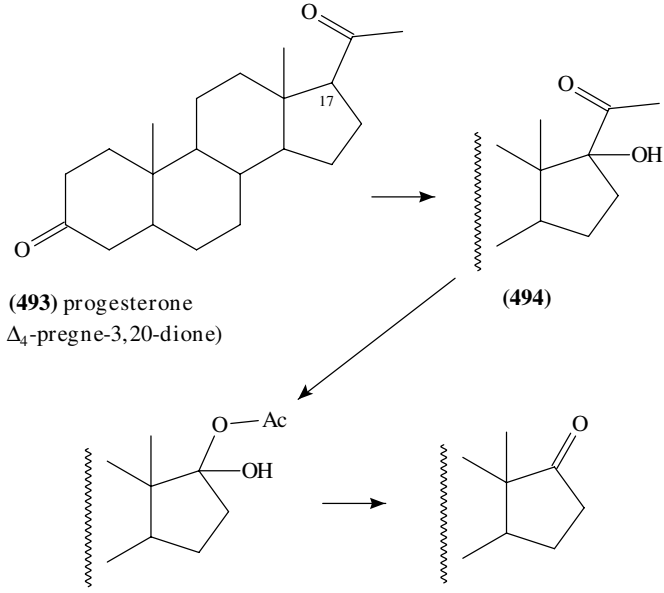


(491) EOS_W



(492) EOS_X

(equations 291a and 291b) and by cleavage of the $C_{(17)}$ side chain (via peroxide chemistry), (equation 292a, 292b), catalysed[580–582] by the enzyme P450CYP17.



(493) progesterone
(Δ_4-pregne-3,20-dione)

(494)

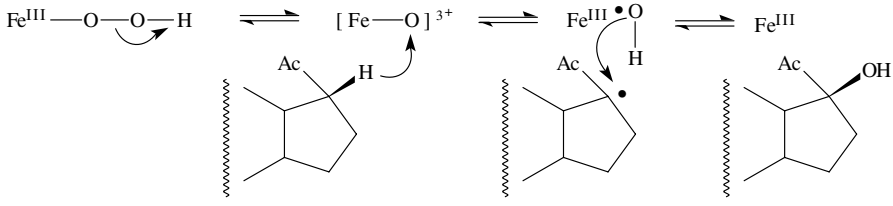
(495) $C_{21}H_{30}O_3$

(496)
Androstenedione

(290)

The pL-independent IEs have therefore been interpreted[580] as indicating that DOD shifts the acid–base equilibrium from ($Fe^{III}-OO^-$) to the protonated intermediate ($Fe^{III}-OOH$) and increases in that way the rate of synthesis of products formed via *oxene chemistry* (inverse SDIE) and decreases the rate of products formed through the *peroxide chemistry*

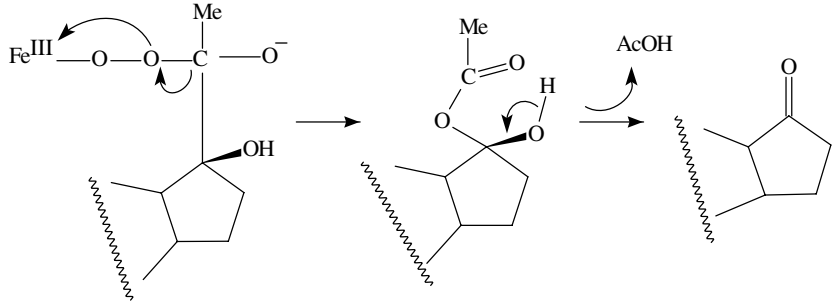
(positive SDIE).



(291a)

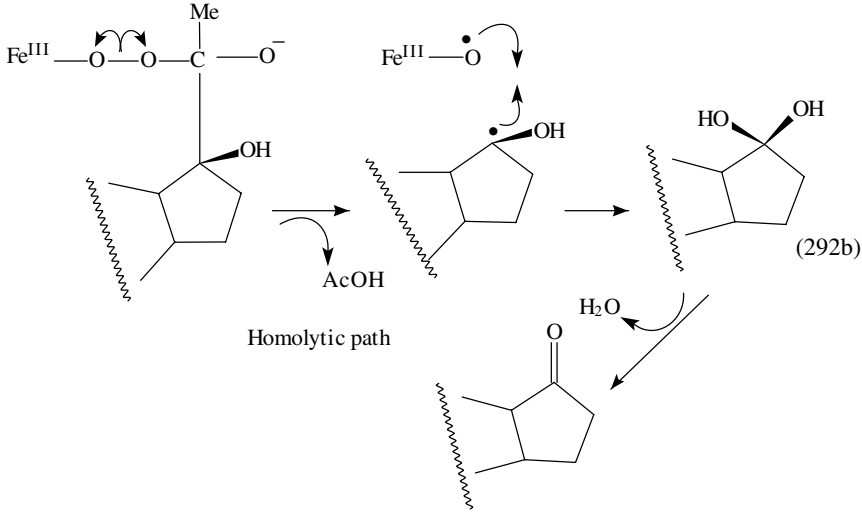
$$Fe^{3+}\text{-}O\text{-}O^{-} + HA \longleftrightarrow F^{3+}\text{-}OOH + A^{-} \text{ and } Fe^{III}\text{-}OOH \longleftrightarrow [Fe\text{-}O]^{3+} + {}^{-}OH$$

(291b)



Heterolytic path

(292a)



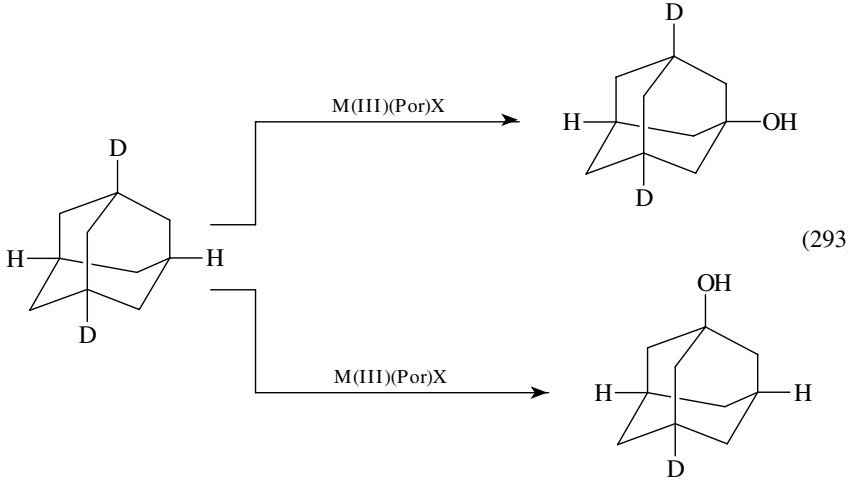
Homolytic path

(292b)

It has been suggested[580] that **494** binds to an unprotonated form of the enzyme in a manner facilitating the $C_{(17)}$ side-chain cleavage via peroxide chemistry[580].

6. D KIE associated with alkane hydroxylation by cytochromes P-450 and intermolecular D KIE in the alkane hydroxylations catalysed by manganese and iron porphyrin complexes

D KIE in the hydroxylation of deuteriated norcamphors[583], **497–499** (k_H/k_D = 3.8), in the hydroxylation[584] of the compounds **501** (k_H/k_D = 11) and **500** (k_H/k_D = 12.8–14.0)[585] as well as in the hydroxylation of several other alkynes[586–598] in the cycytochrome P-450, porphyrin/PhlO(CH_2Cl_2) and in the FeTTPCl/Ph lO(CH_2Cl_2) oxidation systems and in other chemical model systems have been reviewed[599] and partly elsewhere[600,601]. Intramolecular KIEs in the hydroxylation of 1,3-dideuterioadamantane catalysed by iron and manganese complexes of *meso*-tetrakis (2,6-dichlorophenyl) porphyrin and *meso*-tetramesitylporphyrin [M^{III}(TDCPP)Cl and M^{III}(TMP)Cl, M^{III} = Fe or Mn], with $KHSO_5$, NaOCl and PhlO (equation 293), have been found to be 8.71±0.20 (20 °C) and 7.52±0.21 (20 °C) with Fe(TMP)Cl/NaOCl and Fe(TMP)Cl/PhlO, respectively. KlEs of 4.09 ± 0.17 (20 °C) with Fe(TMP)Cl and 4.74 ± 0.17 with Mn(TMP)Cl were obtained for $KHSO_5$ oxidant in benzene solvent.

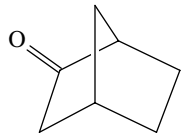


(293)

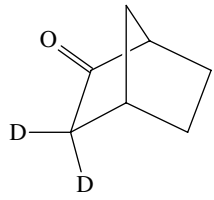
The (A_H/A_D) values less than 0.5 and $[\Delta E_a]^D{}_H$ larger than 1.15 kcal mol^{-1} observed in the oxidations with Fe(TMP)Cl/NaOCl and -/PlO systems, suggest the contribution of tunnelling symmetrical linear H-transfer transition states and a pure metal-oxo species in this case **(502)**. The lower values of k_H/k_D observed when active metal-oxo-like species have been generated by $KHSO_5$ regardless of the metalloporphyrin, have been rationalized by participation of a bent TS involving the leaving group of the oxidant **(503)**.

7. Deuterium and tritium isotope effects in the lactate dehydrogenations by flavocytochrome b_2

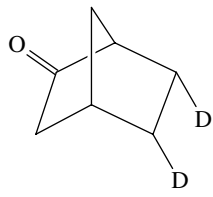
Flavocytochrome b_2 catalyses the oxidation of lactate to pyruvate at the expense of cytochrome C. After reduction of flavin (FMN) by the substrate, reducing equivalents are transferred to heme b_2 and from there to cytochrome C[602]. The mechanism of this process has been studied[603] at 5.0 °C by determining the D KIE in the FMN reduction using L-[2-^{2}H]lactate and wild-type enzyme and also with the Y143F mutant prepared from transformed *Escherichia coli*[604]. Tritium IE in the conversion of [2-^{3}-H]lactate to



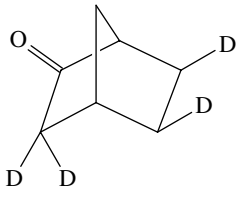
(497a)



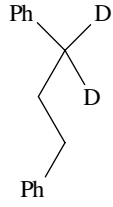
(497b)



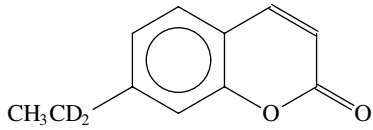
(498)



(499)



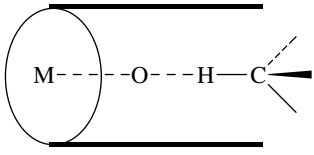
(500)



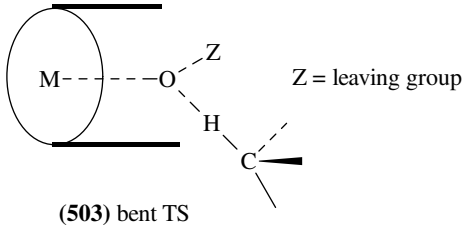
(501)

pyruvate, defined by equation 294,

$$I(V/K) = \ln(1 - f)/\{\ln[1 - f(SA_f/SA_0]\} \tag{294}$$



(502) linear TS



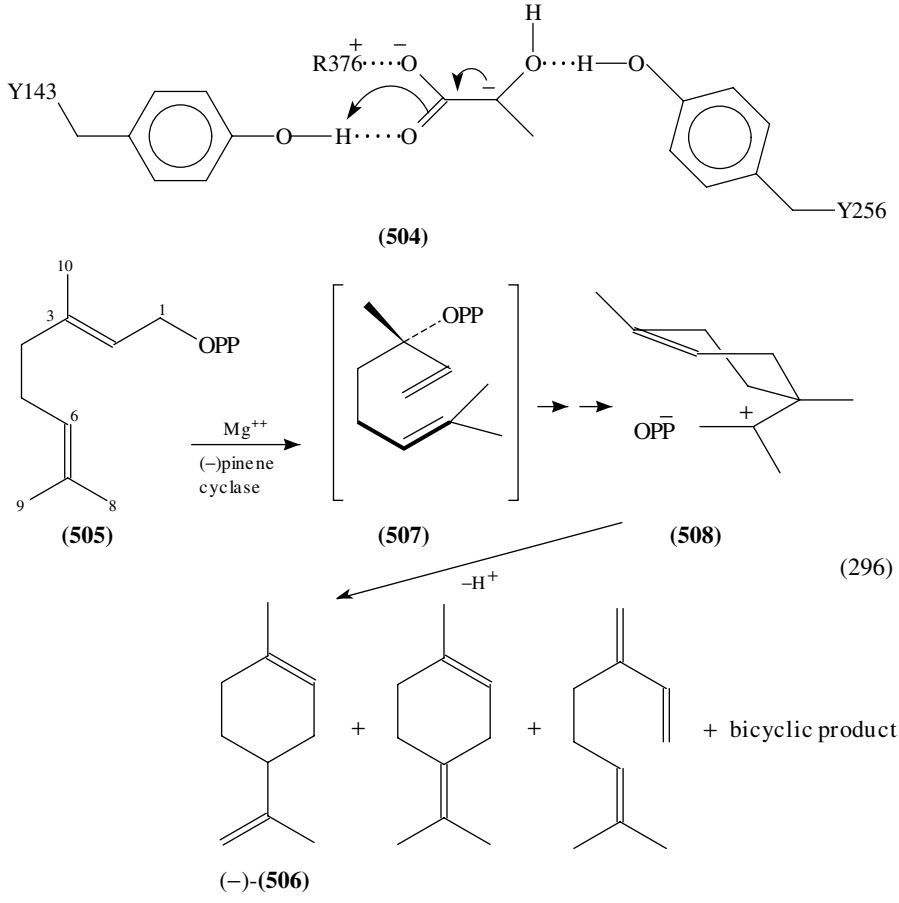
(503) bent TS

where f is the fractional conversion to product, SA_f is the specific activity of the product at the degree of conversion equal to f, and SA_0 is the initial lactate specific activity, has been found to be of 15.8 ± 1.7 and 11.3 ± 0.5 for the wild-type and the Y143F mutant. The detailed analysis of the above results led the authors[603] to the conclusion that the determined hydrogen IEs for FMN reduction are intrinsic IE values [$k_2(H)/k_2H^*$, $H^* = {}^2H$ or ${}^3H$], fully rate determining (k_2 in equation 295), and that therefore the mutation induces a change in the structure of TS of hydrogen transfer. The Tyr 143 phenolic group (in the active side chain of the enzyme) stabilizes the Michaelis complex by H-bonding to a substrate carboxylate, but Tyr 143 does not play the role of electrophilic catalyst which stabilizes the carbanion-like TS **504** formed in the initial step (the hydrogen bond does not appear to be stronger in the TS)[603]. The ${}^{14}C_{(2)}$ and ${}^{13}C_{(2)}$ KIE determinations should help to choose the proper degree of C_α–H bond rupture in the TS for the Y143F mutant.

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} EP \tag{295}$$

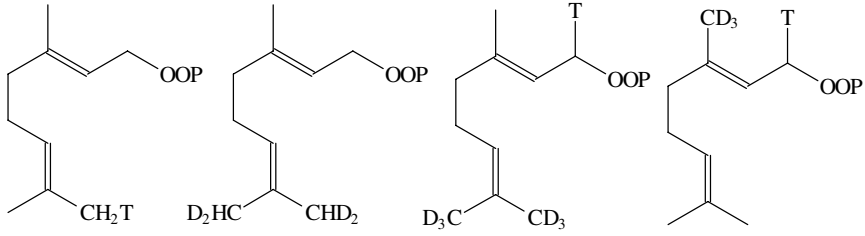
*8. Deuterium and tritium isotope effect study of the methyl-methylene elimination in the enzyme catalyzed biosynthesis of (R)- and (S)- limonenes **(506)***

The mechanism and stereospecificity of the enzyme catalyzed cyclization of geranyl diphosphate, **505** to **506** and other mono- and bicyclic unsaturated products, proceeds according to the established [605–609] mechanism (equation 296) involving a transient α-terpinyl carbonation intermediate **508** (produced from **507**), which by the final proton elimination step yields **506**. Recent tritium tracer and KIE[610] study of this terminating proton transfer supplemented the biosynthesis of **506**.



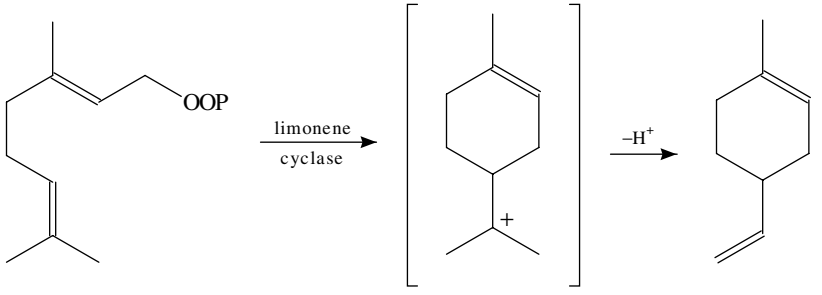
(296)

[8-^{3}H]-**509**, [8,8,9,9-$^2H_4$]-**510**, [1-^{3}H, 8,9-$^2H_6$]-**511** and [1-^{3}H,10-$^2H_3$]-**512** geranyl diphosphates have been synthesized[605] and used in tritium tracer and DIE studies. Degradation of enantiomeric [^{3}H]limonenes produced by cyclization of with (+)- and (−)-pinene cyclase from *Salvia officinalis* showed that methyl-methylene eliminations in this case occur at both the *cis* (55–65%) and *trans*-methyl (45–35%) groups. Terminating eliminations in the formation of **506** catalysed by limonene cyclase from *Citrus sinensis* or *Perilla frutescens* occur exclusively at the *cis* terminal methyl group (equation 297). The intramolecular DIE associated with $CH_3 \longrightarrow CH_2$ eliminations, determined by



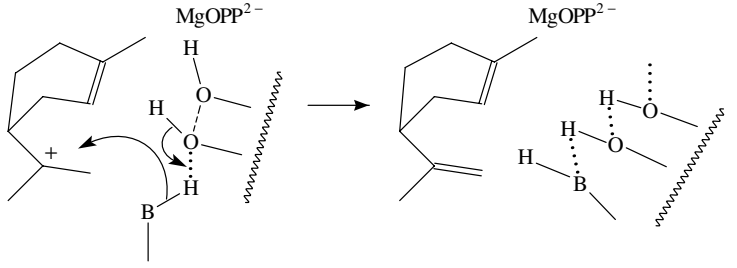
(509) -T **(510)** - D_4 **(511)** - D_6, T **(512)** - D_3, T

incubating **510**-D_4 with (+)- and (−)-pinene cyclase from *S. officialis* and with the (−)-limonene cyclase from *Mentha spicata*, have been found to be $k_H/k_D = 2.3 \pm 0.2$, 5.9 ± 0.5 and 4.0 ± 0.4, respectively. Negligible changes of deuterium content of the bicyclic products have been observed, since in their synthesis no C−D bonds are broken. Remote IEs $k_H/k_D = 1.16-1.27$ of the deuterium substitution at the internal $C_{(10)}$ and terminal methyl group $C_{(8)}C_{(9)}$ on the total rate of monoterpene formation have been observed by incubation of **511**-D_6,T and **512**-D_3,T with pinene and bornyl PP cyclases from *S. officinalis*.



(297)

The sizable secondary-D KIEs observed for **512**-D_3,T are explained by slight destabilization of the intermediate geranyl carbocation/$MgOPP^{2-}$ anion pairs at the enzyme active site, and by the weaker electron-donating capacity of the deuteriomethyl group. Terminal $CH_3 \longrightarrow CH_2$ elimination occurs at the *cis*-methyl group in monoterpene (equation 296) because this *cis*-methyl group is positioned nearer to the negatively charged $MgOPP^{2-}$ leaving group, and the charge separation is less in the TS for proton transfer from the *cis*-Me group to the basic acceptor B(H_2O, imidazole group of the histidine residue) in the enzyme active site (equation 298).



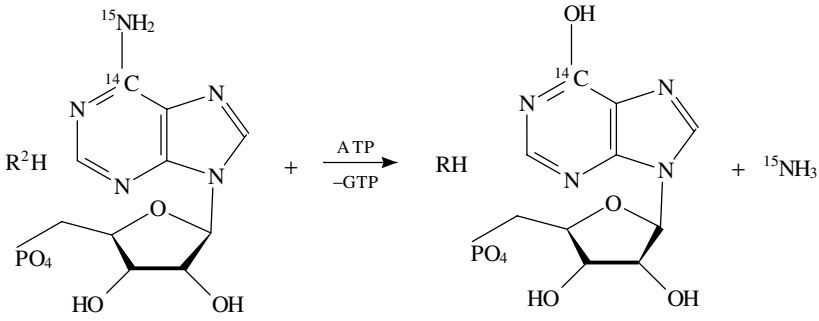
(298)

The direct transfer of the proton to the $MgOPP_2^-$ dianion require considerable movement and reorientation to bring the *cis*-Me and $MgOPP^{2-}$ groups into close proximity.

The differences in primary hydrogen KIE observed are usually related to varying extents of proton transfer in the TS, by nonlinear TS and by tunneling. An attempt has been made[610] to rationalize the different values of intramolecular KIEs by involving processes specific for enzyme catalyzed reactions like e.g., occurrence of conformational inversion *prior* to proton elimination. The sizable secondary KIEs follows also from the general kinetic equation relating the observed k_H/k_D ratios with $(k_i)_H/(k_i)_D$ and $(k_i/k_{i-1})_H$ ratios for consecutive sets of all reversible reactions taking place in the enzyme surface. The initial cyclization step of the enzyme-bound intermediate is an important component of the overall rate of the enzymatic reactions.

*9. Carbon-14 and nitrogen-15 heavy-atom KIEs in the hydrolytic deamination of adenosine 5-monophoshate (AMP **513**) with AMP deaminase*

AMP-aminohydrolase from *Saccharomyces cerevisiae* catalyses the reaction 299, where R^2H is the enzymatic proton donor, Glu633, ATP is an allosteric activator and GTP is an allosteric inhibitor[511,612].

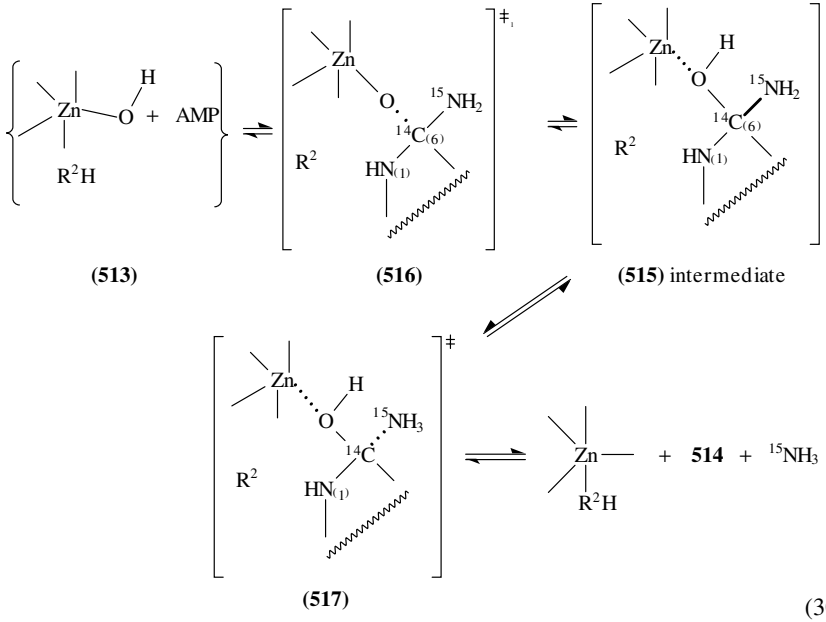


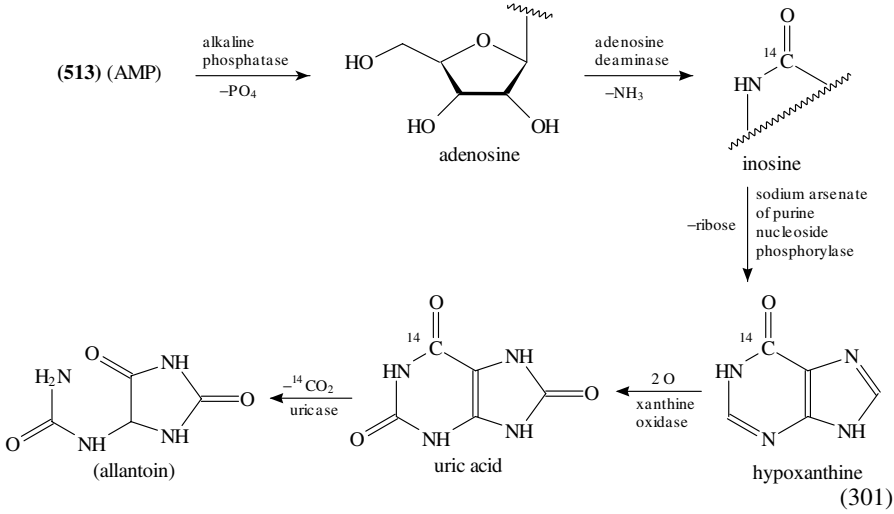
(513) AMP **(514)** IMP (299)

Carbon-14 KIEs for [6-^{14}C]AMP have been found[613] to equal 1.030 ± 0.003, 1.038 ± 0.004 and 1.042 ± 0.003 in the absence of effectors and in the presence of ATP and GTP respectively (ATP = adenosine 5′-triphosphate, GTP = guanosine 5′-triphosphate). The nitrogen-15 IE for [6-^{15}N]AMP was found to be 1.010 ± 0.002. In the presence of ATP the average value of $^{15}(V_{max}/k_m)$ increased to 1.014 ± 0.003. In D_2O, [6-^{15}N] KIE decreased from 1.011 ± 0.001 to 1.007 ± 0.002, The previously determined[612] solvent D_2O effect with AMP substrate was inverse (0.79).

A fully concerted mechanism for reaction 299 has been eliminated as inconsistent with ^{14}C and ^{15}N KIEs and also with the observed inverse solvent D_2O effect. The reaction path for the deamination of AMP has been formulated[613] as a stepwise conversion involving the formation of tetrahedral intermediate **515** characterized by full-bonded hydroxyl and amino groups (equation 300). The TS for slow formation of **515**, resulting from the attack of the hydroxyl from enzyme 'zinc-activated water' at the $C_{(6)}$, is characterized by the $C_{(6)}$ OH bond order of 0.8 ± 0.1 (late TS) and fully bonded NH_2, that is by the nearly complete conversion to sp^3 at $C_{(6)}$, and by nearly complete protonation of $N_{(1)}$, **516**, The protonation of NH_2 (in **515**) and departure of NH_3 (with TS **517**) take place in the subsequent rapid steps as shown in equation 300, Zinc hydroxide is formed prior to attack[514] at $C_{(6)}$. Enzymatic degradation of [6-^{14}C]AMP has been carried out to prove the position of the radiolabel in **513** (equation 301). No radioactivity in the allantoin

generated from [6-^{14}C]AMP has been found, thus only $C_{(6)}$ was radiolabelled in **513**.

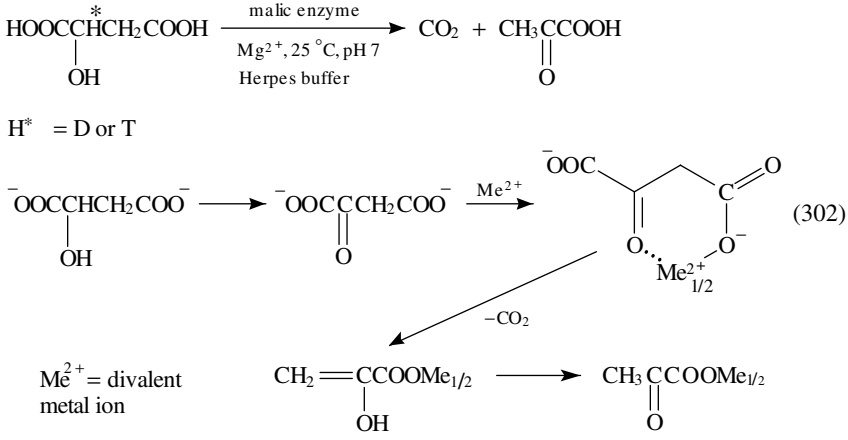




10. Oxidative decarboxylation catalysed by malic enzyme

The problem of stepwise versus concerted oxidative decarboxylation of L-maleate to yield pyruvate CO_2 and reduced dinucleotide catalysed by malic enzyme[615] has been reinvestigated recently[616]. The new D and T KIE determinations, using L-malate-2D

and L-malate-[2^{3}H] (equation 302), combined with ^{13}C isotope effects determined previously[616] led the authors[616] to the conclusion that the stepwise mechanism for oxidative decarboxylation of L-malate with AND(P) changes to a concerted one with alternative dinucleotides such as 3-APAD, where AND denotes nicotinamide adenine dinucleotide, AND(P) denotes nicotinamide adenine dinucleotide 2′-phosphate and 3APAD denotes 3-acetylpyridine adenine dinucleotide, The hydride transfer step is preceding decarboxylation with dinucleotides AND or NADP.



(302)

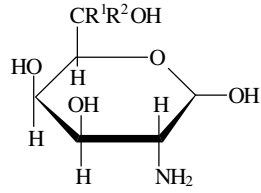
11. Brief review of biochemical studies with isotopes

The ^{13}C KIE associated with the synthesis of methane from acetate by *M. barkeri* (Me carbon of acetate ⟶ methane) has been found[617] to be −21.3% at 37 °C. The isotope effect at the carboxyl portion of acetate was practically the same, Both carbon atoms in acetate are involved in the RDS as expected for reactions catalyzed by carbon monoxide dehydrogenase. The ^{13}C/^{12}C fractionation 'α' of methane produced during microbial oxidation in a forest soil was determined[618] to be 0.978 ± 0.004. This corresponds to ^{13}C KIE, k_{12}/k_{13}, of 1.022 ± 0.004. The T and ^{14}C KIEs in the whole-body with either [1-^{14}C]leucine or [4,5-^{3}H]leucine or [1-^{14}C]α-ketoisocaproate (KIC) and the [4,5-^{3}H]KIC turnover, infused simultaneously to dogs and humans, have been determined[619]. These small differential isotope effects have to be considered when dual isotope infusions are employed e.g. to study the amino acid metabolism.

The pharmacokinetic study of the 1 : 1 mixture of unlabelled (D_0) and fully deuteriated toluene-D_8 showed that toluene-D_8 is a suitable probe for D_0 kinetics[620]. The insecticidal potency of [dimethyl-D_6]methoxychlor has been found[621] to be higher than that of [monomethyl-D_3]methoxychlor. The inverse^{15}N KIEs, $^{15}(V/K)_{H_2O} = 0.995$ and $^{15}(V/K)_{D_2O} = 0.992$ found in the HIV-1 virus aspatric protease (retropepsin) catalysed peptidolysis of Al-Ser-Gl$_n$-AS$_n$-Tyr-Pro-Val-Val-NH$_2$, have been interpreted[622] as indicating that the bonding to the N atom becomes stiffened in the TS of this reaction and that the KIEs arose from protonation of the proline N atom. The reaction sequence in this peptidolysis has been formulated[622]. Emodin deoxygenase transports the 4S hydrogen of NADPH in the rate-determining step[623].

The KIE in the dehydration of fructose to 5-(hydroxymethyl) furfural has been determined[624] and interpreted as arising in the rate-determining addition of H^+ to

4,5,6-trihydoxy-2-oxohexanal, DIEs in the reduction of 1,4-benzoquinones (BQ) and its derivatives and of Me benzoylformate (MBF) with 1-benzyl- 1,4-dihydronicotinamide, [4,4-(H,H)]BzNADH and [4,4-(H,D)]-BzNADH have been determined[625,626] and suggestions concerning the change of the mechanism from single-step H^- transfer for BzNADH oxidation with MBF to a multistep e^-, H^+, e^- transfer for BzNADH oxidation with BQ presented. The problem of product-determining and rate-determining steps in the reduction of BQ with BzNAH has been discussed also[626]. T KIEs in the enzymatic oxidation of tritium D-galactosamine, **518**, have been determined in the presence of galactosooxidase[627]. The amino group affects mainly the formation of the enzyme–substrate complex.



(518) $R^1 = R^2 = H, T$
$R^1 = H, R^2 = T$

The oxygen-18 KIEs in the dopamine β–monooxygenase (D-β–M) reaction have been measured[628]. The trend in ^{18}O isotope effect with reactivity has been explained by assuming that the O—O bond of O_2 undergoes cleavage prior to substrate activation. The D KIE observed in the microsomal oxidative demethylation of the methoxyl group was smaller in the presence of added bovine serum albumin than in its absence[629]. The large primary (k_H/k_D) isotope effect of 60 (at RT and pH 9) has been observed[530] in the oxidation of [11, 11-$^2H_2$]linoleic acid by soybean lipogenase[531]. A primary D_2O isotope effect has been observed[532] at pH 7.0 in the oxidative degradation of tryptophan catalyzed by the hemoprotein, tryptophan 2,3-dioxygenase (Ec. 1.13.1.12). This implies that abstraction of the indole proton is at least partially rate-determining.

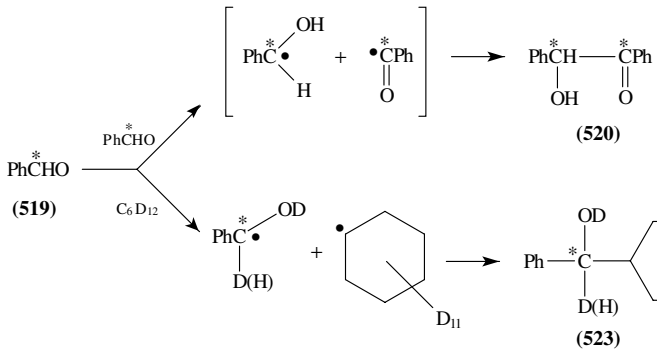
D. Isotope Effects in Photochemical and Physical Processes

1. Photochemistry of benzaldehyde and deoxybenzoin

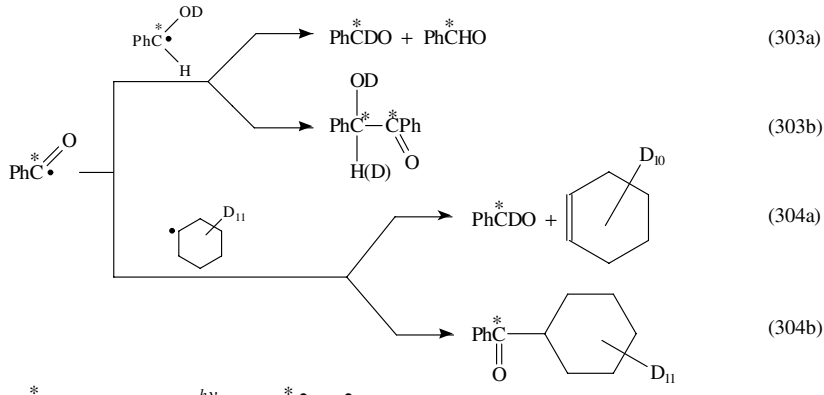
The photochemistry of benzaldehyde (90% $^{13}C{=}O$), **519**, deoxybenzoin (99%) $^{13}C{=}O$), **521**, and *p*-chlorobenzoin (99% $^{13}C{=}O$), **522**, in cyclohexane-D_{12} solution has been studied[633] by spectroscopic techniques, such as ^1H chemically induced dynamic nuclear[634] or electron polarization[635] (CIDNP/CIDEP) or dynamic nuclear polarization[636] (DNP). In all these cases the formation of benzaldehyde-D with emissive $^{13}C{=}O$ polarization has been observed and the results rationalized by intermolecular hydrogen (deuterium) abstraction by the photoexcited ketones from the solvent molecules and by reactions of cage-escaped radicals (equations 303–308), Benzoin, **520**, is formed also.

Beside phenylcyclohexylmethanol, **523**, the dicyclohexyl product **524** has been produced also by irradiation of benzaldehyde in cyclohexane (equation 309). Irradiation of **521** provided 1-cyclohexyl-1,2-diphenylethanol, **525** (equation 310). Benzylcyclohexane, **526**, and dicyclohexyl, **524**, have been formed in secondary encounteres (equation 310a).

It has been documented that the photoexcited deoxybenzoin can abstract H as well as D from appropriate solvents. Hydrogen abstraction by triplet **521** from cyclohexane-H_{12} (rate constant 2.1×10^5 $mol^{-1}\,s^{-1}$) is faster than α-cleavage whereas deuterium abstraction (3.9×10^4 $mol^{-1}\,s^{-1}$) is competitive with α-cleavage (deuterium isotope effect of 5).



(303)

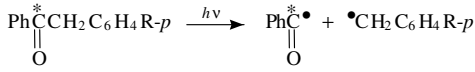


(303a)

(303b)

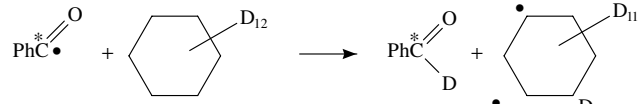
(304a)

(304b)

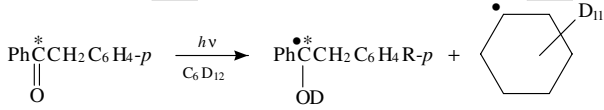


(305)

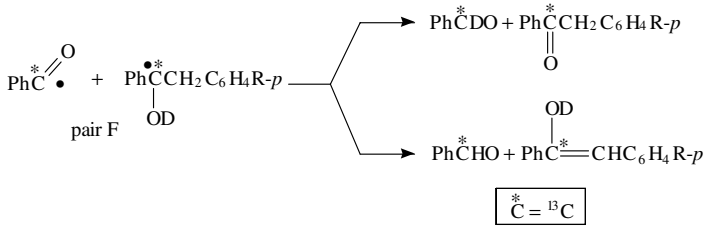
(521) R = H
(522) R = Cl



(306)

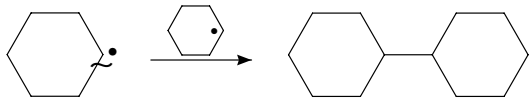


(307)



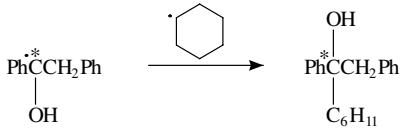
(308)

$\overset{*}{C} = {}^{13}C$



(309)

(524)



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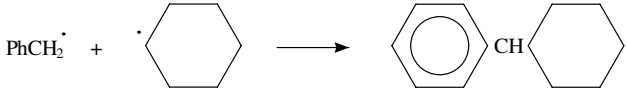
(525)

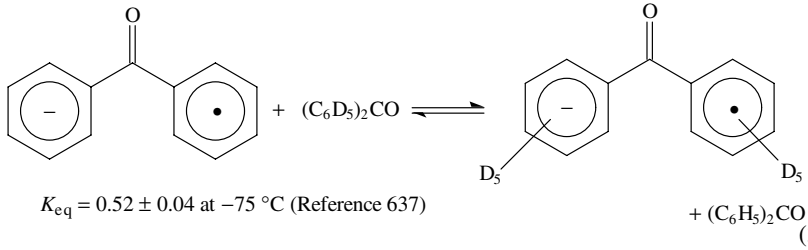


(310a)

(526)

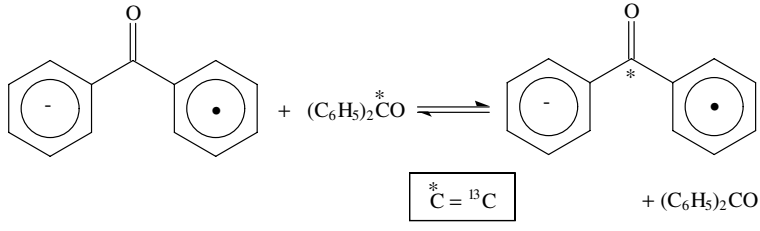
2. EPR, MS and GC study of the equilibrium isotope effects in the electron transfer from ketyls to isotopically different benzophenones

The [sym-dodeca-^{13}C] benzophenone (equation 313) has been synthesized via Friedel-Crafts phenylation of carbon tetrachloride and subsequent dehalogenation of the product using [per-^{13}C] benzene. $C_{12}D_{10}{}^{13}CO$ and $C_{12}H_{10}{}^{13}CO$ were applied[637] in the EPR and MS study of the electron transfer from ketyls to isotopically substituted ketones (equation 311–313). The equilibrium constants K_{eq} at −75 °C, for electron transfer from the anion radicals of polyatomic hydrocarbons ($A^{\bullet -}$) to their isotopic analogues (B), $A^{\bullet} + B \longleftrightarrow A + B^{\bullet}$, in liquid ammonia, when A = benzophenone, have been found to be 0.52, 0.50 and 0.83 for the equilibrium involving B = perdeuteriated benzophenone, [carbonyl-^{13}C] benzophenone and [sym-dodeca-^{13}C] benzophenone.

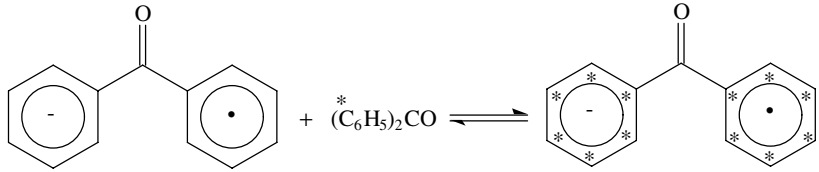


$K_{eq} = 0.52 \pm 0.04$ at −75 °C (Reference 637)

(311)



(312)



(313)

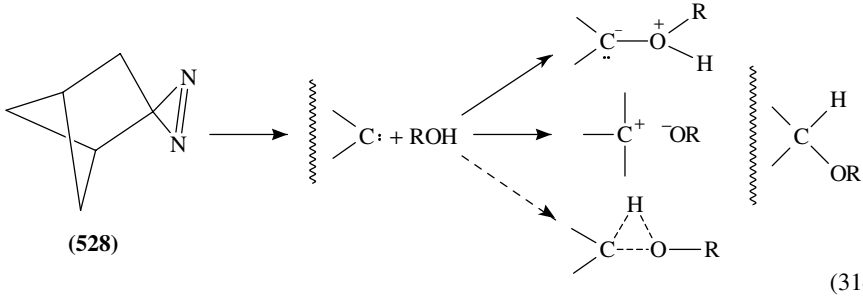
The observed greater attenuation of the electron affinity by substitution of the carbonyl carbon with ^{13}C than in the case of substitution of all the ring carbons combined has been attributed to the fact that the carbonyl moiety has the highest charge and spin density in the benzophenone anion radical. The extremely large values of equilibrium ^{13}C isotope effects by far exceed the magnitude of ^{13}C IEs expected by the statistical mechanics[638] theory of equilibrium isotope effects. The equilibrium ^{13}C IEs in equation 312a have therefore been reinvestigated[639] using the more accurate GC instead of quantitative ESR and mass spectroscopy.

$$Ph_2CO + Ph_2{}^{13}CO^-M^+ \rightleftharpoons Ph_2CO^-M^+ + Ph_2{}^{13}CO \qquad (312a)$$

It appeared[639] that the solution electron affinity of [^{12}CO] benzophenone in liquid ammonia is only 2.1% higher than that of [^{13}CO]benzophenone, and not 100% higher as maintained by Stevenson and coworkers[637]. The source of systematic errors in the ESR and MS methodology of $^{13}C/^{12}C$ determinations which resulted in the unrealistic results in Stevenson and coworkers study has been pointed out by Holm[639]. Some details concerning the improved analytical procedures are described in other work[640].

3. Deuterium study of the reactions of carbenes with OH bond

In the course of studies of the insertion of carbenes, generated in the photolysis of spirocyclic diazarines, **528**, into OH bonds (equation 314) it has been observed[641] that formation of ethers from carbene **527** and ROH(D) is associated with partial rearrangement (equation 315).



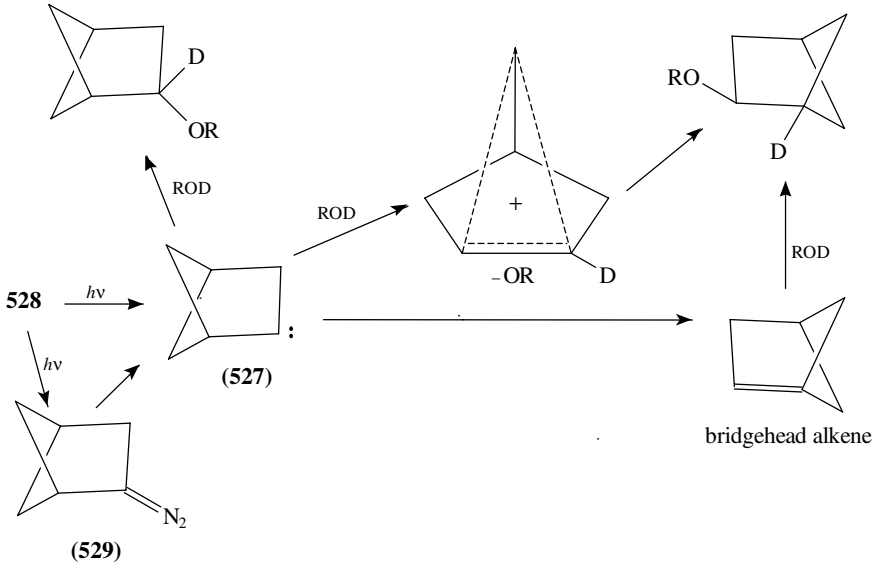
(528)

(314)

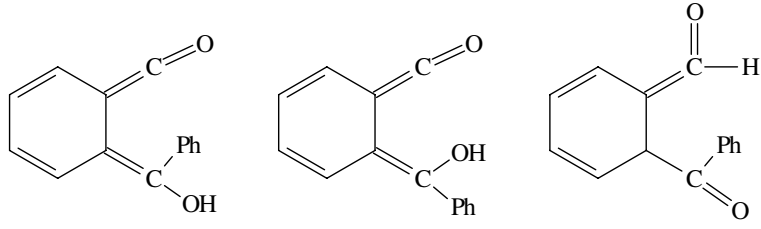
4. Photochemistry of ortho-benzoylbenzaldehyde in D_2O

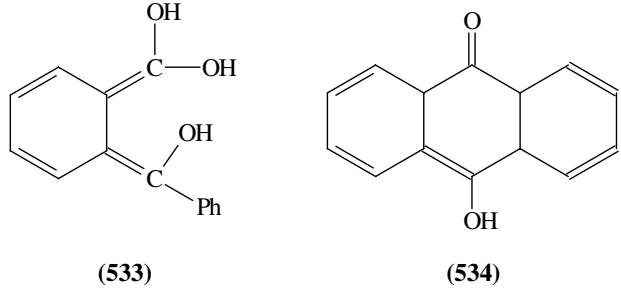
530 and **531** are produced in the laser flash photolysis of *o*-benzoylbenzaldehyde, **532**, in benzene or acetonitrile[642]. At high water concentration (>10 M) a new species **533**

has also been detected. Using D_2O an isotope effect of about 1.5 was found. It has been suggested that **531** is the main precursor of **533**. Dihydroanthraquinone **534** is formed at steady-state irradiation to **532** in deaerated MeOH[642].



529: 527 in 1:3 ratio (315)





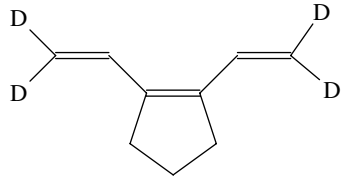
5. A brief review of isotope effect studies in physical, physical-chemical and analytical processes

Dynamics of cyclopentanone, existing in two equally populated forms and of cyclohexanone, existing in single forms, have been investigated[643] by ^{13}C NMR. The separation of $^{13}C/^{12}C$ isotopes caused by the magnetic isotope effect in the recombination of a radical pair with ^{13}C in the carbonyl position in different-sized alkyl sulphate micelles, from sodium octyl sulphate (C_8) through sodium dodecyl sulphate (C_{12}), has been investigated[644,645] and a conclusion has been reached that the behaviour of the radical pair depends on the micelle size[645], on the penetrability of the micelle boundary, on the distance between the two electrons undergoing electron spin exchange interaction and on the viscosity of the micellar core, which in turn depends on the micellar size.

The microwave spectrum of the normal argon–acetaldehyde and of the $Ar-CH_3CDO$ van der Waals dimer has been used to determine their structure[646] which was found to be a non-planar skew, with the Ar binding on top of the C−C−O triangle. The planar or nearly so structure of the Ar–formic acid van der Waals dimer has also been determined[647] from assigning the rotation spectrum of normal, Ar, DCOOH and HCOOH isotopomers.

The IR and Raman spectrum of liquid dicyanoacetylene has been reinvestigated[648] including the isotopic species $NC-^{13}C{\equiv}C-CN$. Three new carbenes generated by pulsed flash pyrolysis have been identified by matrix- ^{13}C IR spectroscopy[649]. The Isotope effect of H-bond stretching vibrations in the one-dimensional model approximation has been investigated[650] and the dependence of the frequency of proton and deuteron stretching vibrations on the distance between equilibrium states of oxygen atoms determined. Rotational analysis of the high-resolution IR spectra of ν_4 and ν_5 bands of formyl chloride has been carried out providing the rotational assignment for the $HCO^{35}Cl$ and $HCO^{37}Cl$ isotopomers[651]. Far-infrared spectra and two-dimensional potential energy surfaces for the out-of-plane ring vibrations of undeuteriated cyclohexanone and its four isotopomers have been constructed[652]. Separation of ^{18}O isotope has been observed in the IR multiple-photon decomposition (IRMPD) of perfluorodimethyl ether and of perfluoropropylene oxide under irradiation with $TEACO_2$ laser[653]. A picosecond, kinetic investigation by optical absorption of protonation of deuteriated diphenylcarbene, Ph_2C:, with H_2O, MeOH, EtOH and 2-propanol has been carried out by detecting[654] the diphenylcarbenium ion, $Ph_2\overset{+}{C}H$.

1,2-Divinylcyclopentene (DVCP-D_0) and its terminally tetradeuteriated isotopomer (DVCP-D_4), **535**, have been studied[655]. Terminal deuteration prolongs the triplet life time, indicating that deactivation in DVCP occurs through vibration involving the terminal hydrogen atoms.



(535)

The IR spectra have been presented and the valence force constants provided[656] for four $Rh^I(CO)_2$ complexes containing Ph and CF_3 substituted β-aminovinylketonato ligands

with various proportions of ^{13}C. Molecular structure and IR spectra of formamide and its deuteriated species have been theoretically reproduced[657]. The IR and Raman vibrational spectra of solid α-chloroacetamides $CH_2ClCONH_2$, $CD_2ClCOND_2$ and $CD_2ClCONH_2$ have been studied and interpreted[658]. Intensities of CH- and CD- stretching overtones in the gas phase vibrational overtone spectra of 1,3-butadiene- and 1,3-butadiene-D_6 have been recorded and analysed, and the effects of vibrational coupling between CH oscillators noted[659]. Isotope effects in the Raman spectra of ^{13}C-enriched C_{60} fullerene have been observed also[660]. Perdeuteriated polystyrene was found to have greater stability than normal polystyrene with respect to oxidation in air[661], but the stability of perdeuteriated *cis*-polyacetylene with respect to oxidation in air was not better than that of normal *cis*-polyacetylene. The dynamics and structural rearrangement in the light and heavy water trimers has been studied by tunable far-IR laser spectroscopy[662]. The ground state rotational spectra of HNCS and its isotopomers have been analysed and their geometry determined[663]. The chemical behaviour of recoil atoms in the solid state, produced by irradiating metallocenes, their derivatives and their inclusion compounds containing Ru, have been studied[664]. A theoretical study of conformations and vibrational frequences of urea, thiourea, selenourea as well as of the corresponding deuteriated compounds has been carried out and the previous experimental IR spectra and their assignments critically examined[665]. The HOCO radical was detected in the gas phase by photoionization MS. The decay of hot radicals showed an apparent isotope effect (DOCO/HOCO), showing that the decay to $H + CO_2$ is dominated by tunnelling[666]. Isotope induced symmetry lowering in C_{60} molecules activated several fundamental modes otherwise IR-inactive[667]. The isotope-dependent anomalous fine structure splitting has been observed[668] in the 14-μm bands of BF_3–CO complexes and interpreted[668]. Natural and deuterium substituted polystyrene targets have been irradiated with energetic ion beams and the *G*-values for primary gas products, H_2, CH_4, C_2H_2, C_3H_4 and C_6H_6 and their various deuterium substituted forms, have been determined[669]. Very large isotope effects have been observed[670] in the multiphoton ionization (MPI) and fragmentation process of benzene at 193 nm. The isotopically labelled complexes[671] *cis*-[Rh(CO)$_2$(PyO)(X)], **536** (X = Cl, Br, PyO, pyridine-N-oxide), containing ^{13}CO and PyO-D_5, have been synthesized and used to assign[671] the internal ligand modes and the skeletal vibration in the IR spectra. The electronic spectra of **536** have also been recorded and analysed. IR spectra of aluminum[^{13}C, ^{18}O]carbonyl complexes, generated in argon matrixes by co-condensation of aluminum atoms and carbon monoxide, have been observed and analyzed[672].

Nearly equal amounts of acetone and acetone-D_6 have been obtained[673] in the collision-induced dissociation (CID) of M(M$_2$CO)[(CD$_3$)$_2$CO]$^+$, **537**, for M = Al, Fe, Co and Cu. Nearly equal losses of the labelled and unlabelled acetones have been observed also in the IR multiphoton dissociation (IRMPD) of **537**. This has been taken as evidence that both acetone ligands in **537** are bound in an equivalent fashion while IRMPD of the ion ScO(acetone)$_2^+$ provides ScO(acetone)(CH$_2$CO)$^+$ and the IRMPD of ScO[(CD$_3$)$_2$CO]$_2^+$ besides ScO[(CD$_3$)$_2$CO](CD$_2$CO)$^+$ yields also the product Sc[(CD$_3$)$_2$CO]$^+$. Influence of isotopic labelling on chain dimension in polymer solutions of deuteriated polystyrene in cyclohexane has been reinvestigated by Schaefer[674].

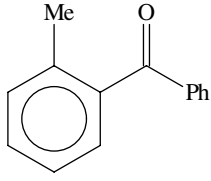
Changes in polystyrene and poly(methyl methacrylate) interactions with isotopic substitution have been observed[675]. Remarkable deuterium isotope effects observed in optoacoustic laser spectra of deuteriated organic vapours[676] can be used to identify these compounds and to detect them also in air at a sub-ppm level. Vapour pressure and miscibility isotope effect studies in H-bonded systems have been reviewed[677]. The kinetics of the ligand exchange between *tetrakis*(acetylacetonato)cerium(IV), and

free acetylacetone (Hacac) in C_6D_6 and CD_3CN, have been studied by ^{1}H-NMR line-broadening[678]. k_{obs} depends on the concentration of Hacac in the acid form, [Hacac]enol (equation 316):

$$\frac{1}{k_{obs}} = q + \frac{r}{[\text{Hacac}]\text{enol}} \tag{316}$$

The deuterium isotope effect on the rate was relatively small. It has been proposed that the exchange proceeds through the formation of a nine-coordinate adduct complex $Ce(acac)_4$Hacac followed by proton transfer from the coordinated Hacac to leaving acac and the ring opening of acac in the adduct complex. The above mechanism is probably valid for the liquid exchanges in other $M(acac)_4$ complexes ($M = Hf^{4+}$, Th^{4+} and U^{4+}). The H/T equilibrium in the system *t*-butylammonium iodide dicyclohexano-18-crown-6-chloroform solution has been studied and the temperature dependence of the separation coefficient $\alpha_{H/T}$ determined[679].

The photochemically induced H/D and H/T isotope exchange between *o*-methylbenzophenone and labelled methanol proceeding through formation of reactive transient neutral photoenols was found to be catalysed by sodium carbonate. The hydrogen kinetic and solvent IE in this system has also been discussed[680]. H/D and H/T exchange in *ortho*-alkylphenyl ketones catalysed by excited semiconductors has been investigated[681]. The photocatalysed H/D and H/T exchange between *o*-methylbenzophenone, **538**, *o*-methylacetophenone, **539**, 5,8-dimethyll-α-tetralone, **540** and MeO[^{2}H], MeO[^{3}H], *i*-PrO[^{3}H] is taking place in the presence of suspensions of inorganic semiconductors, CdS, ZnO and TiO_2. The amount of D and T incorporated into the ketone molecules was proportional to the irradiation time.



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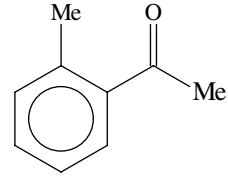

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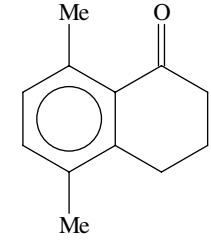


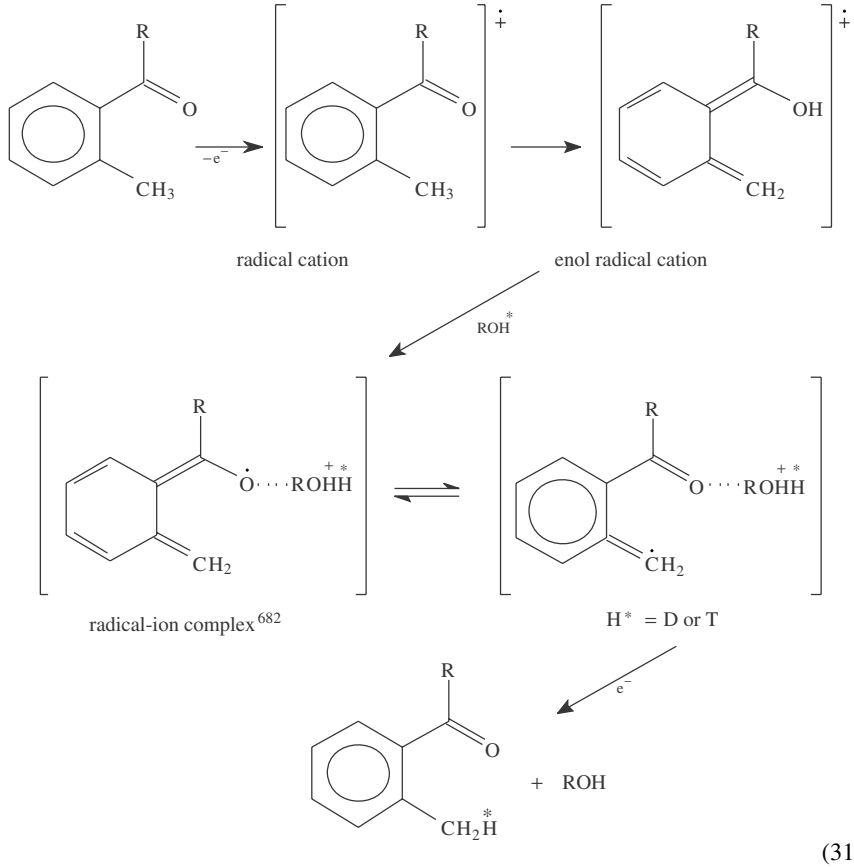
(540)

The % yield of photocatalysed hydrogen isotope exchange was increasing strongly with the increase in of the number of molecules of ketone adsorbed on the semiconductor surface. The adsorption of **538**, **539** and **540** on the surface of CdS, ZnO or TiO_2 is a necessary condition for the exchange to occur. Electron scavengers, such as O_2 and CBr_4, added to the solvent increased the exchange yield, while addition of the hole scavenger 1,2,5-trimethoxybenzene retarded the photocatalysed reaction. The mechanism shown in equation 317 has been proposed to rationalize the above experimental findings.

The k_D/k_T KIE equals 2.27 (CdS), 1.84 (ZnO) and 2.07 (TiO_2) for ketone **539** in labelled methanol indicated that H- transfer is involved in the RDS. No H/D exchange in CD_3OH was observed. This excludes the participation of free radicals in the hydrogen exchange. The possibility of H/H* exchange in the four-centre complex **541** has not been included in the reaction scheme shown in equation 317.

According to equation 317, the incorporation of H* into **538** takes place in the last step following the neutralization. A mechanism of H/H* exchange involving hydroxy hydrogen

radical cation is considered[681] less likely than the one shown in equation 317.



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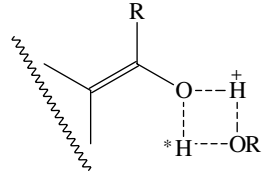
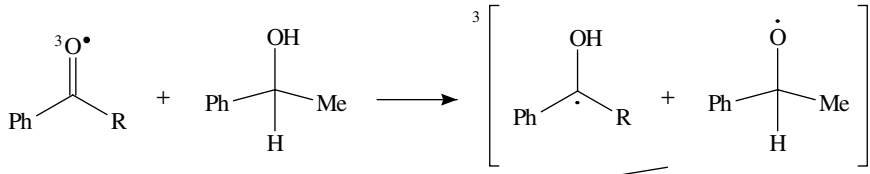


(541)

In the course of irradiation of acetophenone in the presence of 1-phenylethanol, the actual quantum yields for pinacol formation do not exceed 50%, but rise to 71% when PhCH(OD)Me is used for photoreduction of acetophenone in acetonitrile[683,684]. A conclusion has been reached from this inverse DIE that half the reaction of triplet acetophenone with 1-phenylethanol involves abstraction of an OH hydrogen followed by disproportionation of the initial radical pair back to reactants. A transfer of an O-bonded hydrogen to a triplet ketone is taking place (equation 318) besides the abstraction of hydrogen from

carbon by excited ketone (equation 319).



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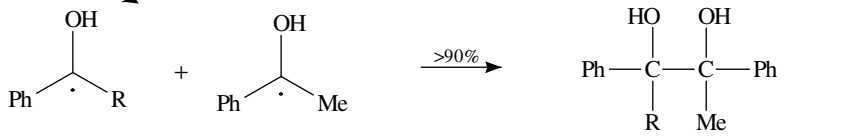

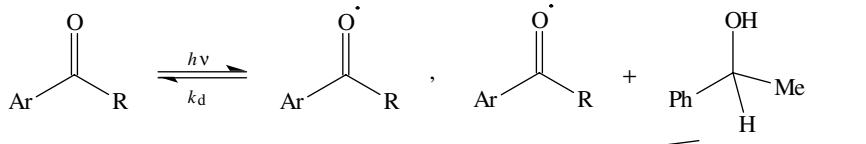

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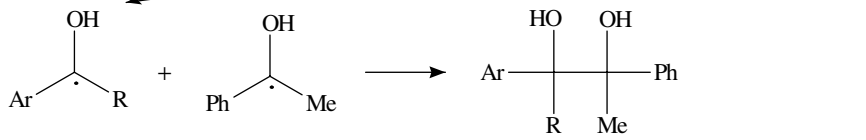


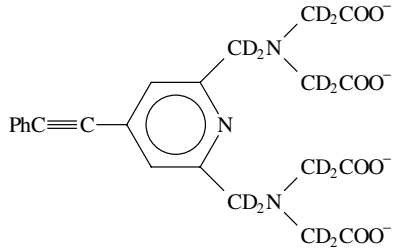
The chemical induced dynamic electron polarization in the acetone ketyl radicals, $(CH_3)_2COH$ or $(CD_3)_2COD$, has been studied by Fourier transform-electron paramaqnetic resonance[685] (FT - EPR). A new method for directly measuring secondary ^{18}O and primary ^{13}C isotope effects by running the reaction under high vacuum (10^{-5} torr) (when CO_2 leaves the solution before significant exchange with the O atoms of water has taken place) was developed[686], and applied to investigate the mechanism and TS structure of the enzymatic decarboxylation of oxalacetate. Variations in HPLC retention time Cs range between 3–7%, depending on the separation conditions and the number and position of the tritium substitution[687]. Isotope fractionation in several common derivatizations of organic compounds preceding their gas chromatographic-combustion isotope ratio MS analysis has been discussed[688]. A kinetic tracer method[689,690] utilizing ^{13}C-labelled exogenous substrates permitted one to compute[690] the respective amounts of glucose and fructose ingested simultaneously that are oxidized during a prolonged exercise.

The NMR determinations of the site-specific hydrogen isotope ratios at natural deuterium abundance permitted one to assess primary and secondary thermodynamic fractionation factors in exchange reactions avoiding the synthesis of selectively labelled reagents and their degradations[691].

Carbonyl–water hydrogen bonding in the $H_2CO–H_2O$ complex and its deuterium-substituted isotopomers has been recently examined[692].

Partially deuteriated vinyl chloride has been used[693] to elucidate its UV photodissociation dynamics. The hydrogen abstraction process by chlorine atom has been found to be the RDS in the reaction of normal and deuteriated alcohols with chlorine atoms generated by pulse radiolysis in CCl_4 at 18 °C[694].

Several protonated, fully deuteriated and partially deuteriated mixed-ligand complexes, $[Os\ (LL)_n(LL)'_{3-n}]^{2+}$, $[Rh(LL)_n(LL'_{3-n}]^{2+}$ ($n = 0$–3), $[Pt\ (LL)_2]^{2+}$, $[Pt(LL'_2]^{2+}$, doped into the single crystal of $[Zn(bpy)_3]\ (C10_4)_2$, where LL and LL′ represent the bpy-H_8 and bpy-D_8 ligands as well as novel Eu^{3+} chelate complexes containing deuteriated 4-(phenylethynyl)pyridine derivatives, **542**, and other organic ligands, have been synthesized to investigate the effect of ligand deuteriation on the highly resolved emission spectra (at 1.5 K) of the above compounds[695–705]. The decay is strictly monoexponential for every compound. The lifetimes increase upon deuteriation. The emission spectra exhibit rich vibrational satellite structures connected with the electronic origins. In the case of perdeuteration, the electronic origin is blue-shifted. Energies of the vibrational modes are red-shifted. The partial deuteration vibrational modes between 400 cm^{-1} and 500 cm^{-1} allow to assign them to M–L modes. The excitation maxima, decay times, quantum yields and luminescence yields of Eu(III) chelates have been determined[702].



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VIII. ACKNOWLEDGEMENTS

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CHAPTER **18**

Nucleophilic attack on compounds containing C=C, C=O or C=N groups

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I. INTRODUCTION

The topic of nucleophilic attack at an sp^2 carbon would be too wide a field to review in one chapter, if one were to discuss all facets and outcomes, some of which are shown in Figure 1. If the nucleophile is anionic an anion is formed, but if the nucleophile is neutral a zwitterion is produced. If X is oxygen or nitrogen, then the outcome can be carbonyl addition, substitution or a Darzens-type reaction. If the X is another carbon then addition leads to conjugate additions or polymerization. Alternatively the nucleophile could be expelled after rotation about the C−C bond to give overall isomerization. Both substitution and cyclization are also observed.

To make the task more manageable this chapter will focus specifically on the interaction between the nucleophile and a double bond and not consider in any depth subsequent steps. We will also only briefly consider reactions in which there is a preassociation or complexation of the double bond with a Lewis acid prior to nucleophilic attack. Finally we shall concentrate on 'conventional' nucleophilic attack and not discuss mechanisms involving single electron processes. In Section II we shall examine the types of double bonds that undergo nucleophilic attack, in particular examining relative reactivity, where available, and models for explaining this order. In Section III we shall review the orbital interactions that control the approach of a nucleophile to the double bond and the associated geometrical constraints. Then in Section IV we shall consider the implications of these constraints on selective reactions.

II. THE TYPES OF DOUBLE BONDS INVOLVING AT LEAST ONE CARBON ATOM THAT UNDERGO NUCLEOPHILIC ATTACK AND THEIR RELATIVE REACTIVITIES

The π system of double bonds represents a region of high electron density such that, in the absence of other factors, double bonds are more prone to electrophilic attack. However,

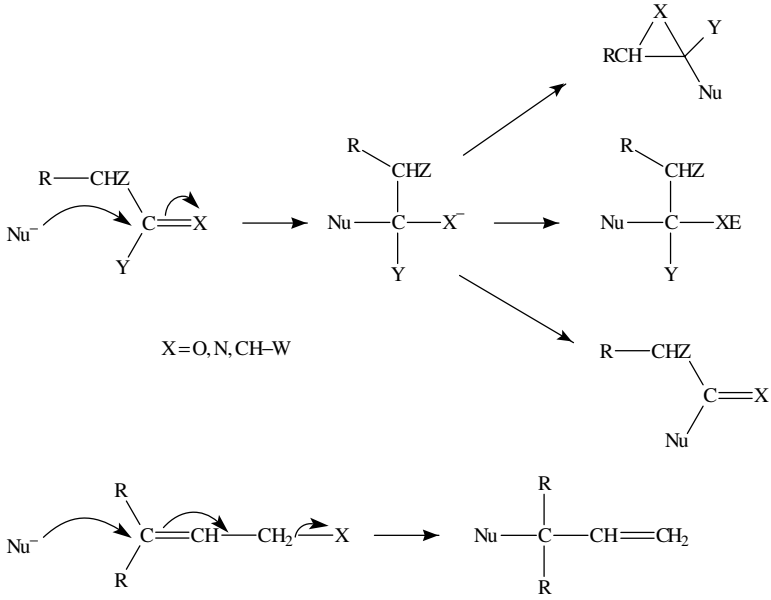
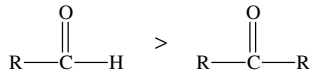
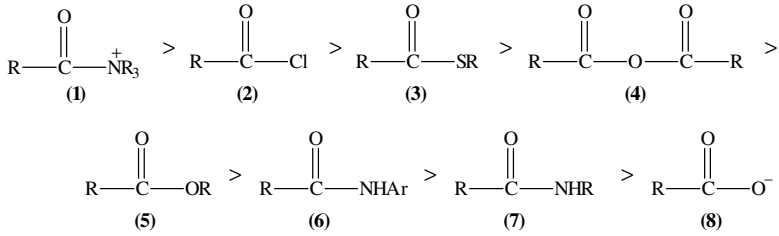


FIGURE 1. Nucleophilic attack of C=X and C=C and possible outcomes

Aldehydes and ketones



Carboxylic acid derivatives



Carbon–carbon double bonds

where X is:

NO_2 > PhCO > SO_3Ph > CHO > MeCO > CO_2Ph > p-$MeC_6H_4SO_2$ > CN > SO_2NMe > CO_2Me > SOPh > 4-pyridyl > $PO(OCH_2CH_2Cl)_2$ > $CONH_2$ > $PO(OEt_2)$ > CONHR > p-$NO_2C_6H_4$ > SPh > Cl > H

FIGURE 2. Examples of carbon double bonds that are prone to attack by nucleophiles and their relative reactivities

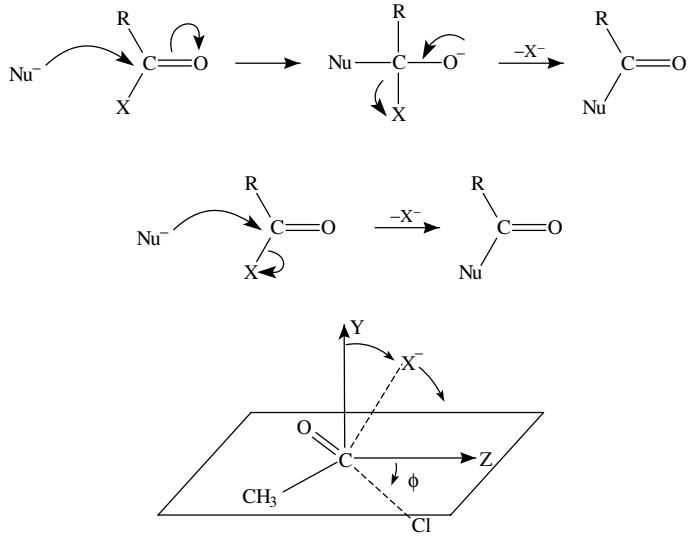
when the electron distribution is polarized in some way such that one carbon of the double bond becomes more electrophilic, then attack by a nucleophile will be possible. Obvious cases of this are C=X species such as aldehydes, ketones, carboxylic acid derivatives and imines. However, carbon–carbon double bonds are also prone to nucleophilic attack when one of the carbons is attached to groups which can polarize the electron distribution of the double bond. In terms of a ground state argument, nucleophiles will attack a C=X to give Nu−C−X^-, if negative charge formation at X is favourable. Again obvious cases are when X is oxygen or nitrogen or suitably substituted carbon, such as a carbon adjacent to a carbonyl where X^- represents an enolate. Of course such arguments involve many simplifications and the range of carbon double bonds attacked by nucleophiles will depend upon such things as the nucleophilicity of the attacking species, solvents, proximity etc. Similarly in some nucleophilic attacks at carbon double bonds Nu−C−X^- species will not appear as intermediates, for example concerted substitutions at sp^2 carbons.

Figure 2 shows the range of carbon double bonds that are prone to nucleophilic attack by conventional nucleophiles together with a measure of relative reactivity where available.

A. Nucleophilic Attack on Carboxylic Acid Derivatives

Theoretical calculations using MNDO and 4-31G basis sets of the frontier orbitals by the group of Yamabe[1] have shown that nucleophilic attack of carboxylic acid derivatives

in the gas phase can proceed via a tetrahedral intermediate or in a concerted process with the carbon-leaving group bond breaking as the carbon nucleophile bond is made (Scheme 1).

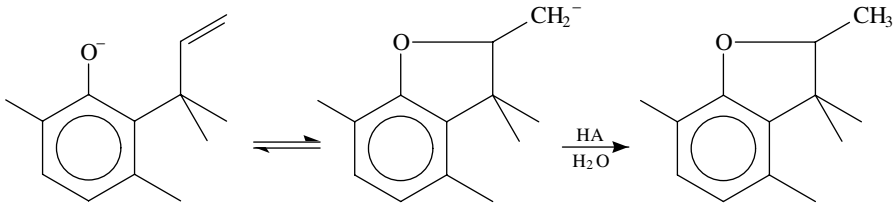


SCHEME 1

Nucleophilic attack involves electron donation to the π^* orbital of the carbonyl; however, the relative reactivity does not reflect the order of these LUMO energy levels. To account for the order it is necessary to consider both the bond-making and bond-breaking processes, that is we need to mix the LUMO with the LUMO + 1 (σ^*_{C-X}). The level of mixing depends upon how close the two LUMOs are. Calculations show that the correct order of energy levels is obtained when φ is 20°. The difference in energy between the LUMO and the LUMO + 1 also predicts whether there is an intermediate along the pathway or not. When the energy difference is small, usually associated with a weak C−L bond, no intermediate is predicted **(1–4)**; however, when the energy difference is large an intermediate is predicted **(5–8)**. Contrary to this conclusion, pulsed ion cyclotron resonance spectroscopy studies of nucleophilic displacements in the gas phase suggest that acyl halides undergo substitution via a tetrahedral intermediate with a range of nucleophiles[2].

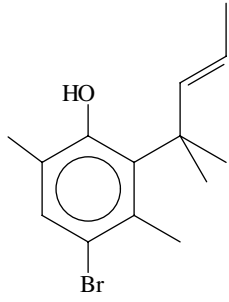
B. Nucleophilic Attack on Alkenes

Whilst nucleophiles do not generally add to unactivated double bonds, they do react if the two groups are close together as part of the same molecule. Evans and Kirby have examined the intramolecular nucleophilic addition of phenolate to unactivated double and triple bonds[3,4]. The nucleophilic phenolate oxygen adds to the double bond up to the point where bond formation, and hence the formation of the primary carbanion, is well advanced. The intermediate ion, **9**, would normally revert to starting material but in the presence of a general acid it can be protonated to give a stable product. Thus, the general acid plays an essential role in avoiding the formation of a complete primary alkyl carbanion in water.



(9)

As expected from Baldwin's rules, with suitable substrates, both regiospecific 5- or 6-*exo* addition could be observed. The electronically symmetrical alkene **10** underwent both 5-*exo* and 6-*endo-trig* addition in a ratio of 18:1. This is in accord with Baldwin's rule in that, whilst both processes are favourable, five-membered rings are formed more readily than six-membered rings. They also showed that 6-*endo-trig* and 6-*exo-trig* were both favourable processes with rate constants differing by a factor of less than 3.



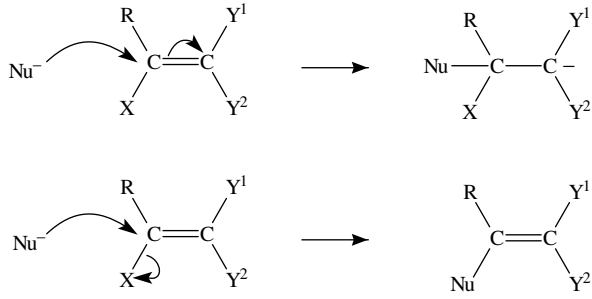
(10)

Similar reactions have been reported in bicyclic systems where the intramolecular reaction of an alcohol with a simple alkene leads to relief of ground state strain[5].

C. Conjugate Additions

1. Mechanistic considerations

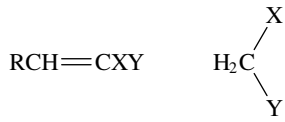
Rappoport has carried out extensive work on nucleophilic substitution reactions. Several excellent reviews have appeared so only brief details are given here[6,7]. There are two possible mechanisms that involve initial attack of the nucleophile, which mirror the behaviour of acyl chlorides: initial attack of the nucleophile to give a carbanion followed by loss of the leaving group or a concerted attack of the nucleophile with loss of the nucleophile (Scheme 2). The former predominates in systems where Y^1 and Y^2 are good electron withdrawers and the leaving group is poor. The latter predominates with a good leaving group and poor electron-withdrawing characteristics of Y^1 and Y^2. The electron-withdrawing characteristics of Y^1 and Y^2 can be evaluated from the pK_a of the carbon acid $CH_2Y^1Y^2$. Based on a variety of evidence, such as the stereochemistry of the substitution and k_{Br}/k_{Cl} and k_{Cl}/k_F element effects, Rappoport proposed that for poor leaving groups, the vinyl substitution would be multistep if the pK_a of the corresponding carbon acid $CH_2Y^1Y^2$ were less than 40. With good leaving groups, such as Cl, Br and



SCHEME 2

OTs, the vinyl substitution would be multistep if the pK_a of the corresponding carbon acid $CH_2Y^1Y^2$ were less than 20. If the pK_a were in the range 20–30 he suggests that the evidence points to a multistep process. However, if the pK_a were greater than 40 the substitution would probably be a single step.

In a third review Rappoport points out the difficulty of trying to construct even a qualitative nucleophilicity scale towards a vinylic carbon[8]. Whilst for a range of nucleophiles, plots of $\log k$ versus a parameter which reflects the nucleophilicity, such as N_+, are sometimes parallel for a range of related alkene substrates, for the majority of reactions studied a constant selectivity relationship does not apply. Each substrate requires a different blend of steric, polar and hard/soft nucleophile arguments to describe the relative reactivities. Bernasconi has correlated the reactivity of carbon–carbon double bonds of the type **11** with the intrinsic rate constant for deprotonation of **12**[9]. Plots of the logarithm of one rate constant versus the logarithm of the other rate constant give reasonably straight lines with a slope which reflects the smaller change in the rate constant for nucleophilic attack on the carbon–carbon double bond. He suggests that in both these reactions the development of resonance and the concomitant solvation of the carbanion lags behind other bond changes and that this lag is less extreme for nucleophilic attack of a carbon–carbon double bond than for proton transfer. He suggests that this lag can be used to explain much of the structure–reactivity behaviour of such systems.



(11) **(12)**

where X and Y are H, CN, $COCH_3$, NO_2, $PhNO_2$

2. Relative reactivities

Shenhav, Rappoport and Patai examined the kinetics of addition of morpholine and pyrrolidine to various activated olefins in methanol and obtained an order similar to Figure 1, as shown in Table 1[10]. They pointed out that data in the literature suggested that CO_2Me and CN are sometimes reversed[11].

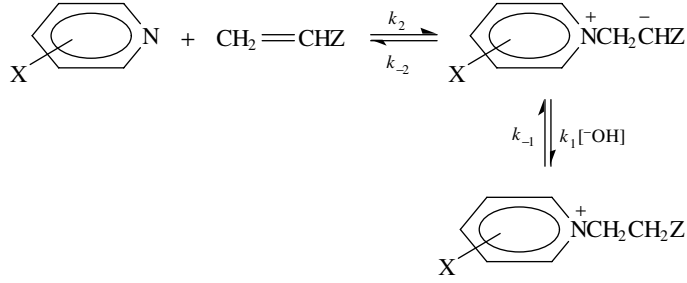
Heo and Bunting have examined the rate-determining steps in conjugate additions and E1cb reactions in aqueous solutions[12]. They examined the reactions between a range

TABLE 1. The relative rates for nucleophilic addition to electrophilic alkenes

Alkene	k (rel)[a]	k_2 (rel)[b]	k (rel)[c]
CH_2=CHCOPh	11300		
CH_2=$CHSO_3$Ph	9000		
CH_2=CHCHO	3600	3900	—
CH_2=$CHCOCH_3$	3400	900	630
CH_2=$CHSO_2CH_3$		140	50
CH_2=$CHCO_2$Ph	400		
CH_2=$CHCO_2CH_3$	29	25	29
CH_2CHCN	16	6	8
CH_2=$CHCONH_2$	1	1	1

[a]Relative rate constants for the addition of morpholine to CH_2=CHZ in methanol[10].
[b]Relative rate constants for the addition of 4-(dimethylamino)pyridine to CH_2=CHZ in aqueous solution[12].
[c]Relative rate constants for the addition of glycine to CH_2=CHZ in aqueous solution[13].

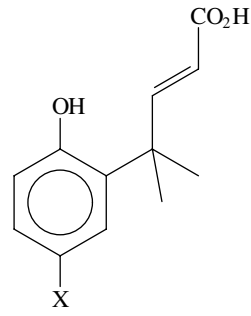
of conjugated double bonds and substituted pyridines and were able to obtain rate and equilibrium data for each of the steps. The relative rates of nucleophilic attack are also given in Table 1. They found that the rates of nucleophilic attack upon these alkenes are much more sensitive to the nature of Z than are the equilibrium constants for addition. The data presented agreed with previous data of Rappoport and Patai[10] and also with data for the addition of glycine to CH_2=CHZ in aqueous solution[13].



By examining the rates of intramolecular nucleophilic cyclization of **13** at different pH values, Kirby has determined the relative reactivity of RCH=CH_2, RCH=$CHCOO^-$ and RCH=CHCOOH towards nucleophilic substitution[14]. The ratios $1:4000:8 \times 10^7$ are in broad agreement with the relative rates, 3×10^4:1, for nucleophilic attack of ammonia on fumaric acid in the neutral and dianionic forms at 135 °C. The relative rates for nucleophilic attack of hydroxide on fumaric acid in the neutral and dianionic forms at 135 °C changed to 3×10^7:1 because of the adverse electrostatic interaction between the hydroxide ion and the dianion[15].

Calculations of reactions of simple nucleophiles such as H^- with carbonyl compounds show that, in the gas phase, there is no barrier. Activation energies in solution arise from desolvation of the nucleophile. However, reactions of a nucleophile with an alkene or an alkyne do have a barrier in the gas phase.

The group of Osman[16] has reported that the incoming nucleophile will align its region of charge concentration with the largest region of charge depletion in the valence shell



(13)

of the electrophile. For acrylic acid systems the nucleophile attacks C(1) above or below the plane at an angle of 115°. Relative reactivities of acrylates to nucleophilic attack are related to the regions of charge depletion on C(1) as given by the minimum in $-\nabla^2 p$ in the valence shell of charge concentration at C(1). This gives the order acrolein, acrylic acid, acrylonitrile and methacrylic acid. The net charge on the electrophilic centre q(C(1)) is not a good parameter of reactivity of C(1) to nucleophilic attack.

For attack of F^- on acrylic acid, first a hydrogen bonded complex is formed which then proceeds to the transition state and then to a stable carbanion. The methyl in the methacrylic acid reduces stabilization of the carbanion as predicted. Subsequent studies using ammonia as the nucleophile indicated that attack proceeded by a rate-determining intramolecular proton transfer from the nucleophile to the ligand, assisted by a discrete water molecule that acts as a catalyst[17]. They predicted that acrolein underwent 1,4-addition, acrylic acid either 1,2- or 1,4-addition and acrylonitrile 1,2-addition.

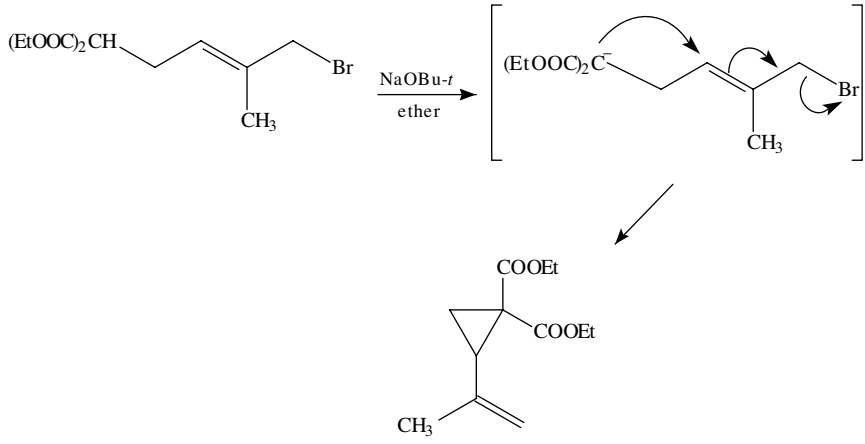
The relative reactivities of acrolein, acrylonitrile, methyl acrylate and methyl methacrylate have also been investigated by means of the Fukui function $f^+(\mathbf{r})$ and its condensed counterpart $f_c{}^+$[18]. These are local properties that help determine the preferred direction for a reagent to approach a substrate. In this instance they also mirror the relative reactivity of different substrates. Both functions correlated well with the experimental data, the LUMO density being a relatively good approximation to the Fukui function. A closely related local property is the condensed local softness $s^+(\mathbf{r})$, which also correlated well with the relative reactivities[19].

D. Nucleophilic Attack on Allyl Systems

Nucleophilic attack at the double bond of an allylic system bearing an α-leaving group has received special attention and has been reviewed extensively[20,21], so only brief details will be given here. Various pathways for substitution have been proposed; however, we shall only concern ourselves with attack at the carbon of the double bond with formation of the carbanion or concerted loss of the leaving group. Magid[20] has thoroughly reviewed the evidence for the mechanism: suffice it to say that some authors favour a concerted process[22,23] whilst others think it a 'myth' and favour the formation of discrete intermediates[24]. There is also competing attack at the carbon α to the leaving group, the extent of which depends upon the presence and size of substituents at the α and γ positions. *Syn* stereochemistry is usually observed with the nucleophile attacking from the same side that the leaving group departs, but the results are often complicated by conformational bias[25]. The preference for *syn* attack is supported by calculations[20]. Nevertheless, *anti*

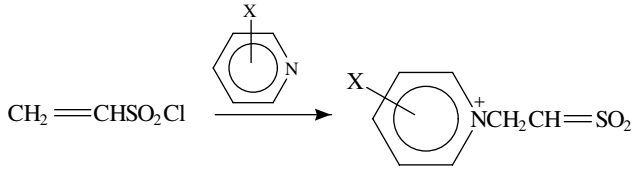
behaviour has been observed[26]. Calculations also suggest that soft nucleophiles give *syn* stereochemistry[27] but anionic nucleophiles give *anti* stereochemistry[28].

Intramolecular nucleophilic attack at the double bond of an allylic system bearing an α-leaving group has been extensively reviewed by Paquette and Stirling[21]. One of the key aspects of such reactions is the limitation of ring size on the trajectory of the nucleophile on the carbon double bond, although examples of 3,4,5 and 6 *exo-trig* reactions are known (for example see Scheme 3)[29]. The stereochemistry of these intramolecular reactions mirrors that of the intermolecular reactions in that the attack is usually, but not always, *syn*.



SCHEME 3

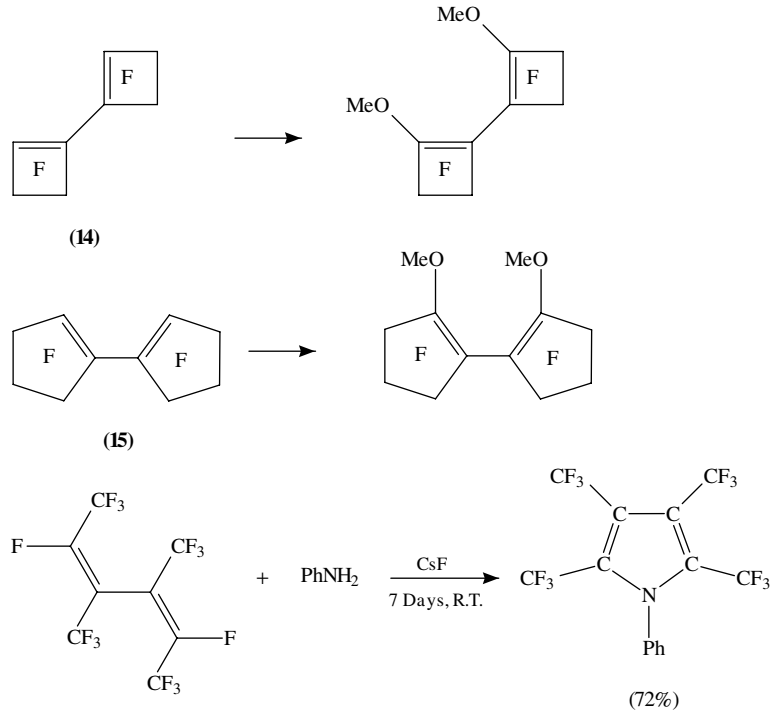
Vinylsulphonyl chlorides undergo a similar reaction. The sulphonyl group activates the double bond to nucleophilic attack with loss of a chlorine to give a sulphene[30]. It was not possible to distinguish whether a two-step process via a zwitterion or a concerted process was involved.



E. Nucleophilic Attack on Halogenated Alkenes

Another series of carbon–carbon double bonds that are prone to nucleophilic attack are halogenated alkenes, where the developing carbanion is stabilized by inductive withdrawal by the halogen. Alkenes bearing fluorines are more prone to nucleophilic attack than the corresponding chloro derivatives. In perfluoro compounds nucleophilic attack occurs preferentially at a terminal $CF_2=$ group and the presence of perfluoroalkyl groups on the double-bond carbon β to attack increases the reactivity due to the formation of a more stable carbanion[31]. This can also be explained using a Frontier Orbital approach, where the presence of the trifluoromethyl group lowers the energy of the LUMO[32]. The

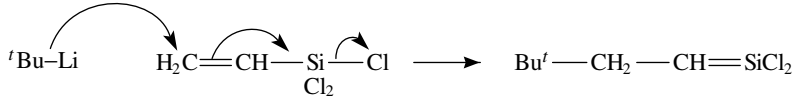
corresponding perfluoro dienes also undergo nucleophilic attack. **14** undergoes nucleophilic attack (Scheme 4) much more quickly than **15** due to the relief of angle strain during formation of the intermediate carbanion[33]. Interestingly, both double bonds undergo nucleophilic attack with overall substitution. This has been used to form fluorinated heterocycles and cyclopentadienes[34].



SCHEME 4

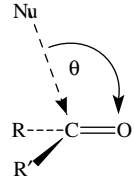
F. Nucleophilic Attack at Other Heterosubstituted Alkenes

Trimethylsilyl groups stabilize α carbanions and thus promote nucleophilic attack at the β position of a double bond. Stork has used α-silylsubstituted vinyl ketones extensively in conjugate addition reactions using enolates[35]. The presence of the trimethylsilyl group stabilizes the enolate produced and thus avoids the problems of reversibility and polymerization. Silylated α,β-unsaturated amidate anions have also been shown to be more prone to nucleophilic attack than their unsilylated analogues[36]. Ordinary vinylsilanes readily undergo nucleophilic attack with strong nucleophiles such as organolithiums and this is one of the methods for generating α-silyl carbanions[37]. This has been used by Auner to make silenes[38].



III. THE ORBITAL INTERACTIONS THAT CONTROL THE APPROACH OF A NUCLEOPHILE TO THE DOUBLE BOND

The approach of a nucleophile to a carbon double bond has been mapped experimentally by Dunitz and Bürgi[39] using crystal structure correlations. This has been reviewed many times[40] and so only the briefest of details will be given here. They examined the X-ray crystal structure of a series of amino ketones where internal proximity or crystal packing led to a range of N...C=O distances. They found that when the N...C=O distance was less than the sum of the van der Waals radii, the closer the nitrogen to the carbonyl carbon the greater the displacement of this carbon from the plane containing the oxygen and the other two substituents. This was accompanied by a lengthening of the C=O. Moreover, the interaction between the nitrogen and the carbonyl carbon was attractive since this displacement was towards the nitrogen. Examination of the series showed that the amine approached the carbonyl on its mirror plane with a trajectory not perpendicular to the carbonyl but with an angle θ of 105°, as shown in Scheme 5.



SCHEME 5

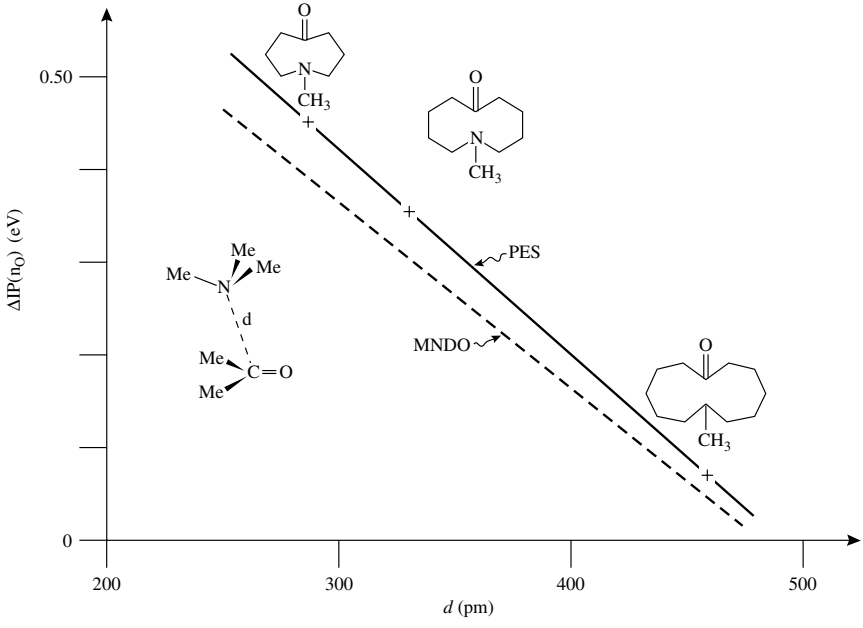


FIGURE 3. The variation with distance of the ionization potential of the n_O orbital as determined by PES. Reproduced by permission of the Royal Society of Chemistry from Reference 41

Rademacher[41] has used a similar approach to examine the properties of species which had energy minima along the Nu. . .C=O trajectory. He employed ultraviolet photoelectron spectroscopy (PES) to examine the energies of the valence orbitals in alicyclic molecules of medium rings (8–12) which involved transannular interactions between a nitrogen and a carbon double bond. He focused on the n_O orbital since theoretical calculations showed this to change in the most coherent manner between reactants and products. Figure 3 shows the variation with distance of the ionization potential of this orbital as determined by PES. This shows the eight-membered ring to have the largest transannular interaction. ^{17}O and ^{13}C NMR indicated that the interaction was largest in the ten-membered system. This difference was explained by phase effects, that is, solvation may affect the conformation of the ring.

Rademacher also examined the addition of nucleophiles to alkenes using MNDO calculations[41]. Here the approach angle is about 120°, maximizing the overlap between the centres involved in bond formation while keeping the overlap involving the other end of the double bond to a minimum. Calculations show that the n_N orbital of an attacking amine correlates with the n_C orbital of the product, whereas the $\pi_{C=C}$ orbital of the alkene correlates with the σ_{CN} of the product. Figure 4 shows how the ionization

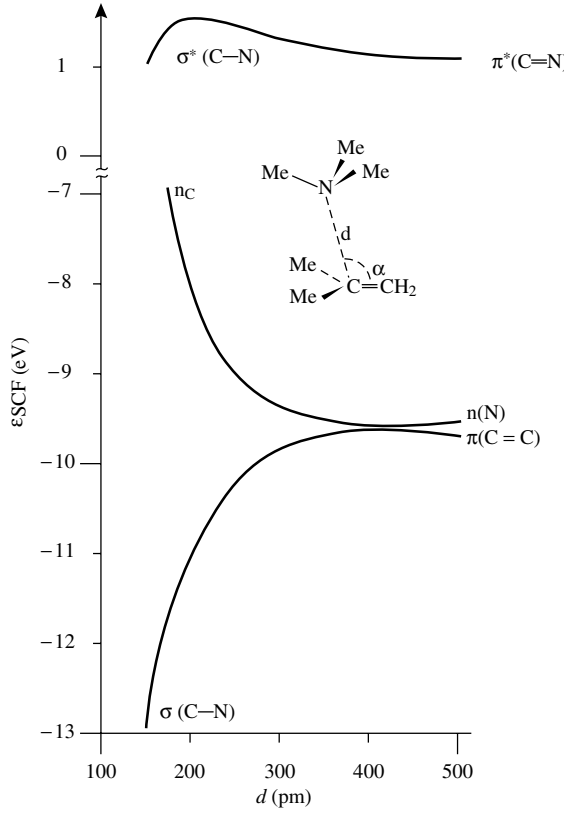


FIGURE 4. Course of the orbital energies for the nucleophilic addition of trimethylamine to isobutene. Reproduced with permission of the Royal Society of Chemistry from Reference 41

potentials determined by PES varied with the approach distance, confirming that such an approach can be used to probe the nucleophilic addition of an amine to an alkene.

A comprehensive analysis of nucleophilic attack on carbon double bonds has appeared[42]. Using GAUSSIAN 80 and 82 the transition states for attack of nucleophiles on alkenes and carbonyls has been determined, as shown in Figure 5. Charged nucleophiles attack alkenes and alkynes with angles between 115° and 130°, as shown by hydride attacking **16** (ethyne) and **17** (propene). The deformation from this angle can occur about

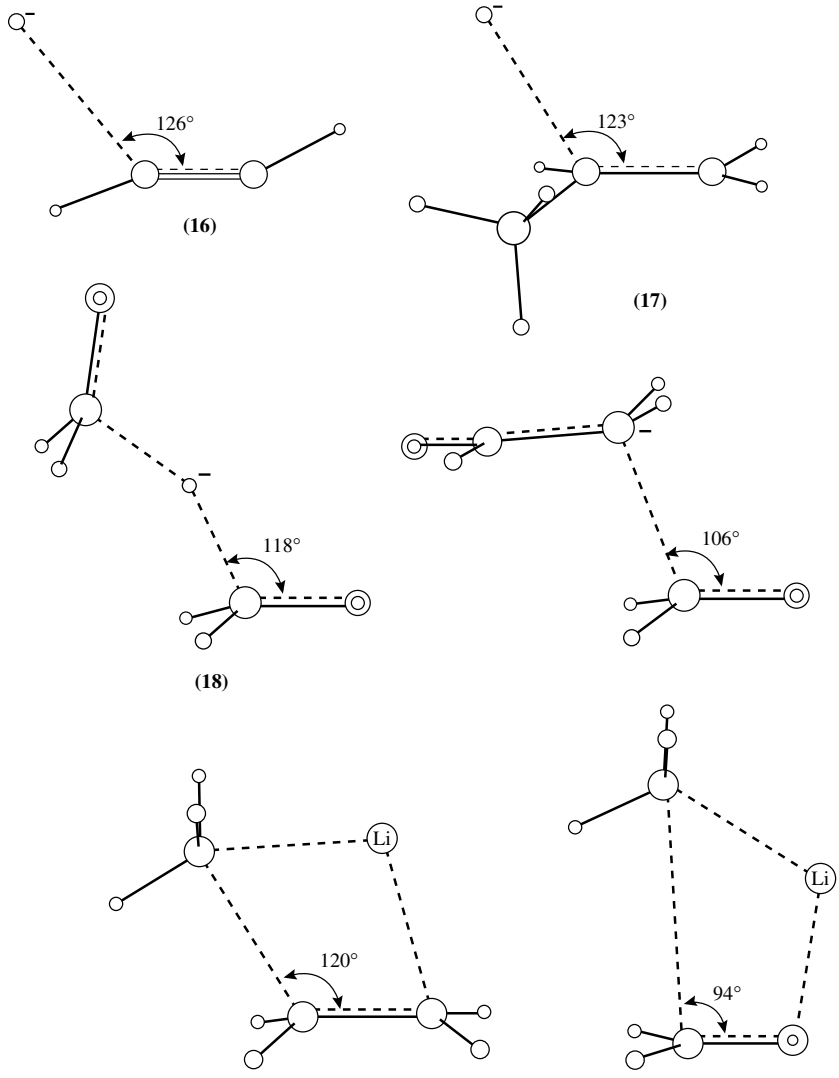


FIGURE 5. The transition states for attack of nucleophiles on alkenes and carbonyls, determined using GAUSSIAN 80 and 82. Reproduced with permission from Reference 42. Copyright (1986) American Association for the Advancement of Science

one-half as easily as the bending of a normal C−C−C or H−C−C angle[43]. As the π bond becomes more unsymmetrical the angle of attack decreases, as shown by **18**, the attack of methoxide ion on methanal. The double-bond component is always bent towards the geometry of the product in the transition state. For alkenes and alkynes, as the substituent(s) on the carbon attacked go beneath the plane of the reactant molecule, the substituent(s) at the other carbon rise above the plane[44]. The addition of organolithiums or metal hydrides involve four-centre transition states, that is, the metal coordinates with the nucleophile and the π system. This leads to smaller angles of attack[45,46].

Frontier Molecular Orbital Theory can be used to describe qualitatively the trajectory of a nucleophile when it attacks a π centre. Two sets of first-order interactions are considered. Firstly the stabilizing interaction of the HOMO of the nucleophile with the LUMO (π^* and σ^* orbitals) of the π system and secondly the destabilizing interaction of the HOMO of the nucleophile with the HOMO (π and σ molecular orbitals) of the π system, as shown in Figure 6.

The angle of attack θ is derived by maximizing the stabilizing interactions and minimizing the destabilizing interactions. Using such an approach Houk and coworkers found that when θ is greater than 90° the destabilization is reduced since the overlap between the two HOMOs is reduced[42]. At the same time, the stabilizing interaction between the nucleophiles HOMO and the double bonds LUMO is increased since the overlap integrals between the nucleophile HOMO and the p orbitals at C_1 and C_2 that make up the LUMO are of opposite sign.

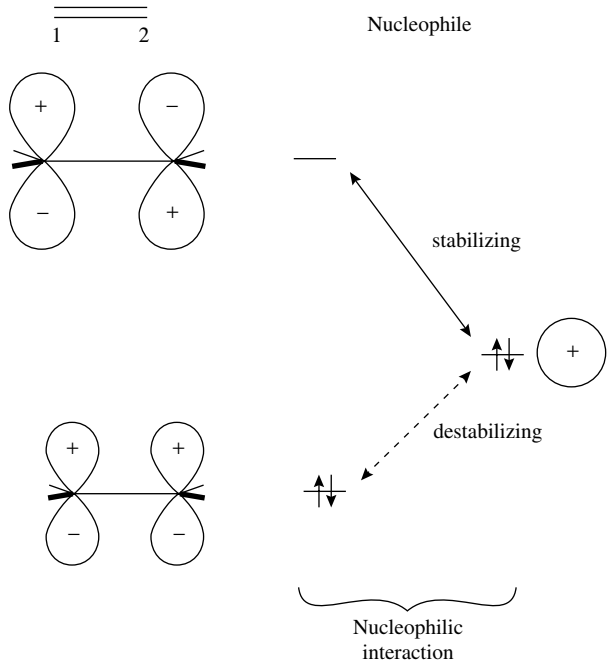
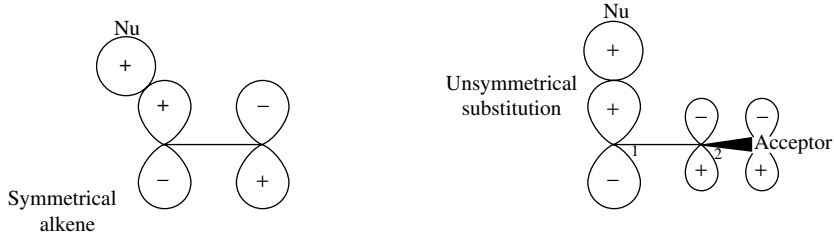


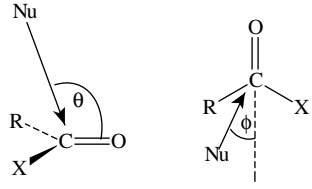
FIGURE 6. Stabilizing interaction between the HOMO of the nucleophile and the LUMO of the π system and the destabilizing interaction between the HOMO of the nucleophile and the HOMO of the π system. Reprinted with permission from Reference 42. Copyright (1986) American Association for the Advancement of Science

Nucleophilic attack on a symmetrical alkene (Scheme 6) occurs with a larger angle than attack at a carbonyl, since an electron-withdrawing substituent on carbon or an electronegative element makes the coefficient of C_1 in the π^* molecular orbital the larger of the two. Since pyramidalization also occurs, the attack angle should approach 109.5° for an unsymmetrical double bond[42]. Liotta and collaborators found that, for carbonyls, as the energy of the frontier molecular orbital of the nucleophile (HOMO) becomes less negative, the angle θ approaches 90°. Thus, since hard nucleophiles have low-lying HOMOs, they will approach at a larger angle than soft nucleophiles that have higher-lying HOMOs[47].



SCHEME 6

Baldwin and coworkers have developed a set of rules that describe the trajectory of nucleophiles when they attack π systems[48–51] (Scheme 7):



SCHEME 7

(i) The angle θ is about 110° when the nucleophile is derived from a first-row element.

(ii) The angle ϕ is determined by the resultant of the vector addition of the trajectories for the main resonance forms, where the magnitude of the vector reflects the relative contribution of the resonance forms.

Thus the angle becomes greater in the series of carbonyl compounds — ketone, amide, ester and carboxylate anion.

When the nucleophile involved a second-row element, the angle θ was smaller, possibly as a result of 3d back-bonding. This means that, as Figure 7 shows, 3- to 7-*exo-trig* ring closures are favoured, as are 6- to 7-*endo-trig*, but 3- to 5-*endo-trig* ring closures are disfavoured. Although the rules are generally applicable, there have been many examples where these rules appear to break down[52]. However, as Johnson points out in a recent review of this area, 'a great deal may still be learnt from the rules, as much in their breach as in their observance'[53]. For example, the disallowed 5-*endo-trig* reaction (Scheme 8) does not occur in base but does take place in acid. Whilst this seems to contradict Baldwin's rules, it has been shown that reaction proceeds with a 5-*exo-trig* mechanism via, after protonation, **19**[54] or, more likely, **20**[55]. This was confirmed by examining the substituent effects of aryl substituents. Electron-donating groups would be expected to slow down the corresponding conjugate additions of enones; however, a rate increase was observed, as a result of stabilization of the intermediate **19** or **20**.

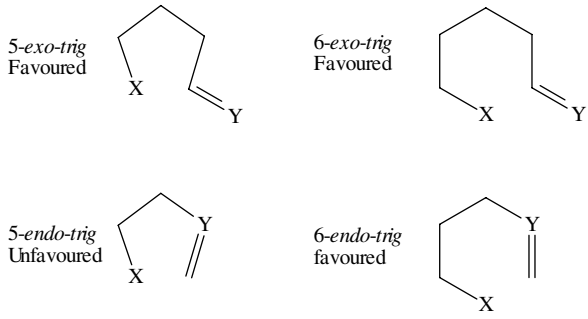
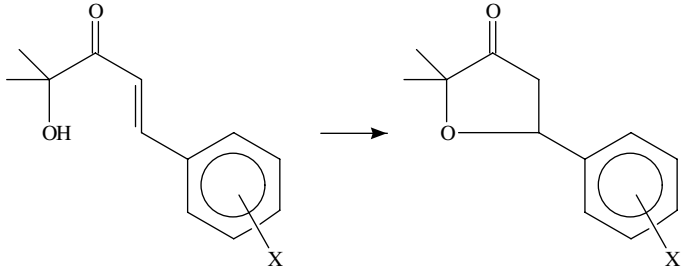
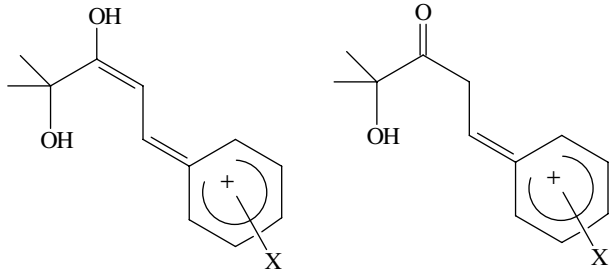


FIGURE 7. Favoured and disfavoured ring closures

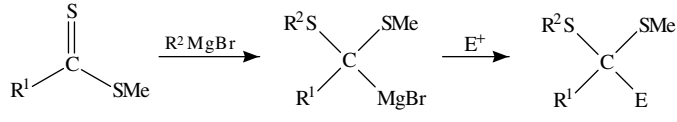


SCHEME 8



(19) **(20)**

Carbon–sulphur double bonds also undergo nucleophilic attack in a similar fashion to carbon–oxygen double bonds except in the cases of thiophilic addition, where the nucleophile selectively attacks the sulphur[56] (Scheme 9).



SCHEME 9

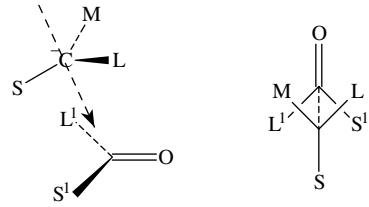
IV. STEREOSELECTIVITY IN NUCLEOPHILIC ATTACK OF DOUBLE BONDS

The direction of approach of the nucleophile on the carbonyl coupled with steric and electronic interactions between the nucleophilic molecule and the substrate lead to stereoselective reactions which have been well studied and for which a number of predictive rules and explanations have been developed.

A difference of only 1.8 kcal mol^{-1} between the free energies of activation of two stereoisomeric transition states leads to a product ratio of 96:4; for enantiomeric transition states this corresponds to an ee of 92%[42]. A difference of more than 2.8 kcal mol^{-1} will give a ratio of greater than 100:1 (ee>99%).

A. Diastereoselective Approach of the Nucleophile on the Double Bond

Calculations have shown that nucleophiles with groups attached, such as a methyl anion, take up a staggered arrangement with respect to the sp^2 centre they are attacking[42]. Based on such an approach of the nucleophile, Bassindale, Taylor and collaborators have proposed an empirical model (Scheme 10) for the nucleophilic addition of prochiral carbanions to prochiral carbonyls in the absence of chelation control[57].

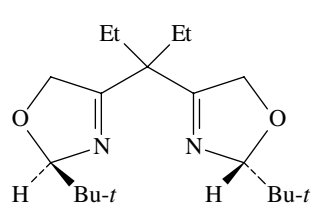


SCHEME 10

The carbanion C-SML approaches the carbonyl S^1L^1CO, where S, M and L represent small, medium and large groups, respectively, such that the smallest group on the carbanion is disposed between S^1 and L^1. The most favoured arrangement of the other groups is with L and S^1 and M and L^1 *gauche*. Other independent studies are in agreement with this predictive model[58,59]. This model assumes no chelation; however, in the presence of chelation other factors influence the stereochemistry of the interaction of the nucleophile with the double bond. For example, analysis of the relative energies of the chair-like transition states involving carbonyls or imines can usually explain the observed diastereoselectivity[60,61]. The presence of chiral auxiliaries can also control the stereochemistry of addition of an achiral organolithium to an aldehyde or unsymmetrical ketone, leading predominantly to one enantiomer[62]. A recent example is the addition of organolithium reagents to imines, which can be made stereoselective (80–90% ee) by the addition of C2-symmetric ligands such as **21** and **22**[63].

B. Stereoselectivity as a Result of a Chiral Centre α to a Carbon Double Bond in the Substrate

A number of models have been developed to predict the stereochemical outcome of the addition of a nucleophile to a carbonyl with a chiral α carbon. One of the first was Cram's rule which was developed on an empirical basis[64]. The generalization is shown in Figure 8a, where L, M and S represent large-, medium- and small-sized groups, respectively, attached to the chiral α carbon. The molecule is imagined to be oriented so



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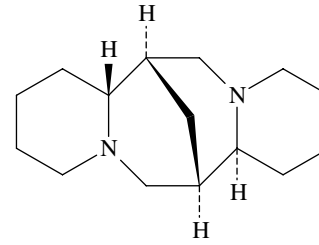


(22)

that the carbonyl group is flanked by the two smaller groups, M and S, with the large group L eclipsed with the alkyl on the other side of the carbonyl. The nucleophile then approaches from the face of the carbonyl with the smallest substituent S. If one of the groups on the chiral α carbon and the carbonyl oxygen are capable of forming a chelate with a metal ion, then a cyclic model has been invoked in which the carbonyl oxygen and the α-heteroatom are held in a coplanar arrangement and attack occurs from the side of the smaller of the remaining α-substituents (Figure 8b). If one of the α-substituents is a dipolar group such as a halogen or an oxyanion, a third possibility has been proposed in which the dipoles of the carbonyl and the α C−X bond arrange themselves to point in opposite directions (Figure 8c)[65]. Again attack occurs from the side of the smaller of the remaining α-substituents.

Felkin's group has developed an alternative approach based on a staggered transition state similar to Figure 8d[66–68]. Here the largest group, L, on the chiral α carbon is placed antiperiplanar to the forming bond The medium-sized group then occupies the sterically

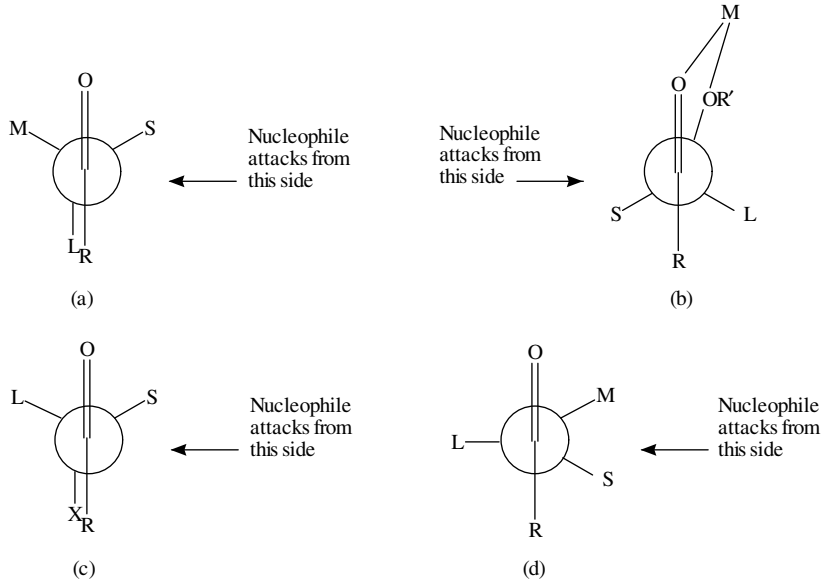


FIGURE 8. Models for predicting the stereochemical outcome of the addition of a nucleophile to a carbonyl with a chiral α carbon

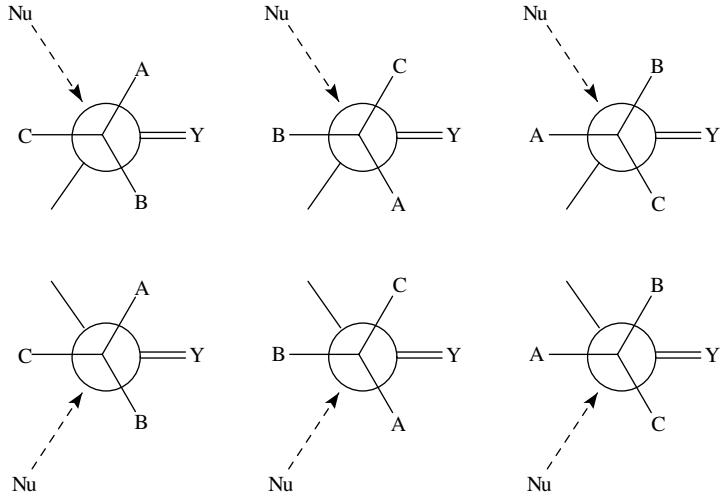
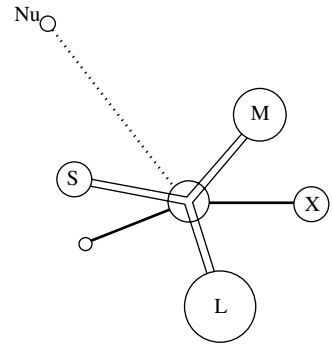


FIGURE 9. Six staggered transition states for the attack of a nucleophile on an unsaturated centre

less congested 'inside' position adjacent to the oxygen of the carbonyl and the smallest group occupies the more sterically congested 'outside' position.

The theoretical basis for these models has been examined on numerous occasions. Calculations have been performed to assess the conformational preferences of single bonds attached to either the nucleophile or the double bond[42,69]. A methyl group attached to C(1) of the double bond will take up a staggered arrangement with respect to the partially formed bond to the nucleophile and the other substituents on the pyramidalized carbon. This confirms that attack of a nucleophile on an unsaturated centre can occur with one of the six possible transition states shown in Figure 9, depending upon the configuration and conformational preferences of the substituents A, B and C. Other nonstaggered conformations will be of higher energy.

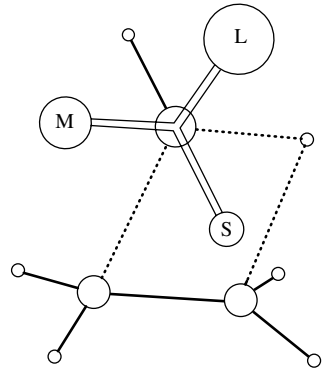
Calculations[42,69] confirm that when only the steric effect of groups is important, the largest group occupies the least crowded position in the transition state and the smallest group the most crowded (Scheme 11).



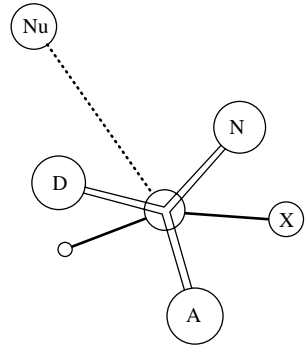
SCHEME 11

In agreement with Felkin's predictions, nucleophilic attack with a large θ has the largest group L *anti* to the incoming nucleophile, since the attacked sp^2 carbon will only be partially pyramidal. The medium-sized group will lie between the incoming nucleophile and the double bond and the smallest group occupy the most crowded position between the incoming nucleophile and the other substituent which will have only moved a little way from the plane of the double bond. As this substituent becomes more bulky, so the differentiation between the crowding of the small and medium group becomes more pronounced leading to higher stereoselectivity.

As θ, the angle of attack, decreases, the differentiation between the crowding of the small and medium group becomes less pronounced, leading to lower stereoselectivity. An example of this is nucleophilic attack on a carbonyl via a four-centred transition state. In extreme cases this can lead to a cross-over in the stereoselectivity so that 'anti-Cram' behaviour is observed (Scheme 12). Here θ is so small that now the space between the substituent and the attacking nucleophile is less crowded than that between the attacking nucleophile and the carbonyl. This 'anti-Cram' behaviour also occurs with enolate alkylations[70]. If the electronic effects of the attached groups A, B and C are important, a different behaviour is observed (Scheme 13). The Anh–Eisenstein model[69] predicts that the most electron-withdrawing substituent, A, will take a position *anti* to the attacking nucleophile so that withdrawal of electrons from the π system is maximized. The most



SCHEME 12



SCHEME 13

electron-donating substituent, D, will take up a position between the attacking nucleophile and the double-bond substituent to minimize electron donation into the π system.

In terms of frontier orbitals, when the electron-withdrawing group is *anti* to the attacking nucleophile, its LUMO σ^*_{C-A} overlaps with the HOMO of the transition state resulting in stabilization, as shown in Figure 10[42]. The HOMO of the transition state is a mixture of the nucleophile HOMO and the carbonyl LUMO (π^*). If the electron-withdrawing group were in either of the other two staggered positions, the stabilization would be less because the overlap decreases the more the electron-withdrawing group is orthogonal to the direction of attack. Overlap of the occupied σ_{C-D} orbital of an electron-donating group with the HOMO of the transition state is destabilizing. Thus it prefers to take up a position orthogonal to the direction of attack and away from the double bond.

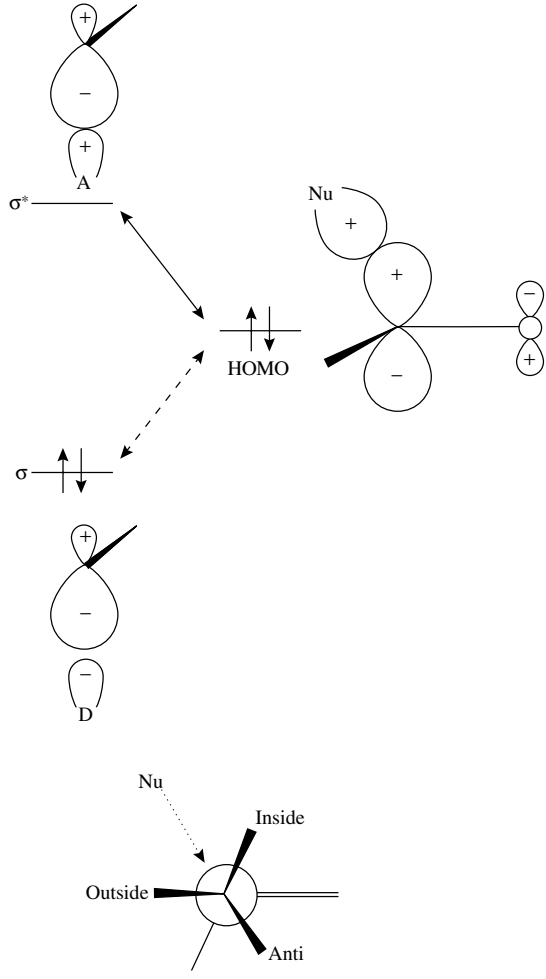
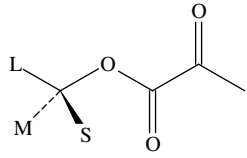


FIGURE 10. Overlap of the LUMO σ^*_{C-A} of an electron-withdrawing group on the α carbon with the HOMO of the transition state. Reprinted with permission from Reference 42. Copyright (1986) American Association for the Advancement of Science

Of course, sometimes steric factors and electronic factors may compete. For example, if the electronic effects of the trimethylsilyl substituent dominate, it will take up a position opposite the carbonyl; however, if its steric factors dominate, it will take up a position *anti* to the incoming nucleophile. Thus one of the problems with this model, with some systems, is determining which group should be placed antiperiplanar to the attacking nucleophile, since its selection depends upon both steric factors and electronic factors. Wong and Paddon-Row have used *ab initio* calculations to model the complete set of diastereoisomeric transition states for the addition of cyanide to propanal, fluoroethanal and 2-fluoropropanal[71]. They found that the most stable transition state has the C−F bond antiperiplanar to the forming Nu−C bond, consistent with the Anh–Eisenstein model. Their results were not consistent with the alternative Cieplak model[72], which suggests mixing of the vacant σ^* orbital of the forming nucleophile bond with the filled σ orbital of the C−L bond is important. Electrostatic effects have also been shown to be important in the nucleophilic addition to β,γ-unsaturated carbonyl compounds[73], which give high stereoselectivity[74]. In non-chelated systems the transition state has the alkynyl group *anti* to the incoming nucleophile, not because of its size (it has little steric demand) but because of electronic effects. Calculations indicate that in the presence of a metal ion and chelation, the alkynyl group occupies the 'inside' position.

Another empirical model is Prelog's rule for predicting the stereoselectivity of nucleophilic attack at the carbonyl of an α-ketoester of a chiral alcohol, $RCOCO_2R^*$[75,76]. The two carbonyls are arranged *anti* and the larger of the substituents on the chiral centre is arranged so that it is *anti* to the O−C bond. Attack of the nucleophile on the carbonyl then occurs from the side with the smallest of the other two groups attached to the chiral centre (Scheme 14). *Ab initio* calculation combined with molecular mechanics calculations[42] have confirmed that the conformation with the largest group *anti* to the O−C bond is preferred and this anchors the positions of the small and medium groups, such that they control the facial selectivity.



Nucleophile attacks from above

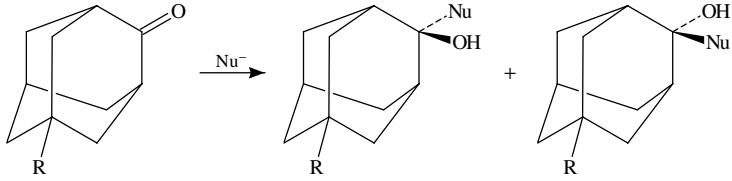
SCHEME 14

C. Stereoselectivity of Nucleophilic Attack on Cyclic Ketones

It is found experimentally that cyclohexanones undergo preferential axial attack with nucleophiles. Klein has explained this preference in terms of the frontier orbitals[79]. The π orbital is distorted about the C=O plane such that the LUMO has a big lobe on the axial side and the HOMO has a big lobe on the equatorial side. Thus for good overlap of the attacking nucleophile HOMO with the carbonyl LUMO, axial attack is preferred. This also reduces the destabilizing interaction of the nucleophile HOMO with the carbonyl HOMO. Shi and Boyd have studied the valence-shell charge concentration of the carbonyl in cyclohexanones and found that the charge density changes only slightly with substituents and is similar on the two sides of the carbonyl[80]. If anything the model predicts the wrong stereoselectivity, thus they conclude that the difference in the extent of electron deficiency between the two sides of the carbonyl does not play a significant role in stereoselectivity.

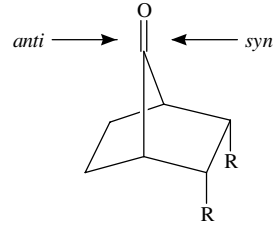
Anh[69,81] has suggested that the interaction of the incipient bonding orbital with the antiperiplanar bond's antibonding orbital affects the relative energy of the transition states,

such that when there is good overlap the transition state is stabilized. Cieplak[72,82] has suggested that the stability of the incipient antibonding orbital is affected by the electron-donating ability of neighbouring bonds. For axial attack the neighbouring bonds are the axial bonds at C(2) and C(6). For equatorial attack the neighbouring bonds are the carbon–carbon bonds C(2)–C(3) and C(5)–C(6). The preferred direction of attack is thus determined by the relative electron-donating ability of these bonds. He proposed that the electron-donating ability of various bonds follows the order C–S > C–H > C–C > C–N > C–O. Thus with cyclohexanone the C–H bonds are more electron-donating than the C–C bonds, thus axial attack predominates. Le Noble's group examined the nucleophilic attack of 5-substituted adamantones to eliminate steric effects[83] (Scheme 15).



SCHEME 15

Electron-donating groups in the 5 position led to mainly *anti* attack, in agreement with Cieplak's proposal, since attack is *anti* to the electron-rich carbon–carbon bonds. When electron-withdrawing groups were used, mainly *syn* attack was observed as expected. Coxon and McDonald have used molecular orbital calculations to examine the facial selectivity of a series of 7-norbornanones with C(2) and C(3) *endo* substituents which exhibit electronic effects on the reaction centre, but, because of the rigid nature of the framework, they do not alter the steric environment in the region of the reaction centre[84]. (Scheme 16). They found that attack of methanol led to a transition state where the forming oxygen–carbon bond is substantially made. The bonds antiperiplanar to the incoming oxygen are little changed, but those antiperiplanar to the carbonyl oxygen are shortened. The presence of electron-withdrawing substituents at C(2) and C(3) leads to shorter bonds *anti* to the C(7)–OMe bond in the transition state. However, electron-donating alkyl groups at C(2) and C(3) have little effect on these bonds. The authors conclude that the Cieplak postulate is not supported by their semi-empirical calculations. Earlier, Mehta had experimentally determined the selectivities for nucleophilic attack of borohydride on 7-norbornanones. The experimental results and those of theoretical calculations are shown in Table 2[85]. The results for the carbomethoxy group were thought to differ because of the difference in the nature of the two nucleophiles: one is charged and the other neutral.



SCHEME 16

Shi and Boyd[80] have studied the barriers to nucleophilic addition of lithium hydride to substituted cyclohexanones. They found that the unsubstituted cyclohexanone had a

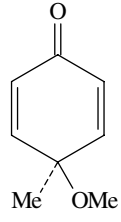
TABLE 2. Observed and calculated *syn*:*anti* ratios for nucleophilic attack on 7-norbornanones

Substituent R	Experimental *syn*:*anti* ratio	Calculated *syn*:*anti* ratio
H	50:50	50:50
Ethyl	20:80	33:67
CO_2CH_3	84:16	7:93
F	—	7:93

larger barrier to attack than the substituted counterparts as observed experimentally[86]. Secondly, the difference between the barriers to axial and equatorial attack was largest for 4-substituted cyclohexanones and that whilst the barrier to axial attack showed little variation with position of the substituent, the barrier to equatorial attack did vary significantly with the position of the substituent, being particularly large when the substituent was axial. They calculated the electron-donating ability of the appropriate bonds for the series of substituted cyclohexanones to see if the pattern matched that predicted by Cieplak and found significant discrepancies.

Shi and Boyd suggest that the difference between the selectivity of 4-equatorially-substituted cyclohexanones and 4-axially-substituted cyclohexanones arises from the change in the direction of the dipole orthogonal to the carbonyl plane. This is consistent with Kamernitzky and Akhrem's proposal that the facial selectivity is 'determined by a difference in the electrostatic fields on the upper and lower sides of the carbonyl double bond'[87].

Wipf has shown that 4,4-disubstituted cyclohexanones undergo nucleophilic attack where the facial selectivity is determined by dipolar control. Thus, compounds of the type **23** underwent nucleophilic attack *anti* to the electronegative substituent at C(4), whereas the fluorinated analogue, **24**, underwent attack *syn* to the oxygen, in accordance with the inversion of the dipole moment. They found that the logarithm of the experimentally observed facial selectivity for nucleophilic attack was correlated linearly ($R = 0.998$) with the calculated dipole moments. The facial selectivities were also shown to depend upon the nature of the nucleophile, hydride ions and alkynyl carbanions being essentially unselective.



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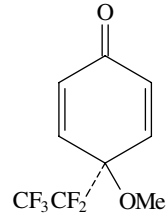
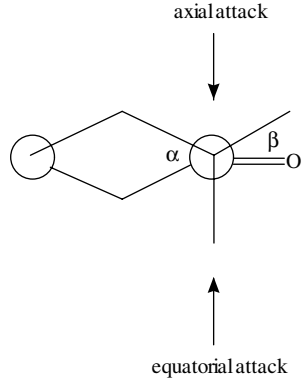


(24)

The preferred direction of nucleophilic attack on cyclohexanones has also been explained in terms of the torsional strain between the forming carbon–nucleophile bond and the adjacent bonds on C(2) and C(6)[66,68,81] (Scheme 17). If the ring is flat, attack from the axial side is staggered whereas equatorial attack is eclipsed. However, if the ring is puckered, attack from the axial side is eclipsed and the equatorial side is staggered. Shi and Boyd have confirmed with calculations at the 6-21G or 6-32G level that the flatter the ring the more axial attack[80].

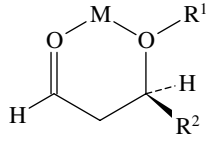


SCHEME 17

One of the problems of modelling the stereochemistry of nucleophilic addition to carbonyls is predicting the influence of metal cations. Some simple force field calculations[88] and steric congestion models[89] have been successful in accounting for the stereoselectivities of hydride reductions of cyclic ketones. Molecular mechanics calculations ignoring the metal ion but using a suitably reduced θ have been successful in explaining the stereoselectivity of $LiAlH_4$ reduction of cyclobutanone and cyclohexanones[42].

D. Diastereoselectivity as a Result of a Chiral Centre β to a Carbon Double Bond in the Substrate

The presence of a chiral centre β to a carbonyl also provides the possibility for chirality transfer upon nucleophilic attack. In cases where there is the possibility of forming an internal chelate, **25**, the stereochemistry is explained by attack of the carbonyl opposite the bulky R^2 group. However, when chelation is not possible, the group of Reetz has suggested that a transition state such as **26** is involved when the chiral carbon has a polar X group which points away from the carbonyl and the nucleophile attacks from the face opposite the bulky R group[77].



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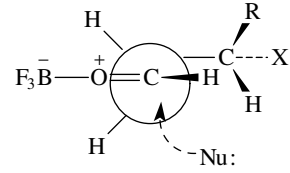
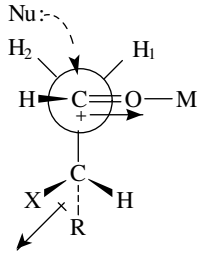


(26)

Evans and coworkers have proposed an alternative model for 1,3-asymmetric induction for nucleophilic additions to aldehydes bearing polar substituents in the β position[78]. The carbonyl is orientated at right angles to the C(α)−C(β) bond in accord with the Felkin assertion that such a staggered arrangement is preferred. Minimization of the interacting dipoles and non-bonded interactions gives the most stable transition state, **27**, with nucleophilic attack of the top face of the carbonyl. Other transition states, such as **28** and **29**, suffer from destabilizing *gauche* interactions of R and unfavourable interactions of



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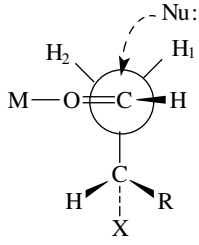

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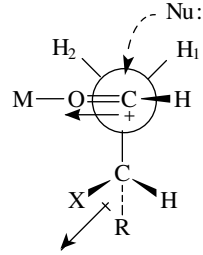
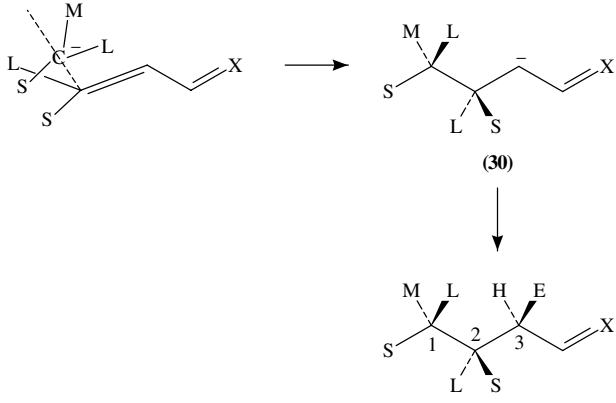


(29)

the two dipoles, respectively. From this model it follows that the selectivity should be enhanced with an increase in the steric bulk of R, as was observed.

E. Stereoselectivity of Conjugate Additions

The stereochemistry of conjugate additions requires similar considerations to those used to predict nucleophilic attack on a carbonyl. Acyclic substrates may yield up to three contiguous chiral centres (Scheme 18). The relative stereochemistry of carbons C(1) and C(2) will depend upon the approach of the two reagents. The stereochemistry of carbon C(3) will depend upon the lifetime of the intermediate **30**; if it has even a short lifetime it will take up the most stable conformation. For example, the base-catalysed additions of ethanol-d and 2-methyl-2-propanethiol-d to ethyl crotonate give a $(2R^*, 3R^*)/(2R^*, 3S^*)$ diastereoisomeric ratio of the addition products of approximately 10:1[90]. The authors[90] suggest the reaction proceeds in two steps and the protonation of the enolate determines the stereoselectivity.



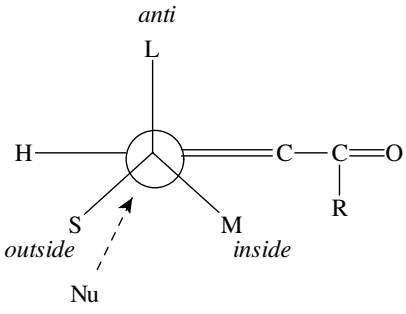
SCHEME 18

The conjugate addition of hydrazine, hydroxylamine, methoxylamine and alkylamines with various alkyl and halegenofumaric acids to give N-substituted aspartic acids can be carried out enantioselectively in the presence of the enzyme 3-methylaspartase[91].

Chiral centres within the nucleophile or the conjugated double bond will control the stereochemistry of the chiral centres that are formed. For example, the Felkin–Ahn model has been applied to nucleophilic 1,4-addition to an α,β-unsaturated carbonyl bearing a

γ-stereocentre. When the carbon–carbon double bond is *trans*, the outside position is the most crowded because of the incoming nucleophile. Hence this position is occupied by the smaller of the groups on the chiral centre. The medium-sized group thus occupies the inside position and the large group directs attack to the opposite face. Whilst such behaviour is often observed[92,93], this is not always the case.

Dorigo and Morokuma have highlighted that the main problem concerned with the 'homologation' of the Felkin–Ahn model to 1,4-additions is identifying the preferred position of the medium-sized group with *cis* carbon–carbon double bonds[94]. Does the presence of the *cis* substituent make the inside or the outside positions the most crowded — does **31** or **32** resemble the transition state? Both models have been used to rationalize the conflicting evidence. For example, nucleophilic attack of the (*Z*)-γ-methoxy α,β-unsaturated esters (Scheme 19) follows the Felkin–Anh model with the C–OMe bond antiperiplanar to the direction of the nucleophilic attack. The larger methyl group occupies the 'outside' position and the hydrogen the 'inside' position, thus avoiding any 1,3-allylic strain[95].



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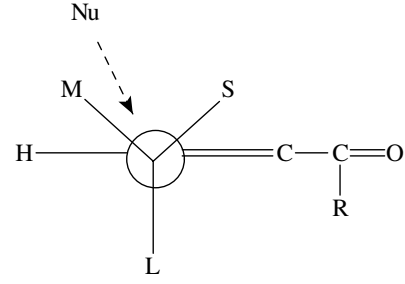

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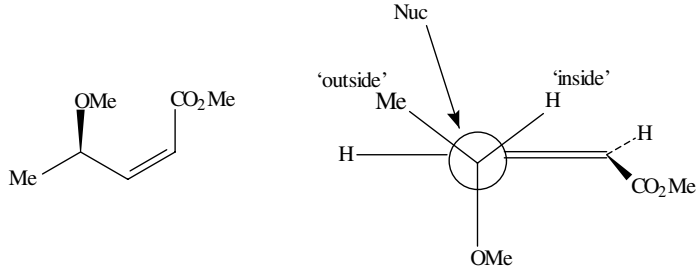
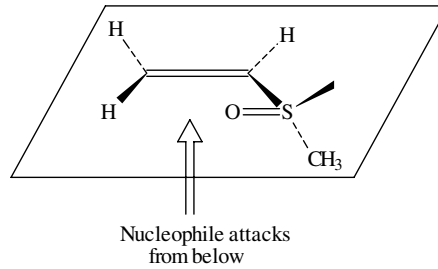


SCHEME 19

Molecular mechanics calculations[96] and *ab initio* studies[94] have been used to resolve the problem, but whilst they go some way to explaining the stereochemical outcomes, there are a number of reactions whose stereochemistry cannot be easily explained.

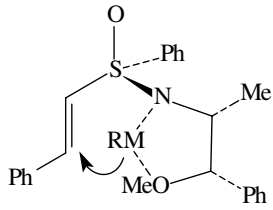
Enantiomerically pure vinyl sulphoxides are highly diastereoselective Michael acceptors with a variety of nucleophiles[97]. However, the transition states that determine the stereochemical outcome are not easy to predict. For example, the nucleophilic attack of piperidine on (−)-(*R*)-(*Z*)-propenyl *p*-tolyl sulphoxide[98] gives a product that can be explained by approach of the nucleophile from the side of the tolyl group, away from

the lone pair, when the S=O and C=C bonds are *cis* coplanar, or by approach of the nucleophile from the side of the oxygen when the lone pair eclipses the double bond. Kahn and Hehre have calculated that the most stable conformation is that with the sulphur–oxygen double bond *cis* coplanar with the carbon–carbon double bond[99]. They predict that hydride ion will attack from the side of the methyl group, contrary to steric considerations, but consistent with the nucleophile avoiding areas of high electron density (Scheme 20). They suggest that examples that are not consistent with this approach may involve ion pairing between the lone pairs and a metal ion which reduces the unfavourable interaction between the lone pair and the incoming nucleophile. The stereochemistry of intramolecular nucleophilic attack on vinyl sulphones is controlled by the stereochemistry of the sulphone and/or any other stereogenic centres in the molecule[100].

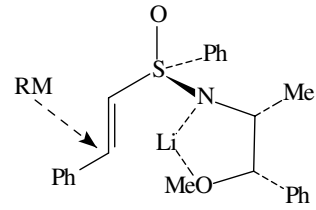


SCHEME 20

Vinyl sulphoximines also readily undergo stereoselective nucleophilic attack. In this case the nitrogen on the sulphur can coordinate any metals and direct attack[101,102]. The sulphur–oxygen bond is thought to be *anti* coplanar with the carbon–carbon double bond and, if the carbanion is associated with the complexed metal, attack from the same side as the nitrogen, **33**, is preferred. If a metal ion is complexed with the nitrogen but the carbanion is not associated with this metal ion, **34**, attack occurs from the opposite side to the nitrogen.

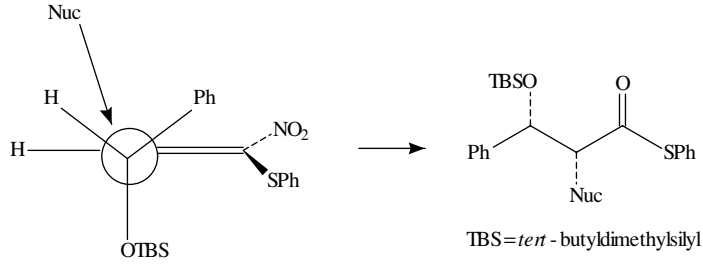


(33)



(34)

The nitro group in **35** (Scheme 21) activates the carbon–carbon double bond to nucleophilic attack. In this case the presence of the adjacent chiral centre led to predominantly one diastereoisomer[103]. The results suggested that in this case 1,3-allylic strain is not important and attack predominantly took place on the conformer with the phenyl occupying the 'inside' position, possibly because of the longer carbon–sulphur bond distance, and the hydrogen occupying the 'outside' position, allowing the nucleophile to approach the nitroalkene in close proximity to the hydrogen. A similar overwhelming



(35)

of the 1,3-allylic strain by factors elsewhere in the molecule has been observed for attack on other nitroalkenes[93,104].

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CHAPTER **19**

Electrophilic additions to double bonds

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I. INTRODUCTION

This chapter represents an update to the previous two editions, published in 1977[1] and 1989[2], and covers the literature of the period 1989–1994 with some references to 1995 papers. It deals mainly with electrophilic additions across the C=C, C=Si and Si=Si bonds and includes both theoretical (*ab initio* calculations, orbital approach, molecular modelling etc.) and experimental aspects. Particular attention is paid to mechanistic studies, facial selectivity and neighbouring group participation. Synthetic utilization of electrophilic addition is discussed only if including substantial mechanistic insight; purely synthetic work is not covered. Aside from the classical reactions, such as hydration, bromination etc., newly included material comprises aziridination (Section VI), attack at C=C bond by an electron-deficient carbon (Section VII) and those electrophilic reactions which utilize a transition or non-transition metal as the electrophile (Section VIII).

A. Reviews

During the coverage period of this chapter, relevant reviews have appeared on the following topics: the principle of hard and soft acids and bases in addition to unsymmetrical alkenes[3]; why does norbornene show selective reactivity on the *exo*-face[4], structure and reactivity of strained olefins having non-planar C=C bonds[5]; additions to bridgehead olefins and enones[6]; utilization of stepwise Ad_E reactions in designing organic syntheses[7]; preparative aspects of addition of electrophiles such as (halogen)$^+$, NO^+, NO_2^+, SO_3H^+, RS^+, RCO^+ and others in the presence of nucleophiles (H_2O, ROH, R_2O, RCO_2H, RCN, RSCN etc.)[8], the role of bromonium ions and β-bromocarbocations in olefin bromination[9]; reactions of N-chloroamines and N-haloamides with unsaturated compounds[10]; novel brominating agents[11], application of [hydroxy(organosulphonyl)iodo]arenes in organic synthesis, including electrophilic additions[12]; diastereofacially differentiating electrophilic additions to chiral bis-allylic diols[13]; stereocontrolled cyclofunctionalizations of double bonds through heterocyclic intermediates arising by electrophile-mediated ring-closure reactions[14]; polyolefinic cyclization via bromination[15]; chemistry of the thiiranium ions[16]; additions of dithio-acids to unsaturated compounds[17], kinetics and mechanism of C–C bond formation by addition of carbenium ions to alkenes[18]; control of electrophilicity in aliphatic Friedel-Crafts reactions by Lewis acids[19]; and the role of charge in synthetically important cationic cyclizations[20].

Increasing importance of the reactions employing organometallics as reagents or catalysts is reflected by the appearance of the reviews on: palladium(II)-catalysed reactions of olefins with oxygen nucleophiles[21]; new aspects of oxypalladation of alkenes[22]; palladium catalysis for intramolecular addition of hydroxy, amino and carboxylic groups[23]; new developments in the palladium-catalysed 1,4-additions to conjugated dienes (Bäckvall reaction)[24]; newly developed asymmetric arylation of olefins (Heck reaction)[25]; nucleophilic addition reactions of cationic iron-π-alkyne and related complexes[26]; and enantioselective *cis*-hydroxylation[27].

The author of this chapter has summarized his work in the area of electrophilic additions and application of transition and non-transition metals in organic chemistry in a personal account[28].

B. General Aspects of Electrophilic Additions

Correlations of ionization potentials (IP) versus relative reactivities of a variety of alkenes towards bromination, oxymercuration and hydroboration clearly show that the reaction rate decreases as the IP is increased[29]; the transition states of the rate-determining steps of oxymercuration and hydroboration are similar, but different from that of bromination[29].

Remote electronic control of the π-diastereofacial selectivity of electrophilic additions has been demonstrated with 7-methylenenorbornanes[30] and 7-isopropylidene benzonorbornenes[31,32] (**1a–1c**; Table 1). Whereas the π-face stereoselection is moderate in the case of additions proceeding through cyclic transition states (epoxidation and hydroboration), it is significantly enhanced in the case of the more polar addition (oxymercuration). Generally, electron-withdrawing groups tend to favour *syn*-addition, while *anti*-attack is dominant for the compounds with electron-donating groups[30]. The results have been rationalized by electrostatic interactions[31] and by the Cieplak[33,34] hyperconjugative model[30] in which the stabilizing interaction between the electron-rich antiperiplanar σ bond and the developing σ^* orbital lowers the transition state energy.

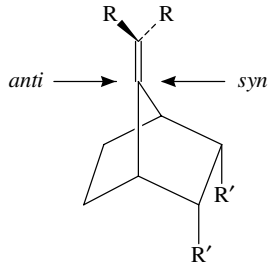
Different electrophilic reagents have been founds to have very different profiles in reactions with benzonorbornenes[2]: *syn* addition is highly favoured by strong electrophiles, such as: CCl_2, $R{-}C{\equiv}O^+$ (R = Me, H) and $Bu^tO(Cl)H^+$, whereas weaker (MCPBA, NBS, O_2, Bu^tOCl) or transvestial[35] (OsO_4, MnO_4^-) electrophiles, which all bear lone-pair electrons, exhibit a preference for *anti* attack[32].

Hyperconjugation appears to be the dominant factor governing the diastereoselectivity of the hydrochlorination of 5-substituted 2-methyleneadamantanes **3** (Table 2)[36]. However, the product distribution for epoxidation suggests that the stereochemical course of electrophilic additions not mediated by carbocations is most likely regulated by direct field effects[36]. Note that, unlike in the previous reactions, the facial selectivity in this case reflects the preference for the nucleophilic attack on the corresponding carbocation.

Distortion of olefin π-orbitals in dibenzobicyclo[2.2.2]octatrienes **4** has been detected[37]. Thus, nitro and fluoro groups give large to moderate bias with preferred *syn* attack (with

TABLE 1. Electrophilic additions to **1**

Compound		*syn*:*anti* ratio		
	R	epoxidation	oxymercuration	hydroboration
1a	CO_2Me	74:26	>95:trace	59:41
1b	CH_2OMe	45:55	40:60	44:51
1c	Et	30:70	17:83	38:62



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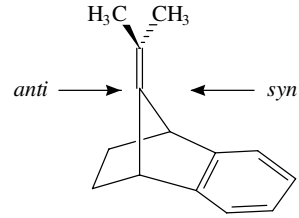

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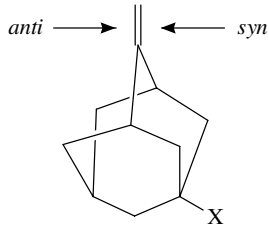

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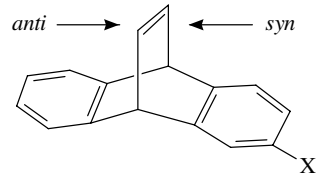


(4)

TABLE 2. Hydrochlorination of **3**

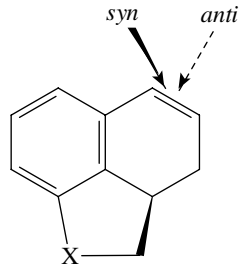
X	*syn*:*anti*
CN	78:13
CO_2Me	72:28
F	90:10
Cl	83:17
Br	78:22
I	66:34
MeO	86:14
Ph	65:35
Me	61:39
Me_3Si	35:65

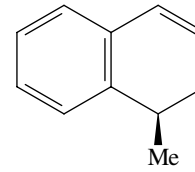
TABLE 3. Electrophilic additions to **4**

X	*syn*:*anti*	
	MCPBA	OsO_4/C_5H_5N
NO_2	77:23	88:15
F	58:42	68:32
MeO	48:52	48:52

respect to the substituent), whereas MeO exhibits a negligible bias (Table 3). These effects have been interpreted in terms of desymmetrization of π-lobes of the olefin orbitals arising from non-equivalent $\pi-\pi$ interaction rather than from an electron-donating or electron-withdrawing effect[37].

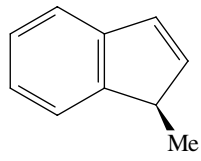
Partial ergot alkaloid substrates of **5** and related, conformationally fixed styrenes **6–8** have been found to undergo electrophilic additions (epoxidation, HOBr addition and

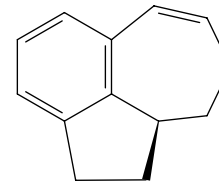




(5a) X = NCOPh
(5b) X = CH_2

(6)





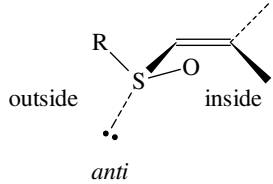
(7) **(8)**

TABLE 4. Electrophilic additions to **5–8**

Compound	*syn*:*anti*	
	MCPBA	NBS/H_2O
4	2:98	2:98
5	1:99	1:99
6	15:85	18:85
7	50:50	—
8	82:18	98:2

dihydroxylation) with a level of stereoselectivity, which cannot be rationalized by steric control (Table 4) but is consistent with electrophilic attack to minimize torsional strain[38].

Both experimental and theoretical studies of the electrophilic additions to vinylic sulphoxides have demonstrated that the π-facial stereoselection can be rationalized by the transition state **9**[39].



(9)

$H_2N—CH=CH—NO_2$

(10)

The possibility of simultaneously finding an electron-hole and an electron pair in a π-system substituted by an electron-withdrawing group (NO_2) and/or electron-donating group (NH_2) has been examined with *cis*- and *trans*-isomers of **10** (push–pull olefins) and for non-vicinal positions[40].

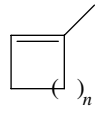
II. PROTON AS AN ELECTROPHILE

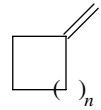
A. Hydration, Addition of ROH and Related Reactions

Data indicative of the relative basicities of C=C and C≡C bonds and relative solvation energies for protonation processes have been obtained from measurements of hydration rates of $RCH{=}CH_2$ and $RC{\equiv}CH$ (R = H, Me, Bu^t) in aqueous H_2SO_4[41]. Enthalpies of hydration of a series of acyclic olefins producing tertiary alcohols have been determined[42,43].

A study of acid-catalysed hydration of norbornenes and nortricyclanes gave α-values for the protonation which correlate well with those for the solvolyses of 2-norbornyl tosylates. This indicates that the first formed cations for both reactions are of a similar character[44].

The activation parameters and solvent deuterium isotope effects for acid-catalysed hydrations ($HClO_4$) of 1-methylcycloalkenes **11–14** and methylenecycloalkanes **15–18** agree with the rate-determining protonation of the double bond. The small Gibbs energy difference between the transition states for hydration of **11** and **15** (1.2 kJ mol^{-1}) contrasts with a large difference in the case of **12** and **16** (11.8 kJ mol^{-1}). The origin of the latter was attributed to the changes of conformation during the protonation of **12**[45]. A carbocation-like transition state is assumed for the $HClO_4$-catalysed hydration of cyclopentene and the mechanism has been formulated as an Ad-S_E2 reaction[46]. The $HClO_4$-catalysed hydration of **14** (at 25 °C) is reversible, whereas the reaction of **18** has been found to be essentially irreversible[47].

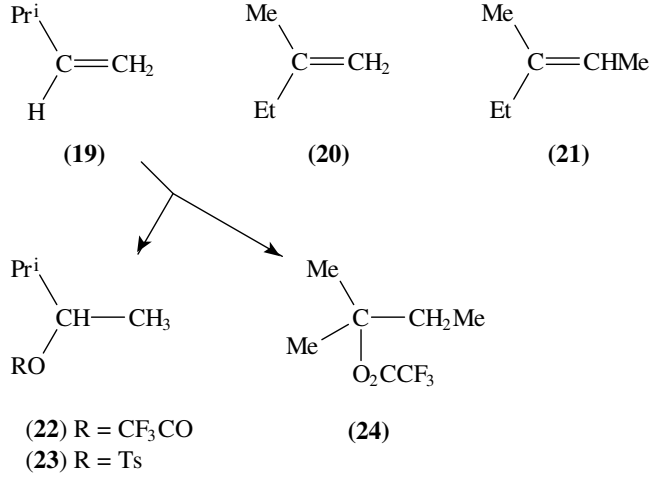




(11) $n = 1$ **(15)** $n = 1$
(12) $n = 2$ **(16)** $n = 2$
(13) $n = 3$ **(17)** $n = 3$
(14) $n = 4$ **(18)** $n = 4$

Investigation of the reactivity of alkenes **19–21** in CF_3CO_2H (neat and buffered with CF_3CO_2K) and in a CF_3CO_2H–MeCN mixture (3:1) shows that **20** and **21**, which form a tertiary cation, react 6.6×10^4 and 5.8×10^4 times faster than **19** (CF_3CO_2H–MeCN, 25 °C). The rates in CF_3CO_2D gave KIEs of 6.8 (**19**; 26.5 °C), *ca* 5 (**20**; −18 °C) and 3.9 (**21**; −18 °C). The isomeric trifluroacetates **22** and **24** are formed from **19** in the same ratio (*ca* 53:47) in CF_3CO_2H and CF_3CO_2D, which indicates that **19** reacts entirely by a carbocation mechanism with no measurable contribution from a molecular addition. The **22**:**24** ratio is close to that observed in the solvolysis of **23**[48].

The hydration rates of isobutylene in concentrated aqueous solutions of heteropolyacids (HPA) such as $H_3PMo_{12}O_{40}$ and $H_3PW_{12}O_{40}$ have been found to be about 10 times higher than those in aqueous mineral acids. This acceleration was attributed to better solubility of isobutylene in concentrated HPA and stronger acidity of concentrated aqueous HPA, as



(**19**) (**20**) (**21**)

(**22**) R = CF_3CO
(**23**) R = Ts

(**24**)

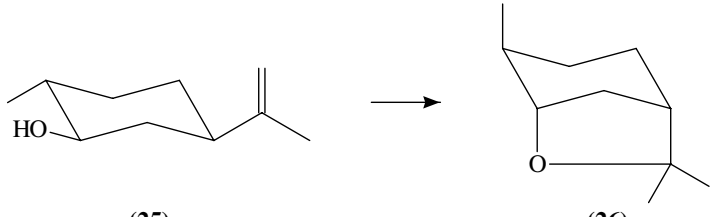
revealed by measurement of the Hammett acidity functions[49–54]. The substrate selectivity is remarkable: competitive hydration of an isobutylene/1-butene mixture below 80 °C exhibits up to 99.9% preference for the formation of Bu^tOH[50].

The relative reactivity, solvent isotope effect (k_H/k_D) and activation parameters for the acid-catalysed hydration of allylic alcohols $CH_2{=}CR{-}CH_2OH$ (R = H, Me) have been found to be similar to those for other alkenes. Whereas the results can be interpreted in terms of the conventional Ad-E2 mechanism, computed values for the life-time of possible carbocation intermediates suggest another feasible mechanism for $CH_2{=}CHCH_2OH$, according to which the nucleophilic attack by the solvent is concerted with protonation[55,56].

Cobalt(II)(salen)$_2$ complex has been found to catalyse the aerobic hydration of styrene in EtOH solution in the presence of Ph_3P, giving the Markovnikov product. Kinetic studies indicate that the rate-determining step is H-abstraction from the solvent by the coordinated O_2 ligand of (O_2)Co(salen)(PPh_3). A mechanism has been proposed for the remaining steps involving an oxymetalation of the C=C bond of styrene by $HOO{-}$Co(salen)(PPh_3)[57].

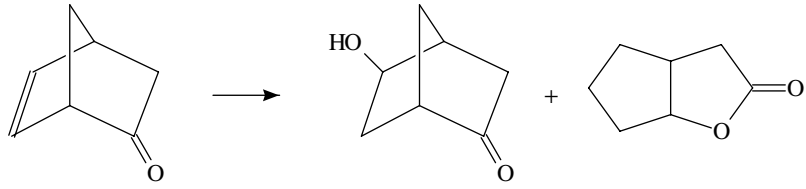
In contrast to the ground-state hydration, the photoaddition of water and of several alcohols to the triplet excited states of *m*-nitrostyrenes affords the corresponding anti-Markovnikov products[58].

Terpenoid alcohols, such as **25**, are cyclized in superacids (FSO_3H/SO_2) under a mixture of kinetic and thermodynamic control. Intermediate oxonium species were identified by ^{13}C NMR[59].



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

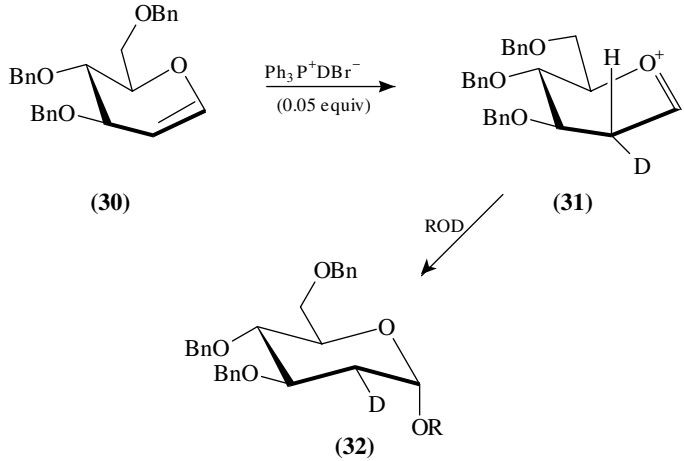
Acid-catalysed hydration of 2-norbornen-5-one **(27)** in aqueous $HClO_4$ results in the formation of hydroxyketone **28** and lactone **29** as the major products. Kinetic measurements suggest complex rearrangement pathways[60].



(27) **(28)** **(29)**

Additions to styrenes in aqueous or alcoholic solutions in the presence of external nucleophiles (e.g. PhSH, EtSH, AcO^- and others) have been investigated. Enhanced nucleophilic selectivity, $k_{(Nu)}/k_{(H_2O)}$, has been observed for photoadditions[61].

The polarized-π frontier molecular orbital (PPFMO) method has been employed to study protonation and sulphenylation of sugar-related dihydrofurans and tetrahydropyrans. The predictions are consonant with the experimental observations[62]. Contrary to expectations, the proton-catalysed addition of alcohols to glycals, such as **30**, has been shown by isotope labelling (^2H) not to be *anti*-diaxial addition. This observation has been rationalized by the initial attack by deuteron from the bottom, giving ion **31**, and by the anomeric effect favouring axial substituent at C-1 **(32)**[63].



(30) **(31)**

(32)

The evidence for perfect synchronization between bond cleavage, bond formation and positive charge delocalization was obtained for the proton transfer from hydronium ion to substituted α-methoxystyrenes $ArC(OMe)=CH_2$[64].

Studies of vinyl ether hydrolysis have demonstrated a strong retardation effect of β-carboxy and β-carbomethoxy groups (2000- to 25,000-fold). The rate profile for (*Z*)-β-methoxymethacrylic acid indicates that ionization of the carboxylate raises the rate of hydrolysis by a factor of 240. It has been proposed that this difference in reactivity of ionized and non-ionized forms of the substrate is due to the conjugative and inductive effect of the substituents, rather than β-lactone formation[65,66].

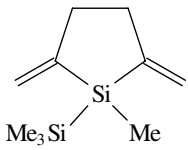
Experimental and theoretical studies of the gas-phase protonation of vinyl ethers, vinyl sulphides and vinyl selenides show, in conflict with the previous studies, that SMe and

SeMe substituents do not stabilize the adjacent positive charge better than does the OMe group. This conclusion is supported by the *ab initio* calculation at the STO-3G and 3-21 levels[67].

The kinetics and mechanism of the acid-catalysed hydration of dihydro-1,4-dioxin have been reinvestigated. The solvent isotope effect ($k_H{}^+/k_D{}^+ = 2.2$) indicates that the reaction proceeds by a rate-determining proton transfer from the catalyst to the substrate[68] rather than by a pre-equilibrium mechanism.

A surface-mediated (SiO_2 or Al_2O_3) addition of hydrazoic acid, generated *in situ* from Me_3SiN_3 and CF_3SO_3H, to 1-methylcyclohexene and 1,2-dimethylcyclohexene has been reported[69]. The reaction obeys the Markovnikov rule and is therefore believed to proceed via the initial protonation of the double bond to generate a carbocation. This mechanism is also supported by the observed non-stereospecificity[69].

Silenes have been found to add alcohols in a non-stereoselective fashion, even if the bond rotation is prohibited by cyclic structures, as in **33**. This is in disagreement with the simple two-step or a concerted four-centred mechanism[70,71]. On the other hand, disilenes (*E*), and (*Z*)-PhMeSi=SiMePh, generated photochemically in an argon matrix at 10 K, react with alcohols (EtOH, Pr^{i}OH, and Bu^{t}OH) via a highly diastereoselective *syn* addition, presumably involving a four-membered intermediate[71]. Addition of alcohols to $PhMeSi{=}SiMe_2$ gives $PhMe(H)Si{-}Si(OR)Me_2$ with high regioselectivity[71].



(33)

B. Additions of Hydrogen Halides and Other Acids

Ethylene, HF and H_3O^+ have been used as a model system in the *ab initio* closed-shell SCF calculation of the acid-catalysed hydrogenation of olefins. While catalysis by HF exhibits bifunctional character, catalysis by H_3O^+ proceeds via initial formation of a carbocation[72].

Ab initio SCF calculations and statistical thermodynamic analysis of the addition of hydrogen halides HX and $(HX)_2$ to ethylene indicate that for $(HF)_2$ and $(HCl)_2$ the termolecular transition states are hexacentric, whereas the bimolecular transition state of the HCl addition is bicentric rather than tricentric reported previously. The driving force for formation of the termolecular transition state in the HF addition appears to be the bonding between C and F. By contrast, in the HCl addition the driving force is the bonding between C and H, as generally accepted for electrophilic additions[73].

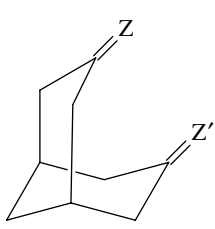
Ab initio 3-21G study of the addition of HF to fluoroethylenes $C_2H_nF_{(4-n)}$ with $n = 0$–4 has been performed, with geometry optimization of all charge-transfer complexes and transition states. The barriers so obtained are in fair agreement with experimental data[74]. Alteration of orbital configuration and hybridization changes in the addition of HBr to ethylene were illustrated in terms of orbital tilting on the basis of the concept of stabilizing and destabilizing second-order orbital interactions. The predominance of *anti*-stereochemistry has also been visualized quantitatively[75].

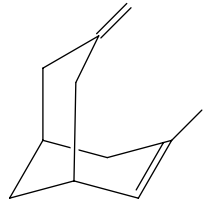
A study of the solid-state hydrohalogenation (HCl, HBr) of 2-methyl-2-butene led to formulation of a mechanism involving the $2HX{\bullet}C_5H_{10}$ complex[76].

Mixtures of gaseous HCl and 1,3-butadiene at 294–334 K and <1 atm of total pressure give mixtures of 3-chloro-1-butene and (*E*)- and (*Z*)-1-chloro-2-butene with the ratio of 1,2- to 1,4-addition products being approximately unity. Kinetic measurements in pyrex cells, using FT IR spectroscopy, revealed that surface catalysis is required and that the reaction most probably occurs between a multilayer of adsorbed HCl and gaseous or weakly adsorbed butadiene. This highly structured process is believed to proceed with nearly simultaneous proton and chloride transfer[77,78].

The mechanism for the uncatalysed and H^+-catalysed reactions of simple quinone methides with solvent and halide ions has been investigated. The observed differences in the isotope effects for addition of HX (X = Hal) and ROH are consistent with a stepwise mechanism for the H^+-catalysed addition of solvent and concerted mechanism for the H^+-catalysed reactions of halide ions[79].

The observed deceleration of the rate of transannular cyclization of a series of olefinic substrates **34** > **36** > **37** > **35** has been rationalized by decreasing electron density on the C-atom undergoing protonation. Negative temperature coefficients for the HCl-catalysed transannular hydrochlorination are consistent with the formation of charge-transfer intermediates. An ion-pair mechanism has been proposed[80].





(**34**) Z = Z′ = CH_2 (**37**)
(**35**) Z = Z′ = C═CH_2
(**36**) Z = CH_2, Z′ = C═CH_2

Asymmetric hydrohalogenation of *trans*-2-butenoic acid has been achieved in a crystalline α-cyclodextrin complex using gaseous HBr at 20 °C and HCl at 0 °C. The products were formed with 58% and 64% e.e., respectively, and were of (*S*)-configuration[81]. This contrasts with the low enantioselectivity of halogenation attempted in the same paper (*vide supra*).

III. ELECTROPHILIC HALOGENS

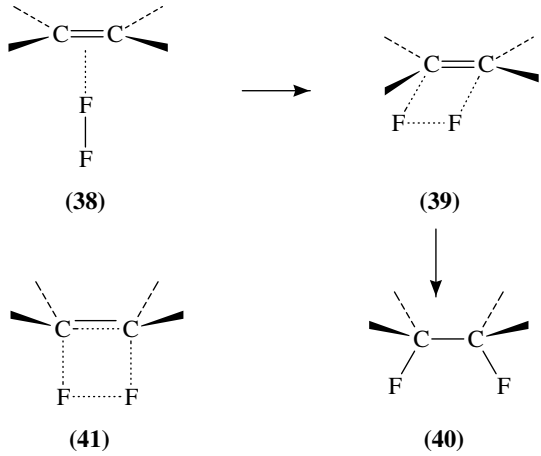
A. Halogenation

The transition-state structures for fluorination, chlorination and bromination were obtained by *ab initio* MO calculation[82]. Chlorination and bromination were found to proceed via three-centred geometries (cyclic halonium ions) leading to *anti*-addition. In contrast, fluorination involves a four-centred transition state which is consistent with the observed *syn*-stereoselectivity[82].

The geometries and relative energies of the singlet and triplet states of ions involved in electrophilic halogenations, namely halogen cations X^+ (X = F, Cl, Br), X_3^+ (X = F, Cl) and hydrohalonium ions H_2X^+ and HX_2^+ (X = F, Cl) were also studied with *ab initio* MO calculations. The monoatomic halogen cations have triplet ground states, whereas most of the triatomic species have singlet ground states. The geometries have been optimized[83].

1. Fluorine

The analysis of the *syn*-addition of molecular fluorine to ethylene at the MP2/6-31 + G level with IRC calculations indicates that F_2 approaches the C=C bond vertically at the middle to form a perpendicular complex **38** as the intermediate. The latter complex then re-orientates to a rhombic-type transition state **39** to give the final *syn*-addition product **40**[84]. This analysis rules out the involvement of the square-type complex **41** proposed earlier. However, these calculations do not clarify the F_2 addition to electron-deficient alkenes, such as acrylonitrile[84].



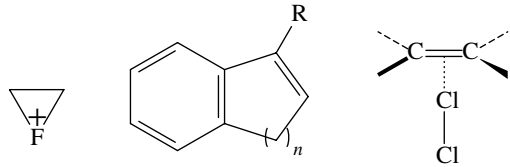
(38) **(39)** **(41)** **(40)**

Further experimental support for a four-centre, concerted addition across the C=C bond as the major mechanism has been obtained by the study of the molecular dynamics of the addition of F_2 to *cis*-d_2-ethylene and the subsequent decomposition dynamics of the vibrationally excited 1,2-difluoroethane-d_2 product isolated in Ar or Xe matrixes at 12K[85].

The long sought epifluoronium ion **42** has now been identified in gaseous phase as a (relatively) stable species[86].

Alkoxyxenon fluorides (ROXeF), generated from XeF_2 on reaction with alcohols, react with indene as positive oxygen electrophiles when $BF_3.Et_2O$ is used as catalyst. By contrast, with proton catalysts they react as apparent fluorine electrophiles[87].

Vicinal difluorides have been obtained on reaction of XeF_2 with triphenylethylene, 9-benzylidenefluorene and tetraphenylethylene in CH_2Cl_2 in the presence of HF at r.t. By contrast, no reaction was observed with $CsSO_4F$ ($\leqslant 30\,^{\circ}C$) unless MeOH had been added. In the latter case, Markovnikov-type fluoromethoxy adducts were isolated[88].



(42) **(43)** $n = 1, 2, 3$ **(44)**

The stereochemistry of fluoroalkoxylation of 1-phenylbenzocycloalkenes **43** with $CsSO_4F$ in alcohols (MeOH, EtOH, Pr^iOH) is ring-size dependent. Thus, predominant *syn*-addition for the five-membered ring, mainly *anti* addition for the six-membered ring, and an almost exclusive *syn* process for the seven-membered ring have been reported. The π-bond disruption in the substrate has been identified as the rate-determining step[89].

The major product of the thermal addition of CF_3OF to trichloroethylene in the gas phase was identified as $CF_3OCHCl-CCl_2F$. Other products, i.e. $CHClF-CCl_2F$ and $CF_3O(CHCl-CCl_2)_nOCF_3$ ($n \geqslant 2$), are formed in minor amounts[90].

2. Chlorine

The geometries of eleven chloronium ions were calculated using 3-21G MO and were classified as being either bridged ('onium') or open structures, depending on the parent olefin. Rather surprisingly, the chloronium ion derived from 2,3-dimethyl-2-butene ($Me_2C=CMe_2$) was found to be an open species, presumably due to the antisymmetric exchange repulsion between an occupied MO of the alkene and the Cl^+ p_π lone pair electrons[91].

The pre-equilibrium molecular complex formed in a mixture of ethylene and chlorine has been characterized using a pulsed nozzle FT microwave spectrometer. The rotational spectrum demonstrated the existence of a C_{2v}-symmetrical complex **44**: the Cl_2 molecule lies along the C_2 axis of ethylene that is perpendicular to the molecular plane and interacts weakly with the π-bond[92].

Chlorination of a variety of vinyl compounds $RCH=CH_2$ (R = Me, Bu^i, Bu^t, CH_2Cl, CH_2Br, CH_2OH, Br, COMe, CO_2H, CN) in alcohols gives a mixture of 2-alkoxy-1-chloro compounds, 1-alkoxy-2-chloro compounds and vicinal dichlorides, the relative proportions of which are dependent on the substituent R, reaction temperature, molar ratio and elapse time[93]. Similarly, chlorination, alkoxychlorination and/or acetoxychlorination was observed with 2-methyl-but-2-ene[94] and 4-substituted cyclopentenes[95].

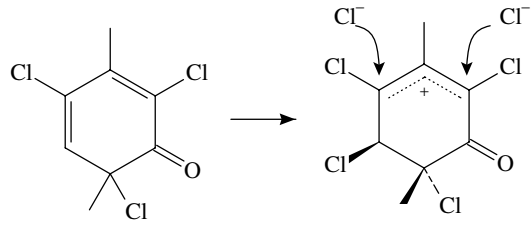
Non-conjugated olefins have been found to undergo *anti*-dichlorination with a MnO_2-Me_3SiCl mixture via a non-chain radical mechanism with $MnCl_4$ serving as the reactive species. Conversion of $MnCl_4$ to $MnCl_2$ during the reaction seems to be an efficient radical-quenching process[96].

Chlorination of ethylene with Cl_2 in $C_2H_4Cl_2$ solution has been studied with and without $FeCl_3$ catalysis at 293–308 K. Simultaneous addition and substitution was detected[97]. The yields of the styrene low-temperature halogenation products with DMF•Cl_2 or DMF•Br_2 have been found to exceed the yields using free halogen in DMF solution[98].

Liquid-phase chlorination of butadiene in the presence of Bu_3N affords a mixture of 1,2- and 1,4-addition products. Kinetic measurements suggest two independent mechanisms: the 1,2-adduct is formed by the attack of Bu_3N•Cl_2 on the butadiene•Cl_2 π-complex, whereas formation of the 1,4-adduct involves Bu_3N-stabilization of the π-complex[99–101].

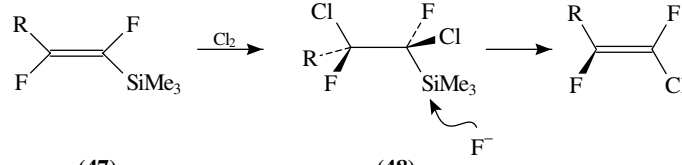
A quantum chemistry study of the reaction of chloroprene with Cl_2 has revealed two transition states for substitutive chlorination, which is consistent with two consecutive processes: chlorination to give a carbocation followed by abstraction of the originally allylic proton. On the other hand, a single transition state was observed for additive chlorination. The potential barriers for the former process lay below that for the latter[102].

Electrophilic chlorination of the trichlorodienone **45** has been found to give two isomeric products resulting from 2,5- and 4,5-addition of chlorine; both processes involve the same intermediate **46**[103–105].



(45) **(46)**

Chlorination of (*Z*)-1-silyl-1,2-difluoroalkenes **47** carried out in the presence of fluoride ions is followed by a stereospecific desilylation which occurs with an overall retention of configuration (**47** → **48**)[106]. The mechanism is believed to involve *syn*-addition of chlorine and the fluoride-mediated elimination of Me_3SiF and Cl^-.



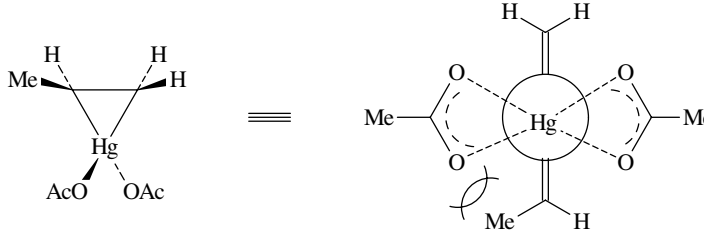
(47) **(48)**

3. Bromine

An MNDO calculation of six bromonium ions derived from ethylene, propene, 2-butene, isobutylene, 2-methyl-2-butene and tetramethylethylene, **49–54** shows energy minima corresponding to symmetrical bridged ions for symmetrically substituted systems **49–51** and highly asymmetric bridged ions for non-symmetrically substituted species **52–54**[107].

(49) $R^1 = R^2 = R^3 = R^4 = H$
(50) $R^1 = R^4 = Me$, $R^2 = R^3 = H$
(51) $R^1 = R^2 = R^3 = R^4 = Me$

(52) $R^1 = Me$, $R^2 = R^3 = H$
(53) $R^1 = H$, $R^2 = R^3 = Me$
(54) $R^1 = R^2 = R^3 = Me$

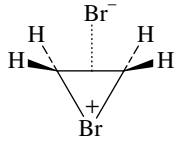


(55)

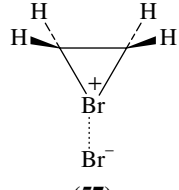
Semiempirical methods at various levels have been used to elucidate the structure of the bromonium ion arising from 2-methylpropene **52** in gas phase[108]. The computed structure turned out to be dependent upon the method employed and the inclusion of the electron correlation and of polarization[107,109]. The computed structure becomes more symmetric (i.e. more bridged) as the quality of the computation method improves. However, the potential energy surface along the C(2)−C(1)−Br mode is very flat and may be easily disturbed by the incoming nucleophile[110]. These factors appear to be significant in the interpreting of the Markovnikov rule[109]. On the other hand, the PPM3 and lower level *ab initio* molecular orbital calculations, carried out for thirteen bromonium ions, suggest the non-symmetrical Markovnikov-type structures for **52** and other non-symmetrical ions resulting from donor–acceptor relations[111]. By contrast, geometries of thirteen mercuronium ions, for example **55**, have been found to be dictated by steric repulsion between the AcO group and the substituent, rather than the electronic effects[111].

A Fukui-type correlation emphasizing the role of the conservation of orbital symmetry has been presented, with formation of bromonium ion as an example. Walsh MOs of bromonium ion have also been discussed with reference to further reactions of bromonium ion with bromide ion, resulting in the formation of *trans*-dibromide[112].

The first theoretical calculations of bromination in solution[110] (in CH_2Cl_2, in MeOH and *in vacuo*), using the polarizable continuum model and Bader's procedure, demonstrated that the Br atom in bromonium ion shares a positive charge equal to or larger than that on the carbon atoms, both *in vacuo* and in polar solvents. This indicates that the basic character of the π-complex does not imply a complete electron transfer from ethylene to Br^+ and that a partial character of σ-complex is present. The charge distribution does not exclude a nucleophilic attack of Br^- or Br_3^- on the bridged Br (which has previously been proposed to account for the reversibility of the bromonium ion formation[113]). *In vacuo*, *trans*-ethylene bromonium bromide **56** is more stable than the *cis*-complex **57** by 12 kcal mol^{-1}, showing that the attack on carbon is favoured over that on bromine in the preparatory step. However, the energy difference is greatly reduced in polar solvents (to 2.9 kcal mol^{-1} in MeOH)[110].

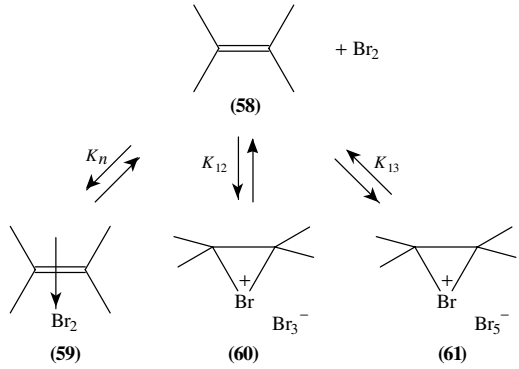


(56)



(57)

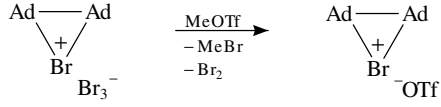
Adamantantylidenadamantane (Ad=Ad) is unique among olefins in that its structure impedes the Br_2 addition from proceeding beyond the stage of bromonium ion[114,115]. An investigation of the Ad=Ad−Br_2 system in 1,2-dichloroethane using stopped-flow and UV spectrometric techniques has shown that an equilibrium is instantaneously established with 2:1, 1:1, 1:2 and 1:3 olefin–Br_2 aggregates (Scheme 1)[116]. Conductivity measurements have confirmed that the 1:1 species is a molecular charge-transfer complex (CTC) while the other three are ionic in nature. The 1:2 and 1:3 species have been identified as the bromonium tribromide and the bromonium pentabromide salts, respectively. The CTC **59** turned out to be surprisingly stable. However, the formation of both **59** and **60** is too fast to be monitored, so that it was impossible to check experimentally if **60** is formed directly from olefin **58** and Br_2 or by a Br_2-assisted ionization of the first formed **59**. Nevertheless, on the basis of the previously proven involvement of CTCs on the reaction coordinate



SCHEME 1

for the ionic bromination of cyclohexene in the same solvent, it seems very likely that **60** arises from **59**. The bromonium pentabromide **61** was found at equilibrium in appreciable amounts at sufficiently high analytical concentrations of Br_2 and was proven to be formed from **60** and Br_2 with the formation constant $K'_{13} = [\mathbf{61}]/[\mathbf{60}][Br_2] = 22.4\ l\,mol^{-1}$. This value is close to that for the formation of $Bu_4N^+Br_5^-$ from $Bu_4N^+Br_3^-$ and Br_2 ($14.3\ l\,mol^{-1}$), which confirms the involvement of bromonium pentabromide ion pairs in olefin bromination at high concentration of Br_2[117].

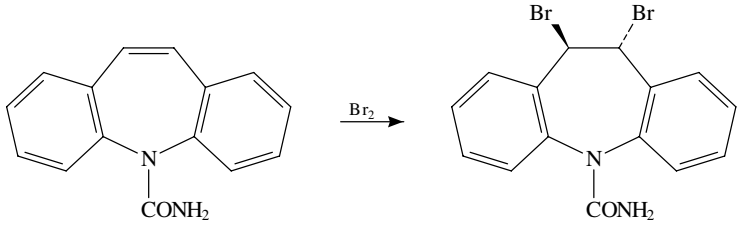
The complication stemming from the equilibrium shown in Scheme 1 was later circumvented by the conversion of **60** to the crystalline triflate **62**, which was isolated and subjected to a detailed NMR and X-ray analysis[118]. An unprecedented, rapid and direct transfer of Br^+ was observed from **62** to acceptor olefins, such as cyclohexene-d_{10} to give the corresponding *trans*-2-bromocyclohexyl trifluoromethansulphonate-d_{10}, indicating that an intermolecular Br^+ transfer from ion to olefin must be considered as competitive with the various product-forming steps during olefin bromination[118].



(62)

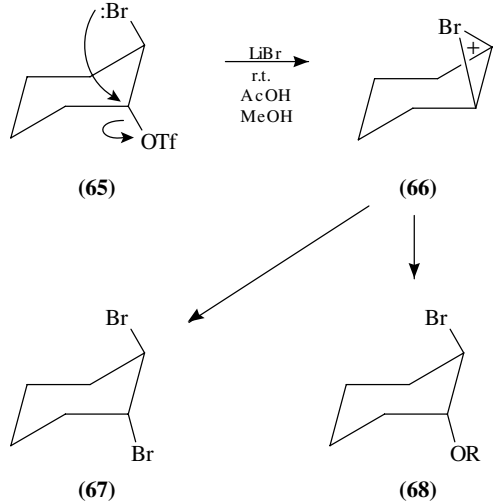
The bromination of dibenzoazepine **63** in 1,2-dichloroethane gives the *trans*-dibromide **64** as the only product. The reaction was monitored spectrophotometrically and found to exhibit a third-order kinetics (second-order in Br_2). A significant conductivity has also been found during the course of bromination. Both spectrophotometric and conductometric measurements are consistent with the presence of Br_3^- salt intermediates at a maximum concentration of *ca* 2% of that of the initial reactants. The X-ray structure of dibromide **64** shows a considerable strain at carbons bearing bromine atoms. The strain appears to be responsible for an easy, spontaneous debromination of **64**, as well as for high barrier for the formation of **64** from the bromonium-tribromide intermediate. That makes possible the cumulation of the intermediate itself during the bromination of **63**[119].

Further convincing evidence for the reversibility of bromonium-ion formation has been gained from the 5*H*-dibenzo[*b*,*f*]azepine model system[113,120,121] (for discussion of previous results, see elsewhere[2]), from kinetic measurements of bromination of tetraisobutyl ethylene (TIBE)[122] and from elucidation of *trans*-2-bromotriflate **65**[123]. The latter compound was solvolysed at r.t. in AcOH and MeOH containing varying concentration of



(63) **(64)**

LiBr and in the presence of cyclopentene as a scavenger olefin. The kinetics, determined by monitoring the formation of strong acids (TfOH or HBr), show that the rate of solvolysis of **65** is dependent on [Br^-] (at a constant ionic strength). In the presence of Br^-, the products are *trans*-1,2-dibromides and bromo-solvates of both cyclohexene and cyclopentene. The cyclopentenyl products have been shown to arise from the electrophilic addition of Br_2/Br_3^- to cyclopentene, while *trans*-1,2-dibromocyclohexane **67** is formed by Br^- capture of the bromonium ion **66** on carbon. The Br_2 required for bromination of cyclopentene results from attack by Br^- on the bromonium ion **66** on Br^+. On the basis of the ratio of the cyclopentyl products to **67**, Br^- capture of the solvolytically produced bromonium ion **66** (by attack on Br^+) is 4–5 times more prevalent than attack on carbon in AcOH, and *ca* 25 times more preferred in MeOH[123].

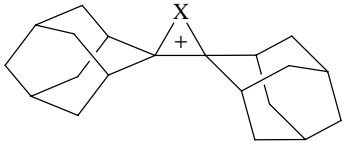


(65) **(66)** **(67)** **(68)**

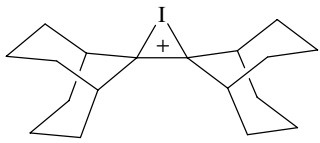
A dynamic NMR investigation of the Ad=Ad/Br_2 system has also provided additional kinetic and thermodynamic evidence for reversible formation of the bromonium ion/Br_n^- pairs. The data revealed that the rate-limiting step for the reversal of a bromonium ion into reagents involves an intermediate having 1:1 (olefin/Br_2) stoichiometry — very likely the charge-transfer complex. Although Ad=Ad cannot proceed past the stage of bromonium ion formation (in which it differs from other olefins), the stages of the reaction up to that point must be considered normal. Therefore, the conclusions arrived at with the Ad=Ad system should be viewed as general[124].

Stable bromonium and iodonium ions **69–71** of Ad=Ad and bicyclo[3.3.1]nonylidenebicyclo[3.3.1]nonane have been characterized by X-ray diffraction[125]. The data have

demonstrated that the three-membered halonium ring is almost symmetrical with the following parameters: Br–C, 2.11 Å; C–C, 1.49 Å; Br–C–C angle, 69.4°; C–Br–C angle, 41.3° for **69** and I–C, 2.48 Å; C–C, 1.45 Å; I–C–C angle, 72°; C–I–C angle, 36° for **70**. The ^{13}C NMR spectra of **69–71**, measured in CH_2Cl_2 at low temperature, indicate that the halonium ion has two perpendicular planes of symmetry. Addition of the parent olefin causes line broadening of signals of the carbons above and below the plane that includes the central C−C bond and is perpendicular to the above two planes. This effect has been attributed to the transfer of X^+ to acceptor molecule. Rate constants for this process have been determined; activation parameters for the exchange between **69** and Ad=Ad are $\Delta H^{\ddagger} = 1.8$ kcal mol^{-1} and $\Delta S^{\ddagger} = -21$ e.u. High-level *ab initio* calculations on the model system $C_2H_4X^+ + C_2H_4 \rightleftharpoons C_2H_4 + C_2H_4X^+$ indicate that the transfer proceeds via an unsymmetrical 1:1 halonium ion/olefin charge-transfer complex intermediate and a D_{2d}-symmetrical transition state[125].



(69) X = Br
(70) X = I



(71)

Greater retardation observed for the bromination of sterically congested adamantylidenealkenes Ad=CRR′ (R = H or Me, R′ = H, Me, Pr^i, Bu^t or *neo*-Pent) compared to isopropylidenealkenes Me_2C=CRR′ has been attributed to a change of mechanism, namely to the inhibition of nucleophilic solvent assistance in the ionization step and/or return resulting from a slow product-forming step[126].

The early stage of electrophilic bromination of tetraisobutylethylene (TIBE) has been examined to detect the formation constant (K_f) for the 1:1 charge-transfer complex (in CH_2Cl_2, AcOH and MeOH). Based on the K_f values, the thermodynamic parameters for CTC formation from TIBE + Br_2 are $\Delta H = -4.2(\pm 0.2)$ kcal mol^{-1} and $\Delta S = -9.5(\pm 0.7)$ e.u. TIBE reacts with Br_2 to afford substitution products, two of which are an initially formed allylic bromide and a more slowly formed diene bromide[127].

The reversibility of the ionization step in olefin bromination (*vide supra*)[121] implies that the product-determining step can also be partially rate-determining[128]. The occurrence of isomerization of *cis*-stilbene to *trans*-stilbene accompanying bromination can be rationalized[129] as follows: a strained *cis*-bromonium species is first isomerized to a *trans*-bromonium tribromide ion pair (through an open β-bromocarbocation). The latter ion pair then releases molecular bromine, producing *trans*-stilbene[129]. The reversibility of bromonium ion and β-bromocarbocation formation has been further elucidated with *p*-substituted stilbenes in 1,2-dichloroethane in the 10^{-1} to 10^{-4} M concentration range[128]. Observed dibromide ratios showed that an open β-bromocarbocation is the intermediate of the bromination of **72a** and **73a** (stabilized by *p*-CH_3), whereas bridged and partially bridged ions are involved with all other olefins **72b–72d** and **73b–73d**. This also determines the extent of reversibility: open β-bromocarbocations do not significantly revert to the olefin, whereas symmetrically bridged bromonium ions, particularly those generated from **72d** and **73d**, are the most prone to reversal. This trend corresponds to a gradual mechanistic shift of rate determination from the ionization step to the product-forming

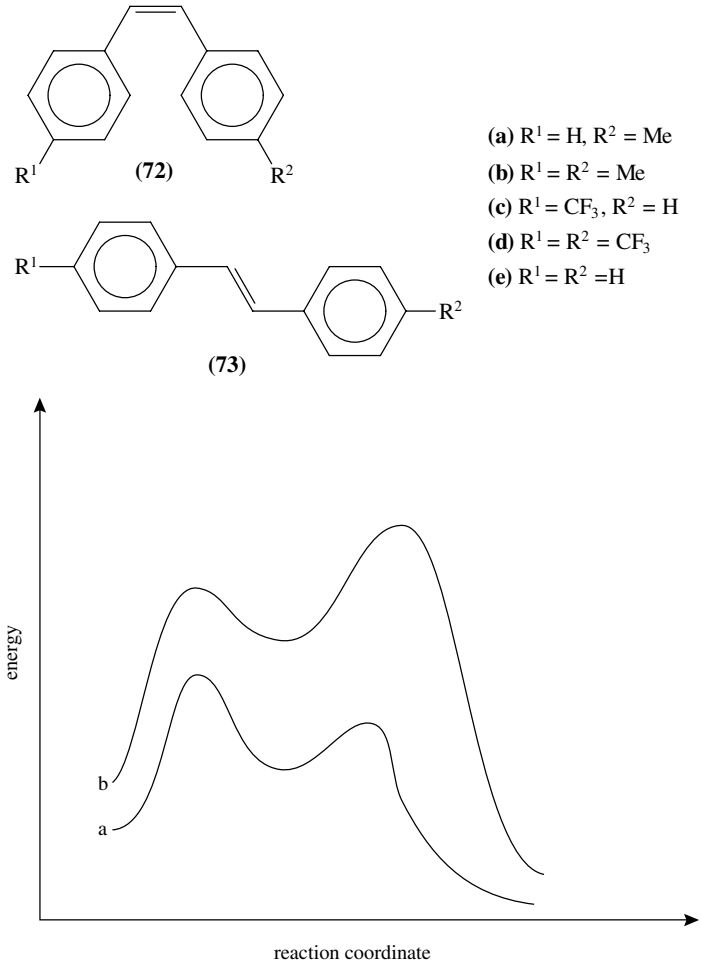


FIGURE 1. Reaction coordinate diagram for the bromination of *trans*-*p*-methylstilbene (a) and *trans*-*p*-*p*′-bis(trifluoromethyl)stilbene. (b). Reprinted with permission from G. Bellucci, R. Bianchini, C. Chiappe, R. S. Brown and H. Slebocka-Tilk, *J. Am. Chem. Soc.*, **113**, 8012 (1991). Copyright (1991) American Chemical Society

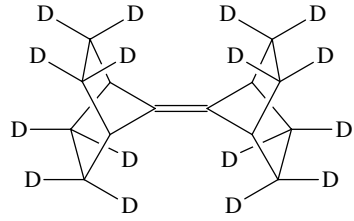
(Figure 1), which is reflected in the dramatic difference in the reaction rate (**73a** was found to react 10^7 faster than **73d**)[128,130].

While bromination of *cis*-stilbene **(72e)** in $CHCl_3$ gives *d*,*l*-dibromide at higher Br_2 concentration, preferential formation of *meso*-dibromide has been observed at lower concentrations[131]. Moreover, at low concentrations, the addition is accompanied by a *cis*–*trans* isomerization of the unreacted olefin (**72e** → **73e**). This behaviour can be rationalized by assuming the reversibility of the formation of the bromonium ions and by their isomerization[131].

An increase by two in the number of alkyl substituents on the double bond has been found to increase in both the K_f and k_{obsd} roughly by a factor of 10^3, indicating

that substituent effects are much more influential on k_{obsd} than on K_f. This may be rationalized by reversible ionization of CTCs to bromonium-bromide ion pairs[132–134], which should result in a decreased ionization rate and, therefore, in a decrease in the k_{obsd} for bromination[132].

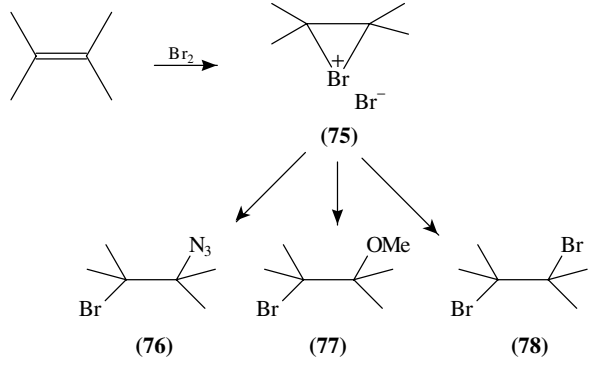
An unusually large inverse secondary deuterium kinetic isotope effect (1.53–2.75, depending on the reaction conditions) has been reported for bromination of the sterically congested olefin **74**. This behaviour can be rationalized by decreased steric hindrance due, in particular, to the *endo*-placement of the deuterium atoms relative to the double bond[135].



(74)

Bromination of 5*H*-dibenz[*b*,*f*]azepine-5-carbonyl, studied at 5, 25 and 50 °C, has demonstrated that the charge-transfer complex ionization cannot be rate-limiting. The collapse of bromonium-tribromide intermediate (having a large negative enthalpy of formation) has been suggested as the most likely rate-determining step[136].

In order to determine the lifetimes of bromonium ions **75**, the product ratios for Br_2 or NBS addition to a series of olefins (cyclopentene, cyclohexene, tetramethylethylene and styrene) in MeOH containing varying concentrations of N_3^- or Br^- have been elucidated[137]. From the **76/77** ratio, the partitioning constant ratios (k_N/k_{MeOH}) for the four olefins have been found as 5.9, 4.9, 9.3 and 2.7 M^{-1}, respectively. The amount of **76** is unexpectedly low (in view of high nucleophilicity of N_3^- as compared to MeOH) which suggests that both N_3^- and MeOH capture a highly reactive intermediate in a non-activation-limited process. Assuming that the N_3^- reacts with the intermediate with a diffusion-limited rate constant 10^{10} $M^{-1}\,s^{-1}$, the respective lifetimes of the ions produced from bromination of the four olefins are 5.9×10^{-10}, 5.0×10^{-10}, 9.3×10^{-10} and 2.7×10^{-10} s, respectively. These values have been interpreted as suggesting the following: (1) the cyclic olefins produce ions that live about 100 times longer than a secondary



(75) **(76)** **(77)** **(78)**

carbocation; (2) tetramethylethylene gives a bromonium ion that lives *ca* 10 times longer than a tertiary carbocation; (3) styrene gives an ion (bromonium or β-bromocation) that is *ca* 40-fold longer-lived than the 1-phenetyl cation[137].

Negative activation energies (*ca* $-60\ kJ\ mol^{-1}$) have been found for the liquid-phase bromination of unsaturated compounds in non-polar solvents and are believed to originate from the association of small amounts of HBr and H_2O present in the system[138].

While bromonium ions are not formed in gas phase[82,139], they are well established intermediates in bromination of olefins in solution. Hence, solvents are of crucial importance for promoting the addition. Kinetic criteria including kinetic solvent isotope effects (ROH vs ROD; R = Me, Et) have been used to estimate the magnitude of the electrophilic and nucleophilic involvement of protic solvents, electrostatic medium effects and the occurrence of internal return in the bromination of olefins[140,141]. The values obtained are consistent with reversible formation of highly congested bromonium ions in protic solvents. The different magnitude of return in protic and aprotic media has also been rationalized by solvent involvement. It appears that in protic media, the main driving force is electrophilic assistance to Br^- departure, as shown by the kinetic solvent isotope effect (KSIE). This participation provides an important contribution to the reaction rate, regardless of the degree of substitution on the olefin. Nucleophilic assistance to positive charge development also contributes but to a smaller extent and depends on the olefin structure: bulky substituents or those that are capable of stabilizing a positive charge by delocalization can attenuate this effect. In halogenated solvents, the driving force is probably bromine assistance to the charge-transfer complex (CTC) ionization (analogous to electrophilic solvent assistance). This results in the formation of Br_3^- so that the product-forming step is energetically more expensive and the bromonium ion formation is reversible. Larger steric effects have been observed for adamantylidene derivatives $Ad{=}CR_2$ (as an extreme) than for other olefins, where the steric congestion is smaller. Thus the experimental rates for addition to $Ad{=}CR_2$ are smaller than ionization rates (in contrast to other olefins) due to the high degree of reversibility of the formation of bromonium ions[140].

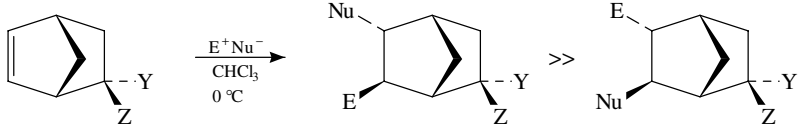
Bromination and oxymercuration have been found to have different rate-limiting steps: formation of the bromonium ion for the former reaction and attack by solvent on mercuronium ion for the latter[142].

A new examination of the bromination and chlorination of acenaphthylene revealed that the relative amount of the *syn*-adduct increased as the solvent polarity decreased. At 4–6 °C the *syn*-dibromide remained unchanged for a year, and hexane was found to be the best solvent for its preparation[143].

Stereoselectivity found for electrophilic additions to norbornene and 1-methoxy-2-cyclohexene is believed to originate from secondary orbital interactions rather than from orbital distorsion at the reaction centre[144]. Rather different results have been obtained from an *ab initio* MO study of the norbornene hydroboration[145].

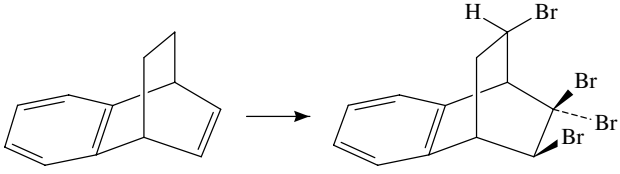
Tuning of the regioselectivity of electrophilic additions by substituents attached to the norbornene derivatives **79** has been reported. Strong preference for nucleophilic attack at C(5) has been confirmed[146]. Bromination of **80** at $-20\,^{\circ}C$ has been found to afford a single product, tetrabromide **81**, arising via a Wagner–Meerwein rearrangement with accompanying aryl migration[147–150]. Unlike the reaction with Se- and S-electrophiles (see below), bromination of **82** with Br_2 or NBS was found to induce skeletal rearrangement and fragmentation[151].

The preference for bromination of C=C vs activated aromatic ring has been elucidated with the aid of model compounds **83** and **84**. Bromination of **83** has been found to occur first at the double bond; with excess of Br_2, subsequent bromination of the aromatic ring has been observed. By contrast, **84** is first brominated in the aromatic nucleus before the

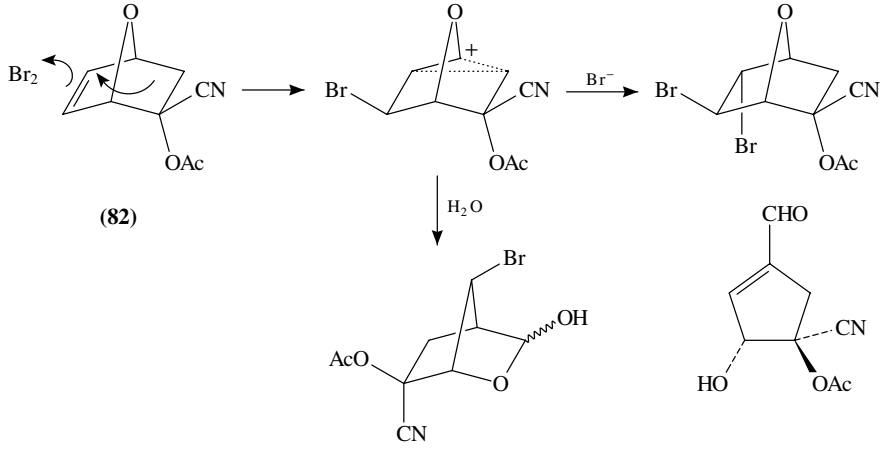


(79)

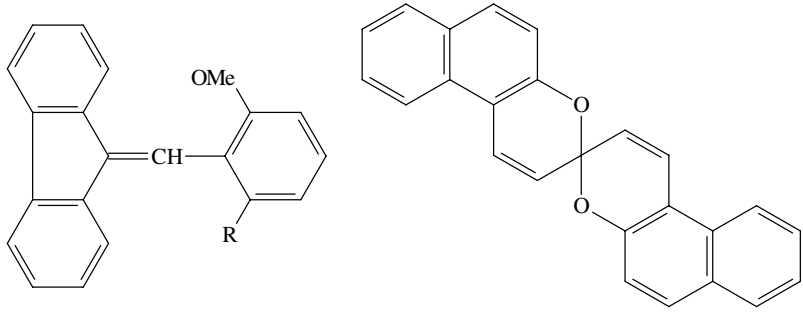
Y = H, OAc, OBn, CH_2OBn
Z = H, CN, OBn, CH_2OBn



(80) **(81)**



(82)

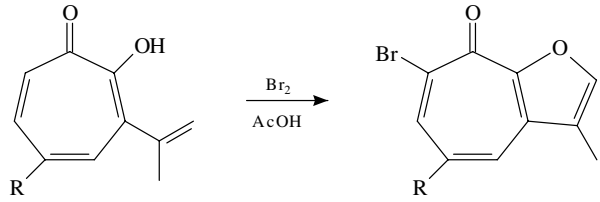


(83) R = H
(84) R = MeO

(85)

double-bond bromination takes place. This divergence has been rationalized in terms of increased steric shielding of the double bond and electron density on the aromatic ring[152].

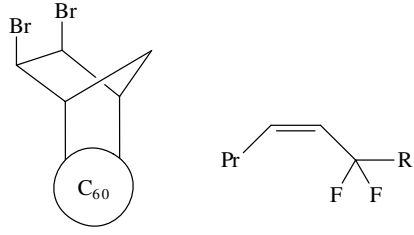
Halogen addition to *endo*- and *exo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-ones has been shown to be dependent on the nature of the reagent and the annulation[153]. The spironaphthopyran **85** has been found to undergo double bromination with remarkable stereoselectivity. The structure of the resulting tetrabromide is in agreement with a mechanism involving initial electrophilic attack at both double bonds from the sides opposite to Ar[154]. Anomalous bromination of cyclohexylidenecylclohexane has been examined[155]. Bromination of 3-isopropenyltropolones **86** (R = H, Me, Pr^i) with Br_2 in AcOH leads to furanobromide **87**, while NBS gives a different product[156].



(86) **(87)**

Although kinetic studies of bromination of methyl (*E*)-cinnamic acid and methyl (*E*)-β-styrylphosphonate suggest analogous mechanisms for both reactions, the stereochemistry of the reactions indicates that product-forming steps of different character must be involved[157].

Bromine has been reported to add *syn* to the double bond of the [60]fullerene-cyclopentadiene adduct; both bromine atoms in the product **88** point away from the cage[158]. Epoxidation also occurs from the face away from the cage[158].



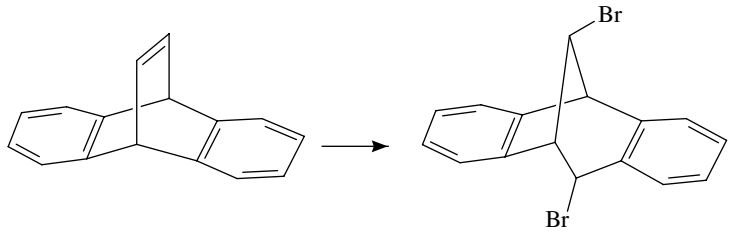
(88) **(89)**

cis–*trans* Isomerization of α,α-difluoroolefin **89** in CCl_4 by a substoichiometric amount of Br_2 has been interpreted as a result of the destabilization of the cyclic bromonium ion in favour of an open carbocation. The latter species is capable of free rotation and of subsequent elimination to afford the *trans*-isomer of **89**. A CF_2 group appears to be more effective in promoting isomerization than aryl in stilbenes[159].

Micellar effects on alkene bromination have been further studied and strong inhibition (10^5–10^6 fold) of the second-order reaction rate constants relative to those in water has been observed. The kinetics and the product distribution suggest that different olefins have different locations at the micellar surface. Kinetics in the presence of added NaBr and *n*-decane support this hypothesis[160]. Selective bromination of alkenes using bromine

and zeolite molecular sieves can be tuned by variation of the order of addition of the reactants[161].

Attempted asymmetric halogenation of *trans*-2-butenoic acid in a crystalline α-cyclodextrin using gaseous Br_2 or Cl_2 at 45–50 °C was unsuccessful, giving very poor enantioselectivity[162]. Exposure of chiral crystals of dibenzobarrelene **(90)** to bromine vapour results in formation of the rearranged addition product **91** in up to 8% e.e.[163].

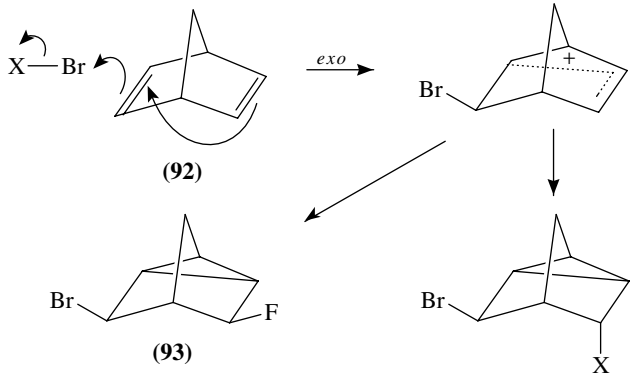


(90) **(91)**

4. Mixed halogens

The stereochemistry of bromofluorination (NBS and $Et_3N{\bullet}3HF$ in CH_2Cl_2) and of electrochemical fluroacetamidation ($Et_3N{\bullet}3HF$ in CH_3CN) of substituted indenes has been studied. The electrochemical reaction was found to be more stereospecific, giving a higher *anti/syn* ratio[164]. Regio- and stereo-selectivity of bromofluorination (with NBS + HF/pyridine) of substituted styrenes is critically dependent on the concentration of HF in pyridine. The reaction appears to be much more selective at low concentrations of HF[165]. Selective Markovnikov-type *anti*-bromofluorination has been achieved by the reaction of alkenes with a mixture of 1,3-dibromo-5,5-dimethylhydantoin and SiF_4[166].

In conflict with previous claims, bromofluorination of norbornadiene **(92)** with an NBS–ET_3N/3HF mixture has been found to proceed exclusively via the *exo*-attack, affording three products **93–95**; the structure of **94** has been revised[167].



(92)

(93)

(94) X = F (38%)
(95) X = Br (5%)

Bromochlorination of olefins such as 1-hexene, ethylene, 3,4-dichloro-1-butene, *trans*-1,4-dichloro-2-butene and 3-chloro- and 3-bromo-propene has been accomplished using

Br_2 and HCl at low temperature; styrene proved inert. A kinetic study with 3-chloropropene showed that the reaction is first-order in both Br_2 and HCl. An ionic mechanism has been proposed for polar solvents, whereas a 'molecular' mechanism is believed to operate in solvents of low polarity[168].

Regioselective (Markovnikov) and stereospecific (*anti*) iodochlorination of several alkenes (e.g. **43**) and alkynes has been described using poly{styrene-[4-vinylpyridiniumdichloroiodate(I)]}[169]. An analogous bromochlorination reagent reacts with substituted styrenes to give products corresponding to those formed by classical methods[170]. *Anti*-stereospecific and regioselective iodochlorination of olefins has also been reported using $PhCH_2N^+Me_3ICl_2^-$. In methanol, iodomethoxylation competes[171]. Addition of IN_3 to 1-phenylcyclohexene affords the expected Markovnikov product corresponding to the *anti*-addition mechanism[172].

B. Hypohalous Acids and Other XOR-type Reagents

Caesium fluoroxysulphate has been reported to add to alkenes (1-hexene, styrene, cyclohexene and others), furnishing vicinal fluorosulphates. The regio- and stereo-selectivity is rather low and may be partially influenced by the solvent; some preference for anti-Markovnikov products and for *syn*-addition has been observed. The slight predominance of *cis*-products seems to be consistent with a concerted mechanism[173].

The chlorination of α,β-unsaturated ketones by Cl_2 in MeOH gives mixtures of Markovnikov and anti-Markovnikov methoxychlorides and dichlorides. Significant increase in the proportion of Markovnikov regioisomers was observed in the presence of acid scavengers, such as pyridine. This effect was ascribed to the elimination of the acid-catalysed mechanism, allowing the chlorination to occur via chloronium ion[174].

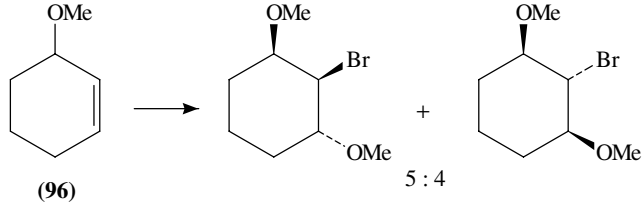
A kinetic model for oxychlorination of olefins has been developed and verified for C_2H_4 on an industrial catalyst[175].

Kinetic analysis of chlorination of 3-thiolene-1,1-dioxide and of $Et_3N^+-CH_2CH{=}CH_2Cl^-$ in water led to an expression for the formation constant K of the Cl_2-alkene π-complex[176]. Chlorination of 1-methylcyclohexa-1,4-diene in alcohols or acids occurs solely at the more substituted double bond and gives mixtures of the corresponding products of dichlorination and alkoxy- or acyloxy-chlorination (Markovnikov-type), respectively[177].

The striking differences observed for the reaction of NBS with allyl alcohol vs crotyl alcohol have been rationalized as follows: with allyl alcohol, formation of the solvated bromonium ion and HOBr are rate-limiting steps. By contrast, with crotyl alcohol, the rate-limiting step appears to be the breakdown of an NBS-crotyl alcohol complex, formed in a fast pre-equilibrium[178].

Bromomethoxylations (NBS/MeOH) of conformationally mobile hydroxy- or methoxy-cyclohexenes and dihydropyrans suggest that the inductive effect of the substituent governs the regiochemistry, as with **96**, whereas the steric hindrance (if present) controls the stereoselectivity (**97**)[179]. In the latter case, however, the possibility of isomerization at the anomeric centre has not been taken into account. It has also been found that compounds with strong steric hindrance, exercised by an axial substituent, may prefer a reversal of the regiochemistry of the nucleophile attack to avoid the interaction of incoming nucleophile with the axial substituent[179].

Substantial amounts of anti-Markovnikov products have been found for bromination of non-symmetrically substituted olefins $RCH{=}CH_2$ in methanol, particularly with bulky R groups (R = Bu^t and Pr^i)[109]. Mechanistic studies of a novel regiospecific hydroxy-bromination, employing CBr_4, O_2 and RO^- (R = Me, Pr^i, Bu^t) as reagents, suggest that both radical and carbanionic intermediates are involved[180].



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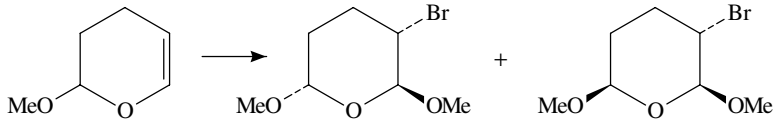


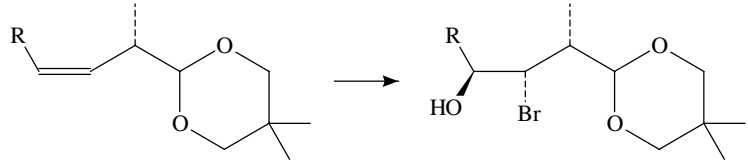
(97)

A dramatic effect of the presence of NBS upon the bromination of α,β-unsaturated ketones with bromine in MeOH has been observed. While in the absence of NBS mostly dibromides are formed, bromination in its presence has been found to afford anti-Markovnikov methoxy-bromides as the major products, e.g. $CH_2{=}CHCOMe \longrightarrow MeOCH_2CH(Br)COMe$[181]. It has been suggested that NBS removes acid, thereby causing a change from an acid-catalysed mechanism to a bromonium ion-type reaction.

Bromination of cinnamic acid with NBS in aq. MeOH gives 2-bromo-3-methoxy-3-phenyl propionic acid, $PhCH(OMe)CHBrCO_2H$. At moderately high $[H^+]$ the reaction is second-order and independent of $[H^+]$, whereas at low $[H^+]$ the rate increases with decrease in $[H^+]$. Succinimide inhibits the reaction[182].

Bromide or chloride anions can now be oxidized to X^+ by *p*-nitrobenzenesulphonyl peroxide. The positive halogen thus formed reacts with olefins via halonium ions[183]. Similarly, $PhSe^+$ can be generated from PhSeSePh[184].

Bromination of (*Z*)-2-methyl-3-alkenal acetal **98** with NBS in DMSO under irradiation affords selectively bromohydrin **99.** The reaction is assumed to proceed via a bromo-radical (generated by irradiation of NBS) that reacts with DMSO to give a yellow intermediate (possibly $BrO{-}SMe_2$) which may further react either with olefin to give the adduct **99** or with water, furnishing hypobromous acid[185].



(98) **(99)**

Hypobromous (HOBr) and hypoiodous (IOH) acids can be generated from $NaBrO_3$ and H_5IO_6, respectively, by reduction with $NaHSO_3$ in $MeCN/H_2O$. Markovnikov orientation and *anti*-stereochemistry has been observed on addition of these reagents to a variety of olefins[186].

Regio- (Markovnikov) and stereo-specific (*anti*) incorporation of MeCN (a Ritter-type reaction) has been observed upon bromination of a series of olefins, carried out in this solvent[187]. The degree of this incorporation depends on the olefin structure and on the initial reagent concentrations and ratios. Thus, when performed at low initial concentrations and with the initial Br_2/alkene ratio $\geqslant 2$, this reaction can be used preparatively[187].

A methyl substituent at a double bond of benzobicyclootadienes has a pronounced effect upon the course of addition of hypoiodous acid. While the unsubstituted derivative **80** has been known to give solely rearranged products, the stabilization of the transient carbocation by the methyl group prevents the rearrangement to some extent[188].

Nitrosonium ion was found to promote iodination of cyclohexene; when AcOH was used as solvent, the *trans*-iodo acetoxy derivative was formed in a good yield. Solvolysis of the latter, followed by saponification, led to a *cis*-diol so that this method can serve as an alternative to the 'wet-Prévost' reaction. The NO^+ cation is believed to promote the formation of 'some positive iodine species' (equation 1). Oxidation by oxygen leads to the regeneration of iodine and NO^+ from nitrosyl chloride[189].

$$I{-}I + NO^+BF_4^- \longrightarrow \text{'}I^+\text{'}BF_4^- + INO \qquad (1)$$

A stereospecific addition of Bu^tOI to β-methylstyrene was observed in the presence of BF_3, yielding Markovnikov products. This result contrasts with the non-stereospecific addition of Bu^tOCl and Bu^tOBr. It has been suggested that the bridging in the intermediate chloronium and bromonium ion derived from PhCH=CHMe is not as symmetrical as in the iodonium ion. Consequently, charge develops on the benzylic carbon in the first two cases, and rotation occurs about the C−C bond[190]. By contrast, a radical mechanism is assumed in the absence of BF_3 as anti-Markovnikov products are formed (both in the dark and upon UV irradiation)[190].

Reactions of Bu^tOI/BF_3, AcOI, ICl or IBr with 1,3-butadiene give mixtures of Markovnikov 1,2- and 1,4-addition products; no anti-Markovnikov 1,2-products have been detected. A radical mechanism was observed for Bu^tOI. Greater 1,4-addition occurs with reagents containing an anion of lower basicity (ICl and IBr). These results have been interpreted as reflecting the charge density and ion-pair stability[191].

Iodoalkoxylation of glycals has been found to furnish *anti*-addition products exclusively[192]. The product distribution is not affected by the electronegativity of the 5-substituent; steric factors appear to affect only the *trans*-diaxial opening of the intermediate iodonium ion[192].

Addition of IN_3 to 1-phenylcyclohexene affords the expected Markovnikov product corresponding to the *anti*-mechanism. Although further chemical transformations of the product seemed to be in conflict with the proposed structure, extensive ^{15}N NMR experiments finally convinced the authors that the original structure was correct[172,193]. Iodination of cyclohexene promoted by silver isocyanate was used to prepare the corresponding *trans*-iodocyanate[194].

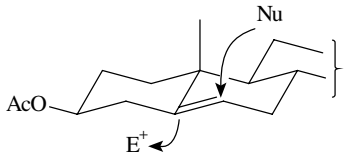
The addition of astatine to ethylene in aqueous solutions forms the expected adduct, $CH_2At{-}CH_2OH$, at various pH values[195]. Monovalent At^+ was found to exist in a hydrated form $(AtOH_2)^+$.

C. Neighbouring Group Participation

Semiempirical MO methods have been employed to determine the reaction surface for intramolecular bromoetherification reactions. Bromonium ions have not been identified as intermediates; instead, the additions involve the formation of a weak olefin/Br^+ π-complex, which is subsequently captured by a proximate nucleophile[196].

Systematic investigation of the stereo- and regio-control of electrophilic additions to cyclohexene systems (steroids in particular) by neighbouring groups allowed formulating certain principles, which govern the reactivities toward representative electrophiles, namely Br^+, I^+, PhSeX, Hg^{2+}, Tl^{3+} and Pd^{2+}[197]. The conclusions that have been arrived at are in full agreement with those previously derived for HOBr and can be summarized as

follows. Stringent stereoelectronic control, resulting normally in the formation of diaxial products (as with cholesteryl acetate **100** and other compounds), can be suppressed, and the regiochemistry of the addition reversed by a neighbouring group in those structures in which the electronic (Markovnikov) effect favours this reaction course. Diequatorial adducts are then formed preferentially, provided the spacer between the neighbouring group and the double bond allows for the formation of at least a five-membered ring, as with **101** (R = H, Me, Ph, NH_2, NHBn etc.) and **102**. However, when the spacer is shorter, as with **103**, exclusive formation of diaxial products is observed again. It has been suggested that while electrophilic additions to cyclohexenes normally proceed predominantly via cyclic 'onium' intermediates, neighbouring group intervention can result in the dominance of 'open' species, stabilized by the interaction with the neighbouring group. This would parallel the well known stabilization of the 'open' intermediates by the aromatic ring in additions to styrenes[197]. This reversion can thus be achieved only with cyclohexene systems containing a non-symmetrically substituted double bond having inherent tendency towards S_N1-like or a borderline mechanism of cleavage of the halonium ion. With 'symmetrical' double bonds, where the preference for the S_N2-like mechanism is strong, the presence of a neighbouring group alone does not suffice to override the stringent stereoelectronic control. Finally, intervention of a neighbouring group residing on the less hindered face of the double bond, as in **104** and **105**, can alter the overall stereochemistry. These observations show that the introduction of a neighbouring group can control the course of electrophilic additions not only to aliphatic olefins and sets the limits for this type of control in highly biased and discriminating cyclohexene systems[197].



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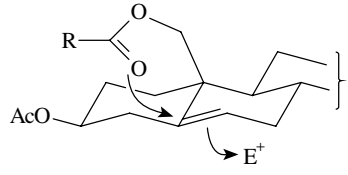

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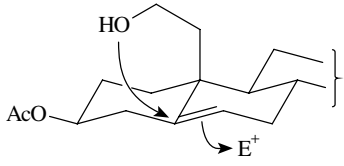

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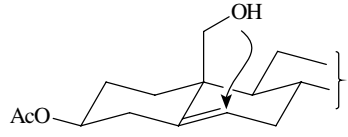

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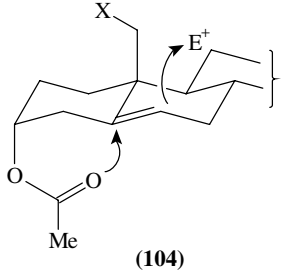

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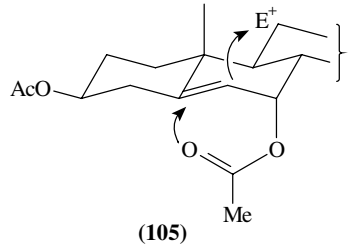
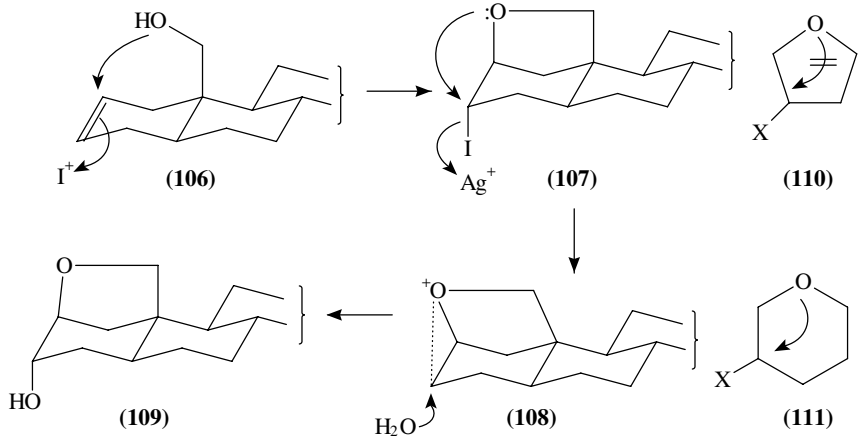


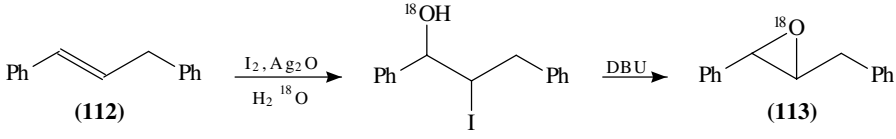
(105)

Remarkable differences have been observed in the reactivity of iodonium reagents generated in different ways ($I_2 + Ag^+$, Tl^+, Ce^{4+}, Cu^{2+}, Bi^{3+} or KI)[197]. It appears that Ag^+ and Tl^+ salts are the best promoters, while reagents generated *in situ* by mixing iodine with Bi^{3+} or Cu^{2+} are much less reactive and can discriminate between di- and tri-substituted C=C bonds. Silver(I)-mediated iodocyclizations of olefinic alcohols are followed by subsequent solvolysis, with an overall retention of configuration, employing a push–pull mechanism (**106** → **109**)[197]. This stereospecific, Koenigs–Knorr-type reaction can occur readily with the iodo intermediates (such as **107**) arising from electrophilic *exo-Trig* ring closure, regardless of the size of the ring initially formed. By contrast, the solvolysis is highly disfavoured for the heterocycles formed in a 5-*endo-Trig* fashion (**110**), as the corresponding transition state would be too strained. However, if a six-membered heterocycle **111** is being formed as the result of a 6-*endo-Trig* cyclization, the subsequent solvolysis becomes possible[197].



The same effects have been found to operate in the Tl(III)-mediated hydroxycyclization: as expected, **106** is readily cyclized to **109**, employing analogous 5(O)^n-*exo-Trig* cyclization and Tl^{3+} as an electrophile[198]. For further comments, see the section on Tl(III) as an electrophile[197,198].

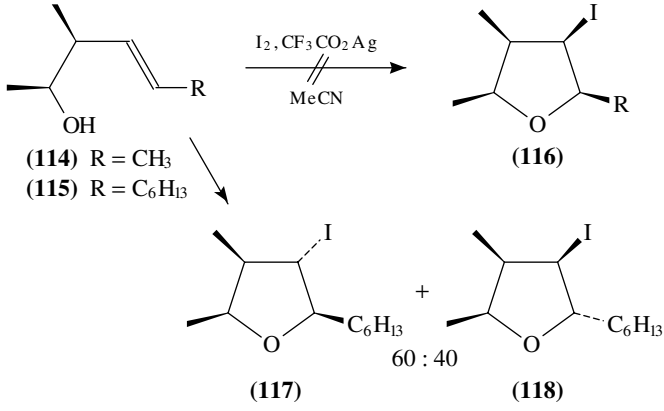
A silver-free alternative to the Woodward–Prévost synthesis of *cis*-1,2-diols has been reported[199,200]. An efficient preparation of ^{18}O-labelled epoxides has been developed (**112** → **113**), based on the silver(I)-mediated I_2 addition carried out in the presence of $H_2{}^{18}O$[201,202].



Kinetic studies of HOCl addition to allylacetic acid revealed the acceleration of lactonization by salts of weak acids (to an extent proportional to their concentration). This effect was attributed to the conversion of HOCl to a more reactive chlorinating agent (a mixed anhydride of HOCl). Non-dissociated allylacetic acid undergoes chlorolactonization approximately 3 times more slowly than its Na salt[203].

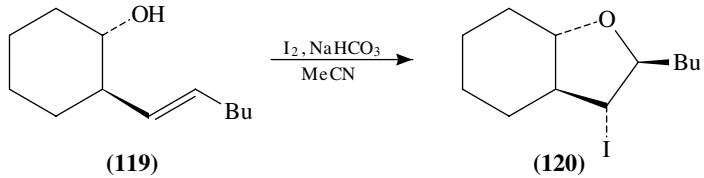
Other halogenation studies have included the stereo- and regio-control by neighbouring groups of additions in both aliphatic and alicyclic series. Allylic oxygen has been shown to have a decisive effect on the stereochemistry of closing up tetrahydrofuran rings via iodo-etherification. Other chiral centres in the substrate appear to have generally little overall influence[204]. A new model for homoallylic chiral induction in iodo-etherification has been proposed on the basis of semi-empirical MO calculation and experimental results[205]. The electrophile-mediated intramolecular cyclization of hept-2-enitols was found to conform to the Hehre model for electrophilic additions to alkenes bearing an allylic oxygen[206].

In 1992, one group of investigators[207] claimed that the stereochemistry of the cyclization of homoallylic alcohols, such as **114**, by means of I_2/CF_3CO_2Ag, formally corresponds to *syn*-addition(!), affording **116**. By contrast, PhSeCl exhibited the expected *anti*-addition. The same dichotomy was reported for several other model compounds. It was noticed that the iodination reaction proceeded well only in MeCN (at temperatures as low as $-40\,^{\circ}C$) and the products were stable under the reaction conditions. No explanation for the unusual outcome of iodocyclization has been offered[207]. These results were soon disproved by another team[208], who demonstrated that the structural assignment by the former group was incorrect. The second group have shown that, e.g., **115** gave a 60:40 mixture of iodocyclization products **117** and **118**, both of which correspond to the expected, clean *anti*-addition[208]. In a letter to this reviewer, the senior author of the first group admitted a systematic mistake in structure determination, associated with the technique of NOE experiments.



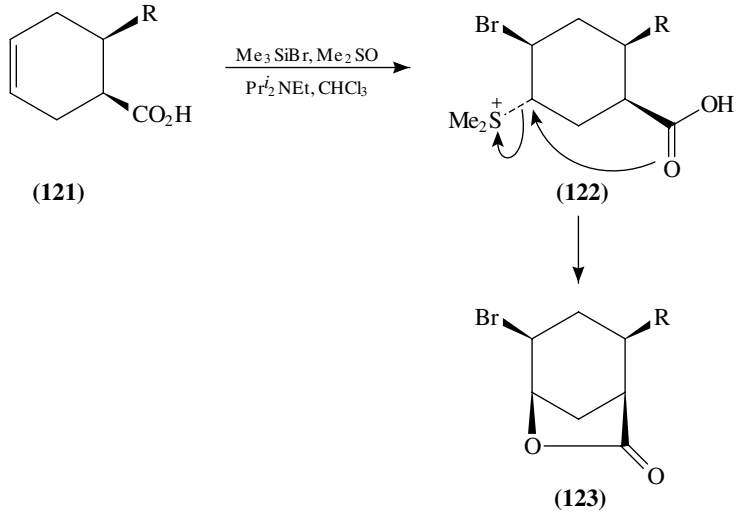
This correction was later confirmed by yet another group[208,209]: the corresponding 5(O)^n-*endo-Trig* cyclization of a number of related hydroxyalkenes has been demonstrated to occur via an ordinary *anti*-addition to the double bond with a very high diastereoselectivity[209]. Meticulous investigation of the NOE effects proved crucial in determining the product structure. A variation on the same theme gave rise to the *trans*-annulated tetrahydrofuranes, again via the 5(O)^n-*endo-Trig* iodoetherification (**119** → **120**)[210,211]. In this case, strictly anhydrous conditions are required in order to prevent the opening of the iodonium ion by water[210].

Another claim for the *syn*-addition (this time for Br^+ and OH) across a double bond has been made[212]. This unusual outcome has been observed for bromolactonization of **121** employing a mixture of Me_3SiBr, Me_2SO and an amine as the source of Br^+. The mechanism is believed to involve the sulphonium ion **122** as an intermediate arising by



(119) **(120)**

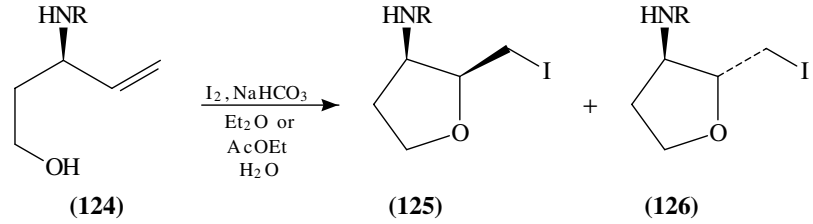
trapping of the initially formed bromonium ion by Me_2SO. The sulphonium group is then replaced by the carboxyl in the subsequent step, to give the *cis*-bromolactone **123**[212].



(121) **(122)** **(123)**

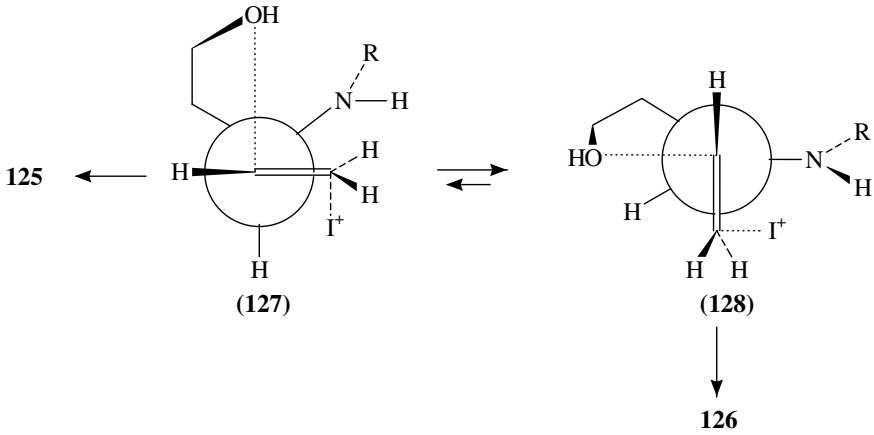
The stereochemistry of iodoetherification of *N*-substituted 3-aminopent-4-en-1-ols (**124** → **125** or **126**) correlates well with the electronic effects of the *N*-substituent. Increasing the electron-withdrawing effect results in the increase of *cis*-isomer **125**. It has been suggested that the sterically less favoured conformer **127** is responsible for the formation of the *cis*-product **125**, whereas the *trans*-isomer **126** arises from the more favoured conformer **128**. The latter conformer should be more reactive toward electrophiles only if there is sufficient donation from the $\sigma_{(C-N)}$ to π-orbitals, which can occur with *N*-substituents of relatively low electron-withdrawing effect, such as MeCO. More electron-withdrawing substituents (e.g. CF_3SO_2) render **128** less reactive than the energetically less favoured **127** which, in turn, is activated toward electrophilic attack due to the $n_N-\pi$ donation, thus changing dramatically the stereochemical outcome[213]. Stereoselective iodoetherification has been reported for *N*-alkenyl-*N*-(2-hydroxyalkyl)anilines[214].

The small differences observed in the reaction rates of ω-alkenyl glycosides **129** and **130** with NBS (2.39×10^{-4} s^{-1} and 6.3×10^{-5} s^{-1}, respectively)[215] may suggest that when the reaction is carried out with a 1:1:1 mixture of NBS, **129** and **130**, the recovered starting material, should be a 1:2:6 mixture of **129** and **130**. In sharp contrast to this expectation, a 23:1 ratio has been found! The authors argue that this result clearly demonstrates the reversibility of the bromonium ion formation: although **132** is obviously generated under the reaction conditions, its consumption to give the corresponding products is apparently slower than that of **131**. Hence, **132** serves as a brominating agent for



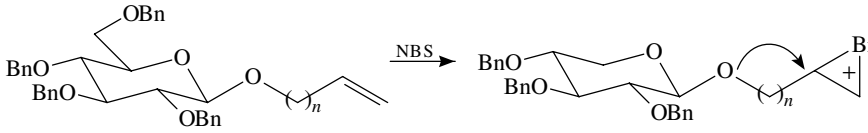
(124) **(125)** **(126)**

R = MeCO	24 : 76
R = CF_3CO	69 : 31
R = Ts	71 : 29
R = $MeSO_2$	79 : 21
R = CF_3SO_2	93 : 7



(127) **(128)**

126



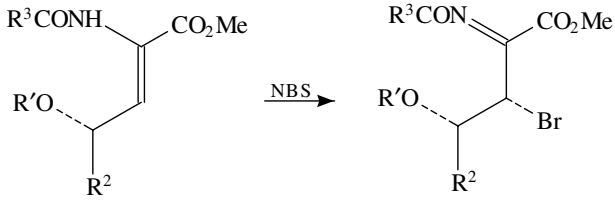
(129) $n = 3$ **(131)** $n = 3$

(130) $n = 4$ **(132)** $n = 4$

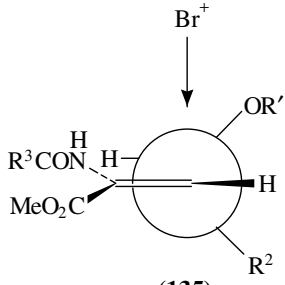
129 which, according to LeChatelier's principle, leads to the absence of the products of its electrophilic opening[215]. Similar transfer has previously been observed between the bromonium ion generated from Ad=Ad to cyclohexene (*vide supra*)[216]. This reviewer feels that although in the present bromoetherification the reaction may not proceed as far as to the stage of bromonium ion (see above[196] for the argument that halocylizations proceed directly from the π-complex), this finding is an important contribution to the general notion that reactions of this type are reversible.

Bromination of γ-oxygenated dehydroamino acids **133** gives predominantly the *syn* product **134**. This outcome has been attributed to an unspecified '*syn*-directing effect' of oxygen **(135)**[217]. However, the reviewer is of the opinion that the nitrogen lone pair

should also play a role in determining the stereochemistry (*vide supra*[218]).



(133) **(134)**



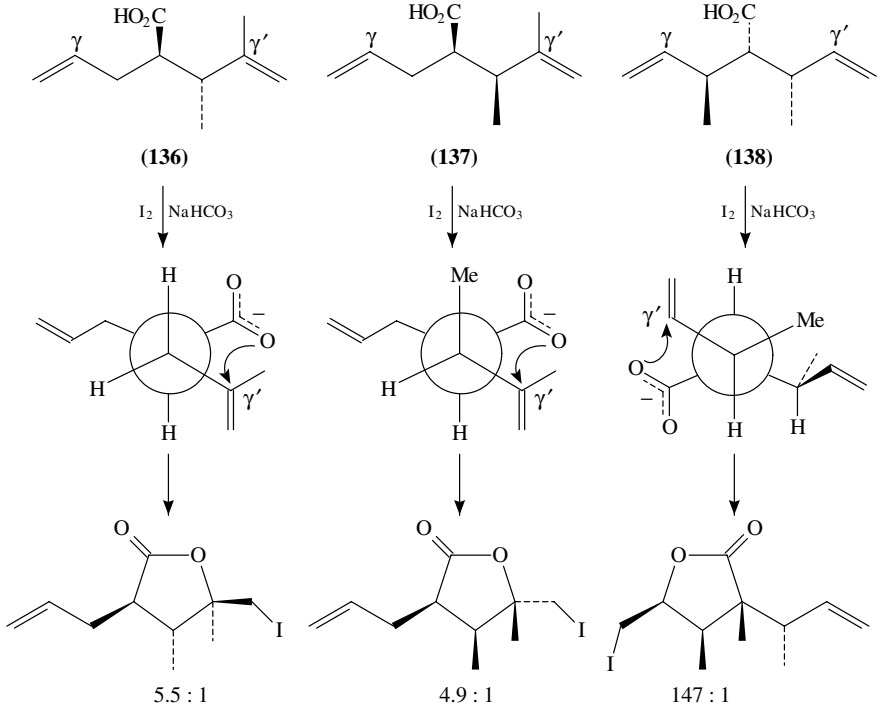
(135)

An iodine-mediated 6(O)$^{\pi,n}$-*exo-Trig* cyclization has been used in the synthesis of (2*S*,4*R*)-4-hydroproline from (*S*)-*O*-benzylglycidol[219]. Stereocontrolled 5(O)$^{\pi,n}$-*endo-Trig* iodoetherification has provided an entry to *trans*-2,5-disubstituted tetrahydrofuran derivatives[220]. On treatment with iodine, trichloroimidates of primary α-allenic alcohols are converted into oxazolines with high stereoselectivity[221].

Electronic control has been found to dominate completely over conformational control in the iodo-lactonization of 1,6-heptadiene-4-carboxylic acids **136** and **137** under kinetic conditions (i.e. the addition is methallyl-selective)[222]. Conformational factors controlling C_γ relative asymmetric induction favour formation of a *trans*-C_β−Me−C'_γ−CH_2I product from **136**, while **137** gives mainly the *cis*-product. In contrast, all three stereoisomers of **138** (*anti,syn*; *anti,anti*; *syn,syn*) undergo kinetic iodo-lactonization favouring a *cis*-C_β−Me−C_γ−CH_2I relationship. The selectivity was rationalized on the basis of conformational control minimizing *gauche* interactions. Thus, conformational control which clearly differentiates C_γ and C'_γ in **138** (147:1) presumably favours methallyl cyclization (C'_γ) in **136**, but does not disfavour methallyl cyclization (C'_γ) in **137**[222].

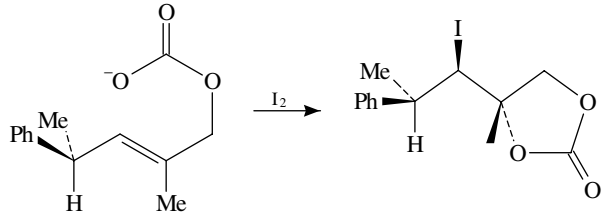
The stereoselectivity of iodolactonization of 2-substituted 4-pentenoic acids (with OH, NHTs or CH_2OH group at C-2) by NIS or I_2 can be increased in the presence of $(Pr^iO)_4Ti$[223]. In contrast, the stereochemistry of analogous haloetherification of 2-hydroxymethyl-4-penten-1-ol is reversed by the addition of $(Pr^iO)_4Ti$[223].

A highly enantioselective iodolactonization has been achieved through face and diastereotopic-group differentiation (for the principle, see elsewhere[224,225]) using (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine **139** → **140**)[226], sultam[227] or other moieties[228] as chiral auxiliaries. All four isomers of 3-hydroxy-4-methyl-γ-butyrolactone have been synthesized by stereoselective iodolactonization and/or epoxidation[229]. An elegant, NBS-induced lactonization of bicyclo[3.2.0]hept-3-en-6-ones **141** has been reported (Scheme 2)[230].


HO2C
γ
γ′
(136)
(137)
(138)
I2 NaHCO3
H
Me
O
I
5.5 : 1
4.9 : 1
147 : 1
MeO
OMe
N
C=O
I2
THF, H2O
(139)
(140) 91% e.e
NBS
DME, H2O
0 °C
(141)
(142)
Br
OH
HO
H2O
CO2H

SCHEME 2

Iodolactonization of the allylic carbonate **143** has been found to proceed with high stereo- and regio-selectivity to produce iodocarbonate **144**. Steering by Ph (i.e. the primary coordination of the electrophile to Ph) has been suggested to account for this result[231].

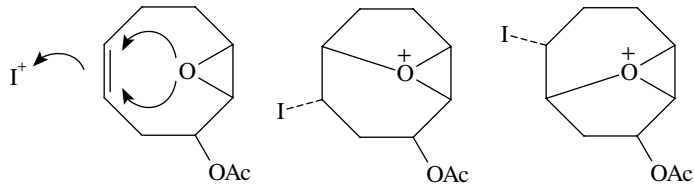


(143) **(144)**

On treatment with NIS, acetoxycyclohex-2-ene has been found to react via $5(O)^{\pi,n}$-*exo-Trig* participation with no migration of the acyl group[232]. To the reviewer's surprise, the authors claimed this behaviour to be unprecedented. This claim is not justified since a number of analogous electrophilic additions, where the acyl did not move, had been reported much earlier[197]. Furthermore, there are examples where the acyl does move, at least partially, giving a mixture of the two possible products[197].

The $5(O)^{\pi,n}$-*endo-Trig* ring closure has been reported for the bromination and iodination of several allenic derivatives[233–237]. α-Carbamoyloxy allenes undergo iodination with $5(N)^{n}$-*exo-Trig* participation[238].

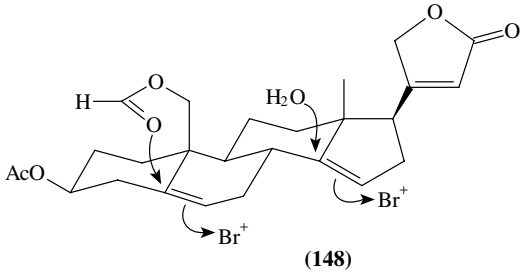
The regioselectivity of the oxirane oxygen transannular participation on iodination of the epoxyolefin **145**, followed by ring opening of the corresponding oxonium ions **146** and **147**, has been rationalized by means of MNDO calculations[161]. These findings have been utilized in model studies towards the synthesis of polyether toxins containing a tetrahydrofuran ring[239,240].



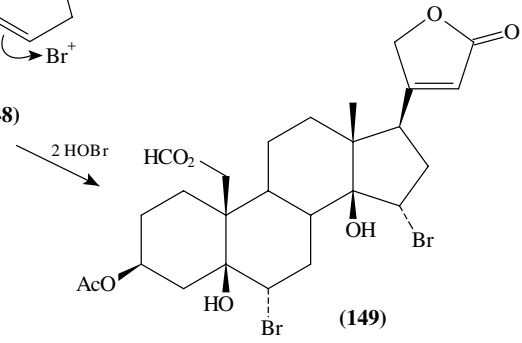
(145) **(146)** **(147)**

Neighbouring group participation has been employed to control the regioselectivity of HOBr addition across a double bond in the crucial step of the synthesis of strophanthidin. Two molecules of the reagent were used in order to introduce two hydroxy groups in one step (**148** → **149**)[241].

Kinetic studies of the transannular iodination of the bicylic dienes **150** (R = H or Me) show that the addition is first order in **150** and second order in I_2. The rate is governed by electrostatic and electron-donor parameters of the solvent[242]. The reaction of brexadiene **151** with electrophiles (Br_2, I_2, CF_3CO_2D and CD_3CO_2D) proceeds with an initial *exo*-attack followed either by direct reaction with a nucleophile or by Wagner–Meerwein rearrangements to give mixtures of products[243]. Addition of hypobromous acid (generated from NBS) to **152** afforded a mixture of two allylic bromides and two products of π-particpation by the aromatic ring[244].



(148)



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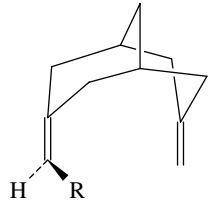

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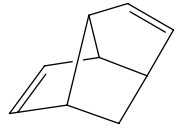

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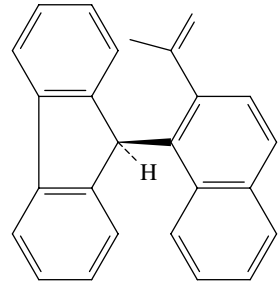
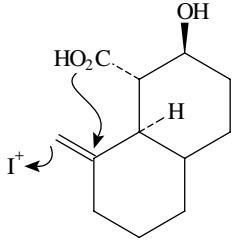


(152)

A detailed study of the iodocyclization of a series of unsaturated hydroxy acids has demonstrated that a ground-state conformational analysis can serve as a reliable indicator of the relative reactivities of various conformations. Thus, while **153** undergoes exclusive iodolactonisation, **154** gives the corresponding iodotetrahydrofuran as the sole product, in full agreement with the MM2 prediction[224].



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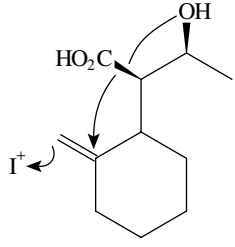

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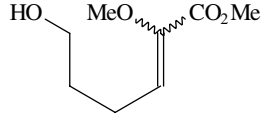
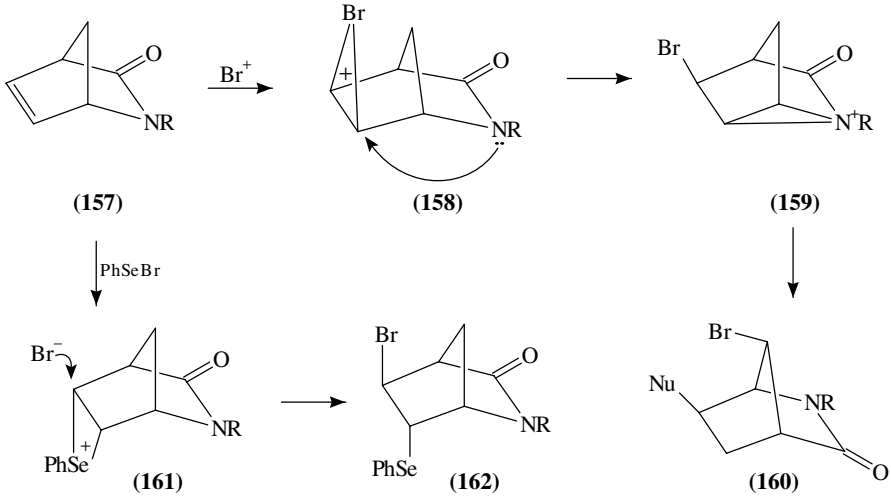


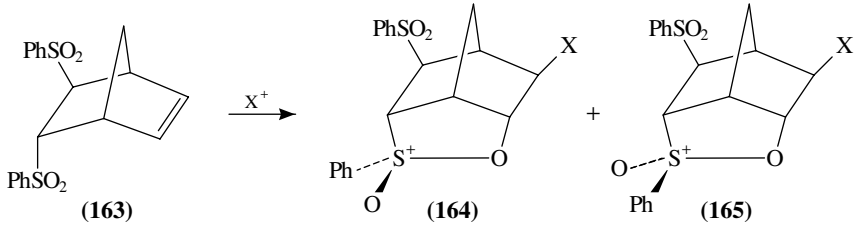
(155) *Z*
(156) *E*

Participation of the pyridine nitrogen in electrophilic additions has been reported[245]. The cyclization of *Z* and *E* isomers **155** and **156** mediated by various electrophiles (MCPBA, PhSeX, NBS, I_2) turned out to be stereospecific; the diastereoselectivity varies with the nature of the electrophilic reagent[246].

While 2-azabicyclo[2.2.2]hept-5-en-3-one **157** has been found to undergo bromination and bromofluorination with participation by the amide nitrogen followed by rearrangement (**158** → **159** → **160**)[247], phenylselenenylation results in a simple addition to afford **162**[247]. This difference has been rationalized as follows[247]: the bulky $PhSe^+$ finds it difficult to approach the double bond from the more hindered face (even if this might have been boosted by neighbouring group participation) so that a normal addition results (via **161**). By contrast, the reversible formation[113] of the bromonium ions allows the equilibrium of two diastereoisomeric ions to be established. The less populated, sterically more crowded ion **158** is siphoned off[248] by fast quenching due to the neighbouring group participation[247]. However, **157** is known to be *exo*-dihydroxylated with MnO_4^- or OsO_4[249], i.e. from the 'more' sterically hindered side, so that this issue is likely to be more complex.

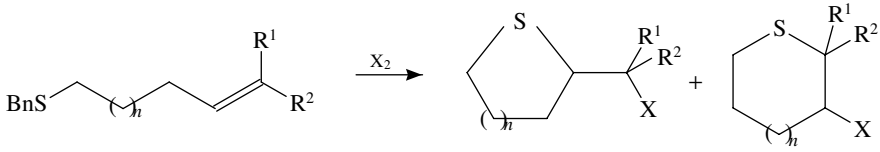


The addition of Cl_2, Br_2 or ICl to 2-*endo*-3-*exo*-bis (phenylsulphonyl)norborn-5-ene **163** in the presence of $AgBF_4$ gives rise to the γ-sulphinium ions **164** and **165**, demonstrating the nucleophilic reactivity of sulphonyl oxygen[250].



Regiochemistry of the electrophilic cyclization of **166** has been studied. Interestingly, 6(S)-*endo-Trig* cyclization seems to be more favoured than the expected 5(S)-*exo-Trig*

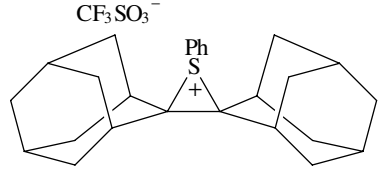
process for $R^1 = R^2 = H$; $R^1 = Me$, $R^2 = H$; and $R^1 = Ph$, $R^2 = H$. By contrast, formation of a five-membered ring becomes substantial for $R^1 = R^2 = CH_3$ (60:40). The 5-*endo-Trig* cyclization is in all cases favoured over the 4(S)-*exo-Trig* closure; the same trend has been observed for *Dig* cyclization of the corresponding alkynes[251]. Further examples of the 5(S)-*endo-Trig* cyclizations have been reported for *o*-thiostyrenes[252].



(166) $n = 0,1,2$ **(167)** **(168)**

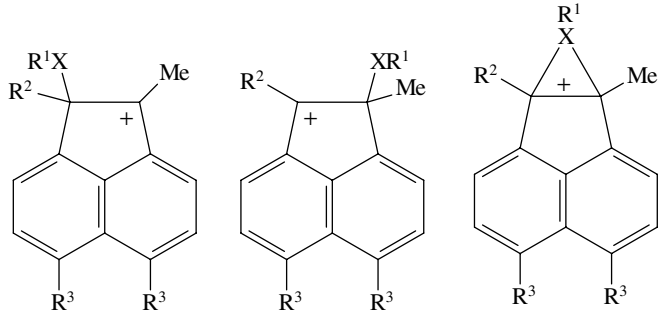
IV. ELECTROPHILIC CHALCOGENS

Addition of PhSCl and related reagents is believed to proceed via cyclic intermediates. The first isolated phenythiiranium ion **169** has been prepared from Ad=Ad on reaction with PhSCl and CF_3SO_3Me (r.t., 10 min) and characterized by single-crystal X-ray crystallography and ^1H and ^{13}C NMR spectra[253]. The dimensions of the thiiranium ring are as follows: (C−S) range 1.909(3)–1.937 (3) Å; (C−C) = 1.500 Å; (C−S−C) = 46.1°; (C−C−S) range 66.3(2)–67.9(2)°. The phenyl ring is approximately orthogonal to the plane of the thiiranium ring, but nearly coplanar with the ring C−S bonds.



(169)

The relative involvement of the cyclic (thiiranium or phenylselenenium) and open species in the addition reactions has been investigated by NMR. These studies have revealed dramatic substituent effects on the relative equilibrium stabilities of ions **170–172**

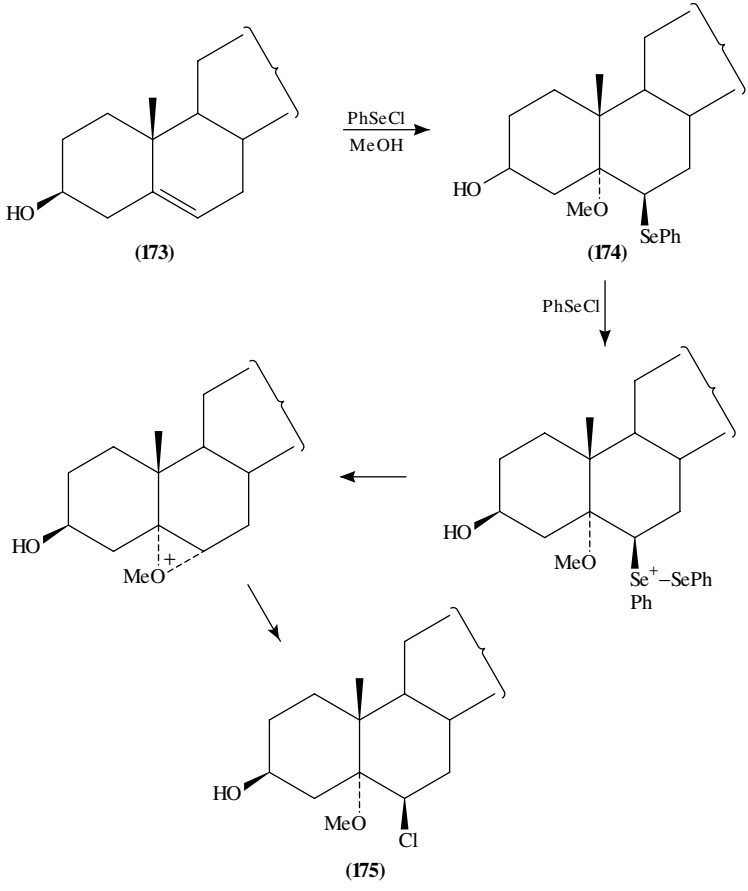


(170) **(171)** **(172)**

(R^1X = MeS, PhS, PhSe, C_6F_5Se, OH, Br; R^2 = Me, CH_2Cl; R^3 = H, Br, Me), that have been generated in superacids from RXCl and acenaphthylene derivatives[254]. In agreement with MINDO/3 calculations, the relative contribution of **172** falls with increasing atom number of X, electron-donating character of R^2 and electron-accepting character of R^3[254].

Kinetic studies of the addition of 2,4-dinitrobenzenesulphenyl chloride to cyclohexene in the presence of $LiClO_4$ have been interpreted in terms of an ion-pair mechanism. A similar conclusion has been arrived at for addition of $(SCN)_2$ to cyclohexene and ring-substituted styrenes, $RC_6H_4CH{=}CH_2$ (R = H, 4-Me, 4-Cl, 3-Cl)[255].

Kinetics of the addition of $4\text{-}RC_6H_4SCl$ (R = MeO, H, Cl) to the ring-substituted styrenes and α-methylstyrenes $4\text{-}R'C_6H_4C(R'){=}CH_2$ (R′ = MeO, H; R″ = H, Me) indicate that the reactivity of the electrophile is governed by the stabilization of partial positive charge in the transition state[256,257]. The transition states for the addition to α-methylstyrenes occur later on the reaction coordinate rather than in the addition to styrenes as a result of differences in localization energy[257]. The relative reactivities of $RC_6H_4CH{=}CH_2$ (R = 4-MeO, 4-Me, H, 4-Cl, 4-NO_2 and 3-NO_2) towards PhSCl are not affected by the solvent[258].



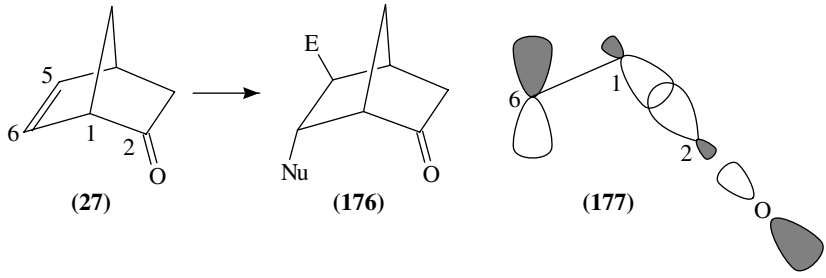
(173) **(174)** **(175)**

SCHEME 3

Irreversible acetoxyselenenylation of terminal and disubstituted olefins has been achieved on addition of PhSeBr in an acetate-buffered solution. Styrenes afford only Markovnikov adducts, while simple terminal olefins and olefins containing an allylic oxygen substituent (RCO_2 or ArO group) furnish 50–80% of the anti-Markovnikov isomer. The product mixture can be isomerized to contain 90–97% of the Markovnikov product by a catalytic amount 6–41%) of $BF_3.Et_2O$ in $CHCl_3$[259].

Excess of PhSeCl and prolonged reaction time are required to convert cholesterol **(173)** in MeOH first to **174** (62% yield), which is gradually transformed into the deselenenylated product **175** (27%; Scheme 3)[260]. Similar reactivity has been reported for α-substituted styrenes[261] and vinyl halides[262].

Kinetically controlled additions of PhSeCl, PhSeBr, PhSeOAc, 2-$NO_2C_6H_4SCl$ and 2,4-$(NO_2)_2C_6H_3SCl$ to bicyclo[2.2.1]hept-5-en-2-one **(27)** proceed in an *anti*-fashion with complete stereo- and regio-selectivity giving adducts **176** in which the electrophile occupies the *exo*-position, while the nucleophile is *endo*-orientated[263–265]. The results are in agreement with the predictions based on MO calculations, which suggest that a carbonyl group, homoconjugated with an electron-deficient centre, can act as an electron-donating remote substituent due to the favourable $n_{CO} \leftrightarrow \sigma_{C(1)-C(2)} \leftrightarrow p_{C(6)}$ hyperconjugation **(177)**[263].



(27) **(176)** **(177)**

Tetraflurobenzobarrelene and its derivatives react with PhSX (X = Cl, Br) in AcOH, $MeNO_2$ or CH_2Cl_2 to afford *trans*-β-halosulphides. Structural rearrangement occurs when these reactions are carried out in systems such as $AgSbF_6/MeNO_2$ and $[(MeS)_2SMe]^+[SbCl_6]^-/CH_2Cl_2$[266].

The electrophilic *anti*-1,2-addition of the elements of MeSF to C=C has been achieved by a one-pot reaction of Me_2S^+-SMe BF_4^- and $Et_3N{\bullet}3HF$ with various types of alkenes[267]. Markovnikov products arise from unsymmetrically substituted olefins. The reaction of 2,6-norbornadiene proceeds with exclusive *exo*-attack on one double bond followed by participation of the second double bond to give rise to two isomeric 3,5-disubstituted nortricyclanes[267]. By contrast, no transannular π-participation has been observed with 1,5-cyclooctadiene. The reaction is believed to occur via the corresponding thiiranium species[267].

PhSeF, generated from Ph_2Se_2 and XeF_2, adds to norbornene predominantly in an *anti*-fashion to afford the non-rearranged adducts, corresponding to *exo*- and *endo*- attack, respectively[268]. By contrast, $PhSeF_3$ gives mainly the products of *syn-exo*-addition and a rearranged derivative in *ca* 7:1 ratio[268].

Predominant *anti*-stereochemistry has been observed for the addition of $TsSNR_2/BF_3.Et_2O$ to olefinic substrates[269]. 4′-Nitrobenzenesulphenanilide (ArNH–SPh) reacts with HBr to generate *in situ* PhSBr, which attacks alkenes or alkynes in a regio- and stereo-selective manner[270].

Oxidation of bis(4-methoxyphenyl)disulphide with ammonium peroxydisulphate generates a reagent that can be utilized to promote *anti*-stereospecific arylthioamidation in acetonitrile[271]. This procedure is also suitable for aryletherification and lactonization[271]. Other methods of generating electrophilic reagents from ArSSAr involve oxidation with $(AcO)_3Mn$[272] and anodic oxidation[273].

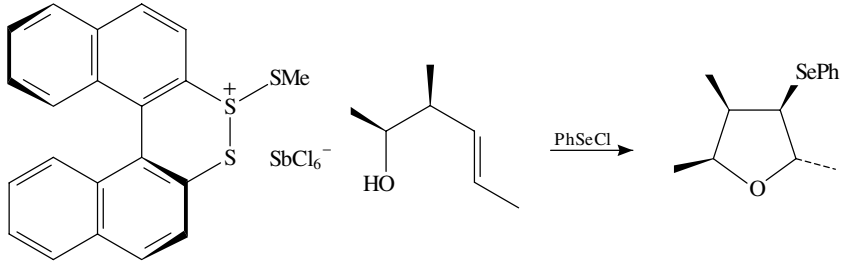
Methoxyselenenylation of olefins can now be effected in one step by oxidation of PhSeSePh with $(NH_4)_2S_2O_2$ in MeOH[274,275]. The reaction is highly regio- and stereoselective giving pure *anti*-products with Markovnikov orientation[274]. When the reaction is carried out in MeCN containing CF_3CO_2H and water, amidoselenenylation products are obtained[275]. Another method of generating $PhSe^+$ relies on the oxidation of PhSeSePh with *p*-nitrobenzenesulphonyl peroxide[276].

Acid catalysis (AcOH) has been investigated for addition of ArSCl to cyclohexene. The acid anion has been found to compete with Cl^- in the formation of the final product[277].

Treatment of olefins with dimethylthiomethylsulphonium salts and triphenylphosphine leads to the corresponding 2-methylthioalkylphosphonium salts[278].

Stereocontrolled glycosylation of furanoid glycals with pyrimidine or purine bases has been accomplished via a Lewis acid-mediated sulphenylation[279].

Enantiopure ditihiiranium salt **178** has been reported to transfer enantioselectively the MeS^+ group to *trans*-hex-3-ene to generate the corresponding thiiranium ion which, in turn, reacts with $MeCN/H_2O$ allowing the enantioselective synthesis of the vicinally disubstituted alkanes with up to 86% e.e.[280].



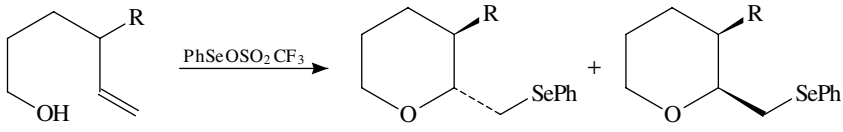
(178) **(114)** **(179)**

Ring-closure reactions of olefins bearing a functional group can now be facilitated using PhSeX/Ag(I)[281], PhSeCl/Tl(I)[197] or PhSeSePh/$(NH_4)_2S_2O_8$ in MeOH, dioxane or MeCN[282]. Both *exo-Trig* and *endo-Trig* cyclizations have been reported[197].

Cyclophenylselenenylation of aliphatic hydroxy olefins results in the formation of polysubstituted tetrahydrofurans with high stereoselectivity (**114** → **179**)[207,208], low temperature (−78 °C) is generally recommended[283]. The 6(O)^n-*exo-Trig* cyclization of 4-substituted 5-hexen-l-ols **180** with PhSeOTf has been found to produce preferentially the *trans*-isomer **181** for R = alkyl or Ph, whereas the *cis*-isomers **182** are favoured when R = OH, OR or R′CO. The stereoselectivities have been rationalized by steric and electronic effects[284]. Phenylselenenyl halides have also been found to effect electrophilic cyclization of olefinic oximes[285,286] (for discussion see the analogous mercuration[286]), generating reactive N-oxides.

Unhindered olefins have been found to react with NaHTe in refluxing EtOH to produce Markovnikov-like dialkyltellurides via an addition process, which is believed to occur through a radical mechanism[287].

A method for acetoxytelluration of olefins has been developed using $TeCl_4$ and AcOLi in AcOH at 80 °C. The reaction is highly *anti*-stereospecific and obeys the Markovnikov



(180) **(181)** **(182)**

rule. Therefore, an ionic mechanism involving a telluronium ion intermediate has been suggested. At 120 °C, formation of vicinal diacetates has been observed, with stereochemistry corresponding to a Prévost-type reaction[288].

V. ELECTROPHILIC OXYGEN: EPOXIDATION

Ab initio calculations have been performed in order to probe the nature of the transition state for epoxidation reactions[289]; the transition state is consistent with an S_N2 attack by the alkene π-bond on the σ- and σ^*-orbitals of the O−O bond[290].

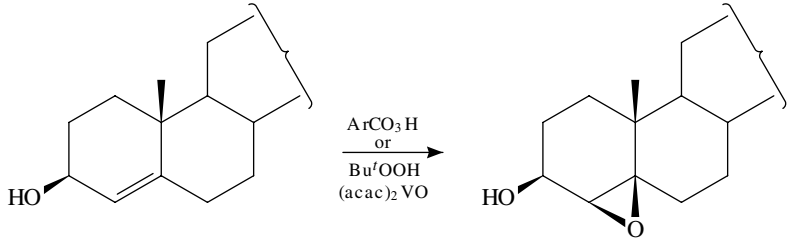
A. Peroxy Acids

Mechanistic studies on the peroxy acid oxidations of isotopically labelled but-2-enes have been reported[291].

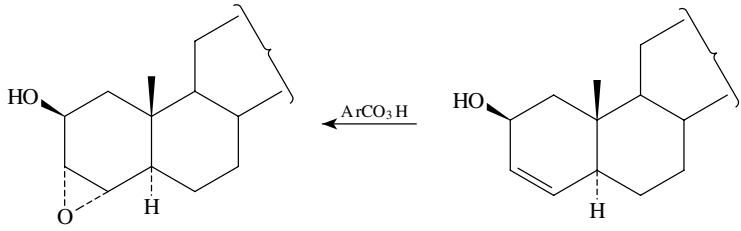
The influence of strain on chemical reactivity has been studied in relation to the MCPBA epoxidations of torsionally distorted alkenes; although in some cases there is a rough correlation between the epoxidation rate and the ionization potential of the alkene, the frontier orbital interaction is not viewed as the dominant factor since conjugated alkenes, which have higher HOMO energies than simple alkenes, are not more reactive to MCPBA[292]. Orbital distortions from remote substituents have been investigated by the MCPBA epoxidation of fluorenes with an alkene group in spiro geometry[293].

The stereochemistry of the epoxidation of A-norsteroids is less predictable than that of the corresponding steroids in view of the flattened nature of ring A and the preferred *cis* fusion of the hydrindane; it has been shown that epoxidation with peroxy acids proceeds predominantly from the β-face in some norsteroids[294].

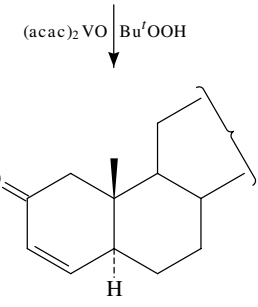
The reactivity of cyclohexene-type allylic alcohols toward epoxidation reagents (peroxy acids or *t*-BuOOH with transition metal catalysts) has been found to be largely dependent on the magnitude of steric hindrance in the substrate molecules. With unhindered (e.g. cyclohexenol) or slightly hindered allylic alcohols, such as **183**, the reaction is dominated by *syn*-stereodirecting effect of the hydroxy group, which results in the exclusive or predominant formation of *cis*-epoxy alcohols **(184)** with both reagents. By contrast, this well-established type of stereocontrol fails with sterically congested substrates, such as **185** (note the 1,3-diaxial interaction of the approaching reagent and the angular methyl



(183) **(184)**



(186) **(185)**



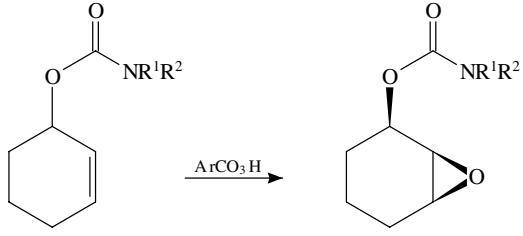
(187)

group), which gives *trans*-epoxy alcohol **186** on MCPBA treatment, while the transition metal-catalysed oxidation with *t*-BuOOH affords the conjugated ketone **187** as the sole product. The latter reaction can serve as a mild procedure for the selective oxidation of hindered allylic alcohols to α,β-unsaturated ketones[295].

The epoxidation of allylic alcohols can be carried out with peroxy acids in aqueous medium. In the case of polyolefinic alcohols, regioselectivity results from control of the pH of the reaction; the proton of the allylic hydroxy group plays a fundamental role when the oxidation is carried out at a high pH[296].

The magnitude of the diastereofacial selectivity in the epoxidation of rigid allylic ethers by *m*-chloroperoxybenzoic acid has been interpreted in terms of Houk's transition-state models[297].

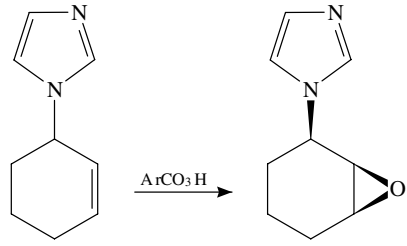
The carbonyl oxygens are responsible for the stereo-directing effects of peroxy acids on the epoxidation of allylic and homoallylic carbamoyloxyalkenes (**188** → **189**)[298]. For other mechanistic investigations of the peroxy acid epoxidations of alkenes, see elsewhere[299–301].



(188) **(189)**

Only the *syn*-epoxide **191** is formed on MCPBA oxidation of the imidazolyl cyclohexene **190**; this selectivity apparently reflects hydrogen bonding between the imidazole and

the approaching peracid[302]. A similar explanation has been used to account for the *syn* selectivity in the epoxidation of some allylic alcohols[303].

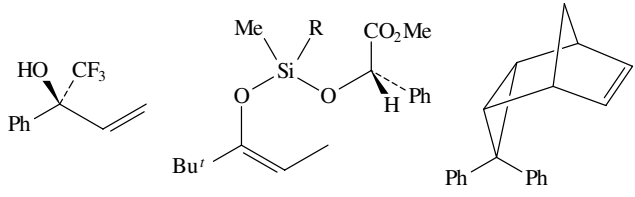


(190) **(191)**

Syn selectivity in the epoxidation of allylic fluorides by peracids has been interpreted by electronic stabilization of the transition state with the electronegative fluorine atom oriented at the inside position[304].

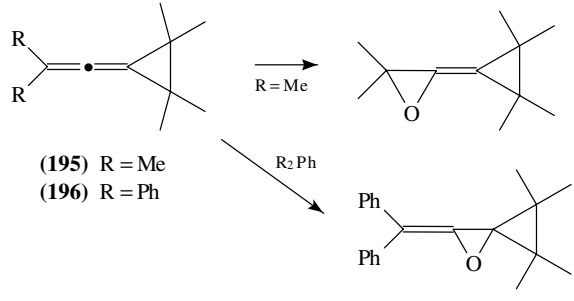
Molecular-orbital calculations indicate that the stereoselective epoxidation of the alkene **192** by peroxy acids arises from stereoelectronic control exerted by a CF_3-C bond orientated *anti* to the alkene plane, in contrast to the previously proposed model for epoxidation of allylic fluoride in which the F−C bond and alkene bonds are in a *syn* arrangement[305].

Silyl enol ethers with stereogenic silicon atoms bearing chiral alkoxy groups on silicon, as in **193**, induce modest stereoselectivity in peracid epoxidation of the enol double bond[306]. Aryl π participation has been observed in the epoxidation of the bicyclooctene **194**[307].

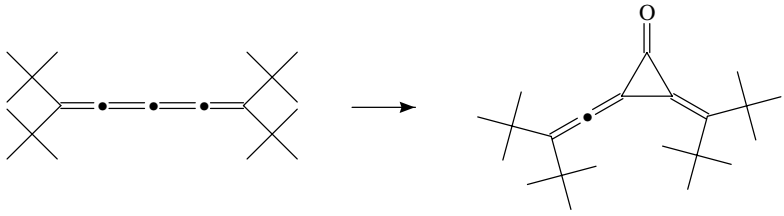


(192) **(193)** **(194)**

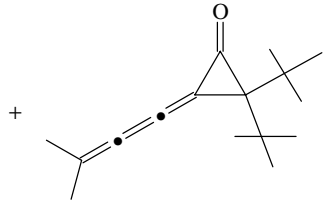
The regioselectivity in the epoxidation of ethenylidenecyclopropanes by MCPBA strongly depends on the double-bond substituents. Thus, with alkyl substituents such as methyl **195**, the adjacent electron-rich double bond is epoxidized, whereas the diphenyl analogue **196** reacts preferentially on the other double bond; both primary products undergo subsequent rearrangements[308]. The MCPBA oxidation of the hindered cumulene **197** gave the cyclopropanones **198** and **199**[309].



(195) R = Me
(196) R = Ph



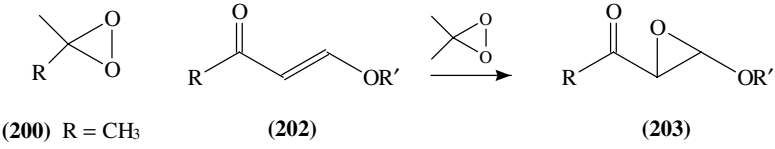
(197) **(198)**



(199)

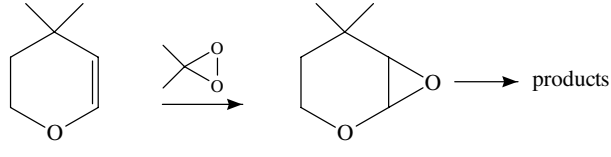
B. Dioxiranes

Dioxiranes, such as dimethyldioxirane **(200)** and methyl(trifluoromethyl)dioxirane **(201)**, are a class of reactive organic peroxides with great potential as oxidants[310]. The main advantage of this methodology is that it makes highly labile epoxides accessible. Thus, for instance, **203** can be obtained by epoxidation of β-oxo enol ethers **202** with dimethyldioxirane[311]. Similarly, the reaction of the dimethyldihydropyran **(204)** with **200** gives the unstable epoxide **205**; secondary deuterium isotope effects indicate a greater degree of rehybridization at the β- than at the α-position in the transition state leading to the epoxide[312].

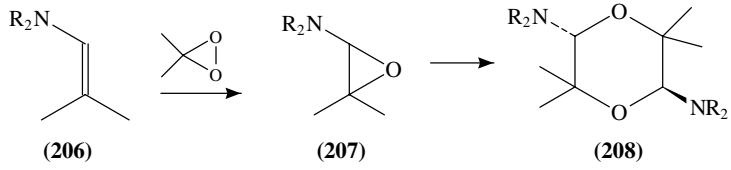


(200) R = CH_3
(201) R = CF_3

(202) **(203)**



(204) **(205)**



(206) **(207)** **(208)**

Electronic and steric effects in the epoxidation of alkenes by dimethyldioxirane have been investigated[313]. Both mechanistic and synthetic aspects of the chemistry of dioxiranes have been reviewed[314,315].

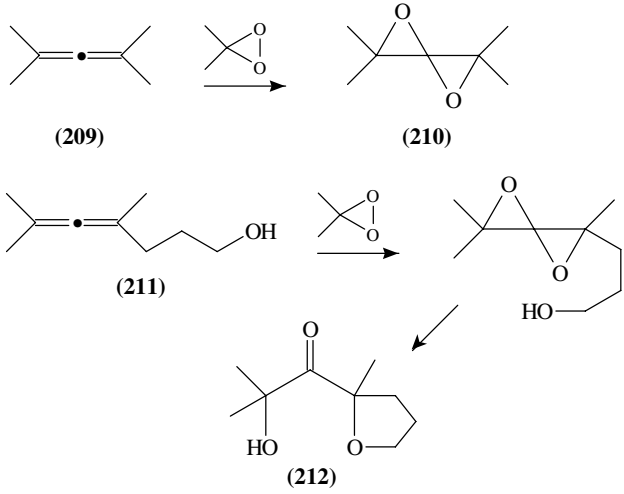
The relative rates of epoxidation of ethyl 4-substituted-(*E*)-cinnamates by **200** gave a Hammett ρ value of -1.53, indicating an electrophilic oxygen-atom transfer[316]; the reaction rate is increased by protic solvents[317].

Dioxiranes react with cholesterol and its acetate to give *ca* 1:1 mixtures of 5α,6α- and 5β,6β-epoxides (in contrast to peroxy acids, that are known to produce *ca* 5:1 mixture)[318].

Dioxiranes have provided the first examples of direct epoxidation of a double bond bearing a trifluoromethyl group substituent by non-biochemical means[319].

Some limitations have been discussed[320] in the dimethyldioxirane oxidation of glucals[321]. Dimethyldioxirane induces epoxidation of enanimes (e.g. **206**), which subsequently dimerize to 1,4-dioxanes **(208)**[322]. The stability of the α-amino epoxides **207** depends on the type of substitution at the nitrogen[323].

Simple allenes **(209)** react with dimethyldioxirane **(200)** to give the corresponding spiro-dioxides **210;** in instances where diastereoisomeric spiro-dioxides are possible, there is usually an acceptable stereochemical preference for epoxidation to occur *anti* to the alkyl substituents[324,325]. Allenic alcohol **211** yields the highly functionalized tetrahydrofuran **212** and tetrahydropyran derivatives by intramolecular nucleophilic addition of the hydroxy group to an intermediate allene diepoxide[324].



(209) **(210)** **(211)** **(212)**

C. Sharpless–Katsuki Epoxidation

Reviews on asymmetric epoxidation[326], with particular emphasis on the Sharpless–Katsuki procedure[327,328], have appeared.

Studies of bis-tartrate esters and other tartrate ligands for titanium-mediated asymmetric epoxidation have provided evidence against the sole intermediacy of monomeric titanium-tartrate species in the parent system[329,330]. Other tartrate ligands have been studied in attempts to gain a better understanding of the mechanism of the Sharpless epoxidation[330].

A systematic study of the Sharpless epoxidation led to the following conclusions: (1) an equimolar complex of titanium tetraalkoxide and tartrate diester [(tartrate)$(RO)_2$Ti] is the

catalytically active template for asymmetric epoxidation; it is much more active than titanium tetraalkoxide alone or titanium tartrates of other than 1:1 stoichiometry and thus exhibits ligand-accelerated catalysis; (2) the rate is first order in substrate and oxidant, and inverse second order in inhibitor alcohol, under pseudo-first-order conditions in catalyst; this is characteristic of a system in which allylic alcohol and alkyl hydroperoxide bind to the same metal centre; (3) the rate of epoxidation is slowed by alkenes with electron-withdrawing substituents, indicating that the olefinic moiety is nucleophilic; (4) increased bulk at several positions in the epoxidation system (the alkyl group of either the tartrate ester of the hydroperoxide or the *trans*-olefinic substituent) results in increased epoxidation rates together with better kinetic resolution and asymmetric induction. Solution-phase and X-ray structure investigations on the detailed structure of [(tartrate)$(RO)_2$Ti] have been reported[331,332].

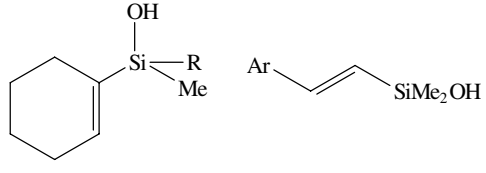
An alternative explanation for the enantioselectivity observed in the Sharpless epoxidation has been proposed[333] but it does not seem to be compatible with the kinetic and other data.

Within limits, an increase in the steric bulk at the olefin terminus of allylic alcohols of the type $R^1CH(OH)CH{=}CHR^2$ causes an increase in the rate of epoxidation of the more-reactive enantiomer, and a decrease in the rate for the less-reactive enantiomer, resulting in enhanced kinetic resolution[334]. However, complexes of diisopropyl tartrate and titanium tetra-*tert*-butoxide catalyse the kinetic resolution of racemic secondary allylic alcohols with low efficiency[335]. Double kinetic resolution techniques can show significant advantages over the simple Sharpless epoxidation techniques[336].

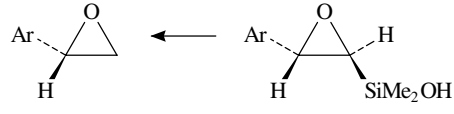
High diastereoselectivity is found in the epoxidation of fluoroallylic alcohols with titanium(IV) isopropoxide and *tert*-butyl hydroperoxide[337]. The anomalous Sharpless asymmetric epoxidation has been used in the synthesis of L-*erythro*- and D-*threo*-sphingosines[338].

The epoxidation of alkenylsilanols parallels that of allylic alcohols in exhibiting good enantioselectivities[339]. Kinetic resolution of the alkenylsilanol **213** by the Sharpless asymmetric epoxidation has been accomplished, with the rate difference for the oxidation of the enantiomers of **213** being unusually high (>11)[340].

Sharpless epoxidation of the alkenylsilanol **214** gave, after protodesilylation of the silyl epoxide **215**, styrene epoxide **216** in 95% e.e.; the stereochemical course of the reaction follows that predicted by Sharpless for allylic alcohols[341].

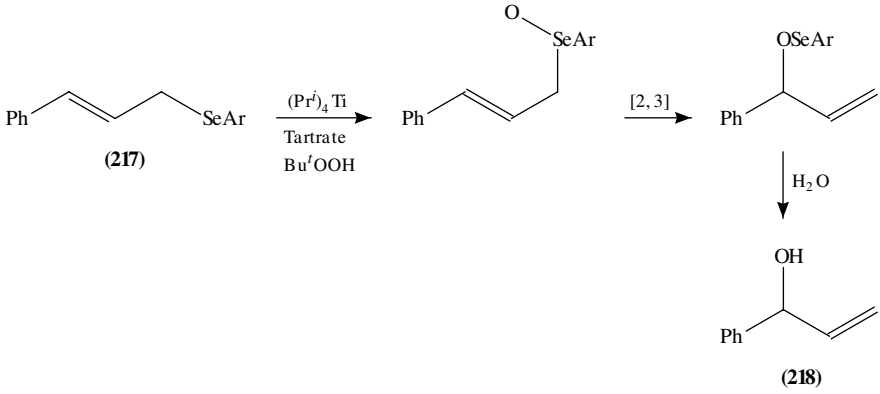


(213) **(214)**



(216) **(215)**

The asymmetric oxidation of sulphides to chiral sulphoxides with *t*-butyl hydroperoxide is catalysed very effectively by a titanium complex, produced *in situ* from a titanium alkoxide and a chiral binaphthol, with enantioselectivities up to 96%[342]. The Sharpless oxidation of aryl cinnamyl selenides **217** gave a chiral 1-phenyl-2-propen-1-ol **(218)** via an asymmetric [2,3] sigmatropic shift (Scheme 4)[343]. For other titanium-catalysed epoxidations, see Section V.D.1 on vanadium catalysis.



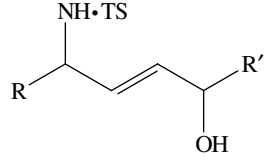
SCHEME 4

D. Other Metal-catalysed Epoxidation Reactions

1. Vanadium

The importance of 1,2- rather than 1,3-allylic strain in the vanadium(V)-catalysed Bu^{t}OOH epoxidation directed by hydroxy groups has been assessed using (*Z*)-3-en-2-ols as model substrates[344].

Epoxidation of both *syn*- and *anti*-5-(tosylamino)-hex-3-en-2-ol derivatives **219** with *t*-butyl hydroperoxide with vanadium or titanium catalysts has been shown to exhibit little stereocontrol ($\leqslant$3:1)[345].

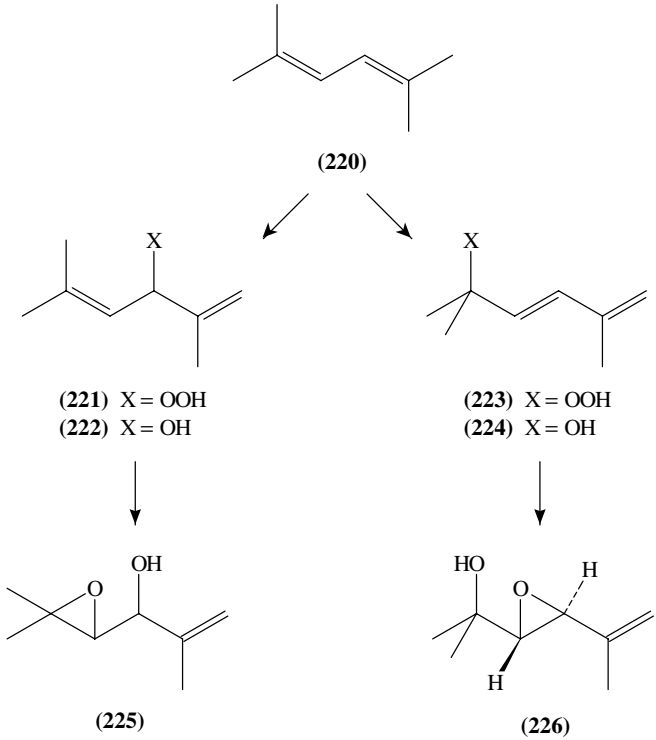


(219)

Stereoselective epoxidation of *β-cis*-homoallylic alcohols by vanadium, tungsten and molybdenum oxo species has been used for the construction of intermediates with four adjacent asymmetric centres[346].

The epoxidation of electron-deficient alkenes with either vanadium or titanium catalysts give *syn*-epoxides[347]; a free hydroxy group and a ketone or ester function are necessary for the reaction to take place, and a modest level of asymmetric induction can be achieved with γ-hydroxyenone substrates and chiral titanium catalysts[348].

In the photo-oxygenation of the diene **220**, use of titanium isopropoxide as oxygen-transfer catalyst afforded exclusively the epoxy-alcohol **225**, whereas a vanadium-peroxo complex gave exclusively the isomeric product **226**; oxygen transfer with a titanium reagent outweighs regio-isomerization whereas the reverse is true for the vanadium catalyst[349]. This procedure has been applied to the regio- and stereo-controlled oxygenation of cholesterol[350].



2. Molybdenum and tungsten

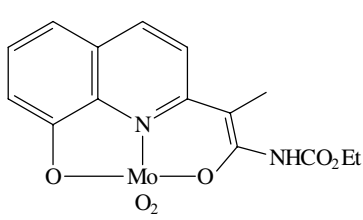
The molybdenum complex **227** is an effective catalyst for epoxidation of alkenes and has allowed the development of the polystyrene-supported peptide-linked epoxidation catalyst **228**[351].

Studies on the epoxidation of unsaturated acids by hydrogen peroxide in the presence of phosphotungstic acid[352] and of alkenes by alkyl hydroperoxides in the presence of molybdenum complexes[353,354] and vanadium oxide[355] have appeared.

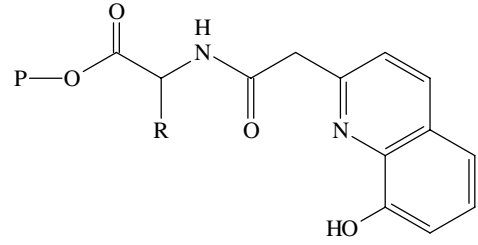
In the epoxidation of alkenes with *tert*-butyl hydroperoxide and a molybdenum oxide catalyst, addition of an aliphatic amine first accelerates the formation of the intermediate **229** and also favours the production of epoxide in favour of the alternative fragmentation to carbonyl compounds (Scheme 5)[356].

3. Manganese

The optically active manganese-salen complexes **230** and **231** are effective catalysts for the enantioselective epoxidation of unfunctionalized alkenes[357–361]. The yield of epoxide



(227)



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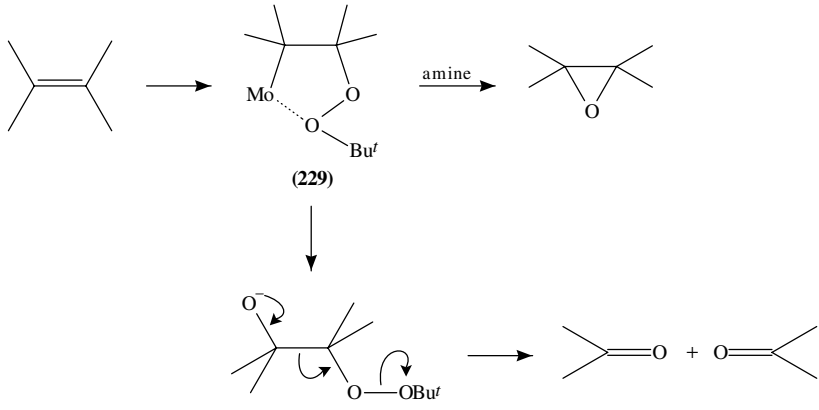
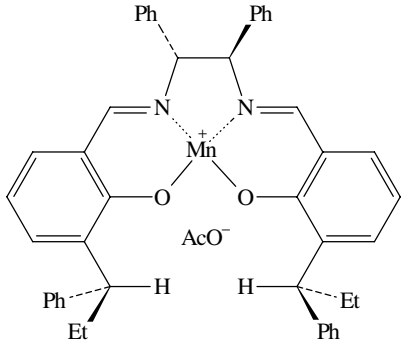
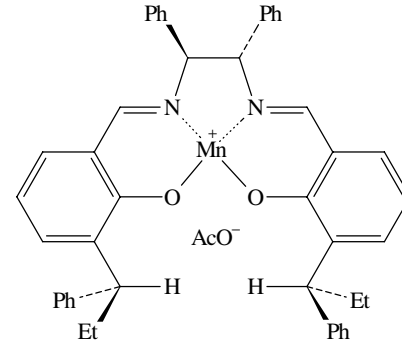


(229)

SCHEME 5



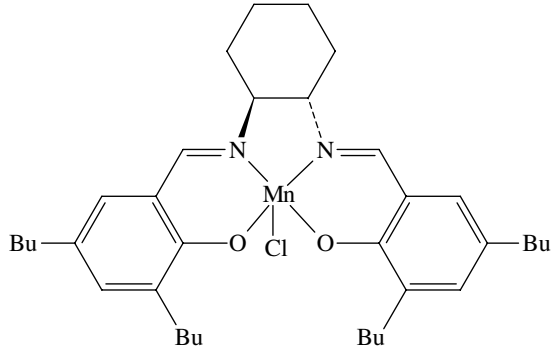
(230)



(231)

diminishes with increasing concentration of the catalysts in the epoxidation of alkenes with iodosylbenzene as oxidant, indicating that rigid coordination of alkene to oxomanganese(V) species does not take place in the rate-determining step[360].

Asymmetric epoxidation of conjugated dienes and enynes catalysed by the chiral manganese(III) complex **232** give monoepoxides exclusively; reactions of *cis*-enynes give *trans*-alkynyl epoxides as the major products with a high level of asymmetric induction[362].

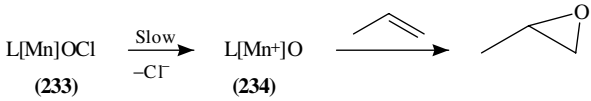


(232)

In the catalytic epoxidation of alkenes by a manganese porphyrin with phase-transfer catalysis and hypochlorite, the yield of epoxide also decreases with decreasing alkene concentration[363]; dibenzo-18-crown-6 has been shown to have an effect on the reaction[364].

The two-phase epoxidation of alkenes by hydrogen peroxide in water–dichloromethane system, catalysed by manganese(III)–porphyrin, is strongly accelerated by addition of catalytic amounts of a carboxylic acid and lipophilic imidazole or pyridine axial ligand[365,366]. Manganese(III)–porphyrin bound to colloidal anion-exchange particles is more active in the selective epoxidation of styrene by aqueous hypochlorite than the same catalyst in aqueous solution[367].

The mechanism of the epoxidation of alkenes by the cytochrome P450 model, sodium hypochlorite–manganese(III) tetraarylporphyrins, involves rate-determining formation of an active species **234** from a hypochlorite-manganese complex **233** (Scheme 6); pyridine or imidazole derivatives, as axial ligands, accelerate this step by electron donation, although the imidazoles are destroyed under the reaction conditions[368].



(233) **(234)**

L = Porphyrine

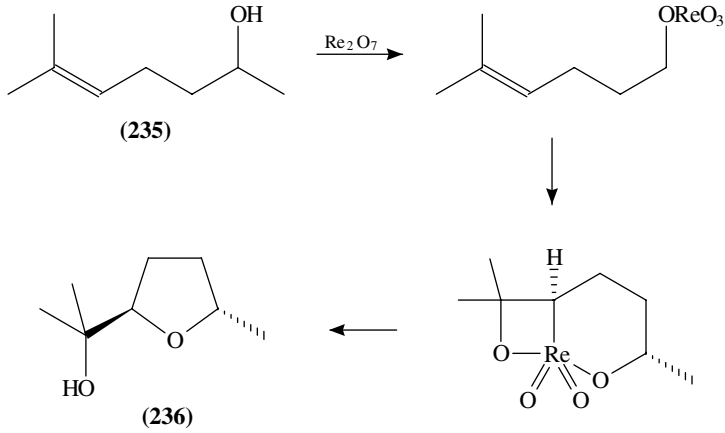
SCHEME 6

4. Rhenium

The oxidation of 5-hydroxyalkenes **235** with rhenium(VII) oxide gives 2-(hydroxymethyl)-tetrahydrofurans **236**; the stereoselectivity has been rationalized by an initial [2 + 2] cycloaddition followed by reductive elimination[369]. The yield and stereoselectivity of such oxidations are the same in both stoichiometric and periodate-catalysed reactions[370].

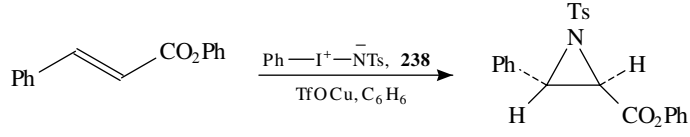
5. Miscellaneous

Sodium perborate in acetic anhydride has been reported to oxidize alkenes to expoxides[371].

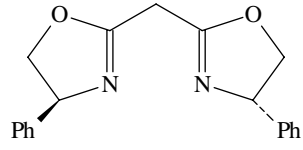


VI. ELECTROPHILIC NITROGEN: AZIRIDINATION

In spite of their inherent ring strain and susceptibility to ring-opening, aziridines are comparatively little used as synthetic relay intermediates by comparison with expoxides. It is the dearth of methods for direct conversion of alkenes into aziridines — aziridination — which is primarily responsible for the relatively little use made of this ring system[372]. In particular, methods for epoxidation of alkenes using peroxyacids or hydroperoxides metal salts do not have nitrogen analogues (see, however, below). Aziridination of alkenes using nitrenes suffers from a lack of chemo- and stereoselectivity. However, Evans[373] and Jacobsen[374] have shown that the copper nitrenoid generated by decomposition of *N*-*p*-tosyliminophenyliodinane aziridinates some alkenes (e.g. **237**) with high enantioselectivity in the presence of copper(I) coordinated to chiral ligands, such as **239**.



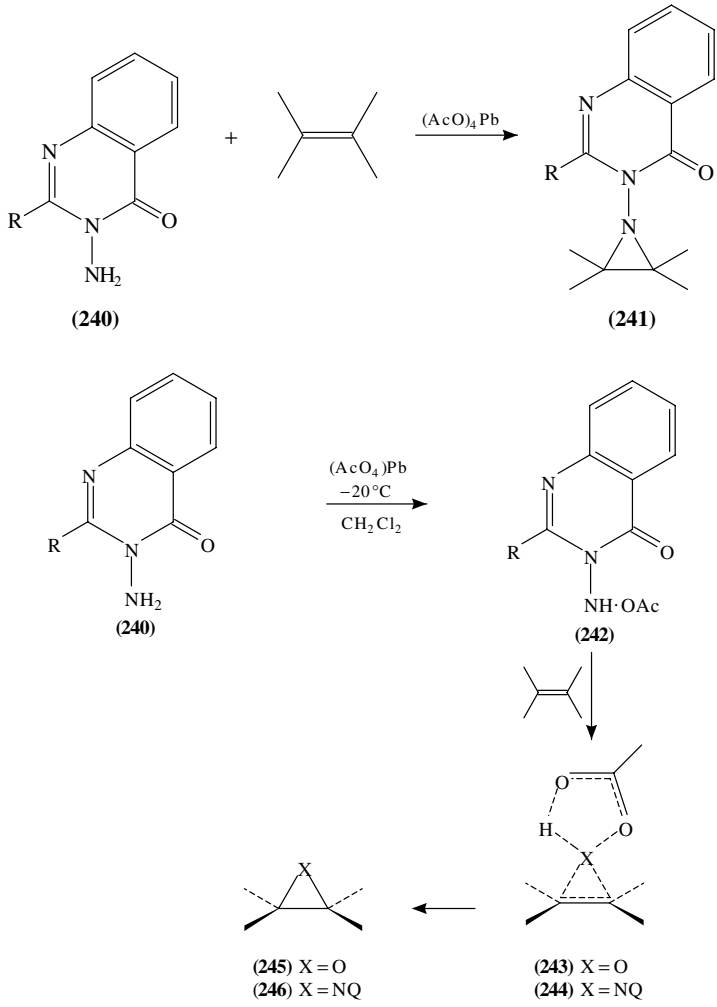
(237) **(239)** 64%; 97% e.e



(238)

A general method for direct aziridination of alkenes, discovered nearly thirty years ago, involved oxidation of a number of *N*-aminoheterocyclic compounds, such as **240**, with lead tetraacetate (LTA) in the presence of the alkene to give **241**[375]. The intermediates in these aziridinations were originally believed to be the corresponding *N*-nitrenes but have recently been shown to be (at least for *N*-aminoquinazolinone **240** and *N*-aminophthalimide) the corresponding *N*-acetoxyamino compounds **242**[375].

It is clear, therefore, that the mechanism of aziridination of alkenes using, e.g., 3-acetoxyaminoquinazolinones (**240**; R = CH_3CO) resembles the Bartlett (butterfly) mechanism by which peroxyacids epoxidize alkenes (Scheme 7). Ironically it has been found recently[376] that the quinazolinonylnitrene, originally thought to be the reactive intermediate (*vide supra*), can be generated from **242** and is also an aziridinating agent with a reactivity profile very similar to, but identifiably different from, **242**.

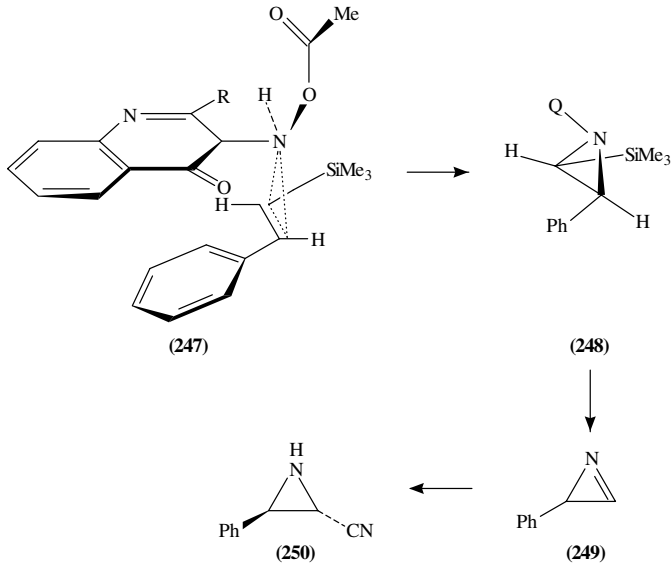


SCHEME 7

The characteristics of aziridination using **242** and its congeners can be summarized as follows: (a) reaction with alkenes is stereospecific with retention of the alkene configuration in the aziridine; (b) reaction takes place in good yields with alkenes substituted with electron-donating groups (e.g. alkyl, phenyl, alkoxy) or with electron-withdrawing groups (e.g. CO_2R, COR), and with only modest excess of the alkene; (c) with allylic alcohols, such as cyclohexenol, addition is highly *syn*-stereoselective (cf

epoxidation with peroxyacids); (d) with chiral 2-substituents on the quinazolinone ring, the aziridination of some prochiral alkenes is highly or completely stereoselective (*vide infra*); (e) the exocyclic nitrogen in **242** is pyramidal and inverting slowly on the NMR time-scale but fast on the time-scale of the aziridination; (f) the yields of aziridines are greatly increased in many cases by the addition of trifluoroacetic acid or hexamethyldisilazane to the reaction mixture.

The presence of the quinazolinone ring in these aziridinations has been invaluable in allowing inferences to be drawn as to the transition state geometry and mechanism of the reaction[377]. Thus, for the aziridination of β-trimethylsilylstyrene, the mechanism is believed to be that shown in Scheme 8 with *endo*-type overlap of the phenyl ring and quinazolinone ring and with an S_N2-type displacement of the acetoxy group from the nitrogen running ahead of the $N-C_1$ bond formation.



SCHEME 8

Removal of the Q group in the ring-opened aziridines can be accomplished by reductive means (SmI_2 or Na/Hg). Alternatively, the aziridine ring can be retained in the removal of Q by the aziridine–azirine–aziridine interconversion shown in Scheme 8 which takes advantage of the leaving-group ability of the Q group. Using an enantiopure R* group $CH_3CH(OSiMe_2Bu^t)$, the aziridine **248** has been obtained highly diastereoselectively and the aziridine **250** in 83%, e.e.[378–380].

VII. ELECTROPHILIC CARBON

A. Addition of 'C^+'

The heats (ΔH_a) of reaction of diarylmethyl tetrachloroborates with 2-methyl-1-pentene were determined[381] by low-temperature calorimetry to be in the range between -53.1 kJ mol^{-1} for $(MeC_6H_4)_2CH^+\ BCl_4^-$ and 33.0 kJ mol^{-1} for the better stabilized $(MeOC_6H_4)(MeC_6H_4)CH^+\ BCl_4^-$. In contrast, the heats of the Lewis-acid-catalysed additions of the corresponding *p*-substituted diarylmethyl chlorides (Ar_2CHCl) are independent of the *p*-substituent ($\Delta H_a = -86.5 \pm 2.7$ kJ mol^{-1})[381].

Kinetic investigation of the reaction of (*p*-anisyl)phenylcarbenium tetrachloroborate with methylenecycloalkanes (ring size 3–12 and 15) exhibits correlation of the second-order rate constants with the solvolysis rates of the corresponding cycloalkyl derivatives[382].

Kinetic studies of the reactivity of allyltrialkylsilanes towards the *p*-methoxy substituted diphenylcarbenium ion revealed an increase of the reaction rate by several orders of magnitude compared to olefins lacking the silyl group[383]. These studies also indicated that the β-silylcarbenium ion is generated in the rate-determining step. The reaction rate, however, is dramatically decreased when one or more alkyl groups on silicon are replaced by chlorine atoms[383].

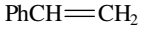
Competition experiments have been carried out to determine the relative reactivities of 23 alkyl chlorides toward allyltrimethylsilane in the presence of $ZnCl_2$. The k_{rel} scale has been found to span 11 orders of magnitude from the least reactive 1-adamantyl chloride to the most reactive bis(*p*-methoxyphenyl)methyl chloride[384]. By contrast, analogous acetals $RCH(OMe)_2$ exhibited very little differences in reactivity[385].

β-(Halosilyl)styrenes undergo dimerization and trimerization on treatment with TfOH via electrophilic addition of the corresponding benzyl cation generated by protonation of the parent molecule[386].

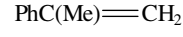
The kinetics of the $SnCl_4$-catalysed addition of 1-chloro-3-methyl-2-butene or (*E*)-2-chloro-3-pentene to isoalkenes (e.g. $Me_2C{=}CHCH_2CH_2CMeClPr$) have been shown to be strongly influenced by steric effects[387].

B. Addition of 'C=O'

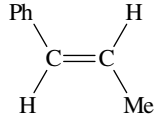
The addition of $CH_2(OMe)_2$ to styrenes **251–254** gives $PhCH(OMe)CH_2CH_2OMe$ in 96% yield from **252**, whereas **252** mostly polymerizes. Addition to **253** is 1.9 slower and affords an equimolar mixture of *erythro*- and *threo*-products, whereas the *cis*-isomer **254** is inert. The reactivities may reflect steric hindrance to planarity in the methylstyrenes, and correspond to the MNDO-calculated heats of formation of the methylstyrene conformers[388].



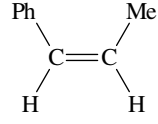
(251)



(252)



(253)



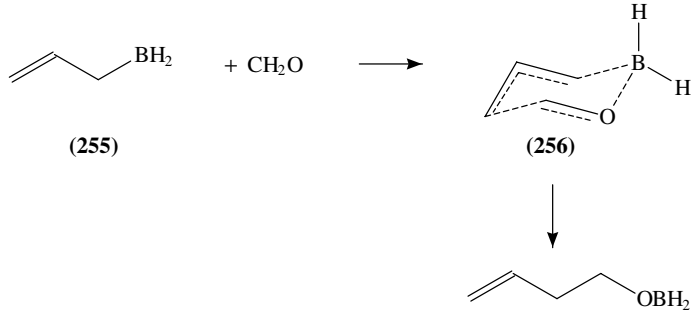
(254)

The reaction of substituted vinylferrocenes with chloromethyl alkyl ethers catalysed by Lewis acids proceeds via an '*exo*' attack to furnish stabilized ferrocenylcarbocations (analogous to benzyl), which are captured by a nucleophile, again in an '*exo*' fashion. As a result, the whole sequence occurs predominantly with retention of configuration[389].

Activated olefins (enol ethers and styrene) smoothly react with acetals in the presence of catalytic amounts of Me_3SiCl and $SnCl_2$ or Ph_3CCl and $(CF_3SO_3)_2Sn$ to produce the corresponding adducts[390].

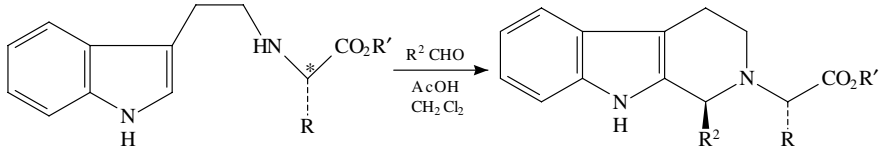
Transition state structures (chair and twist-boat) for the reaction of formaldehyde with allylborane **(255)** and allylboronic acid have been located with *ab initio* calculations at the

3-21G and 6-31G* bases. The chair-like structure of the transition state **(256)** is predicted to be 8 kcal mol^{-1} more stable than the twist-boat[391].



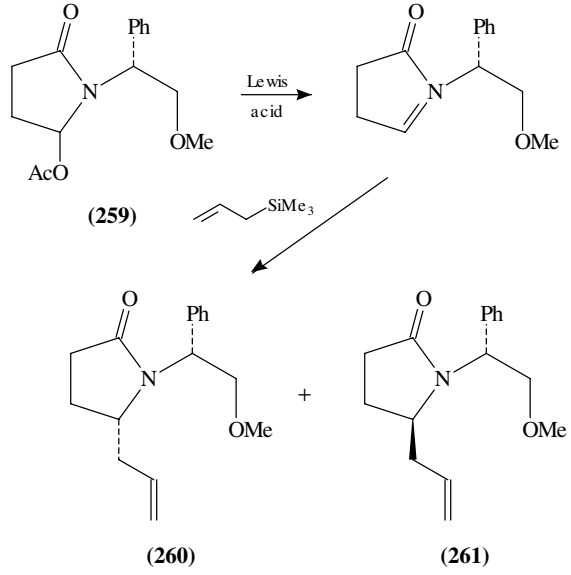
(255) **(256)**

The Pictet–Spengler cyclization of iminium salts, generated *in situ* from *N*-(β-3-indolyl)ethyl substituted amino acid esters **257** and various aldehydes, has been found to proceed with high stereoselectivity (up to 98.5:1.5)[392].



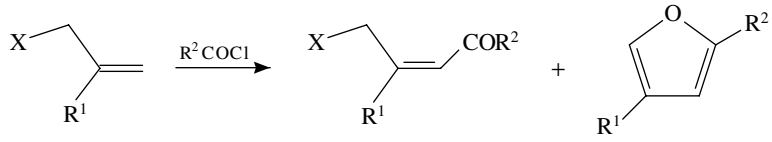
(257) **(258)**

Diastereofacial selectivity in the α-allylation of cyclic α-acyloxy amides **259** derived from succinic or phthalic anhydride can be controlled by the Lewis acid. Thus, while $TiCl_4$ gives **260**, allylation promoted by $SnCl_4$ affords **261**[393]. No rationalization has been offered.



(259) **(260)** **(261)**

Acylation of allylic halides **262** (X = Cl, Br; R^1 = H, Me) by R^2COCl (R = alkyl, cycloalkyl, chlorocycloalkyl etc.) results in formation of (*E*)-acylated products **263** and furans **264** stereoselectively[394].



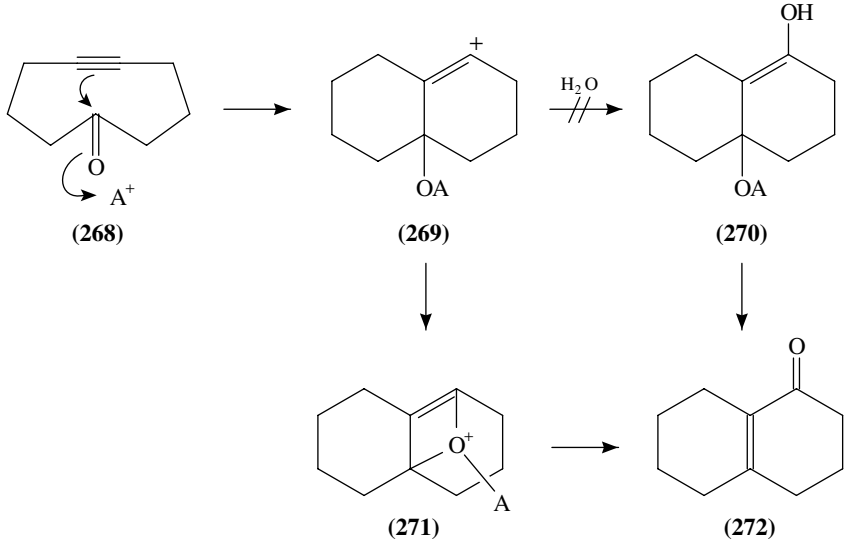
(262) **(263)** **(264)**

The kinetics of trifluoroacetylation of $ArSCH{=}CH_2$ **(265)**, $ArSCH{=}CD_2$, *cis*-ArSCH=CHD and *trans*-ARSCH=CHD with $(CF_3CO)_2O$ imply a mechanism involving slow addition **265** → **266** followed by fast deprotonation **266** → **267**[395].

(265) **(266)** **(267)**

C. Biomimetic Cyclizations and Related Processes

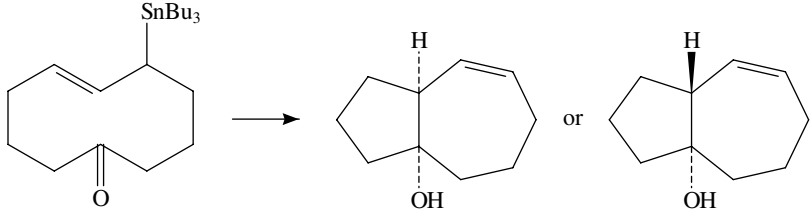
A previously proposed mechanism for the acid-catalysed cyclization of 5-cyclodecynone **(268)** to **272** that involved hydration of the intermediate vinyl cation (**269** → **270**) has now been ruled out, since no significant incorporation of ^{18}O could be observed when the reaction was carried out in $H_2{}^{18}O$. Instead, a new mechanism has been proposed, involving the cyclization of **269** to **271** followed by fragmentation of the C−O bond[396].



(268) **(269)** **(270)** **(271)** **(272)**

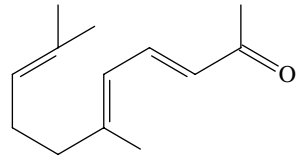
Stereochemistry of the related cyclization of **273** can now be controlled by the choice of reagent to produce either *cis*- or *trans*-fused hydroazulenol **274** or **275**. Thus, the use of fluoride anion or sodium naphthalenide results in the exclusive formation of the *cis*-derivative **274**, while heating in benzene leads to the *trans*-fused **275**. Lewis or Brønsted

acids give *cis/trans* mixtures, with the *cis*-isomer **274** being the major product[397].



(273) **(274)** **(275)**

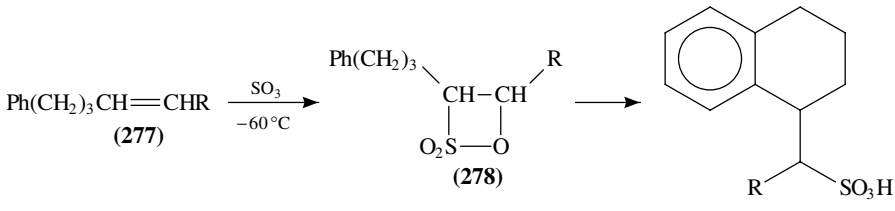
Cationic cyclization of trienone **276** can be controlled by the choice of the reagent. Thus, fluorosulphonic acid in 2-nitropropane at $-70\,^{\circ}C$ afforded a 14:9:1 mixture (70% yield) of cyclic products[398], whereas other acidic conditions (95% H_2SO_4, 85% H_3PO_4 or $SnCl_4$) gave inferior results[398,399].



(276)

Molecular mechanics calculations, carried out in order to explain the regio- and stereo-chemistry of the transannular cyclization reactions of 19-nor-5,10-secosteroidal cyclodecenone systems, correlate well with experiments[400].

Friedel-Crafts cyclization products have been observed for the reaction of **277** with SO_3 in the presence of dioxane as a mediator. The reaction has been shown to occur via β-sultone **278**, initially formed at $-60\,^{\circ}C$, which undergoes a spontaneous conversion to the final product **279** at $> -20\,^{\circ}C$[401].

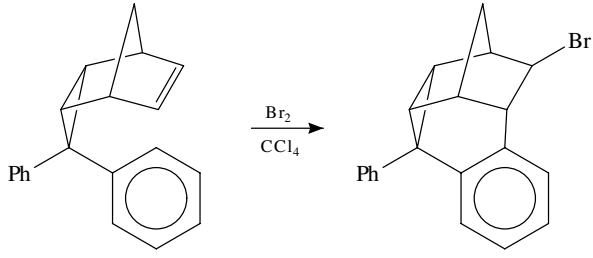


(277) **(278)** **(279)**

π-Aryl participation in bromination of a norbornene derivative has been reported (**194** $\rightarrow$ **280**). Acid opening of the corresponding *exo*-epoxide proceeds in a similar way[402].

Competition of the biomimetic cyclization of epoxides, either with an aromatic ring or with a double bond, has been studied. Evidence for an early transition state has been provided and the biosynthetic implications discussed[403].

The biomitetic polyene cyclizations pioneered by Johnson have culminated in stabilizing the cation[404,405] and extension to the syntheses of pentacyclic triterpenoids in one step from an acyclic precursor(!)[406–409]. Johnson summarized his 50 years of research in a review[410].



(194) **(280)** 33%

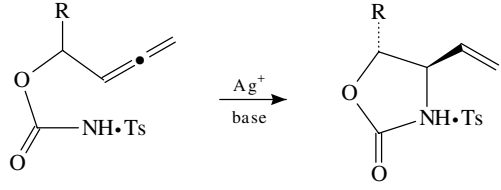
Imminium ion-vinylsilane cyclizations[20], which also belong to this category, are beyond the scope of this chapter.

VIII. ELECTROPHILIC METALS AND ORGANOMETALLICS

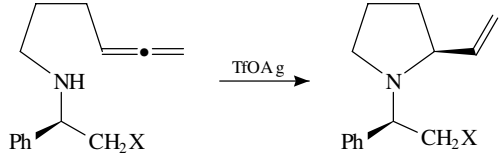
A. Silver

Correlation of ionization potentials with reactivities or formation constants of reactions of alkenes with ArSCl, $MeCO_3H$, Ag^+ and Hg^{2+} revealed that additions whose first step is rate-determining are sterically independent, while those with the second step rate-determining are sterically dependent[411].

In analogy with reactions of amines and amides, allenic tosyl carbamates **281** can also be cyclized on action of Ag(I) to afford predominantly or exclusively *trans*-products **282**[412]. High level of diastereoselectivity (82–99% d.e.) has been reported for the silver(I)-catalysed cyclization of allenic amines **283** (X = CO_2Me, CH_2OH, CONHMe, SPh S(O)Ph, SePh, PPh_2) to give the corresponding 2-vinylpyrrolidine **284**. The highest stereoselectivity has been observed in CH_2Cl_2[413,414].



(281) **(282)**

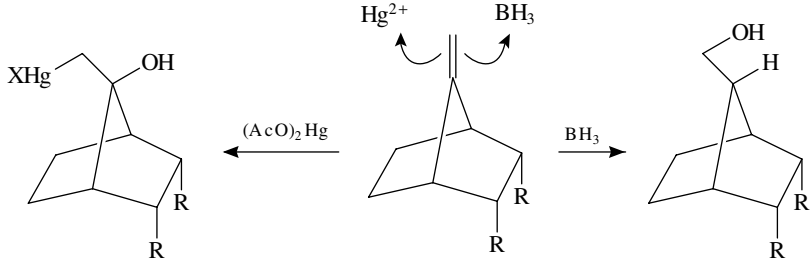


(283) **(284)**

B. Mercury

The PM3 and *ab initio* calculations have been employed to compare mercuronium and bromonium ions **55** and **52**[111]. Experimental comparison of the mechanism of the oxymercuration and bromination has also been made (see the section on bromination)[142].

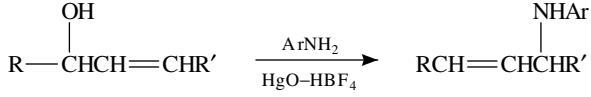
PMB calculations indicate that π-facial diastereoselection in the reaction of 2,3-*endo*-disubstituted 7-methylenenorbornanes **285** with electrophiles such as $(AcO)_2Hg$ or I^+ is determined by electrostatic asymmetry, favouring the electron-richer *anti*-facial attack **285** → **286** (with R = F or CO_2Me)[415]. In contrast, hydroboration is controlled by orbital interactions giving the *syn*-addition product **287**[415]. This is an alternative interpretation of the experimental results reported previously[30].



(286) **(285)** **(287)**

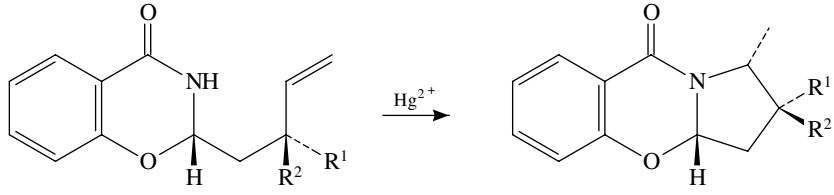
The stereochemistry of addition of Hg^{2+}, RCO_3H and other electrophiles to methylene cyclohexane appears to be controlled stereoelectronically rather than by ordinary steric effects[416].

A catalytic amount of $Hg(BF_4)_2$ facilitates the tandem aminomercuration–deoxymercuration of allylic alcohols by arylamines (**288** → **289**)[418].

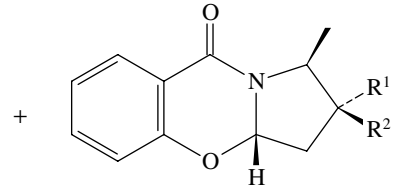


(288) **(289)**

The stereodirecting effect of the allylic alkoxy-substituent **(290–292)** on cycloamidomercuration has been found to be surprisingly high (>4 kcal mol^{-1})[419].

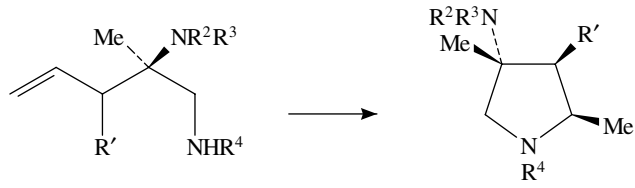


(290) $R^1 = R^2 = H$	12.4	:	1
(291) $R^1 = OBn$, $R^2 = H$	> 50	:	1
(292) $R^1 = H$, $R^2 = OBn$	< 1	:	50

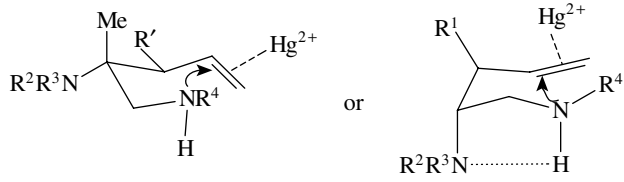


The intramolecular amino- and amido-mercuration of δ-unsaturated-β-amino-amines and carbamates **293** have been found to afford the corresponding 3-aminopyrrolidines

294 in good yields (70–85%) and with high stereoselectivity (⩾95%), which is believed to originate from the favoured, chair-like transition structures **295** or **296**[419].

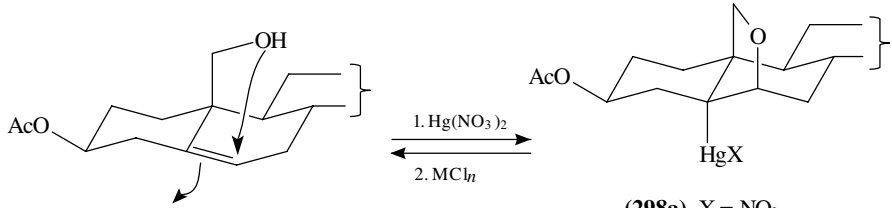


(293) **(294)**



(295) **(296)**

Oxymercuration products having an antiperiplanar arrangement of the C−HgX and C−O bonds (e.g. diaxial as in **298a**) are particularly prone to reversion to the olefin **(297)** when treated with hard reagents, such as NaCl, KBr, $CuCl_2$, $CoCl_2$, HCl etc. The reversal is apparently boosted by the stereoelectronic effect and electrophilic catalysis. By contrast, quenching of the primarily formed organomercurial **298a** with soft reagents, such as CuCl, $PdCl_2$, K_2PtCl_4 etc, reliably affords the desired chloromercurio compound **298b**[420].

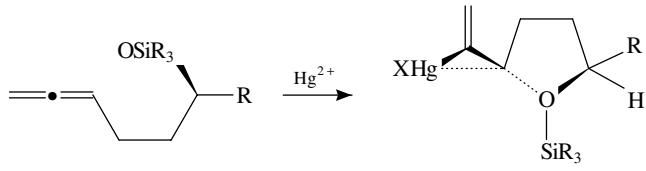


(297)

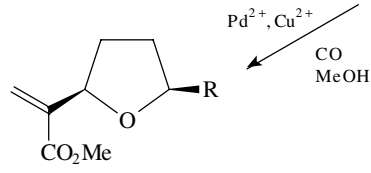
(298a) X = NO_3
(298b) X = Cl

Intramolecular oxymercuration of allene **299** followed by Pd(II)-catalysed carboxymethylation has been found to proceed with excellent *cis/trans* selectivity (>98:2), presumably via the least hindered transition state **300**[421].

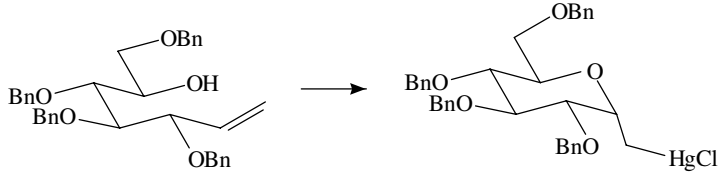
The previously observed[422] preference for the formation of the axial isomer **303** upon mercuration of **302** has now been shown[423] not to originate solely from the coordination of Hg(II) by the adjacent ether oxygen. The latter effect appears to be superimposed upon a kinetic preference for the axial product, which is independent of any directing effect. The authors argued that this behaviour may, presumably, originate from an anomeric effect; some inconsistencies in the literature may be attributed to equilibration of the kinetic products. The authors conclude that experiments carried out under kinetic control should preferentially lead to axial isomers[423].



(299) **(300)**



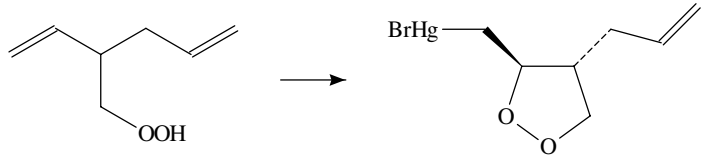
(301)



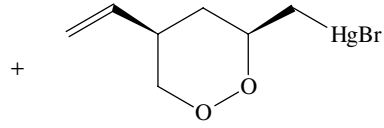
(302) **(303)**

Mercury(II) and other electrophilic reagents for the biomimetic cyclization of 1,5-dienes (e.g. geranylacetone) have been classified in four groups: (1) Lewis acids, such as $SnCl_4$, $SnBr_4$, $(CF_3CO_2)_2Sn$, $BF_3.Et_2O$ etc; (2) bromonium ions; (3) mercurinium ions; (4) phenylselenonium ions. The effect of the choice of reagent upon the stereoselectivity has been discussed[424].

Polar cyclization of diene hydroperoxide **304** has been successfully effected by $Hg(NO_3)_2$ to produce a 2:1 mixture of 1,2-dioxolane **305** and 1,2-dioxane **306**. In contrast, a radical cyclization with $(Bu^tOOCO)_2$ and O_2 or *N*-iodosuccinimide, respectively, is more selective giving only one 1,2-dioxane[425].



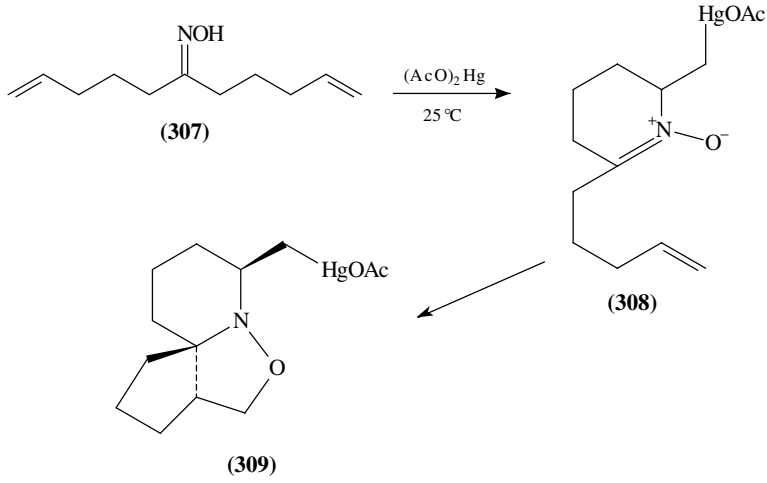
(304) **(305)**



(306)

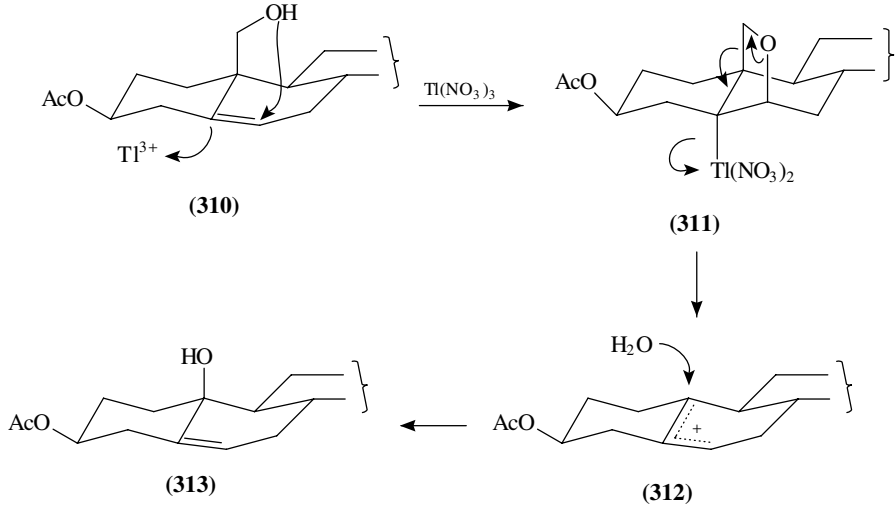
The oxime nitrogen in **307** has been employed as an internal nucleophile in mercuration of a double bond to generate nitrone **308**, which instantaneously underwent the dipolar

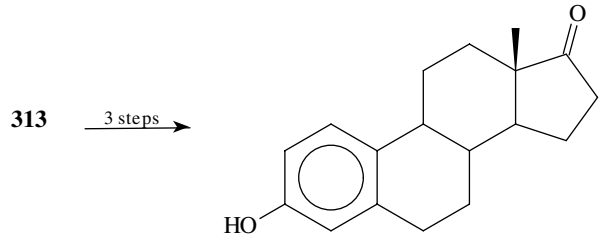
[3 + 2] addition across the other double bond present in the molecule (**308** → **309**)[286]. Analogous reaction has been observed with PhSeX[285].



C. Thallium

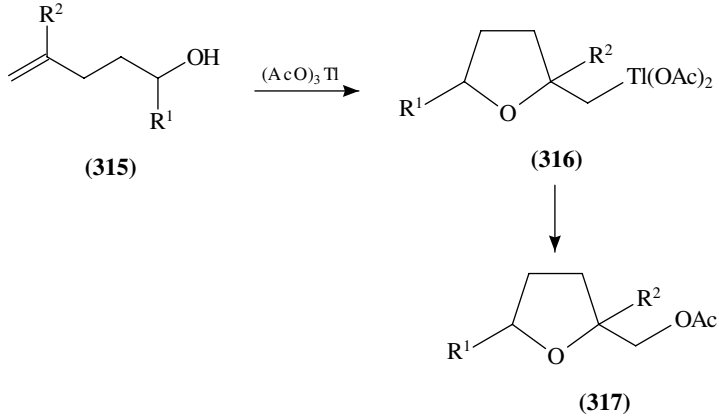
A thallium-mediated, one-carbon degradation of the steroid alcohol **310** has been described. This unusual reaction is believed to proceed via an initial electrophilic ring-closure to **311**, followed by a stereoelectronically controlled fragmentation **311** → **312**, to give 19-nor-derivative **313** as the final product[198]. Interestingly, the same 5(O)^n-*endo-Trig* cyclization is known for the isoelectronic mercury(II) ion (as well as for a range of other electrophiles), but the corresponding organomercurial is stable (*vide supra*)[420,426]. The fragmentation reaction has been employed as the key step in a concise synthesis of estrone **314**[427,428].





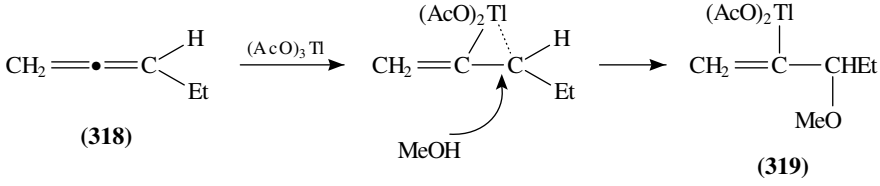
(314)

Intramolecular, thallium(III)-mediated cyclization of unsaturated alcohols **315** has been studied and, in certain instances, the organothalliated primary products **316** isolated and characterized by ^{1}H NMR[429]. The subsequent displacement of $Tl(OAc)_2$ in **316** by OAc has been interpreted as proceeding via S_N2 or S_Ni pathway. However, in light of the previously reported evidence[430,431] the reviewer is of the opinion that involvement of the neighbouring ether oxygen as a participating group is more likely.



(315) **(316)** **(317)**

Methoxythallation of allenes, such as **318**, has been found to occur at the more substituted double bond, and to be far more regioselective than methoxymercuration, giving predominantly the product with $(AcO)_2Tl$ attached to the central carbon **319**[432].



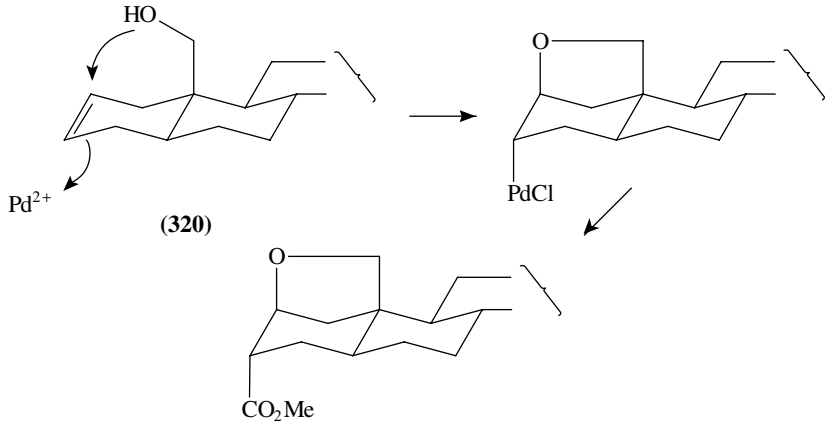
(318) **(319)**

D. Lead

Lead(IV) in acidic media has been found to promote oxidative addition of Cl^-, $CF_3CO_2^-$, AcO^-, $MeSO_3^-$ and ClO_4^- to cyclohexene, 1-hexene and styrene[433]. Sonochemical switching from ionic to radical pathway in the reactions of styrene and *trans*-β-methylstyrene with $(AcO)_4Pb$ has been observed[434].

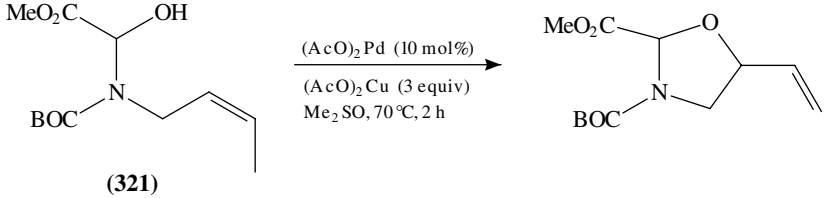
E. Palladium

An improved procedure for cyclopalladation-carbonylation (of e.g. **320**) relies on the addition of CuCl and LiCl to the standard $PdCl_2-CuCl_2$ mixture. This indicates that both the Cu^{2+} and Cu^{+} are required in sufficient concentrations to keep up the cascade of the catalytic cycle. This method is superior to the Hg(II)-mediated cyclization followed by transmetallation with Pd in CO/MeOH[197]. For application in the synthesis of polyether antibiotics, see elsewhere[435].



(320)

Methyl glyoxylate adducts of N-BOC-protected allylic amines **321** have been utilized to construct a new C−O bond by an intramolecular, Pd(II)-catalysed reaction[436]. In analogy, lactones **324a**[437] and cyclic ethers **324b**[438] can be prepared by the Pd(II)-catalysed cyclization of the suitable precursors **322a** and **322b**, respectively.



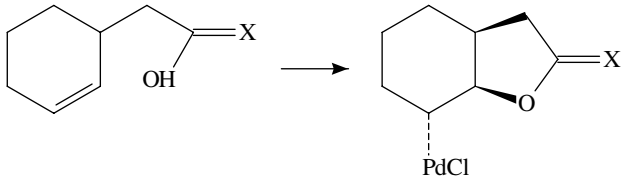
(321)

N-Tosyl carbamates, such as **325**, derived from allylic alcohols, undergo the Pd(II)-catalysed cyclization to furnish oxazolidinones **326** under 1 atm of CO[439]. Analogous Pd(II)-catalysed N-cyclization of allenic N-tosylcarbamates has generated the corresponding vinylpalladium intermediate that could be further alkylated[440].

The Pd(II)-catalysed cyclization of **283** exhibits lower stereoselectivity ($\leqslant$43% d.e.) than its Ag(I)-mediated counterpart (up to 81% d.e.)[413]. A Pd(II)-catalysed 5-*endo-Trig* cyclization of 2-hydroxybut-3-enylamines **327** has been reported to occur with moderate to good yields. The OH group is essential for the cyclization[441].

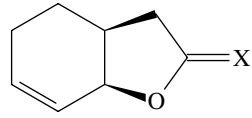
A stereospecific, Pd-catalysed, 5-*exo-Trig* ring closure reaction of **328** has been reported[442,443].

The regioselectivity of the Pd(II)-catalysed hydrocarboxylation of styrene has been elucidated and two different mechanisms have been suggested to account for the differences

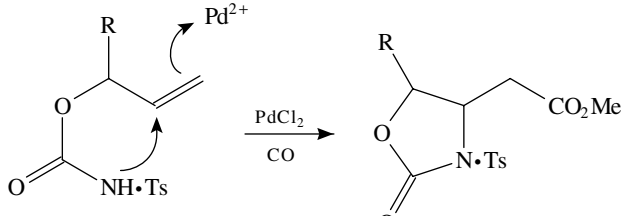


(322a) X = O
(322b) X = H_2

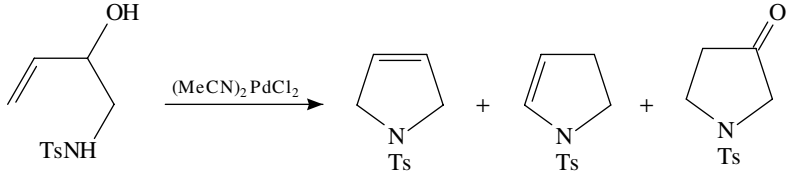
(323)



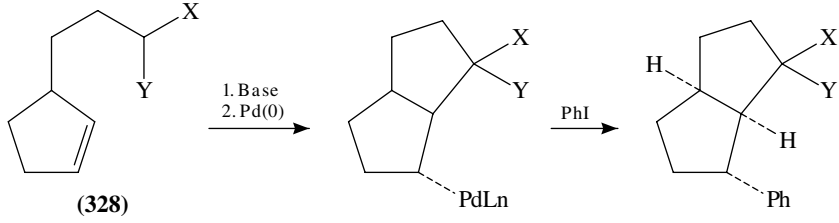
(324a) X = O
(324b) X = H_2



(325) **(326)**



(327)



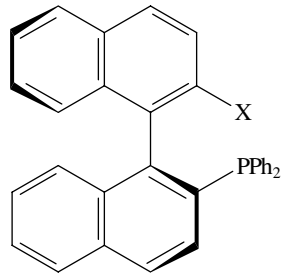
(328)

in activation energy for the formation of the isomeric products $PhCH_2CH_2CO_2H$ and $PhCH(Me)CO_2H$[444].

The DIOP complex of Pd(0) and ethylene, i.e. (DIOP)Pd(C_2H_4), has been found to induce up to 40% e.e. in asymmetric hydrocyanation of norbornene[445]. This complex also

reacts with other alkenes having a low-lying LUMO (e.g. tetracyanoethylene and carvone) while no reaction occurs with cyclopentene and cyclohexene. Detailed examination of the reaction course by NMR led to the formulation of the mechanism, which includes the formation of (DIOP)Pd(H)CN as an intermediate, followed by the rate-limiting reaction of the latter complex with norbornene[445].

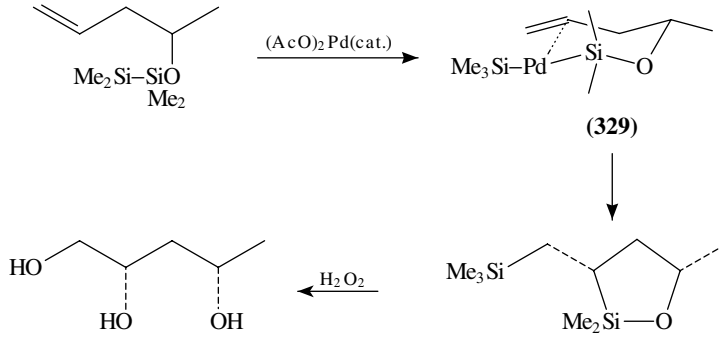
Catalytic asymmetric hydrosilylation of terminal olefins has been developed, using palladium coordinated to the novel binaphthyl ligands **(MOP)**. In all cases **(MOPa–d)**, the enantioselectivity is excellent (⩾90% e.e.). The products can be converted into the corresponding secondary alcohols with retention of configuration[446].



(a) X = OMe
(b) X = OPr^i
(c) X = OCH_2Ph
(d) X = Et

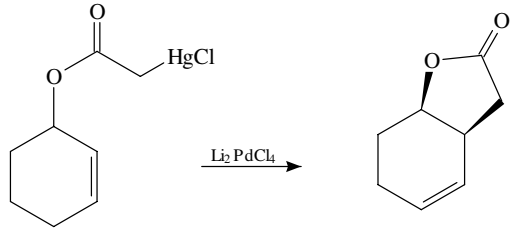
(MOP)

Intramolecular, Pd(II)-catalysed bis-silylation of a C=C bond proved to be highly stereoselective[447]. The reaction is believed to proceed via a chair-like transition state **329**; the product **330** can be oxidized to triol **331**[447].



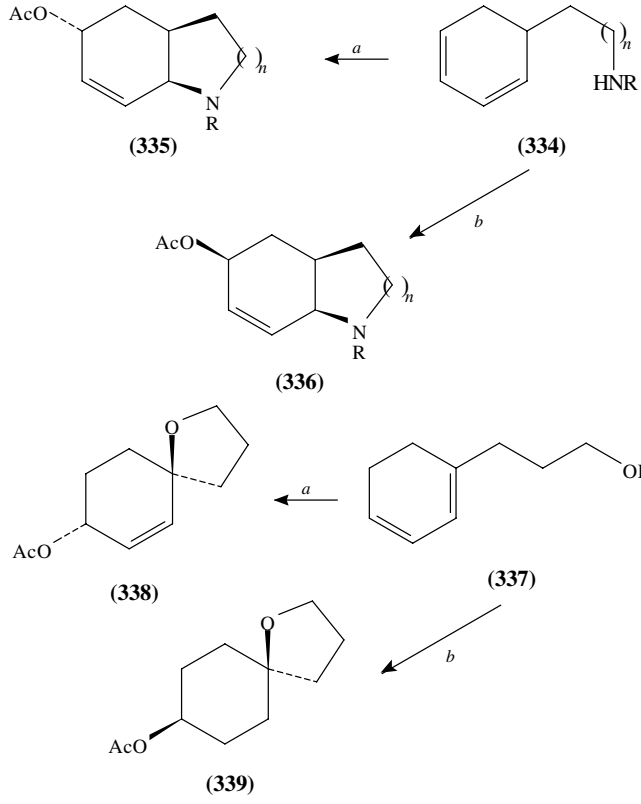
The Heck reaction has now been reviewed[448,449]. Evidence for the formation of zerovalent palladium from $(AcO)_2Pd$ and Ph_3P via a redox process has been provided[450]. This explains the origin of Pd(0) required for certain palladium-catalysed reactions in cases where Pd(II) is added to the reaction as the primary form of the Pd-catalyst. Thallium(I) has been found to accelerate the Heck-type cyclization-carbonylation[451].

Intramolecular Heck reaction of organomercurial **332** has been used to prepare unsaturated lactone **333** by a non-traditional strategy[452]. Sequential, regiospecific C−C and C−N bond-forming reactions via a novel Heck-type coupling have been developed[453].



(332) **(333)**

The rate of the palladium-catalysed Heck-type phenylation of allylic alcohols has been found to be markedly enhanced by addition of tertiary amines[454]. Regioselectivity can be increased, in some cases, by adding Et_4NCl or employing a Wilkinson Rh catalyst (rather than Pd)[455,456]. Another Heck-type reaction involves addition of arenediazonium tetrafluoroborates to α-silylstyrenes to give (*E*)-PhCH=CHAr. A BF_4^--mediated *syn*-elimination of silicon and palladium has been suggested to account for the stereochemistry[457].



(335) **(334)** **(336)** **(338)** **(337)** **(339)**

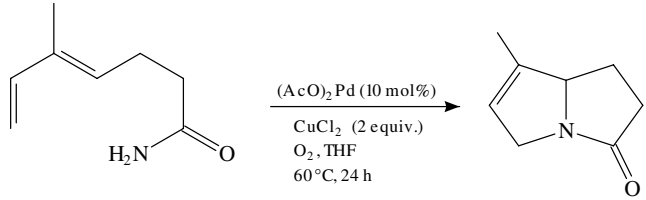
(*a*) $(AcO)_2Pd$, *p*-BQ, AcOH, Me_2CO, AcOLi
(*b*) $(AcO)_2Pd$, *p*-BQ, AcOH, Me_2CO, AcOLi, LiCl
R = Ts, COMe, CO_2Bn, CONHBn

SCHEME 9

Conjugate addition of H_2O, ROH or AcOH to enones and enone enolates can be catalysed by $(MeCN)_2\,PdCl_2$[458,459]. Palladium-catalysed addition of stabilized C-nucleophiles, such as $RCH(CN)_2$ to allenes, has been reported. The reaction proceeds under essentially neutral conditions regio- and, in some instances, stereo-selectively[460].

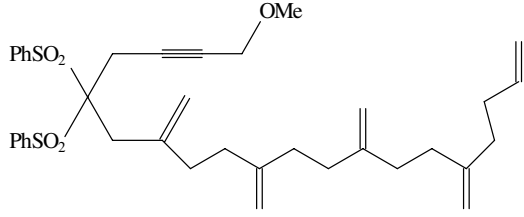
The Pd(II)-catalysed 1,4-oxidation of dienes (Bäckvall reaction) has been extended to the introduction of one oxygen and one nitrogen nucleophile (**334** → **335** or **336**)[461]. This methodology also allows the annulation of tetrahydrofurans, tetrahydropyrans, lactones[462] and spirocycles (e.g. **337** → **338** + **339**)[463,464]. The previously developed dual stereocontrol by adding or omitting LiCl[465,466] has been demonstrated again in all these transformations (Scheme 9).

A novel, intramolecular variant of the Bäckvall oxidation has been developed, which allows one to employ the same nucleophile (NH_2 group) twice, resulting in an overall [4 + 1] annulation, as exemplified by the synthesis of pyrolizidine skeleton (**340** → **341**). In this case, $CuCl_2/O_2$ proved to be superior to *p*-benzoquinone in regeneration of Pd(II). Also, the change of solvent from AcOH to THF had a beneficial effect[467].



(340) **(341)**

Palladium(0)-catalysed coupling of non-conjugated dienes, aryl iodides and stabilized carbon nucleophiles has been developed[468]. An incredibly high yield (86%) of pentacycle **343** has been obtained from a Pd(0)-catalysed zipper reaction of acetylenic pentaene **342**. The reaction is triggered off by a Pd-catalysed cyclization of acetylenic bond and the first olefinic bond[469].



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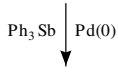
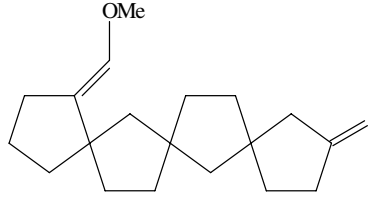
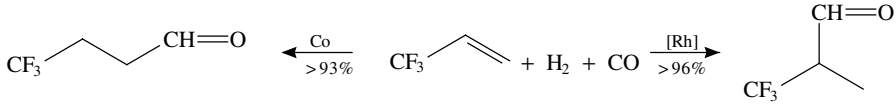




(343)

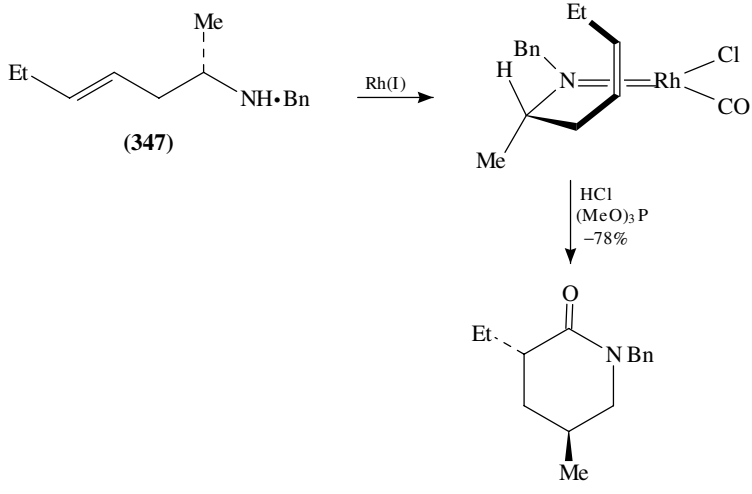
F. Rhodium

Extremely high regioselectivity has been observed for hydroformylation of fluoroolefins $R_fCH{=}CH_2$, catalysed by group VIII transition metals. While a Co catalyst gives the normal product **345** on hydroformylation of **344**, a Rh catalyst gives mostly the isomeric aldehyde **346**[470]. In another study, hydroformylation of 1-hexene was catalysed by rhodium(I) with concomitant isomerization[471].



(345) **(344)** **(346)**

The kinetics of the $Rh_4(CO)_{12}$-catalysed hydroformylation of 2-butenes are consistent with a mechanism involving fragmentation of the catalyst to the active mono- and non-active bi-nuclear Rh-complexes. Interaction of the monomeric $HRh(CO)_3$ with alkene appears to be the rate-limiting step. Binuclear Rh-complexes, predominating in the reaction mixture, serve as a reserve for the active monomeric complexes[472]. Amine-directed, Rh(I)-mediated hydrocarbonylation has been reported (**347** → **348**)[473].



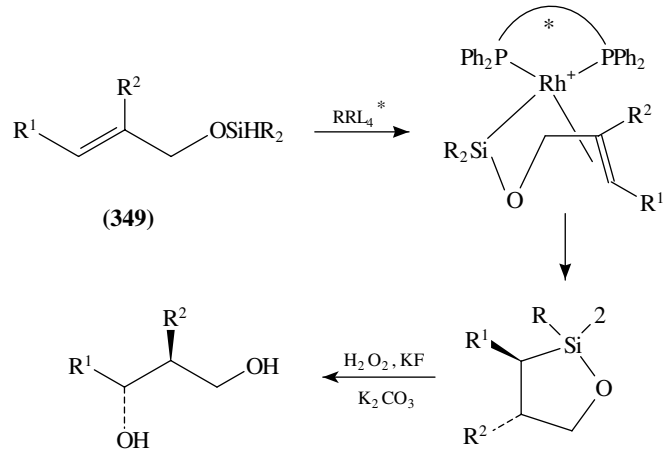
(347) **(348)**

Asymmetric, intramolecular hydrosilylation, catalysed by Rh(I) coordinated to chiral diphosphine complexes, such as chiraphos or BINAP, has been reported to give up to ⩾99% e.e. (**349** → **350**)[474–476].

The efficiency of the tail-to-tail dimerization of methyl acrylate has been further improved, based on a detailed study of the role of the Rh(III)-catalyst, the resting state and the mechanism of the catalyst deactivation[477].

G. Osmium

The systematic study of the origins of high enantioselectivity in the osmium-catalysed dihydroxylation carried out by the Sharpless group has led to defining certain crucial features and ruled out other mechanistic proposals[478–481]. Thus, the dihydroxylation has been



found to be first-order in OsO_4, which rules out the μ-oxo-bridged bis-OsO_4 complex, proposed by Corey[482,483], as a reactive species[478]. The results have also suggested that OsO_4 is coordinated to one nitrogen of the quinuclidine unit, while the role of the second alkaloid group is to create a chiral pocket[478]. Sharpless has proposed a C_2-like symmetrical cavity, created by the quinoline rings, into which olefin is sucked to be dihydroxylated[479,483]. The actual roles of the individual groups of the ligand are summarized in Figure 2[479].

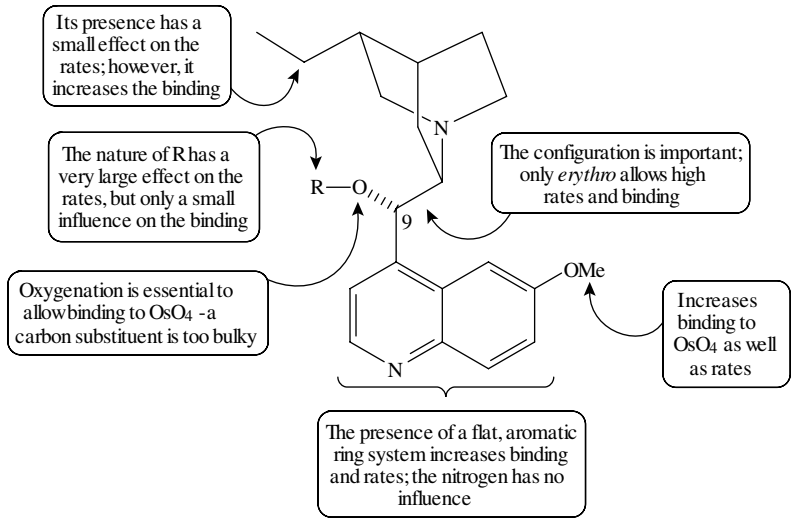


FIGURE 2. Relationship between ligand structure and K_{eq} and ceiling rate constants. The alkaloid core is ideally set up to ensure high rates, binding and solubility. The rates are influenced considerably by the nature of the O9 substituent, while the binding to OsO_4 is almost independent of that substituent. Reprinted with permission from H. C. Kolb, P. G. Andersson and K. B. Sharpless, *J. Am. Chem. Soc.*, **116**, 1278 (1994). Copyright (1994) American Chemical Society

The results further revealed that the saturation rate constants (k_c) are influenced principally by the nature of the O-9 substituent of the cinchona analogues studied, especially if aromatic substrates are used. The observed trends in binding constants (K_{eq}) for OsO_4 and the test ligands show that K_{eq} can be regarded as an approximate measure of the steric hindrance in the vicinity of the ligand-binding site. The binding constants and the saturation rate constants k_c are not correlated, which indicates that the observed rate variations are apparently not caused by variations in ground-state energy due to steric interactions. The rate data have been interpreted in terms of a relative stabilization of the transition state in the case of 'fast' ligands. It has been approximated that a transition-state stabilization may result from stacking of the olefin and ligand substituents; this is consistent with the fact that flat aromatic substrates give much higher rate constants than aliphatic ones. Further support for this hypothesis has been obtained from the solvent effect and Hammett studies, as well as from X-ray data, molecular modelling and NOE experiments on osmium complexes (Figure 3). Phthalazine ligand **351** gives exceptionally high rate

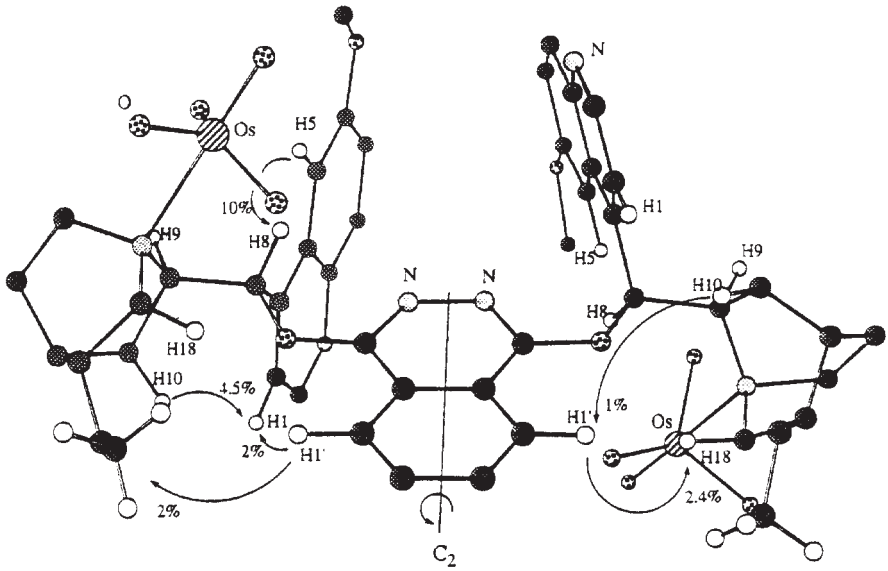
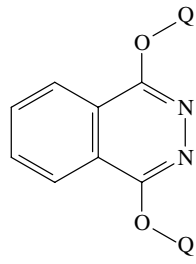


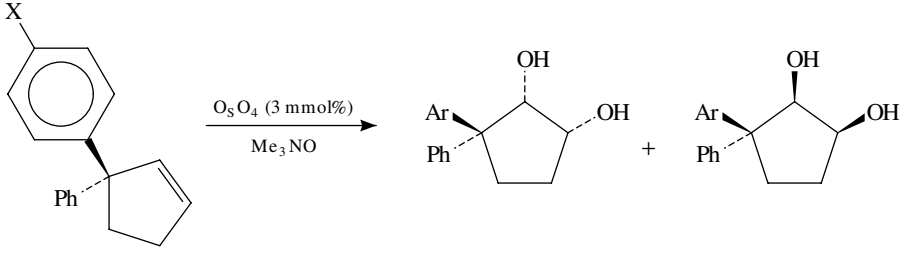
FIGURE 3. Structure of the bis-OsO_4 complex of $(DHQD)_2PHAL$ based on molecular mechanics calculations and NOE experiments. Reprinted with permission from H. C. Kolb, P. G. Andersson and K. B. Sharpless, *J. Am. Chem. Soc.*, **116**, 1278 (1994). Copyright (1994) American Chemical Society



(351)

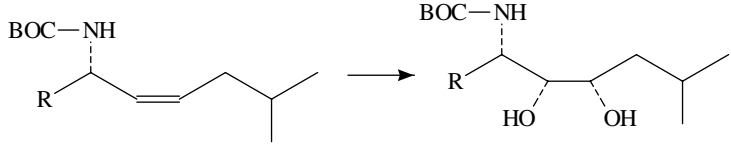
constants with aromatic substrates. This effect can be attributed to a 'binding pocket' created by the phthalazine and methoxyquinoline moieties of the ligand, which enables a particularly good transition-state stabilization for aromatic olefins. The enantioselectivity trends have been found to parallel the rate trends[480]. However, the old question whether the osmylation proceeds via an initial [3 + 2] or [2 + 2] addition remains unsolved as the kinetic experiments cannot differentiate between these two pathways.

Strong evidence for the stereoelectronic control of diastereoselectivity in the catalytic osmylation has been provided by the study of the reactivity of sterically unbiased 3(*p*-X-phenyl)-3-phenylcyclopentenes **352** (X = NO_2, Br, Cl, OMe, NMe_2)[484]. Diastereoisomeric diols **353** and **354** are formed in the ratio varying from 30:70 (for X = NO_2) to 64:36 (for X = NMe_2), as determined by ^1H and ^{13}C NMR spectroscopy. In all cases, the addition occurs predominantly opposite the more electron-rich aromatic ring[484] as predicted by Cieplak's theory[33]. The observed ratios correspond to an overall energy difference of 1.1 kcal mol^{-1}[484].

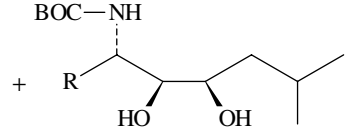


(352) **(353)** **(354)**

The diastereoselectivity of dihydroxylation of allylic amides and carbamates **355** has been found to be dependent on the solvent, the nitrogen protecting group and the substitution pattern of the substrate[485]. In contrast to the '*erythro*' **357** selectivity observed with allylic alcohols, amides and carbamates exhibit '*threo*' **356** selectivity. Stoichiometric osmylations have been found to be more selective than their catalytic cousins. Control experiments have suggested that this is due to the presence of a second catalytic cycle involving osmium glycolate catalyst, which accumulates as the reaction proceeds to completion[485].



(355) **(356)**



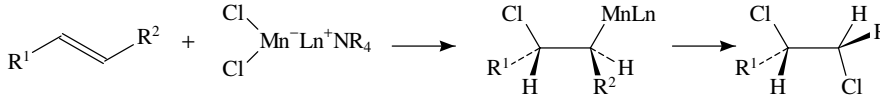
(357)

A stoichiometric procedure for the osmium-mediated, enantioselective aminohydroxylation of *trans*-alkenes RCH=CHR (R = Ph, Et, Pr^i) has been developed employing chiral complexes between *tert*-butylimidoosmium ($Bu^tN{=}OsO_3$) and derivatives of *cinchona* alkaloids. The success of the reaction is dependent on a ligand acceleration effect; corresponding diols are the by-products. The e.e. varies between 40 and 90%[486,487].

H. Other Transition Metals

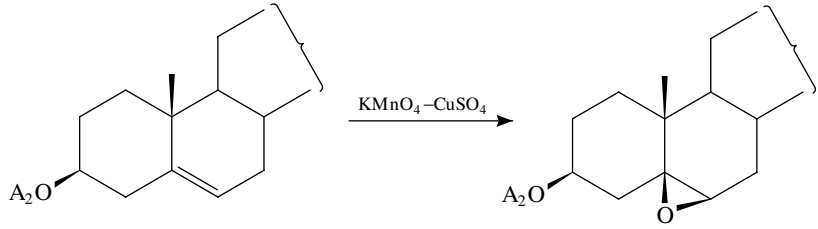
Tungsten η^4-diene cations in both s-*trans* and s-*cis* forms have been synthesized and the influence of the diene conformation on the regiochemistry of nucleophilic attack has been demonstrated[488]. Application of nucleophilic additions to Mo-complexed olefins in the construction of quaternary carbon centres has been summarized[489].

Oxalyl chloride has been reported to react with R_4NMnO_4 to form a chlorine-containing manganese reagent (possibly **358**), that stereospecifically *trans*-dichlorinates olefins[490]. Primary *syn*-addition of the reagent across the double bond to form **359** is assumed, followed by S_N2 displacement of Mn by chloride **359** → **360**[490]. This reaction closely parallels a stereospecific dichlorination effected by means of MnO_2–Me_3SiCl for which a non-radical mechanism has also been proposed[491].



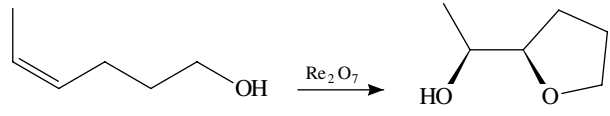
(358) **(359)** **(360)**

Under controlled conditions, the $KMnO_4/CuSO_4$ mixture oxidizes cholesterol **361** to furnish the β-epoxide **362** rather than the α-epoxide, which is normally formed by peroxy acids[492].



(361) **(362)**

5-Hydroxyalkenes **363** have been found to react with Re_2O_7 to produce moderate yields of hydroxymethyl tetrahydrofurans **364** with overall *syn*-stereoselectivity[493].



(363) **(364)**

Ferric complexes $(Et_3NH)Fe^{III}(bpb)X_2$ (X = Cl, OTf) catalyse the epoxidation of olefins by PhIO[494]. Analysis of the by-products led the authors to the formulation of a

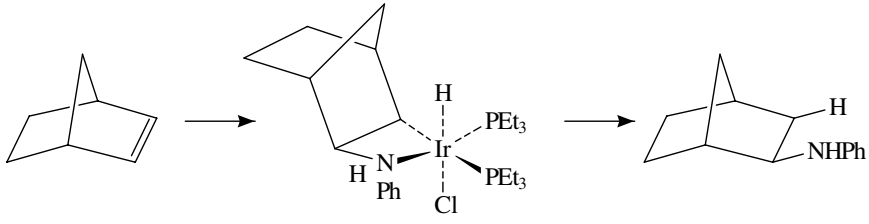
mechanism which involves electrophilic attack on the olefin by the iodine(III) centre in a metal–iodosylbenzene complex. Additional evidence in support of this mechanism was gained from the reaction of $PhI(OAc)_2$ with norbornene or norbornenecarboxylic acid in different solvents[494].

Substitution of one carbonyl by Ph_3P in (diene)$Fe(CO)_3$ complexes results in a change of regiospecificity of electrophilic attack and thus provides an easier access to [(allyl)FeL_4]X salts. Similar Ph_3P substitution in [(dienyl)$Fe(CO)_3$]X complexes decreased reactivity towards nucleophiles[495].

The electrophilic Co(III) complex $\{Cp^*[(MeO)_3P]CoCH_2CH_2\text{-}\mu\text{-}H\}^+BAr_4^-$ [Ar = 3,5-$(CF_3)_2C_6H_3$] has been shown to be an efficient catalyst for the regiospecific hydrosilylation of 1-hexene; $\{Cp^*[(MeO)_3P]CoCH(Bu)CH(SiEt_3)\text{-}\mu\text{-}H\}^+$ has been identified as the catalyst resting state by spectral methods[496]. The ω-alkenyl side-chain in the Co^{II}(salen)-type derivatives reacts with O_2 and MeOH to give products with new Co–C bonds. The reaction is believed to be initiated by electrophilic attack of Co at the C=C bond[497]. Cobalt(II)(salen)$_2$-catalysed aerobic hydration of styrene[57] has been described in Section II.A.

Tailoring of the chiral ligand resulted in the high enantioselection of the nickel-catalysed hydrocyanation of β-vinylnaphthalene[473].

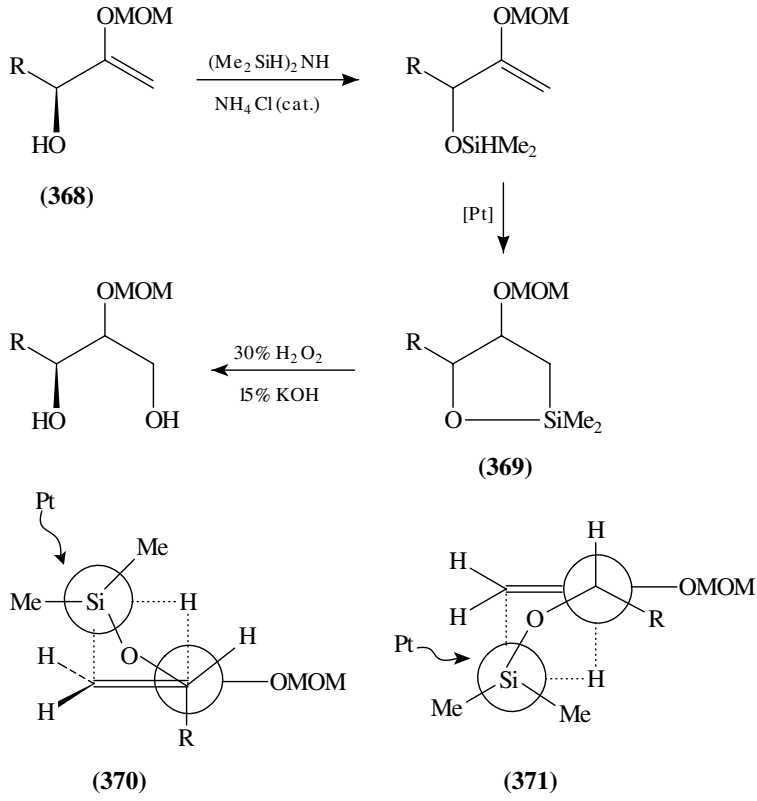
The first successful catalytic amination of an olefin by transition-metal-catalysed N–H activation was reported for an Ir(I) catalyst and the substrates aniline and norbornene **365**[498]. The reaction involves initial N–H oxidative addition and olefin insertion **365** → **366**, followed by C–H reductive elimination, yielding the amination product **367**. Labelling studies indicated an overall *syn*-addition of N–H across the *exo*-face of the norbornene double bond[498]. In a related study, the amination of non-activated olefins was catalysed by lithium amides and rhodium complexes[499]. The results suggest different mechanisms, probably with β-aminoethyl–metal species as intermediates.



(365) **(366)** **(367)**

A highly stereoselective method of anti-Markovnikov hydration[500] relies on the intramolecular hydrosilylation of α-hydroxy enol ethers **368** catalysed by platinum-vinylsiloxane. The origin of the stereoselectivity has been attributed to steric repulsion between the R and OMOM groups in the cyclic transition state **371**. Stereoselectivities attained with OMOM, OEt and OTHP groups (14:1 to >99:1) are much higher than those observed for the corresponding methyl derivatives (6.7:1), suggesting also an important contribution of electronic effects. A rhodium complex, (acac)(COD)Rh, exhibits similar activity but somewhat lower stereoselectivity[500].

The relative rates of platinum-catalysed hydrosilylation of terminal olefins versus internal alkynes have been compared in competitive experiments. Thus, for example, $(EtO)_3SiH$ appears to prefer almost exclusively (97:3) to add to PhC≡CPh vs $PhCH{=}CH_2$, while

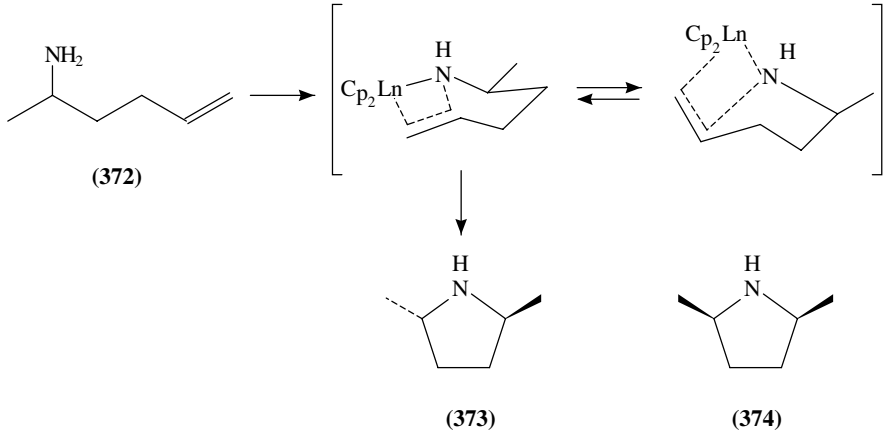


a 1:1 mixture of 2-decyne and 1-hexene gave a 78:22 mixture of the alkyne vs alkene product. The ratios with other model compounds fall into the range of 78:22 to 90:10, showing the higher reactivity of the triple bond. All the olefinic products have the (*E*) stereochemistry[501].

I. Lanthanoids

A detailed kinetic study of the organolanthanoid-catalysed intramolecular hydroamination allowed for the formulation of a catalytic cycle[502]. The stereochemistry appears to be highly dependent on the size of the lanthanide ion, π-ligation, temperature and added exogeneous ligands. Thus, for example, the cyclization of **372** can produce diastereoisomeric mixtures of **373** and **374** in the range of ratios from 1:1 to $\geqslant$50:1[502,99]. The hydrogen from the nitrogen atom migrates to the terminal carbon as revealed by labelling[502]. The reaction is zero-order in substrate over a wide concentration and conversion range. The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values suggest a highly organized transition state. With chiral substrates, high e.e. of the products was achieved; the negligible racemization at long reaction times indicates that the reaction is essentially irreversible[502].

The use of organotyrium catalysts in reductive cyclization of 1,5- and 1,6-dienes has been reported; the yields are in the range of 53–99%. The catalytic species is generated *in situ* by reduction of $Cp_2{}^*YMe$[503].



(372) **(373)** **(374)**

IX. ACKNOWLEDGEMENT

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CHAPTER **20**

Epoxidation of C=X double bonds

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I. ABBREVIATIONS

MCPBA	*m*-chloroperoxybenzoic acid	DET	diethyl tartrate
Bn	benzyl	(+)MPCA	(+)-monoperoxycamphoric acid
PTC	phase transfer catalyst		
THF	tetrahydrofuran	oxone	$2KHSO_5.KHSO_4.K_2SO_4$
TPP	tetraphenylporphyrin		

II. INTRODUCTION

Epoxidation of C=X double bonds is a very active field in organic chemistry. It seems that for almost every type of double bond a special epoxidation reagent has been developed.

One can find quite a few cases of peroxy acids reacting for hours at elevated temperatures with simple alkenes in order to form regular epoxides. More deactivated olefins require lengthy treatment with strongly basic hydrogen peroxide solution.

There are many other reactions devised for oxygen transfer such as various oxidants combined with transition metals with or without macrocyclic hosts and industrial specific epoxidations using oxygen, to name just a few.

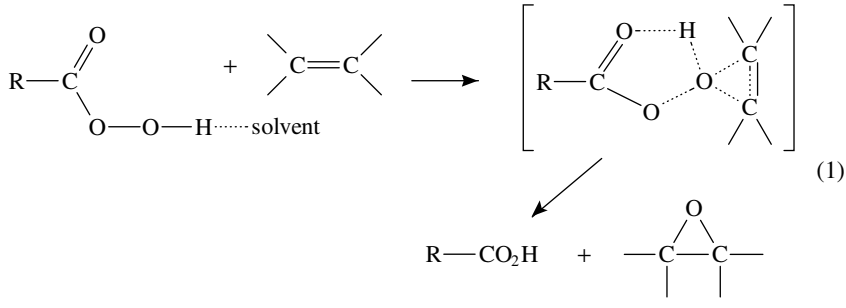
Because of the large number of literature data on epoxidations, we cannot hope to give a full review of all publications that have appeared. We shall therefore restrict ourselves to a brief survey of the still continuing research that has led to the currently accepted interpretation of epoxidations. Using earlier reviews[1–10] as a starting point, we shall mainly discuss the results achieved in the last years. Here recent developments are described by presenting some characteristic new examples.

III. EPOXIDATION OF THE C=C BOND

A. Epoxidation by Peroxy Acids

The epoxidation of olefins by peroxycarboxylic acids is quite important and has been reviewed repeatedly[2,6,9]. The two characteristic features of epoxidations with peroxycarboxylic acids are such that the epoxidations are accelerated by both increasing electron density of the carbon–carbon double bond and electron-attracting groups on the peroxycarboxylic acid.

In coordinating solvents, peroxycarboxylic acids form a complex with the solvent through intermolecular hydrogen bonding[11]. Thus, a well-known cyclic transition state has been widely accepted (equation 1).

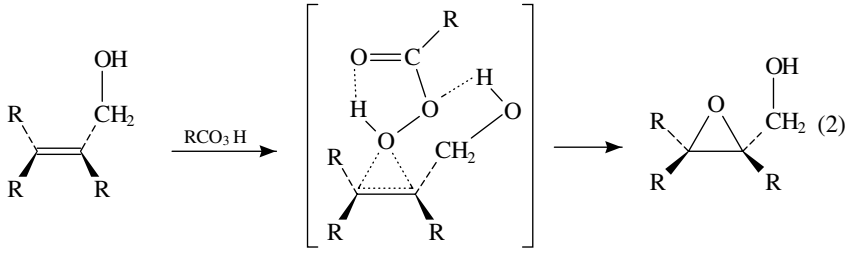


(1)

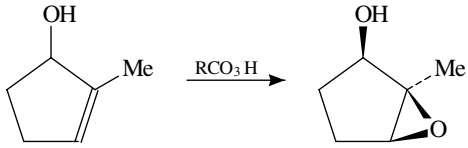
Solvent effects in the peroxycarboxylic acid epoxidations are significant. The epoxidation rates in ether or ethyl acetate are approximately one-tenth of those in benzene or chloroform. The much slower epoxidation with peroxycarboxylic acids with intermolecular hydrogen bonding is indicative of the development of a cyclic transition state.

It is known that peroxycarboxylic acids exist in an intramolecular hydrogen-bonded form in noncoordinating solvents and in an intermolecular hydrogen-bonded form in coordinating solvents such as ether[12,13]. When a coordinating group is present in an olefin, a directed epoxidation could be attained. A typical example is the *syn* epoxidation of acyclic and cyclic allyl alcohols[14–17]. It was postulated that a hydrogen bond formed

between the hydroxyl group and one of the peracid oxygens leads to the delivery of the reagent to the olefin face *syn* to the hydroxyl group (equations 2 and 3).



(2)

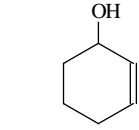
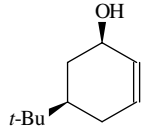
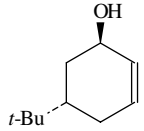


(3)

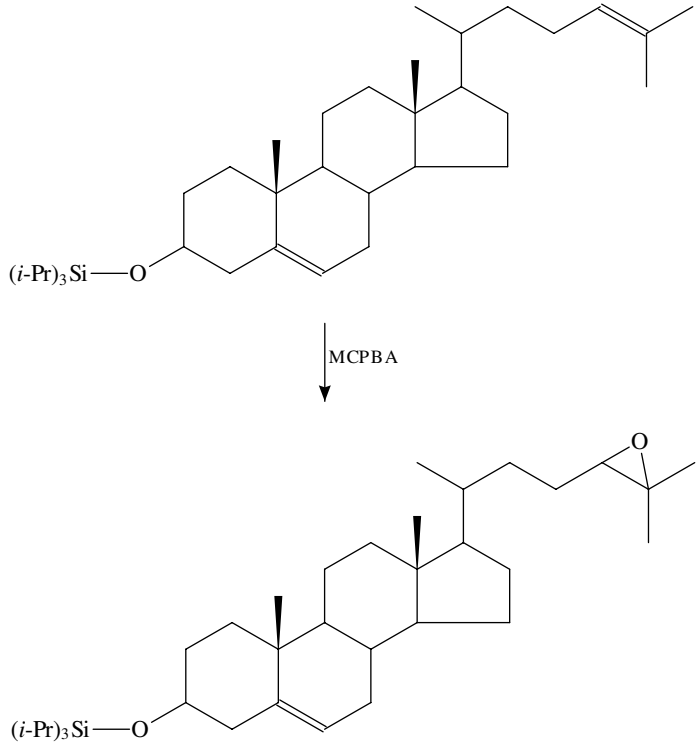
Epoxidation of allylic alcohols with trifluoroperacetic acid offers significantly higher levels of stereocontrol than perbenzoic acid[17] (Table 1).

Comparison of the stereochemical outcomes in entries 2 and 3 of Table 1 implies that the heteroatom functionality directs the oxidation reaction more effectively from pseudoequatorial orientation (the O−C−C=C dihedral angle is 140°). Selective formation of *syn*-epoxides is also known for olefins having carbamate[18], acetal[19], ether[20] and halogen groups[21] in allylic positions. There are many cases in the literature where the epoxidation

TABLE 1

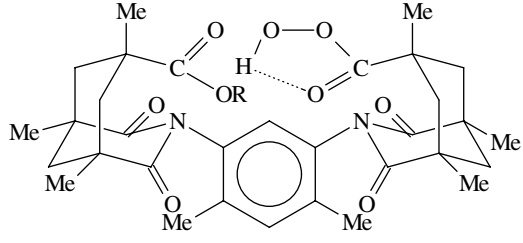
	Entry	*syn:anti* epoxides (MCPBA)	*syn:anti* epoxides (CF_3CO_3H)
1.		24:1	50:1
2.		24:1	100:1
3.		5:1	100:1

process is directed by other functionalities[22–26] (e.g. equation 4).



(4)

For selective epoxidation Rebek and coworkers synthesized highly crowded peroxyacids **(1)** and their naphthalene and acridine homologues and compared their epoxidation rates[27].



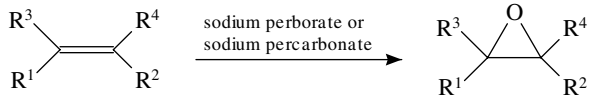
(a) R = Me

(1)

(b) R = Et

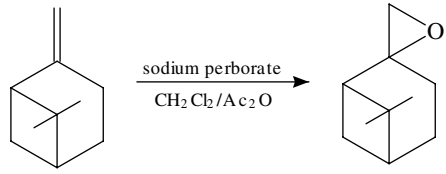
The resulting *cis/trans* ratios for the epoxidation of 2-octenes were 1.2, 5.6 and 7.7 for MCPBA, **1a** and **1b**, respectively, suggesting a high ratio for the U-shaped peroxy acid **(1)**. These results indicate that a stereoselective epoxidation is possible by using highly crowded peroxy acids.

The ability of other peracids[28], sodium perborate and sodium percarbonate[29], to release oxidative species in an organic medium has made them useful reagents in organic synthesis. The oldest organic reaction reported with sodium perborate concerns the formation of peracids (equation 5).



(5)

The formation of peracids as the effective oxidizing species has often been proposed for oxidations with sodium percarbonate in the presence of organic acids or acid anhydrides[30–32]. It was observed that at room temperature and in dichloromethane as solvent, the addition of acetic anhydride induced the epoxidation by sodium perborate of mono-, di- and trisubstituted alkenes, including α,β-unsaturated ketones in a slightly exothermic reaction[33] (equation 6).



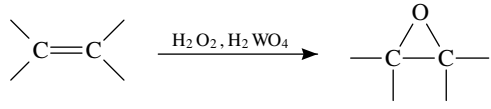
(6)

New epoxidation methods have been developed by the utilization of alkanesulfonic peracids and peroxymonosulfate[34,35].

B. Metal-catalyzed Epoxidations

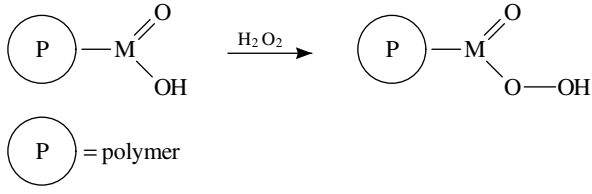
1. Epoxidation by hydrogen peroxide

Hydrogen peroxide is a mild oxidant and its use in olefin epoxidations requires the application of appropriate catalysts. The oxidation with aqueous hydrogen peroxide in the presence of tungstic acid yields the corresponding epoxides (equation 7)[9].



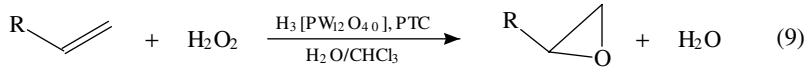
(7)

The catalytic epoxidation proceeds via the formation of peroxytungstic acid. Similarly, other metal catalysts are effective in the H_2O_2 oxidation. Aqueous conditions are not appropriate for epoxidations since epoxides are prone to undergo acid-catalyzed hydrolysis[36]. Polymer-anchored catalysts are conveniently separated from the reaction mixture after catalyzed H_2O_2 epoxidations (equation 8)[9].



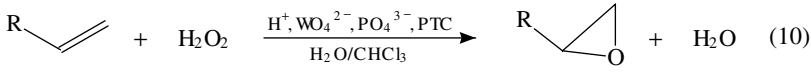
(8)

Polyoxometalates have been used as homogenous catalysts for a wide variety of thermal organic substrate oxidations[37]. This involves the epoxidation of relatively electron poor terminal olefins by H_2O_2 and heteropoly acids, principally $H_3[PW_{12}O_{40}]$, using PTC (equation 9).



(9)

The transformation in equation 9 is similar operationally and mechanistically to the chemistry described in equation 10 (see in References 9 and 38). Here, biphasic H_2O_2-based epoxidations of terminal olefins are effected by tungstate and phosphate.



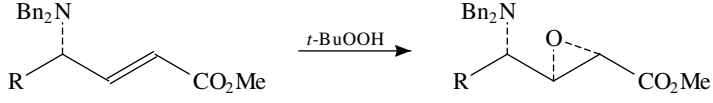
(10)

Similar results are obtained if tungstate is replaced with tungstic acid, WO_3H_2O[39,40]. Under noncatalytic conditions very similar to those in equation 10, the polyperoxometalate $\{PO_4[WO(O_2)_2]_4\}^{3-}$ was isolated and characterized crystallographically[41]. This tetranuclear species was postulated to be the active oxygen transfer agent in equation 10 based on its ability, as an isolated complex, to effect the active epoxidation of terminal olefins[42–44]. Recently the corresponding Mo analogue $\{PO_4[MoO(O_2)_2]_4\}^{3-}$ was isolated and thoroughly characterized[45,46]. Another polyoxometalate disubstituted with a manganese(II) transition metal, $[WZnMn_2(ZnW_9O_{34})_2]^{12-}$, dissolved in an organic solvent by a quaternary ammonium counter cation, was used as a highly effective catalyst for the epoxidation of alkenes[47].

2. Epoxidation by hydroperoxides and other oxidants

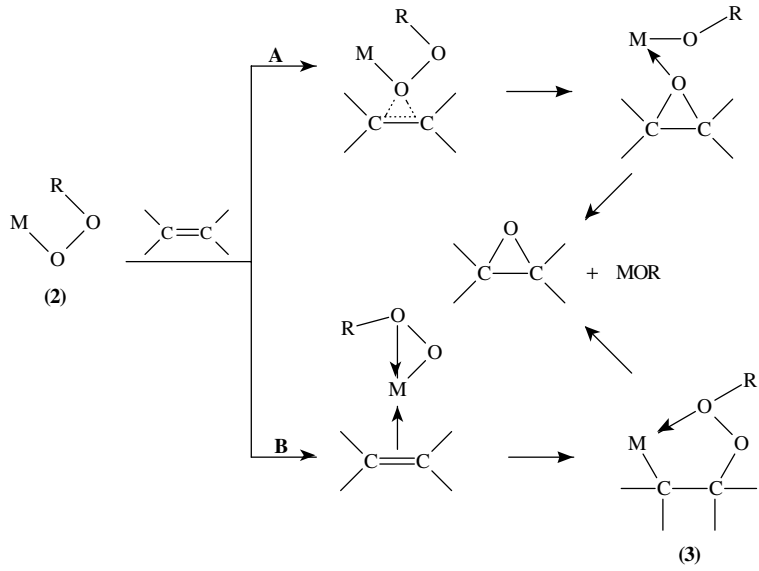
Olefin epoxidation with alkyl hydroperoxides catalyzed by various metal complexes, e.g. Mo, V and Ti, is an important industrial process[9]. Despite intensive studies[48], the detailed epoxidation mechanism has not been clarified. It seems that two alternative pathways[9], **A** and **B** in Scheme 1, each involving a metal alkyl peroxidic complex **(2)**, have been accepted in the literature. Mechanism **A** involves an electrophilic O-transfer to olefins just like the epoxidation process by peroxy acids[49]. Mechanism **B** involves a five-membered dioxametallocyclopentane **(3)**, i.e. it occurs via a pseudocyclic peroxymetalation[50,51]. For the particular case of vanadium, the alkylperoxy complexes were isolated, and pathway **B** was supported by the fact that the relative rates were correlated with the coordinating ability of olefins. The operating pathway seems, however, to change by changing metals, ligands and solvents.

High *syn* diastereofacial selectivity was reported in the formation of the epoxides which are obtained upon epoxidation of γ-amino-α,β-unsaturated esters with a reagent derived from potassium *t*-BuOOH in THF-ammonia[52] (equation 11).



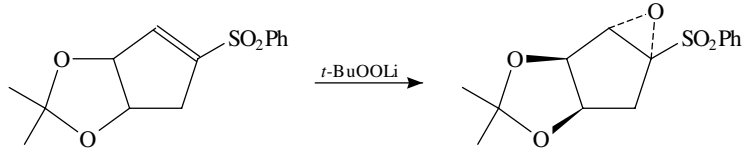
(11)

It was found that the cyclic vinyl sulfone with *t*-BuOOLi yielded only a single stereoisomer. The structure was established as the *anti*-epoxide by an X-ray crystal structure



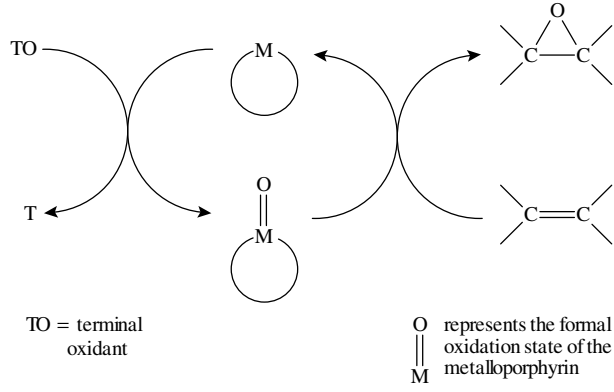
SCHEME 1

determination[53] (equation 12).



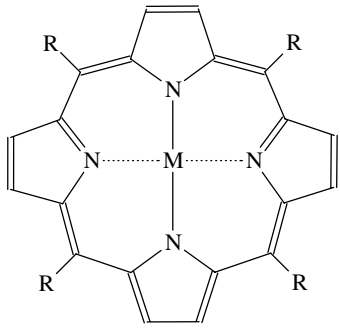
(12)

Another type of catalytic epoxidation is the reaction via *metallo oxo intermediates* (Scheme 2) (see details in Reference 9).



SCHEME 2

In the last decade, transition metal complexes (e.g. metalloporphyrins) have been used to catalyze epoxidation. These entities can reproduce and mimic all reactions catalyzed by heme-enzymes (cytochromes P-450)[54]. Synthetic metalloporphyrins are analogous to the prosthetic group of heme-containing enzymes which selectively catalyze various oxidation reactions. The metallo complexes of Fe, Co, Cr, Mn, Al, Zn, Ru, etc. possessing porphyrin ligands have been mostly studied[55–57]. Porphyrin ligands **(4)** are planar and can possess several redox states of the central metallic ions and hence they can exist as oxo metals.



(4)

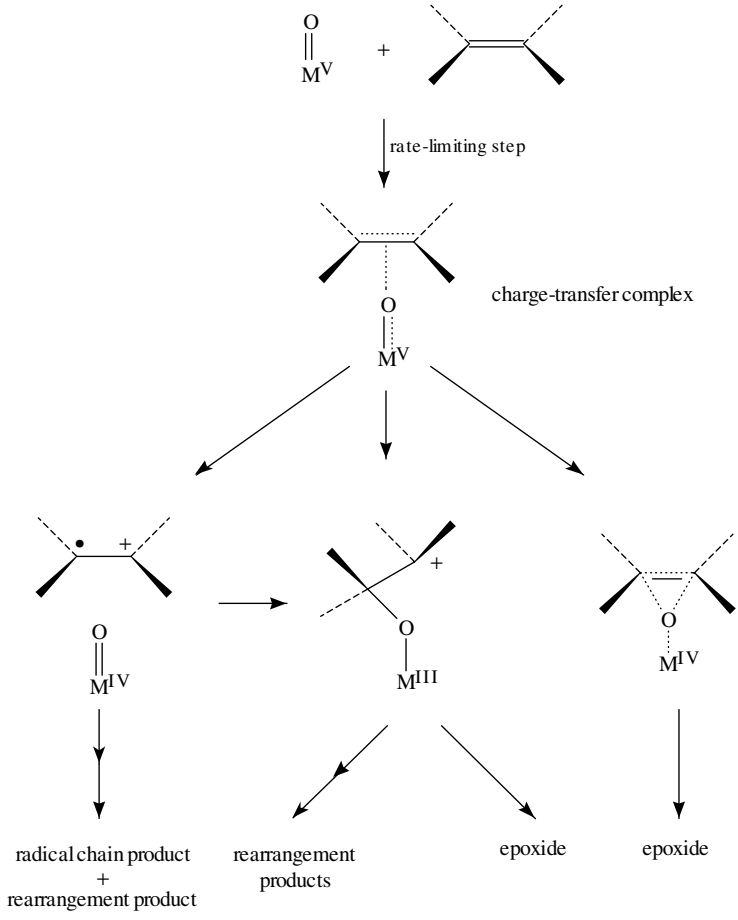
(a) R = H
(b) R = Me
(c) R =
(d) R =
OR′
R′ = glycoside

The high reactivity of these catalytic systems utilizing oxidants such as iodosylarenes[58–62], peracids[63,64], hypochlorites[65–70], alkylhydroperoxides[71,72], hydrogen peroxide[73–75], amine N-oxide[76] and ozone[77] has been described. The mechanism consists of an oxygen atom transfer from oxometalloporphyrins to alkenes with the rate-determining step of the formation of a charge-transfer complex[64] (Scheme 3).

The reactions following the rate-determining step (epoxidation vs rearrangement) were proposed to be dependent on a number of factors that included the oxidation potentials of the alkenes and the active oxidant, the steric and electronic structures of the reactants (steric bulk and geometry of both species and the metal axial ligand of the metallo-porphyrins) as well as the properties of various substrates to undergo rearrangements. Examination of the metal and ligands revealed various features of metalloporphyrin-catalyzed epoxidations. Sometimes, the epoxidation was accompanied by rearrangements and isomerizations indicative of a one-electron transfer from olefin to oxo metals[78–80]. *cis*-Olefins are more reactive than *trans*-olefins in porphyrin-catalyzed epoxidation by iodosylbenzene. For example, *cis*-stilbene is epoxidized by tetraarylporphyrin [Fe(TPP)Cl] **(4c,d)** in 77% yield whereas *trans*-stilbene does not react under the same conditions. In contrast, the use of Mn porphyrin yields a mixture of *cis* and *trans* isomers[81]. High selectivity is induced by sufficient noncovalent interactions between the substrate and the metalloporphyrin. The use of NaOCl as oxidant promotes epoxidation in good yields and with high regio- and stereoselectivities for terpenes and steroids[82]. Dienes can selectively be transformed to monoepoxide[83].

3. Asymmetric epoxidation

Chiral porphyrins, prepared in different ways[84,85] (chiral units attached to preformed porphyrins[84], chiral substituents introduced during the synthesis of porphyrins[86] or chiral porphyrins synthesized without the introduction of chiral groups[69,87–90]), proved to be effective as asymmetric epoxidation catalysts.

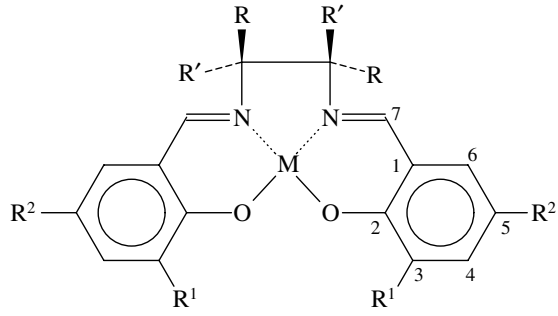


SCHEME 3

Prochiral olefins, such as β-methylstyrene, can be epoxidized with 72% enantiomeric excess, either with 'picket' metalloporphyrins ('basket handle' iron-porphyrin)[91,92] or with bulky ligand porphyrins[93–96]. Chiral binaphthyl bridges give a rigid conformation and a chiral environment to the metallic center, which recognizes the substrate[84]. A serious weak point for the metalloporphyrin-catalyzed epoxidation is the oxidation of the porphyrin rings themselves, resulting in low turnover[9]. The rings may be moderately stabilized by introducing sterically bulky groups or electron-withdrawing groups[97–99].

At present, the best enantiomeric excess with different olefins is achieved by chiral *salen ligands*[100–108]. Contrary to the porphyrin systems, salen complexes **(5)** [i.e. *N*,*N*′-ethylene-bis(salicylidene-aminate) ligands] bear tetravalent and potentially stereogenic carbon centers in the vicinity of the metal binding site.

The reaction of cyclohexene with Mn(III)(salen)/*t*-BuOOH afforded cyclohexene oxide as the single product in the presence of radical inhibitors. When PhIO was used as the terminal oxidant, stereospecific epoxidation could be attained. Similar results were obtained with Co(II)(salen) **(5)**; stereospecific epoxidation took place with PhIO as the

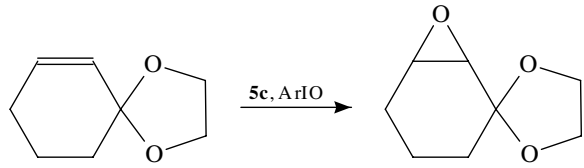


(5)

(a) R = R′ = R^1 = R^2 = R^3 = R^4 = H
(b) (*R, R*); R = R^2 = H, R′ = Ph, R^1 = *t*-Bu
(c) (*S, S*); R′ = R^2 = H, R = Ph, R^1 = *t*-Bu

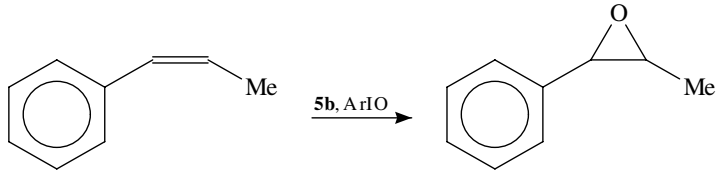
terminal oxidant while the epoxidation with *t*-BuOOH was accompanied by a radical reaction[9].

The asymmetric epoxidations of unfunctionalized olefins without coordinating groups are difficult but very interesting. Jacobsen and coworkers were the first to report asymmetric catalysis with chiral Mn(III)(salen) complexes[101,109]. These systems are generally derived from chiral 1,2-diamino-1,2-diphenylethane. Systematic variation of the steric and electronic nature of different substitutents led to the discovery of catalysts that are particularly effective for the epoxidation[10,102] *trans*-Olefins did not show as good enantioselectivity as *cis* olefins. The enantiomeric excess (ee) is substrate-dependent and can reach 93%[110,111]. The most selective catalyst for the epoxidation of a wide range of olefins is the Mn(salen) complex (e.g. **5c**)[101,111–113] (e.g. equation 13).

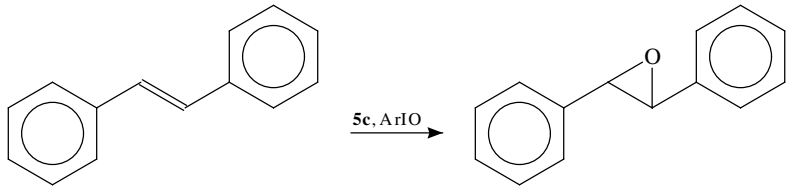


(13)

In the case of *cis*-β-methylstyrene the 84% ee is rather high (equation 14), and also significant is the 33% ee for the epoxidation of *trans*-stilbene for which asymmetry is regarded to be difficult to induce (equation 15).

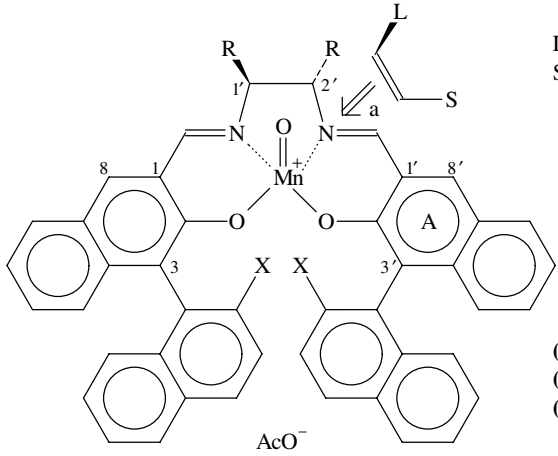


(14)



(15)

Recently, Katsuki and coworkers found that the epoxidation of *cis*-olefins conjugated with alkenyl, alkynil or aryl groups occurs with high enantioselectivity[114]. This interesting substrate-specific enentioselectivity observed in salen-catalyzed epoxidation can be explained by the newly proposed pathway **a** for the olefin access to metal oxo species **(6)**. Two factors, repulsive steric and electronic interactions between the oncoming olefin and the salen ligand, are considered to be responsible for induction of asymmetry: the steric repulsion between the C-3′ substituent in the salen ligand and an olefinic substituent and π,π-electronic repulsive interaction between the salen benzene ring (**A**) and the olefinic substituent bearing π-bond direct a bulkier and more electron-rich olefinic substituent (**L**) away from the C-3′ substituent. On the basis of the newly proposed hypothesis on the mechanism of asymmetric induction, a highly efficient (salen) manganese(III) complex **(6)** was constructed as a catalyst for asymmetric epoxidation[115–119].



L = alkenyl, alkynyl or aryl group
S = alkyl group

(a) R = Ph, X = Me
(b) R = Ph, X = Ph
(c) R = 3,5 $(CH_3)_2C_6H_3$, X = Ph

(6)

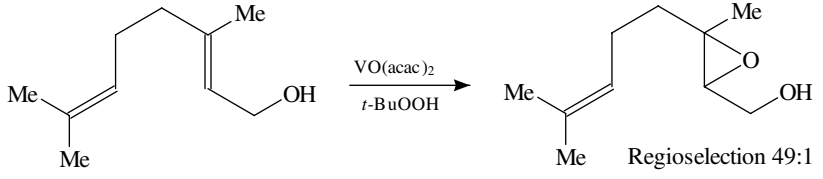
In addition to the above examples the significance of chiral epoxidation is manifested by the appearance of numerous other results (for example, papers[120–125], reviews[126–133] and patents[134–136]).

Among others, new methods for epoxidation have been developed[137–142] and new transition metal complexes[143–147] have also been used.

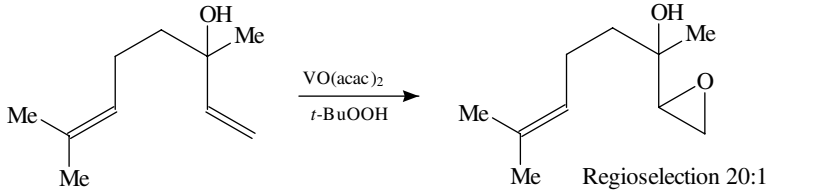
4. Stereoselective and asymmetric epoxidation of allylic alcohols

Stereoselective and enantioselective epoxidations have been treated in detail in recent reviews[8,9]. A typical example is the stereoselective epoxidation of allylic and homoallylic

alcohols[8,9] on vanadium catalysts. The high *syn* selectivity of the vanadium catalyst is due to its strong coordination to the hydroxyl group (equations 16 and 17).

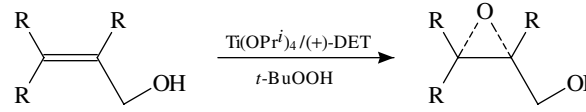


(16)



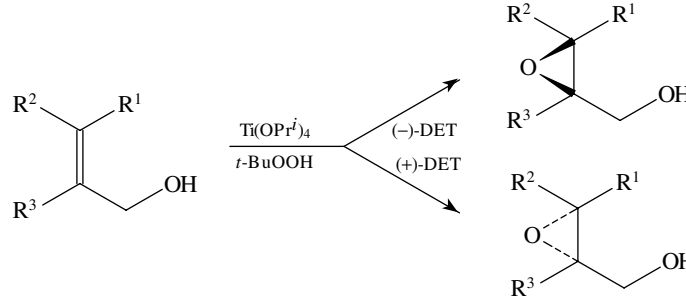
(17)

Katsuki and Sharpless reported the new process of asymmetric epoxidation[8] using a complex of titanium tetraisopropoxide and diethyl tartrate (DET), and *t*-butyl hydroperoxide (equation 18).



(18)

The direction of the attack depends on the diethyl tartrate used in the reaction. The stereochemistry of the epoxidation, therefore, can be correctly predicted (equation 19).



(19)

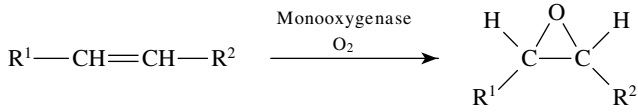
This epoxidation is one of the most useful asymmetric reactions available to the synthetic chemist. The results show that, irrespective of the substitution pattern around the starting allylic alcohol, very good yields and excellent enantiomeric excesses are obtained[148–152].

C. Biological Epoxidations

Epoxides are involved in the metabolism of many aliphatic and aromatic compounds in plants as well as in mammals. Enzyme potentiality allows both regio- and stereospecific

oxygenation reactions, which are very difficult to carry out chemically. The use of enzymes for such reactions is one of the most fascinating applications in bioconversion[153–156].

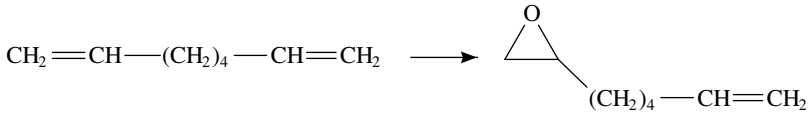
Monooxygenases can activate molecular oxygen incorporating one oxygen atom into the substrate and reducing the other to water. In this way alkenes can be converted into epoxides (equation 20).



(20)

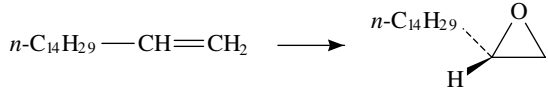
Monooxygenases are found in many living organisms: bacteria, yeasts, insects, plants and mammal tissues. They are used for organic asymmetric reactions either in a more or less purified enzymatic form (cytochromes P-450) or in whole-cell microorganisms (bacteria, fungi).

1,7-Octadiene, which does not contain a terminal methyl group, is selectively converted by *Pseudomonas oleovorans* to the monoepoxide with an enantiomeric excess greater than 80%[157] (equation 21).



(21)

Results show that structural limiting factors exist and that the enzymatic systems do not act on every substrate; thus they act on O-alkylated derivatives[158], but not on allylic alcohols[159]. The epoxide products are generally of the *R* configuration. The epoxidation by *Rhodococcus rhodochrous* showed that the epoxidation rate and enantioselectivity of gaseous alkenes are very high[159]. Different genera of bacteria were tested utilizing ethene, propene or butenes[160,161]. The *Corynebacterium equi* was grown in an inorganic medium containing 1-hexadecene as the sole source of carbon[162]. The epoxidation of linear alkenes with carbon chains longer than 14 and with a terminal double bond proceeds stereospecifically. For example 1-hexadecene gives (*R*)-(+)-1,2-epoxyhexadecane with 100% enantiomeric excess (equation 22).



(22)

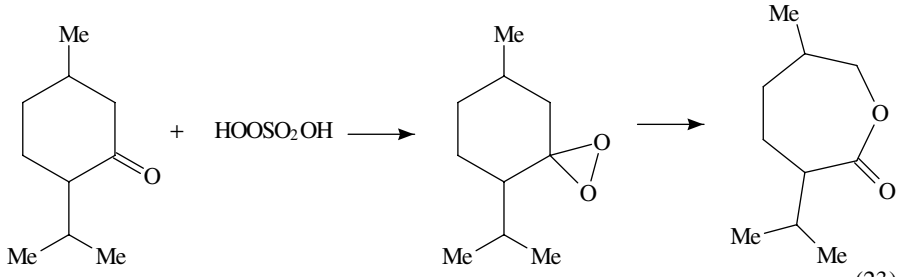
IV. EPOXIDATION OF THE C=O BOND

A. Introduction

The epoxidation of ketones, i.e. the preparation of three-membered cyclic peroxides (dioxiranes), was developed in the 1980s. This field is so new that monographs dealing with the chemistry of peroxides do not mention in yet[163,164].

As early as 1899 Baeyer and Villiger[165] postulated a dioxirane intermediate in the $KHSO_5$ oxidation of menthone to its lactone (equation 23). The first real contribution to dioxirane chemistry was made Montgomery[166]. Careful studies on the decomposition of the caroate ion permitted him to observe the acceleration of the reaction by the addition

of acetone in neutral aqueous solutions.



(23)

The main achievements of dioxirane chemistry can be attributed to the activities of Curci, Edwards, Murray and their coworkers[3,167]. As a result of their detailed, systematic research, dioxiranes have become indispensable reagents in synthetic organic chemistry.

In addition to the review papers written by the leading experts of the field[3,167] other reviews were also published in recent years[9,168,169]. Thus, we give only a short summary of dioxirane chemistry, referring, in the majority of cases, to the results published in the last 2–3 years.

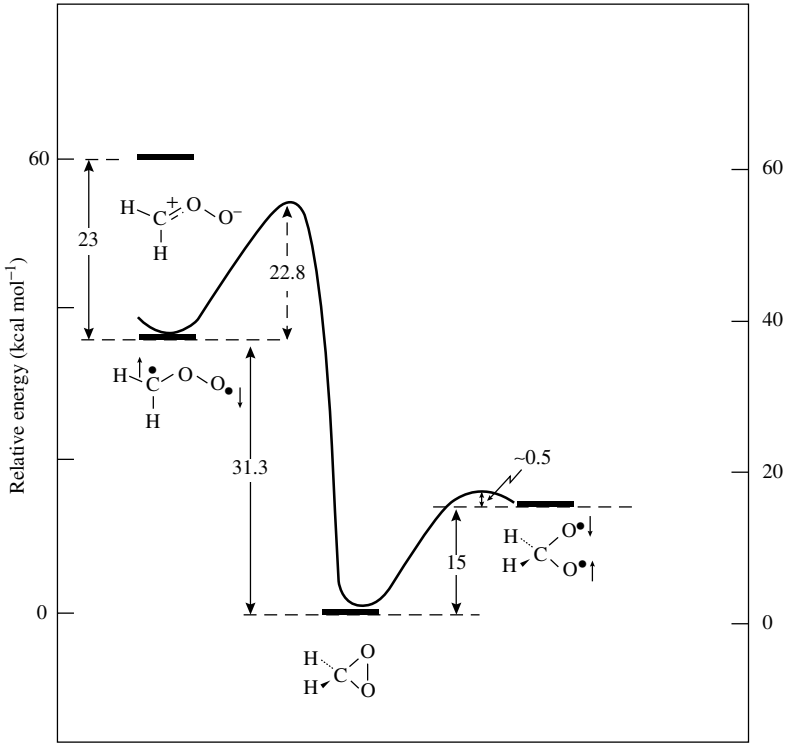
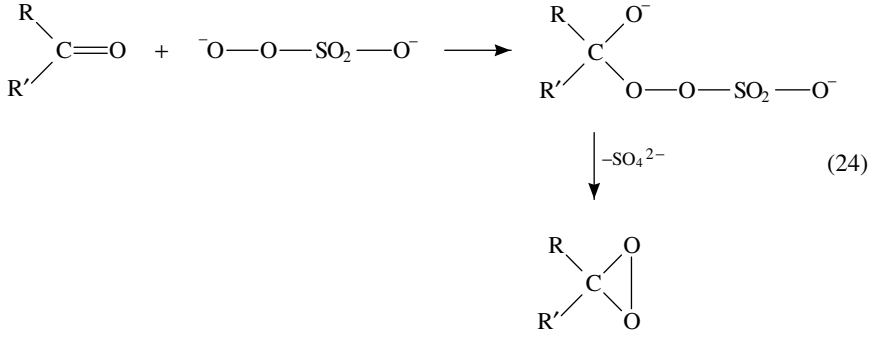


FIGURE 1. Energy diagram of the H_2CO_2 entities[167]

The three-membered dioxirane ring is a strained system. In regard to the thermochemistry of these compounds, a number of theoretical analyses of the H_2CO_2 entity have been performed. The stability conditions are well demonstrated by the energy diagram in Figure 1.

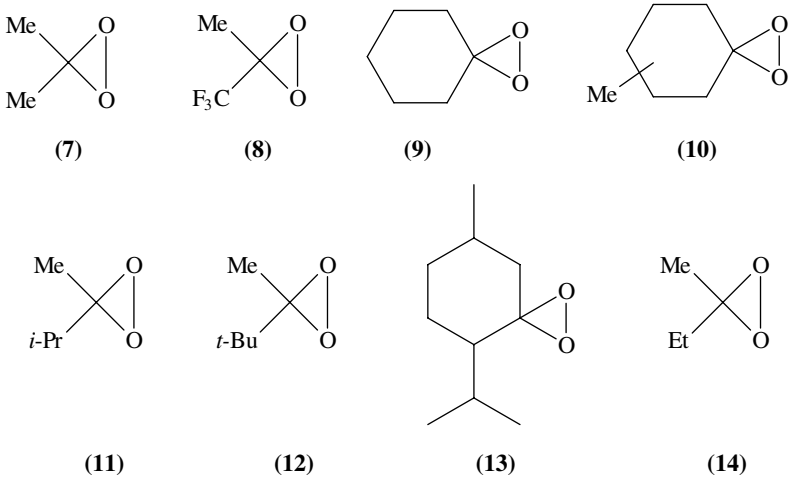
B. Preparation of Dioxiranes

Epoxidation of ketones is carried out by the oxone reagent. The actual oxidizing agent is the caroate ion (equation 24).



(24)

Numerous variations of this method were developed[170–173]. In general, 0.1–0.8 molar solutions of dioxiranes were prepared and used as oxidizing agents. These solutions can be stored in a refrigerator. Epoxidation of many ketones has been carried out in the above way, and the dioxiranes **(7–14)** thus prepared were characterized spectroscopically and also by chemical methods.



(7) **(8)** **(9)** **(10)**

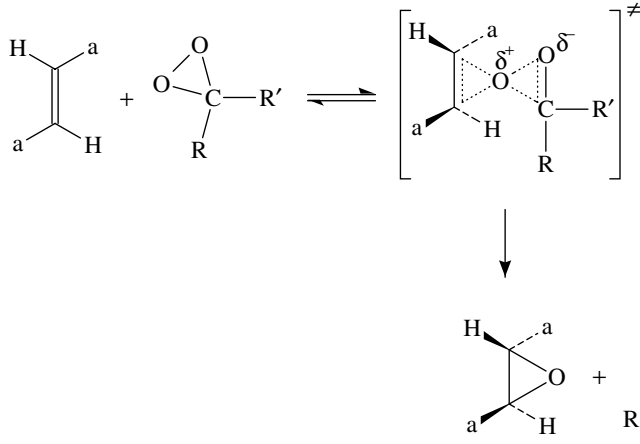
(11) **(12)** **(13)** **(14)**

Dimethyldioxirane **(7)** and methyl(trifluoromethyl)dioxirane **(8)** are the two most effective reagents mainly used in preparative organic chemistry.

C. Epoxidations by Dioxiranes

Dioxiranes can be used for the oxidation of various organic functional groups. The epoxidation of the olefinic double bond and the formation of the hydroxyl group through the oxidation of the C−H bond have been studied most.

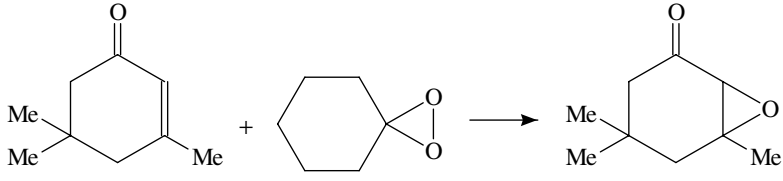
Dioxiranes epoxidize different compounds with C=C stereospecifically and electrophilically (equation 25) in high yield (90–100%).



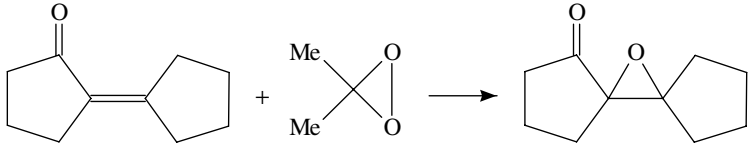
(25)

A kinetic study of the epoxidation showed the reaction to be of the first order with respect to both alkene and dioxirane[174]. A large steric effect was observed in the epoxidation of certain *cis/trans*-dialkylalkenes; the *cis* compounds were found to exhibit reactivities one order of magnitude higher than the corresponding *trans* isomers. This large effect reflects a repulsive interaction between the substituents of the olefin and the dioxirane in the transition state (equation 25)[9].

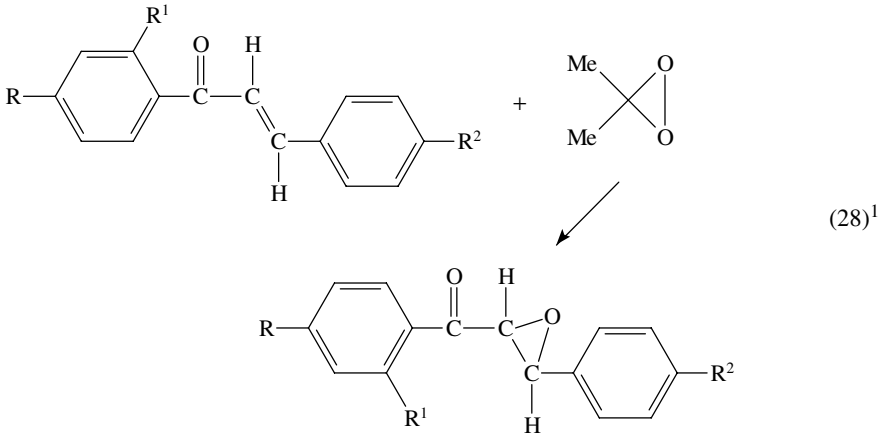
Several characteristic recent examples describing the epoxidation of α,β-unsaturated ketones (equations 26–28) and that of α,β-unsaturated carboxylic esters (equations 29 and 30) are given below.



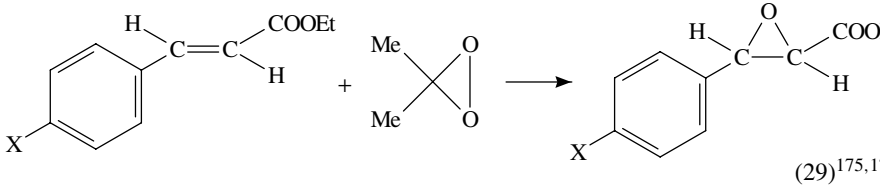
(26)[173]



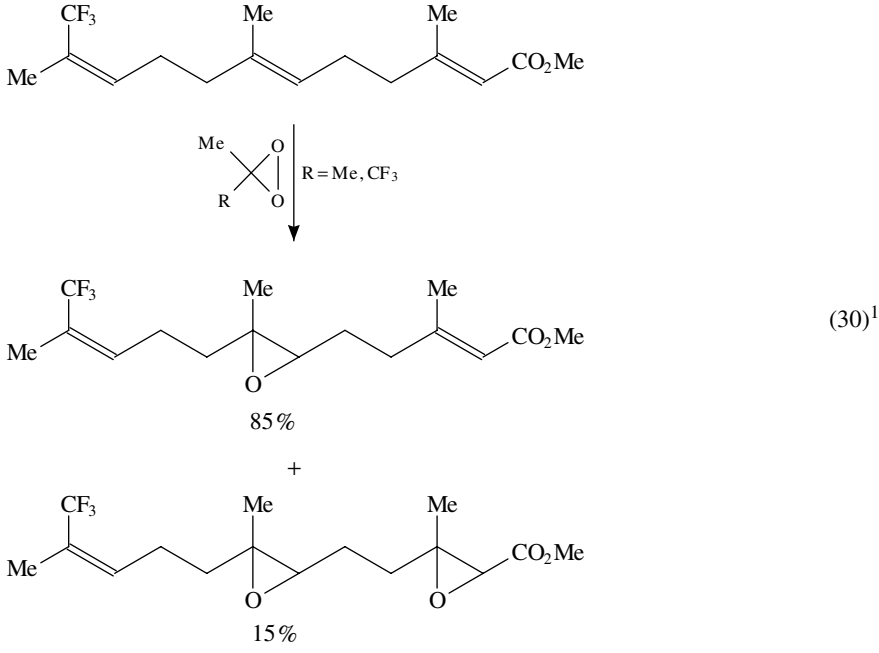
(27)[172]



(28)[172]

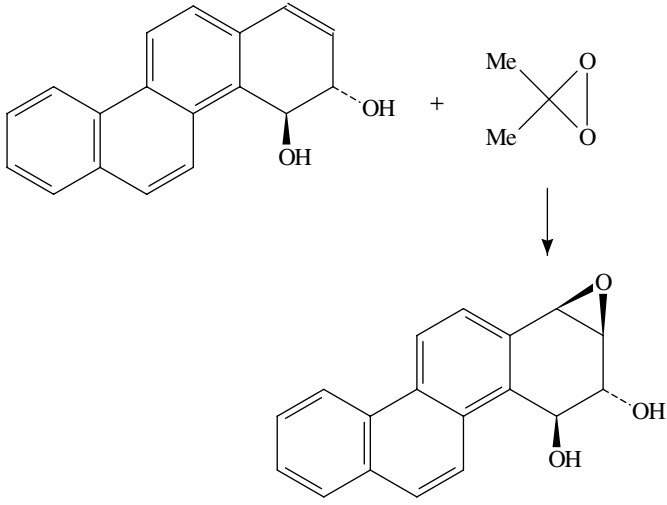


(29)[175,176]

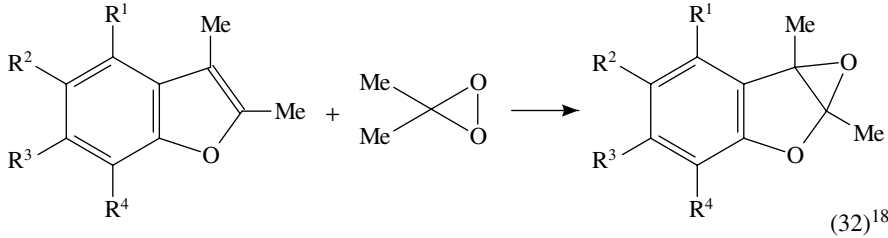


(30)[177]

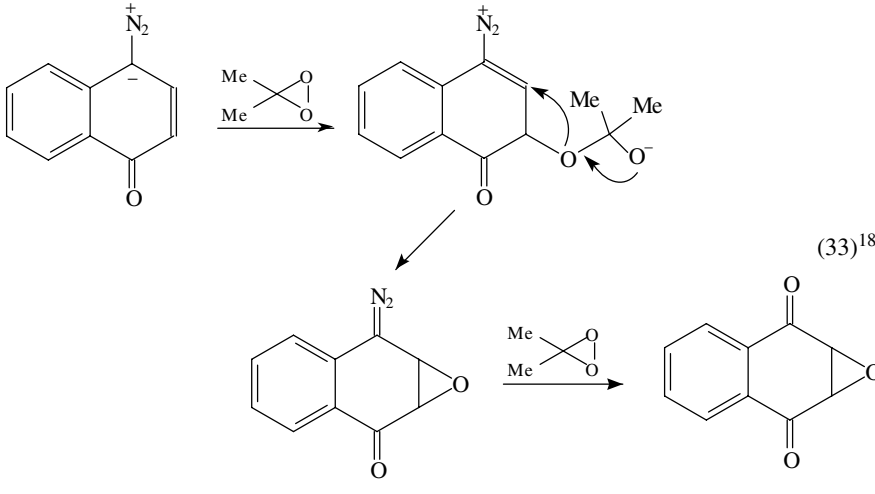
Several new examples for stereospecific epoxidation of compounds with more complicated structures can be seen in equations 31–38.



(31)[178,179]

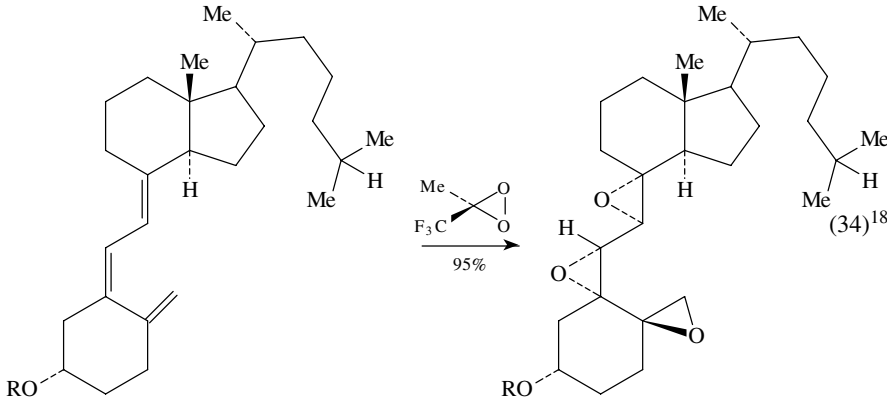


(32)[180]

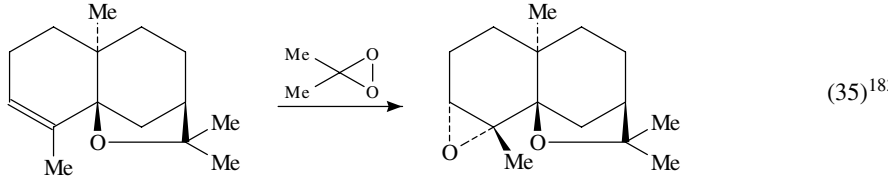


(33)[181]

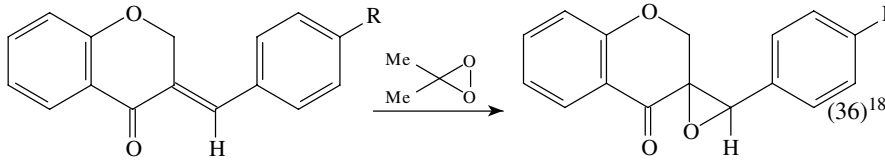
70%



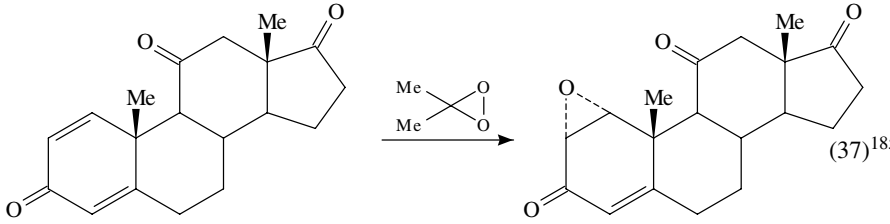
(34)[182]



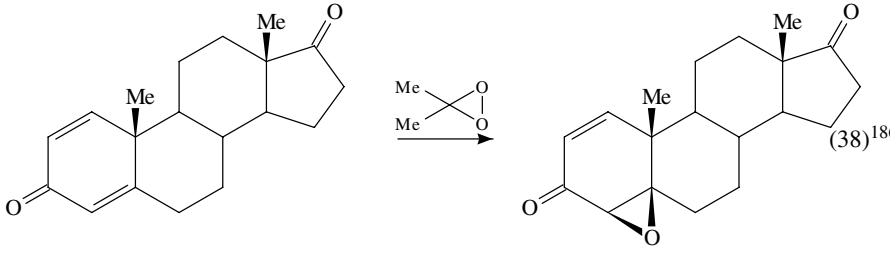
(35)[183]



(36)[184]



(37)[185]



(38)[186]

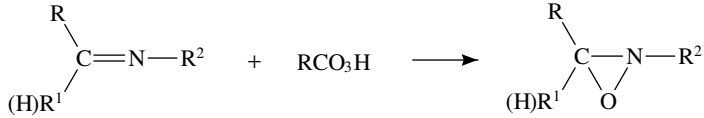
Beside the preparation of epoxides and the formation of OH group[186–190], dioxiranes can also be used to oxidize other functional groups[191–196].

Recent results clearly indicate that synthetic organic chemistry obtained a new, significant oxidizing agent by the epoxidation of ketones. Due to their high reactivity, regio- and stereoselectivity, the use of neutral conditions in their synthetic applications and the easy product recovery, dioxiranes are unique oxidizing agents. The intensive utilization of dioxiranes as versatile oxidizing agents, however, has just started.

V. EPOXIDATION OF THE C=N BOND

A. Introduction

The epoxidation reaction of imines with peroxy acids was discovered by Emmons in 1956[197,198]. The reaction gave oxaziridines in good yield (equation 39).



(39)

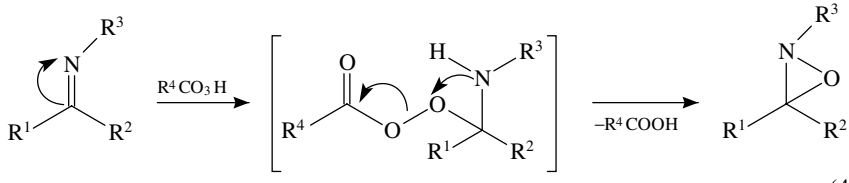
Through the research work of the 40 years since the discovery, the chemistry of oxaziridines has become well known as earlier[4,7,199] and recent[5,9,200] reviews testify. These reviews give detailed information about the development of oxaziridine chemistry and the use of some oxaziridines as oxidizing reagents. In contrast to the vigorous development of the chemistry of dioxiranes fewer new reports were published on oxaziridines in recent years. Nevertheless, it is necessary to give some brief information in this monograph about the epoxidation of imines and the utilization of oxaziridines synthesized in this way. The conclusions are based on the information of the above-mentioned reviews.

Extensive investigations of these compounds have revealed their unusual reactivity. This, undoubtedly, is related to the strained three-membered ring and a relatively weak N—O bond. A consequence of these features is the low basicity of the oxaziridine nitrogen compared to that of amines. Another remarkable property of some oxaziridines is that they possess a configurationally stable nitrogen atom at ordinary temperatures[200].

It is important to underline in this introduction that the importance of oxaziridines as special oxidizing agents is expected to diminish in some fields due to the use of dioxiranes. Their importance, however, is indisputable since oxaziridines as chiral oxidizing agents[201,202] offer greater possibilities than dioxiranes.

B. Preparation of Oxaziridines

The most common method for the epoxidation of imines is the peracid[203–205] and oxone[206–210] oxidation. Two mechanisms have been put forward: the concerted mechanism (analogous to an olefin epoxidation) and the two-step mechanism proceeding through an intermediate. On the basis of recent investigations the latter mechanism seems to be more likely (equation 40)[204,208,211].

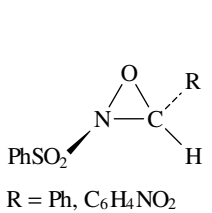


(40)

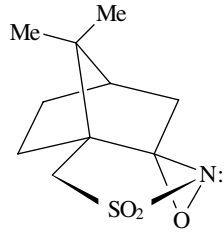
Of peracids, MCPBA and (+)-MPCA are used most often. Oxidation is usually carried out in aprotic solvents, mostly in CH_2Cl_2, $CHCl_3$, or with phase-transfer catalysis. Perfluorinated oxaziridines are prepared in acetonitrile[212,213]. The acid side-product, *m*-chlorobenzoic acid, is insoluble in the solvent and the desired oxaziridine may be prepared in good yield. MCPBA, however, is expensive, and large-scale oxidations are sometimes contaminated with bis(*m*-chlorobenzoyl) peroxide, which complicates product purification[206].

Oxone is an inexpensive and stable oxidizing reagent that is commercially available. Replacement of MCPBA by buffered oxone in toluene results in increased yields, a significant reduction of the reaction time and easier purification of the oxaziridine[206]. In addition, other oxidizing agents were also employed for the epoxidation of imines[214–218].

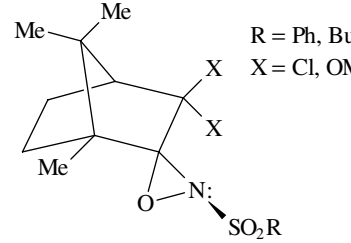
Epoxidation of both aldimines and ketimines is possible. Most oxaziridines formed are stable compounds, especially aldimines containing aromatic substituents, and 2-sulfonyl- and 2-sulfamyl oxaziridines[5]. Generally, *N*-sulfonyloxaziridines are isolated as stable crystalline solids. Certain compounds are widely used in synthetic organic chemistry as oxygen-transfer reagents **(15–17)**.



(15)

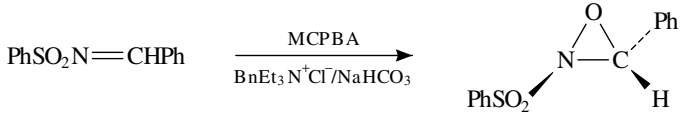


(16)



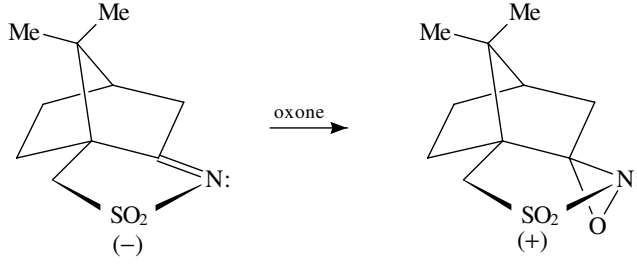
(17)

Biphasic buffered oxidation of sulfonylimines usually suffice for stereoselective synthesis of *trans*-sulfonyl substituted oxaziridines in excellent yields (equation 41)[203].

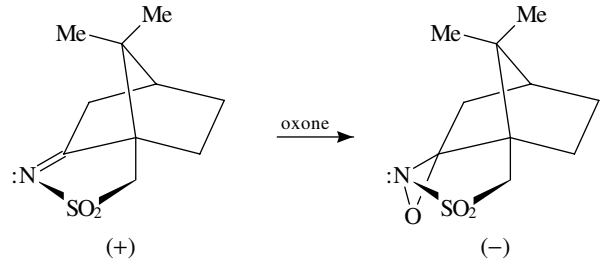


(41)

Chiral 2-sulfonyl- and 2-sulfamyloxaziridines were also prepared in different ways[4,5]. Two examples are given in equations 42 and 43[207].



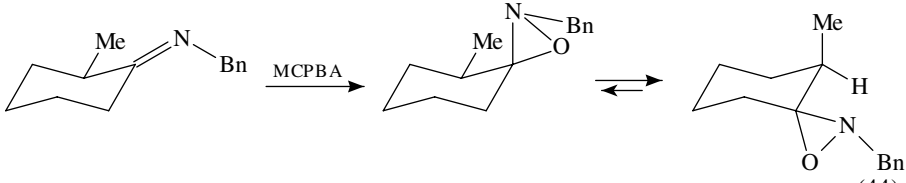
(42)



(+) (−) (43)

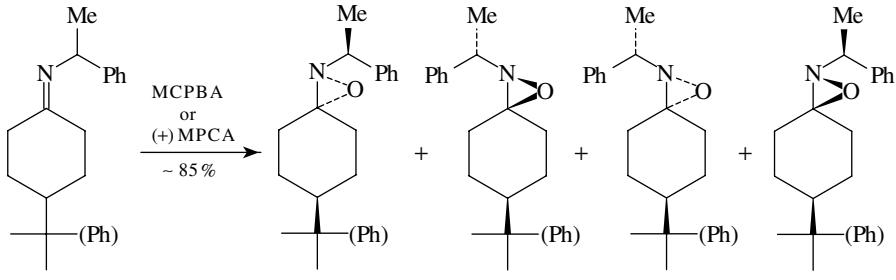
Both isomeric forms of (+)- and (−)-(camphorylsulfonyl)oxaziridines are available by oxidation of the corresponding sulfonimines with buffered potassium peroxymonosulfate (oxone). Since oxidation can only take place from the *endo*-face of the C=N double bond due to steric blocking of the *exo*-face, a single oxaziridine isomer is obtained. The enantiomerically pure sulfonimines can be prepared in three steps in better than 80% yield from inexpensive (+)- and (−)-camphor-10-sulfonic acids. Alternatively they are commercially available[200].

The oxidation of imines derived from substituted cyclohexanones occurs predominantly from the equatorial direction. However, the product oxaziridines can undergo subsequent equilibration to favor a more stable conformation which places the bulkier nitrogen substituent in an equatorial conformation (equation 44)[219].



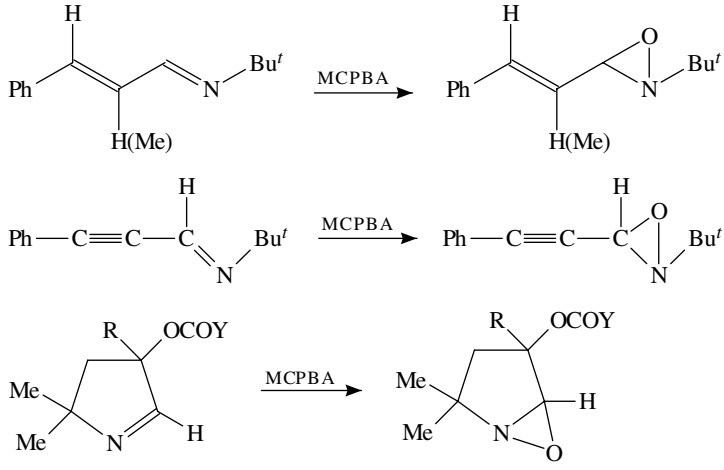
(44)

In another example, the cumulative effect of equatorial attack in prochiral cyclohexanoneimines with diastereoselectivity induced by a chiral nitrogen substituent allowed the synthesis of spirocyclic oxaziridines with a high induction of axial dissymmetry. The major oxaziridine isomer results from both the favored equatorial attack and oxidation *anti* to the chiral nitrogen substituent (equation 45)[204]



(45)

On epoxidation of imines containing several oxidizable functions, significant selectivity was observed in favor of the formation of oxaziridines (equations 46–48)[220–222].

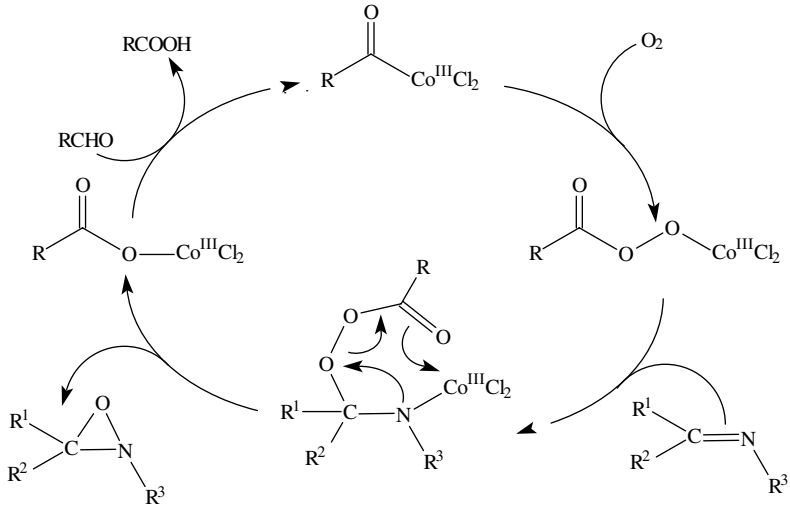


(46)

(47)

(48)

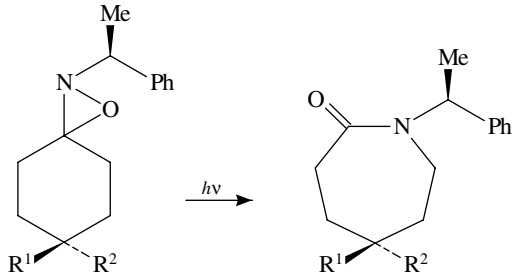
The metal-catalyzed oxidation of imines using molecular oxygen as the final oxidant and aldehydes as co-reductants has been studied[223]. Various transition metal complexes have been tested as catalysts and it is found that cobalt complexes can catalyze the selective oxidation of imines to oxaziridines in good yield (*ca* 80%) (Scheme 4).



SCHEME 4

C. Reactions of Oxaziridines

Considering that the present paper does not intend to analyze the chemical reactions of oxaziridines, we refer only to some publications in this field published in recent years. Certain oxaziridines undergo stereoelectronically controlled photochemical rearrangement into lactams (equation 49)[204,219].



(49)

Oxaziridines are synthetically useful reagents to transfer an oxygen to a variety of substrates. Within this, chiral oxaziridines[5,200,202] attained especially great significance.

The research work of recent years includes predominantly the epoxidation of alkenes[9,200], asymmetric hydroxylations[209,224–228] and the asymmetric oxidation of sulfides to sulfoxides[205,209,229,230]. Optical yields of practical significance were obtained (>90%). A detailed review published in 1991[231] reports about the versatile use of oxaziridines in the field of the electrophilic amination.

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CHAPTER **21**

Strained olefins

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I. BASIC CONCEPTS

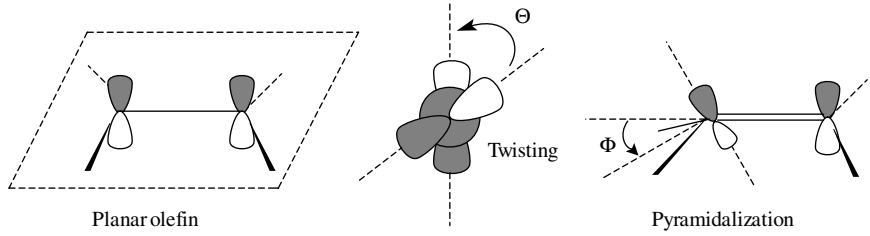
The concept of strain in organic chemistry is based on the experimentally and theoretically well founded structure theory, according to which bond lengths, bond angles, dihedral angles involving four atoms joined by three bonds in sequence, and distances between nonbonded atoms have optimal values, which are determined by the atoms involved and their connectivity. A molecule, in which these parameters can attain their optimal values, is free from strain. In many molecules, restrictions due to space-requiring substituents or cyclic structures prevent one or more of the ideal parameter values being attained. The molecule is subject to strain, and its energy is increased accordingly. A quantity named *strain energy* can be defined as the difference between the heat of formation of an actual strained molecule and that of a hypothetical strain-free molecule with the same atoms in the same bonding arrangement[1]. Mathematical expressions describing the relation between the degree of deviation from an ideal parameter value and the energy of the molecule have been developed, creating a force field for the molecule. Based on the principle that a physical system strives to attain the lowest possible energy, the deformations are distributed over the different degrees of geometrical freedom in the optimal way. This is the basis of the technique of empirical force-field (EFF) or molecular mechanics calculations[2–4], a technique that has had an enormous impact on physical

organic chemistry, permitting highly realistic predictions of the geometries and energies of the different feasible forms of more and less flexible molecules. It is also possible to map the entire energy hypersurface of a molecule and to find reaction itineraries and transition state energies for exchange reactions between different minimum energy forms.

Strong steric strain leads to modifications of the structures and the physical and chemical properties of molecules, and investigations into these changes and the limits for the existence of extremely strained molecules have become important fields of research with challenges for preparative and theoretical chemists alike.

The concept of the steric stability of the C=C bond, manifested in the high barrier to exchange between *cis* and *trans* forms of 1,2-disubstituted ethylenes, is one of the most longstanding dogmas of organic chemistry. The underlying theory, based on sp^2 hybridized carbon atoms, the $\pi-\sigma$ separation and the sideways overlap of the p orbitals to form a π bond, is one of the early triumphs of the MO model[5]. In 'normal' double-bonded systems the sp^2 hybridized carbon atoms and the four atoms bonded to them lie in one plane, the double bond plane. The π bond gives rise to a barrier to rotation around the C−C bond in ethylene corresponding to an Arrhenius activation energy of 65.0 kcal mol^{-1}[6].

However, over the years an increasing number of molecules have been studied, which contain nonplanar C=C bond systems. The deformations are caused by strain, due to bulky substituents or to inclusion of the double bond in cyclic systems, or to both. The deviations can be described as twisting about the C=C bond or as pyramidalization of the carbon atoms, or as a combination of both. In C=C systems with pure twisting the carbon atoms remain sp^2 hybridized, and the bonding energy is diminished because of diminished overlap between the p orbitals. On pyramidalization of a carbon atom the hybridization changes in the direction of sp^3, and the p orbital, which is a component in the π bond, acquires some s character and turns away from the p orbital on the other carbon atom, which leads to diminished overlap and a weakened π bond (Scheme 1). The degree of pyramidalization is often measured by the angle Φ, but a more general pyramidalization analysis based on the π-orbital axis vector (POAV) has been proposed by Haddon[7–9].



SCHEME 1

An experimentally accessible index for strain in bridgehead olefins, *olefinic strain energy* (OS), has been proposed by Schleyer[10,11]. The OS is defined as the difference in strain energy between the olefin in its most stable conformation and the corresponding saturated hydrocarbon, also in its most stable conformation. It can be obtained by equation 1, where ΔH°_H is the heat of hydrogenation of the olefin and 26.1 is the heat of hydrogenation of an unstrained trisubstituted olefin to the corresponding unstrained saturated hydrocarbon. OS values have been derived both by quantum-mechanical (*ab initio* and semiempirical) and by EFF calculations, and OS <17 kcal mol^{-1} in general means that the compound is stable at ambient temperature, $17 <$ OS < 21 kcal mol^{-1} indicates stability in the range $+20$ to $-78\,^\circ$C, while compounds with OS > 21 kcal mol^{-1} can at

most be studied in low-temperature matrix isolation.

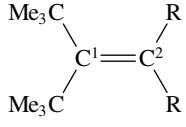
$$OS = \Delta H^{\circ}_{H} - 26.1 \text{ (in kcal mol}^{-1}\text{)} \quad (1)$$

The energetically unfavorable situation with pyramidal carbon atoms in double bonds was early realized by Bredt. His famous rule[12,13], which states that a carbon atom in a C=C bond cannot be a bridgehead in a bicyclic system, is based on studies of camphenes and pinenes and is thus intended to be valid only for five- and six-membered rings.

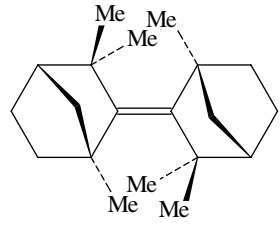
The field of strained olefins has been the subject of numerous reviews[14–18].

II. TETRASUBSTITUTED ETHYLENES

Tetra-*tert*-butylethylene **(1a)** can serve as a symbol for this group of compounds. In spite of ingenious approaches to its synthesis[19,20] it still eludes its pursuers. However, the most recent EFF calculations by Burkert[21] and by Favini and coworkers[22] predict a twist angle of *ca* 45° and a C^1-C^2 bond length of 137.7[20] and 136.0 pm[21], respectively. The latter authors calculated a strain energy of 89.6 kcal mol^{-1}, which means that **1a** should be capable of existence, since other hydrocarbons with much higher strain energies have been prepared, e.g. cubane with 166.9 kcal mol^{-1}. *Syn*-difenchylidene **(2)** is a close analogue of **1a**, but the cyclic structures remove some nonbonded interactions and the twist angle is only 11.8° and the C^1-C^2 bond length 134.9 pm[23], well reproduced by EFF calculations[22].



(1a) R = ^{t}Bu
(1a) R = Ph



(2)

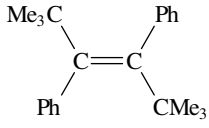
1,1-Diphenyl-2,2-di-*tert*-butylethylene **(1b)** has been prepared and studied by X-ray crystallography[24], and twist angle (24°) and C^1-C^2 bond length (136 pm) as well as other structural details were well reproduced by EFF calculations[22]. Gano and coworkers have studied two isomers of **1b**, viz. *E*- and *Z*-1,2-diphenyl-1,2-di-*tert*-butylethylene (**3a** and **3b**). The former was obtained in low-valent Ti-induced coupling of phenyl-*tert*-butyl ketone and was photoisomerized to **3b**, which in turn could be thermally isomerized back to **3a** with an enthalpy barrier of 31.2 kcal mol^{-1}. The low barrier indicates a high ground-state strain energy, estimated at 27.1 kcal mol^{-1}. The equilibrium mixture contained 0.4% of **3b**, corresponding to an energy difference of 4.2 kcal mol^{-1}[25]. An X-ray crystallographic study of **3b** unexpectedly shows an untwisted double bond with a C=C distance of only 134.3 pm and phenyl groups perpendicular to the double bond. The considerable crowding leads to large C=C–CMe_3 angles (132.7°)[26].

Sakurai and coworkers[27–30] have prepared a series of strongly crowded 1,1,2,2-tetrasilyl-substituted ethylenes (**4a** to **4e**). The twist angle and the lengths of the C^1-C^2 and C–Si bond lengths increase with increased crowding (Table 1). In **4a** and **4b** pure twisting occurs, but in **4d** C^2 and in **4c** both C^1 and C^2, which have

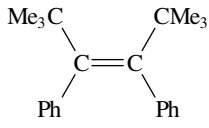
TABLE 1. Twist angles (Θ) and bond lengths in some tetrasubstituted ethylenes

Compound	Θ (deg)	$r_{C^1-C^2}$ (pm)	r_{C^1/C^2-Si} (pm)	Reference
1a	45	137.7	—	21[a]
	45.5	136.0	—	22[a]
1b	24	136	—	24
2	11.8	134.9	—	23
3b	0	134.3	—	26
4a	29.5	136.8	191.5[b]	27
4b	49.6	137.0		28
4c	50.2	136.9	193.0	29
	47.1		191.2	
4d	—[c]	138.1	197.1	30
4e	0	136.7	191.7	30

[a] From EFF calculation.
[b] Normal lengths in unstrained molecules 184–187 pm.
[c] Strongly twisted, but no angles are specified. C^1 with substituents planar, C^2 pyramidal.



(3a)



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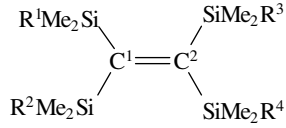
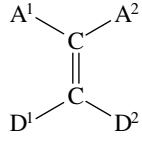


(4a) $R^1 = R^2 = R^3 = R^4 = Me$
(4b) $R^1 = R^2 = Me$, $R^3 = R^4 = {}^t Bu$
(4c) $R^1 = R^3 = Me$, $R^2 = R^4 = {}^t Bu$
(4d) $R^1 = R^2 = R^3 = {}^t Bu$, $R^4 = Me$
(4e) $R^1 = R^2 = R^3 = R^4 = H$

nonidentical substituents, are pyramidal. These compounds are red, and some of them show thermochromic behavior, indicating the existence of more twisted, high-energy conformers. However, the less crowded **4e** is colorless and has a planar double bond.

III. PUSH–PULL SYSTEMS

Twisting is particularly facile when the substituents are of push–pull type (**5**, A^1 and/or A^2 acceptors, D^1 and/or D^2 donors). The A^1A^2C part develops an increasing anion character and the D^1D^2C part an increasing cation character with increasing twist angle, and the loss of π bonding energy in the C=C bond is partly compensated by the delocalization energy of the incipient anion and cation. This stabilization increases and consequently the barrier to rotation about the C=C bond decreases with increasing donor capacity of D^1 and/or D^2 and with increasing acceptor capacity of A^1 and/or A^2. Studies by dynamic



(5)

NMR spectroscopy have shown that push–pull ethylenes with acyl groups as acceptors and amino groups as donors may have barriers to rotation lower than 5 kcal mol^{-1}[31]. If a steric interaction exists between the donor and the acceptor groups in the planar form of such a system, the strain may be relieved by rotation about the C=C bond. The geometry of the system and therefore the angle of rotation is controlled by the balance between the strain energy and the loss of π electron stabilization on rotation. However, the strain may also be released by rotation of the individual donor and acceptor groups around the D–C(=C) and A–C(=C) bonds, which leads to an increase of the C=C barrier. More clear-cut conditions are obtained if the two donor and/or the two acceptor groups are joined in a small (five- or six-membered) cyclic system, which diminishes the deformation of this part of the molecule.

The conformations of push–pull ethylenes are thus determined by an interplay between π-electronic and steric effects, and a schematic subdivision of this group of compounds into three different classes (case 1–case 3) with respect to the two effects has been proposed[32,33]. The energy contributions are discussed as functions of the dihedral angle, Θ, which describes the twist of the C=C bond. The steric energy (E_{ster}) is assumed to have maxima at $\Theta = 0^\circ$ and 180° and the π-electronic energy (E_π) at $\Theta = 90^\circ$ and 270°. During a full 360° rotation, four energy minima are passed.

In case 1 (Figure 1), E_{ster} is small and E_π relatively large, and the energy minima fall close $\Theta = 0^\circ$ and 180°. Most 'normal' push–pull ethylenes fall in this group, and *cis* and *trans* isomers are likely to be observable, at least with NMR spectroscopy unless the symmetry is too high. In case 2 (Figure 2), the relation is the opposite with $E_{ster} \gg E_\pi$. The positions of the energy minima depend on the shapes of the energy curves, but they are likely to fall closer to $\Theta = 90^\circ$ and 270° than to 0° and 180°. If $A^1 \neq A^2$ and $D^1 \neq D^2$, the molecules appear as pairs of enantiomers, which may be separated by substantial

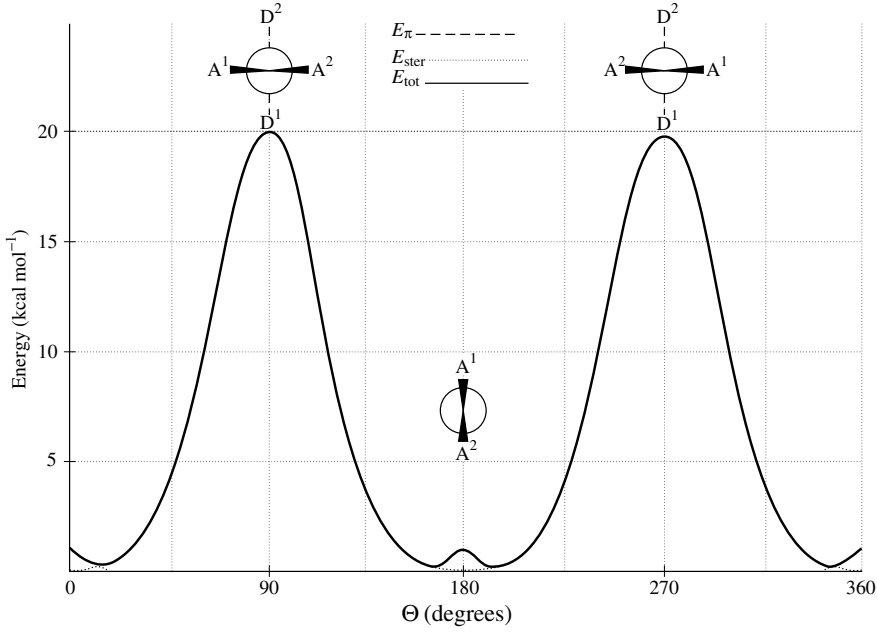


FIGURE 1. Schematic potential energy curve for a case 1 push–pull ethylene. $E_\pi \gg E_{ster}$

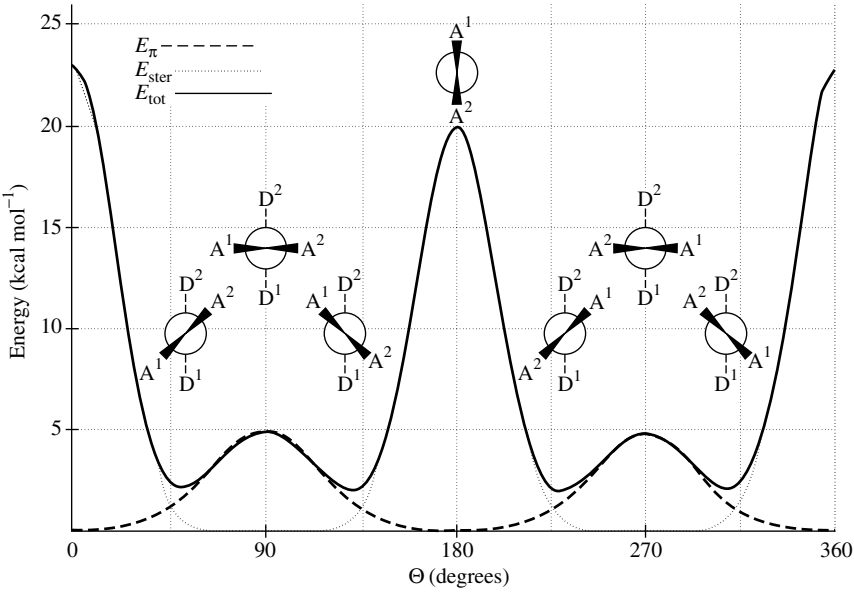


FIGURE 2. Schematic potential energy curve for a case 2 push–pull ethylene. $E_\pi \ll E_{ster}$

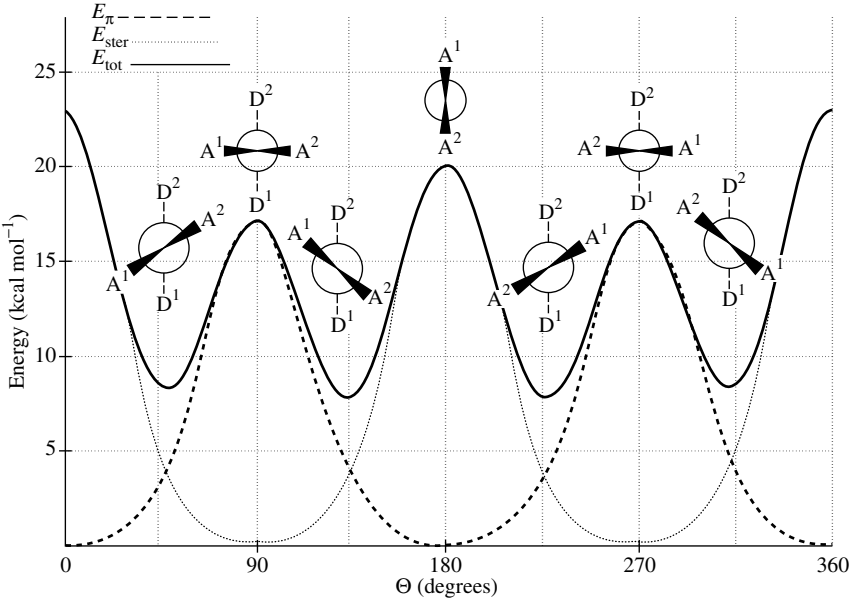
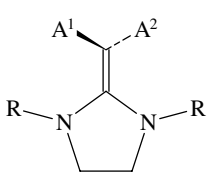


FIGURE 3. Schematic potential energy curve for a case 3 push–pull ethylene. $E_\pi \approx E_{ster}$

steric barriers. As will be discussed below, enantiomers in systems with sufficiently high barriers have been separated, using a chromatographic technique with chiral stationary phases. The barriers have then been measured by monitoring the rate of racemization. Lower barriers can be measured by a dynamic NMR technique[34] if the molecule contains prochiral groups[35], even if $A^1 = A^2$ *or* $D^1 = D^2$. *Cis* and *trans* isomers, on the other hand, are separated by very low barriers and are not likely to be observed separately.

Finally, in case 3 (Figure 3), E_{ster} and E_π are both of similar and substantial magnitude. The energy minima fall in the neighborhood of $\Theta = 45°$, 135°, 225° and 315°, and in systems with suitable barriers and substituents the passages past both the steric and the π-electronic barriers can be followed by NMR spectroscopy.

In this chapter, only case 2 and case 3 systems are of interest. Representatives of the former group are found among compounds **6** and **7** (Table 2). The structural requirements are bulky substituents and a combination of good donor and good acceptor groups. While compounds **6a–6c** can be seen as intermediates between case 1 and case 2 because of their rather weak acceptor groups, compounds **6d** and **6e**, with good acceptor groups, clearly belong to case 2. Because of the larger bond angles in six-membered rings, E_{ster} is larger in compounds **7** than in corresponding compounds **6**, as shown by the larger twist angle (Θ) in **7c** than in **6c** and by the higher $\Delta G^{\#}_{ster}$ in **7d** than in **6d**.



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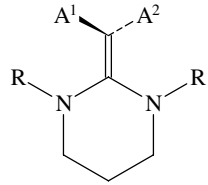


(7)

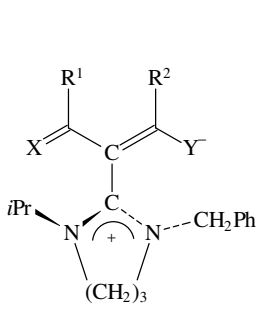
Rather few case 3 systems have been described. The requirement is a strong steric effect and a combination of rather poor donor and/or acceptor groups. The first chosen candidate, **7b**, has good donors and poor acceptors, and it fulfilled the expectations. The ^{1}H NMR spectrum of the benzylic protons showed a singlet at ambient temperature, which changed into an AB system around −70 °C, and into two broad, equally intense AB systems around −130 °C[36]. Raised acceptor capacity as in **7e** leads to an increased

TABLE 2. Free-energy barriers to rotation through the 90° twisted state ($\Delta G^{\ddagger}_{\pi}$, kcal mol^{-1}) and through the planar state ($\Delta G^{\ddagger}_{ster}$, kcal mol^{-1}), twist angles (Θ°) and C^1-C^2 bond lengths (pm) for compounds **6** and **7**

Compound	A^1	A^2	R	$\Delta G^{\ddagger}_{\pi}$	$\Delta G^{\ddagger}_{ster}$	Θ	$r_{C^1-C^2}$	References
6a	4-BrC_6H_4	CN	Me	9.5		41	144.8	38, 39
6b	Ph	CN	CH_2Ph	9.2	<5.0			32
6c	CN	CN	Me			20	140.7	37
6d	PhCO	COMe	CH_2Ph	<5.0	16.5			32
6e	MeCO	COMe	Me			73	146.8	37
7a	Ph	CN	Me	7.4				36
7b	Ph	CN	CH_2Ph	7.3	10.5			36
7c	CN	CN	Me			32	142.9	37
7d	PhCO	COMe	CH_2Ph	<5.0	22.0			32
7e	4-$O_2NC_6H_4$	CN	CH_2Ph		13.9			36
7f	4-$H_2NC_6H_4$	CN	CH_2Ph	8.3	9.7			32

steric barrier and a decreased (to below the limit of detectability) π barrier, while lowered acceptor capacity as in **7f** has the opposite effect.

Coming back to case 2 systems, a number of analogues of **7** with acyl and thioacyl groups as acceptors and with *i*-Pr and $PhCH_2$ groups as substituents on the nitrogen atoms (**8–10**, Table 3) have been resolved by chromatography on swollen microcrystalline triacetylcellulose[40,41], and the barriers to rotation through the planar state have been determined by monitoring the thermal racemization. As expected, replacement of carbonyl by thiocarbonyl groups as acceptors increases the steric barrier both by lowering E_π (C=S is a better acceptor than C=O[42]) and by raising E_{ster}. It is also clear that E_{ster} is increased and E_π is decreased compared to the situation in compounds **8** if the acceptor groups are also included in a ring system. This should lead to an increase in $\Delta G^{\ddagger}_{ster}$, which is borne out by a comparison of the barriers in **8a** and **9b**.



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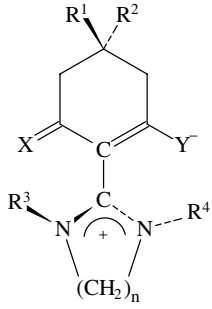

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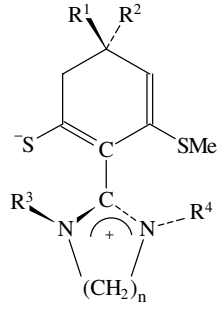


(10)

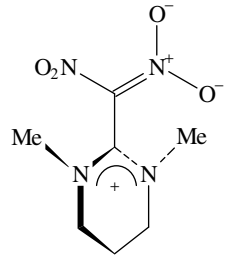
Compounds **9a**, **9c**, **9e** and **10c** have been subjected to X-ray crystallographic studies[43,45] and large twist angles and long C−C bonds have been observed (Table 3). Comparison of **9a** and **9e** shows the effect of the size of the donor ring discussed above, the twist angle Θ being *ca* 5° larger with a six-membered than with a five-membered donor ring. The same effect is responsible for the difference in $\Delta G^{\ddagger}_{ster}$ between **10a** and **10b**. The difference in twist angle between **9e** and **10c** can be ascribed to differences in E_π. The steric effects should be rather similar, but the acceptor part in **9e** contains two and in **10c** only one thiocarbonyl group. Therefore E_π is higher in **10c** and the energy minimum falls at a lower Θ value than in **9e**. The C−C bond lengths in the four compounds are rather similar and show no correlation with the twist angles.

The barriers to passage of the 90° twisted state in case 1 type push–pull ethylenes have been shown to correlate roughly with $\Sigma\sigma_R^-$ of the acceptors[46] and the nitro group should be a better acceptor than acyl and thioacyl groups. Consequently, push–pull systems with two nitro groups as acceptors, like **11** and **12**, show practically perpendicular acceptor parts with $\Theta = 89.0$ and 86.9°, respectively[47].

Case 2 systems like compounds **8–12**, and especially **11** and **12**, are not olefins but are best described as zwitterions of carbanions and amidinium ions. Consequently, the polarity of the molecule should decrease when going from the ground state to the transition state to rotation, contrary to the situation in case 1 systems. This has been supported by AM1 and CNDO calculations[45]. The activation parameters in the two kinds of systems have been studied, and as expected case 1 systems have large and negative, and case 2 systems moderate and positive, activation entropies[48]. The barriers in case 1 systems are considerably lowered, and those in case 2 systems practically unchanged, by increased solvent polarity[48,49].

TABLE 3. Free-energy barriers to rotation through the planar state (kcal mol^{-1}), C^1-C^2 bond lengths (pm) and twist angles (deg) for compounds **8–10**

Compound	n	R^1	R^2	R^3	R^4	X	Y	$\Delta G^{\ddagger}_{ster}$	$r_{C^1-C^2}$	Θ	Reference
8a		Me	Ph			O	O	25.6			40
8b		Me	Ph			O	S	30.3			41
8c		Me	Me			O	S	30.3			41
8d		Me	Ph			S	S	29.9			41
9a	2	Me	Me	CH_2Ph	CH_2Ph	S	S		148.2	80.6	43
9b	3	H	Ph	*i*-Pr	CH_2Ph	O	O	27.8			44
9c	3	Me	Me	CH_2Ph	CH_2Ph	O	O		147.2	78.8	45
9d	3	Me	Me	*i*-Pr	CH_2Ph	O	S	>30.4			41
9e	3	Me	Me	CH_2Ph	CH_2Ph	S	S		146.6	85.1	45
10a	2	Me	Me	*i*-Pr	CH_2Ph			28.9			44
10b	3	Me	Me	*i*-Pr	CH_2Ph			30.4			44
10c	3	Me	Me	CH_2Ph	CH_2Ph				147.6	72.5	45



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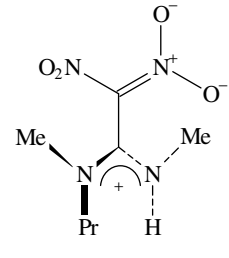

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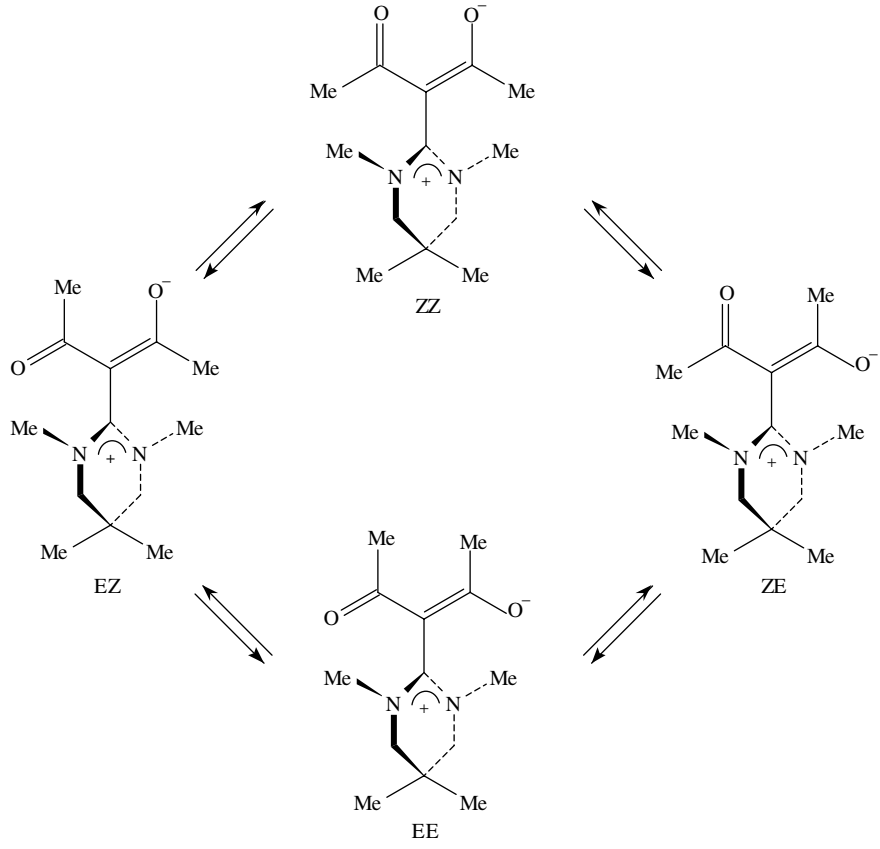
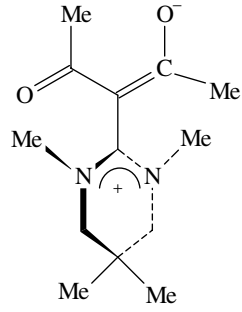


SCHEME 2

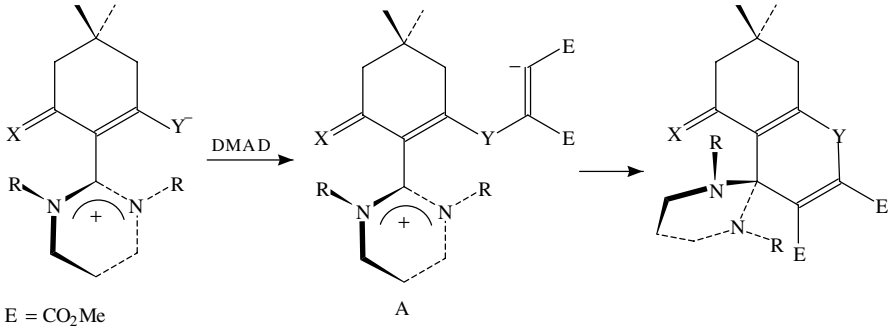
The delocalization in the donor and acceptor parts of case 2 systems leads to considerably hindered rotations around the formal single bonds. The acceptor part of a compound like **13** is similar to the anion of a β-diketone. While the dynamics of the latter one is difficult to study without the intervention of a chelated cation, the acceptor part of **13** is more similar to an isolated β-diketonate ion. A study of **13** by dynamic ^{1}H NMR revealed exchange between three rotamers (*EZ*, *ZE* and *EE*, Scheme 2). The fourth rotamer, *ZZ*,

destabilized by dipole–dipole repulsion, could not be observed, but lineshape analysis revealed that it plays a role as high-energy intermediate in the *EZ*–*ZE* exchange[50].



(13)

Push–pull ethylenes are unreactive toward normal double-bond reagents[51]. The dipolar character of the twisted representatives might have made them attractive substrates for addition reactions with dipolarophiles. However, reactions of a series of typical compounds, analogues of **6** and **7**, with dimethyl acetylenedicarboxylate (DMAD) led to addition of the dipolarophile between a negatively charged oxygen or sulfur atom in the acceptor part and the positive carbon atom in the donor part (Scheme 3), leading to spiro compounds[52–54]. The reaction probably proceeds in steps, since in the presence of water the first adduct (A) is protonated, and the reaction takes a different route[55].



SCHEME 3

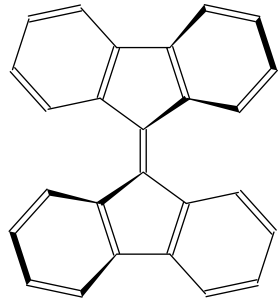
The ultraviolet absorption spectra of a number of untwisted and twisted compounds of the types **5**, **6** and **7** have been studied[43,45] and found to be compatible with the chromophore in the acceptor part. The same was found for the photoelectron spectra of a series of more or less twisted simple push–pull ethylenes[56].

IV. BIS-TRICYCLIC ETHYLENES

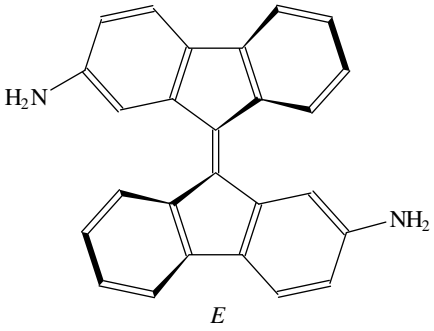
These compounds have long been of interest, among other things because of their generally strong color and the thermochromic, piezochromic and photochromic properties of some of them. Two main types can be recognized, the bifluorenylidenes **14** with

five-membered central rings, and the bianthronylidenes, dixanthylenes, biacrylidenes and the bianthrylidenes **15a–15d** with six-membered central rings. Compounds with seven-membered central rings **(15)** have also been described.

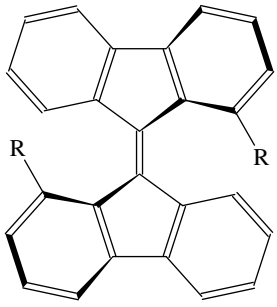
Coplanarity is made impossible by the close approach of the neighboring *peri* hydrogen atoms (H-1, H-1′ and H-8, H-8′/H-9, H-9′), and these compounds have two principal routes to minimize the steric strain based on the mechanisms mentioned in Section I. One way, *twisting*, is to rotate the two halves of the molecule about the formal double bond



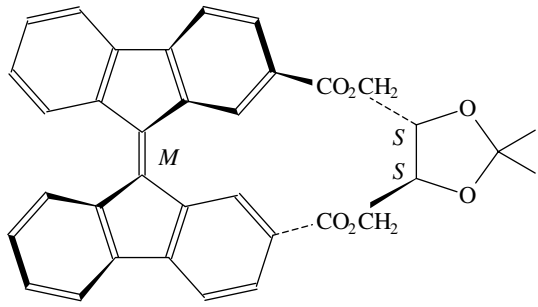
(14a)



(14b)



(14c) R = CO_2Pr-*i*



(14d)

while retaining the planarity of the tricyclic parts, and another, *folding*, is to introduce pyramidalization at the double-bond carbon atoms, leading to *anti-* or *syn-folding* of the tricyclic parts (Scheme 4). A combination of the two routes is also feasible.

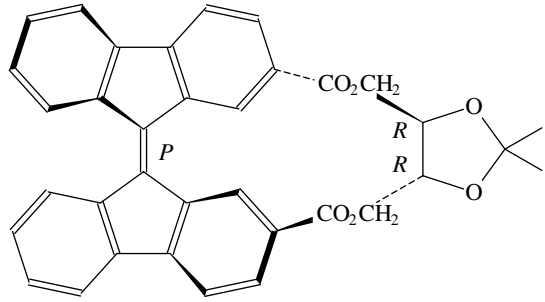
The symmetry properties of the parent compounds **14–16** and their substituted derivatives plays a great role in the analysis of their chirality and dynamic behavior. These properties have been analyzed in detail by Agranat and coworkers[57].

Due to complications in the crystal structure, the X-ray crystallographic analysis of the parent bifluorenylidene **(14a)** for a long time gave conflicting results. However, it is now generally accepted[58,59] that **14a** has a twisted structure. The value of the twist angle depends on how it is measured. The mean angle between the mean planes of the fluorene parts is 42.3°, whereas the mean of the dihedral angles at the 9,9′ bond is 32.8°. The difference is due to a slight deformation of the nearly planar fluorene parts. Molecular force-field[60] and MNDO-PM3[57] calculations have given similar results, with twist angles of 42.9° and 30.2°, respectively. Substitution in the 1,1′,8,8′ positions increases the twist angle, up to 67° in the perchloro derivative[61].

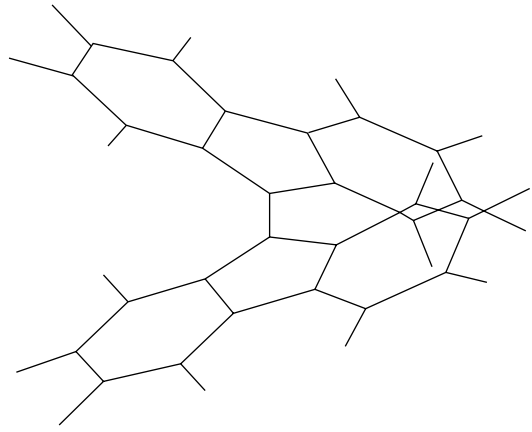
The twist-angle dependence of the energy of the molecule can be expected to be similar to that of the case 3 push–pull systems discussed above (Figure 3) with energy maxima at *ca* 0°, 90°, 190° and 270°. Derivatives, which are unsymmetrically substituted in the individual fluorene units (e.g. 1,1′- or 2,2′-substituted) can exist as enantiomeric pairs of *E* and *Z* forms (Figure 4). Racemization occurs by passage through the planar state and *E*–*Z* exchange by passage through the perpendicular state. The *E* and *Z* forms of 2,2′-diamino-bifluorenylidene **(14b)** were resolved by chromatography already in 1953, and the barrier to *E*–*Z* exchange was found to be 25 kcal mol^{-1}[62].

Early determinations of the barriers for the two kinds of processes employing the temperature dependence of the NMR spectra were made with 1,1′-substituted derivatives with substituents containing prochiral groups, e.g. **14c**[63]. The two kinds of barriers were found to be very similar, *ca* 20 kcal mol^{-1}. However, it is evident that the 1,1′-substituents increase the racemization barrier by increasing the strain in the planar state and lower the barrier to *E*–*Z* exchange by increasing the ground-state strain.

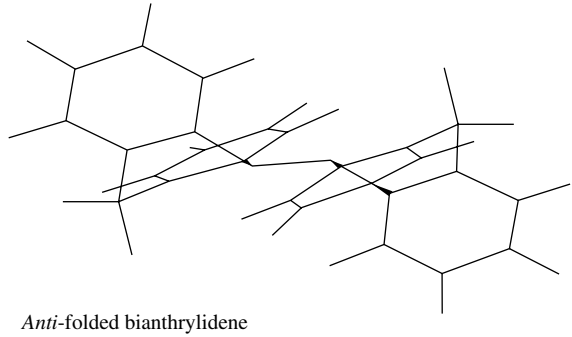
Luh and coworkers have developed a new desulfur-dimerization of thioketals by treatment with tungsten hexacarbonyl to form C=C bonds[64,65]. Application of this reaction to the diester of 9,9-ethylenedithiofluorene-2-carboxylic acid and (*R*,*R*)- or (*S*,*S*)-2,2-dimethyl-4,5-bis(hydroxymethyl)-1,3-dioxolane led to enantiomeric bifluorenylidenes of unknown optical purity with the 2,2′ positions connected by a chiral bridge **(14d, 14e)**[66]. These compounds display high specific rotations, $[\alpha]_D^{22} = +634°$ and $-690°$ for the enantiomers with *S* and *R* configuration of the bifluorenylidene moiety, respectively. They are optically stable, which is ascribed to the rigidity imposed by the dioxolane ring. When the



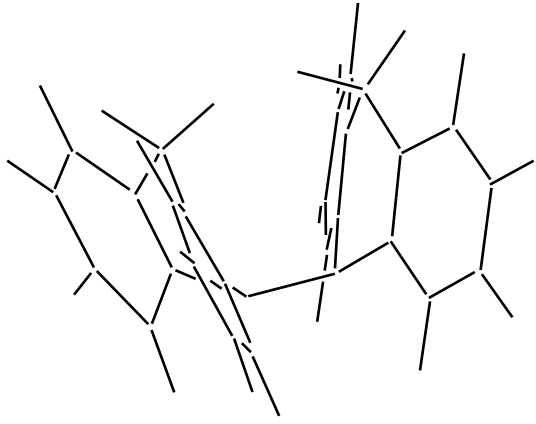
(14e)



Twisted bifluorenylidene



Anti-folded bianthrylidene



Syn-folded bianthrylidene

SCHEME 4

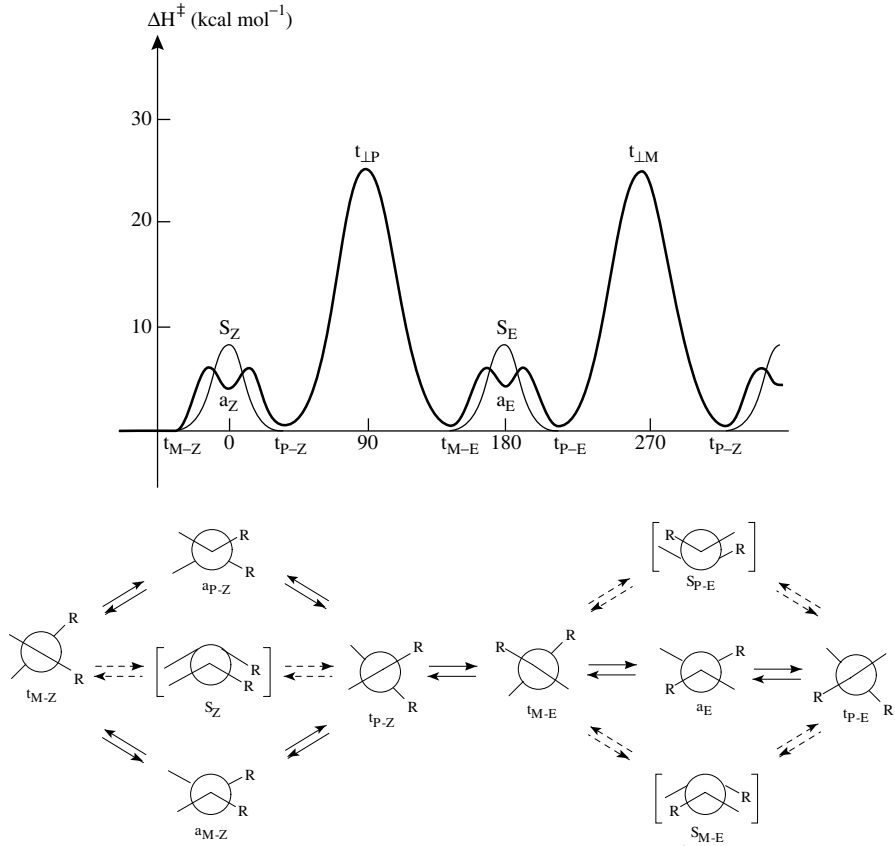
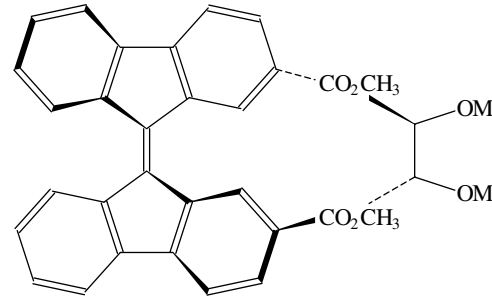


FIGURE 4. Schematic potential energy curve and exchange pathways for a 2,2′-substituted bifluorenylidene

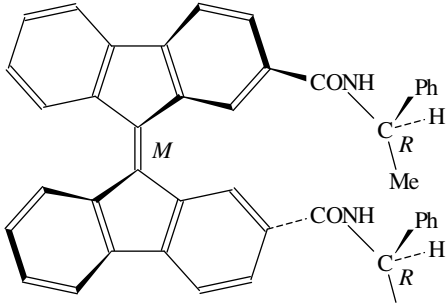
ring is replaced by two methoxy groups **(14f)**, a labile system with low specific rotation is formed, evidently a nearly 1:1 mixture of two rapidly interconverting diasteromers with opposite chiralities of the bifluorenylidene units. The ^{1}H NMR spectrum shows only one set of signals at ambient temperature, but it splits into two sets below $-20\,^\circ$C, corresponding to a barrier to racemization of 12 kcal mol^{-1}. The exchange process is suggested to proceed with pyramidalization at one or both of C-9 and C-9′.

In a following study, Luh and coworkers[67] describe the preparation of the *E* and *Z* isomers of **14g** in the ratio 85:15 by reaction of **14h** with (*R*)-1-phenylethylamine in refluxing dichloromethane. The *Z* isomer of **14g** is shown to rearrange rapidly to *E* in boiling ethanol, although no rate or barrier data are reported. The *Z* isomer of **14g** also shows an equilibrium between (*P*,*R*,*R*) and (*M*,*R*,*R*) forms (epimerization) with a barrier of 11.5 kcal mol^{-1}. A number of 2,2′-di- and polyether- and -diester-bridged analogues are described, and the hydrolysis of one of the latter gave the pure *Z* form of **14h**, not isomerized to the *E* form even at $+160\,^\circ$C.

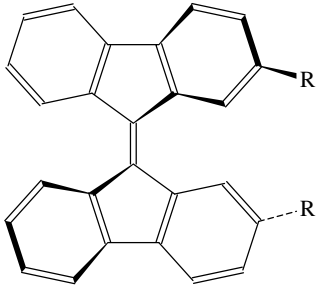
Grieser and Hafner[68] report the preparation of a 1:1 mixture of the *E* and *Z* isomers of bi(cyclohepta[*def*]fluorenylidene), **14i** and **14k**. A racemization barrier of 15.0 kcal mol^{-1}



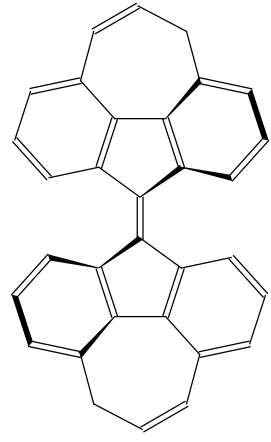
(14f)



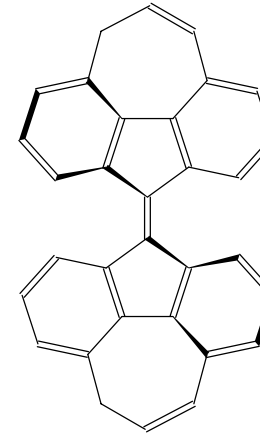
(14g)



(14h) R = CO_2H
(14l) R = Me
(14m) R = Pr-*i*



(14i) *M-E*



(14k) *P-Z*

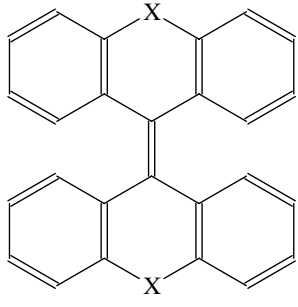
was determined by NMR lineshape analysis. The reason for this comparatively high barrier may be the rigidity imposed by the 4,5 and 4′,5′ bridges.

In a recent work, Agranat and coworkers[69] report studies of the temperature-dependent ^1H and ^{13}C NMR spectra of 2,2′-dimethyl- **(14l)** and 2,2′-diisopropylbifluorenylidene **(14m)**. The free-energy barrier to racemization in **14m** was determined as being

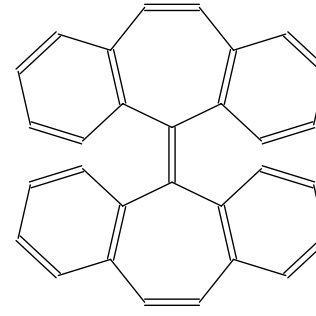
11.5 kcal mol^{-1}, in good agreement with the value for **14g**. A similar study of the $E-Z$ exchange in **14l** gave a barrier of 25 kcal mol^{-1}, fixing the value of this barrier in an unrestrained bifluorenylidene.

Based on PM3 calculations on **14a**, Agranat and coworkers[69] have proposed a detailed mechanism for the dynamic processes in **14l** and **14m** (Figure 4). The racemization is predicted to proceed *via* an *anti*- folded intermediate **a**, which is calculated to be 4.6 kcal mol^{-1} above the ground state **t**; **a** and **t** are separated by a transition state, the energy of which is not reported An alternative but less likely racemization route proceeds *via* a *syn* -folded transition state **s**, 8.2 kcal mol^{-1} above **t**. The $E-Z$ exchange is predicted to occur with a perpendicular transition state $\mathbf{t}_{\perp}$, 25.0 kcal mol^{-1} above **t**. The latter value is in very good agreement with the experimental barrier to $E-Z$ exchange. Passage from $\mathbf{t}_{M-Z}$ to $\mathbf{t}_{P-Z}$ via a planar transition state is very unlikely, since the energy of this state is calculated to be 29.4 kcal mol^{-1} above that of **t**. In the proposed itinerary, every transition state involves at most one edge passage.

X-ray crystallographic studies have shown that bistricyclic compounds with six-membered central rings are *anti*-folded, e.g. bianthrone **(15a)**[70,71] and dixanthylene **(15b)**[72]. The unsubstituted compounds are centrosymmetric, but symmetric tagging, e.g. by introducing equal 2- and 2′-substituents, permits the existence of *E* and *Z* isomers, each of them a pair of enantiomers. Agranat and coworkers[73–79] have used a ^{1}H NMR bandshape technique to study the barriers to $E-Z$ exchange and to racemization in derivatives of **15a–c**, substituted in 2,2′ position with methyl or isopropyl groups. The barriers to the two processes were found to be very similar, indicating a common transition state. The barriers were found to be 20–22 kcal mol^{-1} for **15a** and **15c**, and *ca* 18 kcal mol^{-1} for **15b**.



(15a) X = C═O
(15b) X = O
(15c) X = NMe
(15d) X = CH_2



(16)

Using the force-field method of Warshel and Karplus[80], Korenstein, Moszkat and coworkers[81,82] found three minimum energy conformations for dianthrylidenes. The one predicted to be most stable (A) was the *anti*-folded form found in the crystal[70]; the following one (B) was the twisted form with twist angles in the range 50° to 60°. The third, still higher in energy, is *syn*-folded (E). The calculations predict B to be 2 kcal mol^{-1} above A and E to be another 11 kcal mol^{-1} higher. MNDO-PM3 calculations on dixanthylene **15b**[57] predict an *anti*-folded A form very similar to that in the crystal to be the most stable

one with the *syn*-folded E form 4.1 kcal mol^{-1} and the twisted B form with a 49° twist angle 8.7 kcal mol^{-1} above the ground state. Evidently, forms B and E may be considered as intermediates on the itineraries between the *E* and *Z* and between the *P* and *M* forms.

The energy curve proposed by Agranat and coworkers[75–78] for the interconversions (Figure 5) is similar to that in Figure 4, with the difference that the *anti*-folded forms now are the ground states and the twisted forms are higher-energy intermediates. The interconversions are based on the principle of only allowing one edge passage at a time and not to allow substituted edges to pass one another. The *syn*-folded form E is not considered, and it is not expected to facilitate the interconversions even if it represents an energy minimum on the total energy hypersurface.

In bianthrones **(15a)** the B form is thermally and photochemically[83] accessible, and both the B → A barrier ($\Delta H^{\ddagger}$) and ΔH° could be determined by monitoring the equilibrium and the reaction rate as functions of the temperature[79]. The B → A barrier was found to

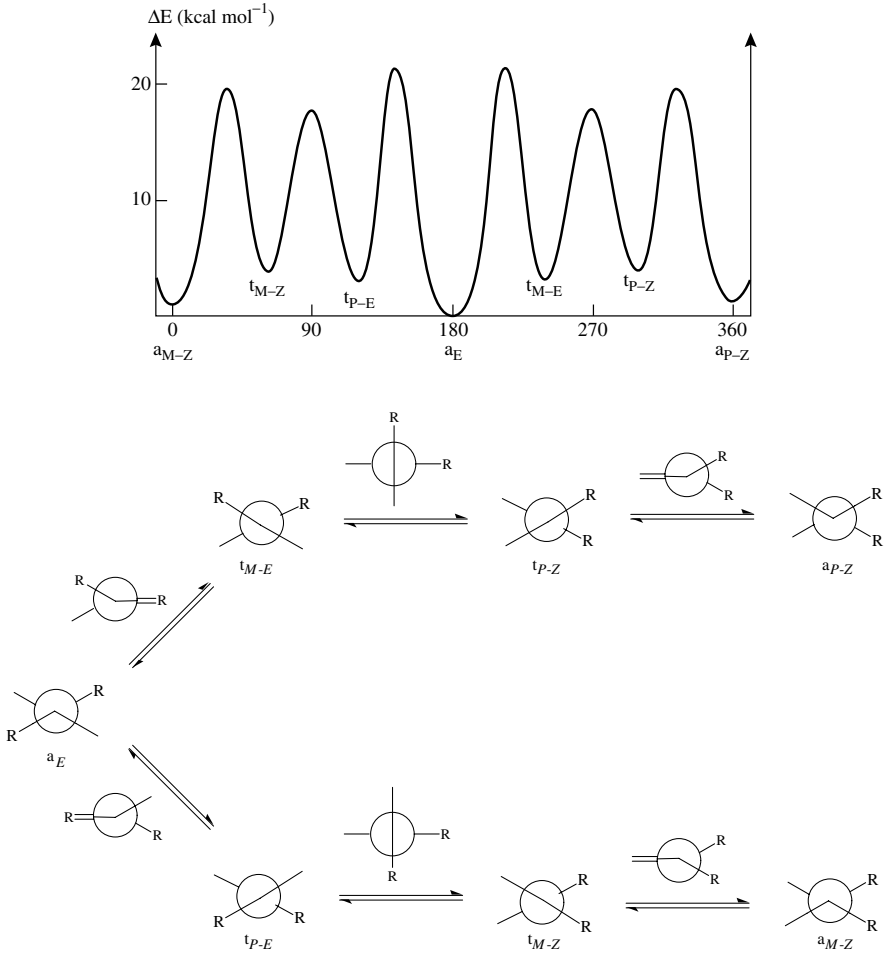


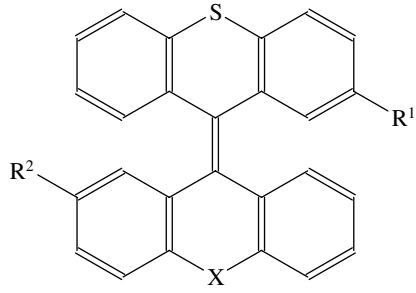
FIGURE 5. Schematic potential energy curve and exchange pathways for a 2,2′-substituted bianthrone

be 16.1 ± 0.7 kcal mol^{-1} and the enthalpy difference 4.2 kcal mol^{-1}, in good agreement with the experimental free-energy barrier of 21.5 ± 0.3 kcal mol^{-1}[78].

The changes in the bianthrones and bixanthylidenes can be followed photometrically, since the visible absorption occurs at much longer wavelength (600–650 nm) in the B form than in the A form (⩽400 nm)[83]. The A → B transition is favoured by high pressure on the crystal (triboluminescence) or in solution[84].

To judge from the double bond lengths (138 pm in **14a**[58], 132 pm in **15a**[70]) the *anti*-folded structure preserves the double bond character better than the twisted one. Semiempirical calculations (CNDO/S) show that the π-overlap across the double bond is much more diminished by a twisting in **15a** than by an *anti*-folding leading to the same increase in H-1−H-1′ and H-9−H-9′ separation. Folding in compounds **14** is unfavorable because of the restraint imposed by the Ar−Ar bond.

Feringa and coworkers[85] have resolved 2-methyl-9*H*-thioxanthene-9-(9*H*-thioxanthen-9-ylidene) **(17a)** and some homo- and heteromerous[57] analogues **(17b–17d)** by chromatography with (+)-polytriphenylmethylmethacrylate[86] as chiral stationary phase. Only the monothio-bixanthylidene **17e** could not be resolved, presumably because the barrier is below 20 kcal mol^{-1}. The 2,2′-dimethyl-bithioxanthylidene **17d** was separated into three components, the centrosymetric *E* isomer and two enantiomers of the *Z* isomer. The racemization barriers for **17a** and **17d** were as high as 27.2 ± 0.2 kcal mol^{-1}, 9.4 kcal mol^{-1} higher than for the analogous dixanthylidene **17b**[76]. The barrier for *E–Z* exchange was also *ca* 27 kcal mol^{-1}, supporting the mechanism discussed above (Figure 5). An interesting correlation was found between the barriers and the aryl-X bond lengths (Table 4), which can be related to the expansion of the central ring. Feringa and coworkers have also studied the thermal and photochemical isomerizations of analogues of **17a** with a view to their use as molecular switches.[87,88]

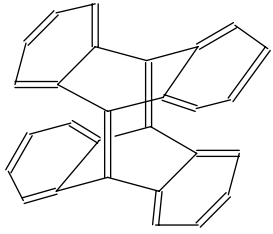


(17a) X = S, R^1 = Me, R^2 = H
(17b) X = CMe_2, R^1 = Me, R^2 = H
(17c) X = NMe, R^1 = Me, R^2 = H
(17d) X = S, R^1 = R^2 = Me
(17e) X = O, R^1 = Me, R^2 = H

A bistricyclic ethylene with seven-membered central rings, 5,5′-bis-5*H*-dibenzo[*a*,*d*]cycloheptenylidene **(16)**, has been found to give two stable steroisomers, one with *syn*- and the other with *anti*-folding[89]. An extreme case of *syn*-folding is represented by 9,9′,10,10′-tetrahydrodianthracene **(18)**[90], in which the anthracene rings in a bianthrylidene are bent backward to the extent of permitting double bonds between the 9,9′ and 10,10′ positions.

TABLE 4. Relation between C−X bond lengths and racemization barriers for compounds **17a–17c** and **17e**[85]

Compound	X	r_{C-X} (pm)	$\Delta G^{\ddagger}_{rac}$ (kcal mol^{-1})
17a	S	177	27.4 ± 0.2
17b	CMe_2	152	25.1 ± 0.3
17c	NMe	142	21.3 ± 0.5
17e	O	138	<20.0



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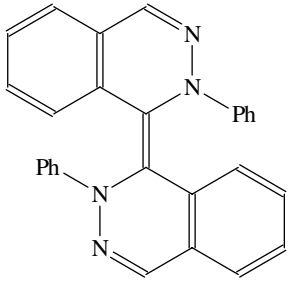


(19)

According to Haddon[9], this compound possesses the most strongly pyramidalized double-bond carbon atoms of all structurally characterized molecules see below (Table 6).

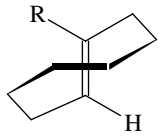
A bis-bicyclic compound, **19**, has been studied by X-ray crystallography and was found to assume an *anti*-folded structure[91].

V. MEDIUM-SIZED *trans*-CYCLOALKENES AND ANALOGUES

Cyclodecene is the smallest cycloalkene, which can accommodate a *trans* double bond without significant deformation of bond angles and/or dihedral angles. The strain energies and structures of smaller *trans*-cycloalkenes have been the subjects of considerable research over the years.

trans- or *E*-1-Phenylcyclohexene has only been observed as an extremely short-lived species on laser photolysis of the *Z* isomer[92]. Seven-membered analogues show much greater stability. *E*-Cycloheptene has been generated photochemically, and the enthalpy barrier to isomerization to the *Z* isomer was measured to be 18.2±1.2 kcal mol^{-1}[93], whereas the corresponding barrier for *E*-1-phenylcycloheptene was found to be 20.9 kcal mol^{-1}[94]. The strain energy of the *E* in excess of the *Z* form of unsubstituted cycloheptene has been calculated to be 20.3 kcal mol^{-1} with a C−C=C−C dihedral angle of 125°, corresponding to an OS value of 19.6 kcal mol^{-1}[95].

The most-studied member of this group is *trans*- or *E*-cyclooctene **(20a)**. The bridging of the *trans*-1,2-positions by a hexamethylene chain imposes too much strain to permit a planar double-bond system. Electron diffraction studies[96] and EFF calculations[95–97] show that the molecule has a crown or twist conformation with a C−C=C−C dihedral angle of 136°. The olefinic carbon atoms are slightly pyramidalized, and the situation at the double bond can be described as a combination of twisting and *syn*-folding. Studies of *E*-1-methyl-cyclooctene **(20b)** show the same kind of deformations, but a diminished C−C=C−C dihedral angle (130.3°) and increased pyramidality at C-1 but diminished at C-2[98].



(20a) R = H
(20b) R = Me

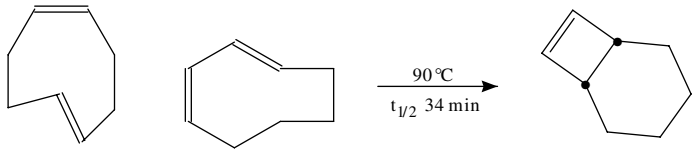
In spite of the deformations, the strain energy in these compounds is not excessive. EFF calculations by Inoue and coworkers[99] predict a difference in strain energy of 9.7 kcal mol^{-1} between *E*- and *Z*-cyclooctene (11.3 kcal mol^{-1} according to Allinger and Sprague[95]) and 11.7 kcal mol^{-1} for the 1-methyl analogues. The strain energy for **20a** is calculated to 6.3 kcal mol^{-1}[95].

E-Cyclooctene is chiral, and it was resolved into enantiomers by Cope and coworkers[100] by separation of diasteromeric platinum complexes containing **20** and (+)-phenyl-2-aminopropane as ligands. Thermal racemization occurred around 150 °C with a rate corresponding to a barrier of *ca* 35 kcal mol^{-1}[101].

The original synthesis of *E*-cyclooctene was performed by a Hofman degradation of trimetylcyclooctylammonium hydroxide[102]. However, photoisomerization of the *Z* isomer has emerged as an attractive alternative. Direct isomerization by irradiation with UV light of 185 nm in pentane gives a photostationary state with an *E*/*Z* ratio of 0.98[103,104], and similar results are obtained by irradiation of *E*-1-methylcyclooctene at 214 nm[99]. A good preparative method is singlet-sensitized isomerization using (poly)alkyl benzene(poly)carboxylates as sensitizers[99]. The mechanism involves exciplex formation with twisted singlet cyclooctene, and by using a chiral singlet sensitizer, e.g. (−)hexa-1-methylheptyl benzenehexacarboxylate at −87 °C in pentane, an enantiodifferentiating transformation of *Z*- to *E*-cyclooctene with an enantiomeric excess (ee) of 52.7% of (+)-*E*-cyclooctene was achieved[105,106]. The ee is strongly sensitive to the nature of the chiral sensitizer and generally increases with decreasing temperature. In fact, reversal of the absolute configuration of the major enantiomer at higher temperatures was observed in some cases, which could be explained as an effect of the entropy of activation. In a later work[107], even better results were obtained with sensitizers containing a phenyl or cyclohexyl group attached to the chiral component of the sensitizer. The highest ee, 63.5%, was reached with tetrakis-8-cyclohexylmenthyl benzene-1,2,4,5-tetracarboxylate as sensitizer at −89 °C. A similar study of enantiodifferentiating *Z*- to *E*- photoisomerization of **20b** has recently been reported[108].

1,3- and 1,5-Cyclooctadienes are also known as *E*,*Z* isomers. *E*,*Z*-1,5-cyclooctadiene **(21)** has been resolved and is stable at not too high temperatures[109]. However, at *ca* 150 °C it undergoes a sequence of Cope rearrangements, ending up in *Z*,*Z*-1,5-cyclooctadiene[110]. The 1,3-analogue **(22)** has been prepared both by stereoselective elimination[111] and by photoisomerization[112]. It has been resolved into enantiomers by chromatography with swollen, microcrystalline triacetylcellulose as stationary phase[113], and optically active **22** has been obtained in 17.6% ee in a stereoselective singlet-sensitized photoisomerization with hexamenthyl benzenehexacarboxylate as sensitizer[114]. Thermal racemization of **22** is not feasible, since already at +90 °C an electrocyclic reaction takes place with appreciable rate, leading to *cis*-bicyclo[4.2.0]oct-7-ene **(23)**[115,116].

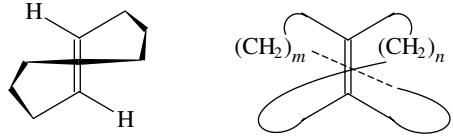
Bouman and Hansen have calculated the CD spectra of (*M*)-**20a** and (*M*)-**22** by *ab initio* methods[117,118]. Positive rotation was predicted for both compounds. The main contribution to the rotational strength in both compounds comes from the twisted *E* double



(21) **(22)** **(23)**

bond. More recently, Hansen and coworkers performed similar calculations for **20a** with a more elaborate basis set and with a similar result[119]. The so-called diene helicity rule[120], which predicts positive rotational strength for dienes with a positive C=C−C=C dihedral angle (*P* helicity for the *E* double bond), is not valid for **22**.

Even in *E*-cyclononene **(24)** the 'jump-rope' movement of the saturated chain is sufficiently hindered to permit the isolation of enantiomers, but the free-energy barrier to racemization was found to be as low as 19.1 ± 0.2 kcal mol^{-1}[121]. A complete EFF search of the conformational space of **24** has recently been published, leading to a barrier of 21.6 kcal mol^{-1}[122]. Earlier EFF calculations predicted the strain energy of **24** to be zero[95].



(24) **(25)**

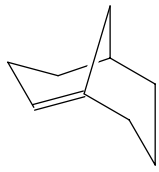
Resolution of *E*-cyclodecene has not succeeded, but its 1,2-dimethyl derivative as well as the corresponding cycloundecene derivative have been obtained in optically active form[123].

An interesting group of bicyclic cycloalkenes, the so-called [*m*,*n*]betweenanes, contain a double bond, which has *E* configuration in both rings **(25)**. Most representatives have *m* and $n > 6$ and have rather low strain or are strain-free[123], but a successful synthesis of a [6.10]betweenane has been reported[124].

VI. BI- AND POLYCYCLIC BRIDGEHEAD OLEFINS

As mentioned in Section I, Bredt's rule prohibits double bonds at bridgeheads. For a time, the rule was assumed to be generally valid, but as exceptions began to emerge around 1950, they were, and are often still referred to as Bredt's rule violators. An early case of a stable though reactive bridgehead olefin is **26**[125,126]. The double bond is part of one *Z*- and one *E*-cycloalkene, and a stable product is expected when $(m + n) \geqslant 5$ in **27**, i.e. the *E*-cycloalkene is eight-membered or larger[127]. However, a number of more strained bridgehead olefins have been studied. A remarkably stable *E*-cycloheptenoid bridgehead olefin is adamantyl-homoadamantene **(28)**, which can be heated to 185 °C without decomposition[128]. The likewise cycloheptenoid **29** is much less stable, but Michl and coworkers have isolated it in matrix and in solution and studied its spectroscopic properties[129].

Using intramolecular Diels-Alder reactions, Lease and Shea[130] have prepared a series of bridgehead olefins, which at the same time are bridgehead lactams with the nitrogen atom at the other bridgehead **(30)**. In these, the C=C double bond and the amide bond are subject to the same kind of distortion. The distortions decrease in the series **30a–30c**.



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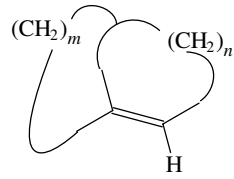

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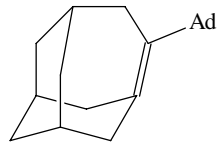

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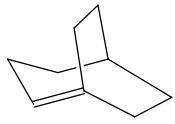

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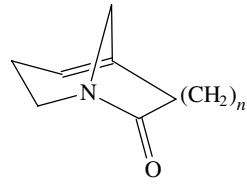
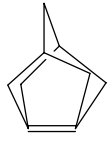


(30a) n = 2
(30b) n = 3
(30c) n = 4

In **30a**, both the amide nitrogen and the double-bond bridgehead carbon are strongly pyramidalized with somewhat twisted bonds but the deformation at the nitrogen is much stronger than that the carbon.

VII. MISCELLANEOUS COMPOUNDS

In suitable tricyclic alkenes, the steric constraints force the double bond to assume a *syn*-folded structure. Borden and coworkers have described some highly strained representatives of the series of bridged bicyclo[3.3.0]oct-1(5)-enes. While the passing existence of **31** could only be inferred from its addition product[131], **32**[132] and **33**[133] could be isolated and studied by a matrix technique, and **34a** was stable at ambient temperature[134]. Its methiodide **34b** was subjected to a study by X-ray crystallography and showed pyramidalization angles (Φ, see Scheme 1) of 20.3 and 12.3°, respectively, at the two double-bond carbons. Hrovat and Borden[135] report *ab initio*, MNDO and EFF calculations of the OS values of **31, 33** and **34c**. The results (Table 5) depend to a great extent on the method, but they fall in the expected order. The OS of cubene **(35)** is calculated to be somewhat larger than that of **31**, but **35** was still predicted to be capable of existence, and as for **31** its formation could be inferred from its reaction products[136].



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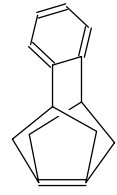

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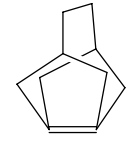

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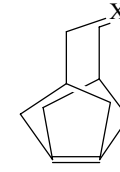


(34a) X = Se
(34b) X = $SeMe^+$
(34c) X = CH_2

(35)

TABLE 5. Olefinic strain energy (OS, kcal mol^{-1}) calculated for compounds **31** and **33–35**[135]

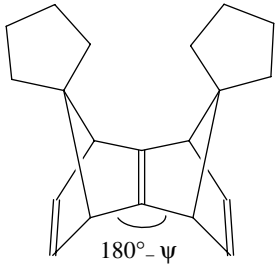
Compound	3-21G		6-31G*			
	SCF	TCSCF[a]	SCF	TCSCF[a]	MM2	MNDO
31	59.5	49.5	62.1	52.3	24.5	66.6
33	38.8	33.3	41.7	37.4	18.2	46.9
34c	16.0	13.9	19.2	17.1	9.8	30.8
35	75.1	63.1	68.2	58.9		

[a]Two-configuration SCF.

TABLE 6. Pyramidalization angles (Φ and ψ) for compounds containing strongly pyramidalized double-bond carbon atoms

Compound	Φ (deg)	ψ (deg)	Reference
36	32.4	22.7	140
18	19.7	44.9	90
34b	20.3	46.2	134
	12.3	42.1	
37	27.3	35.6	142
38	7.0	7.8	143

Weakly pyramidalized double-bond carbon atoms are found in norbornenes[137], an observation that has aroused the interest of theoreticians[138]. The deviation from planarity has been found to increase in *syn*-sesquinorbornenes and even more in analogues containing peripheral double bonds[139]. The largest deviation from planarity has been observed for the *syn*-sesquinorbornatriene **36**[140]. The pyramidalization is measured by two angles, Φ (see Scheme 1) and ψ, the latter being the angle between the planes meeting at the double bond (the flap angle). The values for these angles in **36** together with those for some other compounds containing pyramidalized double-bond carbons are found in Table 6. The Φ value found for **36** is the highest so far reported for a compound isolable at ambient temperature. Analogues of **36** without cyclopentane rings have been prepared, but their study has been hampered by their extreme sensitivity to atmospheric oxygen[141].



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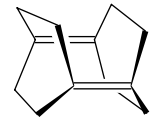

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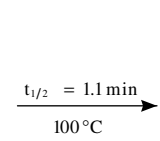
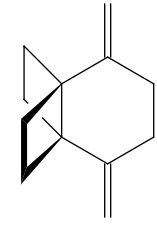
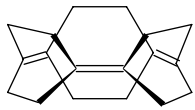




(39)

An interesting series of polycyclic olefins with notable pyramidalization in the lower members is represented by the 'superphanes' **37**[142] and **38**[143]. Their pyramidalization angles are shown in Table 6. While **37** could be obtained as a solid at ambient temperature



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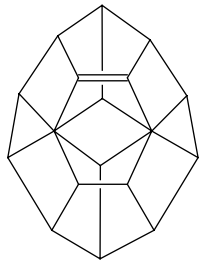

(40)

but underwent a Cope rearrangement to **39** at slightly elevated temperature, **38** could be purified by sublimation and showed mp 259–259.5 °C without decomposition. The He I photoelectron spectrum of **38** shows a small splitting, indicating homoaromatic interaction between the double bonds.

Dodecahedrene **(40)** is a highly strained hydrocarbon, for which calculations predict Φ 42.5° (MM2) and 41.7° (MNDO)[17]. It has not yet been isolated, but there is strong evidence for its formation in a gas-phase ion–molecule reaction in a FT ion cyclotron mass spectrometer[144]. A tetrasubstituted derivative has been studied in condensed phase[145].

VIII. CONCLUSIONS

In the last decades, introduction of new synthetic methods[66,146,147] has increased the availability of crowded organic molecules containing C=C bonds, and methods for preparing and studying labile molecules have been developed and refined. The deformations resulting from the strain in C=C bonds in different environments and the limits for existence of strained olefins have been explored in depth, and the theoretical treatment of strained systems by EFF and quantum chemical methods has developed greatly.

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CHAPTER **22**

Radical anions and radical cations derived from compounds containing C=C, C=O or C=N groups

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I. ABBREVIATIONS

BSA	benzeneseleninic anhydride
CRIP	contact radical ion pair
DCA	dicyanoanthracene
DCB	dicyanobenzene
DCN	dicyanonaphthalene
DMP^+	dimethylpyrrolidinium ion
FI	free ion
MCPBA	*m*-chloroperbenzoic acid
PIET	photo-induced electron transfer
SET	single electron transfer
SSRIP	solvent-separated radical ion pair
TIET	thermally induced electron transfer
TPP	triphenylpyrilium

II. INTRODUCTION

The addition or removal of an electron from a closed-shell organic molecule is a fundamental mechanism for increasing chemical reactivity. Enhanced reactivity results from the diminution of bond orders in the molecule (as a consequence of removing electrons from bonding orbitals or adding electrons to anti-bonding orbitals) and the formation of a *charged*, *paramagnetic* species (i.e. radical cations or radical anions). The focus of this chapter is on the chemistry of radical ions generated from >C=C<, >C=N- and >C=O functionalities, with a particular emphasis on reactions which either have synthetic utility (or the potential thereof), or which are interesting from a mechanistic perspective. The review covers the period 1985–1995.

III. RADICAL IONS OF >C=O CONTAINING COMPOUNDS

A. >C=O Radical Cations

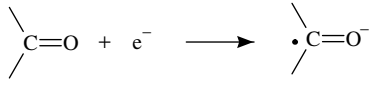
In the gas phase, the chemistry of *radical cations* generated from >C=O containing species is well-documented, especially in the field of mass spectrometry where a number of diverse and particularly diagnostic processes are known such as α-cleavage ($R(CO)R^{\bullet+} \longrightarrow RCO^{+} + R\bullet$) and the McLafferty rearrangement ($R(CO^{\bullet+})CH_2CH_2CH_3 \longrightarrow R(COH)CH_2^{\bullet+} + CH_2{=}CH_2$)[1]. In solution, however, reports of radical cations generated from >C=O containing organic molecules are rare. (For the oxidation of ketones, it is generally the enol form which is actually oxidized)[2]

B. >C=O Radical Anions

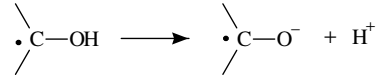
1. Methods of generation

Radical anions generated from ketones (or aldehydes) are referred to as ketyl anions. Common methods for generation of $>C{=}O^{\bullet-}$ are summarized in Figure 1.

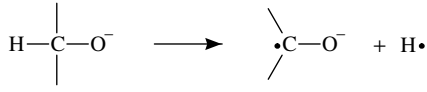
(1) Direct chemical or electrochemical reduction of carbonyl compounds



(2) Deprotonation of ketyl radicals



(3) α-Hydrogen abstraction from alkoxides



(4) Photo-induced electron transfer (PIET)

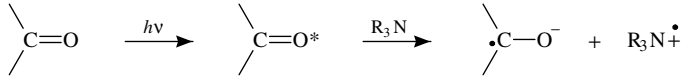


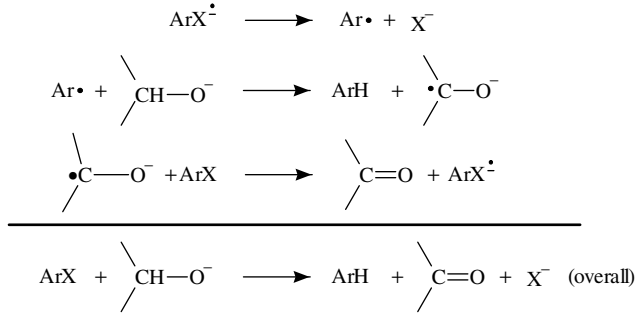
FIGURE 1. Generation of $>C{=}O^{\bullet-}$ in solution

The simplest method for generation of a ketyl anion is via direct reduction (chemically of electrochemically) of an aldehyde or ketone (Figure 1, reaction 1). Historically, it was via direct reduction of a ketone with an alkali metal that ketyl anions were first discovered.

In 1891, Beckman reported that reaction of benzophenone with sodium resulted in a deep blue colored solution[3]. Schlenk and Weickel later suggested that $Ph_2C{=}O^{\bullet -}\ Na^+$ was the species responsible for the blue color[4]. ($Ph_2C{=}O^{\bullet -}\ M^+$ generated in this manner is a common laboratory reagent for the purification of ether solvents.)

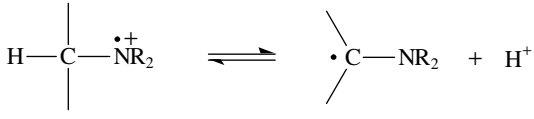
Ketyl anions can also be formed via the abstraction of a proton from a neutral ketyl radical (Figure 1, reaction 2). This process is best depicted as an equilibrium (*vide infra*)[5].

Although less common, ketyl anions can also be generated by removal of an α-hydrogen from an alkoxide (Figure 1, reaction 3). An interesting example where a ketyl anion is formed as an intermediate in this manner is provided by the electrochemically-initiated reduction of an aryl halide by an alkoxide anion via the free radical chain process illustrated in Scheme 1[6].



SCHEME 1

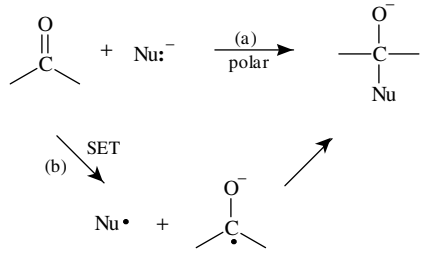
Ketyl anions can be generated photochemically via PIET (Figure 1, reaction 4). In this method, the carbonyl is excited photochemically to its triplet state which is readily reduced by a 3° amine[7]. Initially a ketyl anion/ammonium radical cation pair ($>C{=}O^{\bullet -}/R_3N^{\bullet +}$) is produced. Several distinct ion-pair intermediates have been characterized: contact radical ion pairs (CRIPs), solvent-separated radical ion pairs (SSRIPs) and free ions (FIs). Because each of these may produce different products (e.g. CRIPs may lead to reactions between $>C{=}O^{\bullet -}$ and $R_3N^{\bullet +}$ whereas unimolecular processes may be favored by the free ions), control over the efficiency of CRIP, SSRIP and FI production may be an important consideration in order to maximize the yield of the desired product[8]. Side-products may also arise as a result of the follow-up chemistry of $R_3N^{\bullet +}$. In addition to possessing radical and cationic character, $R_3N^{\bullet +}$ is also an acidic species ($pK_a \approx 10$ for $(p\text{-}MeOC_6H_4)_2NCH_3^{\bullet +}$)[9] and thus subject to deprotonation (equation 1). (In fact, $>C{=}O^{\bullet -}$ may itself serve as the base producing a neutral ketyl radical, $>C(\bullet)OH$.)



(1)

Finally, radical anions of carbonyl-containing compounds are often produced 'unexpectedly' in reactions involving nucleophiles or easily oxidized free radicals. In a seminal 1964 report, Russell, Janzen and Strom noted that ketyl anions could be detected by ESR

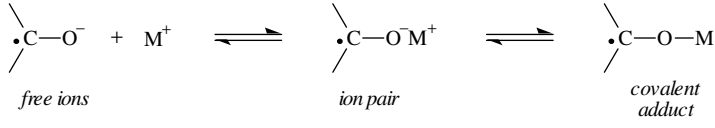
when neutral ketones were treated with a number of common nucleophilic reagents[10]. Since that time, the question as to whether a number of simple organic transformations involving nucleophilic addition to carbonyl compounds proceeds via the traditional polar (two-electron) pathway or via single electron transfer (SET), paths a and b, respectively (Scheme 2), has attracted a great deal of attention. A detailed analysis of the claims (and counterclaims) of electron transfer in nucleophilic and/or radical additions to >C=O is beyond the intended scope of this chapter. It suffices to say that during the period covered by this review, the role of electron transfer has been extensively examined and debated in a large number of reactions involving aldehydes, ketones and other carbonyl-containing compounds (e.g. the Grignard reaction[11], Clemmenson reduction[12], Aldol condensation[13], Wittig reaction[14], Meerwein–Pondorff–Verley reduction[15], reactions with RLi[16], R_2NLi[17], NADH analogues[18], complex metal hydrides[19] and radical-mediated reductions involving $R_3Sn^{\bullet}$[20] and $R_3Si^{\bullet}$)[21].



SCHEME 2

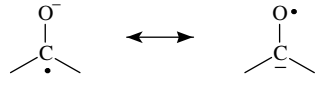
2. Reactions of >C=O•⁻

a. Free ions, ion pairs or neutral free radicals? Regardless of how it is produced, charge balance requires that $>C{=}O^{\bullet -}$ be generated in solution with an appropriate counterion, which in most cases will be a metal cation (M^{+n}). In general, the precise effect of the counterion on reactivity is not very well understood. In principle, a continuum of possible intermediates may exist in solution ranging from free (unassociated) ions ↔ ion pairs ↔ covalent adduct (Scheme 3)[22].



SCHEME 3

Early ESR studies demonstrated that the hyperfine coupling constant (a_{c13}) for ^{13}C(carbonyl)-substituted fluorenone radical anion is counterion-dependent. For the 'free' ion, $a_{c13} = 2.75$ Gauss. In contrast, when the counterion is Li^+, $a_{c13} = 6.2$ Gauss[23]. Consider Scheme 4: For the 'free' ion, canonical structure **1** and **2** are contributors to the resonance hybrid. For the $>C{=}O^{\bullet -}$ / Li^+ ion pair, association of Li^+ with oxygen increases the relative contribution of canonical structure **1** to the resonance hybrid, resulting in greater spin density at carbon. The fact that spin (and charge density) varies as a function of counterion (and presumably solvent) will certainly affect the reactivity of the radical ion. However, very few quantitative studies exist which directly address this point.



(1) (2)

SCHEME 4

It is likely that many of the reactive intermediates discussed in this chapter are nearing the tight ion pair → covalent adduct end of this continuum (e.g. reactions of >C=O with Sm^{+2}, $R_3Sn\bullet$, etc.). Our operational criterion for inclusion of a reaction as involving a radical *anion* centers on whether the paramagnetic intermediate involved in the transformation is sufficiently anionic so as to have nucleophilic properties (i.e. can it be alkylated? protonated?).

b. Overview. Figure 2 summarizes most of the significant reactions of radical anions generated from carbonyl compounds.

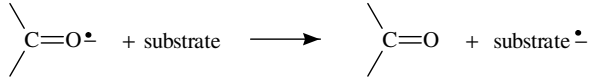
The most fundamental reaction of $>C{=}O^{\bullet -}$ involves electron transfer to another substrate (Figure 2, reaction 1). While at first this process might seem trivial, carbonyl compounds have proven effective electron transfer mediators for the reduction of a variety of substrates.

This mediated reduction process has been utilized extensively in electrochemistry on both a preparative and analytical scale, and is often catalytic. In this process, a mediator, whose reduction potential is more positive than that of the substrate, is reduced electrochemically. The resulting radical anion subsequently transfers an electron to the substrate, regenerating the mediator. The radical anion of the substrate then undergoes further chemistry. Use of a carbonyl compound as a mediator is not mandatory. Carbonyl compounds offer the advantage that with appropriate substitution, their reduction potentials can be tailored over a wide range to suit a large variety of substrates and reactions. This technique is highly effective for obtaining important kinetic and thermodynamic information for substrates which cannot be studied by direct electrochemical methods (e.g. cyclic or linear sweep voltammetry). The interested reader is directed to the work of Savéant[24] and Lund[25].

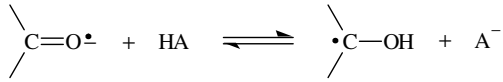
Another fundamental reaction of $>C{=}O^{\bullet -}$ involves its reactivity as a base. In the Brønsted sense, $>C{=}O^{\bullet -}$ may react with a proton donor to produce a neutral ketyl radical ($>C(\bullet)OH$, Figure 2, reaction 2). This is an important process when the reduction of a carbonyl compound is carried out under acidic conditions or in a protic media (e.g. electrochemically, with less reactive reducing reagents such as Mg or Zn, or when $>C{=}O^{\bullet -}$ is produced via PIET and $R_3N^{\bullet +}$ has available α-protons). The follow-up chemistry of $>C(\bullet)OH$ is that of a *neutral* free radical (dimerization to form pinacols, addition to unsaturated compounds, fragmentations/ring-openings, etc.), and thus beyond the scope of this chapter.

Reaction 3, Figure 2, illustrates another variant, the reactivity of $>C{=}O^{\bullet -}$ as a *Lewis* base (e.g. nucleophile) via reaction with electrophilic species. In the specific case of $>C{=}O^{\bullet -}$ reacting with an alkyl halide (R−X), a direct nucleophilic displacement (S_N2) process was initially envisioned. However, it is now evident that these alkylations take place via initial SET: $C{=}O^{\bullet -} + R{-}X \longrightarrow C{=}O + R\bullet + X^-$, followed by $R\bullet + C{=}O^{\bullet -} \longrightarrow R{-}C{-}O^-$. The interested reader is directed to the work of Garst and coworkers[26]. In addition, there has been considerable interest in this chemistry from the perspective of the dynamics and theory of dissociative electron transfer, and the interested reader is directed to the work of Savéant[27] and Lund.[28] (Evidence has recently been presented for a continuous S_N2/SET mechanistic spectrum for the intramolecular reactions of ketyl anions and alkyl halides, Scheme 5)[29].

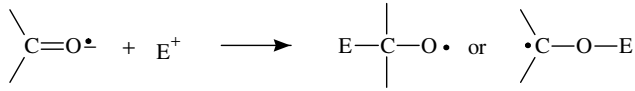
(1) electron transfer



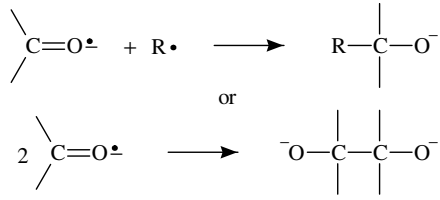
(2) proton transfer



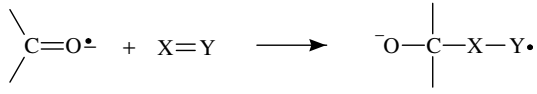
(3) reaction with electrophiles



(4) reaction with radicals or radical ions

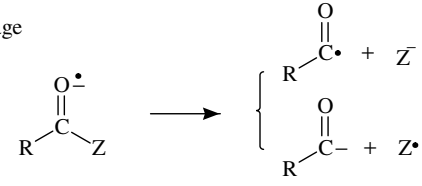


(5) addition to π-systems



(6) fragmentation

(a) α-cleavage



(b) β-cleavage

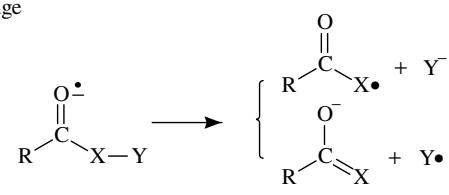
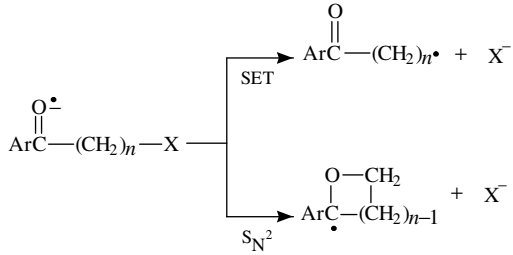


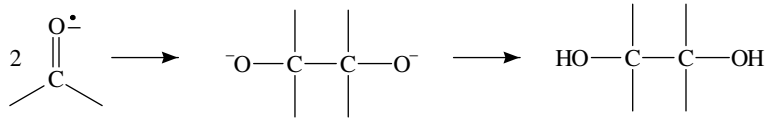
FIGURE 2. Reactions of >C=O•⁻



SCHEME 5

With regard to Figure 2, reactions 1–3: Because the recent work dealing with these reactions is only tangentially related to ketyl anions, these reactions will not be considered further in this chapter. The remaining reactions (4–6) depicted in Figure 2 represent the bulk of the mechanistic and synthetic work which was reported in the 1985–1995 period, and will be the primary focus of the remainder of this section.

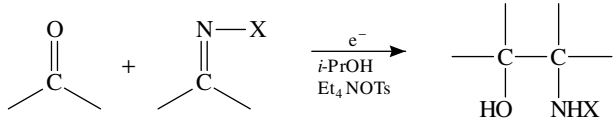
c. Reactions of $>C{=}O^{\bullet -}$ *with radicals or radical ions (pinacolization).* Being paramagnetic, $>C{=}O^{\bullet -}$ is especially reactive towards free radicals and radical ions. The rate constant for reaction of Li^+/benzophenone$^{\bullet -}$ with a 1° alkyl radical is slightly below diffusion-controlled (on the order of 1.5×10^8 $M^{-1}\,s^{-1}$)[26]. A similar rate constant was reported for reaction of 1° radicals with Ph(C=O$^{\bullet -}$)*t*-Bu[30]. The most common reaction of $>C{=}O^{\bullet -}$ with another radical ion is dimerization to form pinacolates, which after workup yield pinacols (equation 2). The rate constant for dimerization of PhCHO$^{\bullet -}$ is 2.4×10^3 $M^{-1}\,s^{-1}$[31].



(2)

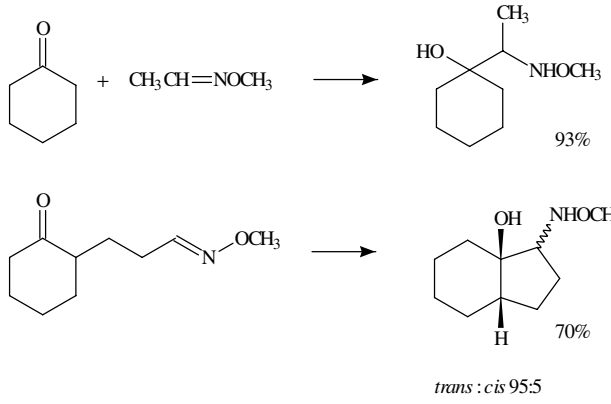
The reduction of carbonyl compounds to form pinacol dimers can be accomplished photochemically, electrochemically or with chemical reducing agents. When conducted under acidic conditions or in protic solvents, pinacols are likely produced by coupling of two neutral ketyl radicals (vs radical anions). The electrochemical reduction is especially complicated in terms of the role of the electrode surface, counterion and solvent, and an excellent review has appeared on the subject[32].

Shono and coworkers[33] have recently reported a novel ketone/imine coupling process (equation 3) analogous to pinacolization. The coupling process was achieved electrochemically, utilizing a Sn cathode. As the results summarized in Scheme 6 illustrate, yields are reasonable for both inter- and intramolecular coupling, although diasteroselectivity was higher for the latter. The suggested mechanism for this reaction is summarized in Scheme 7.

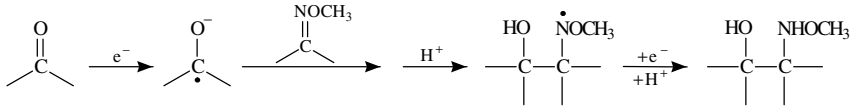


(3)

X = OCH_3, $N(CH_3)_2$



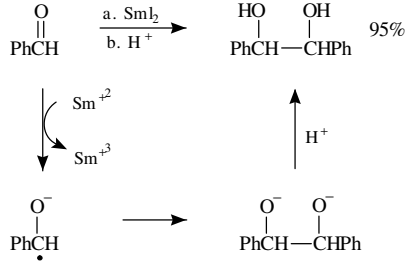
SCHEME 6



SCHEME 7

Recently, SmI_2 has emerged as a potent one-electron reducing agent for carbonyl and other functional groups[34]. (For $Sm^{+3} + e^- \longrightarrow Sm^{+2}$, $E^\circ = -1.55$ V.) As will be seen in several examples in this section, this reagent provides convenient entry into ketyl anion chemistry.

In 1983, Kagan[35] reported that benzaldehyde is conveniently converted into its pinacol dimer by reactions with SmI_2 in 95% yield (*dl/meso* 54: 44, Scheme 8). Ten years later, Kagan also reported that pinacolization of a variety of aldehydes and ketones could also be achieved with $SmBr_2$ in virtually quantitative yield[36].

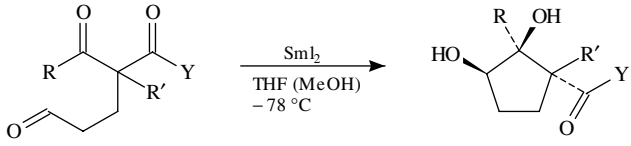


SCHEME 8

An intramolecular variant of this reaction was reported in 1988 by Molander and Kenny (Table 1)[37]. These reactions proceeded in reasonable yields and exhibited extremely high diasteroselectivity (200:1). It was suggested that the aldehyde functionality is first reduced, allowing chelation control of the stereochemistry (e.g. **3**).

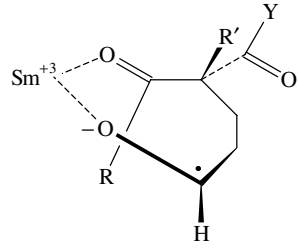
d. Fragmentations of $>C{=}O^{\bullet -}$ (i) α- or β-cleavage of carbonyl radical anions. Radical anions derived from carbonyl compounds may undergo α- or β-cleavage (Figure 2:

TABLE 1. Intramolecular pinacol coupling SmI_2[a]



Y	R	R′	% Yield
OCH_2CH_3	CH_3	CH_3	77
OCH_2CH_3	C_6H_5	CH_3	66
$N(CH_2CH_3)_2$	CH_3	H	50

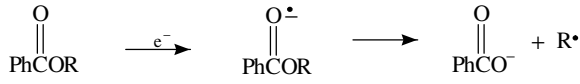
[a]Reference 37.



(3)

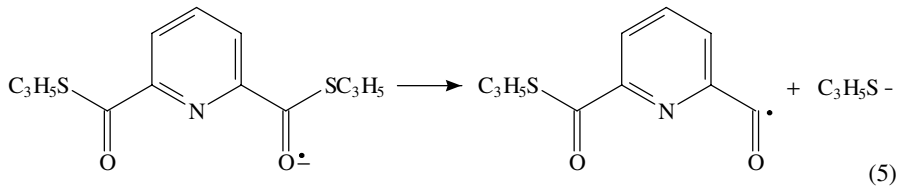
reactions 6a and 6b, respectively). Of the two, β-cleavage is far more common. Two fragments result from this process, R(C=O)X and Y, one of which is a free radical, the other, an anion. As might be expected, the anionic fragment is generally the one which is more able to support a negative charge (i.e. the more stable anion is produced). When X and Y are incorporated in a ring, fragmentation leads to ring opening. Because of the wealth of mechanistic and synthetic interest in ring-opening reactions, this subset of β-cleavage reactions is treated in a separate section.

Esters undergo β-cleavage to yield carboxylate anions and alkyl radicals in accordance with equation 4[38]. Rate constants for these fragmentations have recently been measured via pulse radiolysis, and it was found that the rate of the reaction increases with the stability of the alkyl radical[39].



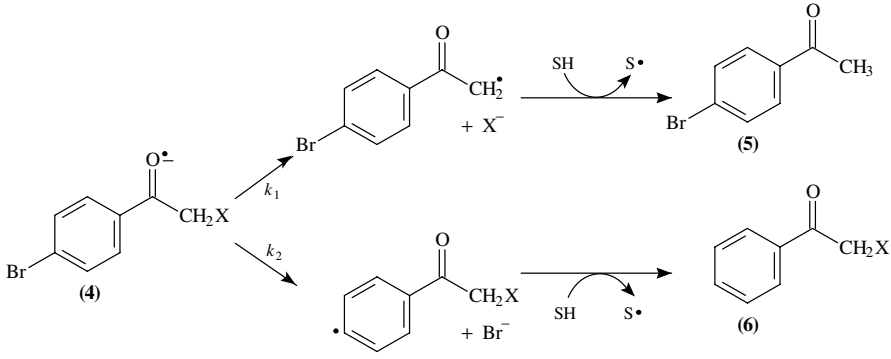
(4)

Thioesters, on the other hand, appear to undergo α-fragmentation to yield acyl radicals and thiolates (equation 5)[40].



(5)

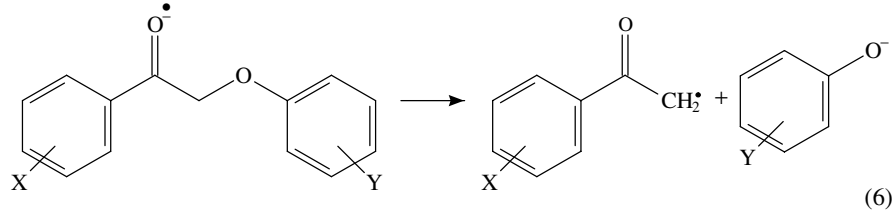
In an extremely clever study, Tanner and collaborators have estimated rate constants for fragmentation of a series of α-haloacetophenones[41]. These rate constants were determined by the intramolecular competition outlined in Scheme 9. Radical ion **4** was generated by reaction with 1,3-dimethyl-2-phenylbenzimidazoline (DMBI). The rate constant ratio (k_1/k_2) was determined by the relative yields of the two products **5** and **6**. With the assumption that the α-substituent does not affect the magnitude of k_2, k_2 was assumed to be equal to 3×10^7 s^{-1} (which had been measured earlier by Wipf and Wightman for the dehalogenation of *p*-bromoacetophenone radical anion)[42].



SCHEME 9

Some of the results of these experiments are summarized in Table 2. The results reveal that the rate increases as the basicity of X^- decreases. For X = Br or Cl, it is assumed that fragmentation occurs via dissociative electron transfer, i.e. fragmentation and electron transfer is concerted; the radical anion $Ph(C{=}O^{\bullet -})CH_2X$ has no significant lifetime.

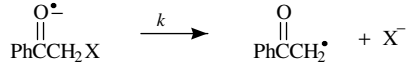
Mathivanan, Johnston and Wayner examined the effect of substituents on the rates of cleavage of α-phenoxyacetophenone radical anions (equation 6)[43]. In this study, the radical anions were generated by trapping solvated electrons produced by laser-induced photoionization of 4,4′-dimethoxystilbene in CH_3CN and DMF. Their results show that the fragmentation rate is enhanced when Y is electron withdrawing, but retarded when X is electron withdrawing.



(6)

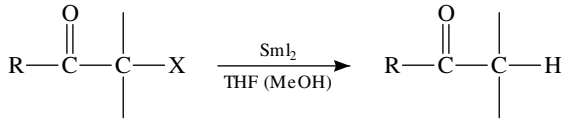
Dehalogenation of α-substituted ketones and esters via radical anions has also been examined for its synthetic utility. As reported by Molander, SmI_2 is an especially effective reagent for this transformation (equation 7)[44]. Yields are typically high (70–100%) for X = Cl, OAc, $OSiMe_3$, $OCOCH_2Ph$, OTs, etc.). A mechanism for the reduction of esters (Scheme 10) has been suggested.

TABLE 2. Rate constants for β-cleavage of several α-substituted acetophenone radical anions[a]

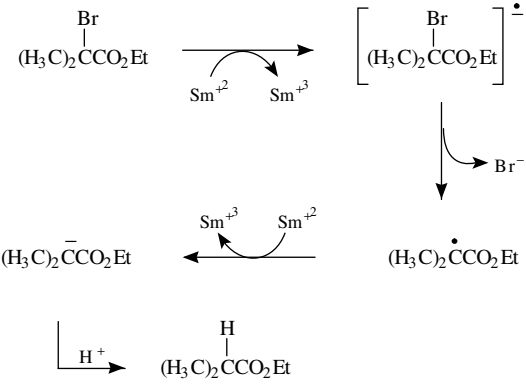


X	$k(s^{-1})$
Br, Cl	$>10^9$
F	5×10^9
$PhCO_2$	6.3×10^9
CH_3CO_2	9.6×10^8
PhO	9.5×10^6
PhS	9.3×10^6

[a]Reference 41.



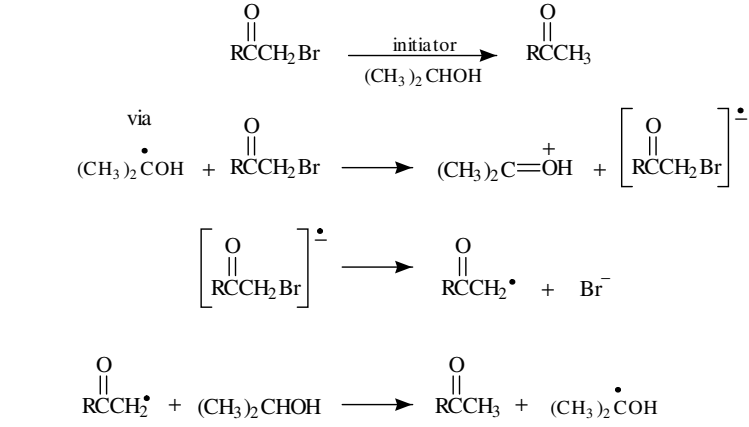
(7)



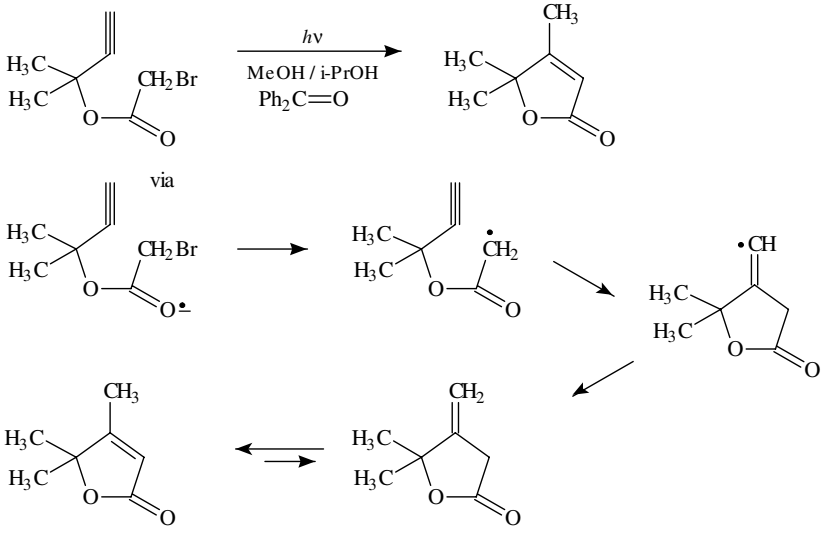
SCHEME 10

Reductions of α-bromo ketones and esters can also be accomplished in a free radical chain process (Scheme 11) using 2-propanol or 2-methyldioxolane[45]. The 2-hydroxypropyl radical is an effective reducing agent with $E^\circ = -1.11$ V vs Ag/AgCl. An application of this chemistry to yield spiro-γ-lactones has been reported (Scheme 12)[46].

(ii) Long-range cleavage involving $>C{=}O^{\bullet -}$. The presence of the $>C{=}O^{\bullet -}$ functionality may induce cleavage of distant C−X bonds, presumably via intramolecular electron transfer. Examples include dehalogenations of ring-substituted benzophenone and acetophenone radical anions which yield aryl radicals. Results from a recent study from the Tanner group are summarized in Table 3[41]. General trends emerge from these results such as leaving group abilities ($I^- > Br^- > Cl^-$; p-X > m-X). Because of extended conjugation in $ArCOPh^{\bullet -}$, these radical anions fragment at a rate one to two orders of magnitude slower than $ArCOCH_3{}^{\bullet -}$.



SCHEME 11

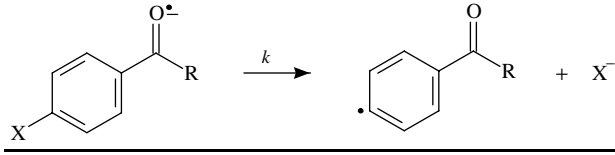


SCHEME 12

In a recent study, Savéant has found that the rates of dehalogenation are affected by solvent and ion-pairing effects[47]. For example, the dehalogenation of *p*-chlorobenzophenone radical anion can be circumvented when the counterion is Li^+ or Mg^{+2}. Savéant has suggested that ionpairing stabilizes the radical anion, thereby retarding the rate of chloride loss. Indeed, the major product when these counterions are present is the corresponding pinacol (Scheme 13).

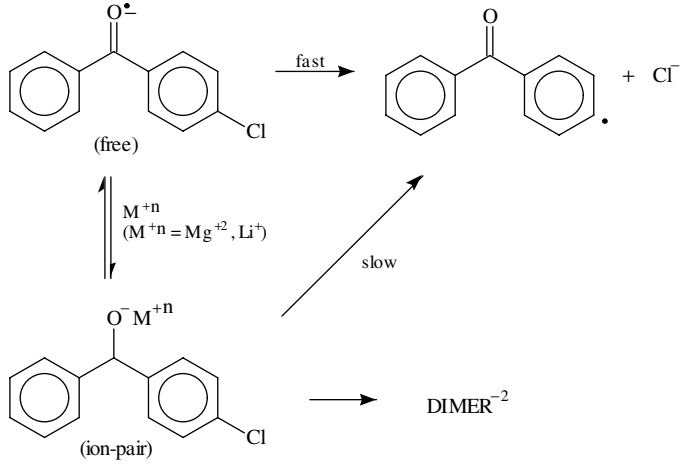
(iii) Ring-opening reactions involving $>C=O^{\bullet -}$. (a) Cyclopropane ring openings. Dissolving metal reductions of aliphatic cyclopropyl ketones usually leads to ring opening, and is a classic procedure for introducing angular methyl groups in steroid synthesis (equation 8)[48]. Ring opening is sensitive to stereoelectronic factors (i.e. the rupturing C−C bond must properly overlap with the π-system of C=O) and generally believed to

TABLE 3. Rate constants for dehalogenation of ring-substituted acetophenones and benzophenones[a]



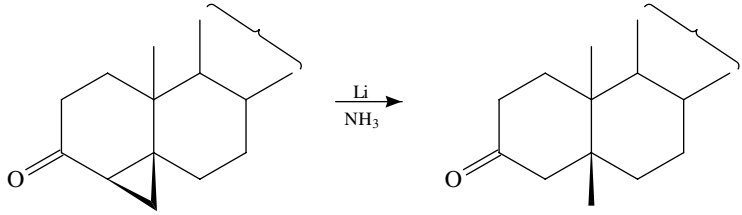
X	$k(s^{-1})$	
	$R = CH_3$	$R = C_6H_5$
p-I	3.5×10^9	—
m-I	1.9×10^8	2.5×10^6
p-Br	3.2×10^7	6×10^4
m-Br	8×10^3	7.9×10^2
p-Cl	3×10^3	29
m-Cl	15	—

[a]Data from Reference 41.



SCHEME 13

involve ketyl anion intermediates[49].

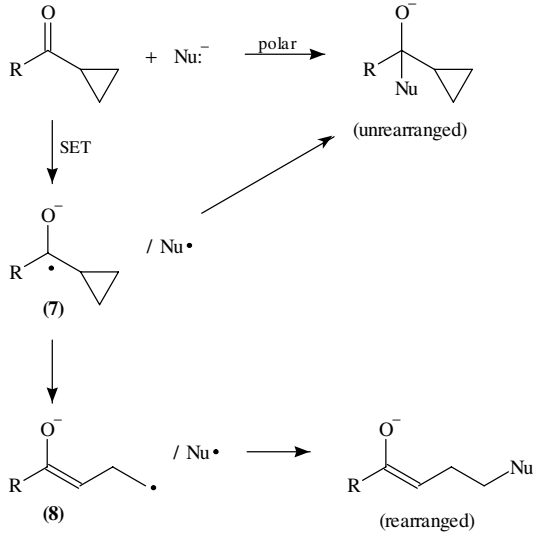


(8)

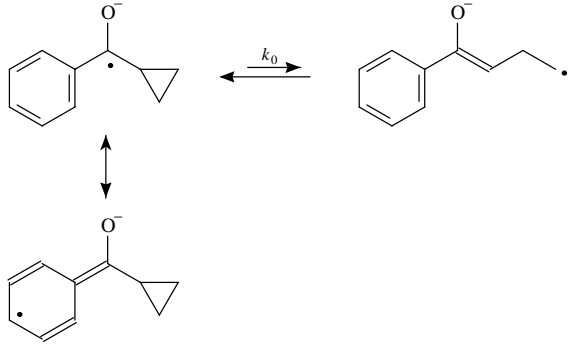
There has been considerable interest in ring opening of cyclopropyl-containing ketyl anions from both a mechanistic and synthetic viewpoint. Cyclopropyl substituents are often

utilized to 'probe' for the occurrence of SET in a variety of transformations involving carbonyl groups such as nucleophilic additions. The general premise of this approach is illustrated in Scheme 14. If the nucleophile reacts with the carbonyl compound via SET, ketyl anion **7** is produced. Incorporation of a cyclopropyl group into the molecule diverts the radical anion (via a β-cleavage reaction driven by relief of cyclopropane ring strain) to yield a ring-opened distonic radical anion **8**. (This ring opening is in direct analogy to that of the cyclopropyl carbinyl neutral free radical which opens to the homoalllyl radical with a rate constant on the order of 10^8 s^{-1}.)[50] Thus, the detection of cyclopropane ring-opened products *might* imply that radical anions were involved along the reaction pathway. There are two important assumptions associated with this approach: (a) ring opening is fast and irreversible, and (b) ring opening can only occur via the SET pathway. In retrospect, it has been found that *neither* is necessarily valid.

In 1990, Tanko and Drumright[51] presented evidence that the ring opening of the radical anion generated from phenyl cyclopropyl ketone (Scheme 15) is *reversible*, with an

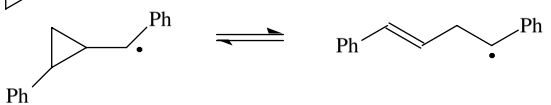
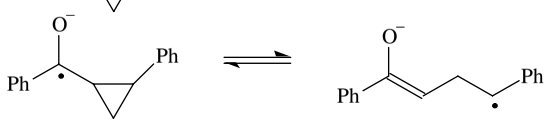
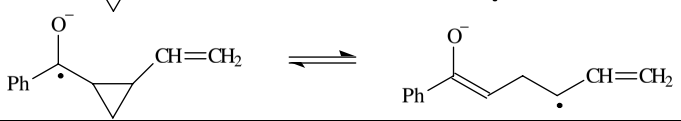


SCHEME 14



SCHEME 15

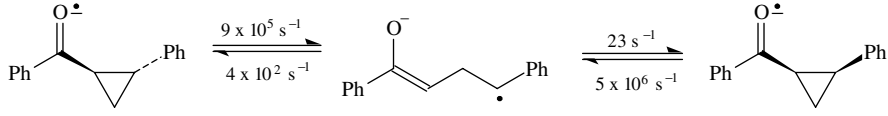
TABLE 4. Effect of substituents on the rate of ring opening of cyclopropylcarbinyl radicals and related radical anions

Reaction	k_1 (s^{-1})	k_{-1} (s^{-1})	ΔH° (kcal mol^{-1})	Reference
	1.2×10^8	5×10^3	−3.1	50
	1×10^6	1.2×10^7	+3.3	53
	3.6×10^8	—	—	54
	$\leqslant 2$	8×10^7	+11	51
	1×10^7	—	−2	52
	$\geqslant 5 \times 10^5$	—	−2	52

equilbrium constant favoring the ring-closed form ($K_{eq} = 2 \times 10^{-8}$; $k_0 = 2\ s^{-1}$)[30]. It was suggested that the relief of cyclopropane ring strain upon ring opening did not sufficiently compensate for the loss of resonance energy of the highly delocalized ketyl anion.

In a subsequent study, it was found that placement of radical stabilizing substituents on the cyclopropane ring *partially* compensates for the loss of resonance energy (by stabilizing the radical portion of the resulting distonic radical anions), but the rate constants for ring opening were still substantially slower than that of the analogous cyclopropyl carbinyl free radicals (Table 4)[52].

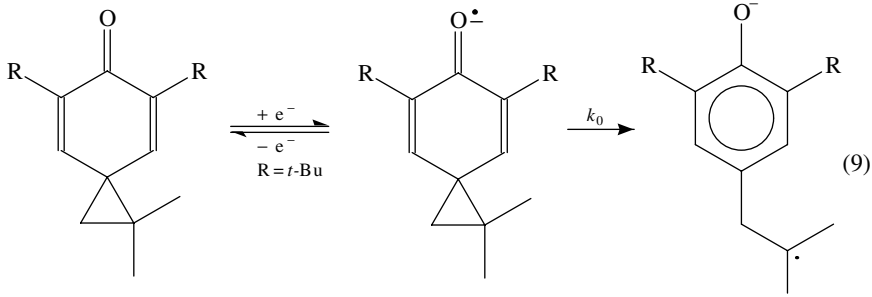
Moreover, it appears that phenyl substitution on the cyclopropane ring does not solve the problem of reversibility. Tanner demonstrated that the radical anion derived from (+)-*trans*-1-benzoyl-2-phenylcyclopropane **(9)** isomerizes to (±)-*trans* and (±)-*cis* (presumably via ring-opened radical anion **10**), providing definitive evidence that even for the substituted systems, ring opening is reversible. Rate constants for ring opening and closing were reported (Scheme 16).



(9) **(10)** **(11)**

SCHEME 16

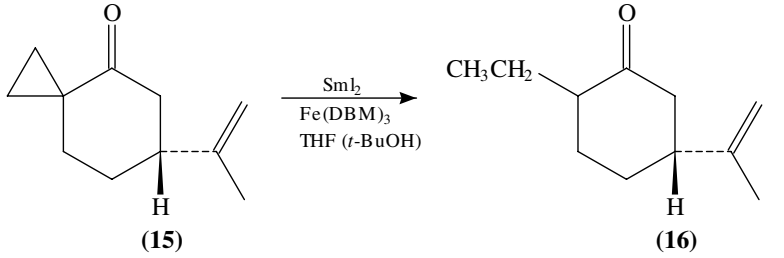
A substrate which appears to solve many of these difficulties has recently been reported. The radical anion generated from spiro compound **12** undergoes ring opening to 3° distonic radical **14** with a rate constant $>10^7\ s^{-1}$ (equation 9)[55]. For this system, relief of cyclopropane ring strain and an *increase* in resonance energy provide the thermodynamic impetus for ring opening (ΔH° for ring opening of this radical anion is estimated to be -20 kcal mol^{-1}).



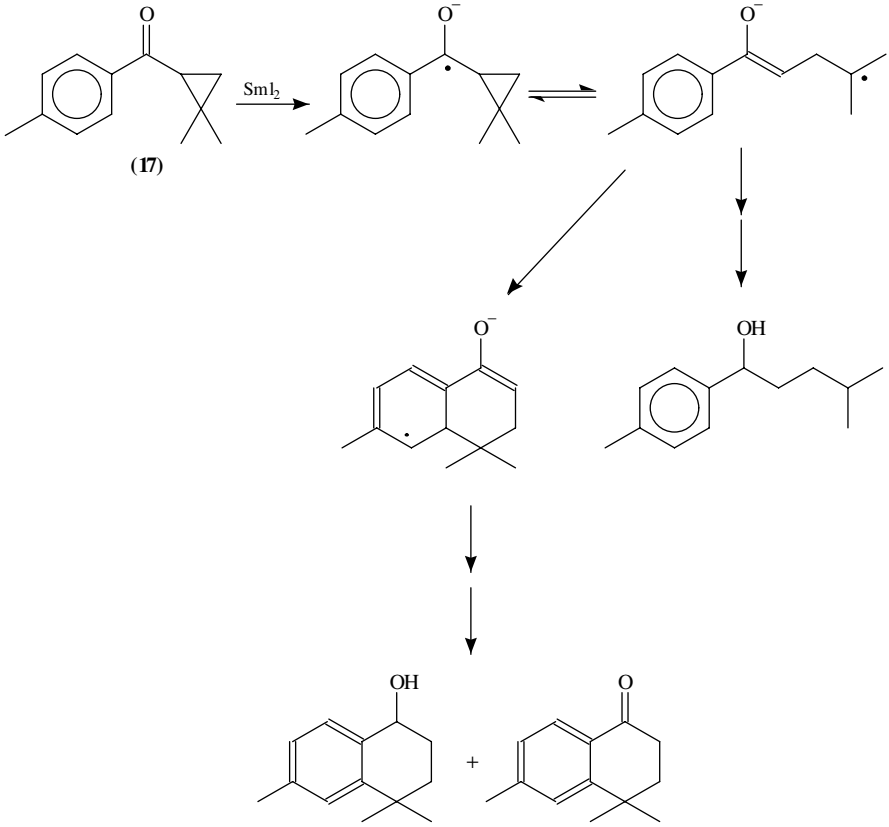
(9)

(12) **(13)** **(14)**

Cyclopropyl groups have been used to probe for ketyl anion intermediacy in reactions of SmI_2 with ketones. In 1991, Molander reported that treatment of cyclopropyl ketone **15** with SmI_2 yields ring-opened product **16** in 81% overall yield (equation 10)[56] Timberlake and Chen reported that several cyclopropyl-ring-opened products result from treatment of **17** with SmI_2 (Scheme 17)[57].



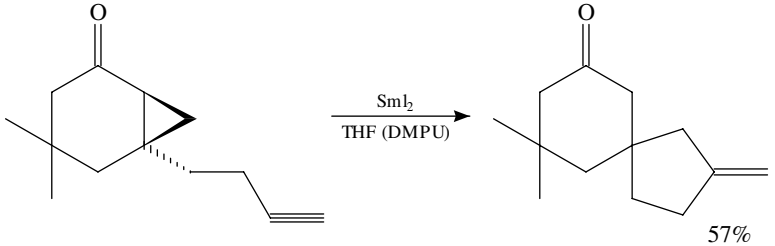
(15) (16) (10)



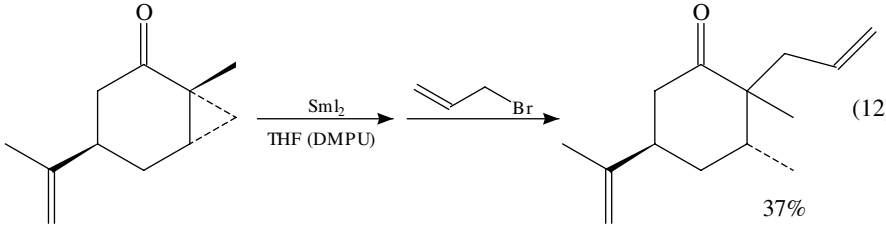
(17)

SCHEME 17

A number of synthetically interesting transformations involving SmI_2-induced ring opening of cyclopropyl ketones were reported by Batey and Motherwell, involving subsequent cyclization of the ring-opened radical ion onto a remote C=C or C≡C. One example from this study is illustrated in equation 11[58a]. Moreover, these authors also demonstrated that it was possible to alkylate the ring-opened enolate anion with electrophilic reagents (equation 12).

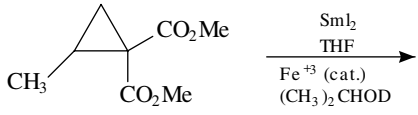


(11)



(12)

Analogous ring opening of cyclopropyl esters with SmI_2 were also reported in 1994 by Imamoto, Hatajima and Yoshizawa (equation 13).[58b]



(13)

(b) Oxirane ring openings. Although analogous to cyclopropanes, ring opening of radical anions generated from α,β-epoxyketones are more complicated mechanistically because (in principle) either C−C or C−O bond cleavage may result. In the case of *neutral* free radicals, this competition is highly substituent-dependent. For unsubstituted oxiranylmethyl radicals, C−O bond cleavage is observed. Radical-stabilizing substituents (vinyl, phenyl) on the oxirane ring tend to favor C−C bond cleavage[59].

There have been very few studies involving ring opening of radical anions generated from α,β-epoxyketones, and in all of these, only C−O bond cleavage has been found. This method has been successfully applied to the synthesis of β-hydroxyketones or esters. These C−O cleavages are thought to produce an enoyl radical and alkoxide anion (path d, Figure 3), although it is not clear that the available experimental evidence rules out path c. (Presumably C−C bond cleavage would proceed according to path a on the basis of thermodynamic considerations.) The influence of substituents, counterion and solvent on the relative importance of these (potentially competitive) pathways, or whether any of these ring openings are reversible, is currently unknown.

In 1992, Hasegawa's group[60] found that irradiation of α,β-epoxyketone **18** in the presence of triethylamine led to ring-opened products, the nature of which varied as a function of solvent and counter-ion (Table 5).

The proposed mechanism for this reaction is summarized in Scheme 18. Irradiation of **18** in the presence of Et_3N yields SSRIP (**21**). Oxirane ring opening is suggested to yield **22**, which, via CRIP (**23**), abstracts a proton from $Et_3N^{\bullet+}$ to yield **25**. Diketone **19** is suggested to arise from a 1,2-hydrogen shift (**22** → **24**), followed by back electron transfer. (Note: Since 1,2-hydrogen shifts are virtually unknown in free radical chemistry, it might be more reasonable to formulate this sequence according to equation 14). The effect of Li^+ on the product distribution is attributed to the fact that Li^+ favors SSRIP

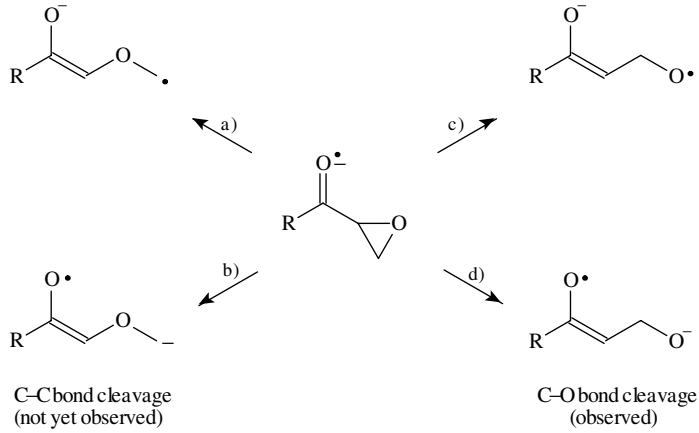
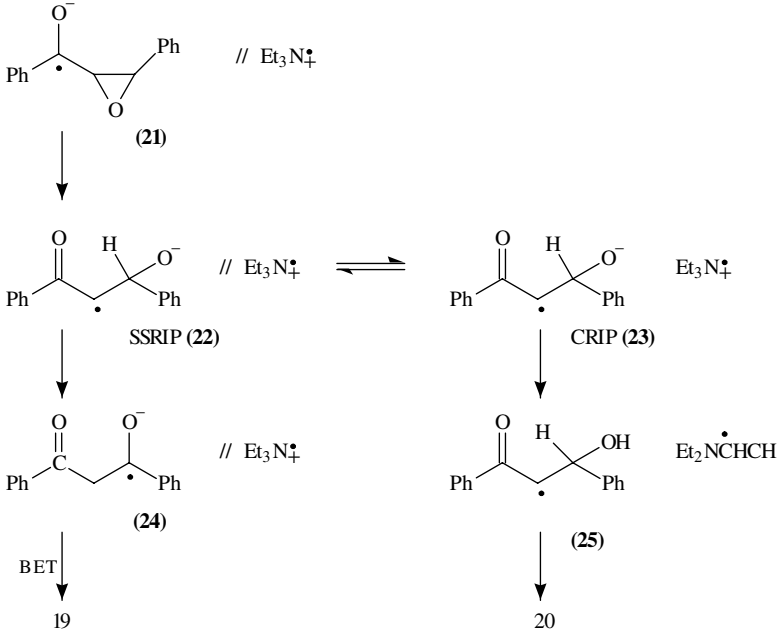
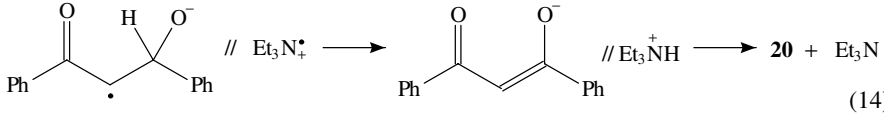


FIGURE 3. Possible ring-opening pathways for α,β-epoxyketone radical anions



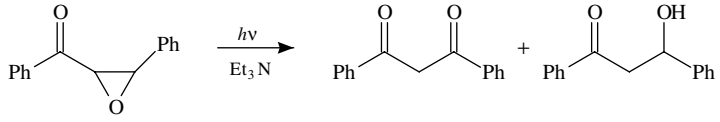
SCHEME 18

formation[8], thereby preventing deprotonation of $Et_3N^{\bullet+}$ at the CRIP stage.



(14)

TABLE 5. Products arising from photoinduced electron transfer to α,β-epoxyketone **18**[a]

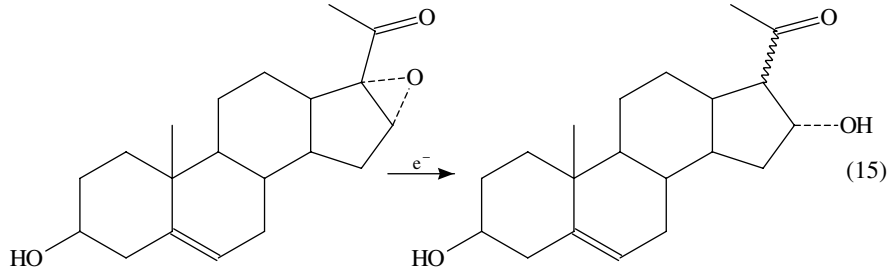


(**18**) (**19**) (**20**)

Solvent	%**19**	%**20**
CH_3CN	60	22
CH_3OH	49	28
CH_3CN/Li^+	70	0

[a]Reference 60.

Ring openings of α,β-epoxyketones can also be accomplished electrochemically, although most of the work in this area deals with the synthetic aspects of this reaction. Shapiro, Gentles, Kabasakalian and Magatti reported that electrochemical reduction of epoxyketone **26** yields ring-opened products **27** and **28** (equation 15)[61]. Although the overall yield for this reaction was quite low (35%), it was noted that chemical reducing agents were ineffective at promoting this transformation.

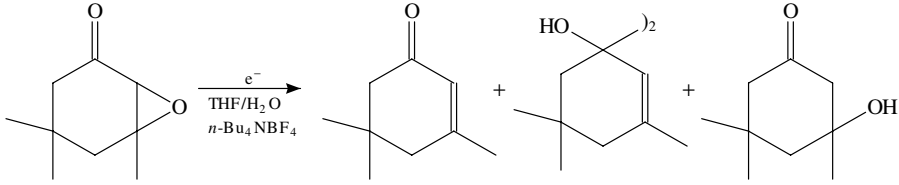


(15)

(**26**)

(**27**) *trans*: 29%
(**28**) *cis*: 6%

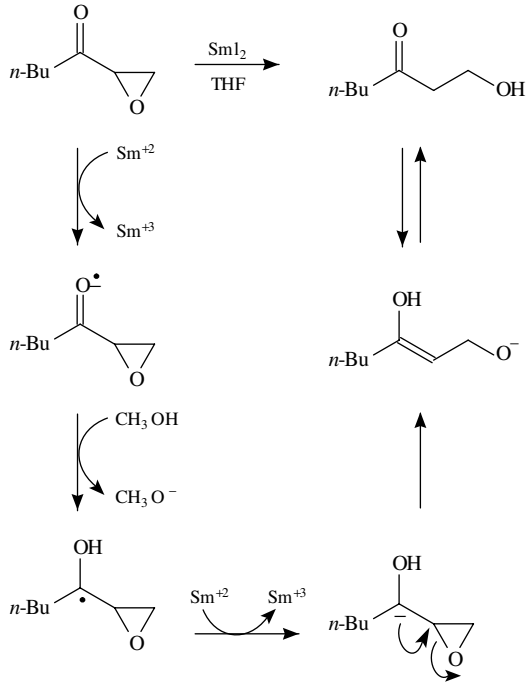
Inokuchi, Kusumoto and Torii reported the electrochemical reduction of epoxyketone **29** at a carbon cathode (equation 16)[62]. In the absence of a proton source, two deoxygenated products (enone **30** and pinacol dimer **31**) were produced in a combined yield of 37%. However, in the presence of a proton source ($CH_2(CO_2Et)_2$), ring-opened product **32** was produced in 65% overall yield.



(**29**) (**30**) (**31**) (**32**) (16)

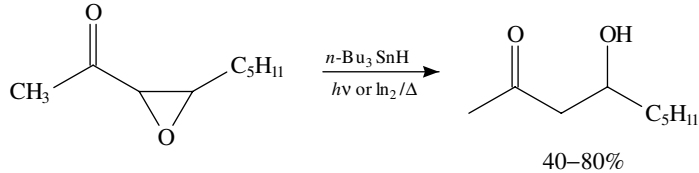
SmI_2-promoted ring opening of α,β-epoxyketones have also been reported. In 1986, Molander and Hahu reported that aliphatic epoxyketones produce ring-opened products

upon treatment with SmI_2 in the presence of methanol in high yield[63]. However, these authors suggest that ring opening occurs after protonation of the initially formed ketyl anion and a second electron transfer (Scheme 19). Analogous ring openings of α,β-epoxyesters have also been reported, proceeding in yields of 30–70% (depending on reaction conditions and additives)[64].



SCHEME 19

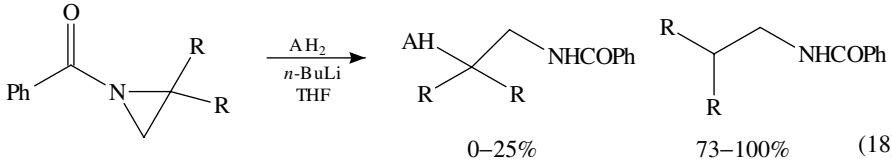
Finally, ring opening of α,β-epoxyketones can be accomplished using n-Bu_3SnH (equation 17)[65]. These reactions can be initiated either photochemically or via a thermal initiator such as AIBN. For the photochemical reaction, initiation occurs via excitation of the ketone to its triplet state, which abstracts hydrogen from n-Bu_3SnH.



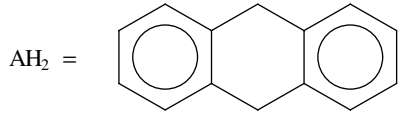
(17)

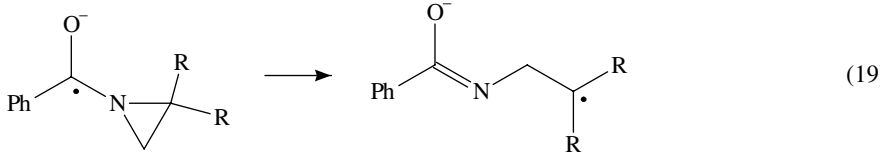
40–80%

(c) Aziridine ring openings. There have been very few reports regarding opening of aziridine rings via ketyl radical anions. In 1989, Stamm's group reported the reductive ring opening of N-benzoylaziridine via reaction with dihydroanthracene and n-BuLi (equation 18)[66]. The key step of their proposed mechanism involves ring opening of an intermediate aziridine radical anion (equation 19).



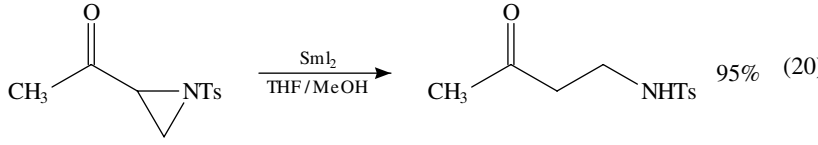
(18)



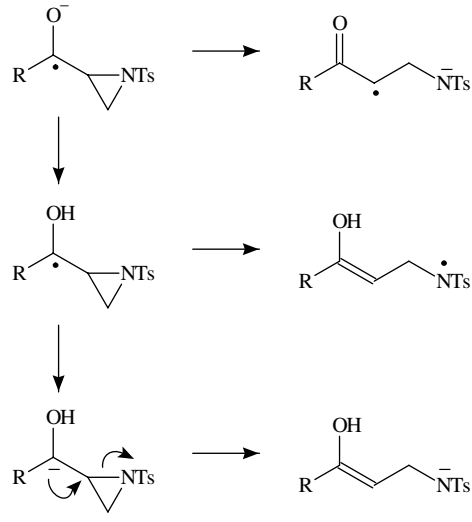


(19)

Ring opening of 2-acylaziridines can be accomplished in high yield using SmI_2 to give masked β-aminoketones (e.g. equation 20)[67]. The details of the mechanism (i.e. whether ring opening occurs at the ketyl anion or ketyl radical stage, or after a second electron transfer, Scheme 20) are unclear at this time.

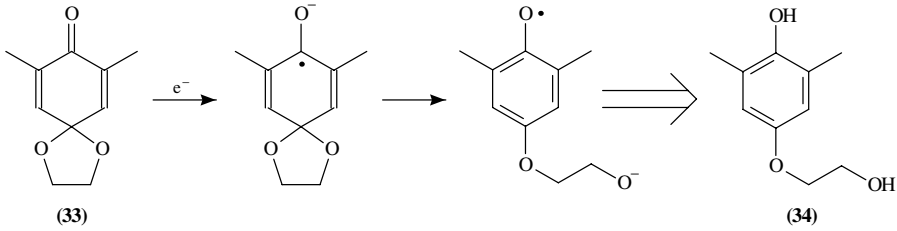


(20)



SCHEME 20

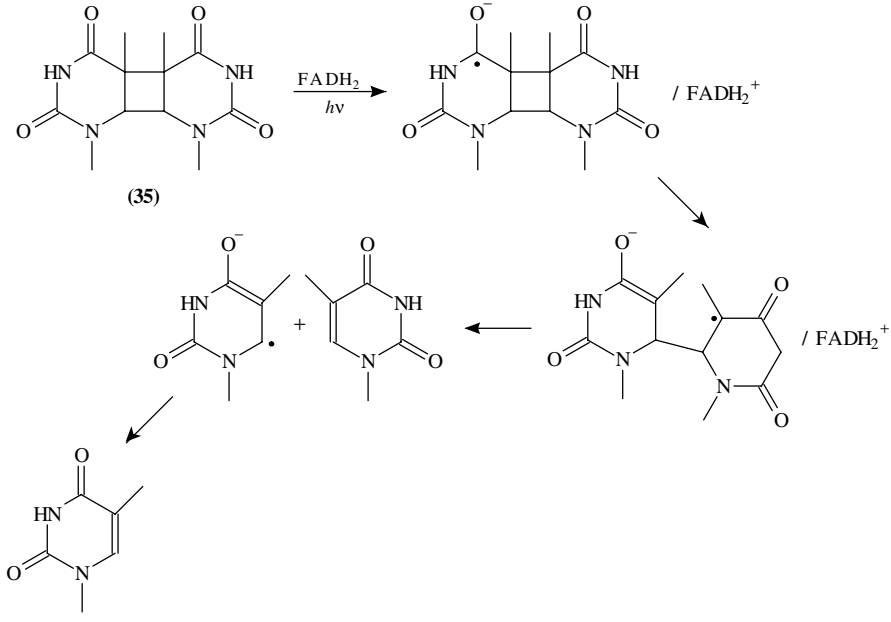
(d) Four- and five-membered ring openings. In 1983, Liotta reported the use of dienone **33** as a probe for SET. The radical anion generated from **33** undergoes ring opening according to Scheme 21[68]. The generation of an aromatic ring provides the thermodynamic driving force for this ring opening. This system has been used to assess the importance of SET in reactions of ketones with $(CH_3)_2CuLi$, RMgX and RLi. Detection of alcohol **34** was cited as evidence for SET in several of these reactions.



(33) **(34)**

SCHEME 21

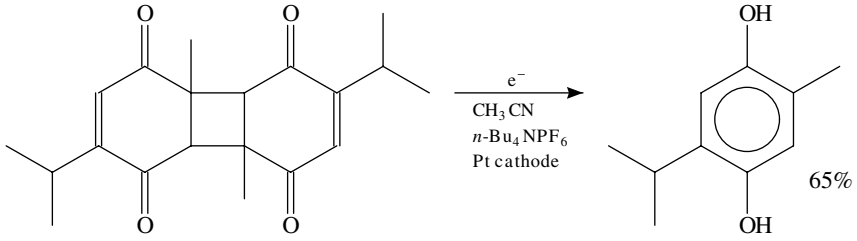
There has been considerable interest in the mechanism of action of DNA photolyase enzymes, which repair pyrimidine dimers in damaged DNA via action of visible light. Several model reactions have given credence to a possible SET pathway. For example, Falvey and coworker reported that the photochemical reaction of dimer **35** with $FADH_2$ results in a retro [2 + 2] cycloaddition according to Scheme 22[69].



(35)

SCHEME 22

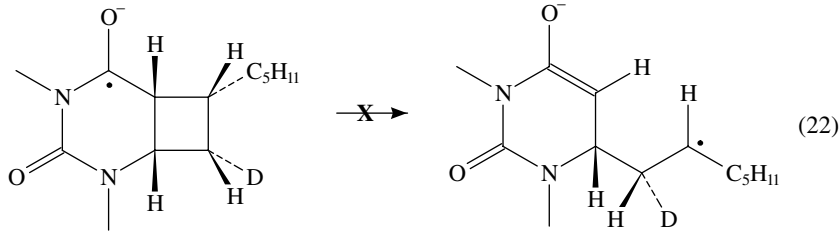
Similarly, electrochemical reduction of **36** results in a 65% yield of the retro [2 + 2] cycloadditon product (equation 21). The rate constant for the conversion **36**$^{\bullet-}$ → **37** + **37**$^{\bullet-}$ was determined to be 3.0 s^{-1} by cyclic voltammetry[70].



(21)

(36) **(37)**

Radical-stabilizing substituents on the cyclobutane ring appear necessary for this ring opening to occur. Yang and Begley found no evidence for ring opening of radical anion **38** (equation 22, generated via PIET using *N*,*N*-dimethylaniline)[71]. Neither ring-opened products nor isomerized starting material (resulting from a reversible ring opening) were detected.

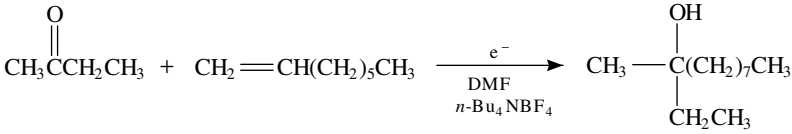


(22)

(38)

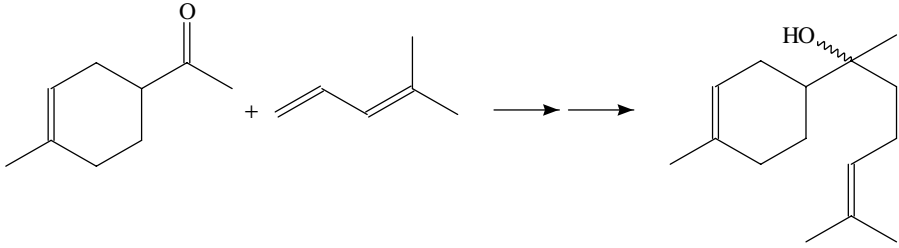
e. Addition of >C=O$^{\bullet-}$ *to π-systems (ketone–olefin coupling reactions).* Generation of >C=O$^{\bullet-}$ in the presence of an olefin (or other unsaturated functionality) may lead to an addition process as outlined in Scheme 23. Depending on the method of generation and the reaction conditions, the radical portion of the adduct may abstract a hydrogen atom from the solvent, or be further reduced to a dianion which can be trapped by electrophiles (usually, but not always, H^+). This methodology is particularly valuable when the addition reaction is *intramolecular*, and is an effective means for the synthesis of five- and six-membered rings.

(i) Intermolecular additions. In 1989, Shono's group reported that aliphatic ketones reduced (electrochemically) in the presence of an olefin yield the ketone/olefin adduct in reasonable yield (e.g. equation 23)[72] presumably via a mechanism analogous to that outlined in Scheme 23. The selection of the cathode material was critical to the success of this reaction; carbon fiber was found to give the highest yield of coupling product. The addition step was sensitive to steric effects, with addition to less substituted double bonds favored. This technology was applied to the one-step synthesis of bisabolol **(39)** in 80% yield (equation 24).

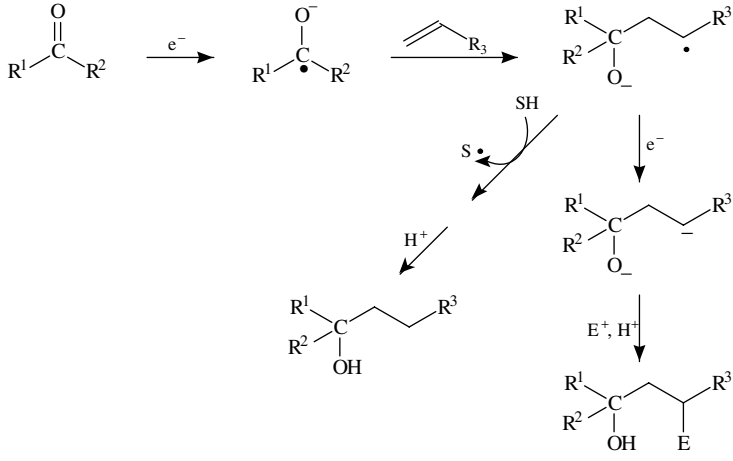


(23)

77%



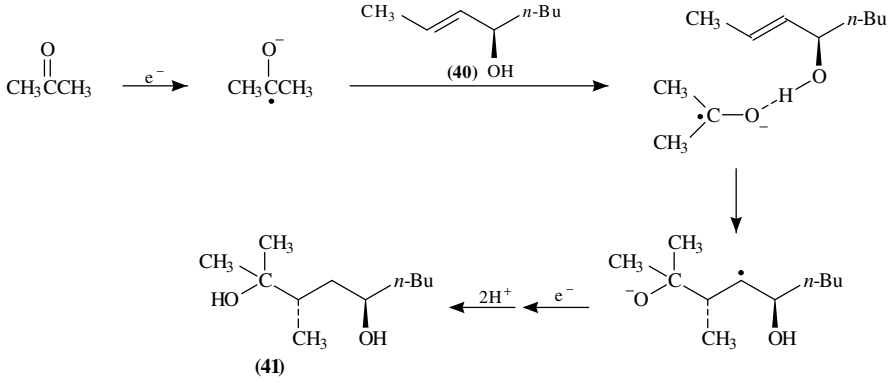
(39) (24)



SCHEME 23

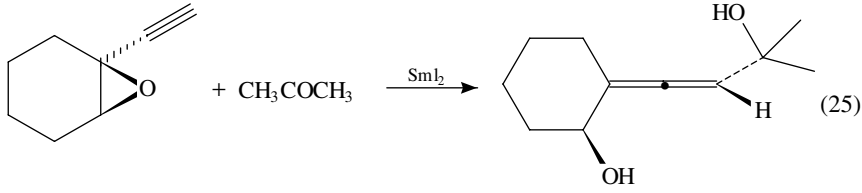
In an interesting extension of this methodology, Shono demonstrated that this reaction was especially effective when an allylic alcohol was utilized instead of a simple alkene. For example, reduction of acetone in the presence of **40** yields adduct **41** in 71% yield and greater than 85% diastereomeric excess[73]. The high diasteroselectivity observed for this process is rationalized to arise from hydrogen bonding interactions between the oxygen of $>C=O^{\bullet -}$ and hydroxyl group of the allylic alcohol which direct the addition to the *si* face of the double bond (Scheme 24).

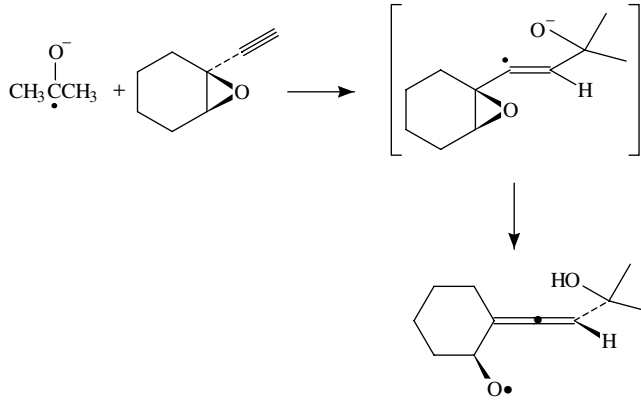
An intriguing variant of this coupling process was reported in 1995. Treatment of acetone with SmI_2 in the presence of **42** resulted in the formation of allene **43** in 81% yield and a 5.7:1 diastereomeric ratio (equation 25)[74]. Although no mechanism was suggested, it is likely that the reaction involves addition of $(CH_3)_2C=O^{\bullet -}$ to the terminal alkyne,



SCHEME 24

followed by subsequent ring opening of the oxiranyl radical (Scheme 25)[75].

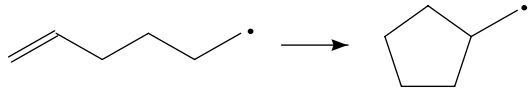




SCHEME 25

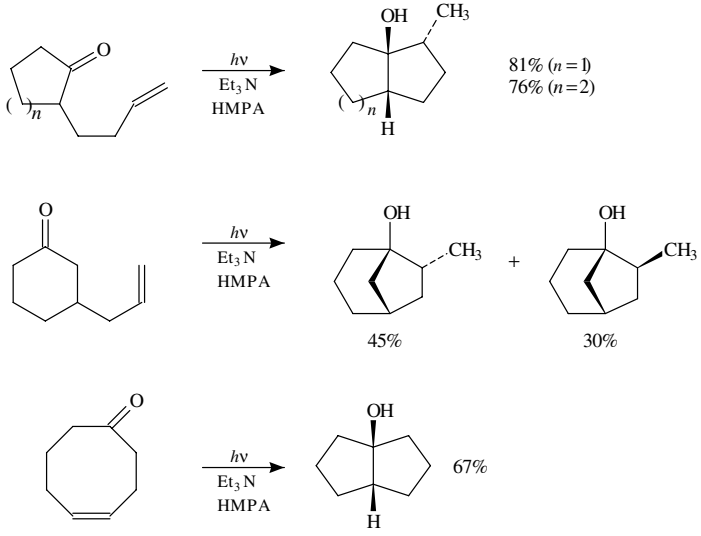
(ii) Intramolecular additions. (a) Intramolecular additions to remote alkene or allene functionalities. When a radical center is created in a molecule possessing a remote C=C or other unsaturated functionality, intramolecular addition may occur resulting in the formation of a cyclic compound. (This reaction is formally the reverse reaction of β-cleavage.) The Δ^5-hexenyl neutral free radical rearrangement (equation 26) is a classic example of such a process. In addition to providing an important mechanistic tool both

for detecting alkyl radical intermediates in a variety of chemical processes and for measuring the rates of competing bimolecular reactions (i.e. a free radical 'clock')[76], this rearrangement has emerged as an important synthetic method for the synthesis of five-membered rings[77]. Over the past decade, numerous examples have been reported of the radical anion equivalent of this reaction, involving intramolecular additions of $>C{=}O^{\bullet -}$ to remote unsaturated functionalities.



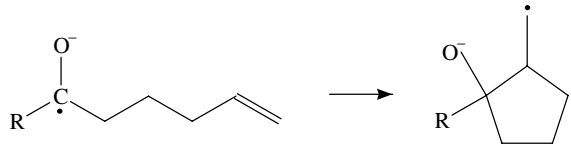
(26)

In 1986, Belotti, Pete and Portella reported that intramolecular ketone/olefin coupling could be achieved via photoinduced electron transfer (irradiation of an aliphatic ketone in HMPA)[78]. Several examples of this chemistry are highlighted below (Scheme 26). Intramolecular additions to C≡C and allenes were also reported with yields in the range 70–80%; however, additions to C≡N were unsuccessful.



SCHEME 26

The centerpiece of this chemistry involves cyclization of a ketyl anion (produced by PIET: $>C{=}O + R_3N: + h\nu \longrightarrow >C{=}O^{\bullet -} + R_3N^{\bullet +}$) as outlined in equation 27.

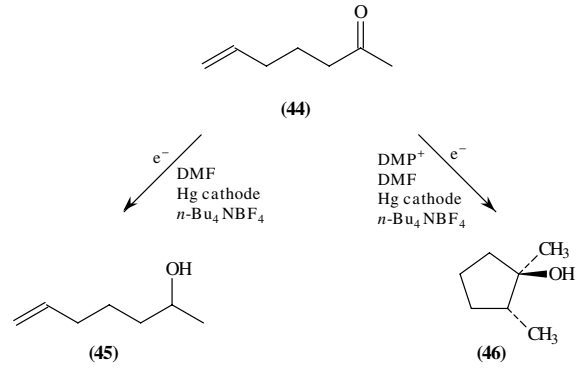


(27)

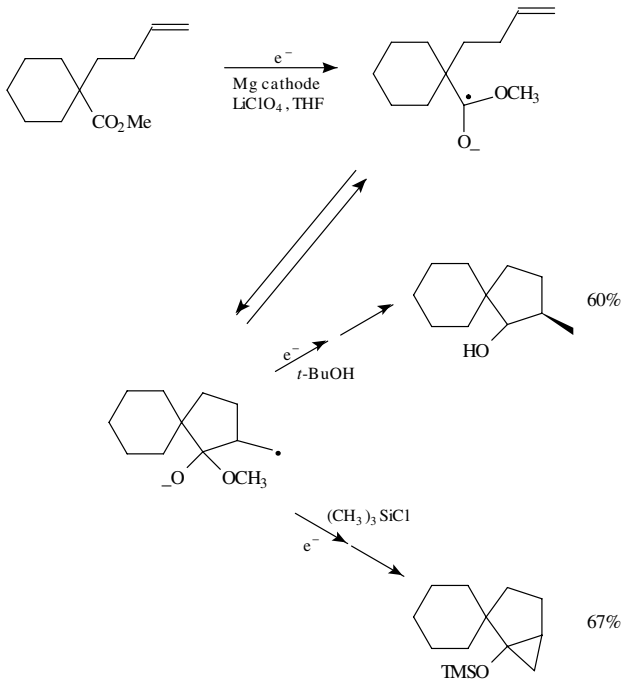
Analogous cyclizations can also be accomplished electrochemically[79]. In 1988, Kariv-Miller's group reported that cyclization of enone **44** could be achieved at a mercury electrode in the presence of dimethylpyrrolidinium ion (DMP^+)[80]. DMP^+ was a critical component for the success of this reaction, as direct reduction in the absence of DMP^+

produced only reduced product **45** (Scheme 27). DMP^+ was found to serve as a mediator (catalyst) for electron transfer to the carbonyl. Reduction of DMP^+ at Hg yields a species of composition $(DMP)Hg_5$, which has been independently prepared. $(DMP)Hg_5$ subsequently reduces the carbonyl compound ($(DMP)Hg_5 + >C{=}O \longrightarrow DMP^+ + 5Hg^\circ + >C{=}O^{\bullet -}$)[81].

Cyclizations involving esters were reported by Shono and workers in 1992 utilizing a Mg electrode[82]. Different products arose when the reduction was conducted in the presence of *t*-BuOH vs $(CH_3)_3SiCl$ (Scheme 28).



SCHEME 27

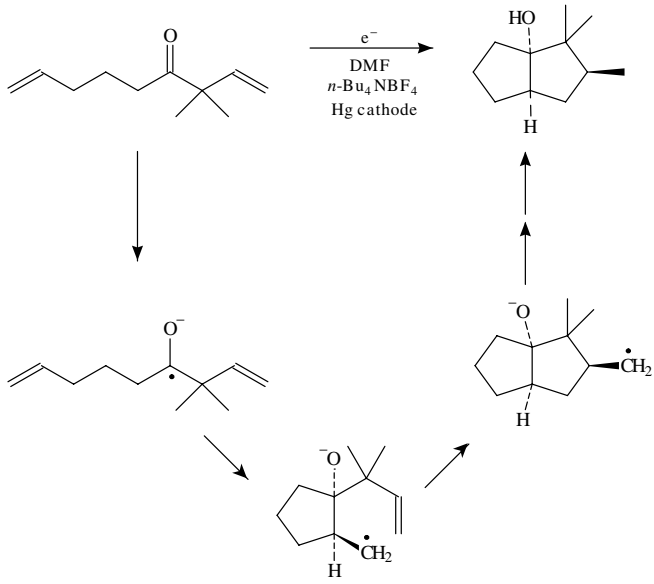


SCHEME 28

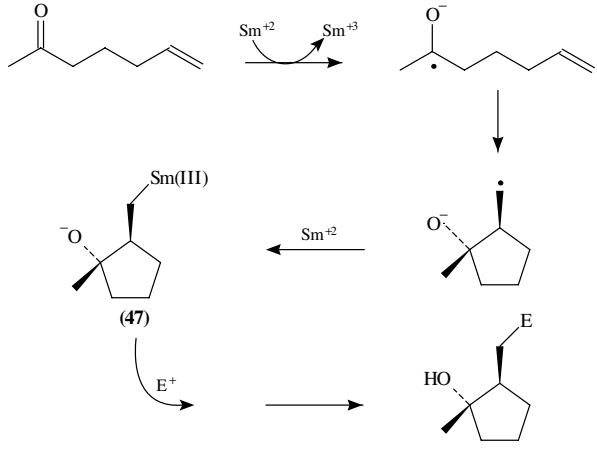
A tandem cyclization was accomplished electrochemically in 1989 (Scheme 29). A 50% yield was reported, depending on conditions[83].

A number of intramolecular ketyl anion/olefin coupling reactions promoted by SmI_2 have been reported since 1985. In general, SmI_2 reactions give extremely high yields and exhibit high diasteroselectivity.

Several examples of intramolecular ketyl anion/unactivated olefin coupling reactions were reported by the Molander group, one of which is illustrated in equation 28[84]. An interesting facet of this reaction is that it is possible to *further* react the cyclized samarium(III) intermediate **(47)** with a variety of electrophiles, thereby enhancing the

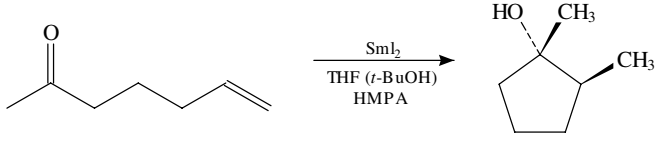


SCHEME 29



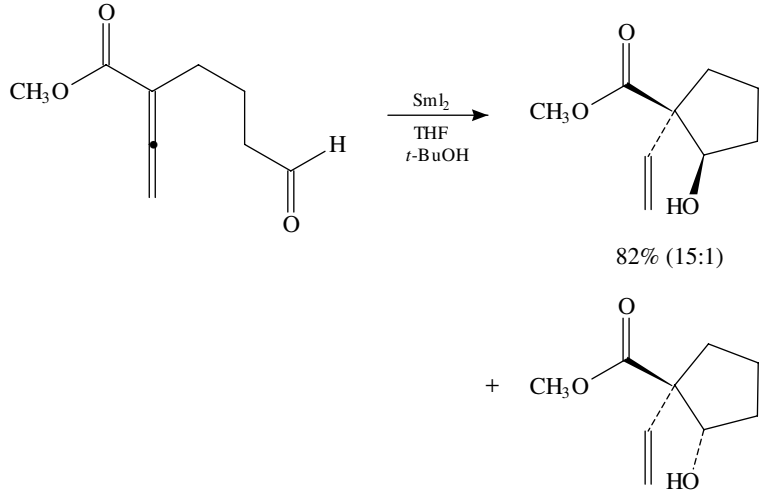
SCHEME 30

synthetic utility of this chemistry (Scheme 30). Electrophiles such as cyclohexanone, benzaldehyde, diphenyldisulfide and carbon dioxide successfully reacted in yields of 65–80%. In sense, this technique is superior to the related cyclizations of the Δ^5-hexenyl radical involving n-Bu_3SnH in that there is no loss of functionality at the radical center after cyclization.



(28)

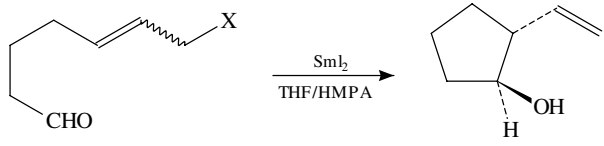
A similar cyclization of a ketyl anion (produced via reaction with SmI_2) onto an allene was reported by Gillmann in 1993 (equation 29)[85] The regiochemistry and high diasteroselectivity associated with this process was explained on the basis of a 'chelation-controlled' cyclization (e.g. TS **48**). The same reduction carried out with n-Bu_3SnH resulted in only a 37% yield and a 5 : 1 ratio of diastereomers.



(29)

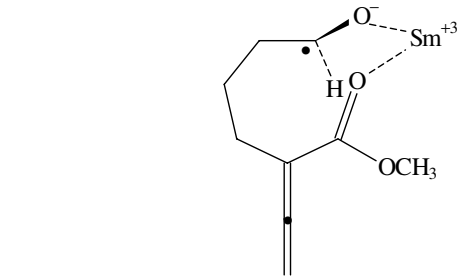
Analogous intramolecular 'chelation-controlled' ketone/olefin couplings with SmI_2, in which Sm^{+3} was complexed in a cyclic manner to the ketyl anion and a β-carbonyl of an ester or amide functionalilty, were reported as early as 1987 (Scheme 31)[86]. The cyclized samarium intermediate **49** could be further reacted with added electrophiles such as aldehydes or ketones[87].

Cyclization of ketyl anions onto allyl sulfides or sulfones were reported to yield 2-vinylcyclopentananols according to equation 30[88].

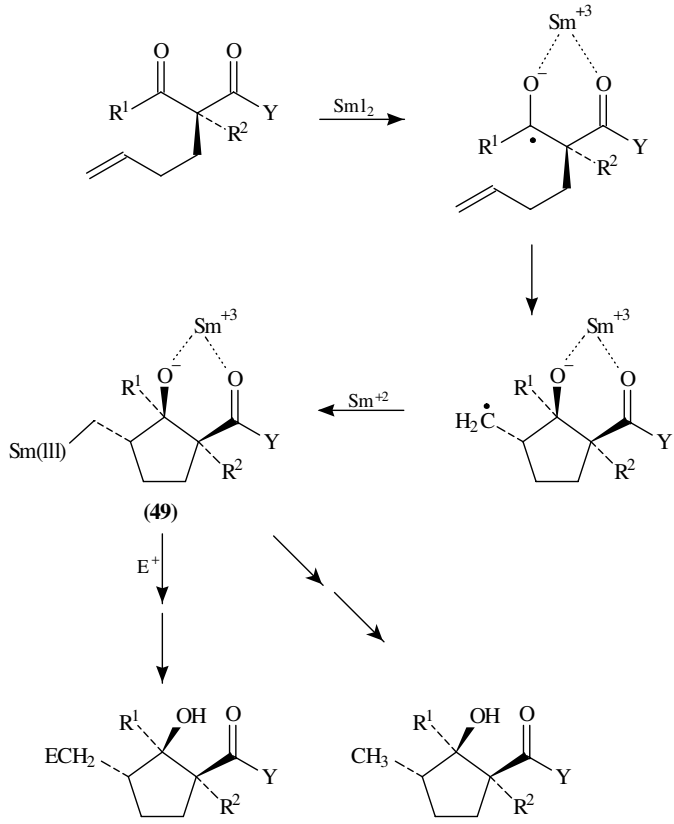


(30)

X = SPh (50%)
X = SO_2Ph (80%)

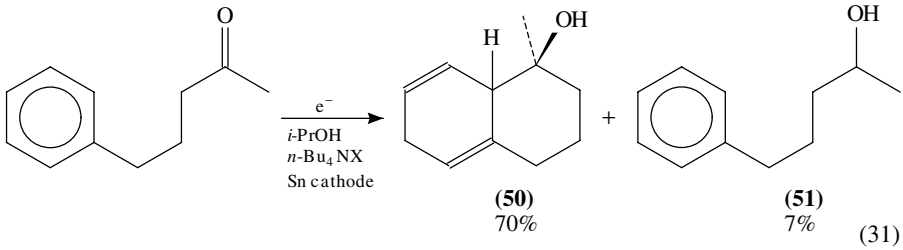


(48)



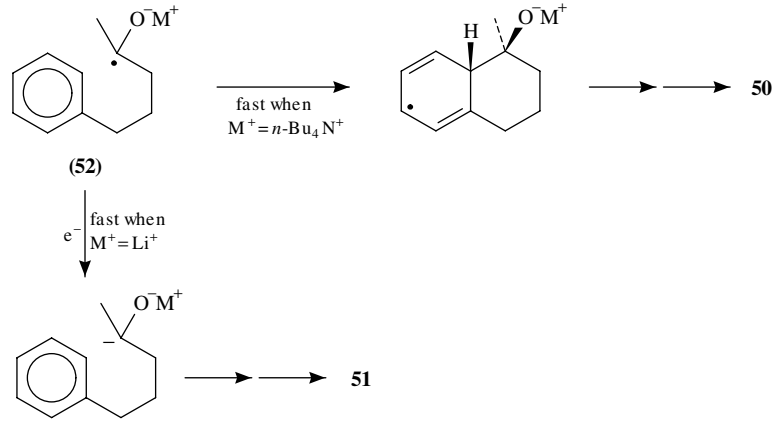
SCHEME 31

(b) Intramolecular additions to other remote π-systems. In 1986, Shono demonstrated the feasibility of intramolecular ketyl anion cyclizations onto an aromatic ring (equation 31)[89]. These reductions were achieved electrochemically in isopropanol, using a Sn electrode and $Et_4N^+X^-$ electrolyte. Use of $LiClO_4$ as an electrolyte yielded only the reduced product **51**.



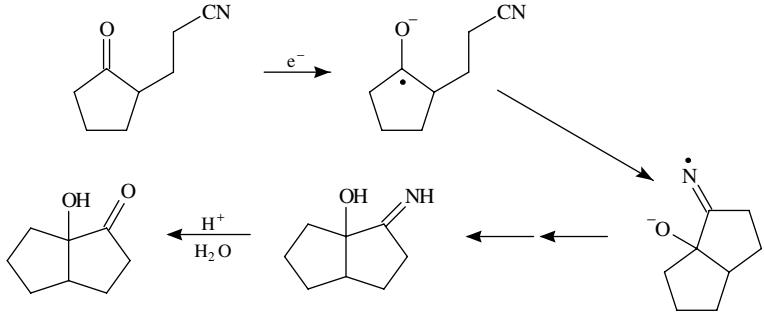
(31)

The effect of the counterion on the outcome of this reaction was attributed to ion-pairing effects (Scheme 32). It was suggested that the ketyl anion **52** is more easily reduced when Li^+ is the counterion, and that this *second* reduction occurs faster than cyclization[90].



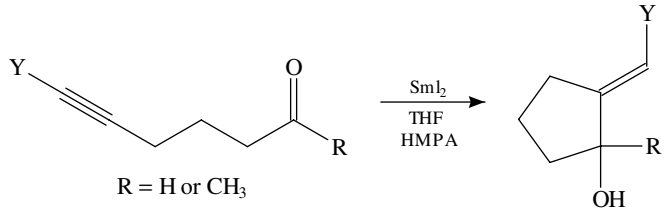
SCHEME 32

Intramolecular cyclizations of ketyl anions (generated electrochemically at a Sn cathode in isopropanol) onto a remote C≡N were reported in 1992[91]. α-Hydroxyketones are produced in yields ranging from 60–80%, depending on the structure of the substrate (Scheme 33).



SCHEME 33

SmI_2-promoted, intramolecular ketone/alkyne couplings were reported in 1990 (equation 32)[92]. Yields were low (30–50%) for unactivated alkynes (Y = H or CH_3), but improved to 50–75% when Y = $Si(CH_3)_3$, Ph or CO_2Et. Also, yields were typically much better for ketones than for aldehydes.



(32)

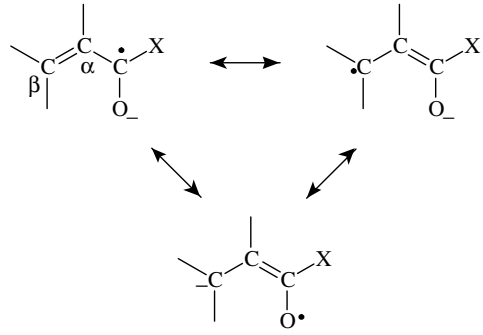
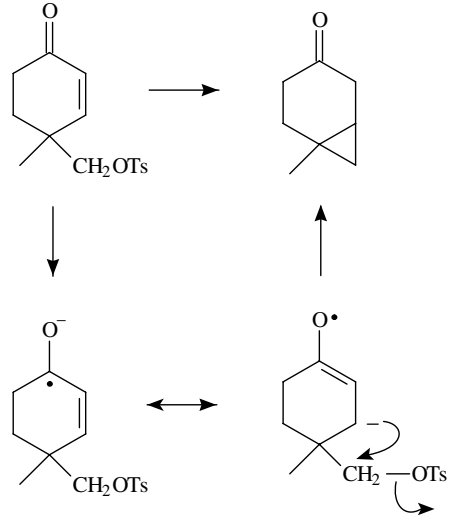


FIGURE 4. Resonance forms of α,β-unsaturated carbonyl compounds

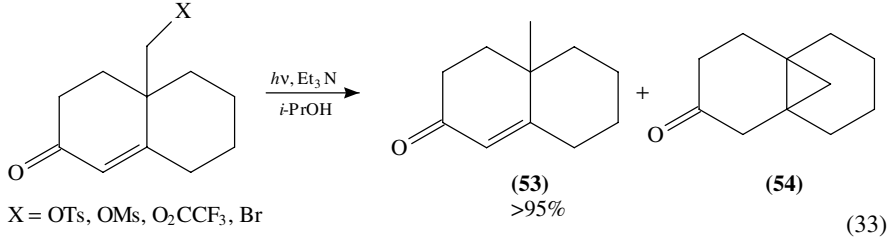


SCHEME 34

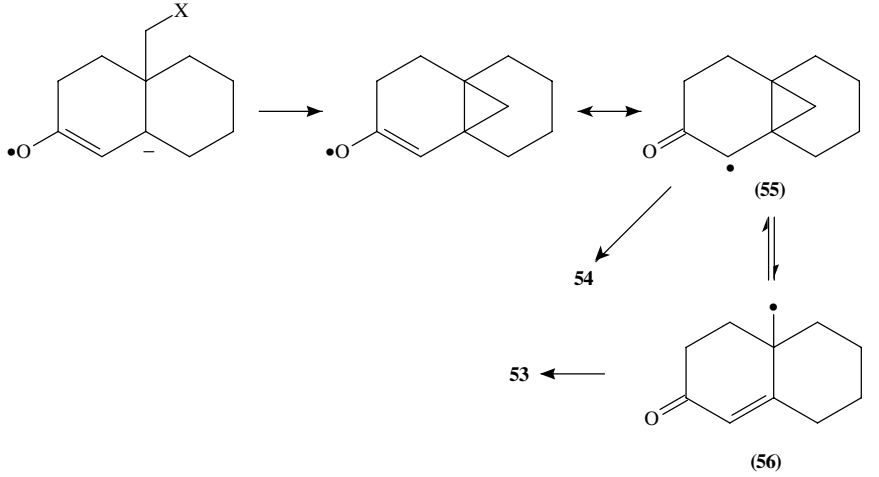
f. Radical anions generated from α,β-unsaturated carbonyl compounds. The principles underlying the chemistry of radical anions generated from α,β-unsaturated carbonyl compounds (mainly aldehydes, ketones and esters) are similar to those discussed earlier for $>C=O^{\bullet -}$ in general. The key difference is that, as a result of the transfer of spin- and/or electron-density to the β-carbon through resonance (Figure 4), new reaction pathways become accessible. There are examples in which the β-carbon seems to be reacting both as a nucleophile and as a radical, several of which are discussed below.

(i) 'Nucleophilic' reactions of $>C=C-C=O^{\bullet -}$. In 1981, Gassman reported that electrochemical reductions of enones possessing a good leaving group at the δ position yield cyclopropanes in excellent (>80%) yields[93]. The mechanism suggested for this process is summarized in Scheme 34. (Similar reductions were achieved in the 1960s by Stork using Li/NH_3, although in much lower yields.)[94]

In contrast, under conditions of photoinduced electron transfer, Givens and Atwater found that the major product of the reaction is C−X reduced product **53** (equation 33)[95]. It was proposed that under these conditions, the cyclopropylcarbinyl radical **55** undergoes further (*reversible*) ring opening (**55** → **56**, Scheme 35). The reversibility of this ring opening was demonstrated by generating radicals **55** and **56** independently via reaction of the corresponding alkyl bromides with *n*-Bu_3Sn•.



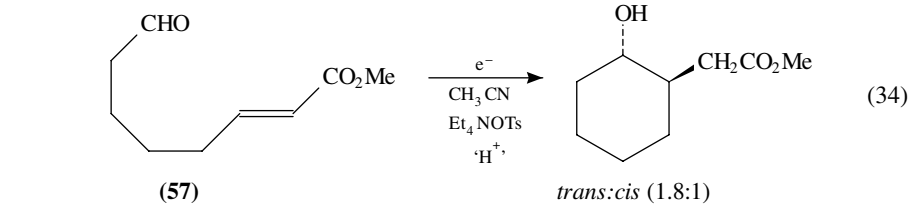
(33)



SCHEME 35

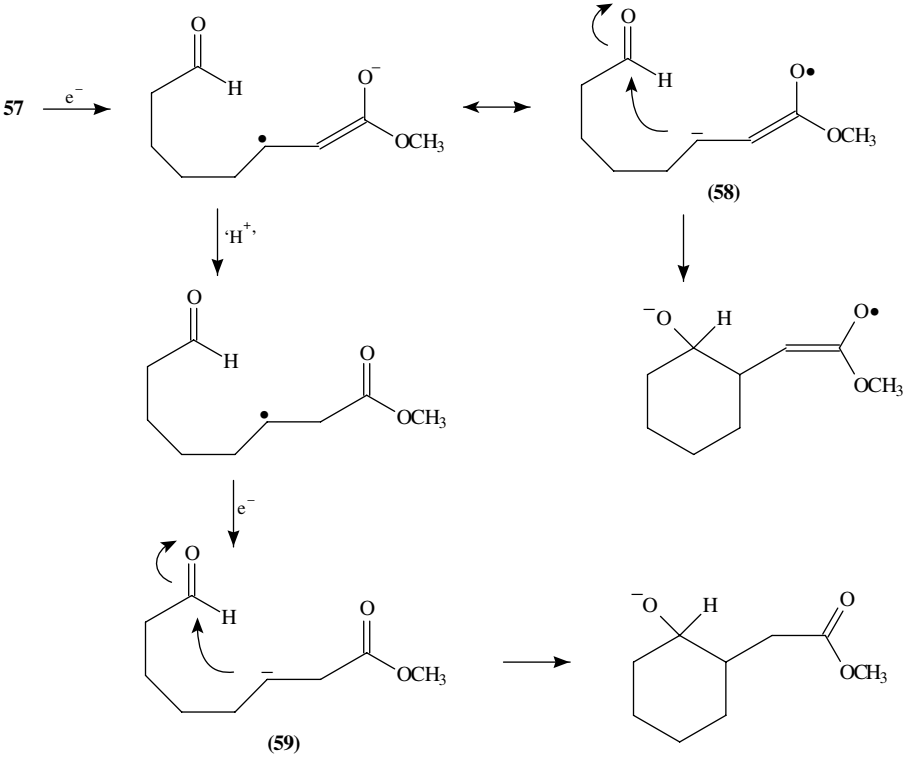
Little's group has reported electroreductive cyclizations involving α,β-unsaturated esters (equation 34)[96]. Based upon CV measurements, the conjugated ester rather than the aldehyde or ketone is suggested to be the electron acceptor. Although direct cyclization of

radical anion **58** was suggested initially, a more detailed mechanistic study suggests that cyclization actually occurs via *anion* **59** (Scheme 36)[97].



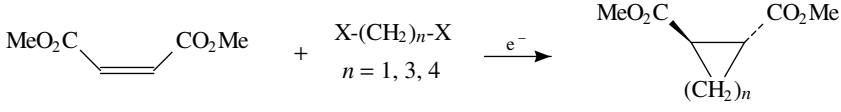
(34)

(57) *trans:cis* (1.8:1)



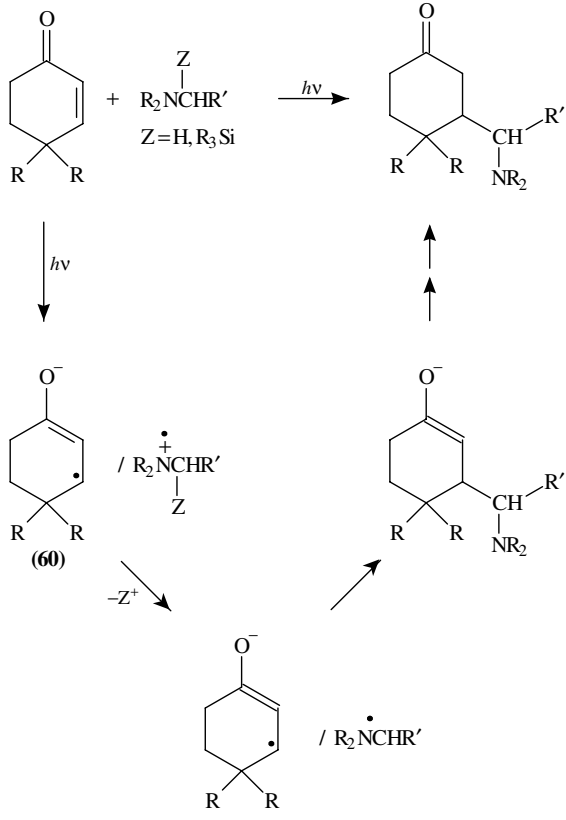
SCHEME 36

The preparation of three-, five- and six-membered rings in modest yield by the electrochemically induced coupling of activated olefins with dihalides has been reported (equation 35)[98]. Use of an aluminum anode was critical for the formation of cyclized product. Application of this technique to the preparation of four-membered rings was unsuccessful.



(35)

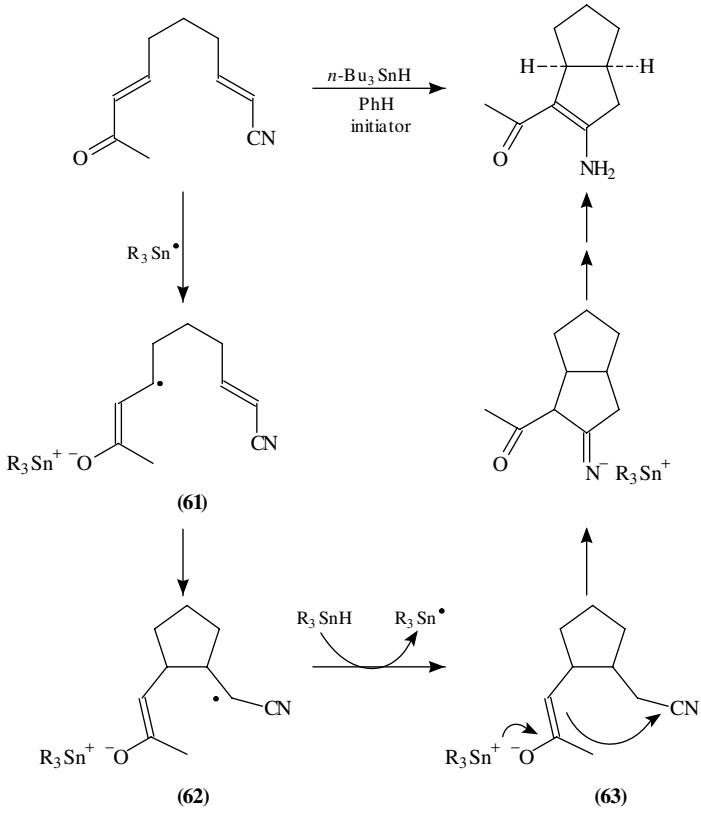
(ii) 'Radical' reactions of >C=C−C=O$^{\bullet-}$. In a series of papers, Mariano reported numerous examples of photochemically-induced inter- and intramolecular coupling reactions of enones with amines[99]. These reactions proceed via PIET (Scheme 37) to generate the radical anion/radical cation pair **60**. Loss of 'Z^+' from the amminium radical cation followed by radical anion/radical coupling leads to the final adduct. An excellent review of this chemistry has recently appeared[100].



SCHEME 37

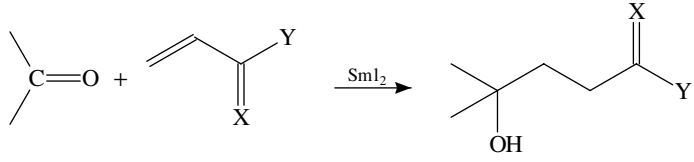
Enholm has reported tandem cyclizations induced by R_3SnH (Scheme 38)[101]. The initial cyclization is a Δ^5-hexenyl-type cyclization of the initially formed radical anion (**61** → **62**). After hydrogen transfer from R_3SnH, the resulting tin enolate **63** undergoes nucleophilic addition to the nitrile.

(iii) Miscellaneous ketone (aldehyde)/activated olefin couplings. SmI_2-promoted coupling of aldehydes or ketones with α,β-unsaturated ketones, esters and nitriles have been reported (equation 36). These reactions have been suggested to involve the addition of >C=O$^{\bullet-}$ to the activated alkene[102], although the inverse (>C=C−C=X$^{\bullet-}$ + >C=O ⟶) seems more likely since activated alkenes are more easily reduced than simple aldehydes and ketones. This coupling reaction can also be promoted by Mg in CH_3OH[103], although mechanistically this is more complicated because the sequence of proton vs



SCHEME 38

electron transfers is less clear.



(36)

IV. RADICAL IONS OF >C=C< CONTAINING COMPOUNDS

A. Chemistry of Radical Cations Derived from Carbon–Carbon Double Bonds

As will become evident in this section, in the net transformation from reactant → product transformations many of the synthetically useful reactions involving >C=C<$^{\bullet+}$ are analogous to those involving neutral, un-ionized carbon–carbon double bonds (e.g. the Diels-Alder reaction, oxidation/reduction reactions, nucleophilic addition etc.). However, many of the reactions involving a *neutral* >C=C< often require the presence of an activating substituent in order to make the alkene more electron-deficient. In a sense, one-electron oxidation of an alkene to its radical cation provides a simple and unique mechanism for increasing the electrophilic (and, of course, radical) properties of

a >C=C< group *without* having to resort to the incorporation of a substituent. Consequently, radical cation pathways provide a useful alternative in cases where classical synthetic methodologies are not applicable.

1. Methods of generation

Cation radicals may be generated by direct or indirect electrochemical oxidation of the molecule of interest, and many such oxidations are synthetically useful. However, several other methods are also available, which fall into two broad categories: thermally-induced electron transfer (TIET) and photo-induced electron transfer (PIET).

Synthetically important TIET acceptors are dominated by various triarylaminium cation radical salts ($Ar_3N^{\bullet+}$)[104]. Aminium cation radicals may also be generated electrochemically *in situ* from the corresponding amines[105]. High-valent complexes based upon Ce(IV), Fe(III) etc. have also proven useful as one-electron oxidizing agents for radical cation generation[106].

Photo-induced electron transfer takes advantage of the fact that the excited state of many compounds (typically possessing electron-deficient π-systems) are strong oxidants. Important PIET acceptors include the dicyanobenzenes (DCB), -naphthalenes (DCN) and -anthracenes (DCA), but other more exotic PIET acceptors include 2,4,6-triphenylpyrrilium (TPP)[107] and *N*-alkylacridinium salts. The latter compounds (with long-chain alkyl groups) are particularly useful as PIET acceptors in solvents of medium to low polarity[108]. TPP salts are typically used as PIET acceptors for reactions such as the cation radical Diels-Alder reaction, which requires the use of a minute quantity of catalyst. Use of these compounds is applicable to a wide range of dienes[109].

2. Reactions involving >C=C<$^{\bullet+}$

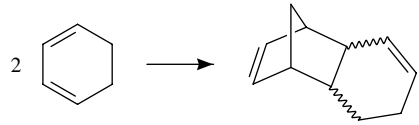
a. Cation radical 'pericyclic' reactions. Over the past decade, several examples of pericyclic reactions induced or catalyzed by the removal of an electron from an olefin have been reported. Three reviews by Bauld cover this group of reactions, especially the so-called 'hole-catalyzed Diels-Alder' reactions. The first review is primarily concerned with the initial work in Bauld's laboratory[110]. The second[111] and third[112] are more comprehensive reviews which cover the field of radical cation 'pericyclic' reactions in general, through about 1988 and 1989, respectively. After a brief introduction, this section will focus primarily on more recent developments so as not to duplicate material already covered by the existing reviews.

(i) The 'hole-catalyzed Diels-Alder' reaction. Bauld reported that treatment of cyclohexadiene with $Ar_3N^{\bullet+}$ led to an unusually facile Diels-Alder reaction (Table 6). It was suggested that radical cations were involved as intermediates in a chain process, and the name 'hole-catalyzed Diels-Alder' reaction was coined. The proposed mechanism is summarized in Scheme 39.

Since this initial report, there has been considerable controversy over whether these reactions actually involve radical cations. The alternative possibility is a cationic mechanism. (In many cases, $R_3N^{\bullet+}$ serves as an indirect source of H^+[113]. However, this Brønsted-acid-catalyzed pathway can be effectively suppressed by the addition of a hindered base.)

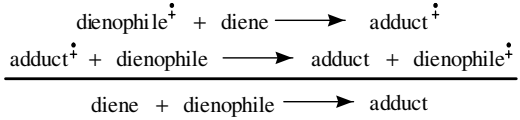
More recently, however, it has been suggested that carbocation intermediates might result from the addition of an amminium ion (through the aromatic ring) to a π-bond[114]. Recently, this controversy seems to have been definitively settled: Most hole-catalyzed Diels-Alder reactions actually *do* involve cation radicals[115], except for the addition of tetracyanoethylene to electron-rich alkenes[116].

TABLE 6. Diels-Alder reaction of cycloheda-diene[a]



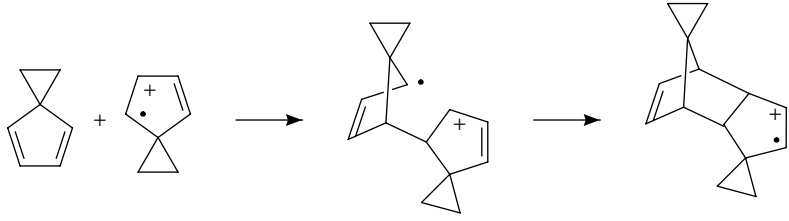
Conditions	Yield	*endo:exo*
200°C, 20 h	30%	4:1
5–10 mol% $Ar_3N^{\bullet+}$, 0 °C, 15 min	70%	5:1

[a]Reference 110.



SCHEME 39

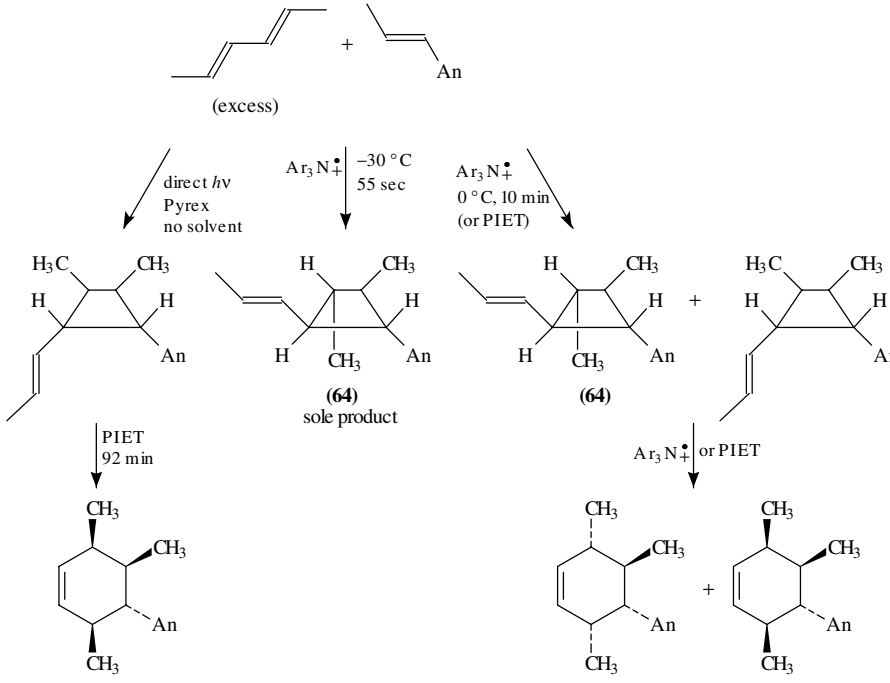
Quotation marks are used to describe the 'hole-catalyzed Diels–Alder' reaction because of the fact that these are Diels–Alder reactions only in the sense that they yield the same products. Mechanistically, however, they are distinct and are generally considered to occur in a stepwise, rather than concerted, manner. Results obtained from CIDNP experiments suggest that an intermediate, ring-opened radical cation may be involved in the reaction (Scheme 40)[117].



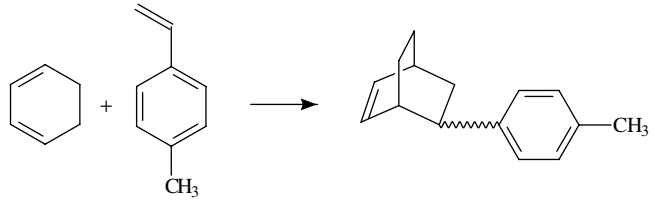
SCHEME 40

Additional evidence for a stepwise pathway is provided by the fact that a 'two-step' Diels–Alder reaction is observed, in which a formal [2 + 2] reaction gives a vinylcyclobutane **(64)** which then rearranges to the formal [4 + 2] product (Scheme 41, An = *p*-$CH_3OC_6H_4$)[118]. It has been shown that orbital symmetry control does not operate in these reactions: Symmetry-allowed and symmetry-forbidden reactions may take place with equal facility depending upon the conditions[119]. It has also been shown that the obtention of formally [4 + 2] or [2 + 2] products depends on many factors, including solvent and whether it is the diene or the dienophile which is ionized[120].

Typically, electrochemical oxidation of cyclohexadiene gives only polymer[121]. However, when extreme care is used a low yield (38%) of the Diels–Alder adduct with *p*-methoxystyrene is obtained, with an enhanced *endo/exo* ratio compared to the same reaction using PIET (Scheme 42)[122]. For most purposes PIET gives sufficiently high



SCHEME 41



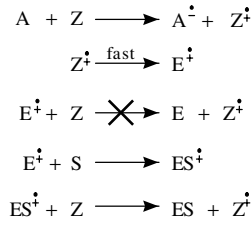
	Electrochemically-induced	PIET-induced
Yield:	22%	28%
endo/*exo*:	9:1	4:1

SCHEME 42

endo-selectivity. Nevertheless, selectivity may be altered somewhat by varying reagent or electrolyte concentrations, by using different PIET acceptors or by selective quenching[123].

Important general aspects of the cation-radical 'Diels–Alder' reaction and other cation-radical sigmatropic reactions are summarized below:

- There is a wide range of possible catalysts available for initiating the reaction. In addition to organic salts, oxidants such as hydrated or anhydrous $FeCl_3$[106a] and ceric ammonium nitrate[106a,124] have proven effective.
- Electrochemical methods should be avoided because their chief electrooxidative reaction involving olefins is polymerization.

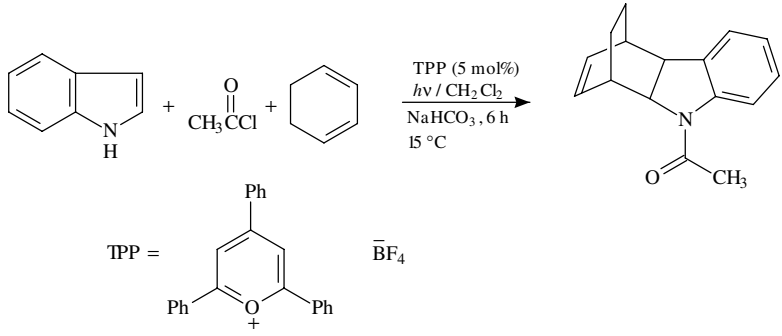


A = acceptor, S = substrate,
Z = (*Z*)-stilbene, E = (*E*)-stilbene

SCHEME 43

• Cation radicals of (*Z*)-alkenes isomerize to the more stable (*E*)-isomer before adding to a substrate (Scheme 43). Despite this, in the case of stilbene, it is often found that none of the (*E*)-isomer is recovered from the reaction mixture. This is due to the fact that electron transfer from (*Z*)-stilbene to (*E*)-stilbene$^{\bullet+}$ is highly endothermic[111,125].

Indoles, which are especially electron-rich and thus unsuitable for ordinary Diels–Alder reactions, have performed successfully in the cation-radical reaction as dienophiles (Scheme 44)[107] and as dienes (Scheme 45)[126]. Interestingly, the site of annulation (across the C–C or the C–N bond) in vinylindole cation radicals (functioning as dienes for eneamine dienophiles) may be manipulated by varying the substituent on the enamine and thereby altering its push–pull nature (Scheme 45).

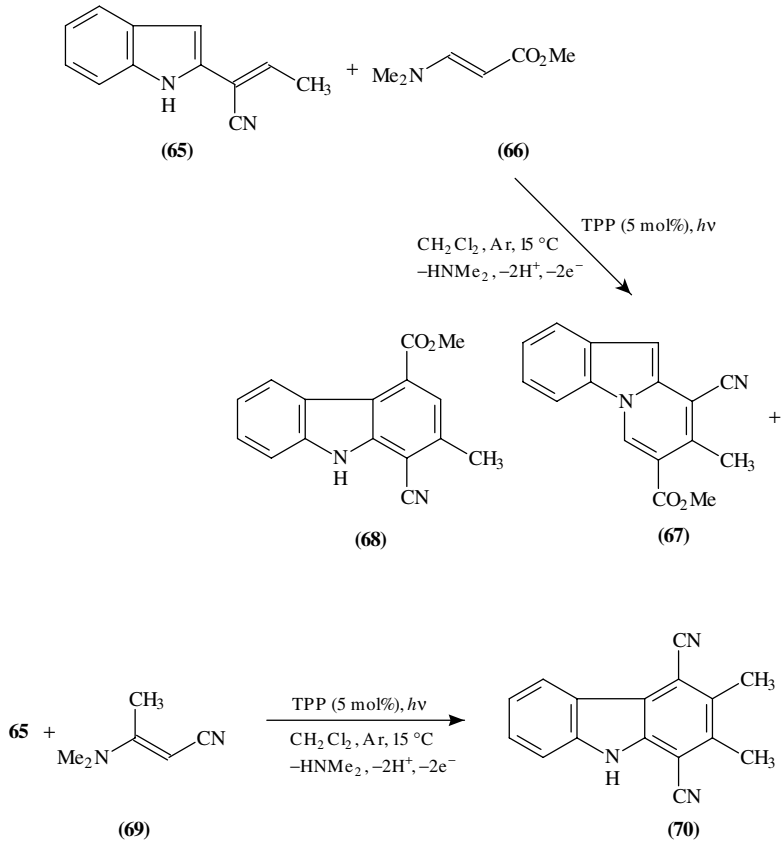


SCHEME 44

For the indole, methyl sustitution at the 2-position (i.e. **71**) appears to sterically block C–C annulation vs C–N annulation (Scheme 46)[126*a*]. Note also that electrochemical methods are only useful for the substituted vinylindoles, as unsubstituted indoles passivate the working electrode. The results of cycloadditions of substituted enamines **66** and **69** to vinylindoles **65** and **71** are summarized in Tables 7 and 8.

Another interesting variation on hole-catalyzed Diels–Alder chemistry involves the use of electrochemically-oxidized phenols as dienes. A set of cycloaddition reactions leading to bicyclic products was reported in 1991, beginning from polysubstituted phenols[127]. This work strongly implicated cation **74** by showing that the same products were obtained when **74** was generated independently via Brønsted acid/base reactions (Scheme 47).

Similarly, phenoxonium ion **75** was believed to be a key intermediate in the intramolecular process (Scheme 48)[128].



SCHEME 45

TABLE 7. Results of PIET-induced cycloaddition of indole diene **65** with dienophile **66**[a]

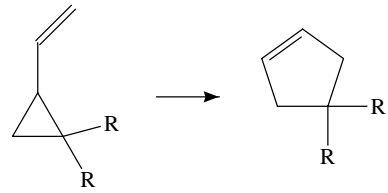
[**66**] (mmol L^{-1})	mol% of TPP[b]	67:68	Yield (%) (**67** + **68**)
7.7	8	3.5:1	85
5.9	6.9	2.6:1	80
2.7	6.1	1.5:1	75

[a]Reference 107.
[b]TPP = 2,4,6-triphenylpyrilium tetrafluoroborate.

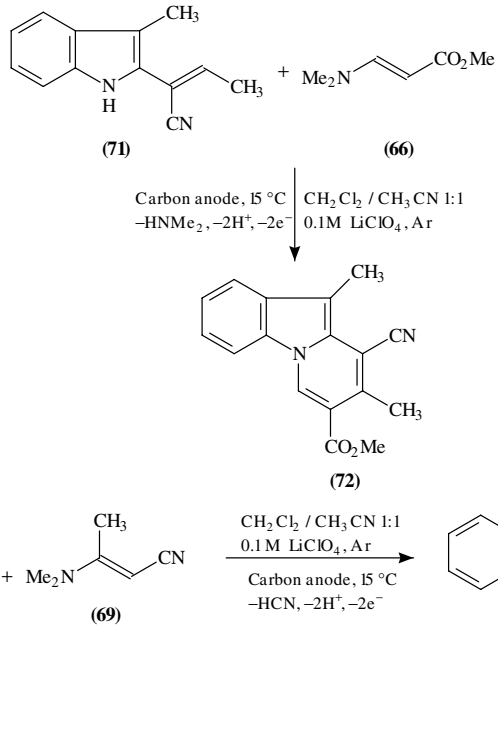
A later study of the intermolecular addition suggested that electron transfer between the phenoxonium ion and alkene is an important pathway to products (Scheme 49)[129].

(ii) Vinylcyclopropane rearrangements. The vinylcyclopropane → cyclopentene rearrangement (equation 37) has emerged as an important method for the preparation of functionalized cyclopentenes[130]. Formally, the thermal process is symmetry-forbidden, and exhibits an activation energy of 50 kcal mol^{-1}[131]. This reaction can also be induced

photochemically, or via the use of appropriate Lewis acids.



(37)

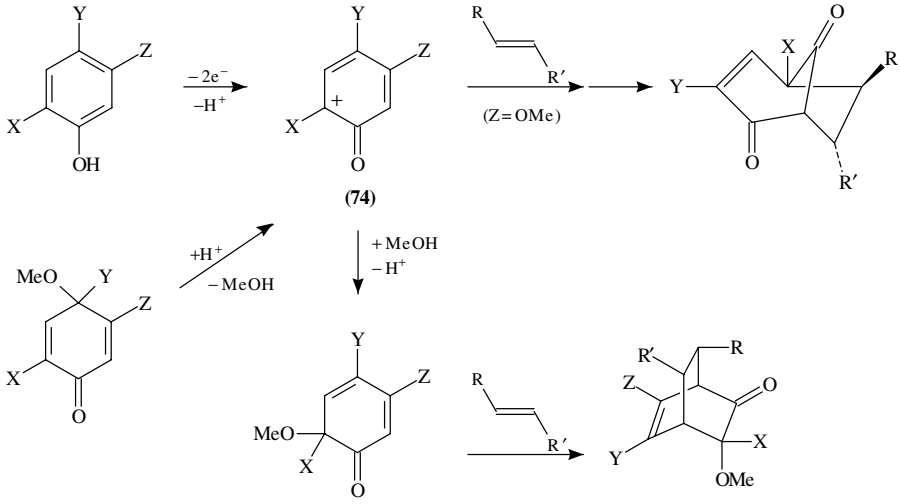


SCHEME 46

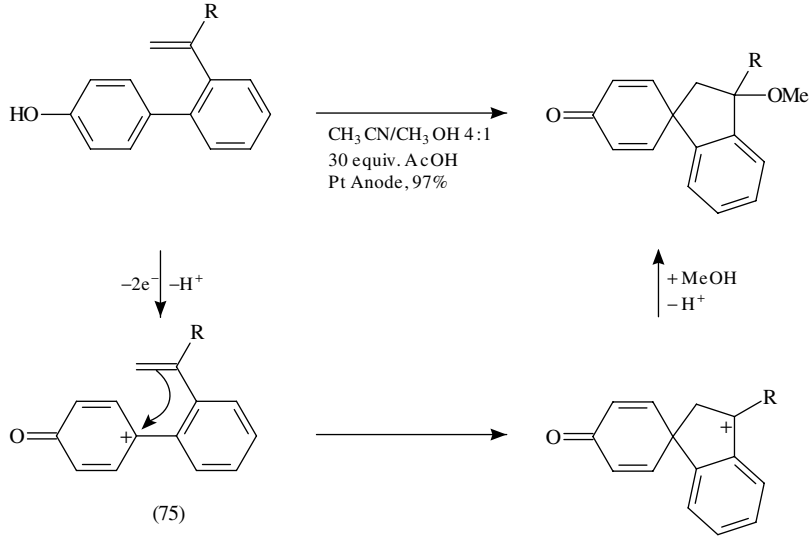
TABLE 8. Results of PIET- or electrochemically-induced cycloaddition of indole dienes with dienophiles[a]

Diene	Dienophile	Initiation[b]	Time (h)	Product (yield %)
65	**66**	PIET	5.5	**67** (74), **68** (22)
71	**66**	e-chem	2	**72** (32)
65	**69**	PIET	6	**70** (13)
71	**69**	e-chem	2	**73** (29)

[a]Reference 126.
[b]PIET = 5 mol% 2,4,6-triphenylpyrilium tetrafluoroborate, hν; e-chem = carbon anode, 0.1 M $LiClO_4$.



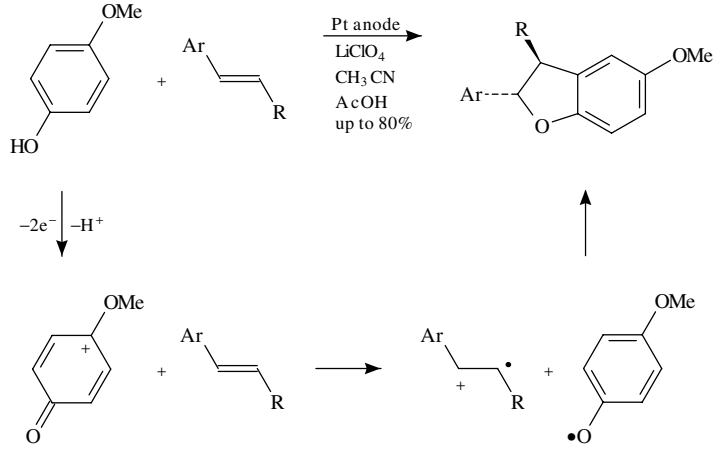
SCHEME 47



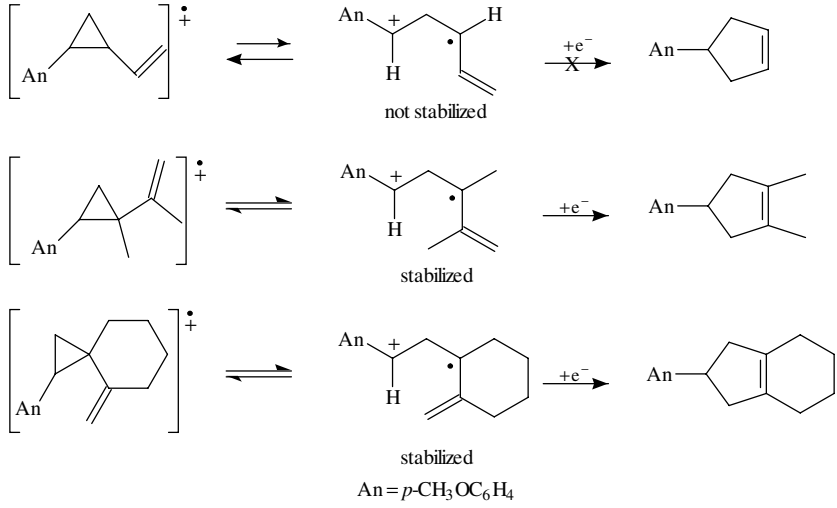
SCHEME 48

In 1988, Dinnocenzo and Conlon reported a radical cation variant of this reaction (Scheme 50)[132]. Most of the relevant material pertaining to this reaction has been recently reviewed[112].

Some question, however, exists as to the extent of ring-opening which exists in cyclopropyl and vinylcyclopropyl cation radicals[133]. Addressing this point, an elegant 1994 study found that (1*R*,5*R*)-(+)-subinene$^{\bullet+}$ (**76**, which cannot rearrange to a cyclopentene



SCHEME 49

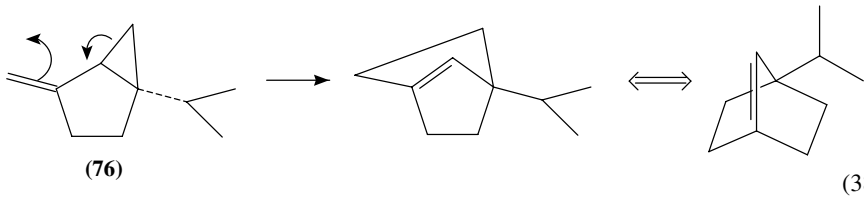


Conditions: 10 mol% Ar_3NSbCl_6
CH_3CN, 22 °C, 5 min

SCHEME 50

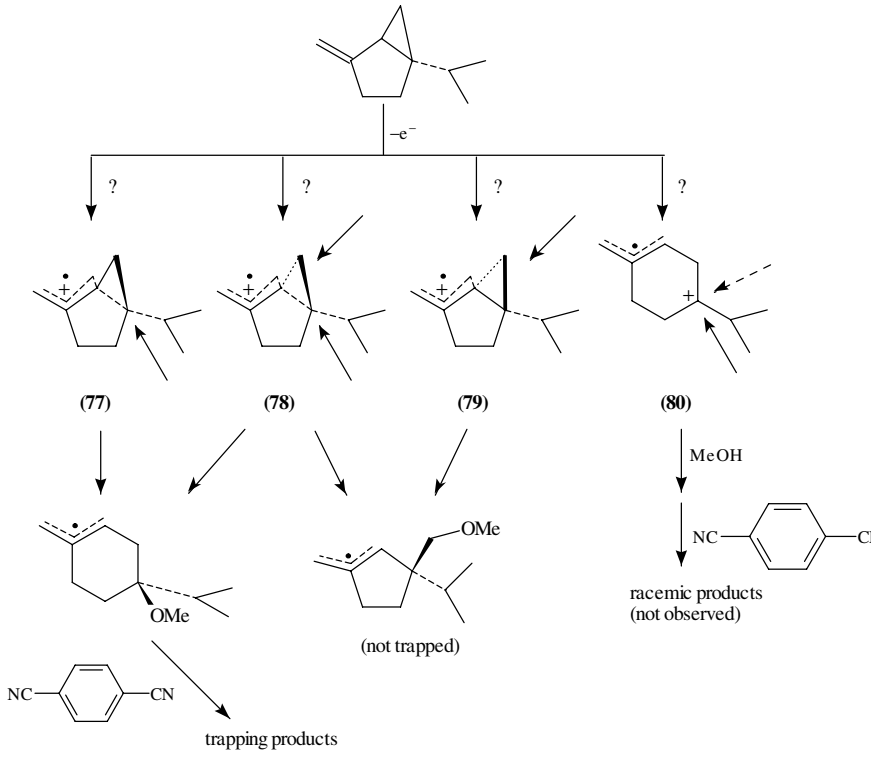
because such a rearrangement would lead to a bridgehead double bond, equation 38) behaves as a stereorigid vinylcyclopropane radical cation (Scheme 51)[134]. Four possible spin- and charge-delocalization patterns are possible in this vinylcylopropane cation radical, **77** → **80**. Ring-opened radical cation **80** would be expected to lead to a racemic mixture of products. However, this was not found and the product showed optical activity. Further elucidation of the products, formed by trapping of the cation radical with methanol and DCB anion radical, showed that the spin and charge distribution in sabinene$^{\bullet+}$ was

as shown in **77**.



(76)

(38)

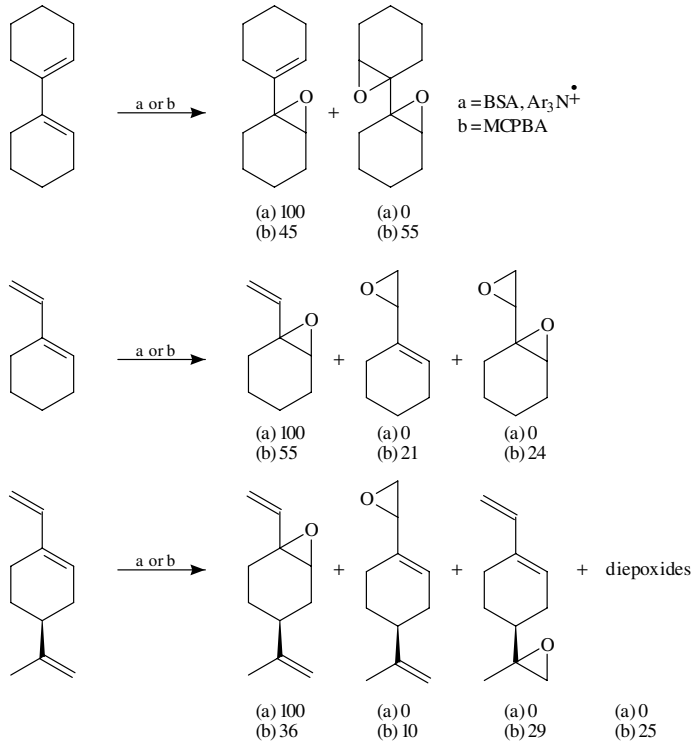


SCHEME 51

(iii) Epoxidations of alkenes. Hole catalysis has been proposed as a mechanism for epoxidations in the presence of TIET acceptors. In epoxidations using SeO_2 or benzeneseleninic anhydride (BSA) in the presence of aminium cation radicals, Bauld and Mirafzal reported 60–90% yields, with complete regiospecificity, over a wide range of dienes and trienes. Their results are compared to the results of epoxidations using *meta*-chloroperbenzoic acid (MCPBA) in Scheme 52 and Table 9[135].

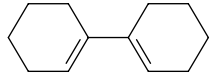
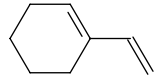
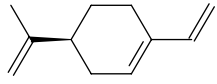
However, most of the debate in this area has been over the mechanism of epoxidation by cytochrome P450 (c-P450) and its analogs. c-P450 is a monooxygenase whose active center is an iron(III) porphyrin[136]; its catalytic cycle is shown in Scheme 53[137].

The two basic mechanistic possibilities for c-P450 epoxidations are summarized in Scheme 54. Path a represents an entirely covalent pathway involving oxidative addition

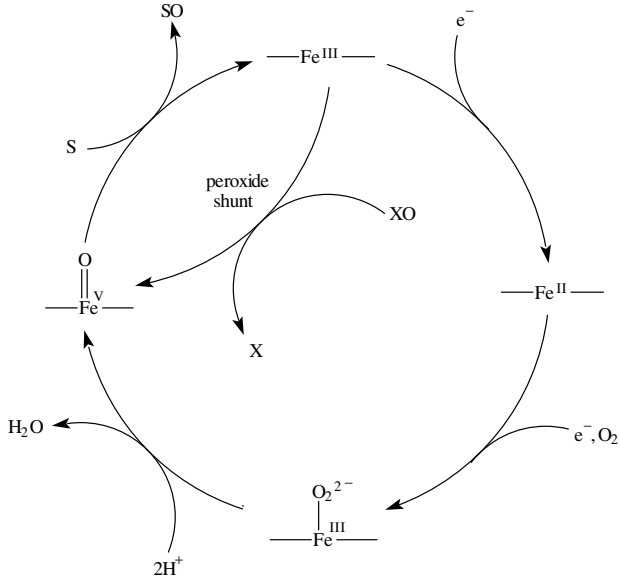


SCHEME 52

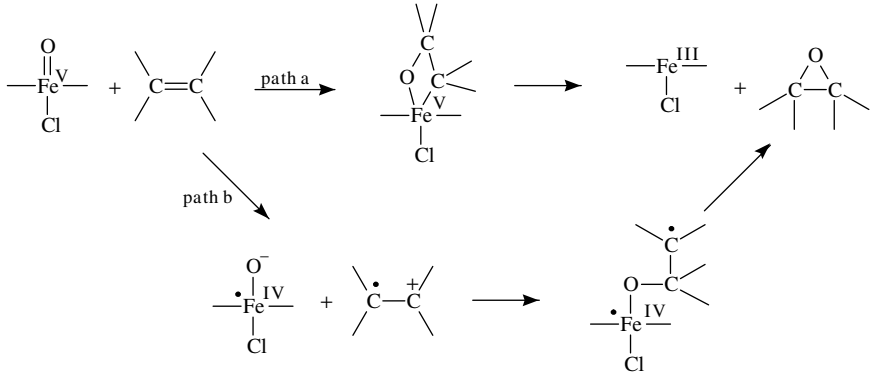
TABLE 9. Results of hole-catalyzed epoxidation[a]

Substrate	Oxidant	% Yield, GC (isolated)[b]
E-stilbene	SeO_2[c]	80 (60)
Z-stilbene	SeO_2	80 (58), epoxide of *E*
1,1-diphenylethylene	SeO_2	70 (42)
β-methylstyrene	SeO_2	60 (35)
α-methylstyrene	SeO_2	65 (38)
Z-stilbene	BSA[d]	85 (65), epoxide of *Z*
	BSA	83 (63)
	BSA	76 (61)
	BSA	72 (56)

[a] Reference 135.
[b] Column chromatography on silica gel.
[c] SeO_2, 500 mol%, Ar_3NSbCl_6, 20 mol%; CH_2Cl_2, 0 °C to RT, 1 h. Quench with K_2CO_3/CH_3OH
[d] BSA 100 mol%; Ar_3NSbCl_6, 20 mol%; CH_2Cl_2, 0 °C. 10 min. Quench with K_2CO_3/CH_3OH.



SCHEME 53



SCHEME 54

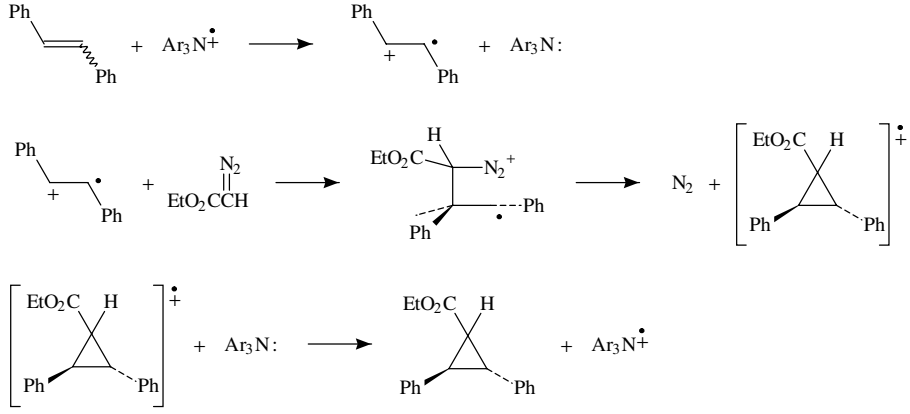
and reductive elimination. Path b supposes the intermediacy of either caged or solvent-separated radical ions (path b).

Initially, the products of these reactions suggested radical ions were involved[138]. In particular, when hexamethyl Dewar-benzene was epoxidized with MCPBA, the nature of the products depended on whether or not the iron(III) porphyrin hemin was added to the reaction mixture[138b]. Furthermore, when *Z*-stilbene was epoxidized with dioxygen, catalyzed by (tetraphenylporphorinato)iron(III) chloride, *E*-stilbene appeared in the reaction mixture[139].

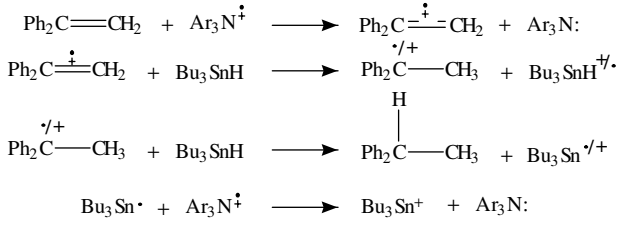
However, there has never been general agreement that alkene cation radicals were involved[140]. It was pointed out that choice of a c-P450 model will strongly influence the results: When manganese porphyrins were used, retention of alkene configuration

depended on the oxidation state of the metal[141]. A 1989 paper by Garrison, Ostovic and Bruice[142] concluded that the rate-determining step in metal-porphyrin-catalyzed epoxidations was formation of a CT complex between the metal and the alkene, and that whether an alkene cation radical is involved is sensitively dependent on the details of that complex.

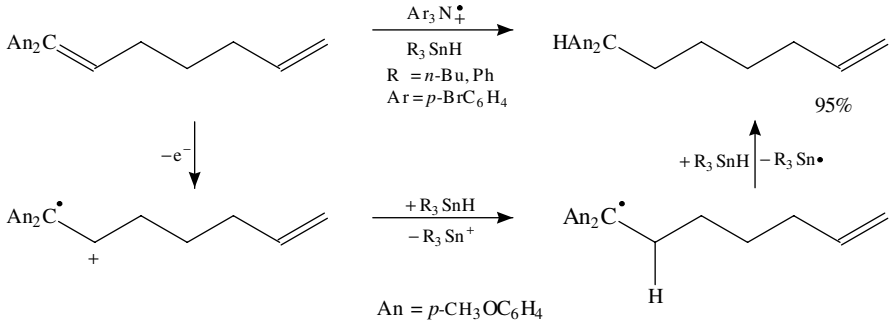
Independent rate studies by Bruice and Castellino[143] and by the Bauld group[144] concluded that any alkene radical cation must have a lifetime less than about 10^{-12} s, ruling out any meaningful role in the reaction for the free species. More recent work has generally concluded that no alkene cation radical is involved in epoxidations catalyzed by iron(III)



SCHEME 55



SCHEME 56



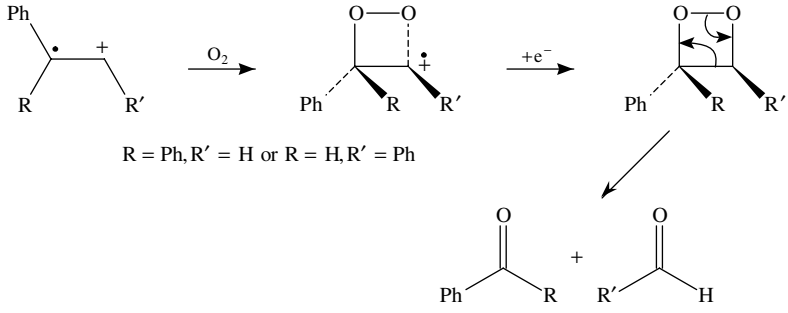
SCHEME 57

porphyrins[145], and a recent report in which hexamethyl Dewar-benzene was used as a radical scavenger in epoxidations catalyzed by c-P450 itself showed no trace of radical products[146].

(iv) Cyclopropanations of alkenes. 'Hole-catalyzed' cyclopropanation provides a useful means of adding a carbene equivalent to electron-rich alkenes under mild conditions. It has been established that the aminium-catalyzed reaction has a radical cation chain mechanism (Scheme 55)[147], and that the reaction does not proceed via the relatively unreactive diazomethane radical cation[148], since ethyl diazoacetate does not decompose in the presence of aminium salt and nonionizable alkenes[116].

b. Oxidation/reduction of alkenes. (i) Hydrogenation. 'Hole-catalyzed' hydrogenation reactions were first reported in 1992, and follow a radical mechanism which destroys the triarylaminium cation radical, at a stoichiometric ratio of two moles of aminium to one of alkene (Scheme 56)[149]. These reactions, though limited to easily-ionizable double bonds, are quite useful as they allow the selective reduction of the more easily-ionized double bond of a polyfunctional molecule in very high yield (Scheme 57)[150].

(ii) Oxygenation. The general form of this reaction involves the cleavage of a radical cation generated from an electron-rich alkene to give a benzophenone (from 1,1-diarylethylenes) or a benzaldehyde (from stilbenes). It is generally accepted that it proceeds via peroxy species, as shown in Scheme 58[151].

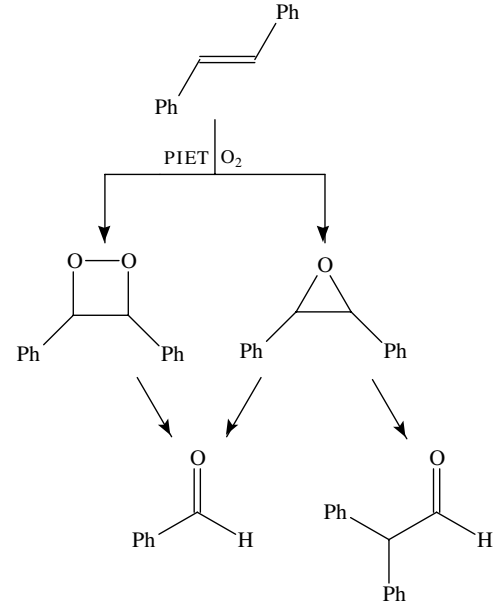


SCHEME 58

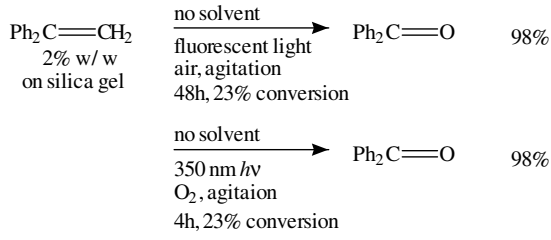
However, it has been recently suggested that oxirane intermediates also play a part in this reaction, producing some of the minor products (Scheme 59)[152]. Dienes do not appear to be good substrates for this reaction, at least not with triplet oxygen, as the cation-radical 'Diels-Alder' dimerization is much faster unless the alkene is sterically hindered[153].

Several electron acceptors have been used for this reaction, the most interesting of which are silica gel and other chromatographic supports as PIET acceptors in an efficient, solvent-free reaction (Scheme 60)[154]. These oxygenations are carried out with 2% substrate by weight adsorbed onto silica gel, acidic alumina or Fluorisil. These reactions work quite well when the resulting powder is agitated in air under an ordinary fluorescent light, but yields and reaction times may be dramatically improved by the use of pure, flowing oxygen and a 350-nm light source (Table 10).

In the solution phase, cation radical oxygenations are considerably enhanced by the presence of weak nucleophiles such as acetate[155]. The nucleophile is believed to function as shown in Scheme 61. Use of tetraethylammonium acetate in acetonitrile for photooxygenations considerably increases the yield of benzaldehydes and reduces the yield of minor products over a range of substituted stilbenes, as shown in Table 11.



SCHEME 59

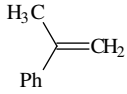
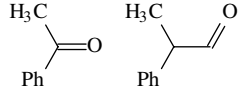
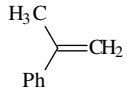
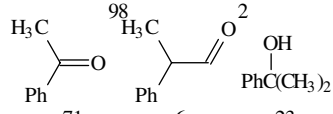
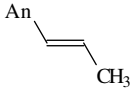
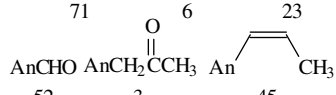
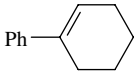
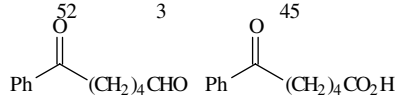
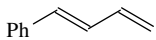
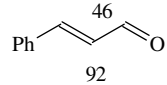
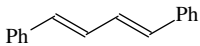
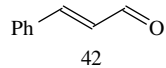


SCHEME 60

Recently, a general synthesis of α-formyloxycarbonyl compounds was reported. Yields ranging from 35–90% were achieved via electrochemical generation of enol carbonate cation radicals in DMF[156]. The cation radicals are trapped by the solvent, and the resulting formiminium ion is hydrolyzed during workup. The mechanism is shown in Scheme 62.

c. Nucleophilic addition to alkenes promoted by one-electron oxidation. In general, nucleophilic addition to alkenes only occurs when the alkene is activated by an electron-withdrawing substituent (e.g. a Michael addition). Oxidation of an alkene to its radical cation, however, provides a means decreasing π-electron density, without having to introduce a substituent. Hole-catalyzed nucleophilic addition to electron-rich alkenes also yields the anti-Markovnikoff product. In hole-catalyzed nucleophilic addition to asymmetric stilbenes, addition of an amine nucleophile occurs at the carbon bearing the less electron-donating aryl group, probably because of greater stabilization of the resulting distonic radical cation (Scheme 63, An = p-$CH_3OC_6H_4$)[157].

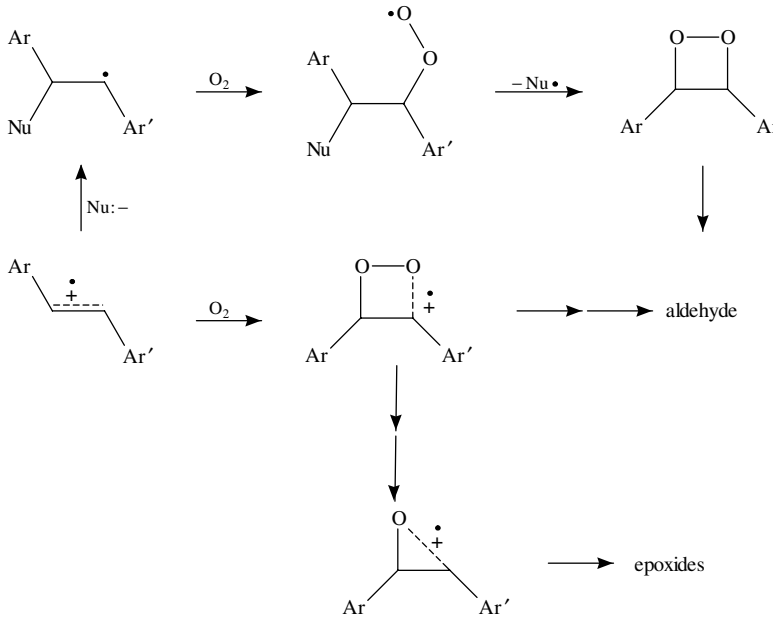
TABLE 10. Yields of solvent-free alkene photooxygenation on silica or alumina[a]

Compound	Adsorbent, gas[b]	Time (h)	Conversion (%)	Yield (%)
$Ph_2C{=}CH_2$	silica air	48	23	$Ph_2C{=}O$ 98; Ph_2CCH_3(OH) 2
$Ph_2C{=}CH_2$	alumina air	48	75	$Ph_2C{=}O$ 97; Ph_2CCH_3(OH) 1; Ph_2CHCHO 2
$Ph_2C{=}CH_2$	silica O_2	4	25	$Ph_2C{=}O$ 98; Ph_2CHCHO 2
$Ph_2C{=}CH_2$	alumina O_2	4	60	$Ph_2C{=}O$ 96; Ph_2CHCHO 1
	silica air	4	3	 98; 2
	alumina air	4	41	 71; 6; 23
	silica O_2	4	23	 52; 3; 45
	silica O_2	22	85	 37; 46
	silica air	72	64	PhCHO 8;  92
	silica air	72	98	PhCHO 53;  42

[a]Reference 154.
[b]'Air' includes irradiation under fluorescent light; 'O_2' includes irradiation by a 350-nm source. Alumina is acidic.

Addition of nucleophiles to 1,1-diarylethylenes has also been reported to give the anti-Markovnikoff product[158], interestingly, solvent polarity may have a strong effect on the stereochemistry of addition (Scheme 64), though no mechanism has been suggested which explains this result[158b].

d. Oxidative C−C *bond-forming reactions*. A variety of synthetically useful C−C bond-forming processes involving $>C{=}C<^{\bullet+}$ intermediates have been reported, several of which are summarized herein. These oxidations may be carried out electrochemically, via PIET, or chemically. Ceric ammonium nitrate and copper(I,II) systems have also found a use in oxidative cyclization reactions[159], as well as electrochemically-generated halonium (X^+) ions[160].



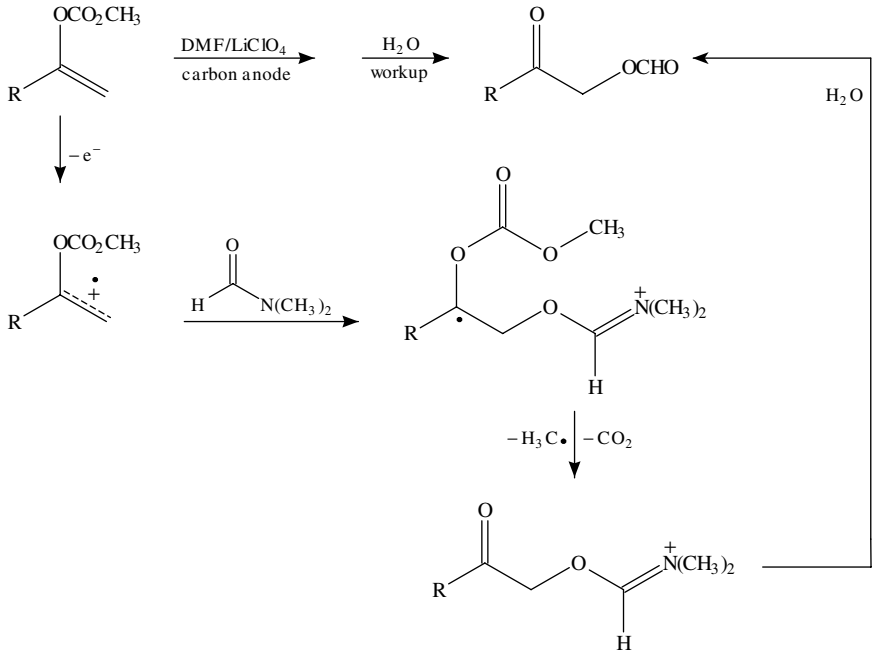
SCHEME 61

TABLE 11. Results of photooxygenation of substituted stilbenes (PhCH=CHAr) with 9-cyanoanthracene catalyst in the presence of tetraethylammonium acetate (yields given in percent)[a]

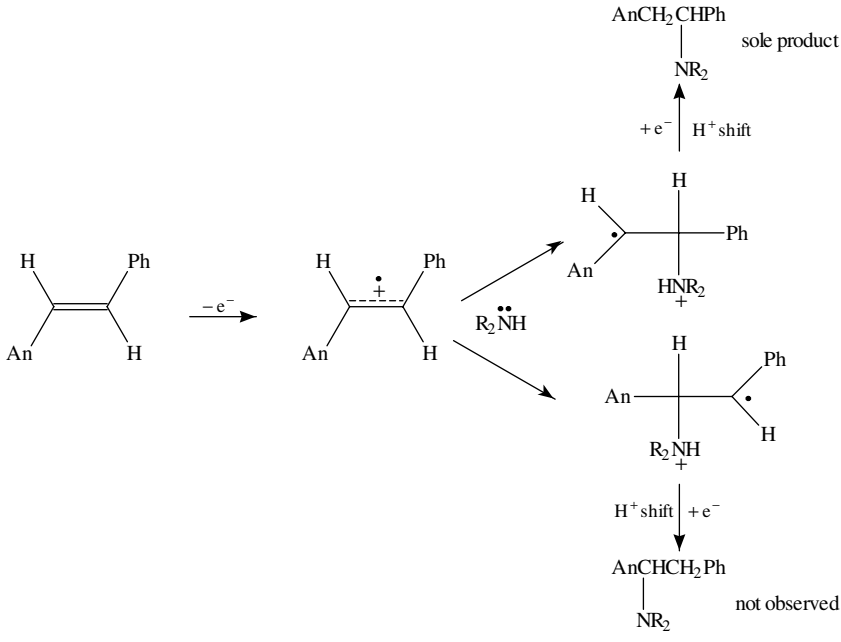
Ar	Solvent	PhCHO	ArCHO	Epoxide	Other[b]	Recovery (*Z*:*E*)
Ph	MeCN	79				20 (5:5)
Ph[c]	MeCN	37		13	4	29 (4:6)
4-MeC_6H_4	MeCN	82	77			0
4-MeC_7H_4[c]	MeCN	28	24	24		7 (7:3)
4-MeOC_6H_4	MeCN	93	66			0
4-MeOC_6H_4[c]	MeCN	31	19	65		38 (4:6)
3,5-$(MeO)_2C_6H_4$	MeCN	53	44			61 (7:3)
4-MeC_6H_4	CH_2Cl_2	32	23		44	72 (3:7)
4-MeOC_6H_4	CH_2Cl_2	46	34	20	10	5 (0:1)

[a]Reference 155.
[b]Benzil (Ar=Ph) or Ph(AcO)C=CHAr (solvent = CH_2Cl_2).
[c]No acetate salt added.

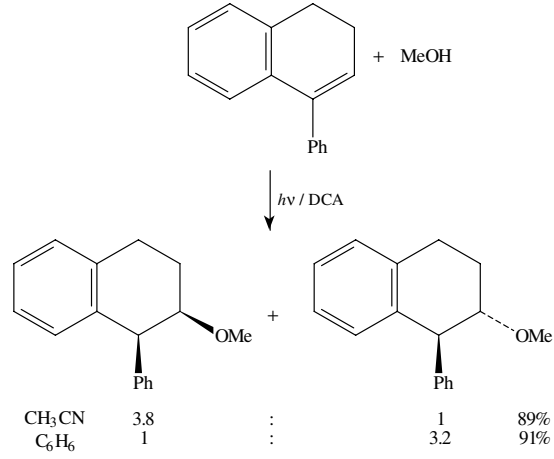
Perhaps the most useful type of alkene substrates for these reactions are enol ethers, enol esters and vinyl sulfides. Silyl enol ethers have excellent electron-donor properties, with an ionization potential of about 8 eV and an oxidation potential in various solvents of approximately 1.0–1.5 V vs SCE[161]. These compounds are easily synthesized by reaction of an enolate with a chlorosilane. (A very recent report synthesized a variety of silyl enol ethers with extremely high stereochemical yield, using the electrogenerated amidate of 2-pyrolidinone as the base.)[162] An interesting point is that the use of oxidative or reductive cyclization reactions allows carbonyl functionalities to be ambivalent, either oxidizable or reducible (Scheme 65)[163].



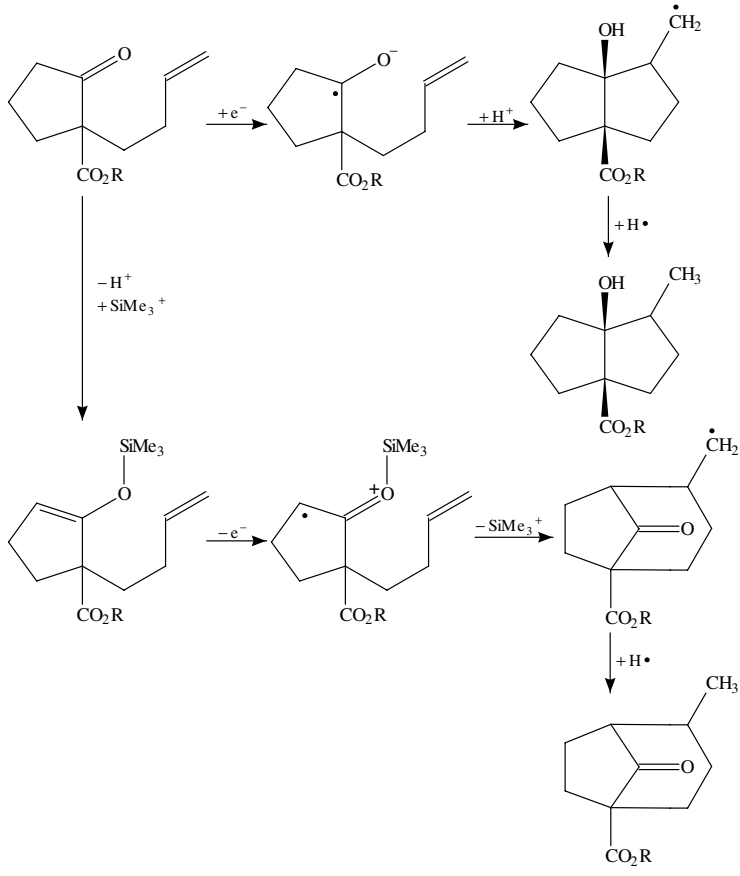
SCHEME 62



SCHEME 63



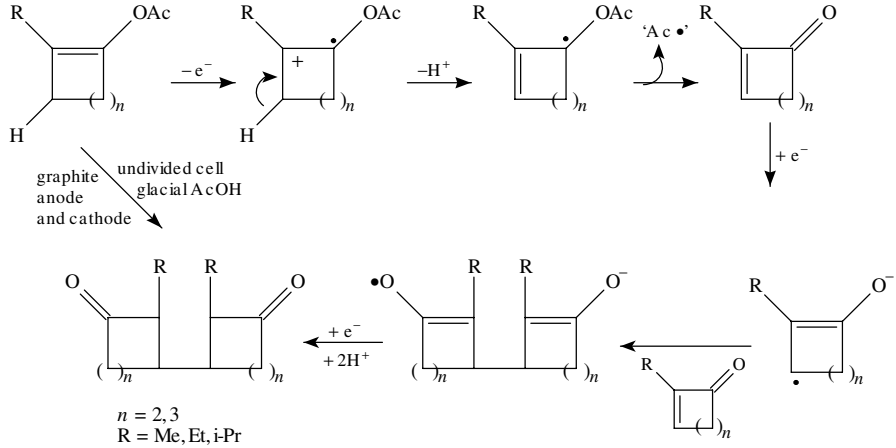
SCHEME 64



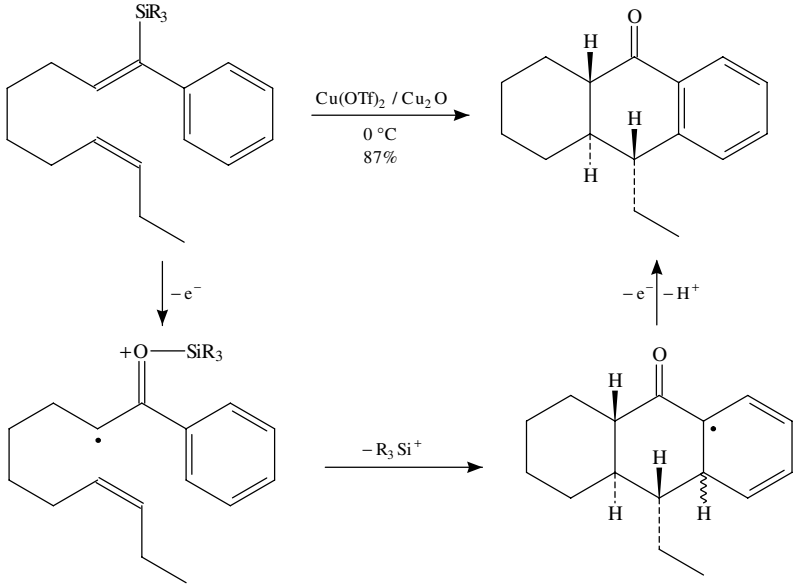
SCHEME 65

Anodic oxidation of cyclic enol esters with β-hydrogens leads to allyl radicals, which then lose 'acyl radical' to form α, β-unsaturated ketones. When the electrolysis is performed in an undivided cell, these are converted by the cathode into enolate anion radicals, which then couple to form β-dimers (Scheme 66)[164].

However, the greatest amount of work in the area of intramolecular cation-radical coupling reactions involves annulation of less ionizable alkenes (or alkynes) with enol ethers or vinyl sulfides. Typically, these reactions are used to form six-[159,163] or five-membered[165] rings, usually stereospecifically (Schemes 67 and 68, respectively). As seen

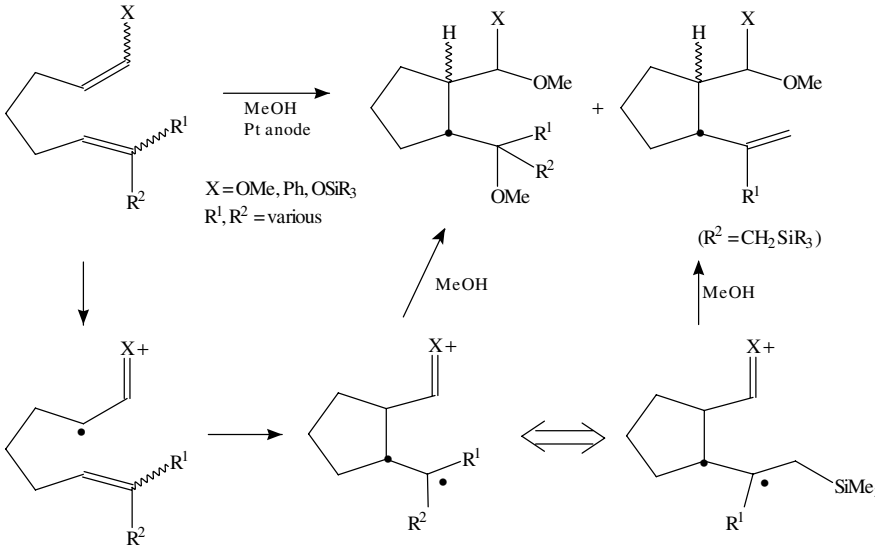


SCHEME 66

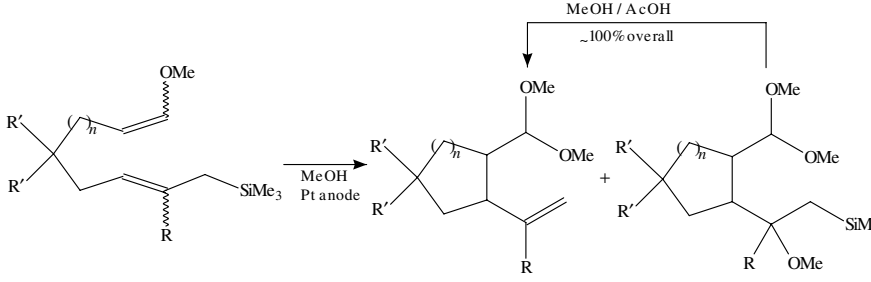


SCHEME 67

in Scheme 68, intramolecular anodic coupling of enol ether cation radicals to allylsilanes in methanol leads to vinylcycloalkanes. This may be exploited as shown in Scheme 69[166].



SCHEME 68



SCHEME 69

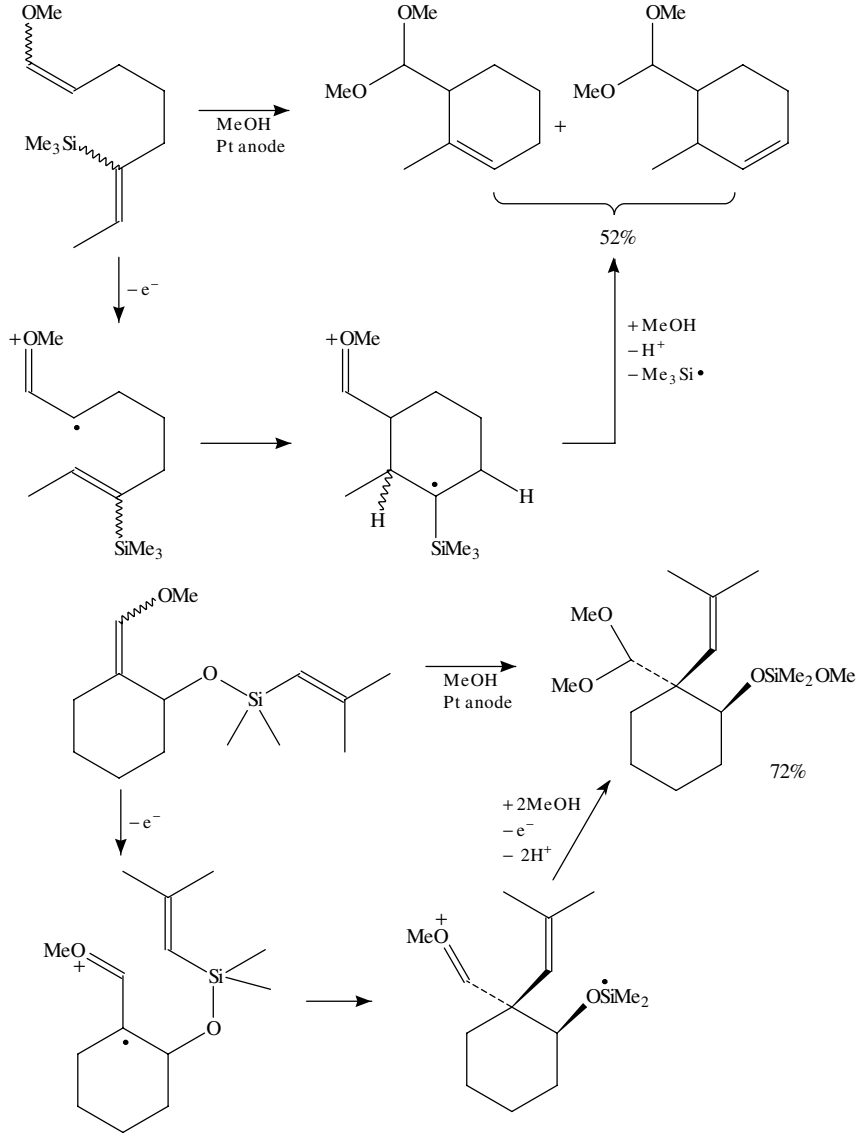
Intramolecular anodic coupling of enol ethers to vinylsilanes generates carbon–carbon bonds while breaking the vinyl–silicon bond; this may be used either to form new rings or to place a vinyl group where it is needed (Scheme 70)[167].

Alkyl enol ethers and vinyl sulfides may also be oxidatively annulated onto electron-rich aromatic rings (Scheme 71)[168].

In a fine display of the versatility of the technique, the Moeller group has produced fused, bi- and tricyclic enones stereospecifically in good yield (Scheme 72)[169].

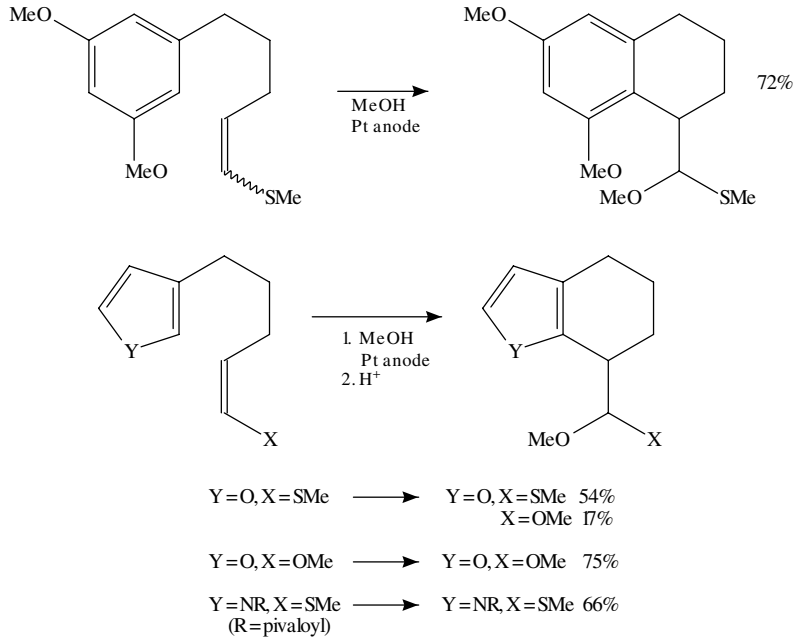
3. Reactions involving >C=C<$^{\bullet-}$

Generally, carbon is not sufficiently electronegative such that alkene radical anions can be generated in solution without the presence of at least one activating substituent,



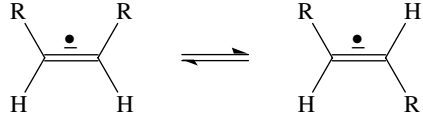
SCHEME 70

typically Ar, NO_2, C≡N or C=O. Because of this requirement, and by virtue of the fact that both charge and spin are delocalized over the entire π-framework in such systems, it becomes somewhat a matter of semantics as to whether such species are truly 'alkene' radical anions. The most numerous examples of such species, radical anions involving a C=O activating substituent generated from α, β-unsaturated ketones, aldehydes and esters, have already been discussed separately in the context of reactions involving $>C=O^{\bullet -}$. This section completes the presentation of the chemistry pertaining to $>C=C<^{\bullet -}$.



SCHEME 71

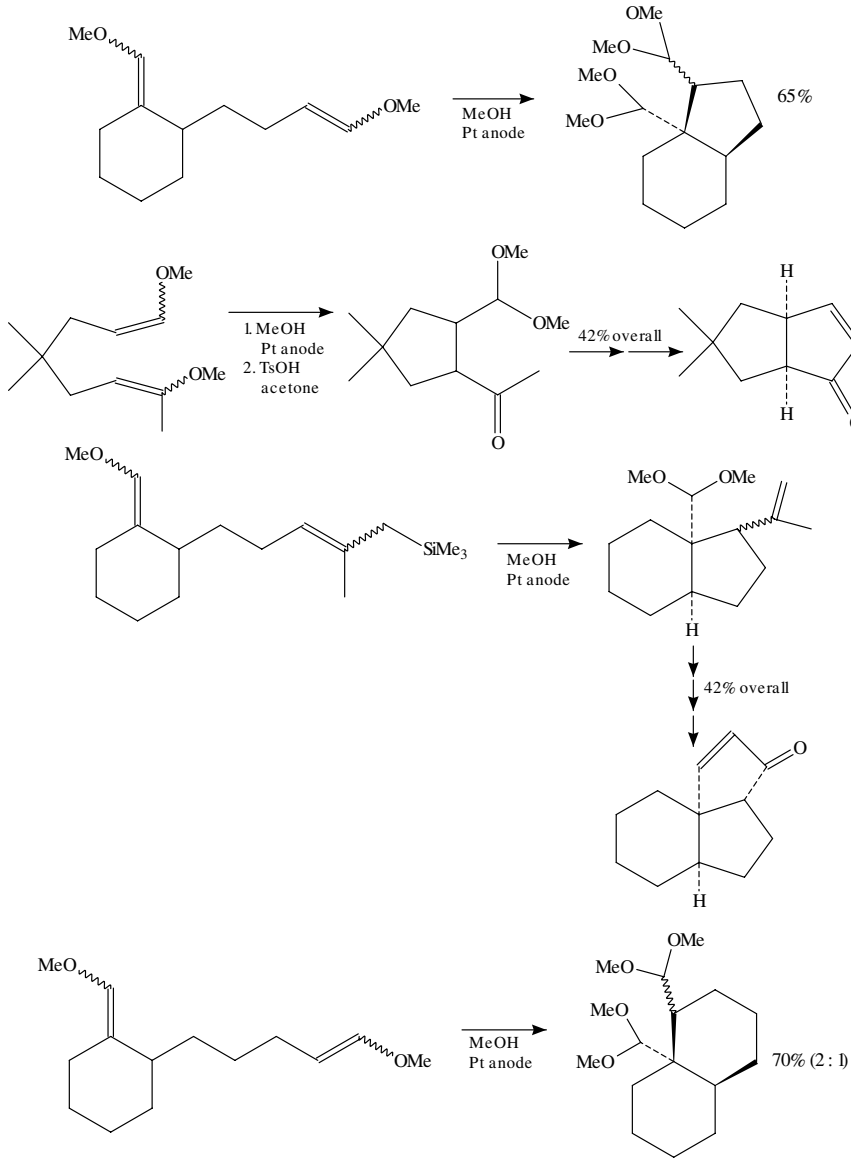
a. Z → E isomerization. One of the most studied reactions of alkene radical anions is $Z \rightarrow E$ isomerization (equation 39)[170]. Addition of an electron to the π^* orbital of an alkene results in a reduced π-bond order, and the barrier to rotation becomes significantly less than that of the neutral alkene. The kinetics of this process has been studied extensively, and this particular property of alkene radical anions has been used to 'probe' for single electron pathways in several reactions[171].



(39)

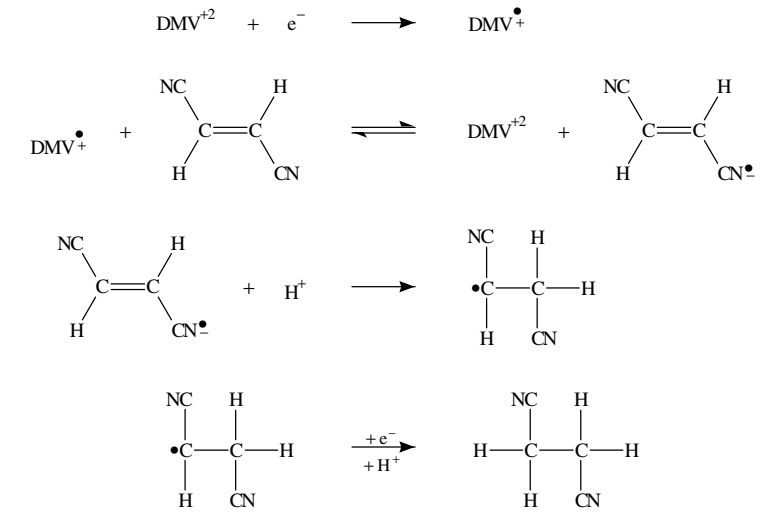
b. Reduction/dimerization of alkenes. The electrochemical reduction of alkenes can lead to the formation of the corresponding alkanes or dihydro dimers[172]. Recently, an example of an electrocatalytic variant of this process, the reduction of fumaronitrile, was reported[173]. On the basis of results obtained from cyclic voltammetry, a mechanism for the process was suggested (Scheme 73, DMV^{+2} = 4, 4′-dimethyl-1,1′-trimethylene-2,2′-dipyridinium ion).

An investigation recently demonstrated that upon one-electron reduction vinylcyclopropanes undergo cyclopropane ring opening with retention of C=C (Scheme 74, $DBB^{\bullet -}$ = 4, 4′-di-*t*-butylbiphenyl radical anion)[174]. Substrates without phenyl substitutents on the cyclopropane ring were found not to react under the reaction conditions, suggesting that the phenyl group, rather than the >C=C<, was the electrophore. Initial ring opening was suggested to proceed at the radical anion stage, in analogy to the cyclopropylcarbinyl → homoallyl radical rearrangement.

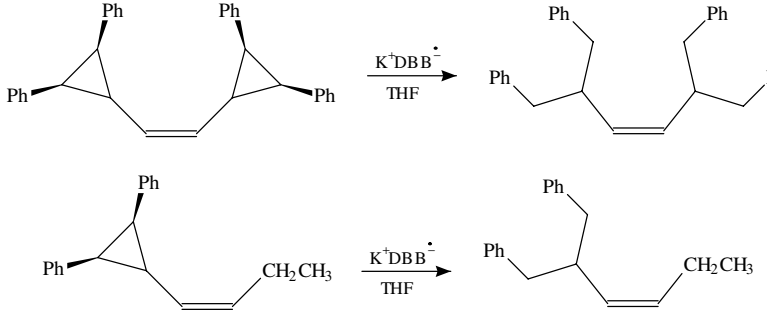


SCHEME 72

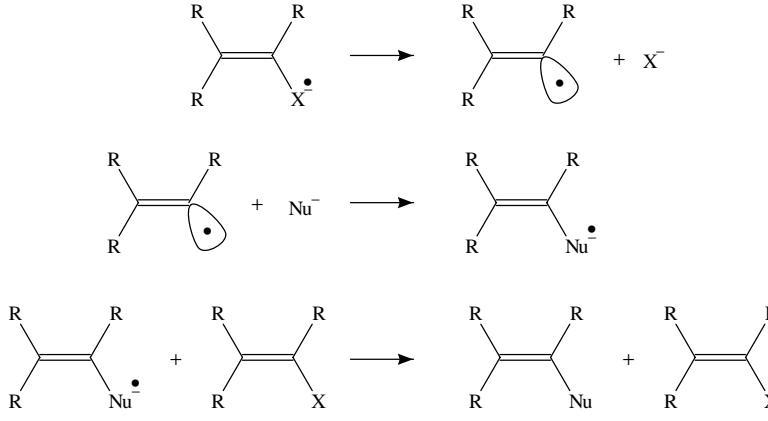
c. The vinylic $S_{RN}1$ reaction. In 1970, Bunnett's group found that several aryl halides react with various nucleophiles via a free radical chain process and suggested the name '$S_{RN}1$'[175]. (A similar mechanism for nucleophilic substitution in aliphatic and benzylic systems had been discovered by Russell and Kornblum in 1966.)[176] Evidence was subsequently presented which suggested that, in addition to aryl halides, several vinyl halides also underwent nucleophilic substitution by the $S_{RN}1$ mechanism (Scheme 75)[177].



SCHEME 73



SCHEME 74



SCHEME 75

In 1994, it was found that several reactions thought to proceed via the vinylic $S_{RN}1$ mechanism were contaminated by a nonradical, α,β-elimination/addition pathway (equation 40)[178]. However, this elimination/addition pathway becomes inaccessible when substrates without β (or β') hydrogens are utilized. Thus, the reaction of pinacolone enolate (t-Bu(CO)CH_2^-) with 1-bromo-1,2,2-triphenylethylene was touted to be the first 'unequivocal' example of vinylic substitution exclusively by the $S_{RN}1$ pathway.

$$\mathrm{R{-}CH{=}CH{-}X} \xrightarrow[\text{-NuH, X}^-]{\mathrm{Nu}^-} \mathrm{R{-}C{\equiv}CH} \xrightarrow{\mathrm{NuH}} \mathrm{R{-}CH{=}CH{-}Nu} \qquad (40)$$

V. RADICAL IONS OF >C=N− CONTAINING COMPOUNDS

In contrast to radical ions generated from alkenes or carbonyl compounds, substantially fewer recent reports have appeared which describe the chemistry of radical ions generated from the >C=N− functional group. This situation likely results from the relative obscurity of the >C=N− group (compared to >C=O and >C=C<), rather than specific problems with the chemistry, per se. Based upon the limited data available, and as might be anticipated, $>C{=}N{-}^{\bullet+}$ chemistry appears to be analogous to that of $>C{=}C{<}^{\bullet+}$, while $>C{=}N{-}^{\bullet-}$ chemistry is reminiscent of $>C{=}O^{\bullet-}$.

A. >C=N− Radical Cations

1. Overview

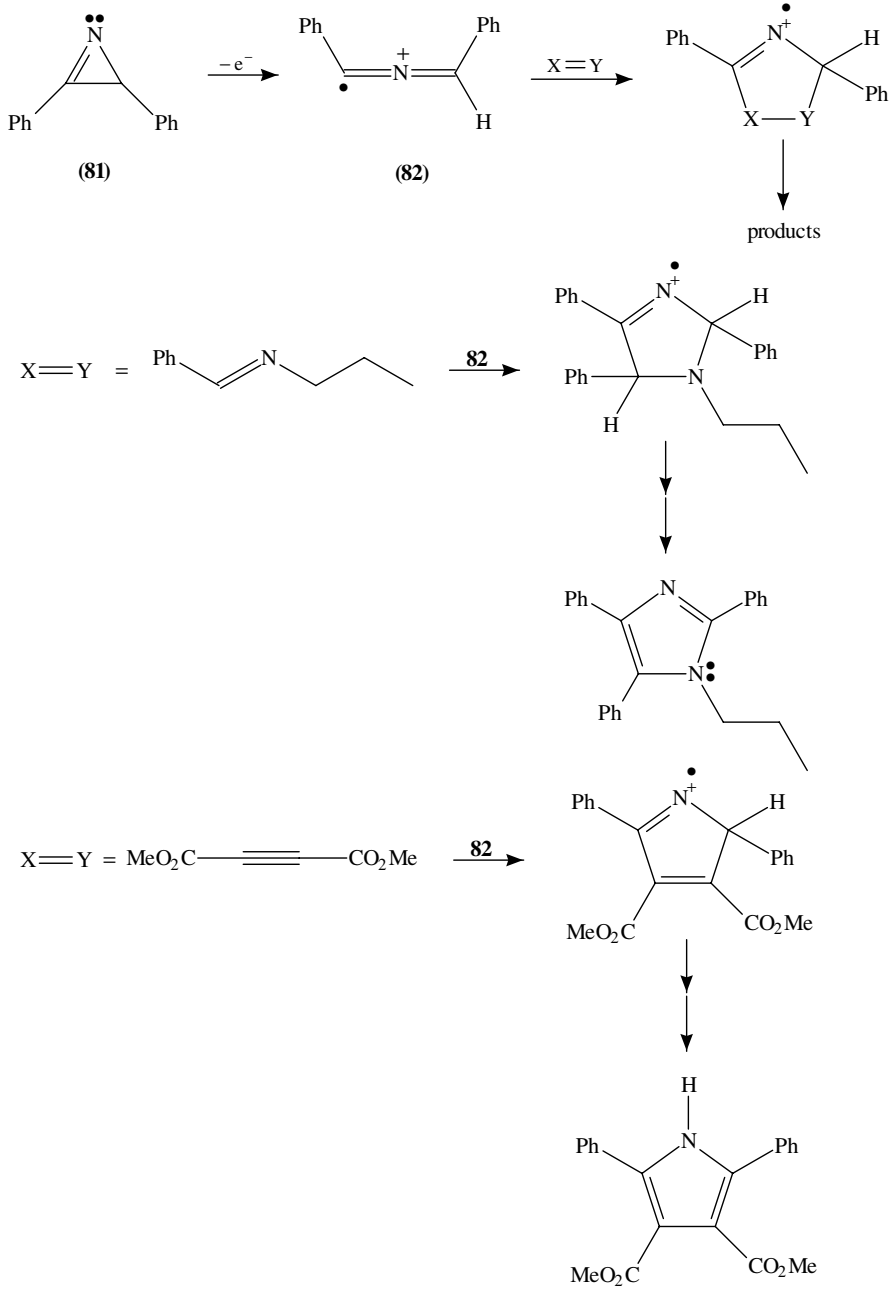
Several reports appear in the more recent literature of syntheses using electrochemical or PIET oxidation of compounds containing >C=N− bonds. These fall into three categories based upon a mechanism or presumed mechanism: Cycloadditions, nucleophilic attack on $>C{=}N{-}^{\bullet+}$ cation radicals and radical annulations. The latter will not be reviewed here[179] as none of the annulations appears to involve $>C{=}N{-}^{\bullet+}$ cation radicals. It should be pointed out that it is by no means certain that the electronic structure of $>C{=}N{-}^{\bullet+}$ is that of a π-cation radical rather than of an iminium cation radical (Figure 5). As will be seen below, reactivity appears sometimes in one guise and sometimes in the other.

2. Reactions of >C=N-$^{\bullet+}$

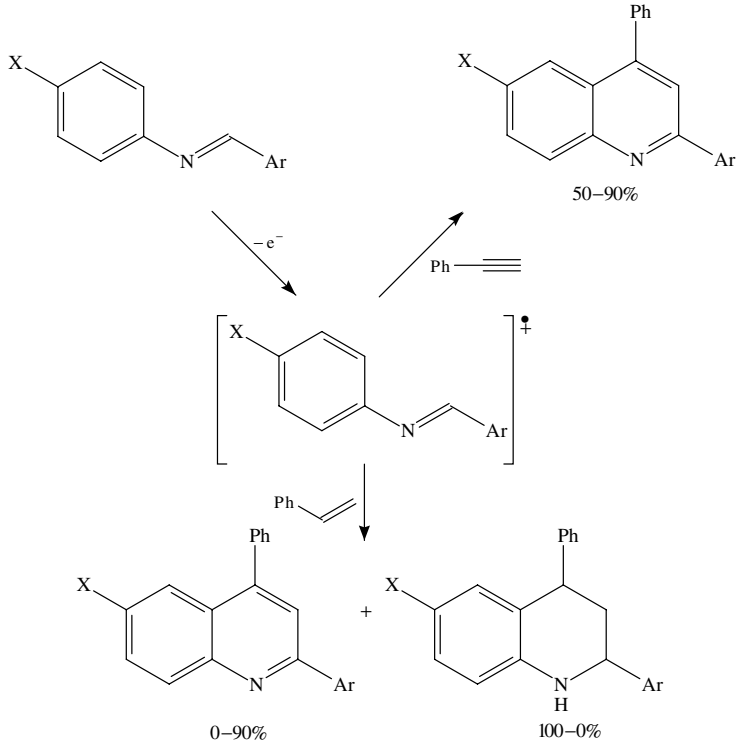
Azirene$^{\bullet+}$ cation radicals **(81)** have proven useful as 1,3-dipole equivalents for cycloaddition reactions. Several heterocycles, such as pyrrolines, imidazoles, pyrroles and porphyrins, have been synthesized from azirenes in low to moderate yields, via PIET using DCN or DCA as electron acceptors (Scheme 76)[163].

Cycloadditions of alkenes and alkynes onto imine cation radicals have been reported, with the cation radicals generated by either PIET mediated by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)[180], or by TIET mediated by $FeCl_3$[106b]. The reaction is shown in Scheme 77.

FIGURE 5. Possible electronic states of $>C{=}N{-}^{\bullet+}$


Ph
Ph
(81)
−e⁻
Ph
Ph
H
(82)
X═Y
Ph
H
Ph
X—Y
products
X═Y =
Ph
82
Ph
H
Ph
Ph
H
Ph
Ph
Ph
X═Y = MeO2C—≡—CO2Me
82
Ph
H
Ph
MeO2C
CO2Me
H
Ph
Ph
MeO2C
CO2Me

SCHEME 76



SCHEME 77

Keteneimines will also undergo electrochemical hole-catalyzed cycloaddition reactions, producing dimers and even trimers as shown below (Scheme 78)[181]. Adventitious water or the replacement of aryl α-hydrogens leads to somewhat different products (Scheme 79)[182].

Dimers **83** and **84** will undergo electrochemical oxygenation, replacing 'Ph_2C' with 'O' (Scheme 80)[183].

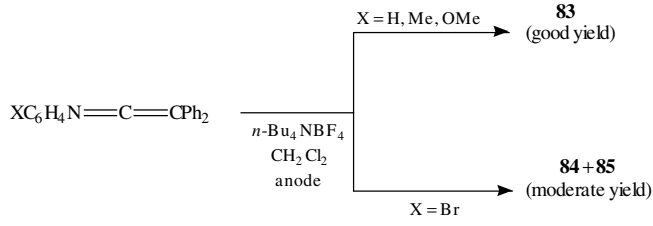
Another recent report of ring closings involving C=N cation radicals, generated by anodic oxidation, appears to involve intramolecular nucleophilic attack (Scheme 81)[184].

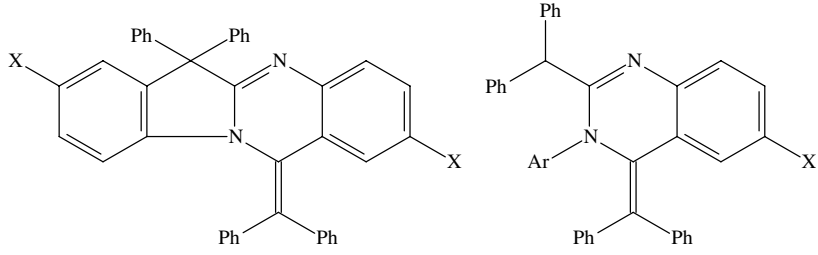
B. >C=N− Radical Anions

Because they are isoelectronic, it is reasonable to expect that imine radical anions (>C=N−$^{\bullet-}$) would exhibit chemistry analogous to that of >C=O$^{\bullet-}$. Such does appear to be the case, based upon the limited information available.

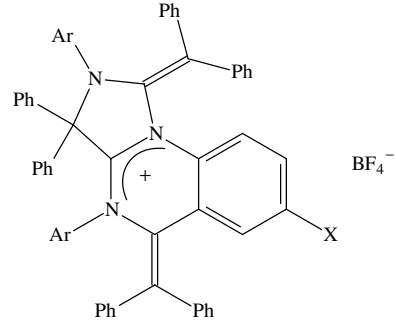
Imine radical anions appear to be substantially more basic than their ketyl anion counterparts. In 1991, Zhan and Hawley reported that $Ph_2C{=}NH^{\bullet-}$ (generated via the electrochemical reduction of benzophenone imine) was a sufficiently strong base to deprotonate weak carbon acids whose pK_a values were as high as 33[185].

Imamoto and Nishimura reported a SmI_2-induced coupling of imines in direct analogy to the pinacol coupling of aldehydes and ketones (Table 12)[186]. However, no mechanistic



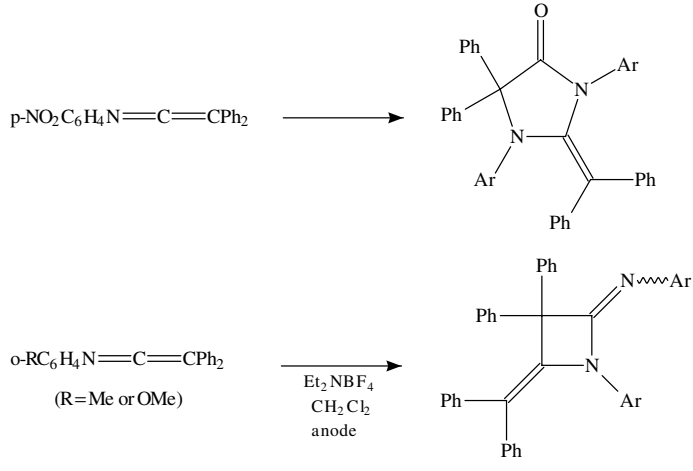


(83) (84)

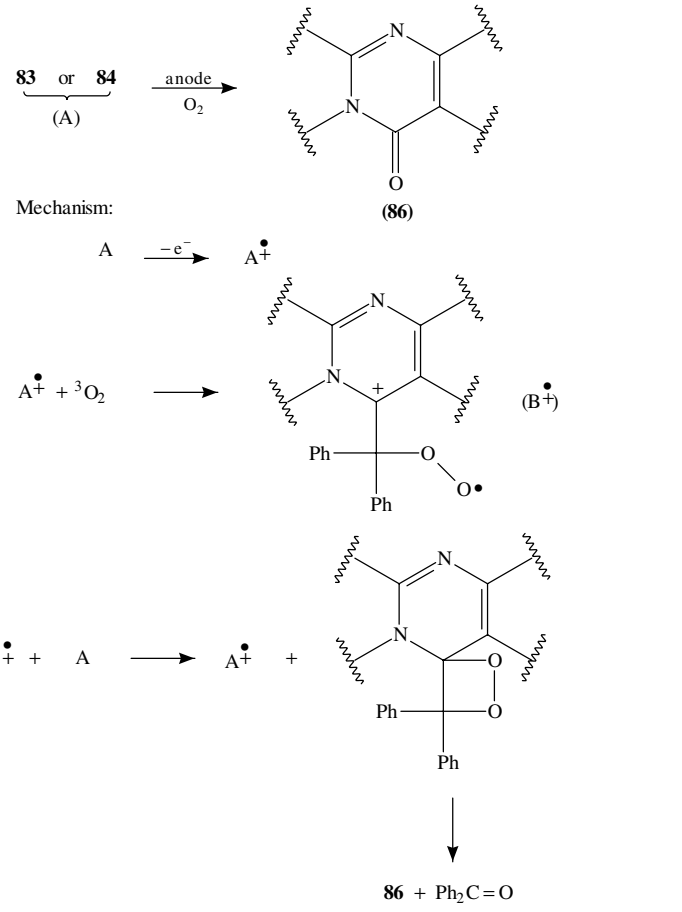


(85)

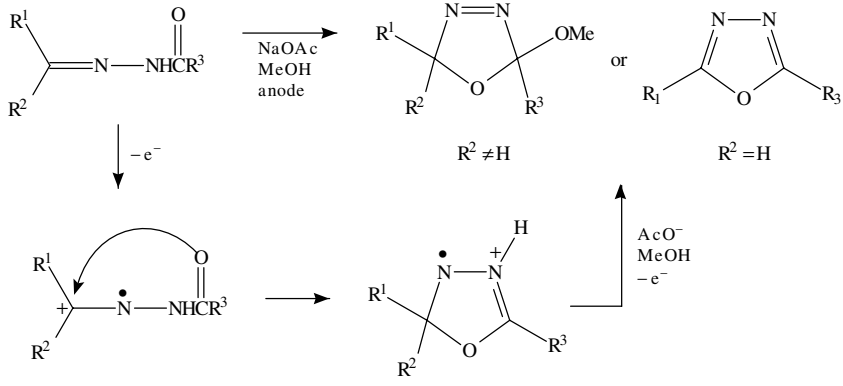
SCHEME 78



SCHEME 79

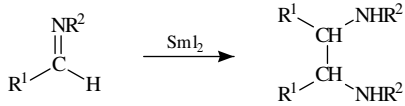


SCHEME 80



SCHEME 81

TABLE 12. SmI_2-promoted coupling of imines[a]



R^1	R^2	% Yield
Ph	Ph	93
Ph	p-$CH_3C_6H_4$	84
Ph	CH_2Ph	38
Ph	t-Bu	10

[a]Reference 186.

details were provided, nor was any data available regarding the diasteroselectivity of the process.

VI. CLOSING REMARKS

Hopefully, this chapter has provided the reader with an appreciation of the diverse range of chemical transformations which may be achieved based upon the chemistry of radical ions. Over the past fifteen years, neutral free radical processes have enjoyed a transition from 'mechanistic curiosities' to their present status as important tools in the synthetic repertoire. It is likely that the same will hold true in future years for radical ions.

A number of mechanistic challenges remain. Unlike neutral free radicals, radical ions also possess charge and thus their reactivity is sensitive to environmental effects (i.e. counterion, solvent). Thus, there remains much that needs to be learned both about this important class of intermediates, as well as about the role of these environmental factors, before this chemistry can be completely understood and exploited.

VII. ACKNOWLEDGMENT

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CHAPTER **23**

The thiocarbonyl group

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I. INTRODUCTION

This monograph covers the period 1989–1995 and is partially an update of the work by Schaumann[1]. The scope is essentially the same, attention being focused primarily on thioaldehydes (thials) and thioketones (thiones). In keeping with the spirit of Reference 1, only some new developments in the field of thioketene, hetero cumulene and thioquinone chemistry are considered. Because of the fast evolution in the field, the spirit is somewhat different and physicochemical and theoretical topics are emphasized. Whenever possible, systematic comparisons with homologous carbonyl compounds, a natural yardstick, are carried out.

During the last seven years, some important reviews have appeared. They are either general and cover synthesis, reactivity and properties of thiocarboxylic acids and their derivatives[2], thioformyl compounds[3] and thials and thiones[4,5], or more specific. The latter include synthesis and reactivity[6–10] as well as photophysics[11,12], photochemistry[11,13,14], radical reactions[15,16], mass spectrometry[17], photoelectron spectroscopy[18] and electrochemistry[19] of various families of thiocarbonyl compounds.

The last seven years have also witnessed important developments in the field of thiocarbonyl chemistry. Synthetic and reactivity studies have maintained their steady growth. New or improved experimental methods have been applied to the study of the physicochemical properties of these compounds as well as to the generation and observation of important fleeting species. In particular, flash vacuum thermolysis (FVT or FVP)[20] and neutralization–reionization mass spectrometry[21–22].

Thanks to advances in computer technology, a number of theoretical studies have been performed that shed light on structural and spectroscopic properties as well as on the reactivity of thiocarbonyl compounds both in the ground and in excited electronic states.

In this review, quantitative aspects of the structure and reactivity of these compounds are treated first. New developments in the fields of synthesis and reactivity are examined next. As a consequence of their relevance for the development of new materials[23–27] and the possibilities they offer for analytical purposes, the number of studies in which thiocarbonyl compounds act as ligands of a variety of metal ions has increased in an almost explosive way. Recent reviews[28–30] are also available on specific families of coordination compounds involving thiocarbonyl ligands. A concise survey of the present status of these studies is presented in the last section.

When warranted by their importance, mention shall be made of the biological or technological aspects of some compounds and reactions. A serious effort was made in order to minimize overlaps with previous reviews.

II. ENERGETICS AND STRUCTURE OF THIOCARBONYL COMPOUNDS. THEIR INFLUENCE ON REACTIVITY AND PHYSICAL PROPERTIES

A. Molecular Properties

As indicated earlier, quantum-mechanical methods, particularly molecular orbital (MO) treatments, are tools used to explore essentially all fields of thiocarbonyl chemistry. Hence, we shall first review the current status and scope of this methodology with respect to a number of important topics. This shall be followed by a survey of the experimental and theoretical data available on the thermodynamics, structure and selected aspects of the reactivity of these compounds.

1. Quantum mechanical studies

a. Molecular orbital (MO) treatments. These theoretical studies are not free, in some cases, from discrepancies between theory and experiment, as we shall illustrate later. Most of these discrepancies simply reflected the inadequacy of the theoretical model used to study a particular problem. We have thus considered it useful to provide a short analysis of the performance of the theoretical models most often used in the framework of *ab initio* molecular orbital theory, in order to outline the minimal computational requirements necessary to get reliable theoretical predictions when dealing with sulfur compounds in general and with thiocarbonyl compounds in particular.

Since in many instances we shall try to compare the properties of thiocarbonyl compounds with their carbonyl analogs, we recall that, in general, the theoretical treatment of sulfur containing systems is more demanding, essentially because of the larger number of electrons in the sulfur atom. This has restricted the *ab initio* calculations to relatively small compounds or to the use of small basis sets. Until quite recently, high level *ab initio* calculations were only reported for a few, small thiocarbonyl systems.

An adequate description of the geometries and electronic properties of sulfur containing compounds requires the inclusion of supplementary d functions in the basis set. Some theoretical work has explicitly analyzed the role of these supplementary d functions, in particular for hypervalent molecules. Patterson and Messmer[31], by means of a generalized valence bond (GVB) treatment of sulfur oxides, concluded that the role of d functions on the S atom is primarily to allow the orbitals to attain their optimum shapes while remaining mutually orthogonal. This implies that the orbitals obtained with a basis set supplemented with d functions are more flexible and are wrapped around the cores more effectively than those obtained from a basis without d functions, thus maximizing the electron–nuclear attraction. They also concluded that the role of d functions in electronic structure calculations of hypervalent molecules differs from that in normal molecules, where they act as polarization functions. This conclusion is somewhat at variance with that by Magnusson[32], who found that although the level of participation of supplementary d functions in the wavefunctions of hypervalent systems is greater than in normal molecules, there is no difference in the role of the d functions, which are required to properly respond to the rapidly varying molecular potential in the internuclear space. In any case, both studies clearly illustrate the need of including d functions in the treatment of sulfur containing systems. In later work Magnusson[33] has shown that whether molecules are hypercoordinated or not, d functions provide a fairly constant 13 kcal mol^{-1} of the MP4 correlation energy per valence shell electron pair. He also showed that while for Hartree–Fock calculations d functions behave as polarization functions, for correlated

calculations their major role is to provide angular correlation. Furthermore, the d function role in the correlated wavefunction seems to be quite independent of the sp basis set level.

In summary, it seems well established that supplementary *d* functions are indispensable in molecular orbital calculations of sulfur containing compounds. This is particularly true for thiocarbonyl compounds, wherein the anisotropy of the electrondensity distribution around sulfur is significantly greater[34] than that around oxygen in carbonyl systems.

The need for a well-balanced basis set for the theoretical treatment of sulfur derivatives is also clear. In particular, a proper description of the angular correlation cannot be achieved by including supplementary d functions exclusively on the sulfur atom since, as has been shown by Magnusson[33], supplementary functions on peripheral atoms (for instance O in SO_2) contribute more to the correlation energy than the functions centered on the central sulfur atom. Similarly, some discrepancies between Hartree–Fock optimized geometries for 6-thioguanine obtained when d functions are included exclusively in the sulfur atom[35] with regards to those obtained when d functions are centered on all heavy atoms of the molecule[36], may have their origin in the unbalanced character of the former basis set.

Not all the molecular properties present the same sensitivity to details of the basis set used to expand the molecular wavefunction. Thus, Alkorta[37] analyzed the geometric and electronic properties of 22 sulfur compounds by means of *ab initio* calculations and local density functional (LDF) methods. He showed that, while a minimal STO-3G(d) basis set yields standard deviations of 0.033 Å for the bond lengths and 3.595° for the bond angles, the standard deviations when a 6-31G(d) basis set is used are reduced to 0.012 Å and 1.688°, respectively. However, both basis sets behave rather poorly as far as the dipole moments are concerned. The STO-3G(d) calculations yield too small values for this magnitude, with a standard deviation of 0.558 D, while the 6-31G(d) calculations predict dipole moments which are too large, with a standard deviation of 0.315 D, which does not change significantly when a second set of d functions is added to the basis set. It is only when electron correlation effects are taken into account, at the second-order Møller–Plesset perturbation theory [MP2/6-31G(d) level], that the calculated dipole moments come closer to the experimental values. For this set of compounds, the LDF results provide, in average, the best dipole moments of all methods analyzed in that paper, though it consistently yields too large bond distances for the atoms bonded to sulfur. Although there are in the literature systematic studies of the performance of different density functional methods to describe molecular properties of first-row compounds[38], there is no similar study for sulfur containing systems. Nevertheless, density functional methods will likely become a very good and economic alternative to the standard *ab initio* methods.

It is fortunate that the *trends* of structural effects on the structures of thiocarbonyl compounds are largely basis-independent. Important examples shall be discussed later.

Abboud and coworkers[39] have found the C=S bond length to vary within very narrow limits ($1.60\ Å \pm 0.1\ Å$) for a wide set of thiocarbonyl derivatives, which includes 27 different molecules as well as substituents of different nature [CH_3, OH, NH_2, OCH_3, F, Cl, SCH_3, $NHCH_3$, $N(CH_3)_2$, C_2H_5, OC_2H_5]. Similar behavior is observed when comparing the C=S optimized bond lengths for thiocarbonyl cyanide[40], thiopropynal[40] and thioformyl cyanide[41]. These findings are consistent with the conclusions of Mó and collaborators[42] in the sense that the electronic charge density at the C=S bond critical point, for the same series of compounds, is also quite insensitive to the nature of the substitutent. In this respect, it is worth noting that the thiocarbonyl group, similarly to the carbonyl group[43], is hard to perturb[42]. However, the thiocarbonyl group seems to conjugate better than the carbonyl group. Actually, the most significant structural difference between carbonyl and thiocarbonyl cyanide is that the C–C bond is significantly shorter

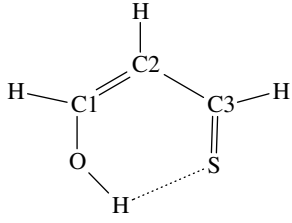
in the latter (1.437 Å vs 1.462 Å) while the corresponding stretching force constant is significantly higher (5.687 vs 5.076 mdyne/Å)[40]. Something similar is found when the C−C bond lengths in propynal and formyl cyanide are compared with those in thiopropynal[40] and thioformyl cyanide, respectively. The significant shortening of the C−C bond adjacent to the C=S linkage is presumably due[40] to the release of electron density into the conjugated system, which is more favorable in the case of thiocarbonyl compounds because of the smaller electronegativity of sulfur.

b. Electron correlation effects. From the discussion in the preceding section it seems clear that some molecular properties, and in particular a correct description of the electronic charge distribution of the molecule, require unavoidably to take into account electron correlation effects. However, these effects are also important in obtaining reliable structures and energetics.

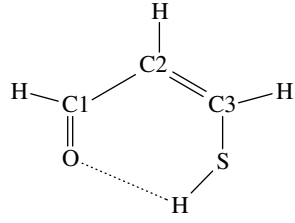
(i) Effects on structures. Correlation effects on molecular geometries are, in general, not negligible. For instance, geometries obtained at the MP2 level are in very good agreement with the experimental structures when a 6-31G(d) basis set is used[44]. Similarly, when the comparison of experimental and theoretical structures is carried out in terms of the rotational constants, the MP2/6-31G(d) values present a relative error ten times smaller than that found at the HF/6-31G(d) level[45].

The computational cost is considerably higher when the geometry optimization is carried out at the correlated level rather than at the Hartree–Fock level. We draw attention, however, to the fact that some aspects of the molecular structures can only be reproduced when electron correlation effects are taken explicitly into account. The fluoro, chloro and bromo disubstituted derivatives of thioformaldehyde are a paradigmatic example. The C=S bond of thioformaldehyde is reduced by about 0.020 Å, 0.010 Å and 0.014 Å in thiocarbonyl difluoride, dichloride and dibromide, respectively[46–51]. This experimental finding is not reproduced by Hartree–Fock calculations[52] which predict the C=S bond to be elongated by 0.006 Å on going from CBr_2S to CF_2S, contrary to experimental observation. Only when electron correlation effects are taken into account, at the MP2/6-311G(d,p) level, is the experimental trend fairly well reproduced[52] (shortenings of 0.020, 0.008 and 0.013 Å, respectively).

Significant changes in optimized geometries due to electron correlation contributions are also of relevance for systems which present intramolecular hydrogen bonds. We shall present here, as a suitable example, the case of monothiomalonaldehyde **(1a)** and its thienol tautomer **(1b)**, since in this case the characteristics of the intramolecular hydrogen bonds depend strongly on the inclusion of electron correlation effects in the theoretical treatment.



(1a)



(1b)

In Table 1 we present the optimized geometries of both systems obtained at the HF level by using a triple zeta plus polarization basis set[53] and at the MP2/6-31 + G(d,p)

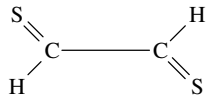
TABLE 1. *Ab initio* optimized geometries for the tautomers **1a** and **1b** of monothiomalonoaldehyde (bond lengths in Å, bond angles in degrees)

	C_1-C_2	C_2-C_3	C_3-S	C_1-O	C_1-H	C_2-H	C_3-H	$X-H^a$	HB^b	OC_1C_2	$C_1C_2C_3$	C_2C_3S	C_1OH	C_3SH
1a HF[c]	1.352	1.426	1.644	1.300	1.074	1.072	1.078	0.957	2.246	128.1	125.7	128.7	112.4	—
MP2[d]	1.371	1.426	1.654	1.329	1.083	1.081	1.088	0.999	2.043	125.7	124.6	127.5	107.6	—
1b HF[c]	1.471	1.331	1.749	1.191	1.093	1.075	1.075	1.330	2.153	125.9	126.7	131.4	—	98.5
MP2[d]	1.455	1.362	1.729	1.243	1.100	1.083	1.084	1.340	1.951	125.3	125.6	129.5	—	95.0

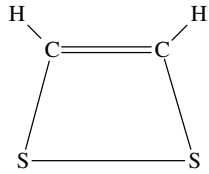
[a] X = O, S.
[b] HB represents the length of the corresponding hydrogen bond measured as the X- - - -H distance.
[c] HF/TZP optimized values taken from Reference 53.
[d] MP2/6-31 + G(d,p) optimized values taken from Reference 54.

level[54]. It can be seen that differences between both sets of values are sometimes greater than 0.05 Å for bond lengths and greater than 3° for bond angles, respectively. However, the most dramatic changes affect the hydrogen bonds, which upon inclusion of electron correlation effects become more than 0.2 Å shorter. As we shall discuss in forthcoming sections, these structural changes will be reflected by the energetics of the corresponding hydrogen bonds.

Other valence tautomerisms such as that between 1,2-dithioglyoxal **(2a)** and 1,2-dithiete **(2b)**, are also interesting examples of dramatic effects of electron correlation on optimized structures. As illustrated in Table 2, only optimizations carried out at the MP2 level, using either a 6-31G(d) or a 6-31+G(d,p) basis set[55,56], are able to reproduce correctly the experimental bond lengths of the most stable conformer, 1,2-dithiete, while HF optimizations yield too short C−C bond lengths and too long C−S linkages.

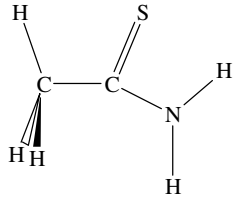


(2a)



(2b)

Electron correlation effects have been found to be also significant as far as the internal rotation of thioamides is concerned[57]. MP2/6-31G(d) geometry optimizations[57] indicated the eclipsed conformer **(3)** as the stable structure of thioacetamide, while this conformer was predicted to be a first-order saddle point at the HF/6-31G(d) level[57].



(3)

Very few geometry optimizations of thiocarbonyl derivatives have been carried out at a level higher than MP2/6-31G(d). Table 2 clearly shows, for the particular case of 1,2-dithiete **(2b)**, that the effect of enlarging the basis set from 6-31G(d) to 6-31 + G(d,p) has very little effect on the optimized geometry. Something similar has been found by

TABLE 2. *Ab initio* optimized geometries for 1,2-dithiete **(2b)** (bond lengths in Å, bond angles in degrees)

	C−C	C−S	C−H	S−S	CCS	HCS
HF/6-31G(d)[57]	1.324	1.765	1.071	2.095	102.6	125.5
MP2/6-31G(d)[55]	1.352	1.755	1.083	2.112	102.5	125.2
MP2/6-31 + G(d,p)[56]	1.358	1.755	1.079	2.114	102.4	125.3
Exp.[59]	1.350	1.753	1.080	2.096	102.3	126.7

TABLE 3. MP2-optimized geometries for some thiocarbonyl derivatives XYC=S (bond lengths in Å, bond angles in degrees)

System	Basis set	C−X	C−Y	C=S	X−C−S	Y−C−S
X=Y=H	6-31G(d)[137]	1.095	1.095	1.580	121.0	121.0
	6-31 + G(d,p)[116]	1.086	1.086	1.617	121.9	121.9
	6-311G(d,p)[53]	1.090	1.090	1.613	121.9	121.9
	TZP[a136]	1.087	1.087	1.622	121.9	121.9
X=H, Y=CN	6-31G(d,p)[41]	1.086	1.434 (1.184)[b]	1.624	115.1	123.5
	6-311G(d,p)[41]	1.091	1.434 (1.178)[b]	1.622	115.1	123.4
	D95[163]	1.090	1.446 (1.191)[b]	1.632	115.0	122.8
X=H, Y=F	6-31G(d)[116]	1.089	1.345	1.598	126.4	123.9
	6-31 + G(d,p)[116]	1.085	1.362	1.595	127.6	123.5
	6-311G(d,p)[53]	1.089	1.337	1.596	126.3	124.0
X=H, Y=Cl	6-31G(d)[116]	1.088	1.734	1.606	123.8	125.6
	6-31 + G(d,p)[116]	1.085	1.735	1.607	123.8	125.7
	6-311G(d,p)[53]	1.088	1.735	1.603	123.8	125.8

[a]These values correspond to a CCSD(T)/TZP geometry optimization.
[b]C−N bond length.

Csaszar[41] for thioformyl cyanide, when comparing MP2/6-31G(d,p) and MP2/6-311G(d,p) optimized structures (see Table 3).

Table 3 also shows the negligible differences between MP2/6-31G(d) and MP2/6-31 + G(d,p) optimized geometries for thioformaldehyde and some monosubstituted derivatives. Table 3 includes also the optimized geometry for thioformaldehyde reported by Martin's group[58]. This optimized geometry was obtained using the coupled cluster method with all single and double excitations augmented with a perturbative estimate of the effect of triplet excitations [CCSD(T)]. The close agreement between this CCSD(T) optimized geometry and the MP2 ones clearly illustrates the rather small effects of correlation contributions beyond second order. Hence, we may conclude that, in general, the MP2/6-31G(d) approach will provide reasonably accurate structures for thiocarbonyl compounds, although for anionic species the MP2/6-31 + G(d) structures should be more reliable[59], since a proper description of the electronic charge distribution of anions requires the inclusion of diffuse functions in the basis set[60].

(ii) Effects on the energetics. Electron correlation effects are particularly important as far as the energetics of the systems is concerned. Sulfur containing compounds provide also good examples to illustrate this point.

The thiol–thione tautomerism is particularly sensitive to the inclusion of these effects. Unfortunately, there are not many theoretical studies on this tautomerism in which electron correlation effects are included. In most studies, they are considered only for the evaluation of the total energies but using HF optimized structures. It is generally agreed, however, that electron correlation effects cannot be neglected if reliable results are sought in these systems[36]. This has a physical basis, related to the fact that in thiol/thione tautomerism there is a significant change in the nature of the bonds on going from the thiol, which has a S−H bond, to the thione, where the S−H bond has been replaced by an O−H or an N−H linkage. The works of Leszczynski[35], and of the groups of Lapinski[61], Parchment[62] and Alhambra[36] among others, clearly show the significant effects of second-order electron correlation effects on the stabilization of the thiol forms. In some particular cases there still remain significant discrepancies regarding the experimental energy differences between the different tautomers and the aforementioned theoretical estimations. This is particularly

true for diazinethiones, where SCF + MBPT(2) calculations predict the thiol tautomer of pyridine-2-thiol to be 6.6 kcal mol^{-1} more stable than the thione one[63], in clear contrast with the experimental evidence which reduces this difference to 2.4 ± 0.2 kcal mol^{-1}[63]. This was taken as an indication that electron correlation effects beyond second order might be important, at least for this particular system. This was indeed ratified by a recent paper[62] where it was shown that the thiol/thione energy difference decreases to 3.6 kcal mol^{-1} when evaluated at the QCISD(T) (Quadratic Configuration Interaction including single and double excitations and estimating the contribution of the triples to the energy in a perturbative way)[64], which is practically correct to fifth order.

These results indicate that an accurate description of the energetics of the system would require what is usually called high level *ab initio* calculations, where the energy of the system is practically correct to fifth order and the basis set of a 'near limit' quality. No doubt such calculations are very expensive and only feasible for very small systems, which are not of interest when one is dealing with thiocarbonyl derivatives, where the parent compound, thioformaldehyde, has already 34 electrons. Pople and coworkers[65] have developed a theoretical scheme, usually called Gaussian-2 (G2) theory, which provides total energies effectively at the quadratic configuration interaction QCISD(T)/6-311 + G(3df,2p) level, with a moderately large computational effort. G2 theory is in general accurate to ±0.1 eV for dissociation energies, ionization potentials, electron affinities and proton affinities. This general procedure has been also applied with success to reproduce accurately heats of formation, which are obtained by substracting the atomization energies from known enthalpies of formation of the isolated atoms. In particular, the G2 heats of formation of thioformaldehyde and its cation are reported[66] to be in good agreement with experimental data. Further examples shall be examined later.

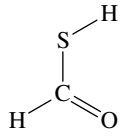
It seems quite obvious that the evaluation of heats of formation requires unavoidably high level *ab initio* calculations, since high-order electron correlation effects are very important when breaking the different bonds of a molecule. Nevertheless, in thiocarbonyl chemistry there are examples of other processes, such as valence or thiol/thione tautomerisms, where these high level calculations are required to get results in agreement with experiment. An example of this discrepancy between experiment and calculations, when the latter are not carried out at a sufficiently high level of accuracy, is provided by 1,2-dithioglyoxal **(2a)** and its valence tautomer 1,2-dithiete **(2b)**. There is experimental evidence from PES[67], gas-phase microwave studies[68] and low-temperature matrix IR spectroscopy[69] which shows that **2b** is more stable than **2a.** *Ab initio* studies at different levels (see Table 4), including different basis sets and fourth-order correlation calculations, fail to predict the correct stability of 1,2-dithiete. Jonas and Frenking[70] have shown that the correct stability order **2b** > **2a** is obtained only when a set of f functions is

TABLE 4. Relative energies (kcal mol^{-1}) of 1,2-dithiete **(2b)** with respect to 1,2-dithioglyoxal **(2a)**

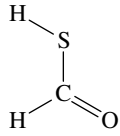
HF/3-21G(d)//HF/3-21G(d)[57]	+6.60
HF/6-31G(d)//HF/6-31G(d)[57]	+5.00
MP2/6-31G(d)//MP2/6-31G(d)[69]	+5.45
MP4(SDQ)/6-31G(d)//HF/6-31G(d)[57]	+6.09
MP2/6-31G(2d)//MP2/6-31G(d)[69]	+0.72
MP2/6-31G(3d)//MP2/6-31G(d)[69]	+3.39
MP2/6-31G(2df)//MP2/6-31G(d)[69]	−6.79
MP2/6-31G(3df)//MP2/6-31G(d)[69]	−5.35
MP2/6-31G(2d 2f)//MP2/6-31G(d)[69]	−8.46
G2(MP2)[56]	−3.39

added to the basis set. González and coworkers[56] have shown that the correct stability of **2b** is well reproduced at the G2(MP2) level of theory, this tautomer being found to be 3.4 kcal mol^{-1} more stable than **2a**.

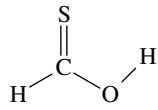
Another example is provided by the relative stabilities of the different conformers of thioformic acid. It is well established that the s-*cis* thiol form **(4a)** of this compound is the global minimum, the s-*trans* conformer **(4b)** being 0.16 kcal mol^{-1} less stable. *Ab initio* calculations at the Hartree–Fock level using different basis sets (see Table 5) also predict the s-*cis* thiol conformer to be the most stable, but fail to yield the correct energy difference, which at the HF/6-31G(d) level is still about three times greater than the experimental value. This situation does not change appreciably when electron correlation effects are included at second order, and the MP2/6-31 + G(d,p) energy difference is still almost three times too large. Only when higher-order correlation contributions are included in the theoretical treatment by means of G2(MP2) calculations is the correct energy gap between both conformers obtained.



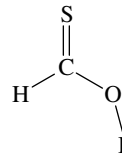
(4a)



(4b)



(4c)



(4d)

Finally, we should mention that there are also some extreme cases that are not well described even at the G2 level of theory. The most significant examples are the sulfur oxides. Neither the atomization energy of SO nor that of SO_2 are correctly reproduced by G2 theory[65,71]. For the particular case of sulfur monoxide and some of its derivatives, Esseffar and collaborators[72] have shown that the dissociation energy of SO and the heat of formation of HSO can only be accurately reproduced by using a very large basis set of the 6-311 + G(5d2f,2p) quality at the quadratic configuration interaction QCISD(T) level, which includes contributions to the energy beyond the fourth order.

2. Thermodynamic aspects

As a consequence of the high reactivity of these compounds, experimentally determined standard enthalpies of formation, $\Delta_f H^\circ_m$, for thiocarbonyl compounds are quite scarce.

TABLE 5. Relative stability (kcal mol^{-1}) of the s-*cis* **(4a)** conformer of thioformic acid with respect to the s-*trans* **(4b)**

HF/3-21G[117]	−2.80
HF/3-21G(d)[117]	−1.80
HF/4-31G(d)[205]	−2.44
HF/6-31G(d)[117]	−1.50
MP2/6-31 + G(d,p)[72]	−1.60
MP2/6-311G(d,p)[72]	−1.30
G2(MP2)[72]	−0.62
Exp.[206]	−0.67

Pilcher[73] has recently reviewed the experimental data for a variety of carbonyl and thiocarbonyl compounds. Enthalpies of formation for dithiocarbonic acids, $R_2N{-}C(=S)SH$, thioamides and thioureas were determined by standard calorimetric methods. For an important, older review on the thermochemistry and thermochemical kinetics of sulfur-containing compounds, see work of Benson[74].

$\Delta_f H^\circ_m$ values for thioformaldehyde, H_2CS **(5)** have been obtained by several workers using mass-spectrometric techniques. The most recent results, together with data for formaldehyde **(6)** and several thiocarbonyl and carbonyl compounds, are presented in Table 6.

Over the last few years, high level *ab initio* calculations have been performed on **5, 6** and simple cognate species. As indicated earlier, these calculations, either alone or combined with experimental data, have led to the determination of several energetic magnitudes of great relevance. These values were arrived at by combining the appropriate G2 energies (which include the zero-point energy correction) with the formation energies at 0 K for the various atoms. At 0 K, the standard enthalpies of formation, $\Delta_{f0} H^\circ_m$, are the same as the standard energies of formation. Representative results are given below.

a. Bond energies and enthalpies. It should be kept in mind that different definitions have been used by different workers and great care should be exercised when comparing their results. Pilcher[73] defines bond enthalpies in terms of the enthalpy of atomization of a molecule, $\Delta_a H$, the enthalpy for reaction 1:

$$\text{Compound (gas)} \longrightarrow \text{Atoms (ground state, gas)} \tag{1}$$

$$\Delta_a H = \Sigma \text{ bond enthalpies } -\Delta_f H^\circ_m(\text{compound, gas}) \tag{2}$$

In order to derive bond enthalpies, Pilcher selects 'those molecules for which it is reasonable to assume absence of strain energy and stabilization energy'.

Representative results for relevant bonds are given in Table 7.

TABLE 6. Thermochemical data for representative thiocarbonyl and carbonyl compounds[a]

Compound	$\Delta_f H^\circ_{298}$(g), exp	$\Delta_{of} H^\circ_m$(g), exp
$H_2C{=}S$ **(5)**	27.3 ± 2.0[b]	$\leqslant 29.9 \pm 0.9$[b]
	$\leqslant 28.9 \pm 0.9$[b,c]	28.3 ± 2.0[b,c]
$H_2C{=}O$ **(6)**	-25.96 ± 0.12[d]	-26.67 ± 1.5[g]
$CH_3C(=S)NH_2$	3.04 ± 0.29[d]	
$CH_3C(=O)NH_2$	-56.96 ± 0.19[d]	
$C_6H_5C(=S)NH_2$	24.71 ± 0.19[e]	
$C_6H_5C(=O)NH_2$	-24.0 ± 0.2[f]	
$(NH_2)_2C{=}S$	5.47 ± 0.38[e]	
$(NH_2)_2C{=}O$	-58.70 ± 0.50[e]	
$[(CH_3)_2N]_2C{=}S$	10.73 ± 0.55[e]	

[a] All values in kcal mol^{-1}.
[b] From Reference 75.
[c] Upper limit.
[d] From Reference 76.
[e] From Reference 73.
[f] From Reference 77.
[g] From Reference 78.

TABLE 7. Bond enthalpies according to Pilcher[73]

Bond	Enthalpy[a]
C−C	85.67
C−H	97.37
C=O	166.25
C−O	84.49
O−H	107.95
C=S	137.3[b]
C−S	70.26
S−H	86.16

[a] All values in kcal mol^{-1}.
[b] Obtained using $\Delta_f H^\circ_m$ **(5)** from Reference 75.

Bond dissociation energies, D_0 (A−B), defined by equation 3, have been determined experimentally by Berkowitz and coworkers using photoionization mass spectrometry[75].

$$A - B(g, 0\ K) \longrightarrow A \cdot (g, 0\ K) + B \cdot (g, 0\ K) \qquad D_0(A{-}B) \tag{3}$$

These results are summarized in Table 8 and portray the energy changes for the stepwise atomization of **5**. Data for **6** are given for comparison purposes.

The high quality of the G2 results allows one to use bond energies computed at this level for quantitative studies. Representative results are given in Table 9.

Some important conclusions derived from the results given in Tables 6 to 9 are as follows: (1) Computed and experimental D_0 values are in excellent agreement. (2) By all criteria, CO bonds in H_2CO and CO are stronger than CS bonds in H_2CS and CS. The differences between the two homologous couples are, however, quite important,

TABLE 8. Experimental bond energies, D_0[a], for **5, 6** and species derived therefrom

Bond	D_0
H−HCS	$\leqslant 95.0 \pm 0.5$[b]
	$\geqslant 93.0 \pm 0.5$[b]
H−CS	$\leqslant 47.7 \pm 2.0$[b]
	$\geqslant 44.1 \pm 1.2$[b]
H_2C−S	$\geqslant 129.4 \pm 1.1$[b]
	131.0 ± 2.0[b]
H_2C−O	177.6 ± 1.5[c]
HC−S	$\leqslant 137.9 \pm 2.0$[b]
	$\geqslant 134.3 \pm 1.0$[b]
C−S	169.8 ± 0.6[b]
C−O	255.4 ± 1.5[c]

[a] In kcal mol^{-1} at O K.
[b] From Reference 75.
[c] Using data from References 79 [$\Delta_f H^\circ_0$ (CH_2)] and 78 [$\Delta_f H^\circ_0$ **(6)**].

TABLE 9. Standard enthalpies, $\Delta_{of}H^{\circ}_{m}$ (g) and dissociation energies at O K, D_0, computed at the G2 level for **5** and **6**[a]

Compound	$\Delta_{of}H^{\circ}_{m}$ (g)
5	28.7[b]
6	−29.5[c]

Bond	D_0
H−HCS	93.7[b]
H−CS	46.0[b]
H_2C−S	131.6[b]
C−S	170.5[b]
H−HCO	87.9[b]
H−CO	13.4[b]
C−O	258.0[c]
H_2C−O	180.7[c]

[a] All values in kcal mol^{-1}.
[b] From Reference 66.
[c] From Reference 80.

namely 46.6 and 85.6 kcal mol^{-1}, respectively (see Table 9). (3) The CH bonds in H_2CO and HCO· are significantly weaker than those in H_2CS and HCS·. (4) The CS bond in H_2CS is substantially weaker than the CO bond in H_2CO. Its stability, however, is appreciably higher than that of many 'strong' single bonds (see Table 7) and barely 12 kcal mol^{-1} lower than that of the CC bond in C_2 H_4 (computed using Pilcher's scheme). Thus, *the apparent instability of thiocarbonyl compounds is not a consequence of the intrinsic weakness of the thiocarbonyl group but rather follows from the fact that other atomic arrangements are energetically more favorable*. In this respect, if we consider the thiol–enethiol equilibrium embodied in reaction 4, use of the data given in Table 7 leads to an upper limit (i.e. neglecting resonance stabilization of the enethiol) for $\Delta H_{(5)}$ of −17 kcal mol^{-1}, a substantial value.

$$CH_3CSH \rightleftharpoons H_2C{=}CHSH \qquad \Delta H_{(4)} \tag{4}$$

From a chemical standpoint, the decomposition of the energies of the double bonds into the corresponding σ and π components, E_σ and E_π, is important. Unfortunately, this is a conceptual division and these quantities are not quantum-mechanical observables. Thus, approximate methods have been devised to estimate these contributions.

In the case of **5** and **6**, Schleyer and Kost[81] used reactions 5 and 6 to compare the energies of the C=X double bonds with those of the single bonds C−X:

$$H_2CX + CH_4 + XH_2 \longrightarrow 2CH_3{-}XH \qquad \Delta E_{(5)} \tag{5}$$

$$CH_3{-}XH \longrightarrow CH_3\cdot + \cdot XH \qquad \Delta E_{(6)} \tag{6}$$

(X = O, S)

$\Delta E_{(7)}$ provides D_0(C−X), taken as a measure of E_σ, the contribution of the σ bond to the overall stability of the C=X bond; $\Delta E_{(5)}$, when substracted from $2D_0$(C−X), is intended to yield an estimate of the total energy of the bond, $E_{\sigma+\pi}$. The π bond contribution, E_π, is given by $E_{\sigma+\pi} - E_\sigma$. Representative results, based on experimental data, are given in Table 10.

TABLE 10. σ and π contributions to the stabilities of C=X bonds[a]

C=X	E_σ	E_π	$E_{\sigma+\pi}$	Reference
C=C	86.1	70.6	156.6	81
		62		82
C=O	89.4	98.8	188.2	81
		77		82
C=S[b]	68.7	57.2	125.9	81
		51.8		82

[a] All values in kcal mol^{-1}.
[b] Original data revised using the $\Delta_{of}H^\circ_m$ (g) value for **5** from Reference 78.

Schmidt's group[82], developed a scheme based on the definition of E_π as the enthalpy change at 0 K for reaction 7:

$$H_2C\cdot - X\cdot \longrightarrow H_2C{=}X \qquad E_\pi \tag{7}$$

This magnitude can be determined by combining the enthalpy change at 0 K for the hydrogenation reaction 8 with the appropriate bond dissociation energies:

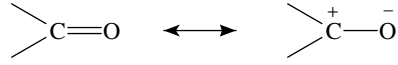
$$H_2C{=}X(g) + H_2(g) \longrightarrow CH_3 - XH(g) \tag{8}$$

Selected results are also given in Table 10.

Although the two sets of data are not identical, they nevertheless define the same pattern:

$$E_\sigma(CS)/E_\sigma(CC) \approx E_\pi(CS)/E_\pi(CC) \approx 0.80 \text{ and } E_\sigma(CS)/E_\sigma(CO) \approx E_\pi(CS)/E_\pi(CO) \approx 0.66$$

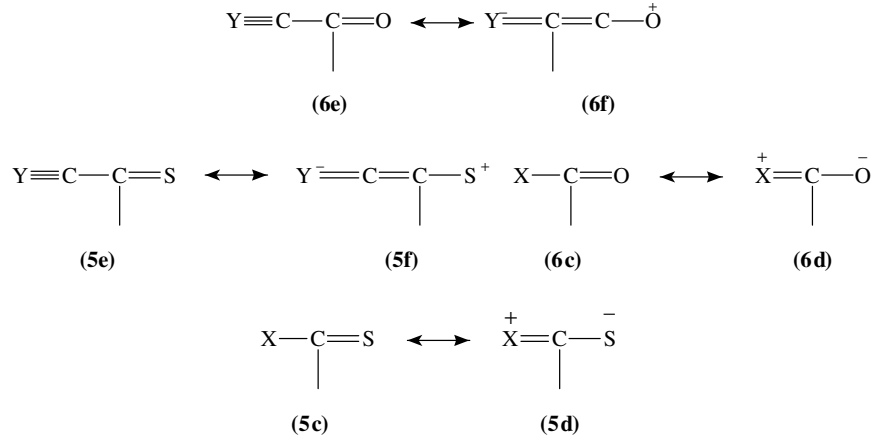
An important contributor to the enhanced stability of the CO bond relative to that of the ethylenic double bond originates in the sizable contribution of the limiting structure **6b**.



(6a) **(6b)**

This follows from the difference between the electronegativities of oxygen and carbon[1]. As indicated by Wiberg and coworkers[83–85], the Coulombian attraction between C and O contributes significantly to the overall stability of the bond. It is remarkable that, even in the presence of electron-donor substituents, structures such as **6b** are very important in the case of carbonyls and much more so than in the case of thiocarbonyls[83]. The importance of structure **6b** brings about a reduction in the bond order of the carbonyl group: 1.371 vs 2.026 for C_2H_4. At variance with this, the bond order in the thiocarbonyl group of **5** reaches 1.718[81]. Other factors are to be considered when comparing the stability of the thiocarbonyl and carbonyl bonds. They were very ably examined by Kutzelnigg[86].

b. Conjugative and electronegativity effects. In substituted carbonyl and thiocarbonyl groups, conjugation between the π systems of these groups and the electronic systems of

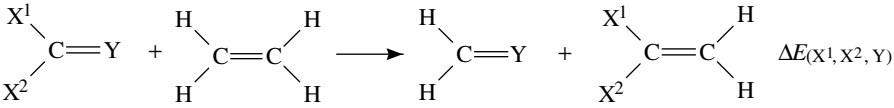


(6e) **(6f)** **(5e)** **(5f)** **(6c)** **(6d)** **(5c)** **(5d)**

appropriate symmetry of the substituents can take place. These interactions may confer importance to limiting structures such as **5d**, **5f**, **6d** and **6f**.

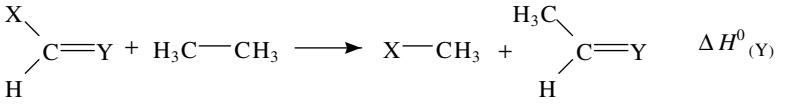
This, in turn, will affect the energetics of the molecules, their rotational barriers and their reactivity. The relative importance of these structures will be determined to a large extent by the difference in electronegativities between oxygen and sulfur as well as by the ability of X and Y≡C to either donate or receive electrons. The electronegativities of X and Y≡C also play a key role, as they strongly affect the degree of polarization of the carbonyl and thiocarbonyl groups (including *both* σ and π bonds. Several schemes have been set forth for the purpose of quantifying the influence of substituents on the stability of both families of compounds.

(a) Abboud and coworkers[39] have used the families of reactions 9:



(Y = O, S) (9)

Wiberg and coworkers[83–85] have used reactions 10:



(Y =O, S) (10)

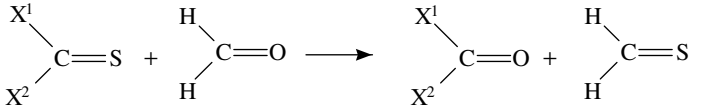
Most of the energetic data used in these studies were obtained by computational methods [6-31 G(d)[39] and G2[83]]. We present in Table 11 a set of data taken from these studies as well as from Notario's work[87].

(b) A direct way of comparing substituent effects on both families is by means of the isodesmic reactions 11 and 12, related to reactions 9 and 10, respectively.

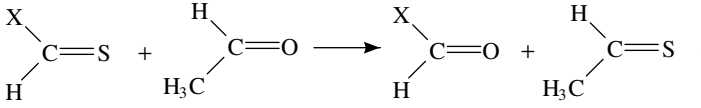
TABLE 11. Values of $\Delta E_{(X^1,X^2,S)}$, and $\Delta H^{\circ}_{0(O,S)}$, for reactions 10, 12 and 13

X_1	X_2	$\Delta E^{a,b}_{X^1,X^2,S)}$	$\Delta E^{a,b}_{X^1,X^2,O)}$	$\Delta E^{a,b}_{(O,S)}$	$\Delta H^{\circ}_{0(O,S)}{}^{a}$
H	H	0(0)[c]	0(0)[c]	0(0)[c]	
CH_3	H	3.5	6.2	−2.7	(0)[c]
NH_2	H	18.9	21.5	−2.6	−2.1
OH	H	16.4	26.5	−10.1	−6.1
F	H	4.1	19.6	−15.5	−10.3
Cl	H	0.2	8.3	−8.1	
CH_3	CH_3	1.6	10.2	−8.6	
NH_2	CH_3	17.2	24.1	−6.9	
OH	CH_3	17.0	30.2	−13.2	
F	CH_3	6.2	22.9	−16.7	
Cl	CH_3	−0.4	13.5	−13.9	
NH_2	NH_2	12.6	39.8	−27.2	
OH	OH	17.0			
F	F	6.4	25.6	−19.2	
Cl	Cl	−7.1	11.9	−19.0	
CN	H	−13.6	−6.8	−6.8	
NO_2	H	−9.8	−2.4	−7.4	
BH_2	H	4.3	−0.7		

[a] All values in kcal mol^{-1}.
[b] Defined in the text.
[c] Reference value.



(11)



(12)

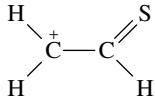
Values of $\Delta E_{(O,s)}$ and $\Delta H^{\circ}_{0(O,s)}$ are also given in Table 11. This table lists data for potential electron-donor substituents. Relative to hydrogen, most of them exert a stabilizing effect.

Some conclusions derived from these data are as follows: (1) Substituent effects on carbonyl groups are systematically larger (in absolute value) than those on thiocarbonyl. (2) Electron-donor groups always exert a stabilizing effect. (3) Substituent effects are not additive.

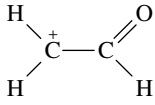
$\Delta E_{(H,X,S)}$, $\Delta E_{(H,X,O)}$ and $\Delta E_{(O,S)}$ can be analyzed in terms of the Taft–Topsom formalism[88] wherein these effects are decomposed into electronegativity, polarizability, field and resonance contributions, respectively measured by the descriptors σ_χ, σ_α, σ_F and σ_R. In view of the size of the database, only two parameters are used. Linear combinations of σ_χ and σ_R lead to a reasonably good description of the ΔE values indicated above. The main semiquantitative conclusions of such an analysis are as follows:

(1) Electron-donation effects (structures **6d** and **5d**) are quite important and stabilizing in both cases. According to Wiberg[83], this effect is relatively more important in the case of thiocarbonyls. Structures **6f** and **5f** do not seem to exert a sufficiently strong stabilizing effect, the overall effect in the case of cyano and nitro derivatives being moderately

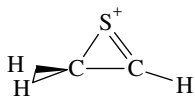
destabilizing. The mutual repulsion of the dipoles also comes into play. This fact notwithstanding, the recent determination of the PES of thioformylcyanide by Pfister-Guillouzo and collaborators[89] provided direct proof of the relevance of structure **6f**. These authors analyzed their experimental results in terms of a correlation diagram showing that the overlap between the π_{CS} MO of H_2CS and one of the degenerate π_{CN} orbitals of HCN leads to a strongly stabilized in-phase combination essentially isoenergetic with the original MO of H_2CS. Elecron-donation from the thiocarbonyl group to CN and C≡CH groups is also confirmed by analysis of the stretching frequencies and bond lengths in thiopropynal and formyl cyanide[40]. Similar behavior is also found in α-thiocarbonyl cations. As shown by Creary's group[90], the thiocarbonyl cation **(7a)** displays features suggestive of substantial thiocarbonyl conjugation. For instance, comparison of bond lengths of **7a** with those of the corresponding carbonyl analog **7b**, in particular the significant shortening of the C−C bond (from 1.475 Å in **7b** to 1.403 Å in **7a**), indicates that thiocarbonyl conjugative stabilization of a cationic center is more important than carbonyl conjugation. It must be mentioned that, despite the stabilization of **7a** due to thiocarbonyl conjugation, the most stable cation corresponds to the cyclic **7c** form, which lies 28.1 kcal mol^{-1} below the open **7a** form[90].



(7a)



(7b)



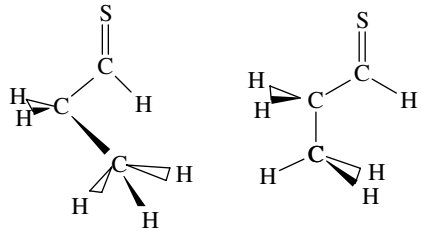
(7c)

A strong resonance stabilization is also found for 4-sulfomethylenecyclopropene **(8a)**. Bachrach and Liu[91a] have estimated that the delocalization energy for **8a** is about 4.4 kcal mol^{-1} higher than that of the carbonyl analog **8b**. This finding was explained in terms of the lower electronegativity and larger polarizability of sulfur[91a]. These and other cyclopropenes have been studied by Burk and coworkers[91b].

(8a) **(8b)**

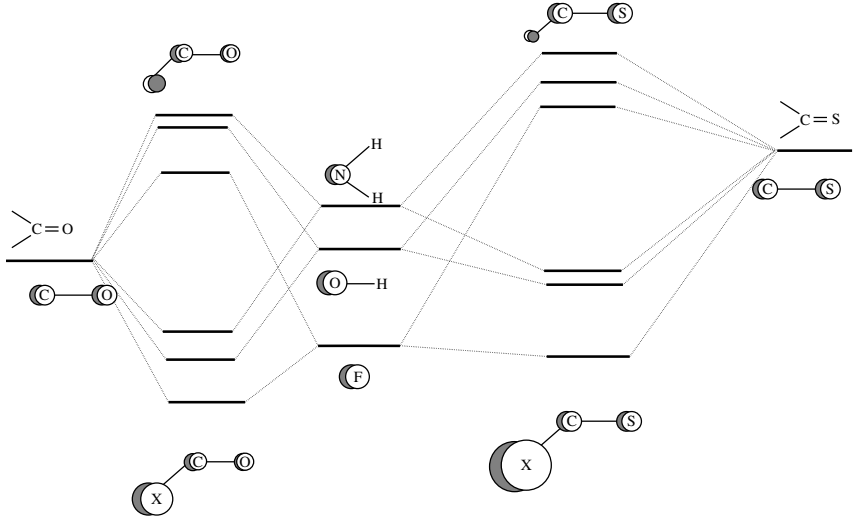
The lower electronegativity of sulfur with respect to oxygen explains also the shortening of the C−C bond in thioketones with respect to the corresponding ketones[92]. In the most stable conformer of thioaldehydes[93], thioketones[92,94,95] and thioamides[57,96], the methyl groups show a systematic preference to eclipse the C=S bond. This is also the most common situation as far as carbonyl derivatives are concerned. However, when this comparison is carried out for further terms in the series of aldehydes, some differences appear with respect to the analogous thioaldehydes. *Ab initio* calculations[95] show that, similarly to what has been found for thiols and thioethers[97−98], thiopropionaldehyde preferentially adopt the *gauche* conformation **(9a)**, in contrast to the analogous oxygen compounds which generally adopt the *trans* **(9b)** form[97].

(2) The role of electronegativity determines an important difference between the two families. For thiocarbonyl compounds, the contribution is small and barely at the limit of statistical significance. In the case of the carbonyls, the contribution is large and stabilizing.



(9a) **(9b)**

$\Delta E_{(O,S)}$ and $\Delta H_{(O,S)}$ essentially reflect the influence of electronegativity and, to a lesser extent, that of resonance. The only positive value of $\Delta E_{(O,S)}$ in Table 11 pertains to the BH_2 substituent and illustrates the role of electronegativity. This property is also largely responsible for the ranking of the MOs of F, OH and NH_2. The analysis of the influence of electron donation and electronegativity of the substituents on carbonyl and thiocarbonyl groups in terms of MO diagrams has been carried out elsewhere[39]. The discussion to follow is based on the MO diagram given in Scheme 1. It allows the comparison of substituent effects on **5** and **6**.

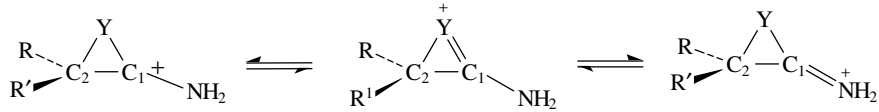


SCHEME 1

For simplicity, we start our analysis with the carbonyl compounds. The highest occupied MO (HOMO), Ψ_8, of **6** is essentially an oxygen lone pair, while the next one, Ψ_7, is a C−O π-bonding orbital. Upon substitution there are two dominant interactions, those involving the Ψ_7 π-MO and those affecting the lower σ-MOs. The Ψ_7 MO interacts with the appropriate MO of the substituent (NH_2, OH, F) leading to a stabilized π-MO (in-phase combination) and to a destabilized π-MO (out-of-phase combination). These interactions are quantitatively different depending on the substituent. For the amino and hydroxyl groups they are quite strong because the interacting MOs are close in energy, while they are very weak for fluorine, whose π-type orbital is much lower in energy than Ψ_7. Hence, for the fluorine derivative, the in-phase and out-of-phase combinations have

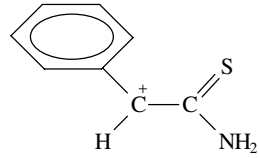
strong contributions from the fluorine orbitals and from the C=O subunit orbitals, respectively, while for amino and hydroxy substituents, these weights are more evenly balanced. From the energetic point of view, this implies that the out-of-phase combination will be much higher in energy when the substituents are NH_2 or OH than when the substituent is fluorine. A quantitative calculation shows that in the first two cases this orbital becomes the HOMO of the system (see Scheme 1). Thus, while as in the parent compound (basically an oxygen lone-pair), in formaldehyde and formic acid this orbital lies below the aforementioned π-MO. Scheme 1 also shows that these π-interactions are slightly more favorable for OH than for NH_2 substituents, since for the former both interacting MOs are almost degenerate. There is a second interaction which affects the lower energy σ orbitals of C=O. These interactions become more effective as the electronegativity of the substituent increases. In constrast to π-orbitals, the σ-MOs of the parent compound contain a contribution from the hydrogen atom orbitals. When hydrogen is replaced by a more electonegative system, the contribution of the substituent orbitals to the corresponding σ-MO increases significantly. This implies that the larger the electronegativity of the substituent, the lower the participation of the carbon orbitals to the corresponding MO should be. This perturbation should be reflected in a greater C^+-O^- polarity of the carboxylic bond and hence in a stabilization. For the thiocarbonyl series the situation is qualitatively similar but quantitatively different from carbonyl systems. The MOs of the parent compound **(5)** are analogous to those in **6** and follow the same ranking of energies. However, π-interactions are now less favorable because the π-MO of the C=S subunit lies higher in energy than that in C=O. As a consequence, the energy gap with respect to the substituent orbitals increases (see Scheme 1). This is reflected in the fact that, while formamide presents the two HOMOs in a reversed order with respect to formaldehyde, in thioformamide the order is the same as in thioformaldehyde. Scheme 1 also shows that the interaction is now more favorable with the orbitals of the NH_2 group than with those of the OH. This is in good agreement with the results of Table 11, which show that while the carbonyl system is more stabilized by hydroxy than amino substitution, the opposite holds for thiocarbonyl compounds.

Hopkinson and coworker[99] have just published *ab initio* MO calculations at MP2(FULL)/6-311G(d,p) or MP2(FULL)/6-31G(d,p) levels on carbocations $RR'CCHO^+$, $RR'CCHS^+$, $RR'CCONH_2^+$ and $RR'CCSNH_2^+$ where R and R′ = H, CH_3, *c*-C_3H_5 and C_6H_5. Primary (R = R′ = H), secondary (R = H, R′ = alkyl or phenyl) and tertiary (R = R′ = CH_3) prefer the cyclic oxiranyl or thiiranyl structure **10**, with open structures such as **11** being a transition structure for ring opening. Tertiary carbocations with R = R′ = phenyl or cyclopropyl and the 9-thioformamidyl-9-fluorenyl cation **(12)** have an open structure. These authors provide strong experimental evidence suggesting that **12** has indeed this open structure. Isodesmic reactions show $CONH_2$ to be weakly stabilizing in the methyl cation, and $CSNH_2$ has a larger stabilizing effect, roughly equivalent to that of a methyl group. An α-thioamide substituent is less stabilizing in the ethyl cation and even less stabilizing in the isopropyl cation. In $C_6H_5CHCSNH_2^+$ the $CSNH_2$ group is slightly destabilizing and, by extrapolation, is more destabilizing in $Ar_2CCSNH_2^+$.



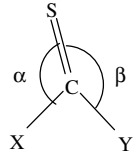
(10a) **(10b)** **(10c)**

(Y = O, S)



(11)

In unsymmetrically substituted thioketones, the thiocarbonyl group is often calculated[92,39] to be significantly bent towards one of the substituents. The tilt (see Scheme 2) is consistently away from electropositive groups and towards electronegative ones. In general, the tilt found for thiocarbonyl compounds is smaller than that exhibited by the carbonyl analogs. This difference has been explained by Sudhakar and Chandrasekhar[93] in terms of the energy differences between the thiocarbonyl *n* orbital and the carbonyl *n* orbital. Since the former lies higher in energy than the latter, tilt angles will no longer be determined by simple two-orbital interactions as in the case of carbonyl compounds, involving the carbonyl *n* orbital and a σ^* orbital from the substituent, but by three-orbital and four-orbital interactions.

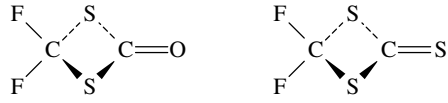


SCHEME 2

3. Structural aspects

a. Experimental structural data. (i) Structure. Clouthier and Moule[100] have critically compiled and thoroughly discussed the available structural data for **5**, **6**, acetaldehyde, thioacetaldehyde, acetone, thioacetone and the formyl and thioformyl halides, $X_2C{=}Y$ (X = F, Cl, Br, Y = O,S), ClC(O)F and ClC(S)F both in the ground and in various excited states. This is a major reference in the field. Schaumann[1] also provides relevant information on small carbonyl and thiocarbonyl molecules.

Mack and collaborators[101] have used electron diffraction for the purpose of determining the structures of 4,4-difluoro-1,3-dithietane-2-one **(13a)** and 4,4-difluoro-1,3-dithietane-2-thione **(13b)**.

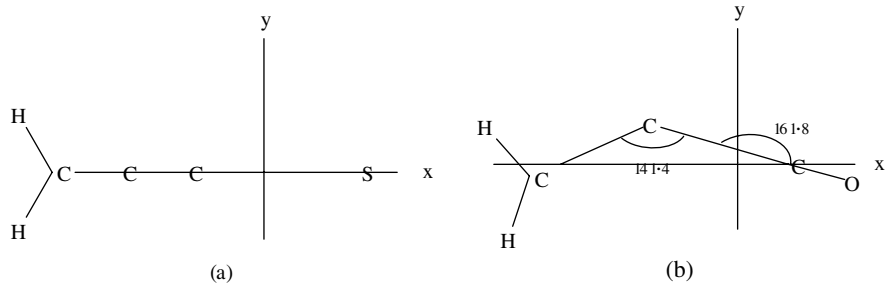


(13a) **(13b)**

The comparison of their results with data for the open-chain compounds dimethyldithiocarbonate, $(CH_3S)_2C{=}O$ **(14)**[102] and dimethyltrithiocarbonate $(CH_3S)_2C{=}S$ **(15)**[103] sheds light on the influence of cyclation on the structure and orbital interactions of thiocarbonyl compounds. A particularly important feature is the decrease in C=O and C=S bond lengths upon cyclation. This follows from the reduction of the $S{-}C(sp^2){-}S$ angles

(*ca* 8° in both cases) since, as pointed out in studies involving four-membered carbonyl compounds[104], the two hybrids involved in the C(sp^2)−S bonds appreciably increase their p-character upon cyclation and, by orthogonality, that involved in the C=X (X = O, S) increases its s-character. Thus, in **13a** and **13b**, this carbon shows an enhanced electronegativity with respect to **14** and **15**.

Brown and coworkers[105] used microwave spectroscopy to determine the structure of propadienethione $H_2C{=}C{=}C{=}S$ **(16)** through the analysis of the rotational constants for several of its isotopomers (obtained by pyrolysis of cyclopenteno-1,2,3-thiadiazole and deuterated derivatives). The main structural parameters are shown in Scheme 3a. A most remarkable (and yet unexplained) feature is the fact that this molecule has a C_{2v} geometry, while propadienone, $H_2C{=}C{=}C{=}O$ **(17)** is 'kinked'[105], as shown in Scheme 3b.



SCHEME 3

High-resolution FTIR studies of thioketene-H_2, -HD and -D_2 have allowed the determination of the r_s molecular structures of thioketene[106]. On going from ketene to thioketene, a marked change in the methylene group geometry is observed, such that a small decrease in the CH bond length and a substantial reduction of the HCH angle (2.8°) occur. This was interpreted as an indication of a larger p-character of the C−H bonds of thioketene. Relevant parameters for the couple thioketene/ketene are as follows: r_s(CH) (Å) = 1.0796(36)/1.0825(15); r_s(CC) (Å) = 1.3144(24)/1.3137(721); r_s(CS) (Å) = 1.5542(26); r_s(CO) (Å) = 1.1620(721); $<_s$= 119.7(30)/121.56(15).

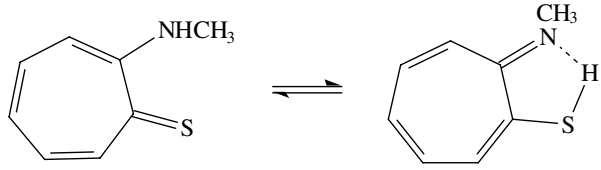
(ii) Dipole moments. Table 12 summarizes experimental data for selected carbonyl and thiocarbonyl compounds. The first two sets present remarkable features: (a) In benzene

TABLE 12. Experimental dipole moments (in Debye units) for selected thiocarbonyl and carbonyl compounds

Compound	X = O	X = S
Tropone/tropothione	4.30[a]	3.88[a]
2-Methoxythiotropone		5.10[b]
2-Methylaminotropone/2-methylaminotropothione	3.36[b]	4.73[b]
$H_2C{=}X$	2.332[c]	1.647[c]
$H_2C{=}C{=}X$	1.422[c]	1.021[c]
$H_2C{=}C{=}C{=}X$	2.297[c]	2.064[c]
$H_2C{=}C{=}C{=}C{=}X$	1.9767[c]	
$C_6H_5C(=X)N(CH_3)_2$	3.85[d]	4.71[d]

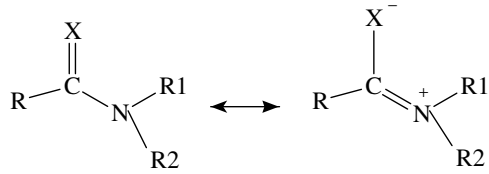
[a] Reference 1, solution values.
[b] Reference 107, benzene solution at 20.0 °C.
[c] Reference 108, gas phase.
[d] Reference 109, benzene solution at 30.0 °C.

solution at 20 °C, the dipole moment of 2-(methylamino)tropothione **(18)** is much higher than that of the carbonyl homolog while the opposite holds for the parent compounds. The situation is intriguing, because Machiguchi's group[107] has shown that under these experimental conditions **18** actually exists as a rapidly equilibrating mixture of the thione and ene-thiol **(19)** forms. Furthermore, because of the very different lengths of the C=O and C=S bonds, the comparison of the dipole moments is by no means straightforward. These problems call for further study. (b) As indicated by Brown[105], the available results for the cumulene–thione series display a pattern of alternance with the parity of the number of carbon atoms similar to that displayed by the carbonyl homologs. It is possibly related to the 'even/odd' factor relevant in the $X{=}C{-}(C)_n{-}C{=}Y$ systems[108]. Data by Lumbroso and Curé[109] on benzamides and thiobenzamides are discussed below, in connection with the problem of internal rotations.



(18) **(19)**

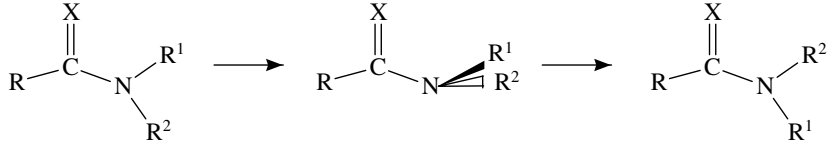
b. Rotational barriers. (i) C–N *internal rotation in thioamides*. In general, the geometry of amides and thioamides tends to be planar owing to the contribution of the mesomeric form **20b**.



(20a) **(20b)**

This is also reflected in quite high rotational energy barriers, which surprisingly are greater for thioamide than for the amide analogues.

Ferreti and coworkers[110] have carried out an analysis of over 300 crystal structures of species which contain the $R(X{=})C{-}NR_1R_2$ molecular fragment. In this survey it was found that, in the crystal, inter- or intramolecular forces can induce out-of-plane deformations of the fragment, so that the *cis–trans* isomerization pathway involves a transition state **21b**.



(21a) **(21b)** **(21c)**

These movements are well represented by a potential energy surface of two internal coordinates which represent the rotation around the C−N bond and the degree of nitrogen pyramidalization, respectively. One of the most significant quantitative results is that the activation barrier for the *cis–trans* isomerization is lower for amides than for thioamides. The available experimental data suggest, and the theoretical estimates point also in the same direction, that the nitrogen inversion barriers are larger for thioamides. The dipole moment analysis of amides and thioamides carried out by Lumbroso and Curé[109] showed that the C−N rotational barriers for *N*, *N*-dimethylacetamide ($MeCONMe_2$) and *N*, *N*-dimethylbenzamide ($PhCONMe_2$) are also smaller than those of the corresponding sulfur analogs, *N*, *N*-dimethylthioacetamide ($MeCSNMe_2$) and *N*, *N*-dimethylthiobenzamide ($PhCSNMe_2$), respectively. From the mesomeric moments of these species it was concluded that these increases in the rotational barriers parallel the increase in the estimated contributions of mesomeric forms **20b**. These results are in agreement with the *ab initio* calculations of Wiberg and Rablen[83], who found that at the G2 level the rotational barrier of thioformamide is 2.0 kcal mol^{-1} higher than that of formamide. Similarly, the out-of-plane bending vibration is predicted to have a considerably higher frequency for thioformamide than for formamide and the corresponding potential much stiffer. This is also interpreted in terms of a greater contribution of the **20b** mesomeric structure. Following the arguments given by Wiberg and Rablen[83], this would imply that, quite unexpectedly, there is a greater transfer of π charge from nitrogen to sulfur in thioformamide than from nitrogen to the oxygen atom in formamide. In the latter case the oxygen of the C=O group has a considerably large negative charge which comes essentially from the carbon atom. Hence, in amides the carbonyl carbon is electron deficient and the nitrogen lone pairs interacts with the carbon leading to a C−N double bond character. In thioamides, the carbon is not electron deficient and the nitrogen π charge is transferred to the uncharged sulfur atom. This charge allocation on sulfur requires very little energy due to the large size of this atomic system. This better conjugation of the amino group with the thiocarbonyl system was also postulated by Abboud and coworkers[39] for both neutral and protonated thiocarbonyl compounds.

A semiempirical study of rotational barriers of various thioamides and thioureas was published by Feigel and Strassner[111a] and a careful, high level *ab-initio* study of formamide and thioformamide has been carried out by Chu and coworkers[111b].

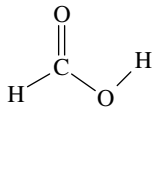
(ii) Methyl and alkyl rotations in thiocarbonyl compounds. As in the case of propionic acid[112,113], *ab initio* MO calculations at the 3-21 + G(d) level predict that thiolpropionic acid adopts preferentially the *syn* conformation around the C_α−C bond. However, the estimated rotational barrier is higher for the thiocarbonyl compound, which is rationalized in terms of unfavorable steric interactions between the α-CH_3 group and the C−S bond. The greater van der Waals radius of the sulfur atom with respect to the oxygen atom renders these interactions greater in thiocarbonyl compounds than in carbonyl derivatives. The same sort of interactions explain the preference for *skew* forms as far as thionpropionic and dithiopropionic acids are concerned[114], as well as the preference for a *gauche* conformation for thiolformate, thionformate and dithioformate[115]. In all cases the calculated rotational barriers for the latter species are also consistent with the importance of α-$CH_3 \ldots S$ steric interactions.

As we have mentioned above, the eclipsed rotamers of thioacetamide and thioacetaldehyde were found to be[114] the global minima of the corresponding potential energy surfaces at the MP4/6-311 + G(d,p) level. However, the rotational barrier is significantly lower (0.24 kcal mol^{-1}) for thioacetamide than for thioacetaldehyde **(22)** (1.4 kcal mol^{-1}). Since the π-character of the C=S bond is higher in thioacetamide, it was assumed[114] that staggered orientation of the methyl group is stabilized by increasing the polarization of the C=S bond.

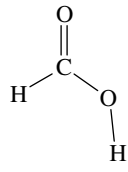
c. Thiol–thione tautomerism. (i) Thioformic acid. The simplest system which is susceptible of presenting a thiol/thione tautomerism is thioformic acid, and probably because of its simplicity it has received a great deal of attention. It is now well established that the thiol form **4a** is more stable than the thione form **4c**. Most *ab initio* calculations agree in predicting **4a** to be about 3 kcal mol^{-1} more stable than **4c**. Even when high level *ab initio* calculations are used[116] this difference is still of the order of 3.1 kcal mol^{-1}. It is important to emphasize that most of this energy difference has its origin in the much smaller zero-point vibrational energy of the thiol form. This is a direct consequence of replacing a O−H bond by a S−H linkage. Since the former has a harmonic vibrational frequency (*ca* 3500 cm^{-1}) significantly higher than the latter (*ca* 2600 cm^{-1}), the corresponding zero-point energy correction is about 1.9 kcal mol^{-1} higher. As we proceed in the present section this finding will be common, to all the thiol/thione tautomerisms.

It is, however, interesting to note that according to the calculations of Nguyen's group[117], the thione form **4c** has a much smaller ionization energy than **4a**. Accordingly, a reversed stability ordering is observed for the corresponding ionized species, and $\mathbf{4c}^{+\bullet}$ turns out to be 22.0 kcal mol^{-1} more stable than $\mathbf{4a}^{+\bullet}$.

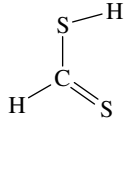
Another interesting problem related to the thiol/thione tautomerism in thioformic acid is the relative stability of the s-*cis* **(4a)** and s-*trans* **(4b)** conformers of the thiol form. As we have mentioned in the preceding section, the former is 0.7 kcal mol^{-1} more stable than the latter. A much larger energy difference is predicted to exist, at the *ab initio* level, between the s-*cis* **(23a)** and s-*trans* **(23b)** forms of formic acid ($\propto$6.2 kcal mol^{-1}) or between the same conformers of the thione form of thioformic acid **(4c, 4d)** ($\propto$6.5 kJ mol^{-1})[118].



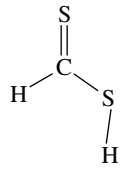
(23a)



(23b)

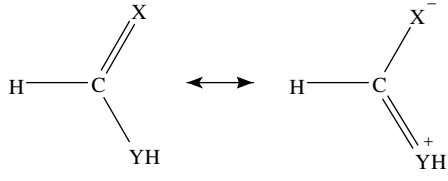


(24a)



(24b)

However, similar estimations yield a s-*cis*/s-*trans* **(24a/24b)** energy gap in dithioformic acid, HC(=S)SH, almost equal to that predicted between forms **4a** and **4b** of thioformic acid. These significant differences were explained in terms of the relative degree of mesomerism within the −C(=X)Y− fragment (see Scheme 4) and the strength of the X. . .H(Y) intramolecular hydrogen bonding in the s-*cis* form. It is hard to believe, however, that the geometrical arrangements in formic or thioformic acid may favor the existence of an intramolecular hydrogen bond. To clarify this matter we have optimized the geometries of the thiol and thione forms of thioformic acid at the MP2/6-31 + G(d,p)



SCHEME 4

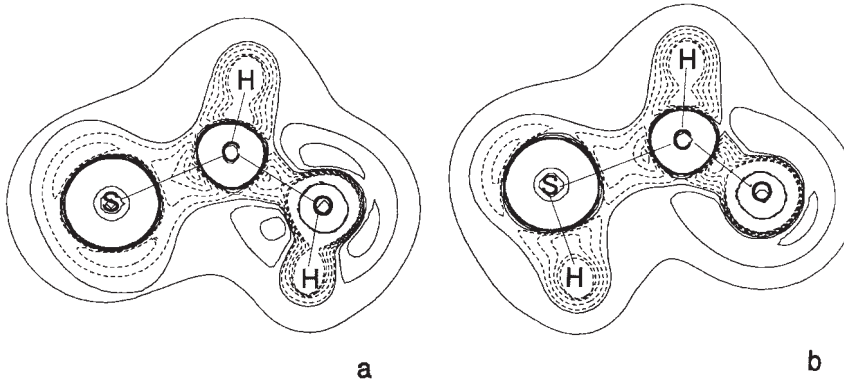
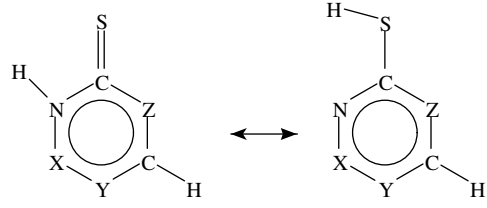


FIGURE 1. Contour maps of the Laplacian of the charge density of forms **4c** (a) and **4a** (b), respectively. Positive values of the Laplacian are denoted by solid lines and negative values by dashed lines. Contour values in a.u. are ±0.05, ±0.025, ±0.50, ±0.75 and ±0.95

level, in order to carry out a Bader topological analysis[43] of their electronic change densities. In Figure 1 we present the Laplacian of the electronic charge density for the s-*cis* conformers of both thiol **(4a)** and thione **(4c)** forms.

These figures clearly show that X...HY intramolecular hydrogen bonds exist neither in the thiol form nor in the thione form. This is also confirmed by the fact that no bond critical point was found in the X...HY regions. We must conclude then that the substantial differences between the s-*cis*/s-*trans* energy gaps between thiol and thione forms are related to the low electronegativity and high polarizability of sulfur atoms with respect to those of oxygen. In the thione form, the positive charge of the hydroxylic proton is significantly greater than the positive charge of the SH proton in the thiol form. On the other hand, the former polarizes a sulfur atom, while the latter interacts with an oxygen atom which is much less polarizable than sulfur.

(ii) Mercaptopyridines and diazinethiones. Thioderivatives of oxopyridines and oxodiazines (see Scheme 5) play an important role in various fields of biochemistry and they have attracted much interest.



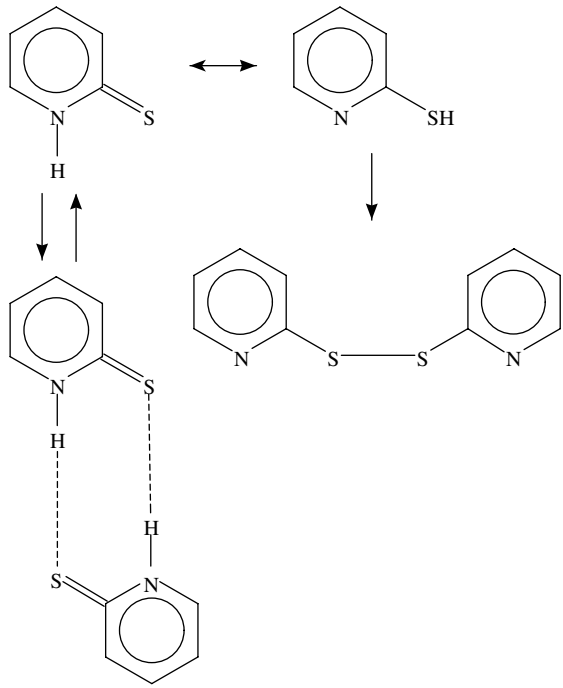
X = Y = Z = CH
X = N, Y = Z = CH
Y = N, X = Z = CH
X = Y = CH, Z = N

SCHEME 5

Since the pioneering work of Beak and coworkers[119], there exist much evidence[120,121] that for these systems, the thione/thiol tautomeric equilibrium strongly depends on the

medium. In gas-phase and in nonpolar solvents the thiol form usually predominates, while either in polar solvents or in the solid state the thione form is usually more abundant. At the beginning of the nineties more evidence in the same direction as well as quantitative relative abundances of the different stable tautomeric forms have been reported.

For the particular case of 2- and 4-mercaptopyridines and 2-mercaptopyrimidines and by means of absorption UV-VIS spectroscopy, Stoyanov and collaborators[122] have shown that polar solvents shift the thiol/thione tautomerism towards the thione form, while in dilute solutions of nonpolar solvents the thiol form predominates. However, one of the most significant contributions of this work[122] is the observation of self-association. It also favors the thione forms and is followed by quantitative transformation of the thiol form into the corresponding symmetrical disulfides (see Scheme 6). More importantly thione-disulfide process is reversible in water, which can be of some relevance in biological systems.



SCHEME 6

The most complete investigation on the thiol/thione tautomerism of thiopyridines and thiodiazines was carried out by Adamowicz and coworkers[61,63,123], who presented combined theoretical and experimental IR spectroscopic studies of Ar and N_2 matrix-isolated compounds for the whole series.

The *ab initio* calculated energies were obtained at the SCF level, followed by the evaluation of the second-order electronic correlation contribution with the many-body perturbation theory [SCF+MBPT(2)]. These calculations were performed on HF/3-21G(d) optimized geometries and include the zero-point vibrational energy corrections.

These authors also show that irradiation by UV light strongly influences the tautomeric equilibria for oxopyridines as well as for thiopyridines and thiodiazines. More importantly, this provided a reliable method to determine the relative abundance of thiol and thione

forms. The thiol/thione experimental ratio was usually obtained by measuring the changes in the IR band intensities after several minutes of UV-vis irradiation of the matrix. Since for matrix-isolated compounds only intramolecular reactions may be expected, one may apply the formula

$$[\text{thiol}]/[\text{thione}] = 0.96\, I/(I^{\text{UV}} - I) \tag{13}$$

where I is the intensity of a band of the thiol form in the initial spectrum and I^{UV} is the intensity of the same band after irradiation. Alternatively, a similar estimated ratio may be obtained from the sums of intensities of all the observed bands scaled by the sums of their theoretically predicted intensities,

$$\frac{[\text{thiol}]}{[\text{thione}]} = \frac{\sum_{\text{obs}} I^{\text{exp}}(\text{thiol}) \sum_{\text{obs}} A^{\text{th}}(\text{thione})}{\sum_{\text{obs}} A^{\text{th}}(\text{thiol}) \sum_{\text{obs}} I^{\text{exp}}(\text{thione})} \tag{14}$$

From the aforementioned procedures the thiol/thione ratios summarized in Table 13 were obtained for these kinds of systems. It is noteworthy that 2-thiopyrimidine was found to exist in inert gas matrices exclusively in the thiol form[124], while 3-thiopyrazine was found only in the thione form, since no trace of the SH absorption was observed[123].

From the determination of the relative abundances of thiol and thione forms and assuming that in the gas phase the thermodynamic equilibrium exists between monomeric tautomers, it was possible to estimate the free energy differences between the tautomers, which are also given in Table 13.

The results summarized in Table 13 show a tendency of a decreasing thiol/thione ratio on going from 2-thiopyrimidine to 3-thiopyrazine. This tendency is also reproduced by the *ab initio* molecular orbital calculations and has been explained[123] in terms of the ability of the sulfur atom to behave as a proton acceptor with respect to the endocyclic nitrogen atom of 2-thiopyridine or 2-thiopyrimidine. On the other hand, attachment of a proton to the sulfur atom yields an aromatic bonding structure which tends also to stabilize the system. In 3-thiopyrazine, on the contrary, the presence of two adjacent endocyclic nitrogen atoms enhances their ability to become proton acceptors and the thione form is favored. An intermediate situation corresponds to 4-thiopyrimidine where the two nitrogen atoms are separated by a CH group.

Although *ab initio* calculations reproduce qualitatively the aforementioned trends, it must be noted that there exist significant discrepancies from the quantitative point of view[61] regarding the predictions of theory and experiment with regards to the relative

TABLE 13. Ratio of concentrations of the tautomeric forms [thiol]/[thione] for mercaptopyridines and mercaptodiazines (ΔG gives the free-energy differences between both tautomers, in kcal mol^{-1})

System	[thiol]/[thione]	ΔG	
		Exp.	*Ab initio*
2-Thiopyridine	30.0/1.0[62]	2.4 ± 0.1[62]	3.6[61]
2-Thiopyrimidine	very large[a59]		6.5[62]
			4.6[122]
4-Thiopyrimidine	5.1/1.0[61]	1.1 ± 0.1[61]	8.2[124]
	5.9/1.0[60]		
2-Thiopyrazine	350.0/1.0[60]		
3-Thiopyrazine	very small[b122]		<0.1[122]

[a] 2-Thiopyrimidine was found to exist only in the thiol form.

[b] 3-Thiopyrazine was found to exist only in the thione form.

stabilities of the thiol vs the thione forms. The particular case of 2-thiopyridine was already discussed in the previous section, but there are also significant differences as far as 4-thiopyrimidine and 3-thiopyrazine are concerned. In the latter case it can be seen that the only *ab initio* calculations available[123] predict the thione form to be only 0.1 kcal mol^{-1} more stable than the thiol one, when experimentally only the thione form is observed. On the contrary, the considerably large stability of the thiol form of 2-thiopyrimidine estimated by Contreras and Alderete[125] at the MP2/6-31 G(d) level seems to be consistent with the fact that only the thiol form is observed in the gas phase and in matrices. The predominance of the thiol form of 2-thiopyrimidine is also predicted by MNDO semiempirical calculations[126].

These studies clearly show that the thiol form is systematically favored by the zero-point energy corrections, which are 2.5 to 3.5 kcal mol^{-1} higher for the thione forms[91a]. This difference reflects mainly the large frequency gap between typical N−H stretching modes, which are observed at about 3400 cm^{-1}[123], and the S−H stretching displacements, usually observed for these systems around 2600 cm^{-1}. This represents the most significant difference with respect to the corresponding carbonyl derivatives, where the enol form is only slightly favored (about 0.5–1 kcal mol^{-1}) by the zero-point vibrational energy correction. Hence, in general, the replacement of oxygen by sulfur enhances the relative stability of the fully aromatic thiol forms[61]. Thus, while the [thiol]/[thione] ratio for 2-thiopyridine is about 30, for 2-pyridinone the [hydroxy]/[oxo] ratio was about 2.6[123]. Similarly, while the free energy difference between the thiol and thione forms of 2-thiopyridine and 4-thiopyrimidine are 2.4 ± 0.1 kcal mol^{-1} and 1.1 ± 0.1 kcal mol^{-1}, respectively, for the oxygen analogs the free energy difference between the oxo and hydroxy tautomers was estimated to be 0.3 and 0.14 kcal mol^{-1}[119].

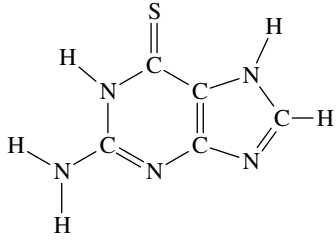
It must be also emphasized that UV-vis irradiation favors the formation of the thiol conformer. A typical example is provided by 3-pyridazine, which, as we have mentioned above, is found exclusively in the thione form. However, one hour of UV-vis irradiation ($\lambda > 330$ nm) of matrix-isolated 3-thiopyrazine caused a nearly complete disappearance of the initial IR spectrum and the new observed spectrum fits well with the predicted spectrum of the thiol form, which was taken[123] as evidence that the photoproduct is the thiol tautomer. A similar conversion of the thione tautomeric form into the thiol tautomer upon UV-vis irradiation was also observed for 2-thiopyridine[63] and for 4-thiopyrimidine[123].

When the thiol/thione tautomerism of 2-thiopyridine was studied in an amorphous, highly disordered, solid layer[63], the observation of two broad bands of the IR spectrum at 2898 and 2412 cm^{-1}, corresponding to the NH and the SH stretchings, confirmed the existence of both thiol and thione forms. Quite interestingly, in the crystalline state the molecules of 2-thiopyridine adopt only the thione form and appear bonded via pairs of N−H...S hydrogen bonds forming cyclic dimers[63]. The predominance of the thione forms in condensed media is expected on the basis of the much higher dipole moments of these forms[63,123]. These experimental findings are consistent, for the particular case of 2-thiopyrimidine, with the *ab initio* self-consistent reaction field (SCRF) calculations of Contreras and Alderete[125], who predicted the thione form to be 5.5 and 5.8 kcal mol^{-1} more stable than the thiol form in DMSO and water, respectively. It is worth noting that solvation effects are rather similar for thio- and oxo-derivatives, since in general the oxo tautomers of oxoazines also have much larger dipole moments than the hydroxy forms[127], so a reversal of stability is predicted in polar media, where the oxo form is usually more stable. These similarities apply also to other molecular properties. The SCRF study of 2-thiopyrimidine mentioned above[125,126] showed that the introduction of a solvent reaction field has little effect on the structure of the thiol tautomer, whereas for the thione the change in the structure on going from the gas-phase to solution is rather significant,

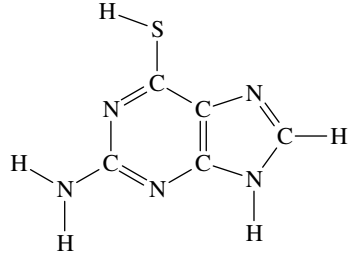
affecting essentially the C−S bond which becomes 0.03 Å longer and the C−N linkage which becomes 0.017 Å shorter. Similarly, in a SCRF study of 2-pyridone it was found[127] that the solvent has little effect on the structure of the hydroxy form while changes in the molecular geometry of the keto tautomer (whose C=O bond lengthens by 0.01 Å while the C−N bonds shorten by 0.005 Å) are sizeable. Similarly, for both carbonyl and thiocarbonyl derivatives large frequency shifts are calculated upon solvation. In both cases a red shift of about 40 cm^{-1} is predicted for the C=O and the C=S stretchings in going from the vapor phase to solution.

(iii) Thioguanines and thiopurines. Closely related to the tautomerism presented in the previous subsection are the tautomeric equilibria in the series of thioguanines and thiopurines. However, in the period of time under review, very few experimental studies have been reported for these systems and we are only aware of that of Santhosh and Mishra[128], although some theoretical studies at the *ab initio* and semiempirical level have been published.

The structures and properties of the tautomers of 6-thioguanine were first investigated, at the *ab initio* level, by Leszczynski[35]. The geometries were optimized at the HF/3-21G(d) level and the final energies obtained at the MP2/6-31G(d) level. The most important conclusion of this work is that the most stable tautomer is the thione form **25a**, while the thiol structure **25b** is only 0.6 kcal mol^{-1} less stable. However, due to the large difference in dipole moments the alternative thione form **25c** was predicted to be strongly stabilized in polar solvents. These results are in good agreement with the experimental work of Santhosh and Mishra[128], who conclude that all the observed transitions of the electronic spectra of this molecule can be explained if one assumes that only the **25a** and **25c** thione species are present in solution. Furthermore, while at neutral or acidic pH the absorption peak observed near 340 nm can be unambiguously assigned to the **25a** thione form, the peak observed near 320 nm at the alkaline pH seems to be due to the **25c** thione form. Hence, Santhosh and Mishra[128] conclude that in going from the neutral or acidic pH to the alkaline pH, the thione **25a** is converted into the thione form **25c**. Similar tautomers are found to be stable in solution for 6-thiopurine.

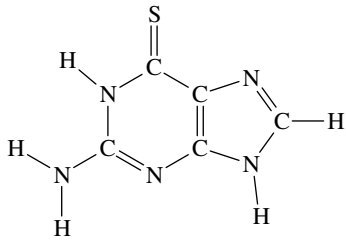


(25a)

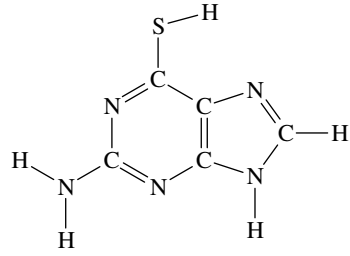


(25b)

A more refined theoretical model was applied later by Alhambra and coworkers[36] in a study of the stabilities of the different tautomers of 6-thioguanine and its protonated species. In this work geometry optimizations were carried out at the HF/6-31G(d) level and final energies were obtained at the MP2/6-311++G(d,p) level. On the other hand, the effect of water on the tautomeric equilibrium was explored using a SCRF approach. In contrast with the conclusions of Leszczynski[35], Alhambra's group[36] concluded that in the gas phase, 6-thioguanine is found predominantly in a thiol tautomeric form **25d** (not



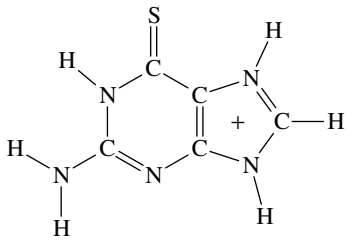
(25c)



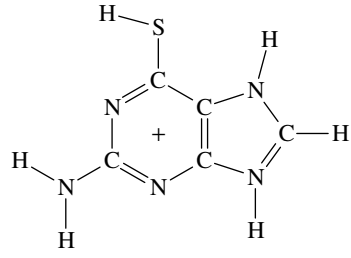
(25d)

considered in the work of Leszczynski), which is predicted to be 3.4 kcal mol^{-1} more stable than the thione form **25a**. Also significantly, the thiol tautomer **25b** is found to be also much more stable (2.5 kcal mol^{-1}) than the thione form **25a**.

These discrepancies were explained in terms of the differences between the optimized geometries used[36]. Another important conclusion in the work of Alhambra's group[36] is that water has a dramatic effect on the charge distribution of 6-thioguanine leading to important changes in the tautomer population, where only thione tautomers **25a** and **25c** should be found. Protonation of 6-thioguanine in the gas phase yields the **25e** thione form as the most stable species, although the **25f** thiol tautomer is very close in energy. Protonation in aqueous solution, where the N1(H) thiones are the main tautomers, occurs at the free imidazole nitrogen, leading to the most stable protonated tautomer **25e**. Finally, it must also be indicated that the AM1 semiempirical method fails to reproduce[129] the stability order predicted by high level *ab initio* calculations. Hence, the conclusions of Contreras and Alderete[130,131], who use this method to study the tautomerism in 6-thiopurine, should be taken with caution.

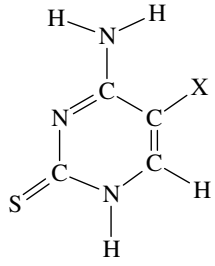


(25e)

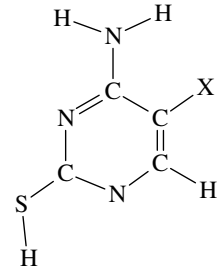


(25f)

The work of Rostkowska's group[132] on 2-thiocytosine and 5-fluoro-2-thiocytosine deals with molecular systems which are closely related to thioguanine. Similarly to what was found for mercaptopyridines and mercaptodiazines, the IR absorption spectra of these two compounds show that when the interactions with the environment are weak, as in low-temperature matrices, both molecules exist only in the amino-thiol forms **26a**, while in the crystalline phase the amino-thione forms **26b** predominate. In this work the observed IR absorption bands in the spectra were assigned to the theoretically calculated normal modes. These *ab initio* calculations were carried out at the HF/6-31G(d,p) level.

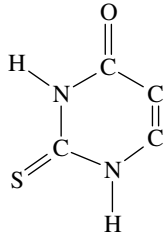


(26a)

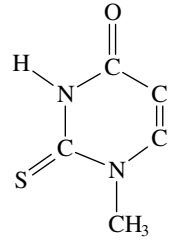


(26b)

(iv) Thiouracils. Thiouracils represent quite a rich tautomerism since oxygen and sulfur may compete, within the same system, as proton acceptors. The first experimental study on the tautomerism of thiouracil derivatives is that of Rostkowska's group[133], where the IR and UV absorption spectra of 2-thiouracil and its N1-, N3-, O- and S-alkyl derivatives, isolated in the gas phase and also isolated in inert low-temperature matrices, are reported. These spectra establish unambiguously that 2-thiouracil as well as its N1- and N3-methylated derivatives exist in the vapor phase and in the inert matrices only in the oxo-thione tautomeric forms **(27)**, **(28)**, **(29)**.



(27)



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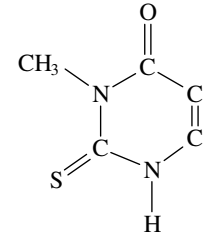
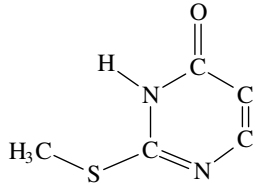
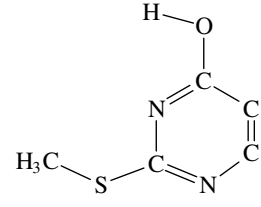


(29)

Also importantly, the same forms are found to be the most stable ones in the solid state and in solution. In contrast, isolated S2-methylthiouracil molecules under the same conditions exist in equilibrium between the 4-oxo and the 4-hydroxy tautomeric forms (**30a** and **30b**).



(30a)



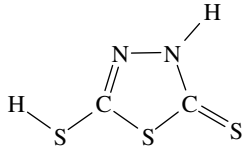
(30b)

These conclusions were ratified in a second paper[134] which includes also 2,4-dithiouracil. The appearance of the N1H and/or N3H stretches and the absence of the SH and OH stretches in the spectrum of 2- and 4-thiouracil confirmed that these molecules exist only in the oxo-thione form. Similar findings for 2,4-dithiouracil showed that this molecule exists only as a dithione tautomeric form in an inert matrix. The spectra of S-methylated thiouracils are substantially different: they present an absorption in the typical NH stretching range and another one near 3570 cm^{-1}, which is the region characteristic for the OH stretching modes.

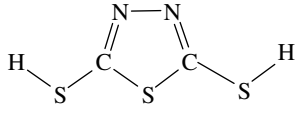
These two factors strongly suggest that S-methylated thiouracils are present as a mixture of oxo and hydroxy tautomers. The ratio $K(o/h) = [oxo]/[hydroxy]$ was determined, in a similar way to that outlined above for thiopyridines and thiodiazines, for the radio of experimental absorbances of the NH and OH stretches and the ratio of the absolute integrated molar absorption coefficients of these modes. This ratio could then be used to estimate the free energy difference between both tautomers. The values obtained were $K(o/h) = 0.36$, $\Delta G = 0.61$ kcal mol^{-1} for 2-methylthiouracil and $K(o/h) = 0.12$, $\Delta G = +1.2$ kcal mol^{-1} for 4-methylthio-6-methyluracil. The most important conclusions of these experimental works have been ratified by subsequent *ab initio* calculations[134,135], which showed that the oxo-thione tautomers of both 2- and 4-thiouracil were the most stable ones. The large dipole moments of these oxo-thione tautomers permit one to conclude that these forms will also be the most stable in polar solvents. The S2-methyl derivative is predicted to be a mixture of oxo and hydroxy forms in agreement with the experimental evidence, although the latter predicts a ratio 1 : 1 and the calculations 1 : 10. Similar discrepancies appear when the relative stabilities of the 4-substituted thiouracil compounds are considered, which indicates that more precise *ab initio* calculations are needed if one tries to attain quantitative agreement with the experimental values. It is also interesting to note that according to the predictions of Les and Adamowicz[135], the hydroxy-mercapto form is close in energy to the oxo-thione tautomers, likely due to the stabilization caused by the aromatic structure which adopts the pyrimidine ring in this tautomer. Also, similar to what has been found for thiopyridines and thiodiazines, both electron correlation effects and zero-point energy corrections are essential to predict correctly the relative stabilities within the series.

(v) Thiadiazoles. The thiol–thione tautomerism of some thiadiazoles, such as 2,5-dimercapto-1,3,4-thiadiazole (DMTD) and related compounds, has attracted some attention because these compounds are of potential use in the production of antiwear additives for engine lubricating oils.

The tautomerism of DMTD (**31a**, **31b**), as well as those of 5-amino-1,3,4-thiadiazole-2-thiol (AMTD) (**32a**, **32b**) and 5-methyl-1,3,4-thiadiazole-2-thiol (MMTD) (**33a**, **33b**), were investigated by means of FT-Raman and FT-IR spectroscopic techniques by Edwards and coworkers[136].

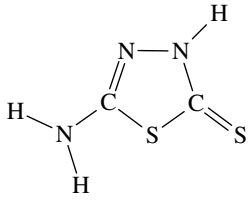


(31a)

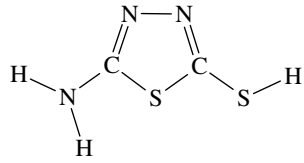


(31b)

The first member of the series was the subject of some controversy since previous IR, UV and pK_a measurements[137] suggested that tautomer **31a** was the most stable form, while ^{15}N NMR spectroscopy studies suggest that an equilibrium exists between forms **31a** and



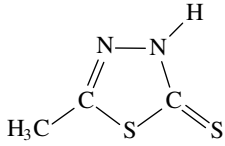
(32a)



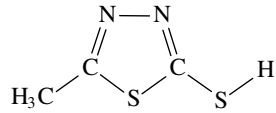
(32b)

31b, with the equilibrium strongly favoring the latter. This is confirmed by the FT-IR and FT-Raman spectra, since the highest frequency transitions are observed at 2519 and 2485 cm^{-1}, corresponding to the S−H antisymmetric and symmetric stretching modes, respectively. On the contrary, AMTD seems to be essentially in the thione form **(32b)**.

This conclusion is consistent with the main features of the IR and Raman spectra, which show transitions at 3267 and 3187 cm^{-1} assigned to the antisymmetric and symmetric NH_2 stretches, as well as a band at 2923 cm^{-1} which is assigned to the N−H stretching mode of the thione tautomer, while a very weak S−H stretching absorption at 2526 cm^{-1} is indicative[136] of only a small proportion (less than 5%) of the thiol form **32a**. Similar conclusions were reached for MMTD. The presence of a band at 3051 cm^{-1} which is assigned to the NH stretching mode, and the existence of an extremely weak band in the Raman spectrum at 2529 cm^{-1} assigned to the SH stretch, are indicative that the thione form **33a** is predominant with respect to thiol tautomer **33b**.



(33a)

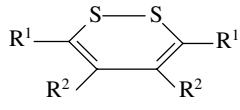


(33b)

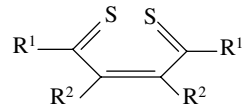
(vi) Valence tautomerism. α, β-Unsaturated thiocarbonyl compounds may exist in an equilibrium with a cyclic form[130]. Among these valence tautomerisms, the equilibria between α-dithiones and 1,2-dithietes have received some attention recently, in particular with 1,2-dithioglyoxal due to the discrepancies between theory and experiment regarding its stability relative to 1,2-dithiete. As we have already mentioned, this disagreement disappears when a sufficiently high level of theory[56,69] is used to describe both systems. Thus, it can be considered well established, from both the experimental[137,67,138] and theoretical[69,70] points of view, that 1,2-dithiete is more stable than 1,2-dithioglyoxal. The estimated barrier height for this tautomeric process was estimated to be 4.6 kcal mol^{-1} at the MP2/6-31G(2df)//MP2/6-31G(d) level of theory[56].

Very recently a theoretical study of the tautomerism between 1,2-dithiins and dithiones was published[139]. Contrary to 1,2-dithiete, 1,2-dithiin **(34a)** is a nonplanar heterocycle with an energy barrier of inversion via the fully conjugated planar structure of 8.3 kcal mol^{-1}, estimated at the MP2/6-31G(d) level. Similarly to what was found for 1,2-dithiete with respect to 1,2-dithioglyoxal, the cyclic unsubstituted 1,2-dithiin is predicted to be about 15 kcal mol^{-1} more stable than the open-chain dithiones (**34b–34d**).

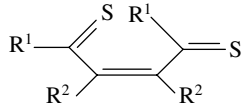
Some substituted dithiins are predicted to be less stable than the corresponding isomeric dithiones. For instance, the 3,6-diamino-substituted derivatives are predicted to more stable



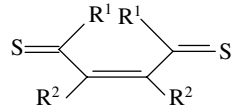
(34a)



(34b)

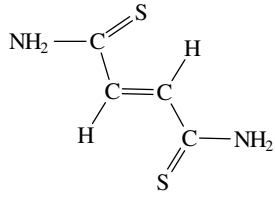


(34c)

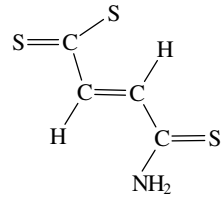


(34d)

in the open-chain forms **35a** and **35b** than in the cyclic form. This may imply, as pointed out elsewhere[132], 'that the synthesis of 3,6-diamino-1,2-dithiins reported in the literature should be considered with caution'.

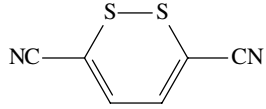


(35a)



(35b)

At variance with the above, it was found[139] that substitution of the 3,6-positions by acceptor groups such as nitrile favors the ring structure **36** with respect to the open-chain forms.



(36)

The influence of fluorine substitution on the torsional potential of 1,2-dithioglyoxal has been examined by Toro-Labbé[140]. However, this study has been carried out at a minimal basis set level, which yields quite poor molecular geometries. This implies that the trends shown for the torsional potentials are only of a qualitative value. The work of Cimiraglia and coworkers[141] on variation-perturbation CIPSI calculations of the first excited states of 1,2-dithiete and 1,2-dithiin permits one to rationalize the main features of their electronic absorption spectra.

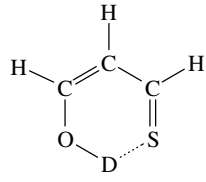
(vii) Intramolecular hydrogen bonds. Some of the tautomerisms which can take place in some thiocarbonyl derivatives, such as thioxoketones or thioaldehydes, involve intramolecular hydrogen bonds. The energetics of the tautomerism and intramolecular hydrogen bonding of monothiomalondialdehyde was investigated by Millefiori and Millefiori[142] at the *ab initio* level. This study illustrates once more the dramatic effects of both electron

correlation effects and zero-point energy corrections. The former tend to favor the thione form **(1a)**, while the inclusion of the zero-point energy correction strongly favors the thiol tautomer **(1b)**, which at the MP2/6-31G(d,p) level is predicted to be the most stable form. However, on passing from the vapor phase to polar solvents the thione form is stabilized with respect to the thiol form. A rough estimate of solute–solvent interaction energies in water by the reaction field continuum model[143,144] suggests that forms **1c** and **1d** are stabilized by 1.5 and 2.5 kcal mol^{-1} with respect to **1a** and **1b**, respectively.

The effects on the characteristics of these intramolecular hydrogen bonds of CH_3, OH, F and CN substitution at C3 were investigated in a subsequent paper[145]. The corresponding optimized structures indicated that the structure of the ring, in both the enolic and thiolic forms, is stable towards substitution. It was also predicted that the hydrogen bond strength in the thial tautomer is systematically weaker in the substituted compounds. However, for the thiol tautomer, CN substitution and CH_3 substitution imply a slight strengthening of the hydrogen bond. From these results it was concluded that the tautomeric equilibrium is significantly shifted towards the enolic form by $-$CN and $-CH_3$ substitution, while it is little affected by fluorine substitution. In the $-$OH derivative, by contrast, the thiolic structure seems to be preferred. It must be noted, however, that the relative values reported by Millefiori and Di Bella[145] do not include the corresponding zero-point vibrational corrections.

Trimethyl substitution leads to a strengthening of the hydrogen bond, which is dramatically large for the thial form. However, following the arguments of Craw and Bacskay[53], the extremely large hydrogen bond energies reported[145] may be biased by the fact that the reference structure used to define them contains a considerable amount of nonbonded repulsion contributions. Actually, when the reference rotamer used is free from the O...S repulsion[53] the calculated hydrogen bond energies are about half those reported by Millefiori and Di Bella[145]. It should be noticed, however, that in this paper it is stated that the enolic form is energetically the most stable one, since these authors did not include the zero-point energy correction.

The most accurate calculations reported on this particular tautomerism are those of González and coworkers[54], who show that at the G2(MP2) level the thiol tautomer is slightly (0.2 kcal mol^{-1}) more stable than the thial form. This work also shows that high-order correlation contributions stabilize the thial form. The characteristics of the hydrogen bonds of both tautomers were characterized by means of a Bader's[43] topological analysis of their electronic charge densities. This treatment showed that the hydrogen bond of the thial form is sizeably stronger than that of the thiol tautomer, the charge density at the corresponding bond critical point being almost twice for the former than for the latter. Hence, the greater stability of the thiol structure is mainly a consequence of its much smaller zero-point vibrational energy. In the same paper *it was shown that deuteration leads to a reversal of the stabilities of these forms, the thial tautomer* **1aD** *being 0.5 kcal mol^{-1} more stable than the thiol one*.



(1aD)

Theoretical studies, at the semiempirical level, on intramolecular hydrogen bonding in dithio analogues of malonaldehyde have also been reported[146–148].

4. Infrared and Raman spectra

The IR spectroscopic information on thiocarbonyl compounds is not abundant because of the instability of these compounds. Hence, much of the information on harmonic vibrational frequencies is of theoretical origin. Actually, the first conclusive evidence for the existence of the simplest thiocarbonyl system, thioformaldehyde, was not reported until 1970[149]. In fact, thioformaldehyde is unstable with respect to polymerization centered on the C=S bond and it must be synthesized through pyrolysis or photolysis of stable organic precursors and then detected immediately after it is formed. Nevertheless, nowadays there is already rather precise information on the fundamental vibrational modes of this species, not only in the ground state but also in some excited states. In this respect the reader is referred to the review of Clouthier and Moule[100] on the spectroscopy of carbonyls, ketenes and nitriles, where the effect of substitution by sulfur, selenium and phosphorus is analyzed thoughtfully. In the latter review[100] the reader will find a complete discussion of the vibrational frequencies of thioformaldehyde and its isotopomer D_2CS in their ground states as well as in the a^1A_2 and a^3A_2 excited states. Information on the vibrational frequencies of the ground, S_0, as well as of the S_1 and T_1 excited electronic states of the following thiocarbonyl halides: F_2CS, Cl_2CS, Br_2CS, ClFCS and BrClCS is also given. For thioacetaldehyde, thioacetone and thioketene the available information on the fundamental vibrational frequencies of their ground electronic states is also complied.

Since the most relevant information on infrared spectra of thiocarbonyl derivatives published prior to 1989 has been compiled and discussed in the aforementioned review, we shall concentrate our attention on those papers published after the review of Clouthier and Moule[100].

One of the most striking characteristics of the IR spectra of thiocarbonyl compounds is the fact that the C=S stretching mode appears very often coupled with other vibrational modes. This sometimes renders it very difficult to make an unambiguous assignment of the C=S stretching absorption, particularly for cyclic compounds such as thiopyridines, thiouracils, thiodiazines, etc., where the C=S stretching vibration is very often coupled with ring in-plane bending motions. Hence, for these species the C=S stretch is not a good group vibration. This is likely the case for other noncyclic thiocarbonyl derivatives XYC=S, such as: (a) X = Y = $N(CH_3)_2$; (b) X = $N(CH_3)_2$, Y = OCH_3; (c) X = OCH_3, Y = SCH_3; (d) X = Y = $NHCH_3$; (e) X = C_2H_5, Y = OCH_3; (f) X = CH_3, Y = OC_2H_5; (g) X = CH_3, Y = $N(CH_3)_2$, for which the HF/6-31 G(d) calculated harmonic vibrational frequencies[42] also predict a significant coupling of the C=S stretch with other vibrational modes. The experimental values reported in the literature concerning C=S stretching frequencies have been summarized in Table 14.

Many thiocarbonyl derivatives such as thioformic acid, thiopyridines, etc. present a thiol–thione tautomerism, so in those cases where the thiol form dominates the C=S stretch is not observed, or the band is very weak, while a typical S–H stretching frequency is found. This is very characteristic and is usually observed around 2600 cm^{-1} (2540 cm^{-1} for the thiol form of thioformic acid[150], 2495 cm^{-1} for s-*cis* dithioformic acid[118], 2601 cm^{-1} for 2-thio-4-neopentoxy uracil in Ar matrices at 14 K[131]; 2615, 2610, 2604, 2601 and 2617 cm^{-1} for the thiol tautomer of 2-mercaptopyrimidine[124], 2-pyridinethiol[63], 4-pyrimidinethiol[123], 3-pyridazinethiol[123] and the amino–thiol tautomer of 2-thiocytosine[132], respectively. The theoretical results of Mo's group[42] point in the

TABLE 14. C=S stretching frequencies for some thiocarbonyl compounds

Molecule	ν (C=S)	Reference
H_2CS	1059.2	154
D_2CS	936.2	154
Thioformic acid	935, 1160, 1238, 1460[a]	150
HDCS	778	106
Thiouracils	1100–1150	133
Imidazoline-2-thione	520–910[a]	172
Tetramethylcyclobutane-1-one-3-thione	1305	175
Thiosaccharin	1040, 1220, 1380[a]	170
Thiopyridines and Thiopyrimidines	400–1200[a]	63, 123
4*H*-Pyran-4-thione	722–1168–1226[a]	169
1,3-Dithiole-2-thione derivatives	1000–1070	168

[a]Combined with other vibrations.

same direction and show that for the protonated species of a wide set of thiocarbonyl derivatives, the HF/6-31G(d) calculated harmonic vibrational frequencies for the S−H stretch are between 2586 and 2671 cm^{-1}.

Thioformaldehyde. As indicated above, there is an impressive amount of spectroscopic data concerning the IR spectra of thioformaldehyde[100]. In particular, the S_1-S_0 and T_1-T_0 electronic transitions were identified as rovibrationally resolvable band systems in the visible region[151], from which it was possible to conclude[152] that thioformaldehyde was near-planar in the S_1 excited state, in clear contrast with formaldehyde. This particular problem was analyzed in detail by Dunlop and coworkers[153] by means of pyrolysis jet spectroscopic techniques. Some of the vibrational frequencies in the S_1 excited state were reported, which modify slightly previous values given elsewhere[154]. In particular, the CH_2 bending mode, the antisymmetric C−H stretch and the CH_2 rocking mode are observed at 1334.5, 3054.9 and 785.2 cm^{-1}, respectively, rather than at 1316, 3081.3 and 799 cm^{-1}, which were the values previously reported by Clouthier and Ramsay[154]. Also, a detailed description of the rovibrational energy level structure of this excited state is presented. The analysis of these data using the semirigid invertor model confirm that thioformaldehyde has a planar equilibrium structure in the S_1 excited state, while formaldehyde adopts a nonplanar equilibrium structure with an out-of-plane angle of 34°[155]. It was also found that while upon excitation the C=O bond of formaldehyde lengthens 0.12 Å, the C=S linkage of thioformaldehyde becomes only 0.09 Å longer.

Another problem related to the IR spectrum of thioformaldehyde concerns the in-plane CH_2 deformation, which was the subject of some controversy regarding its assignment. The group of Turner[156] reported a band origin of 1447.0 cm^{-1}, while that of Clouthier[157] reported a higher value, 1457.3 cm^{-1}, from a single rotational level resonance fluorescence study. This discrepancy was resolved by McNaughton and Bruget[158] who obtained a high-resolution spectrum of this band as well as a high-resolution pure rotational spectrum of thioformaldehyde in the region of 16–60 cm^{-1}. The origin of the CH_2 deformation band was determined to be 1455.5 cm^{-1}, in closer agreement with the value previously reported by Clouthier and coworkers[157]. Improved ground state constants were also reported for the ^{32}S and ^{34}S species.

McNaughton and Bruget[158] gave the gas-phase IR spectrum of thioglyoxal and assigned the ν_3, ν_5 and ν_7 fundamental bands.

From the theoretical point of view the work of Leszczynski and collaborators[159], should be mentioned, where the calculated harmonic vibrational frequencies of thioformaldehyde were compared with those of formaldehyde and selenoformaldehyde. The largest discrepancy (120 cm^{-1}) between calculated and experimental vibrational frequencies was found for the aforementioned CH_2 in-plane deformation.

Thiocarbonyl halides. In the period covered by this review we are only aware of the theoretical study of Kwiatkowski and Leszczynski[52] where the harmonic vibrational frequencies of all possible symmetric and asymmetric halides, including F, Cl and Br, are reported. These harmonic vibrational frequencies were obtained at both the HF/6-311G(d,p) and MP2/6-311G(d,p) levels of theory. Comparison with the experimental values, when available, clearly show that electron correlation contributions are essential for reliable prediction of the relative intensities of the IR absorption bands. For HFCS, HClCS and FBrCS species, for which the experimental spectra are not known, the C=S stretching bands are predicted to appear at 1206, 1108 and 1264 cm^{-1}, respectively.

Thioformic acid and dithioformic acid. The calculated HF/6-31G(d) harmonic vibrational frequencies of the different tautomers of thioformic acid (**4a–4d**) are compared with the experimental values[150] elsewhere[118]. For this comparison the calculated harmonic frequencies were scaled following the procedure proposed by Blom and collaborators[160,161]. The agreement between calculated and experimental values is quite good and confirms that for the s-*cis* thioformic acid **(4c)** there is a significant coupling of the C=S stretch with other modes. The greater C=S contribution is predicted for the absorption band observed at 935 cm^{-1}. More importantly, the theoretical study for dithioformic acid (**24a**, **24b**) allowed the assignment of the reported experimental bands[120]. As for thioformaldehyde, the C=S stretching mode contributes to bands observed at 1381, 1047 and 711 cm^{-1}.

Thioformyl and thiocarbonyl cyanides. The long-sought for IR spectrum of this compound was obtained by Wentrup and coworkers[162]. S=CH−CN was prepared by Flash Vacuum Pyrolysis (FVP) of allyl cyanomethyl sulfide and condensed in an argon matrix. The absorption frequencies(in cm^{-1}) and the intensities (in km mol^{-1}) corresponding to the five bands observed were: υ_2, CN stretch (2221, 17); υ_3, CH rock (1320, 11); υ_4, CS stretch (1103, 10); υ_5, CC stretch (889, 8); υ_8, CH wag (824, 26). These assignments were made on the basis of MP2/6-31G(d) calculations. The spectrum of formyl cyanide is reported and discussed elsewhere[163].

Thioketene. Many of the characteristics of the vibrational spectrum of thioketene were known prior to 1989, however some details of its ground-state rotational constants were not known with enough accuracy, considering the work of Winnewisser and Schäfer[164]. Duncan and Jarman[165] and later Jarman and Kroto[106] carried out high-resolution FTIR studies of this compound and its deuterated isotopomers. The nine fundamental vibration wavenumbers (cm^{-1}), υ_1 to υ_9, corrected for Fermi resonance as given by Jarman and Kroto[106] for the gaseous material are as follows: 3020, 1757, 1357.97, 850, 698.09, 404 (matrix sample), 3107.33, 921.60 and 356 (matrix sample). The C=S stretching is found at 1757 cm^{-1}, a very high value, certainly reflecting substantial changes in the hybridization of the thiocarbonyl carbon. Values for ketene are given by Kroto and McNaughton[166].

The effects of substituting O by S or Se on the harmonic vibrational frequencies of ketene was investigated from a theoretical point of view[167]. For this purpose the harmonic vibrational frequencies of ketene, thioketene and selenoketene were calculated at the MP2/TZP level. Similar differences from those observed between the fundamental frequencies of ketene and thioketene are expected between the former and selenoketene. In particular, a red-shifting of both the CH_2 symmetric and antisymmetric stretching modes and the CCX bending was predicted, while a sizeable blue-shifting of the C−C stretching and the CH_2 wagging should be expected.

Thiopyridines, thiodiazines, thiouracils and related compounds. The IR spectra of thiopyridines and thiodiazines were obtained in inert gas matrices and, in some cases, in the crystalline state. In most cases the assignment was carried out by comparing the experimental IR spectra of matrix-isolated and crystalline compounds with the spectra obtained by means of *ab initio* calculations. In this way the characteristic bands associated to the C=S stretching and bending vibrations of 2(1*H*)-pyridinethione[63] were found at 2610 and 884 cm^{-1}, respectively, for the molecule isolated in an inert matrix, where the thiol form dominates. Although in the crystalline state the bands are perturbed, in particular those corresponding to the vibrations of the NH and CS groups, it was found[63] that the positions of the bands due to ring and CH vibrations are close to their counterparts in the spectra of matrix-isolated compounds. The NH band, on the contrary is considerably broadened and red-shifted, while the NH bending is also broadened but blue-shifted. The bands which present a greater contribution of the CS stretch are slightly red-shifted in the crystal with respect to the matrix, while the C=S out-of-plane bending is blue-shifted. For 2-mercaptopyrimidine a band at 2615 cm^{-1} in the IR spectrum of the molecule isolated in argon or nitrogen matrices was found[124]. This very characteristic band was assigned to the SH stretching and indicates that the thiol form dominates. One important conclusion of these studies is that, in general, the absolute intensity of the SH stretching band is about 13 times lower than the absolute intensity of the NH stretching band. This finding could be used to estimate the thione/thiol ratio in the matrix. The SH in-plane bending was observed at 907 cm^{-1}, while the SH torsion appears at 312 cm^{-1}. As is common for all the thiol derivatives of pyridine and diazines, the C−S stretching vibration is very often coupled with ring in-plane motions, while the C−S wagging is usually coupled with ring out-of-plane displacements. For the particular case of 2-pyrimidinethiol two bands, where C−S wagging and ring torsions are coupled, were observed at 777 cm^{-1} and 475 cm^{-1}. For the thione form, the strong band found at 1189 cm^{-1} was assigned to the C=S stretching[124], coupled with a bending vibration of the ring.

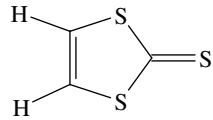
The thione forms of 4(3*H*)-pyrimidinethione and 3(2*H*)-pyridazinethione present the NH stretching bands at 3394 cm^{-1} and 3400 cm^{-1}, respectively[123]. When these frequencies are compared with those of the corresponding oxo analogues, they are found to be lower. The C=S stretching mode contributes to several normal modes for which frequencies are spread from 1200 to 400 cm^{-1}, the most considerable contribution being that to the band found near 440–450 cm^{-1}. The corresponding thiol forms present characteristic low-intensity SH stretching bands at 2604 and 2601 cm^{-1}, respectively[123]. The SH in-plane bending vibrations are observed at 894 and 889 cm^{-1}.

The IR absorption spectra of 2-thiocytosine **(26a)** and 5-fluorothiocytosine **(26b)** in low-temperature inert gas matrices and in thin polycrystalline films were reported by Rostkowska and coworkers[132]. In the isolated molecule in matrix only the spectra of the thiol forms were observed, while in the polycrystalline films the amino-thione forms dominate. The band due to the SH stretching is observed at 2617 cm^{-1} for 2-thiocytosine and at 2619 cm^{-1} for 5-fluorothiocytosine, although in both cases these bands are very weak. The SH bending motions are placed in the 950–890 cm^{-1} spectral region. For the thione forms, it was found from comparison with HF calculated values that the C=S stretching contributes to bands around 1100, 870, 650 and 430 cm^{-1}.

The FT-Raman and FT-IR spectra of mercaptothiadiazoles were reported by Edwards and coworkers[136]. The 2,5-dimercapto-1,3,4-thiadiazole **(31a)** IR spectrum has two fundamentals at 2519 cm^{-1} and 2485 cm^{-1}, which were assigned to the S−H antisymmetric and symmetric stretching modes, respectively. Both bands present a significant broadening, which is believed to be due to the presence of hydrogen bonds involving the SH groups. The C−S stretching modes are observed as antisymmetric and symmetric combinations at

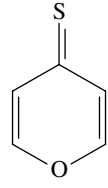
714 and 658 cm^{-1}, respectively. The corresponding 5-amino derivative, 5-amino-1,3,4-thiadiazole-2-thiol **(32b)**, present a very weak band at the typical S−H stretching region (2526 cm^{-1}), which is indicative that only a very small amount of the thiol tautomer is present. This is consistent with the observation of a band at 2923 cm^{-1}, which was assigned to the NH stretching mode. The strong Raman and IR band at 765 cm^{-1} has been assigned to the C−S stretching mode. Similarly, a Raman spectrum of 2,5-methyl-1,3,4-thiadiazole-5-thiol shows an extremely weak band at 2529 cm^{-1} corresponding again to the SH stretching, which indicates the predominance of the thione form. The weak bands in the 600–500 cm^{-1} region of the Raman and IR spectra were assigned to the C−SH stretching mode[136].

A complete analysis of the FT-Raman spectra of 1,3-dithiole-2-thione **(37)** and a series of related compounds were reported by Dyer and collaborators[168]. The bands at 3092 and 3075 cm^{-1} have strong sharp features corresponding to the CH stretch. The absorption at 1512 cm^{-1} was attributed to the C=C stretching. Although this is a rather low value for a typical C=C stretching vibration, the downshift in frequency was interpreted as being due to aromaticity in the ring[168]. The bands at 1077 and 1038 cm^{-1} were associated with the C=S stretching motion and its coupling to S−C−S motions. Depolarization ratio measurements show that the band observed at 512 cm^{-1} is highly polarized. This strongly suggests it to be associated with the ring-breathing motion.



(37)

Somogyi and coworkers[169] have reported a FT-IR gas-phase spectrum of 4*H*-pyran-4-thione **(38)**, which was interpreted using a general valence force field from *ab initio* calculations at the HF/4-21G level. The C=S stretching is assigned to a band at 1168 cm^{-1}, although it seems clear that this mode contributes to different bands in the spectrum, namely ν_5, ν_6 and ν_9. The in-plane C=S bending is observed at quite a low frequency (300 cm^{-1}), while the out-of-plane bending contributes to two b_2 bands found at 685 and 415 cm^{-1}.



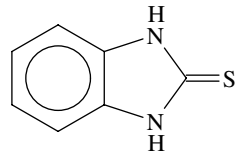
(38)

In a paper by Grupce and collaborators[170], the infrared spectra of protiated and partially deuterated thiosaccharin is reported in the N−H, N=D and C=S stretching regions. Although, as is common for these kinds of compounds, the C=S stretching mixes in more or less proportion with other vibrational modes, at least the three bands observed at 1380, 1220 and 1040 cm^{-1} present significant contributions from the C=S stretch.

The IR spectra of 2- and 4-thiouracils together with their N1- and N3-methylated derivatives (**27–29**) and 2,4-dithiouracil in low-temperature inert matrices were obtained by Rostkowska's group[133] and the strongest and most characteristic bands related to C=O, C=S and C=C stretching modes discussed. For 2- and 4-thiouracil the C=O stretch appears at 1732 and 1752 cm^{-1}, respectively. Methylation at N1 does not change the frequency of the C=O stretch for 2-thiouracil strongly. However, the C=O stretching modes of the methylated derivatives of 4-thiouracil are red-shifted with respect to the unsubstituted parent compound. It was also found that the C=C stretch, around 1650 cm^{-1}, is very sensitive to sulfur substitution. For 2-thiouracil and all its derivatives the absorption in this region is weak, while for 4-thiouracil and all its derivatives it is as strong as the C=O stretch. This is explained[133] in terms of the couplings between different modes. In 2-thiouracil the C=C stretch is coupled (out-of-phase) with the C=O stretch. However, when the S atom is substituted at the C4 position, as in 4-thiouracil, the C=C no longer couples with the C=S stretch.

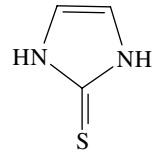
There are also significant differences between 2- and 4-thiouracil in the 1500–1600 cm^{-1} spectral region, where the former presents relatively strong absorptions while for the latter only very weak bands are found. For all the thiouracils investigated the C=S stretch is located in the region 1100–1150 cm^{-1}, except for the S-methylated derivatives. Strong absorptions which were assigned to out-of-plane displacements of the C=O groups were observed in the 750–800 cm^{-1}.

Bigotto[171] reported the IR and Raman spectrum of benzimidazol-2-thione (**39**), in the polycrystalline state and in the region from 4000 to 180 cm^{-1}. The strong band observed at 3150 cm^{-1} was assigned to the NH stretching mode, while the C−H stretching modes are observed at 3050–3070 cm^{-1}. The skeletal displacements appear grouped as A_1 and B_2 fundamentals. The former are observed at 1624, 1501, 1462, 1279, 1234, 1199, 1020, 971, 819, 603 and 419 cm^{-1}, while the latter are found at 1579, 1375, 1258, 1213, 614, 481 and 264–253 cm^{-1}. The A_1 band at 419 cm^{-1} is found to have a strong C=S stretching character. The bands at 970, 919, 850 and 741 cm^{-1} were assigned to the C−H out-of-plane bending fundamentals, while the out-of-plane N−H binding is observed at 705 cm^{-1}.



(39)

The Raman and IR spectra of imidazoline-2-thione (**40**) were reported by Sathyanarayana and coworkers[172]. As for other thiocarbonyl derivatives the C=S stretching is coupled to other vibrational modes. In general, when, as in this case, the C=S group is attached to a strongly conjugated nitrogen atom, a large contribution is found for a band near 500 cm^{-1}, due to extensive coupling of the vibrations and the contribution of the $S^--C=N^+$ mesomeric form. Thus for imidazoline-2-thione, similarly to imidazolidine-2-thione[173] and thiazoline-2-thione[174], the C=S stretching contributes to a medium intensity band at 520 cm^{-1} and to another medium intensity band at 910 cm^{-1}. The C=S bending mode was assigned to a band at 340 cm^{-1}, while the C=S out-of-plane bending was attributed to a weak band at 250 cm^{-1}.



(40)

Shurvell[175] and collaborators have published the Raman and IR spectra of tetramethylcyclobutane-1-one-3-thione and the fully deuterated derivative. For this compound, the C=O stretching was observed as a very strong Fermi doublet at 1811–1782 cm^{-1}. For the deuterated species this doublet is red-shifted and was found at 1808–1775 cm^{-1}. The C=S stretching mode was assigned to a band of medium intensity at 1303 cm^{-1} and 1302 cm^{-1} in the IR and Raman spectra, respectively, and the same for the deuterated species are found at 1306 cm^{-1} and 1309 cm^{-1}, respectively.

Ethylene dithione. This interesting molecule has been generated by means of Neutralization–Reionization Mass Spectrometry (NRMS)[176] by Sülzle and Schwarz by flash pyrolysis, with subsequent isolation of the products in an argon matrix by the groups of Maier[177] and of Wentrup[178] as well as by Tesla coil discharges in Ar/CS_2 mixtures (including various isotopomers of CS_2) by Andrews and coworkers[179]. Although it had initially been suggested that in the ground state C_2S_2 is a singlet[177], there seems to be increasing evidence that it is a triplet. The latter works[177–179] provide IR data for this compound. The $D_{\infty h}$ symmetry of this molecule leaves one of three stretching vibrations (out-of-phase CS stretching) and one of the two degenerate bending vibrations as IR-active. They have been reported at 1179.7 and 1904 cm^{-1}[177]. Further details on the structure and properties of this compound as well as on cognate cumulene-dithiones have been given by Sülzle[180]. Various papers[176–179] report *ab initio* calculations on the stability, structure and vibrational spectrum of C_2S_2. They were extremely valuable for the purpose of establishing the structure and confirming the formation of this molecule.

1,2,3,4- pentatetraene-1,5-dithione (C_5S_2). This compound was obtained by Maier and coworkers[181] by photolysis or flash pyrolysis of appropriate precursors. These authors succeeded in obtaining the IR spectrum of the argon matrix-isolated material. They detected the absorptions at 2105.0, 1687.9 and 783.5 cm^{-1}, which were attributed, on the basis of PM3 calculations, to the three IR-active stretching modes υ_4 to υ_6 (assuming $D_{\infty h}$ symmetry).

Thioacetaldehyde. Maier and coworkers obtained this compound by flash pyrolysis of allyl ethyl sulfide in an argon matrix[182]. Its IR spectrum does not show a characteristic C=S stretching band. A comparison of the observed spectrum with the calculated one [the MP2/6-31G(d) level] allowed the identification of the molecule and further showed the extensive coupling between the normal C=S stretching mode and other normal modes.

5. Electron paramagnetic resonance spectroscopy (EPR)

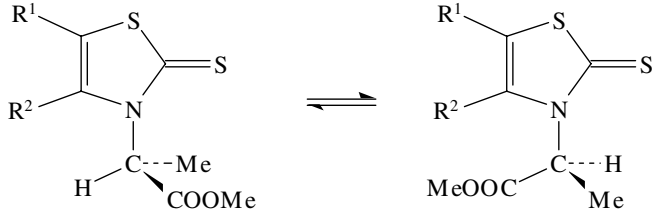
Davies and Neville[183] have reported the first EPR spectra of several radical anions of simple aliphatic thioaldehydes and thioketones in fluid solutions. They were generated (in the absence of *tert*-butyl peroxide) by photolyzing solutions of the appropriate potassium thiolates in *tert*-butyl alcohol. Coupling constants, a[n(α-H)] and a[n(β-H)], and g values were reported for $RHC{=}S^{-\bullet}$ species (R = Me, Et, C_7H_{15} and C_6H_5) as well as for $(CH_3)_2C{=}S^{-\bullet}$. These experiments suggest a significant spin delocalization from carbon onto sulfur, the effect of this on the a(C-α) coupling constant being offset by some degree

of pyramidalization at the carbon center. The authors further showed the great similarity existing between these EPR spectra and those for the homologous carbonyl radical anions. They also determined the spectrum of cyclohexanethione radical anion and analyzed it in connection with the time scale of the ring inversion. Placucci and coworkers[184] have reported the EPR spectrum of the thioaldehyde radical anion $H_2C{=}CHCH{=}S^{-\bullet}$[184] obtained under conditions similar to those used by Davies and Neville[183], that is, the photolysis of the allyl thiolate, *but* in the presence of *tert*-butyl peroxide. This allowed these workers to obtain the spectra of both *E* and *Z* rotational isomers of this species. The origin of this isomerism can be traced back to the restricted rotation around the C−CS bond. Neville and Davies could only detect one of the rotamers under their working conditions. Placucci and colleagues had already reported the EPR spectrum of the radical anion of thiobenzaldehyde, $C_6H_5CHS^{-\bullet}$ **(41)**, and 2,4,6-tri-*tert*-butylthiobenzaldehyde and deuterated derivatives[185]. This important study showed, *inter alia*, that: (i) Similarly to those of the radical anion of benzaldehyde, $C_6H_5CHO^{-\bullet}$ **(42)**, the $a[(\alpha-H)]$ values of **41** indicate that these corresponding to the pair of *ortho* hydrogens (positions 2 and 6) as well as to the pair of *meta* hydrogens (positions 3 and 5) are not equivalent. This suggested that the radical adopts a planar (or quasi-planar) conformation with a substantial barrier to the Ar−CHS rotation. (ii) A comparison of the data for **41** and **42** shows that the a_H values corresponding to the aromatic hydrogens in **41** are smaller than those of **42,** in agreement with the observation that the C=S moiety is less able than the C=O one to delocalize the unpaired electron into the aromatic ring.

Alberti and coworkers have reported the EPR spectra of several adducts of group VI radicals with thioketones[186].

6. ^1H and ^{13}C NMR spectra

These spectra were routinely obtained for most of the compounds discussed in forthcoming sections. Specific studies were performed on selected compounds such as: (i) (+)-(*S*)-4,5,6,7-tetrahydroimidazo-9-chloro-5-methyl-6-(3-methyl-but-2-enyl)imidazo [4,5,1-*jk*] [1,4] benzodiazepin-2(1*H*)-thione (9-chloro-TIBO)[187] and (ii) series of metal chelates derived from 1,2-dithiol-3-thion-4,5-dithiolate (dmt)[188]. The equilibria between 2-ethoxycarbonylthiolane-3-thiones and their (*Z*)-enethiol tautomers were also studied by these techniques[189]. It was found that the equilibrium is largely shifted in favor of the enethiols. ^1H NMR was also used to study the *syn*–*anti* conformational equilibria of seven *N*-(1-methoxycarbonylethyl)-Δ^4-thiazoline-2-thiones with *S* conformation of the chiral rotor **(43)**[190]. A variety of substituents were used.



(43)

To our knowledge, very few systematic studies of the NMR spectra of thiocarbonyl compounds have been carried out that allow a good comparison with the homologous

carbonyl derivatives. An important study was carried out by Barbarella, Bongini and coworkers[191,192]. They determined the ^{13}C chemical shifts, $\delta(^{13}C)$, of the C=X carbon in series of compounds $[(CH_3)_3C]_2C{=}X$ (X = NH, O, S, Se)[191]. The values (in ppm relative to TMS) are, respectively, 193.5, 218.0, 278.0 and 292.5. These results agree with the fact that the C atom in C=S is deshielded by several tens of ppm with respect to that in the homologous carbonyls[193,194]. These authors further examined the problem using Pople's expression for the local paramagnetic term σ_p, considered to be the dominant contributor to $\delta(^{13}C)$[195]. This treatment links this magnitude to ΔE, the mean electronic excitation energy, that in this particular case is essentially determined by the energy of the $n \rightarrow \pi^*$ transition. It was further calculated that this term is preponderant. ΔE is then linked to λ_{max} for the longest-wavelength absorption maximum in the UV-vis region. The experimental values for the same compounds (in nm) are as follows: 195, 298, 540 and 706. There is an excellent correlation between $\delta(^{13}C)$ and λ_{max} for these compounds[193]. This led the authors to conclude that *for this family, the chemical shift variation is dominated by the energy factor*. De Marco and Doddrell[194] examined the effect of replacing a *t*-Bu by a $(CH_3)_3Si$ group for both ketones and thioketones. This allowed one to quantify the influence of the electronegativity of the substituent and to confirm the existence of linear relationships between the $\delta(^{13}C)$ values for carbonyl and thiocarbonyl compounds (see References 1 and 196). Sliwka and Liaanen-Jensen have synthesized and examined the spectroscopic properties of a set of carotenoid thiones[197]. They determined $\delta(^{13}C)$ for the C=S groups of these molecules and their carbonyl homologues and found again adherence to a linear relationship.

B. Low-lying and Excited States

1. UV-visible spectroscopy

Over the last few years, several excellent reviews have been published on this subject. That of Clouthier and Moule[100] is a comprehensive study of the information available on the optical spectroscopy of small carbonyls, thiocarbonyls and selenocarbonyls. Electronic transitions, their vibronic structures and the geometrical structures of various excited states were treated in detail. The case of thiones in solution was discussed by Steer and Ramamurthy[11]. Two major reviews were also published later on the photoreactivity[14] and photophysics and photochemistry[12] of thiocarbonyls. These topics are obviously related to the relative energies of the ground and excited states of these compounds. Schaumann[1] provides a coverage of earlier work.

Both experimental and theoretical studies[14,39] reveal that the sulfur p-type orbitals (n_s) and the $\pi_{C=S}$ orbitals are higher in energy when compared to those of the corresponding carbonyl compounds, whereas the $\pi^*_{C=S}$ orbital is lower in energy than that of the corresponding carbonyl group.

It is known[1] that the long-wavelength band in the visible region (400–700 nm) can be attributed to a dipole forbidden $n \rightarrow \pi^*$ transition. This band is appreciably red-shifted with respect to the same transition in carbonyls. As indicated elsewhere[14], owing to the strong overlap between the $^1n \rightarrow \pi^*$ and $^3n \rightarrow \pi^*$ transitions, it is often difficult to differentiate these transitions in thiocarbonyl compounds. High-intensity absorption bands at short wavelengths (UV) are observed that are attributed to the allowed $\pi \rightarrow \pi^*$ transition ($S_0 \rightarrow S_2$). In the case of thioketones, this transition generally occurs in the near-UV (see Table 14). The electron promotion is largely localized on the C=S moiety. These transitions are broad and exhibit poorly resolved vibrational structure, even

in inert perfluoroalkane solutions or in low-temperature matrices[11]. Rydberg transitions, much higher in energy ($190 < \lambda < 230$ nm), can also be observed, particularly for aliphatic thiones. In the case of thiocarotenes[197] the $\pi \rightarrow \pi^*$ transition is substantially red-shifted, because of extensive electronic delocalization, and overlaps the $n \rightarrow \pi^*$ transition in the visible region of the spectrum. In the case of the 2-amino and 2-methylaminothiotropones[107] this transition seems to be very weak or absent, a feature likely related to their tautomerism.

It is important that, while for large thiones the equilibrium C=S bond lengths in the S_1 and T_1 states are similar to those in S_0, the situation may be quite different for S_2. Thus, even for stable aromatic thiones, the S_2–S_0 absorption profiles suggest that the excited-state geometries are considerably distorted relative to their ground states. In particular, the C−S stretching frequency drops markedly in the excited state, the C−S bond being elongated by up to 0.5 Å in some cases.

Becker and coworkers have published[198] a very thorough study of the photophysics and photochemistry of coumarins, chromones and their thione homologues.

We present in Table XV some experimental data published over the last few years. Data on thioketones can be found elsewhere[191,192].

From a computational standpoint, the study of excited states is much more involved than that of ground states. Clouthier and Moule[100] report several high-level calculations.

TABLE 15. Wavelengths (λ_{max}) and ($\log \varepsilon$) for electronic transitions of selected thiocarbonyl and carbonyl compounds

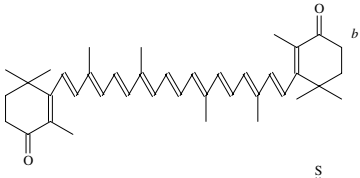
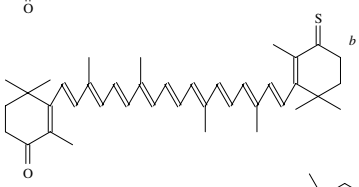
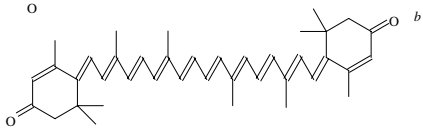
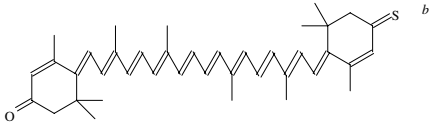
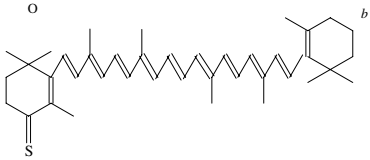
Compound	λ_{max} (nm) and ($\log \varepsilon$)
$(t\text{-}C_4H_9)_2$ CO[a]	298 ($n \rightarrow \pi^*$)
$t\text{-}C_4H_9(CO)Si(CH_3)_3$[a]	367 ($n \rightarrow \pi^*$)
$(t\text{-}C_4H_9)_2CS$[a]	540 ($n \rightarrow \pi^*$)
$t\text{-}C_4H_9(CS)Si(CH_3)_3$[a]	606 ($n \rightarrow \pi^*$)
 [b]	476 ($n \rightarrow \pi^*$)
 [b]	496 ($n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$)
 [b]	495
 [b]	527 ($n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$)

TABLE 15. (*continued*)

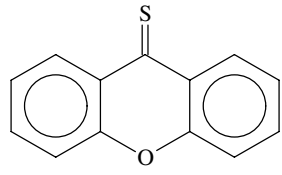
Compound	λ_{max} (nm) and (log ε)			
 [b]	467			
 [b]	490 ($n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$)			
Tropothione[c]	224 (3.89)	253 (3.97)	371 (4.18)	610 (1.67)
2-Methyl tropothione[c]	227 (3.99)	255 (4.10)	376 (4.18)	628 (1.62)
2-Phenyl tropothione[c]	226 (4.44)	252 (4.32)	378 (4.01)	612 (1.65)
2-Amino tropothione[c]	239 (3.82)	281 (4.30)	442 (4.07)	
2-N-methylamino tropothione[c]	241 (3.92)	286 (4.41)	454 (4.12)	
2-Hydroxytropothione[c]	236 (4.05)	267 (4.23)	416 (4.12)	
2-Methoxytropothione[c]	246 (4.02) 268 (4.16)		396 (4.19) 544 (2.07)	620 (1.72)
2-Thiomethyltropothione[c]	225 (4.16) 304 (4.45)		424 (4.09) 564 (2.03)	604 (1.59)
C_2S_2	<230[d]	360–395[e]		
C_5S_2[f]			305	582
C_5O_2[g]	231 (5.38)	4.35 (2.18)		

[a] From Reference 191.
[b] In CH_2Cl_2, values from Reference 197.
[c] In hexane, from Reference 107.
[d] Ar matrix at 12 K, from Reference 177.
[e] Ar matrix, from Reference 179.
[f] In MeCN, from Reference 177.
[g] In *c*-C_6H_{12}, from Reference 201.

The S_1 energy surface is essentially built up from the $^1(n_0, \pi^*)$ state. Very recently, multireference configuration interaction studies were performed on the singlet[199] and triplet[200] states of **5**. The first study indicates that the S_2 surface is composed of (π, π^*), (σ, π^*), (n, 4s), and (n^0, π^{*2}). The former three states have very similar equilibrium energies and are separated by low barriers. The diabatic $^1(\pi, \pi^*)$ state was shown to be planar, whereas $^1(\sigma, \pi^*)$ and $^1(n^0, \pi^{*2})$ are nonplanar. The $^1(\sigma, \pi^*)$ state is considered to be the photoreactive state in S_2 since it lies slightly lower in energy than (π, π^*), can be easily populated by internal conversion and has a low oscillator strength with the ground state. The latter study indicates that the $^3(\sigma, \pi^*)$ state is found in the same energy region as S_2. This is potentially relevant for the understanding of the photochemistry associated with the S_2 state.

Janoschek has studied by *ab initio* techniques the UV spectra of various carbon suboxides and subsulfides[201,202].

Steer and coworkers[203] have performed electrochromism studies on pyranthione (4*H*-pyran-4-thione) **(38)** and xanthione **(44)**. They found that the magnitude of the change in the dipole moment upon excitation, $\Delta\boldsymbol{\mu} = |\boldsymbol{\mu}(S_2) - \boldsymbol{\mu}(S_0)|$ is close to 2 D. The transition dipole moment for the $S_0 \rightarrow S_2$ transition is parallel to the direction of the ground state dipole moment, i.e. along the C_2 axes which contains the C=S bond.



(44)

2. Photoelectron spectroscopy (PES)

This is the choice technique for probing the ground and low-lying electronic levels of molecules. The PES of sulfur-containing compounds was reviewed in 1991[18].

Some uses of this technique, in combination with mass spectroscopy, have been discussed earlier.

The combination of FVT with PES has allowed the study of several, highly reactive species. Thus, Pfister-Guillouzo and colleagues[89] have succeeded in obtaining the various ionization potentials (IP) and assigning the various electronic levels of thioformyl cyanide. Their results (IP in eV and MOs) are as follows: 10.1 (n_s), 11.8 ($\pi_{CS} - \pi_{CN}$), 12.8 (π'_{CN}), 13.7 ($\sigma_{CN} - \sigma_{CS}$), 14.1 ($\pi_{CS} + \pi_{CN}$) and 15.2 ($\sigma_{CN} + \sigma_{CS} + n_N$). They mean *inter alia* that there is a sizable transfer of electron density from the CS to the CN groups, as indicated by the 0.8 eV lowering of the n_s orbital with respect to that of **5**. Also, the $\pi_{CS} + \pi_{CN}$ orbital is stabilized with respect to the π_{CS} and π_{CN} orbitals of **5** and HCN, while the out-of-phase combinations are barely affected. This situation can be compared to that prevailing in thioxoethanal, H−C(=S)C(=O)−H (**45**), also studied by the same group[204]. *This unique system allows one to examine directly the electronic interaction between a carbonyl and a thiocarbonyl group*. The effect is appreciably smaller: the n_s orbital is stabilized by some 0.34 eV with respect to **5** while the n_o orbital (of the C=O group) is practically unaffected (relative to **6**). The π_{cs} orbital was slightly stabilized (0.21 eV) relative to **5** while the π_{co} orbital was moderately destabilized (0.4 eV) relative to **6**. According to the authors, this is evidence of the opposing roles of field and resonance effects. Other species have also been examined by this combination of techniques[205,206].

III. SYNTHESES

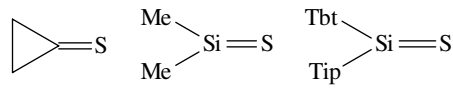
Sulfur plays a pivotal role in many transformations (chiral sulfoxide auxiliary, powerful electron-withdrawing sulfone substituent) and it is a very effective metal radical scavenger in the form of thiocarbonyl group. The radical chemistry associated with the thiocarbonyl group will not be discussed in this chapter but it has been reviewed recently[207−213].

At the same time, thiocarbonyl-derived heterocycles are conveniently employed as key intermediates for the preparation of a plethora of both synthetic and natural products ranging from macrocyclic lactones to the powerful HIV-inhibitor TIBO[214]. Heterocyclic thiones are not included in this chapter. The interested reader is referred to a number of recent reviews[215−222], while this chapter will focus on the synthesis and reactivity of thioaldehydes, thioketones, thioketenes and thioquinones. The material will be organized according to Schaumann's review[1] although a few new sections have been included. Only the major advances achieved since Schaumann's publication shall be examined. The syntheses of thioaldehydes and thioketones have been the subject of recent reviews[223−225], which include their use in C−C bond-forming reactions[226]. Following Schaumann[1] this section is organized according to the type of bond being formed and the reagent used. However, some new subsections (sulfines, reactions with organometallics, ene reactions) are arranged according to individual subjects.

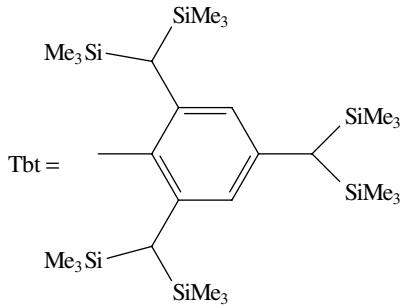
As discussed in Section II, thiocarbonyl compounds differ from their carbonyl counterparts in at least two important characteristics. Because of the higher energy of the sulfur p orbitals, they are much more reactive as electron donors. On the other hand, the C=S bond is also much less polarized than the C=O bond, due to the smaller difference in electronegativities between carbon and sulfur. The latter fact leads to the reactions of the thiocarbonyl group being less selective than those of the carbonyl group. This happens, for instance, in the case of nucleophilic additions (see Section IV.C), and an enhanced reactivity against dipoles has also been observed (see Section IV.E.3).

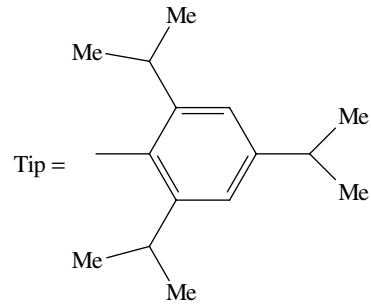
In general, simple thioaldehydes such as thioacetaldehyde and thiobenzaldehyde are extremely reactive and immediately oligomerize. This considerably restricts their potential use in organic synthesis. However, thioaldehydes can be stabilized in several ways: by bulky substituents (Bu^t, Me_3Si,...), π-donor groups at the thiocarbonyl carbon (heterocyclic rings) or by coordination to a transition metal. The latter strategy has experienced a steady growth in recent years and we have added a new section on this particular subject (see Section III.K). In spite of their intrinsic instability, thioaldehydes can be prepared by many methods and used as transient intermediates, provided that the requisite reagent is present and compatible during the preparation. To achieve this purpose one of the most useful techniques has been Flash Vacuum Thermolysis (FVT)[20].

Thioketones are more stable than thioaldehydes and Campaigne has given a personal account on the early development of their chemistry[7]. Although there are many methods to prepare thioketones, the simplest cyclic thione, cyclopropanethione **(45)**, still remains unknown and it has been the subject of theoretical calculations[91,227], Interestingly, the silicon analog dimethylsilathione **(46)** has been formed by thermolysis of silylthioketenes and characterized by analysis of the reaction products[228]. Very recently, kinetic stabilization with bulky substituents has allowed the isolation of pure silanethione **(47)** for the first time[229].



(45) **(46)** **(47)**

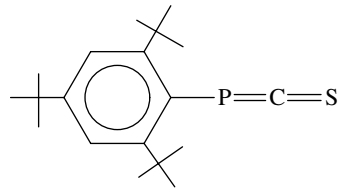




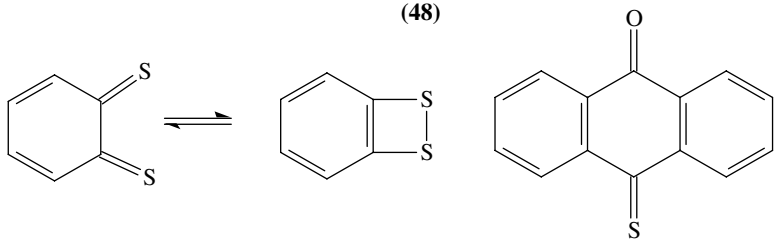
As for thioaldehydes, the stability of thioketenes is largely influenced by the nature of the substituents and bulky groups tend to stabilize this functional group. Electronic factors such as those originating in silicon, phosphorus or trifluoromethyl substituents lead to a similar result. In general, however, the synthesis of monomeric thioketenes is difficult and requires the use of special techniques such as FVT, matrix isolation at low temperatures or generation under conditions which allow trapping *in situ* of the transient species. The

chemistry of thioketenes has been reviewed by Schaumann[230]. Based on the isolation of its dimerization product[231], the phosphorus analog, phosphathioketene **(48)**, has been claimed to be a reactive intermediate.

In spite of many synthetic efforts, thioquinones **49** still remain very elusive and only the anthraquinone member **51** has been isolated as a stable compound[232]. In this case, the reason for this is the higher stability of the cyclic forms, benzothietes, **50** (see Section II).



(48)

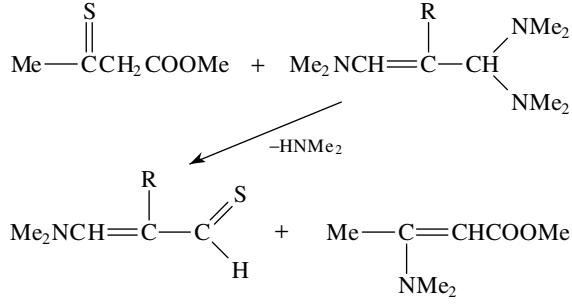


(49) **(50)** **(51)**

During the preparation of this manuscript two new reviews on thioaldehydes and thioketones[233] and on thioketenes[234] have appeared.

A. Formation of the α-Carbon–Thiocarbonyl Bond

Conjugated ω-dimethylamino thioaldehydes have been formed in the reaction of aminals with thioacetoacetates (equation 15)[235].

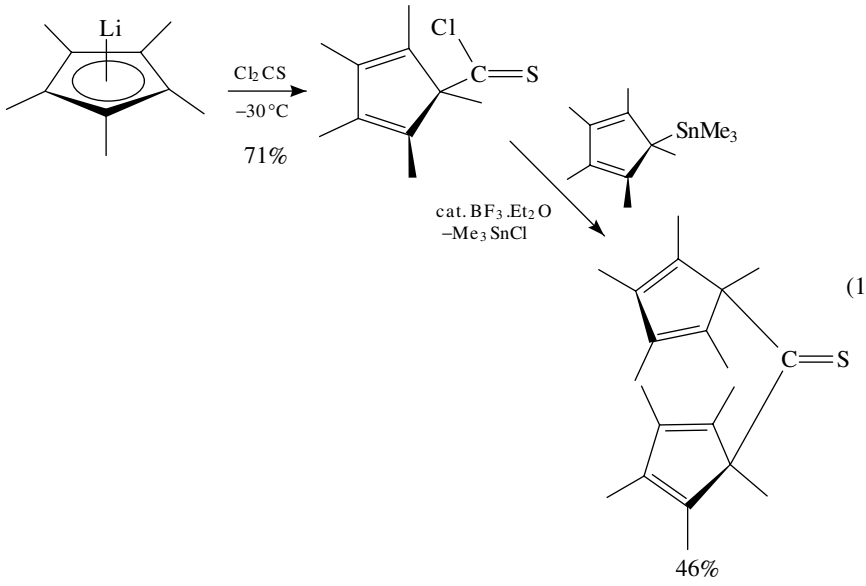


(15)

R = H, Me

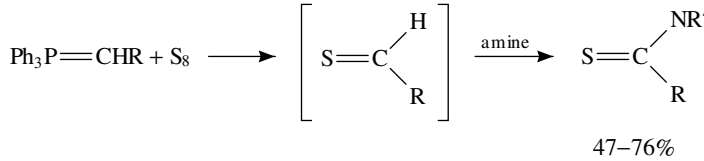
Pentamethylcyclopentadienyllithium by treatment with thiophosgene affords a carbothioyl chloride which, in the presence of boron trifluoride-etherate, reacts with a stannane

yielding a thioketone[236], which is very prone to undergo intramolecular [4+2] cycloadditions even at room temperature (equation 16).



(16)

The reaction of phosphorus ylides with elemental sulfur gave thioaldehydes, which were trapped *in situ* by treatment with secondary amines to afford the corresponding thioamides (equation 17)[237].

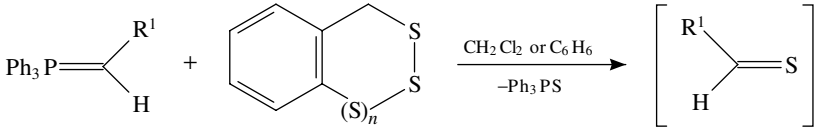


(17)

R = CO_2Me, CO_2Et

Amine: morpholine, dimethylamine, piperidine, pyrrolidine.

The transient thioaldehydes can also be trapped with dienes giving the corresponding Diels-Alder adducts in good yields. These reactions are carried out in toluene under reflux. Milder conditions (reflux in dichloromethane or benzene) have been reported by Sato and Satoh for a similar transformation which involves cyclic polysulfides instead of elemental sulfur[238] (equation 18). The aldehydes obtained were trapped in Diels-Alder reactions.

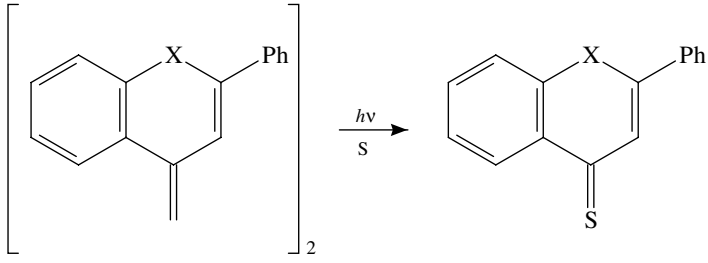


(18)

n = 2, 3

B. Addition of Sulfur to Carbenes

The ethylene linkage in dithioflavylene can be cleaved either by sulfur under drastic conditions (280 °C) or photolytically (under reflux in toluene) giving higher yields[239] (equation 19).



(19)

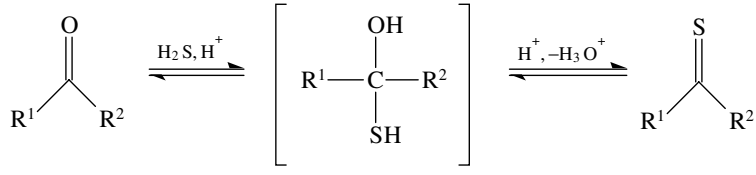
X=O, S 63–68%

C. Thionation of Carbonyl Derivatives

1. Carbonyl compounds

Thionation of carbonyl groups is the most frequently used route for the obtention of thiocarbonyl compounds and many methods are known to achieve this transformation[223]. Brillon[240] has reviewed the different reagents employed in the O/S exchange, which traditionally has been accomplished by using inorganic sulfides, but in recent years Lawesson reagent[241,242] has become the method of choice.

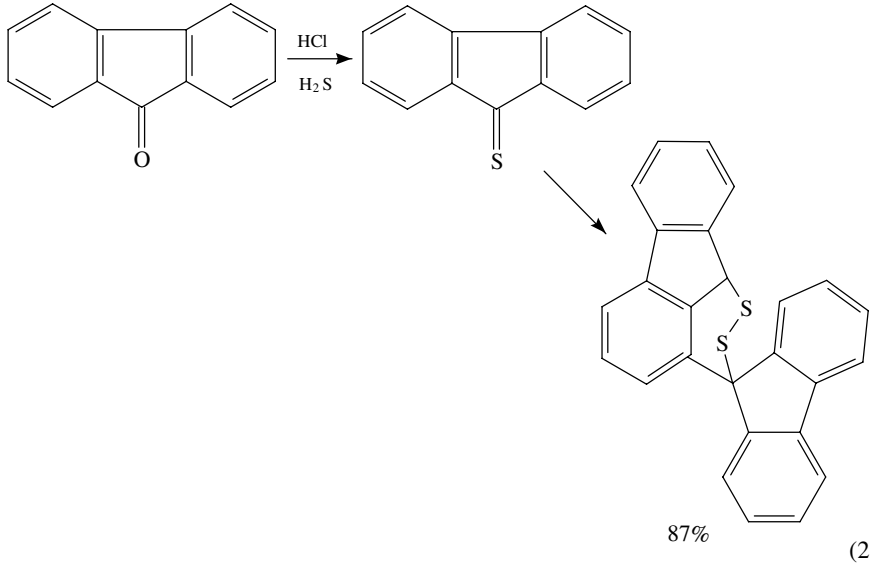
a. Hydrogen sulfide (H_2S). The use of hydrogen sulfide in the presence of an acid catalyst, usually hydrogen chloride, is a classical method for the preparation of thiocarbonyl compounds. The reaction proceeds by reversible protonation of the carbonyl group, which facilitates substitution at carbon by H_2S to give a mercapto hydroxy hemiacetal which eliminates to afford the thiocarbonyl group (equation 20).



(20)

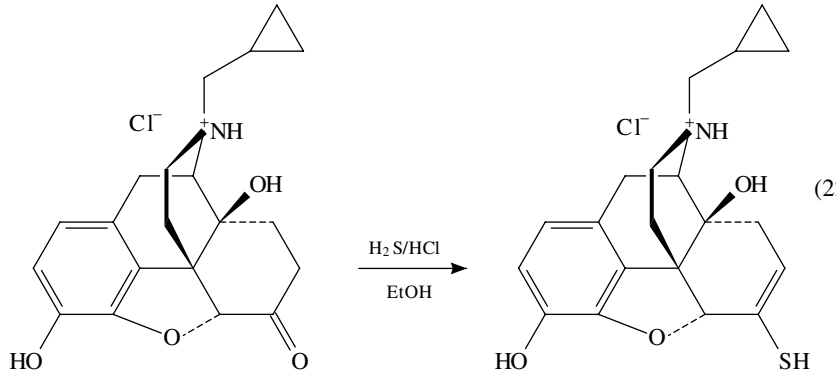
This exchange process is acid-catalyzed in both steps and special care must be taken to avoid polymerization of the final products. This is usually effected by working at low temperatures, when good yields and clean products are obtained.

This method has been applied to the preparation of enaminothioketones[243] although sometimes the yields are very low (30%)[244]. The dimerization product is obtained in the reaction of fluorenone with H_2S/HCl[245], and the pyrolysis of the dimer leads to the hydrocarbon rubicene (equation 21). However, almost quantitative yields of monomeric thiofluorenone can be obtained by performing the reaction at lower temperatures and with higher concentrations of H_2S/HCl[246].



(21)

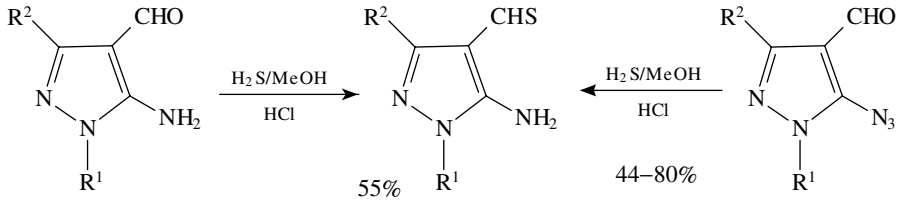
Naltrexone is an opioid antagonist which has been thionated with the system H_2S/HCl at $-78\,^{\circ}C$ to give the crude enethiol (equation 22)[247] which is further oxidized to the corresponding disulfide.



(22)

Although this combination of reagents has not been applied to the preparation of normal aldehydes due to the high instability of these compounds, it has proven very useful in the obtention of some heterocyclic thioaldehydes, especially those belonging to the pyrazole and indole series[248] (equation 23). The authors claim that yields are higher than using Lawesson reagent and, if present, concomitant reduction of the azido group takes place.

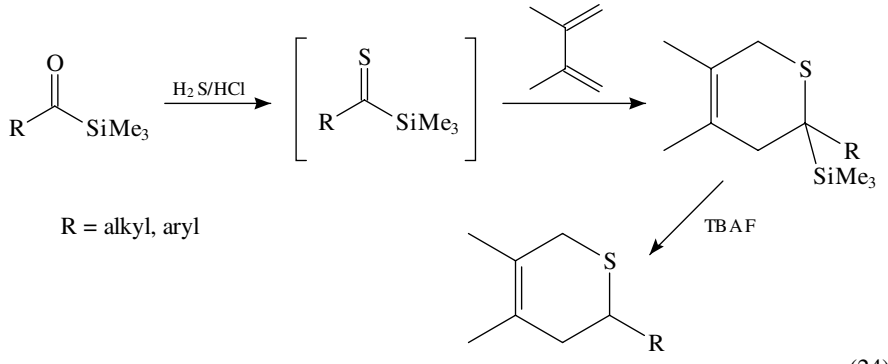
The problem of the synthesis of thioaldehydes has been partly circumvented in recent years by using silyl thioketones as their synthetic equivalents. This clever methodology was introduced by Italian chemists and they have successfully exploited many different applications of these compounds, which have been reviewed by Bonini[249]. In this



R^1, R^2 = Me, Ph, *t*-Bu

(23)

approach, acylsilanes are converted into silyl thioketones by using H_2S/HCl. The thiones, with different stabilities, were trapped *in situ* with 1,3-dienes affording the corresponding Diels-Alder cycloadducts, which then can be desilylated with tetrabutylammonium fluoride (TBAF) to give the thioaldehyde adduct (equation 24), thus proving the synthetic equivalence of silicon with an achiral or even 'chiral' proton[250].



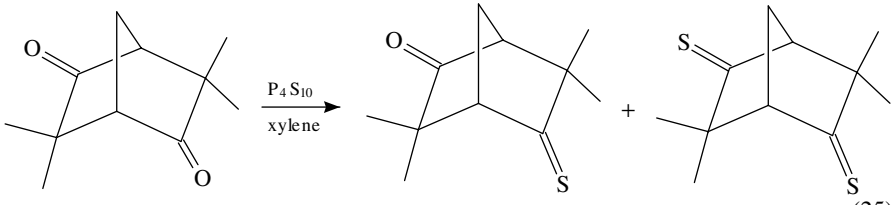
(24)

In an extension of this method, *ω*-haloacylsilanes were transformed by H_2S/HCl into the corresponding silyl thiones, which underwent enethiolization on base treatment and subsequent intramolecular cyclization to afford a range of cyclic sulfides[251].

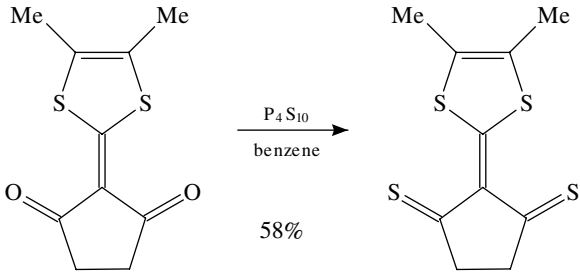
b. Phosphorus decasulfide (P_4S_{10}). This compound, also known as phosphorus pentasulfide P_2S_5, is the phosphorus-based inorganic reagent most frequently employed and its use for the sulfurization of carbonyl groups has spanned over a century. The major problem associated with P_4S_{10} is its poor solubility in organic solvents at 25 °C. Therefore, thionation reactions with P_4S_{10} are generally performed at high temperature in HMPT, pyridine or *o*-dichlorobenzene. Taking into account the mechanism proposed for this reagent[252], several *in situ* derivatives obtained by combination of P_4S_{10} with sodium bicarbonate or sodium carbonate have been introduced[240].

In recent years, P_4S_{10} has been successfully applied to the synthesis of bridged thioketones (adamantanethione, thiofenchone and thiocamphor)[253] and other bicyclic thiones[254] (equation 25).

The synthesis of organic metals containing either a tetrathiafulvalene (TTF) system[255] or a trimethylenemethane (TMM) system[256] (equation 26) has been accomplished by thionation with P_4S_{10}.

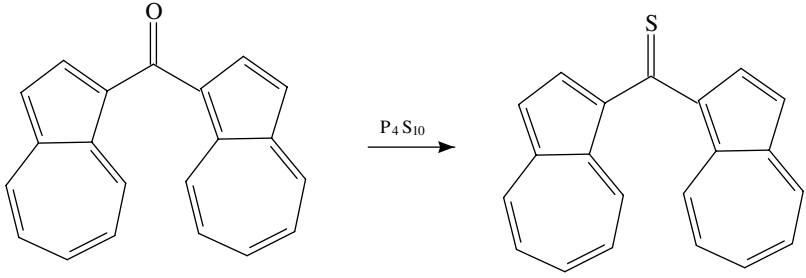


(25)

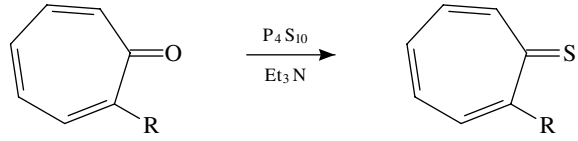


(26)

P_4S_{10} has also been utilized in the preparation of 1*H*-pyridine-4-thiones, useful in the synthesis of modified cephalosporins[257]. However, attempted thionation of diacylketene thioacetals with P_4S_{10}–Et_3N in acetonitrile at low temperature afforded the primary dealkylation product and not the thionated one[258]. Azulenyl thioketones (equation 27a)[259] as well as tropothione derivatives[260,261] bearing an electron-donating group at the C-2 position (equation 27b) (see also Section II) have also been obtained by thionation with P_4S_{10}. In the latter syntheses, the use of 'polar' solvents (dichloromethane, acetonitrile) was crucial for the success of the reaction. These substituted tropothiones are thermally stable and do not dimerize in the solid state at room temperature.



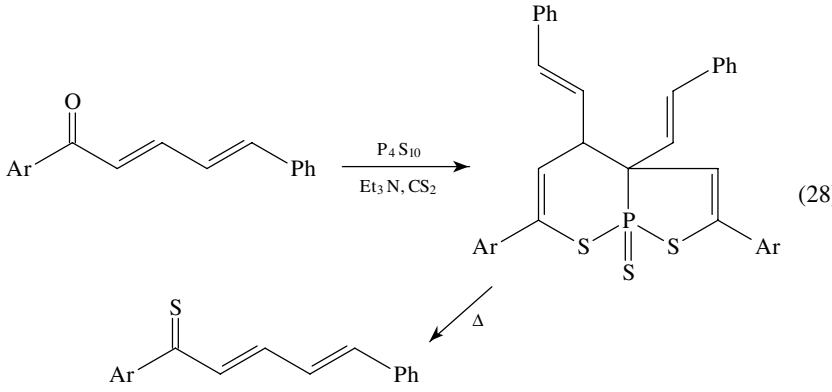
(27a)



(27b)

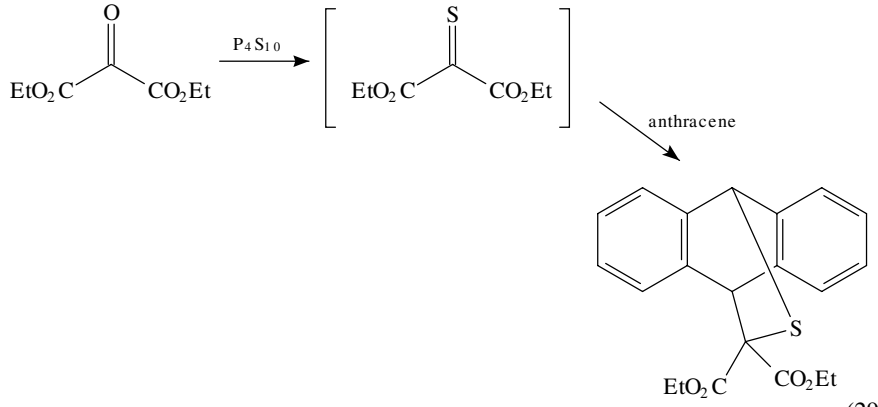
R = H, Me, Ph, NH_2, NHMe, OH, OMe, SMe

Treatment of dienyl aryl ketones with P_4S_{10} affords phosphorus-containing heterocycles which generate dienyl aryl thioketones upon heating[262] (equation 28).



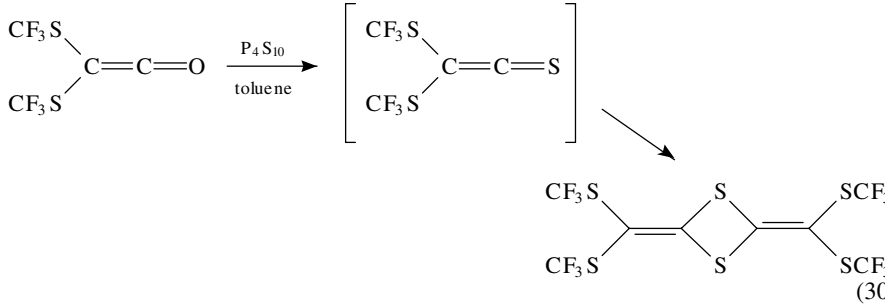
(28)

In a related approach, α,β-unsaturated thioketones, formed *in situ* by thionation with P_4S_{10} of the corresponding ketones, undergo intramolecular hetero-Diels-Alder reactions[263]. Diethyl thioxomalonate was formed from diethyl oxomalonate and phosphorus pentasulfide (equation 29) and was trapped as a Diels-Alder adduct[264].



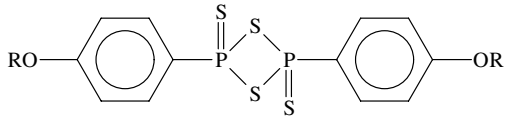
(29)

Attempts to prepare a halogenated thioketene by refluxing a number of different precursors with P_4S_{10} in toluene yielded only the cyclic dimer and the corresponding 1,3,4-trithiolan (equation 30)[265].

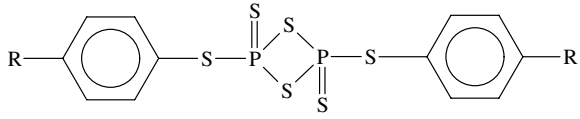


(30)

c. Phosphetane compounds: Lawesson reagent. Lawesson reagent **52**[241,242], very efficient, versatile and soluble in benzene, toluene and xylene, has replaced most of the classical reagents discussed above. Other useful media are THF, HMPT, DME or *o*-dichlorobenzene. The mechanism of thionation with Lawesson reagent has been studied[266] and different analogs such as Belleau's reagent[267] **(53)** or Yokoyama's reagents[268] (**54**, **55**) with increased solubility in these solvents have been prepared.

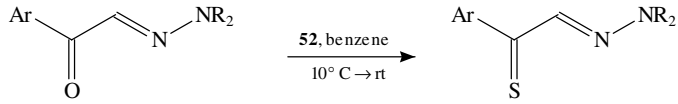


(52) R = CH_3
(53) R = Ph



(54) R = H
(55) R = OCH_3

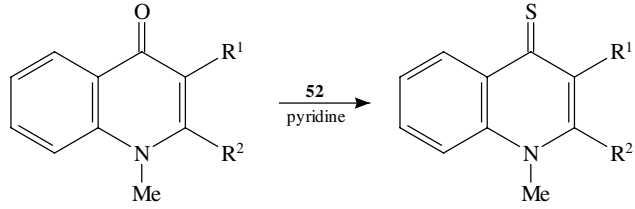
Lawesson reagent is the most widely used for thionation reactions and has been applied to a wide variety of syntheses[240] such as those of camphorthione[269], enaminothiones[270], thiochromone[271] and different diaryl and aryl alkyl thiones[272]. In addition, hydrazonothioacetophenones have been prepared from the corresponding carbonyl compounds under controlled conditions[273]. The heterodienes thus obtained underwent [4 + 2] cycloadditions (see Section IV.E.4) affording different heterocyclic systems (equation 31).



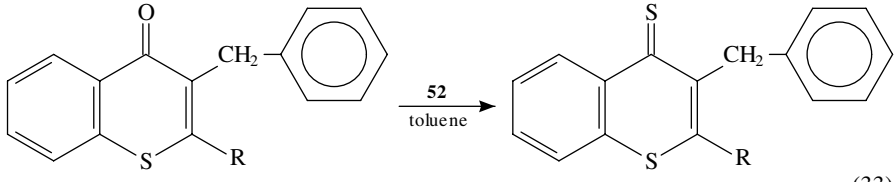
(31)

NR_2 = NMe_2, piperidine.
Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4

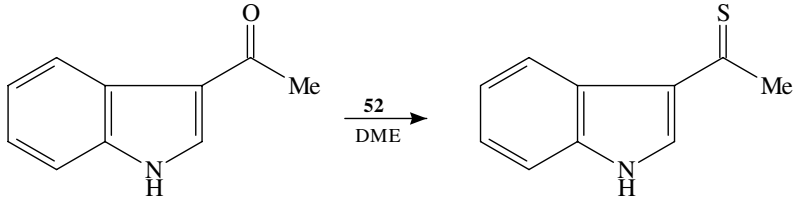
Quinoline-4-thiones[274] (equation 32), 3-benzyl-1,4-dithiochromones[275] (equation 33), 4-thioisoflavones[276] and different pyrrole[277] and indole derivatives[277–279] (equation 34) have also been obtained with Lawesson reagent.



(32)

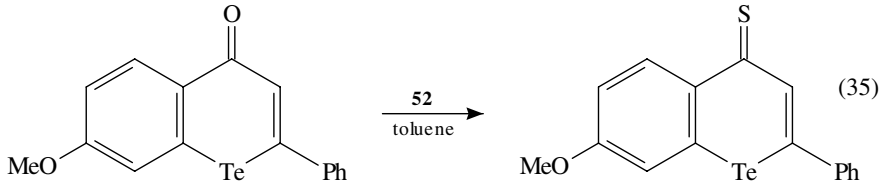


(33)



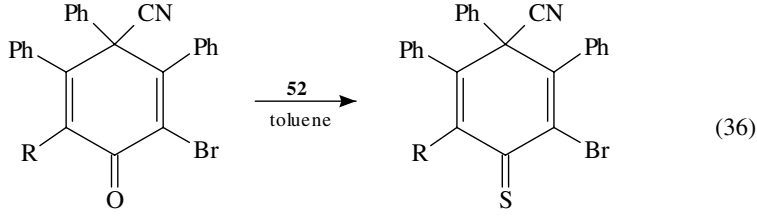
(34)

Even tellurium analogs of chromones and flavones have been prepared with Lawesson reagent[280] (equation 35).



(35)

Reagent **52** has also been very successful in the preparation of highly conjugated systems such as cyclohexadienethiones[281] (equation 36) and cyclobutanethiones[282] (equation 37). In the latter example, depending on the reaction conditions, it is possible to isolate the mono- or the dithione.

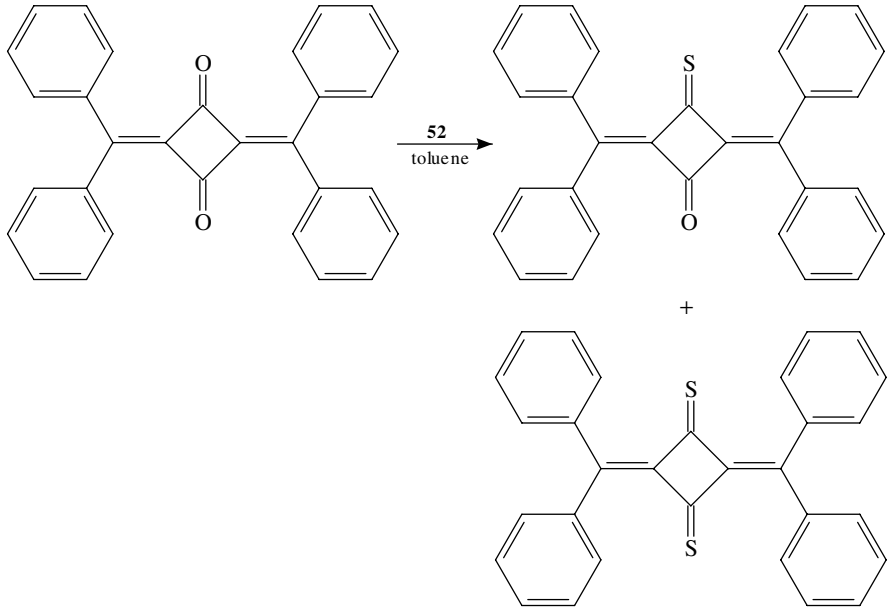


(36)

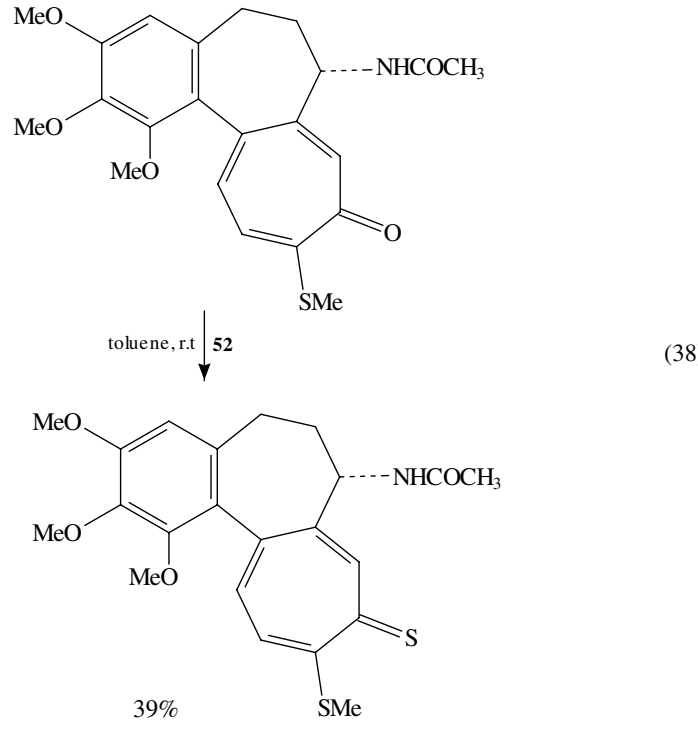
R = H, Br

The thiocarbonyl group is a classic bioisosteric replacement for the carbonyl group which has been widely exploited in medicinal chemistry. This is illustrated with the preparation of thioketones derived from thiocolchicine[283] and isothiocolchicine[284] which exhibited high antitubulin activity (equation 38).

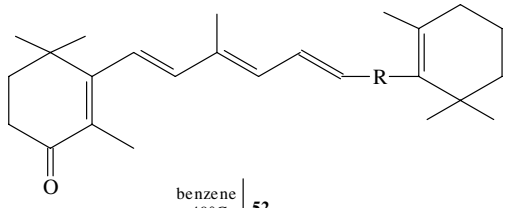
Again in the field of natural products synthesis, Lawesson reagent has found application in the obtention of sulfur carotenoids[285] (equation 39) and thionated steroids[286] (equation 40).


O
O
52
toluene
S
O
+
S
S

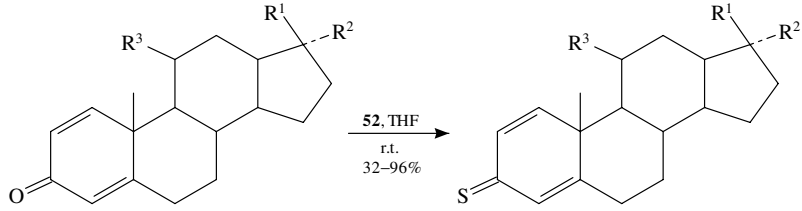
(37)


MeO
MeO
MeO
NHCOCH3
O
SMe
toluene, r.t
52
MeO
MeO
MeO
NHCOCH3
S
SMe
39%

(38)

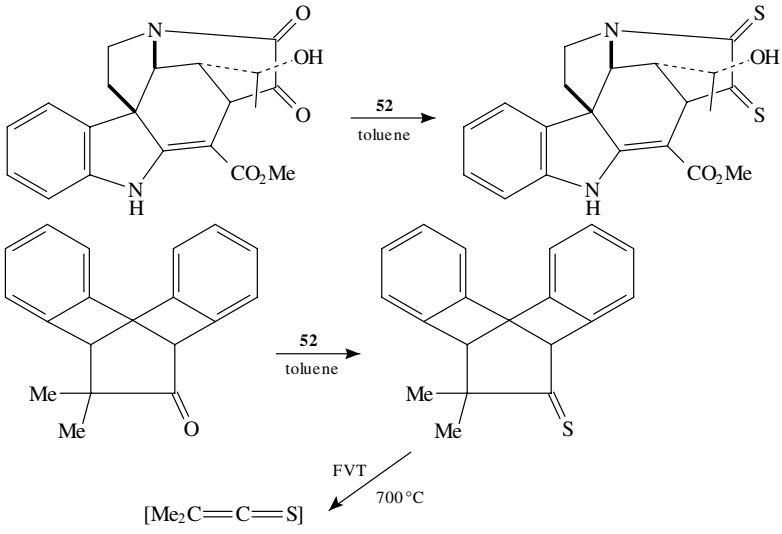


(39)



(40)

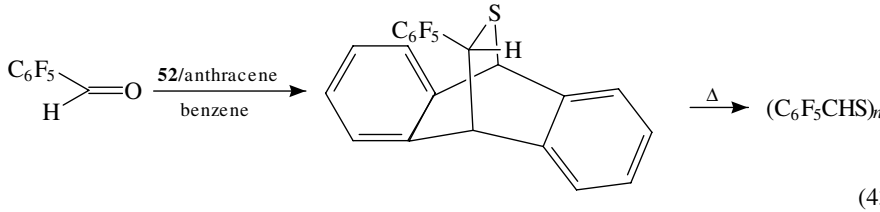
The versatility and selectivity of the Lawesson reagent is also evidenced in the synthesis of the highly complex alkaloid 19-hydroxytubotaiwine[287], in which a ketolactam is transformed into a thionethiolactam (equation 41). Also, Diels-Alder cycloadducts can be thionated with **52** and, upon thermolysis at high temperatures (FVT), afford the corresponding thioketenes which are trapped *in situ*[288] (equation 42).



(41)

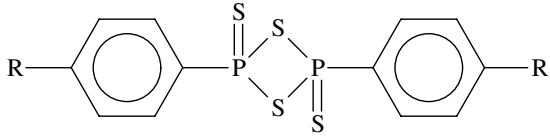
(42)

In situ combination of Lawesson reagent and anthracene allows reactive thioaldehydes to be formed and subsequently trapped as Diels-Alder cycloadducts, as illustrated in the case of pentafluorothiobenzaldehyde[289] (equation 43), which is very reactive and polymerizes rapidly.

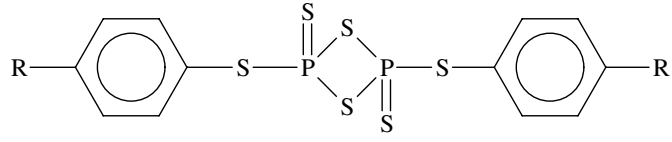


(43)

Several groups have developed a range of modified Lawesson reagents, such as **56** introduced by Sandström and coworkers[290] and employed in the synthesis of twisted push–pull ethylenes[290,291]. Reagent **56** is somewhat more stable than **52** and these authors recommend DME as the solvent of choice. The groups of Heimgartner[292] and of Nicolaou[293] have modified Yokoyama's reagents (**54**, **55**) by preparing analogs **57–59** which have been used primarily for the thionation of amides[292] and lactones[293]. Finally, Davy has reported a number of bis(alkylthio) derivatives of **57** which have found wide application in the preparation of dithioesters[294,295].



(56) R = SCH_3

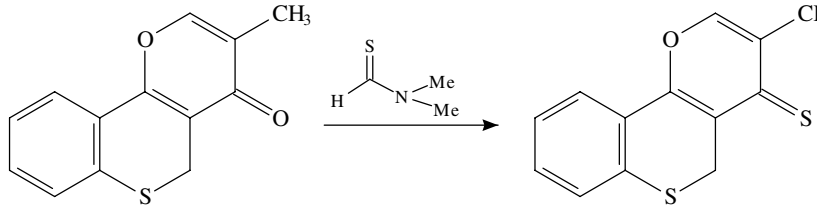


(57) R = CH_3[292]
(58) R = F[293]
(59) R = Cl[293]

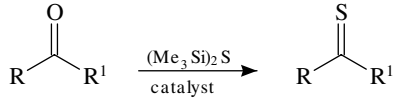
d. Other reagents. In addition to phosphorus sulfides, boron sulfides such as B_2S_3 have been used as mild sulfuration reagents. This reagent is generated *in situ* by treatment of BCl_3 with bis(tricyclohexyltin) sulfide[296,297] and it has been applied to the thionation of nonenolizable diketones[298]. On the other hand, dimethylthioformamide was employed in the preparation of naphthothiopyranopyranthiones[299] (equation 44).

Another reagent with limited application in thionation reactions has been S_2Cl_2, which afforded intermediates leading to 1,3,4-oxadithiolanes[300]. However, among the different thionating reagents developed in recent years the most successful has been bis(trimethylsilyl) sulfide, which in the presence of a catalyst affords thioaldehydes

and thioketones under mild conditions. The selection of the catalyst is important and $CoCl_2.6H_2O$ for thioaldehydes[301,302] and trimethylsilyl triflate for thioketones are preferred[302,303] (equation 45).



(44)



(45)

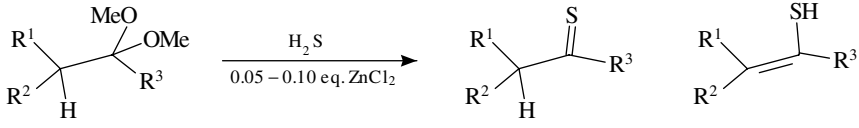
R^1 = H,$SiMe_3$, catalyst: $CoCl_2$. $6H_2O$

R^1 = alkyl, vinyl, catalyst:$TfOSiMe_3$

As usual, thioaldehydes were trapped *in situ* as Diels-Alder adducts and the intramolecular version of this strategy using a catalytic amount of butyllithium has also been reported[304].

2. Acetals

Dimethyl acetals have been treated with hydrogen sulfide in the presence of zinc chloride to afford tautomerically pure aliphatic thioketones **60** (equation 46)[305].



R^1, R^2, R^3 = alkyl

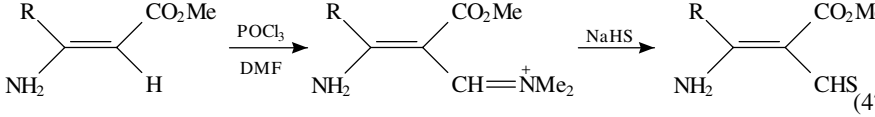
(60) **(61)**

(46)

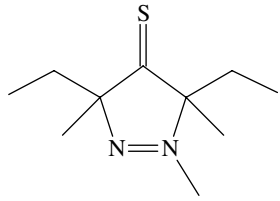
Enethiols **61** are tautomerically stable isomers of thioketones **60** and, in contrast to enols, enethiols have been isolated and characterized. This method provides a route for the selective synthesis of enethiols by deprotonation of **60** and quenching with trimethylchlorosilane, since under these conditions no isomerization takes place.

3. Imino derivatives

This approach is illustrated by the reaction of several immonium salts, obtained by Vilsmeier reaction with sodium hydrogen sulfide (equation 47) to afford a series of stable enamino thioaldehydes[306].



(47)



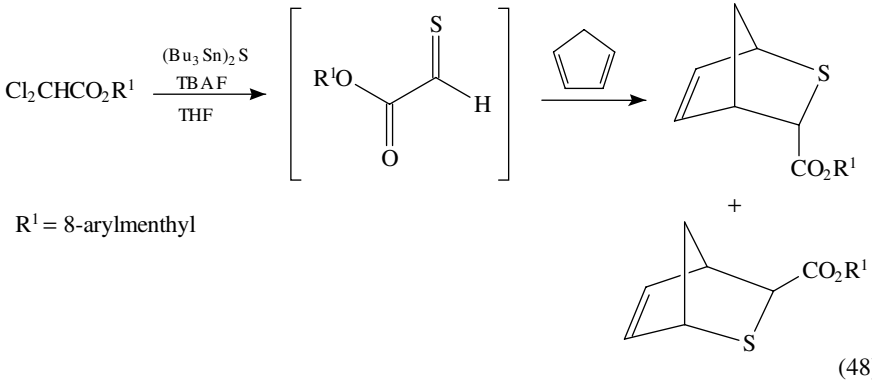
(62)

(63)

Other examples include the preparation of pyrazolinethiones[307] **62** and cyclopropenethiones[308] **63**.

4. Halogen exchange

Optically active α-alkoxycarbonylthioaldehydes were prepared from the corresponding α-dichloroacetates by treatment with bis(tributyltin)sulfide and tetrabutylammonium fluoride[309]; 8-arylmenthols were used as chiral auxiliaries and the thioaldehydes underwent asymmetric hetero-Diels-Alder cycloaddition (equation 48).

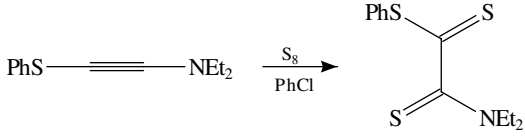


R^1 = 8-arylmenthyl

(48)

D. Addition Reactions to Alkynes and Alkenes

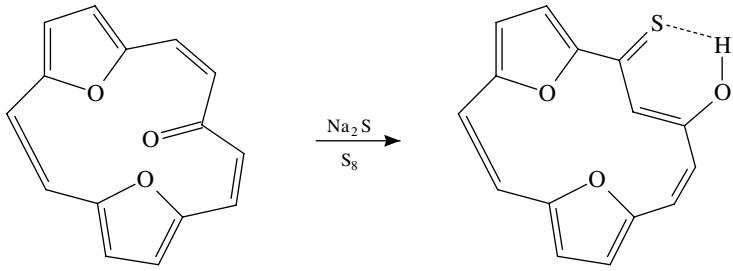
The addition of lithium hydrosulfide to acetylene affords enethiol systems[310] and the addition of elemental sulfur to diethylaminoacetylenes yields α-dithiocarbonyl compounds[311,312] (equation 49).



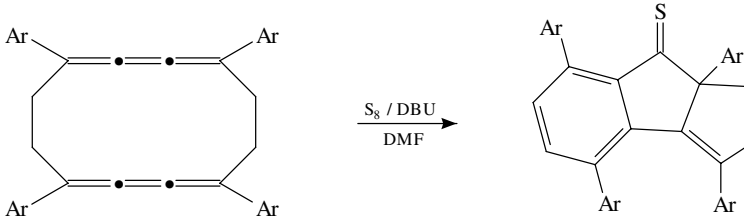
(49)

Two reactions which involve addition of sulfur reagents to alkenes have been reported for the first time. In the first, a mercapto[15]annulenone can be prepared from an annulenone by heating with sodium sulfide and elemental sulfur[313] (equation 50). In the second, addition of sulfur to cyclic cumulenes gave rise to a series of interesting cyclizations, the

final products being the tricyclic thiones in 22–27% yield[314] (equation 51).



(50)



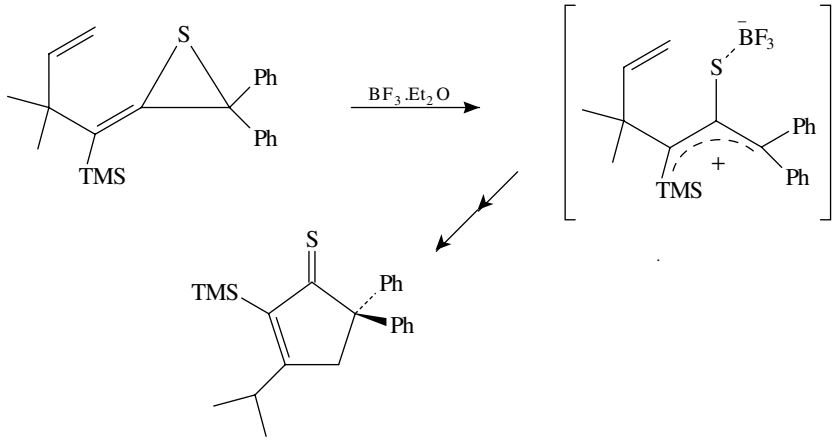
(51)

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

E. Elimination Reactions

1. C,C cleavage

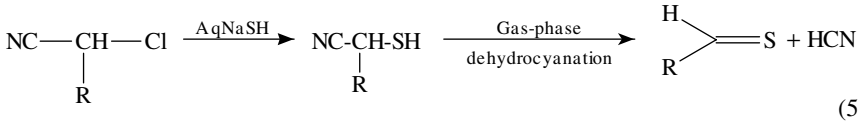
The reaction of thiiranes with $BF_3 \cdot Et_2O$ results in the formation of cyclopentenethiones, by a new type of cyclization via the initially generated thioallyl cations[315,316] (equation 52).



(52)

Photodissociation of thiophene yields several products among them thioketene, $CH_2{=}C{=}S$, produced by C,C cleavage[317]. More synthetic utility possesses the thiocyanohydrins which, by vacuum-gas phase dehydrocyanation, yield the corresponding reactive thioaldehydes[318] (equation 53). These thiocyanohydrins can be mono- and

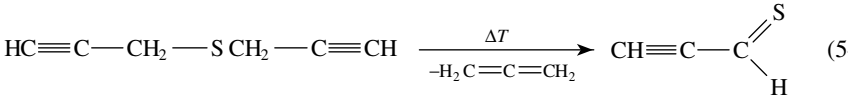
dialkylated and also have been applied to the synthesis of thioketones[319].



(53)

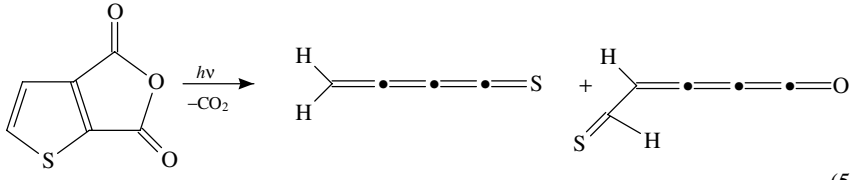
2. C,S cleavage

Cleavage of a C−S bond to give a thiocarbonyl derivative can be induced thermally, photochemically or by appropriate reagents[1]. Thermolysis has been carried out for mechanistic studies rather than for synthetic purposes and has been applied to the preparation of propynethial starting from propargyl sulfide in a flow system[320] (equation 54).



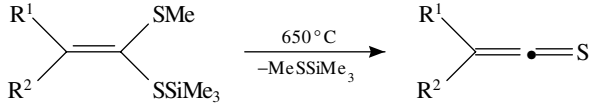
(54)

Photolysis of a thiophene anhydride in an argon matrix at 12 K yielded a mixture of a thioketene and a thioaldehyde[321] (equation 55).



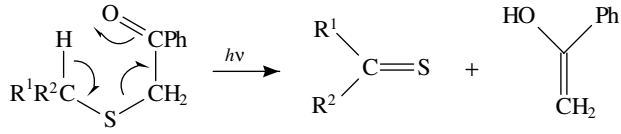
(55)

As mentioned earlier, flash vacuum thermolysis (FVT) is a very useful technique for the synthesis of reactive species[20]. It has been applied to the synthesis of thioketenes[288] (equation 56), such as propadienethione, which were trapped by reaction with dimethylamine.



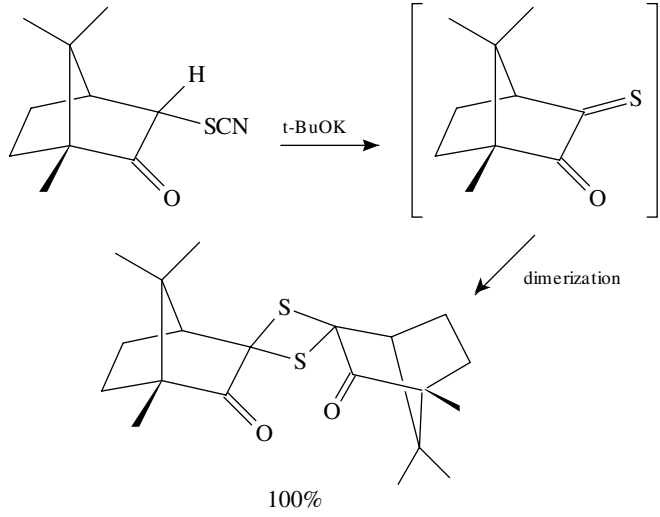
(56)

Highly reactive thiocarbonyl derivatives have been prepared by photochemical Norrish-II-type cleavage of phenacyl sulfides **64** (equation 57). This mild and flexible route has been used by the group of Vedejs in key steps for the synthesis of natural products such as cytochalasans[322] and macrolide antibiotics[323]. In the first case, a reactive thioaldehyde was generated by photolysis using the fragmentation of a phenacyl sulfide and the carbonyl compound was trapped *in situ* as Diels-Alder adduct in 66% yield[322]. On the other hand, a similar approach yielded a reactive thioketone which was trapped in a 1,3-dipolar cycloaddition[323].



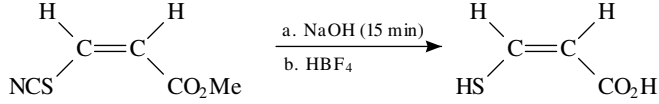
(64) (57)

In addition to pyrolysis or photolysis, S,C cleavage may be induced by nucleophiles (or bases) in substrates with an electrophilic (or acidic) center and a leaving group next to the sulfur[1]. This is exemplified in the treatment of a bridged thiocyanate with potassium *tert*-butoxide leading to an α-oxo thioketone which spontaneously dimerizes (equation 58)[324].



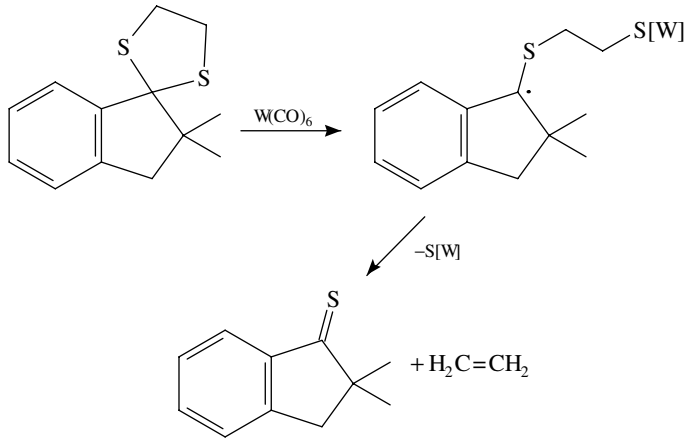
100% (58)

Similarly, the S−CN bond in thiocyanates can be cleaved affording the corresponding thiolate anions which may be protonated to enethiols[325] (equation 59).



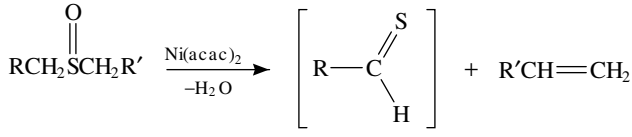
(59)

This approach has also been applied to heterocyclic systems such as thiazolidine-2,5-dithiones, which by treatment with base in the presence of a nucleophile afford a number of pyrroline thiones[326]. Thiopyrilium salts also undergo ring cleavage to yield thiobenzophenones in low yield[327]. Applications to thioquinanthrene salts have also been reported[328]. Finally, it is interesting to note that a thioketone has been invoked as intermediate in the $W(CO)_6$-mediated desulfurdimerization of dithioketals[329] which represents an unprecedented type of fragmentation of the dithiolane moiety. This result can be explained considering that group 6 metal carbonyls are thiophilic and C−S bond cleavage is thus favoured[329] (equation 60).



(60)

Another new application has been the use of complexes such as $Ni(acac)_2$ and $Pd(acac)_2$, as catalysts in the fragmentation of dialkyl sulfoxides, which yielded reactive thials isolated by reaction with 1,3-dienes[330] (equation 61).

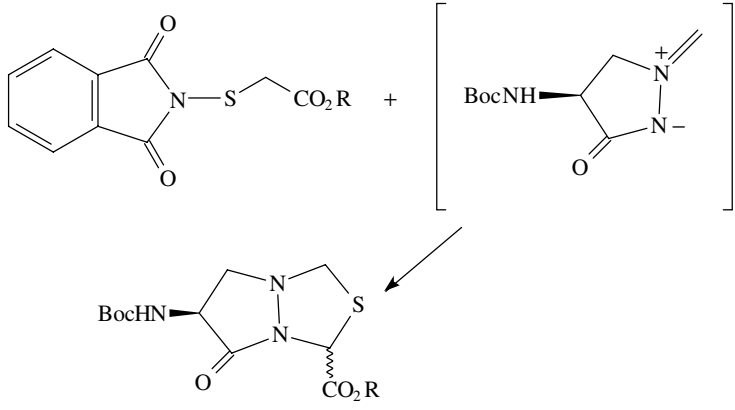


(61)

R = Alkyl, Aryl

3. S,N cleavage

The cleavage of the S−N bond in a phthalimidesulfenyl derivative may be achieved with base yielding a thiocarbonyl compound, which is trapped either as [2 + 4] cycloaddition product[331] or in a 1,3-dipolar reaction[332] (equation 62).

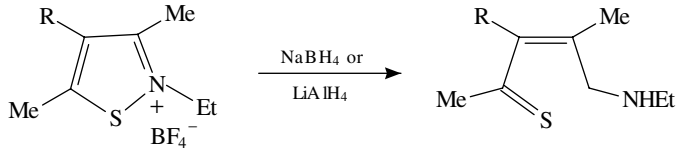


(62)

R = Alkyl

N-Alkylisothiazolium salts undergo ring cleavage when treated with complex metal hydrides ($NaBH_4$, $LiAlH_4$) affording high yields of β-enaminothioketones[333]

(equation 63). Many functional groups remain unchanged.

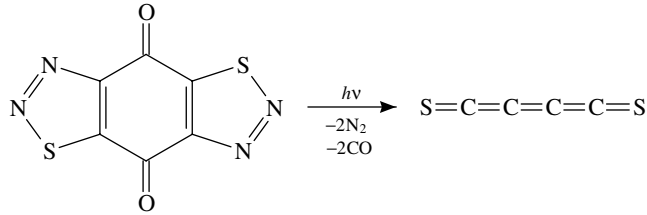


R = H, I, CN, NO_2 , CO_2 Et

82–93%

(63)

The S,N cleavage can also be accomplished by matrix photolysis of several heterocycles which undergo extrusion of N_2 and CO to afford heterocumulenes[334] (equation 64), characterized by UV and IR spectra (see Section II).

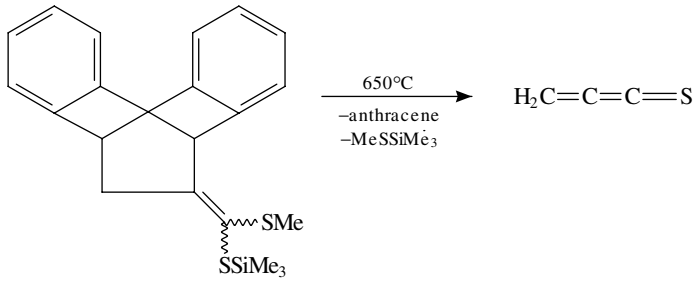


(64)

An organometallic-based strategy for the cleavage of isoxazoles catalyzed by $Co_2(CO)_8$ has been reported by de Wang and Alper[335].

4. S,Si cleavage

Ripoll and coworkers[288] have reported the cleavage of silylated ketene dithioacetals under flash vacuum thermolysis (FVT) conditions[20], which allowed the synthesis of propadienethione by combining this process along with the retro-Diels-Alder reaction (see Section III.F.5). Propadienethione was not isolated, but it underwent addition of the nucleophiles present in the reaction mixture[288] (equation 65).

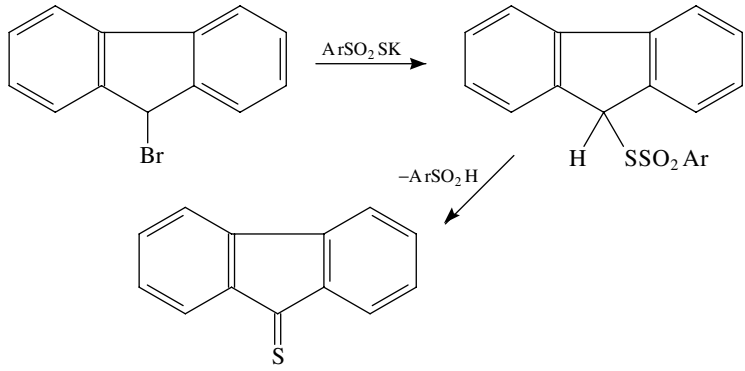


(65)

5. S,S cleavage

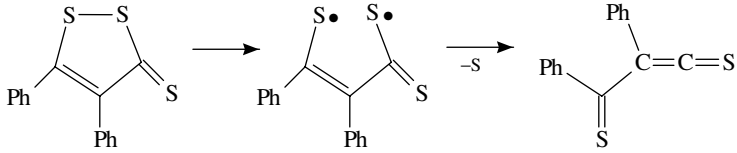
The cleavage of a S–S bond has been extensively used for the preparation of thiocarbonyl compounds and this elimination can be induced thermally or by base

(E1cB mechanism)[1]. Thus, 9-thiofluorenone was prepared from the corresponding *p*-toluenethiosulfonate[336] (equation 66).



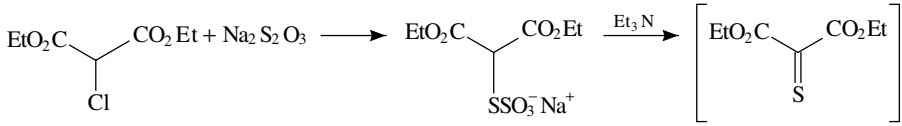
(66)

Thioacylthioketenes are formed by FVT of various 1,2-dithiole or dithietane derivatives[337,338] (equation 67) via a free radical mechanism.



(67)

Another classical strategy involves the use of Bunte salts **65** to generate diethyl thioxomalonate[339] (equation 68) or several transient thioaldehydes[340], which undergo smooth cycloaddition with many dienes[339], including the dienic system of thebaine[340]. In this case, transformation of the adducts gave rise to a variety of opiate agonists.



(65)

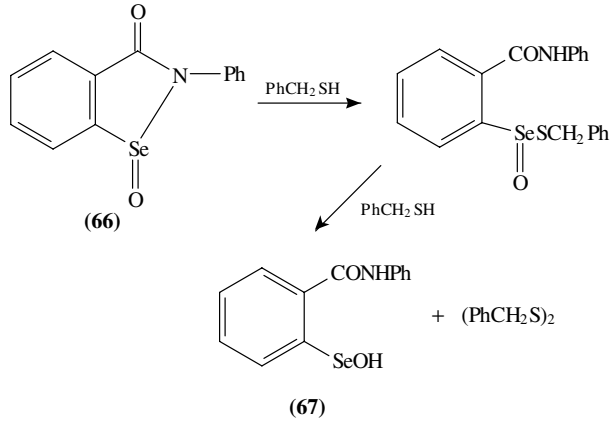
(68)

Disulfides treated with DABCO afforded thioketenes which were trapped with cyclopentadiene[341] and photolysis of polysulfides produced a range of thione[342] and dithione[343] derivatives in low yields.

6. S,Se cleavage

An interesting reaction has been reported by Glass and coworkers[344] consisting of the attack of a selenium heterocycle, Ebselen oxide **66**, by α-toluenethiol (equation 69). In this reaction thiobenzaldehyde has been invoked as intermediate and could be trapped with cyclopentadiene. In the absence of a diene, dibenzyl disulfide is isolated instead of

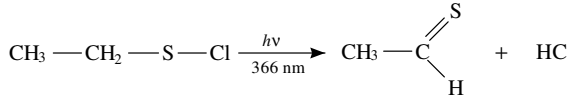
the thial along with selenenic acid **67**.



(66) **(67)** (69)

7. S,halogen cleavage

The elimination of HCl from the corresponding sulfenyl chlorides has been used in the synthesis of thioacetaldehyde[182]. The removal of HCl was accomplished by photolysis of ethanesulfenyl chloride in an argon matrix at 12 K (equation 70).

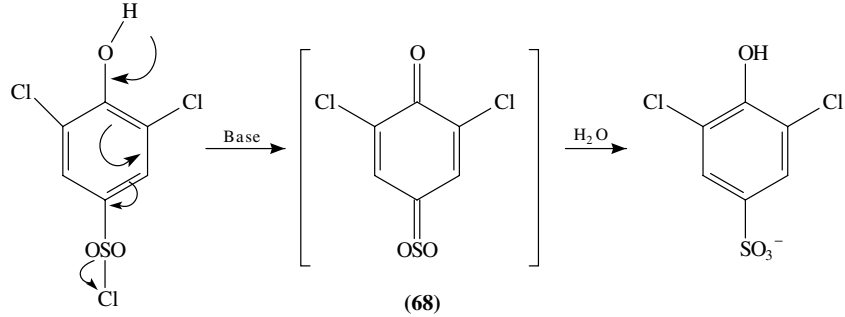


(70)

Related compounds such as alkanesulfonyl chlorides by treatment with base afford sulfene intermediates, which undergo attack by nucleophiles (H_2O, alcohols, amines, ...) present in the reaction mixture. Although sulfenes have been the subject of intense studies[345,346] it has been impossible so far to succeed in the isolation of even one of them.

Other labile thioaldehydes, such as $EtO_2CCH{=}S$, have been prepared and trapped with anthracene[347] (equation 71). On the other hand, a 1,6-elimination of HCl featured as key step in the generation of highly reactive monothioquinone *S*, *S*-dioxides **68** as depicted in equation 72[348]. the final products being the corresponding sulfonic acids.

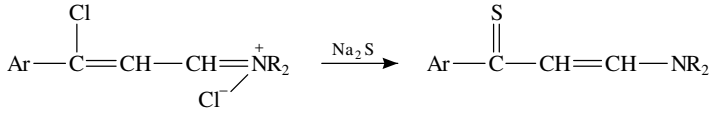
$$EtOOCCH_2SCl + Et_3N \longrightarrow [EtOOCCH{=}S] \tag{71}$$



(68) (72)

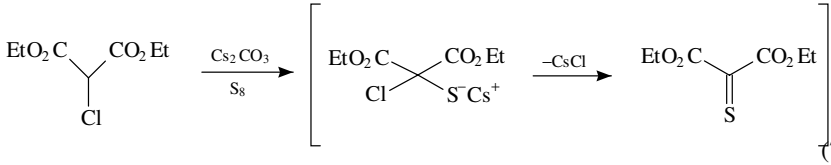
8. C,halogen cleavage

Here we report the thionation of amidinium chlorides (Vilsmeier salts) with sodium sulfide to give the corresponding enaminothioketones[349,350] as shown in equation 73[349].



(73)

A new method for the preparation of diethyl thioxomalonate, already prepared from Bunte salts[340] (Section III.E.5), has been introduced by Abelman[351]. In this approach, diethyl chloromalonate was reacted with cesium carbonate in the presence of elemental sulfur to yield the thioxoester which underwent a facile [4+2] cycloaddition (equation 74).



(74)

F. Cycloreversion Reactions

As stated by Schaumann[1], cycloreversion is the thermally or photochemically induced cleavage of two σ bonds in a carbo- or heterocyclic ring without involvement, in general, of a reagent. Fragments with π bonds are formed and, under the appropriate conditions, this strategy, together with the direct thionation of carbonyl compounds, represents the most common method for the preparation of a wide array of thiocarbonyl compounds.

1. [2+1] Cycloreversion

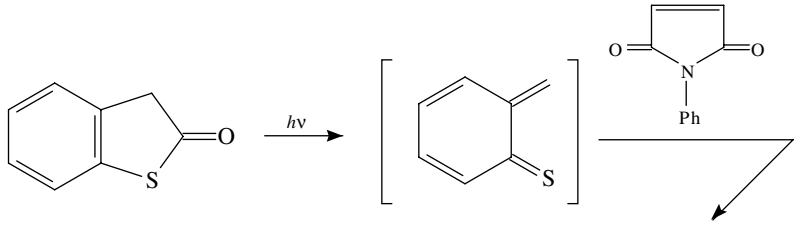
Hypervalent three-membered thiaheterocycles have been claimed as intermediates which undergo cheletropic extrusion of thiones[352]. This approach, however, has found scant application as a synthetic method.

2. [4+1] Cycloreversion

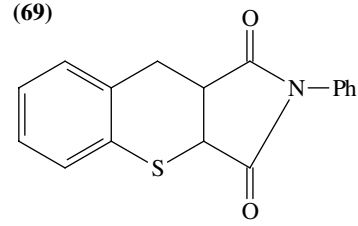
This route has been commonly used for the preparation of α,β-unsaturated thioketones such as *o*-thioquinonemethides[353] **69**, which were trapped with dienophiles as illustrated in equation 75.

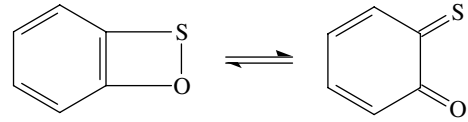
3. [2+2] Cycloreversion

[2+2] Cycloreversions are well documented in the organic literature and were reviewed by Schaumann and Ketcham[354] a number of years ago. This strategy has been primarily applied to the synthesis of thioquinone derivatives and thioketenes. Several precursors to these compounds have been reported. Thus, 1,2-oxathietanes **70**, which are isolable at moderate temperatures in organic solvents, undergo a formal [2 + 2] cycloreversion via a biradical species to yield monothio-*o*-benzoquinones[355,356] **71** (equation 76). This process is a valence tautomerization which occurs spontaneously under the experimental conditions employed.



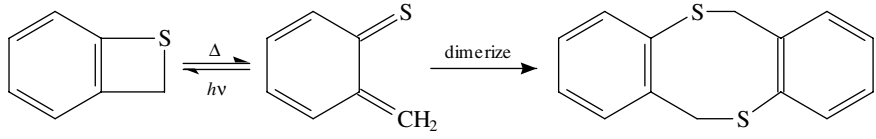
(69) (75)



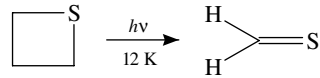


(70) **(71)** (76)

Similarly, thietanes have been the subject of intense studies aiming at the preparation of *o*-thiobenzoquinone methides **69**, which can be prepared by thermal ring opening of benzothietes **72** as depicted in equation 77[357–359]. The dienes **69** thus formed can be trapped by dienophiles in hetero-Diels-Alder reactions or undergo spontaneous dimerization. Very recently, thermally generated **69** was applied to the preparation of fullerene derivatives[360]. Also, the parent compound, thietane **73**, and the corresponding deuterated derivative have been the subject of photochemical studies[361]. Photolysis of thietane in an argon-matrix at low temperature proved to be a clean source of thioformaldehyde which usually polymerizes to a cyclic trimer (trithiane) under normal conditions (equation 78).



(72) **(69)** (77)

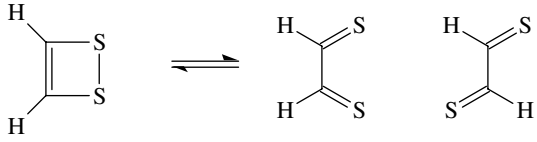


(73) (78)

Quantum chemical studies of these electrocyclic ring-opening[355,356,362] show that benzothietes are thermodynamically more stable than *o*-thioquinonemethides.

1,2-Dithietanes **74** have been studied as appropriate sources for their valence tautomers 1,2-dithiones **75a**, **75b** (equation 79) and theoretical calculations have been carried

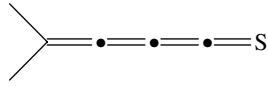
out[363,364]. Further details are given in Section II.



(79)

(74) **(75a)** **(75b)**

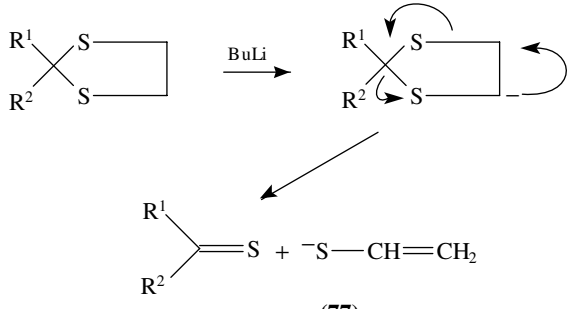
Studies in the benzene series have been reported by Bock and Rittmeyer[365] by carrying out the thermal fragmentations in the gas phase. Finally, few examples of the application of [2+2] cycloreversions in the preparation of thioketenes have been reported[321]. Irradiation in an argon-matrix of 2,3-thiophenedicarboxylic acid anhydride afforded, among other products, thioketene **(76)** in 20% yield.



(76)

4. [2+3] Cycloreversion

Five-membered heterocycles have been frequently used in the generation of thiocarbonyl compounds, and 1,3-dithiolanes and 1,3-dithianes are the most common precursors for these transformations which have been reviewed by Schaumann[366]. These [3 + 2] cycloreversions are based on the generation of a negative charge, by using a strong base (BuLi is preferred), on the five-membered ring. The resulting anion gives an instantaneous cleavage into a thioketone along with an anionic fragment **77** (equation 80).

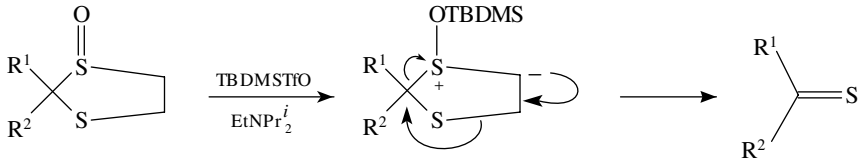


(80)

(77)

Since ketones are readily converted into 1,3-dithiolanes by reaction with 1,2-ethanedithiol and $BF_3.Et_2O$ as catalyst, this is a flexible method for the preparation of thioketones. However, this type of chemistry cannot be applied to the synthesis of thioaldehydes because treatment with base of a dithiolane (or derivative) formed from an aldehyde (R^1 or R^2 = H) preferentially gives an 'umpolung'[367] reaction by removal of the acidic hydrogen α to both sulfur atoms[223]. In the case of thioaldehydes, 4,5-disubstituted dithiolanes with electron-withdrawing groups have been utilized in order to avoid 'umpolung' reactions.

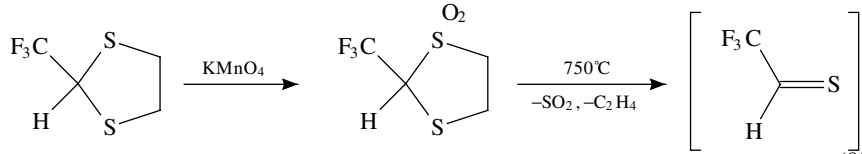
Milder conditions for this cleavage have been achieved by using more reactive analogs such as sulfonium salts or silyl derivatives of the corresponding sulfoxides. The latter strategy is depicted in equation 81[368].



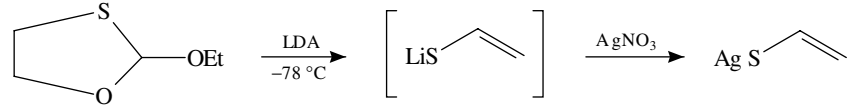
(81)

The corresponding 1,3-dithiolane *S*-oxides were prepared by oxidation of the thioacetals with *m*-chloroperbenzoic acid (mCPBA) and, notably, this approach has proven successful in the obtention of both thioaldehydes and thioketones.

Pyrolytic methods involve the use of dithiolane *S*, *S*-dioxides as starting materials which, upon heating, afford reactive thioaldehydes, such as trifluorothioacetaldehyde, trapped as the Diels-Alder adduct[369,370] (equation 82). In equation 80 an enethiolate was formed, and this feature has been employed also in the cleavage of the oxathiolane **78**. The silver vinylthiolate **79** thus obtained was applied in the preparation of new antibacterial cephem derivatives[371].

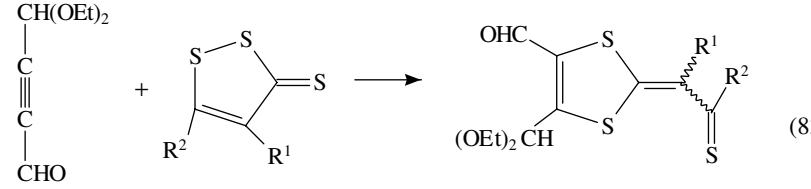


(82)



(78) **(79)**

A related reaction is the cycloaddition of 1,2-dithiole-3-ones **80** onto a number of electrophilic alkynes such as acetylenedicarbaldehyde or its monoacetal. It affords different stable thials or thiones[372] (equation 83).



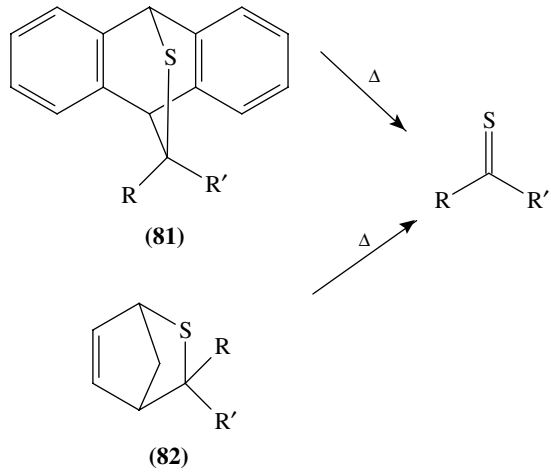
(83)

R^1, R^2 = H, Me, Ar

(80)

5. [2+4] cycloreversion. Flash Vacuum Thermolysis (FVT)

Retro-Diels-Alder reactions giving thiocarbonyl compounds are favored when simultaneously a comparatively stable diene is formed[1]. This is the case with anthracene and cyclopentadiene Diels-Alder adducts **81** and **82** which, upon heating, afford a wide array of thioaldehydes and thioketones (equation 84). These adducts are stable at room temperature and have become a convenient way of storing very reactive thiocarbonyl compounds. Cyclopentadiene is the cheapest and most reactive diene for use in Diels-Alder reactions. Also, strain in the bridged cycloadducts facilitates retro-Diels-Alder cleavage[224].

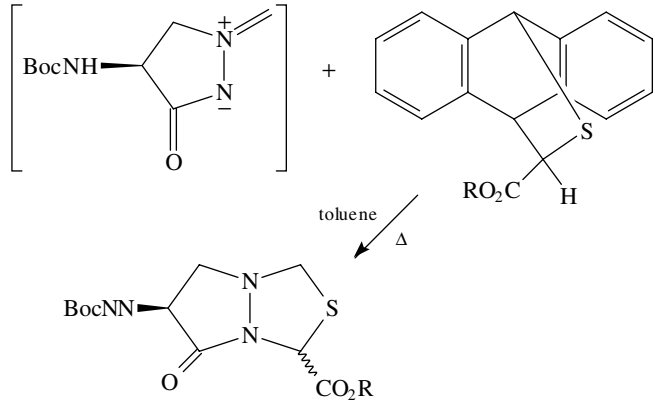


(81) (84)

(82)

Besides common pyrolytic techniques to decompose these cycloadducts, in recent years Flash Vacuum Thermolysis (or Pyrolysis) (FVT or FVP) has found increasing application[20,373]. FVT is a very clean and efficient way of generating (in the gas phase) transient species for spectroscopic or chemical investigations. It generally involves using temperatures in excess of 400 °C and pressures of less than 10^{-4} mbar for the vacuum pyrolysis, and isolation of the free thiocarbonyl compound in a liquid nitrogen trap or argon matrix[223]. In practice, a precursor is vaporized under vacuum in an oven where it is cleaved into (generally) two molecules. One of them is the molecule to be studied which can be trapped at the oven exit by an appropriate volatile reagent (such as another diene) or spectroscopically characterized either in the gas phase (IR, PES, MS, ...) or in the condensed phase after cooling, as mentioned above (IR, UV, NMR). The second molecule formed must be unreactive towards the one being studied and, ideally, they should be easily separable, for instance by selective crystallization of the unreactive by-product. However, simple volatile by-products whose spectra are well known and do not hinder the desired identification, such as N_2 or ethylene, are acceptable[20].

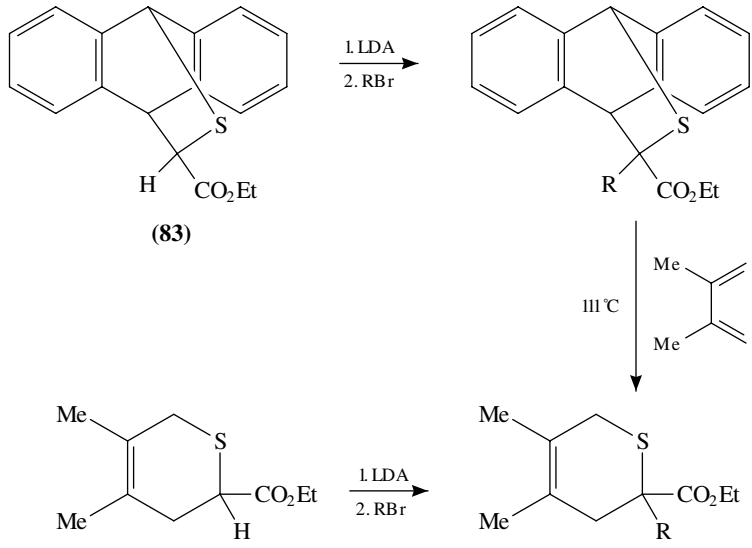
Thermal cycloreversion of the adducts can be accomplished at a convenient rate when heated in toluene under reflux. If a new diene is present in the reaction mixture, the thioaldehyde thus generated in the retro-Diels-Alder reaction may give a new adduct. Therefore, adducts **81** and **82** act as thioaldehyde or thioketone transfer reagents. These adducts dissociate reversibly on heating, thus ensuring that the concentration of the labile species remains very low. For this reason, polymerization is not a serious problem especially in the case of thioaldehydes[224]. The transient thiocarbonyl compounds can be trapped not only by dienes but also by 1,3-dipolar cycloadditions[332] (equation 85).



(85)

R = H, Et, allyl

An interesting feature of adducts **81** and **82** is that they can be additionally functionalized by alkylation with a strong base, usually LDA, using a range of alkyl halides (equation 86)[224,374], thus providing a route for the generation of reactive thioketones. Kirby and coworkers have applied the thermal cycloreversion in the synthesis of thiashikimic acid derivatives[375] (equation 87).



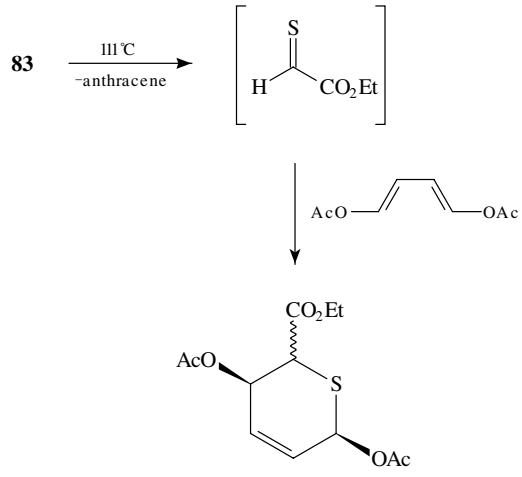
(83)

(86)

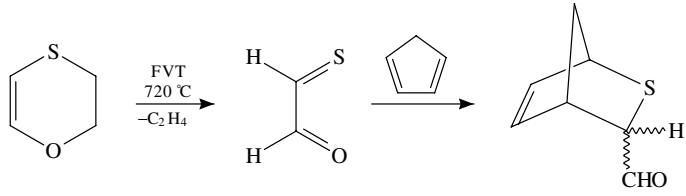
R = Me, Et, allyl, benzyl

Unsaturated 1,3-dithianes also afford thioketones on heating[215].

FVT, initially applied to the synthesis of methanethial and the corresponding *S*-oxide[376], was also the key reaction for the generation of thioxoethanal[377] and thioxoethanal *S*-oxide[378] using as precursors the corresponding 2,3-dihydro-1,4-oxathiin derivatives (equation 88). The reaction products were characterized by chemical trapping with dienes and by PE spectroscopy in addition to low-temperature IR and NMR spectroscopy.



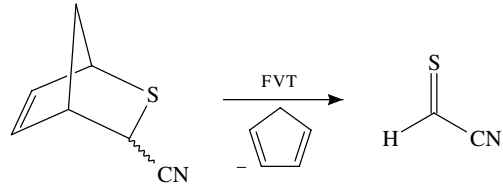
(87)



(88)

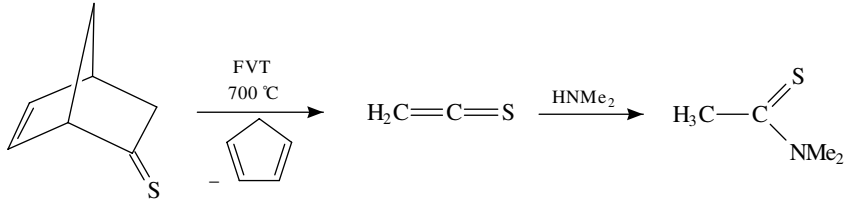
53%

The same strategy has also been applied to the preparation of α-oxothiones[379] and thioformyl cyanide[89] (equation 89), which were characterized by PE and IR spectroscopy.

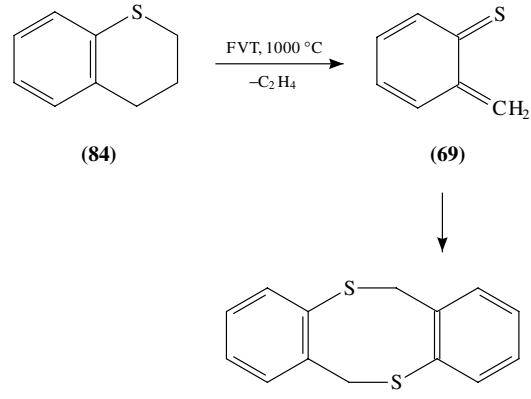


(89)

Thioketenes were generated by FVT of the bridged cycloadducts and were trapped with dimethylamine[288] as shown in equation 90. Thiochromane **84** underwent complete cycloreversion under FVT conditions affording *o*-thioquinonemethide **69**, which spontaneously dimerized[380] (equation 91).



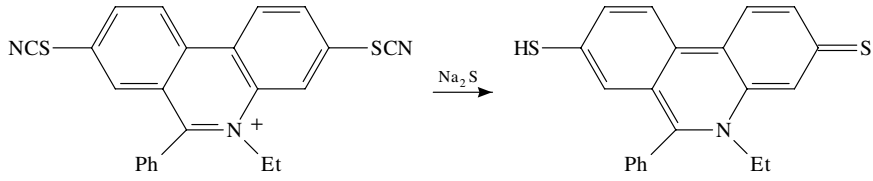
(90)



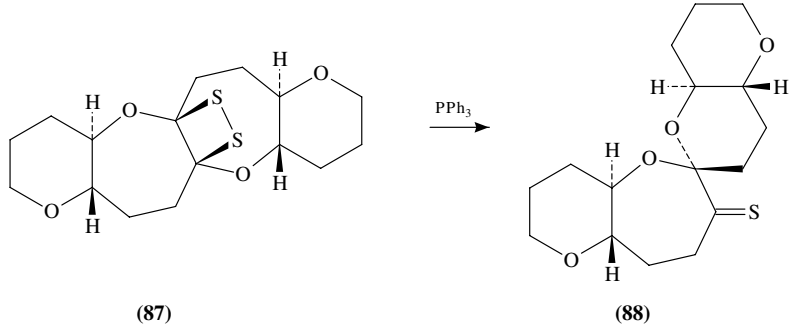
(91)

G. Reductive C,S Cleavage

Aqueous sodium sulfide reduced the aryl thiocyanate **85**, prepared from ethidium bromide, affording the air-sensitive dithiol **86** in 63% yield[381] (equation 92). Also, Nicolaou's group has reported on the cleavage of dithiatopazine **87**, a stable 1,2-dithietane system with loss of one sulfur atom and formation of a rearranged thioketone **88**[382] (equation 93).



(92)



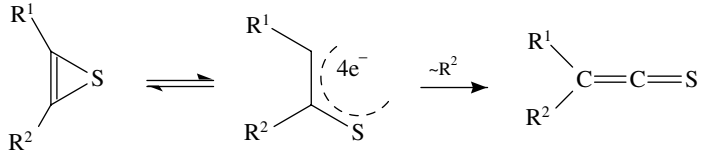
(93)

H. Sigmatropic Shifts

1. [1,2] Shifts

Thioketenes can be formed by 1,2-sigmatropic shifts occurring through the four-electron species **89** which may be considered as a diradical, as a 1,3-dipole or as a carbene[1]. In

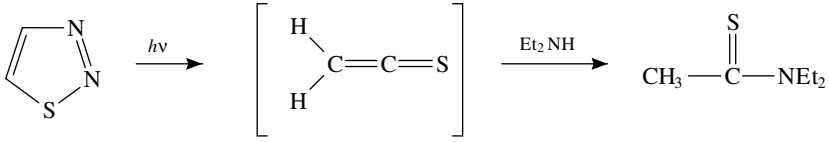
addition, **89** may cyclize to a thiirene **90** (equation 94).



(94)

(90) **(89)**

The most convenient sources of species **89** are 1,2,3-thiadiazoles **91**, which are valence tautomers of the unknown α-diazothioketones. Loss of nitrogen from **91** may be achieved by irradiation or by thermolysis. Larsen and coworkers[383] examined the irradiation of **91** in the presence of diethylamine and isolated *N*, *N*-diethylthioacetamide in high yield, which implies trapping of thioketenes during photolysis. Mechanistic studies excluded thiirene as the intermediate in the photolysis at 150 K (equation 95).

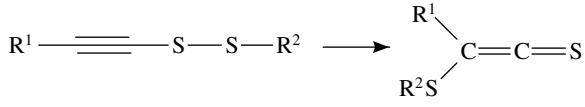


(95)

(91)

2. [1,3] Shifts

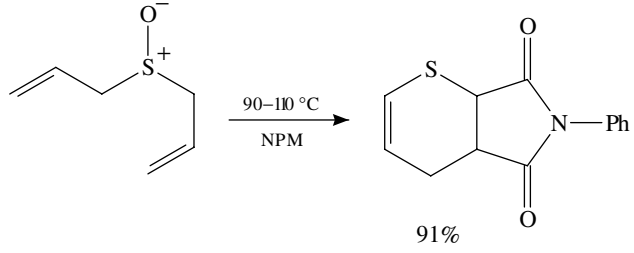
Thioketenes may be formed from 1-alkynyl disulfides by [1,3]sigmatropic shift at −78 °C[384] (equation 96), and are generally stable in solution at room temperature for a few hours.



(96)

3. [2,3] Shifts

Block and Zhao reported the thermal transformation of diallyl sulfoxide **(92)** into 3,4-dihydro-2*H*-thiopyrans, the thioacrolein Diels-Alder adducts, in good to excellent yields[385] (equation 97).



(97)

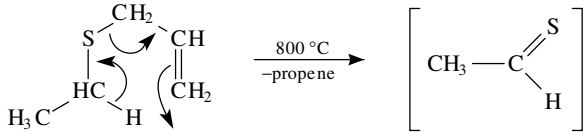
(92) **(93a)**

The reaction does not afford the expected product, thioacrolein S-oxide, but the thial, and the authors propose as mechanism the initial and reversible [2,3]sigmatropic rearrangement of the allylic sulfoxide to give an allyl sulfenate which undergoes attack by a second molecule of sulfoxide. Further transformations, such as trapping with *N*-phenylmaleimide (NPM), of this intermediate yield **93a**. This result is in striking contrast with the pyrolytic behavior of allylvinyl sulfone which undergoes [3,3]sigmatropic rearrangement[386], and diallyl sulfide which suffers a retro-ene reaction[387].

I. Retro-ene Reactions

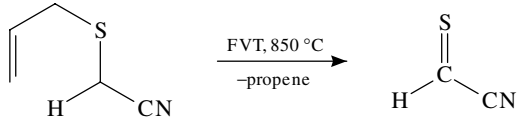
In recent years some applications of retro-ene reactions in the generation of thiocarbonyls have appeared. The retro-ene reaction is a symmetry-allowed process which resembles both [2 + 4] cycloreversion and a [1,5] sigmatropic shift of hydrogen. It usually requires high temperatures, therefore FVT has become very widespread in these reactions.

Flash pyrolysis in an argon matrix of allylethylsulfide afforded thioacetaldehyde characterized by comparison of experimental and calculated IR spectra[182] (equation 98) (see Section II).

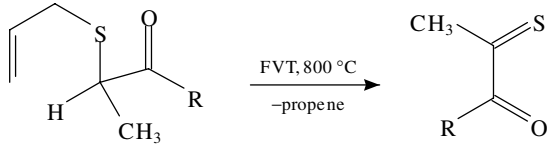


(98)

Thioformyl cyanide was generated under FVT conditions by retro-ene cleavage of allyl cyanomethyl sulfide as shown in equation 99. Spectroscopic properties of this compound are discussed in Section II. Note that thioformyl cyanide had already been prepared by retro-Diels-Alder reaction (see Section III.F.5).



(99)



(100)

R = H, Me

In similar way, the simplest α-oxothione was obtained by retro-ene reaction of the corresponding allyl sulfide[379] (equation 100) and characterized by IR spectroscopy. Upon FVT at higher temperatures (R = Me, 900–1000 °C) subsequent loss of carbon monoxide took place yielding thioacetone[379].

J. Isomerizations

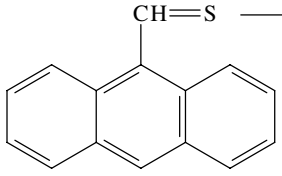
An original isomerization of thiadiazolidine-ones into triazolidin-one-thiones has been achieved enzymatically[388]. The enzymes used were bovine and equine glutathione

S-transferase (GST), glutathione (GSH) being the cofactor. These heterocyclic systems are strong peroxidizing herbicides.

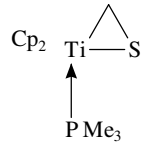
K. Organometallic Derivatives

Although due to limitations in space organometallic applications lie beyond the scope of this overview, their increasing use in recent years for the generation and stabilization of thiocarbonyls will be summarized briefly in this section and leading references will be given.

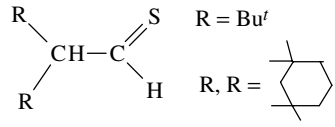
As mentioned at the beginning of Section III, free thioaldehydes tend to polymerize. They can be stabilized by coordination to metals, and several complexes with π-bonded thioaldehydes have been prepared, but only a few in which the thioaldehyde is σ-bonded have been reported[389]. Aromatic and heteroaromatic thioaldehyde pentacarbonyltungsten(0) complexes have been prepared in good yields[390] and, for instance, complex **93b** is very stable. Grubbs and collaborators have reported the obtention of a titanocene η^2-thioformaldehyde triphenylphosphine complex **94**[391]. In related work, Ando and coworkers[392] have prepared the first stable enethiolizable thioaldehydes **95** via the corresponding zirconocene η^2-thioacyl complexes.



(93b)



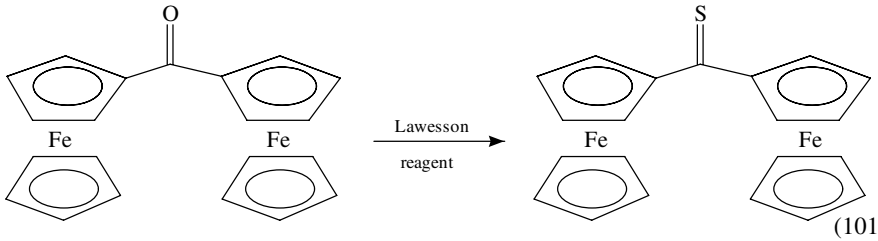
(94)



(95)

In addition, several metal-coordinated thials have been described in studies pertaining to hydrodesulfurization (HDS) reactions. This catalytic process is used to remove sulfur from organosulfur compounds present in fossil fuel feedstocks by reaction with hydrogen and a transition metal (Rh, Ir) and possesses both commercial and environmental importance[393,394].

A different strategy has been the utilization of organometallics, such as acylferrocenes, as stabilizing groups in thionation reactions either with P_4S_{10}[395] or with Lawesson reagent[396] (equation 101).



(101)

IV. CHEMICAL PROPERTIES OF THIOCARBONYL COMPOUNDS

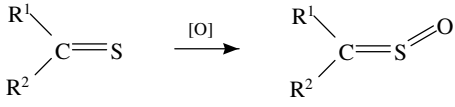
In general, thiocarbonyl compounds tend to dimerize or polymerize and this side-reaction must be considered even in the presence of other reagents[1].

In addition to the typical behavior exhibited in a wide array of reactions by the carbonyl group, attack by nucleophiles and reactions leading to C−S single bonds are generally favored. The energetic reasons for this behavior have been discussed in Section II. Likewise, thiocarbonyl groups show a rich variety of cycloaddition reactions, ranging from 1,3-dipolar to [4 + 2] cycloadditions, and α, β-unsaturated thiones may behave either as dienes or dienophiles[226].

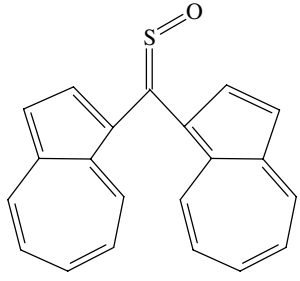
A. Oxidation. Synthesis of Sulfines

The oxidation of thiocarbonyl compounds to give thiocarbonyl *S*-oxides (sulfines) is a characteristic reaction. Sulfines are nonlinear sulfur-centered heterocumulenes with the general structure $R^1R^2C{=}S{=}O$ and their synthesis and reactions have been reviewed by Zwanenburg and by Maccagnani[397]. These compounds are formally derived from sulfur dioxide by replacement of one oxygen atom by a carbon atom, and the name sulfines (also called thione *S*-oxides) was coined by Sheppard and Dieckmann[398] in 1964 to indicate the structural relationship with thione-*S*,*S*-dioxides, which are known as sulfenes. Sulfines, in particular aliphatic sulfines, are in general less stable than their thiocarbonyl precursors, making their isolation sometimes difficult, and frequently they have been trapped with 1,3-dipoles or dienes[1,226]. An important structural property of sulfines is that they can exist as stable geometrical isomers in agreement with their nonlinear nature and, in the case of stable sulfines (such as chlorosulfines), *E*- and *Z*-isomers are known with different properties[397,399−401].

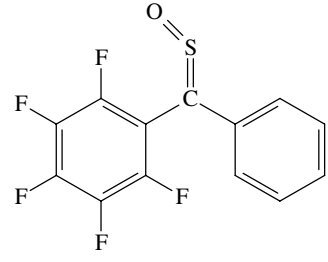
The chemistry of sulfines has experienced steady growth in recent years and many synthetic applications have been described[399−405]. Among the different methods reported for the generation of sulfines[399−406], still the most versatile and generally accepted is the oxidation of thiocarbonyl compounds (equation 102). Hydrogen peroxide and, in some special cases, ozone and singlet oxygen have been used as oxidation reagents, although peracids, and in particular mCPBA, are the oxidizing agents of choice[397]. Stable sulfines **96**[259] and **97**[289] were obtained in good yields by oxidation of the corresponding thiones with monoperphthalic acid.



(102)



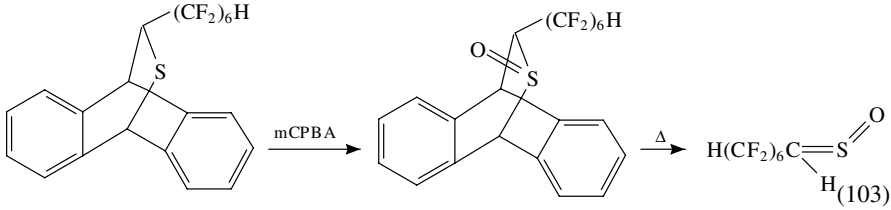
(96)



(97)

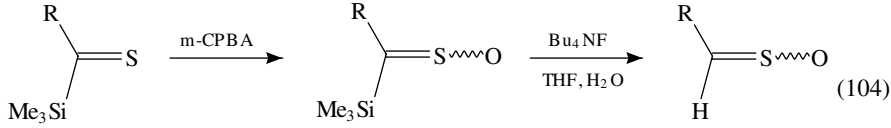
The oxidation of a Diels-Alder adduct may be achieved with mCPBA and the resulting product affords, by thermal cleavage, the corresponding sulfine[224,264,407] (equation 103)

in a strategy primarily developed by Kirby[224].



(103)

In the sulfur literature only a few examples of thioaldehyde *S*-oxides **99** (monosubstituted sulfines) have been reported due to the low stability of these compounds, and they were not prepared by oxidative methods since the starting thioaldehydes are also very unstable. These problems were circumvented by using silyl thioketones[249,250] as precursors which, by controlled oxidation with mCPBA, afforded the corresponding thioacylsilane *S*-oxides **98**. These sulfines were subsequently desilylated with Bu_4NF (equation 104) and the stereochemistry of this process has been studied in detail[408]. This indirect route has been applied to the preparation of aromatic and aliphatic, not enethiolizable, thioaldehyde *S*-oxides.

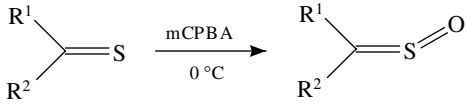


(104)

R = Ar, Bu^t

(98) **(99)**

For aliphatic thioketones, when an appreciable amount of enethiol is present, oxidation leads to divinyl disulfides[397]. However, Metzner[409,410] has carried out the selective oxidation of symmetric and unsymmetrical aliphatic thioketones to afford quantitatively the corresponding sulfines (equation 105).



(105)

R^1, R^2 = Me, Et, Pr, Pr^i, Bu^s, $C_5H_{11}{}^n$

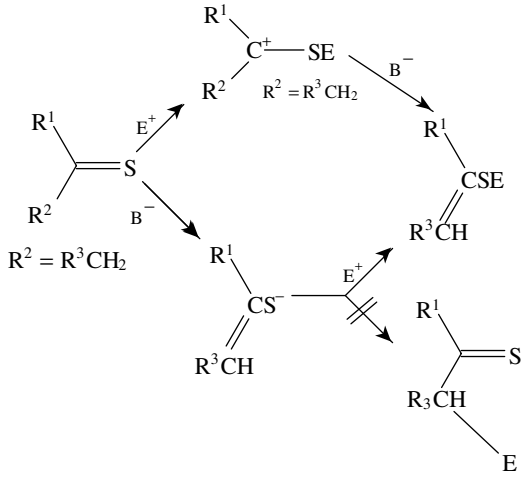
The authors carefully checked that the starting materials were devoid of isomeric enethiols and divinyl disulfides were not detected. This remarkable finding has considerably expanded the synthetic applications of sulfines.

When overoxidation takes place by using peracids, *N*-sulfonyloxaziridines have been proposed as selective and mild oxidizing agents[411]. Oxidation of Michler's thioketone with chlorine, resulting from the decomposition of chloroform, yielded a compound without sulfur in the molecule[412].

B. Electrophilic Additions

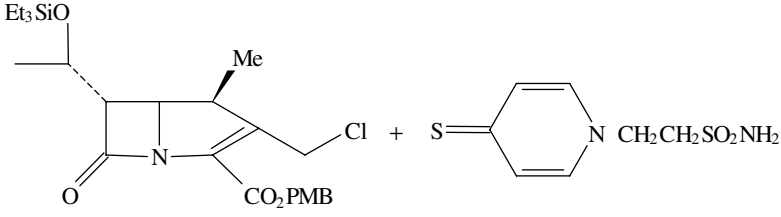
Due to the highly nucleophilic and polarizable thiocarbonyl sulfur, thioketones react with a large variety of electrophiles E^+. In the case of thioaldehydes and thioketenes this

chemistry is not yet fully developed[1]. The primary product of attack by E^+ is a salt, and for enethiolizable thiones the electrophilic attack is regiospecific on the thiocarbonyl sulfur, leading to the formation of C−S single bonds. It is never observed on the α-carbon, in sharp contrast with the behavior of the carbonyl group (equation 106)[1,226].



(106)

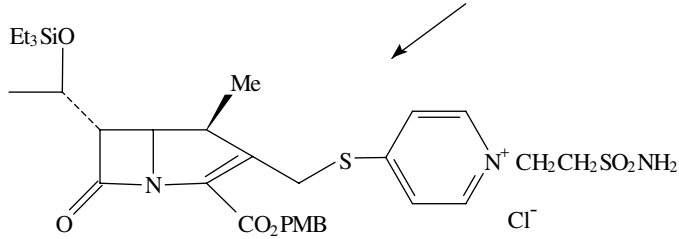
The simplest electrophilic attack, protonation, has been studied in the case of α,β-unsaturated 3-aminothiones[413] and the reaction with common electrophiles, such as alkylation, takes place with methyl iodide in the case of activated thiones, such as diazulenyl thioketone[259] and phenantridine systems[381], yielding the corresponding thioethers. *N*-substituted thiopyridone **100** reacts with carbapenem chloride **101**, leading to the corresponding quaternized compounds which exhibit good antibacterial properties[414] (equation 107).



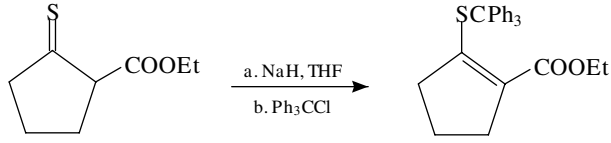
PMP = p-methoxybenzyl

(101) **(100)**

(107)

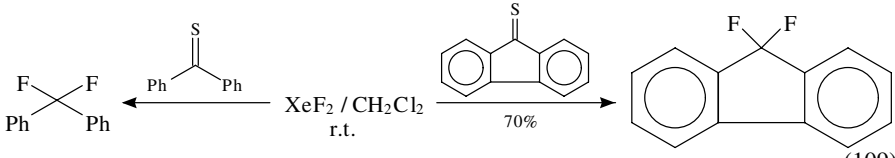


In the case of β-thioxoesters, deprotonation with base followed by alkylation gives rise to reaction on the sulfur atom[415] (equation 108).



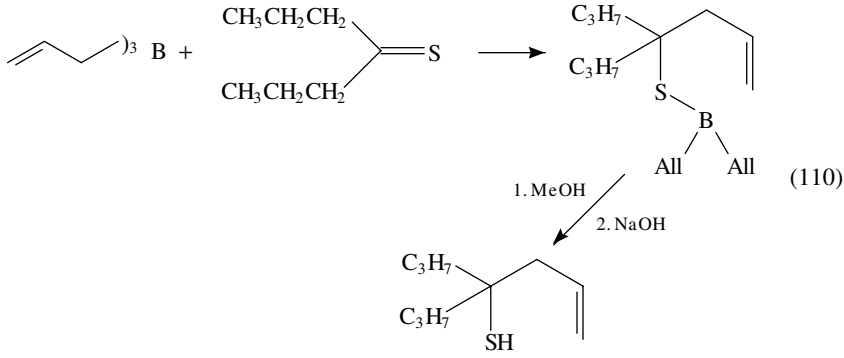
(108)

N-Alkylpyridyl disulfides are potent sulfenylating agents and react smoothly at sulfur with thiones, the reaction being driven by extrusion of 1-alkyl-2-thiopyridone[416]. In this case an additional S−S bond is formed. Another S-hetero bond is generated by halogenation. Xenon difluoride is a mild and selective electrophilic fluorinating agent which reacts with diaryl thioketones, yielding difluoro derivatives[417] (equation 109).



(109)

Sodium ethenethiolate affords by reaction with a variety of dibromosulfides, a range of vinyl thiovinyl sulfides[418]. A new application has been reported which consists of the allylboration of thioketones, useful in the preparation of homoallyl mercaptans[419] (equation 110) and other adducts[420].



(110)

C. Nucleophilic Additions

It has already been mentioned that thiocarbonyl compounds are much more reactive than their carbonyl congeners, but, at the same time, due to the low polarity of the C−S unit, they also react much less selectively. Thus, nucleophilic additions may occur either at the carbon (carbophilic addition, Section IV.C.1) or at the sulfur atom (thiophilic addition, Section IV.C.2), as shown in equation 111. This feature is in striking contrast with the behavior of the carbonyl group, which only undergoes nucleophilic attack on the electron-deficient carbonyl carbon, this being the cornerstone of the synthetic applications of oxo

compounds[1]. Metzner has reviewed the reactions with nucleophiles[226] and we will only highlight the major advances recorded in this area.

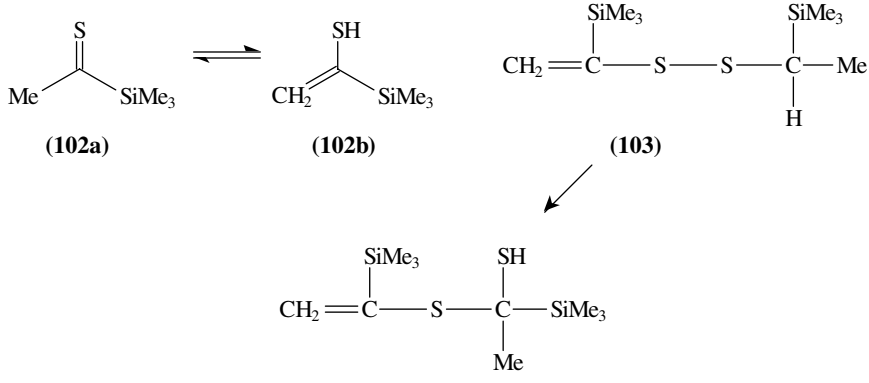
(111)

carbophilic addition thiophilic addition

In the case of α, β-unsaturated thioketones, nucleophiles attack at the β-carbon and the mechanism of aminolysis of 3-alkoxy and 3-alkylthio enaminothiones has been studied[421]. Likewise, addition of amines to α-thioxoketones gives rise to enaminothiones[422].

1. Addition to the thiocarbonyl carbon

The protons located α to the thiocarbonyl group are quite acidic and therefore thiocarbonyl compounds are easy to deprotonate with a variety of bases, the most common being lithium diisopropylamide (LDA). As a consequence of the remarkable ability of sulfur to stabilize a negative charge, the resulting species of this deprotonation are generally written as enethiolates **102b** rather than being metalated on the α-carbon[226]. In comparison with enolates, enethiolates are thermally and configurationally stable and behave as ambident nucleophiles. For instance, dimerization of thione **102a** yielding **103** and **104** can be rationalized only in terms of a thiophilic and a carbophilic addition, respectively, of the enethiol form to another molecule of the thione[250].

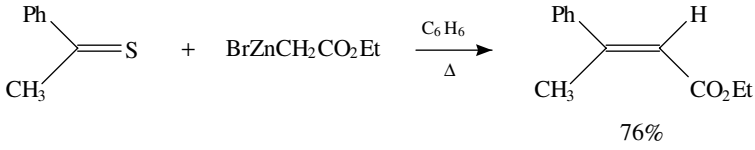


(102a) **(102b)** **(103)**

(104)

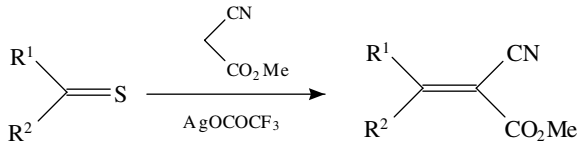
Reactions of different organometallic species with thiocarbonyl compounds have been extensively investigated and been shown to proceed both in a carbophilic and a thiophilic fashion. However, other reactions can be observed simultaneously such as reduction, double addition, coupling, deprotonation and formation of enesulfides[1,226,423]. A complex pattern appears in the reactions of thioketones with lithium or Grignard reagents[424]. The first application of Reformatsky reagents in C−C bond formation by reaction with

thiocarbonyl compounds has been recently reported[425] (equation 112).



(112)

A related reaction is the silver(I) ion-mediated desulfurization–condensation of a number of thioketones with different active methylene compounds, such as malononitrile, methyl cyanoacetate etc.[426] (equation 113), which takes place under mild basic conditions.



(113)

As previously mentioned (Section III.A) the reaction of phosphonium ylides with elemental sulfur afforded thioaldehydes which, by addition of amines, yielded the corresponding thioamides[237]. Another application involved the reaction of cyanothioacetamide with a β-thioxoketone to give a pyridine-2-thione[217].

Okazaki's group[427] has investigated the reaction of sterically hindered thioketones with organolithium and Grignard reagents and found that in the first case the major product was that resulting from the attack at the carbon (carbophilic reaction), whereas with organomagnesium compounds the major products were the reduced ones. Surprisingly, selenoketones afforded mainly selenophilic products. The reaction of thiofluorenone with sulfinates has been studied[336].

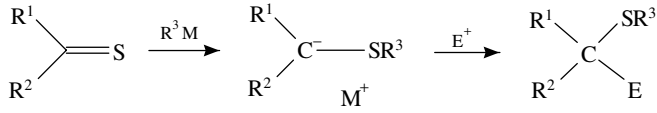
The reaction of thioketenes, generated by flash-vacuum pyrolysis (Section III.C.1.b), with secondary amines affords the corresponding thioamides and is the standard trapping procedure for these unstable compounds[288] (equation 114).

(114)

2. Addition to the thiocarbonyl sulfur

The reaction of organolithium and -sodium derivatives and of Grignard reagents with aliphatic and aromatic thioketones is well documented[1,226]. Thiophilic addition is frequently reported, thus confirming the prediction of a possible reverse polarity of the thiocarbonyl compared to the carbonyl function[423] (equation 115). As mentioned earlier (Section IV.C.1) other competing reactions can be observed (carbophilic addition, reduction, double addition and formation of enesulfides). Viola and coworkers have reviewed the thiophilic reactions of thiocarbonyl compounds with C and S-nucleophiles[428] and proposed a relationship between thiophilic reactions and the redox behavior of the system. Thus, thiocarbonyl compounds undergo easier reduction than their carbonyl counterparts and also afford commonly thiophilic addition products whereas the carbonyl group only

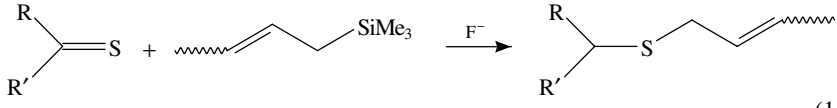
undergoes nucleophilic attack on the carbonyl carbon.



(115)

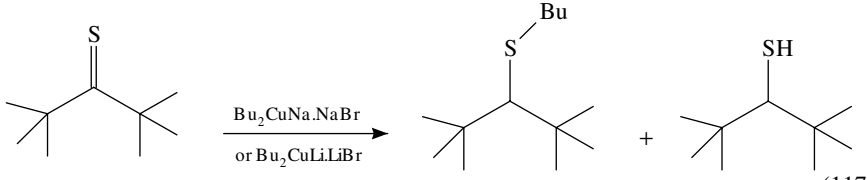
The basic reaction pioneered by Beak's group[429] has been studied by many other groups and also silyl thioketones behave similarly[249,250], yielding α-silyl sulfides in good yields. These thiophilic reactions are probably facilitated by the silyl group due to its stabilizing effect on the intermediate α-silyl carbanion. The silyl sulfides can be used for further synthetic purposes, especially by making use of fluorodesilyation in the presence of carbon electrophiles, such as aldehydes and enones[249].

A major advance in this area is represented by the fluoride ion-promoted addition of allylsilanes to thioketones[423] (equation 116) giving the compounds arising from a direct thiophilic addition, namely the corresponding allyl sulfides.



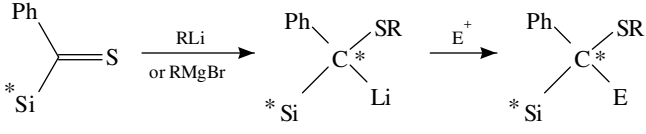
(116)

This regiochemical outcome contrasts with previous observations and the inversion of regiochemistry at the thiocarbonyl group also occurs with benzylsilanes[423]. The dependence of the regiochemistry on the nature of the organometallic species used is illustrated thus when lithium organocuprates are used, instead of allylsilanes, a clean carbophilic addition occurs[423]. Related to this, treatment of di-*tert*-butyl thioketone with sodium or lithium organocuprates affords a substantial proportion of thiophilic addition along with the reduction product[430] (equation 117).



(117)

Sodium cuprate yielded less reduction product and less thiophilic addition product than lithium cuprate at both -50 and $0\,^{\circ}C$. In the case of silyl thiones chiral at silicon, the reactions with organolithium derivatives and Grignard reagents produce α-silylsulfides with medium to good levels of asymmetric induction and, interestingly, the asymmetry induced at the α-carbon is retained in the subsequent desilylation[431] (equation 118), the process being stereoselective.



(118)

*Si = α-Napht., Ph, MeSi R = Me, Bu^n, Bu^t, Ph, *p*-Tol E=H,D

D. Reduction

The reduction of thiocarbonyl groups may lead to a variety of products: thiols, methylene compounds, sulfides etc. The reactions to achieve S/O exchange, namely desulfurization reactions, will be summarized in Section IV.G. There is a short review dealing with the reduction of the thiocarbonyl group[432]. As mentioned earlier, sometimes concomitant reduction of the C=S bond takes place in the reactions of thiones with organolithium or organosodium reagents, and thiols along with the corresponding addition products are obtained[430].

Reduction of diaryl thioketones with ytterbium metal affords a mixture of the corresponding thiols and diarylmethanes together with products arising from homocoupling reactions (equation 119)[433].

$$Ar_2C{=}S \xrightarrow[2,\ H_3O^+]{1,\ Yb} Ar_2CHSH + ArCH_2Ar + Ar_2C{=}CAr_2 + Ar_2CHCH\ CAr_2 \qquad (119)$$

The use of sodium telluride under aprotic conditions allows the transformation of aromatic thioketones into hydrocarbons in good yields[434], as shown in equation 120. Interestingly, when this reaction is carried out with sodium telluride in aqueous media the original ketones are generated.

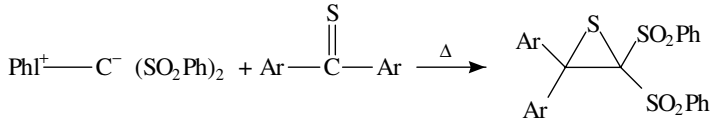
$$Ar_2C{=}S \xrightarrow[DMF,\ \Delta]{Na_2Te} Ar_2CH_2 \qquad (120)$$

E. Cycloaddition Reactions

Thiocarbonyl compounds are excellent reaction partners in all types of cycloadditions, especially 1,3-dipolar (Section IV.E.3) and Diels-Alder reactions (Section IV.E.4). They have been frequently used in the trapping of unstable thiocarbonyl derivatives[1].

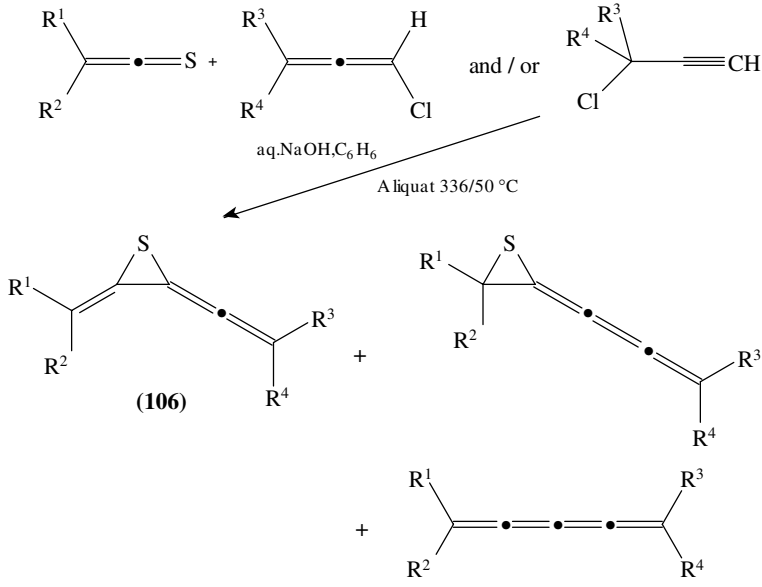
1. [2+1] Cycloaddition

Carbenes add to the CS π bond in diarylthiones to give thiiranes by way of a [2 + 1] cycloaddition[1]. The carbene species may be generated from diazo compounds, from organomercury compounds or from phenyliodonium bis (aryl- or alkyl-sulfonyl) methylides **105**. Very few examples of this type of reaction have been described and equation 121 shows the application to the case of thiobenzophenones, although the yields reported were low[435] and several side products, such as benzothiophenes, were found. Using haloallenes or haloalkynes as source of carbenes under phase transfer conditions, various types of allene episulfides **106** have been generated by the alkenylidene carbene addition to thioketenes[436] (equation 122) although yields are moderate.



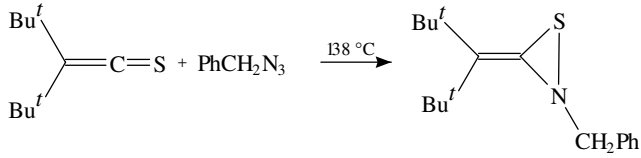
(121)

(105) Ar = *p*-Tol



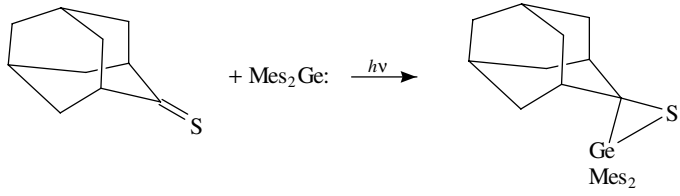
(122)

The thermal formation of a nitrene has been invoked to account for the result in the reaction between a sterically hindered thioketene and benzyl azide[437] (equation 123). Although initially a 1,3-dipolar cycloaddition between the C=S bond and the azide was expected, the temperature of the reaction (138 °C) led to decomposition of benzyl azide into benzyl nitrene and the subsequent [2 + 1] cycloaddition.



(123)

In addition to carbenes and nitrenes, organometallic species such as germylenes **107** have been utilized in [2 + 1] cycloadditions and, upon reaction with thioketones, afforded the corresponding thiagermiranes which are very stable and do not decompose even when heated to their melting point[438] (equation 124).

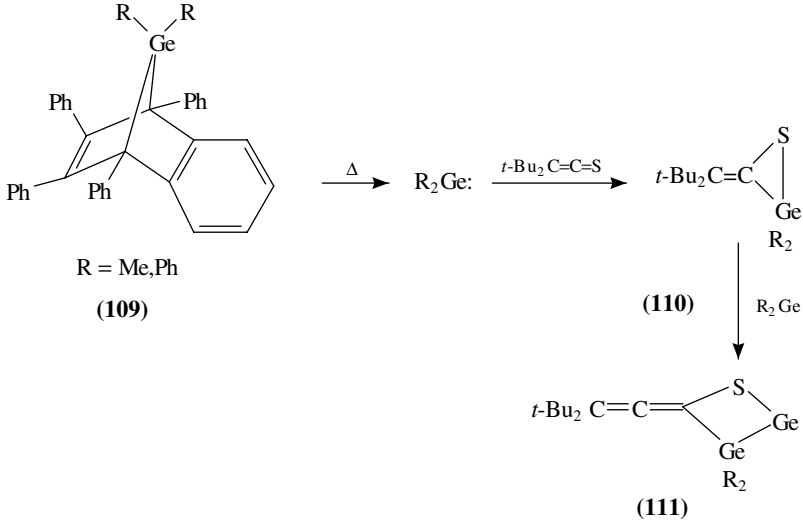


(124)

(107) **(108)**

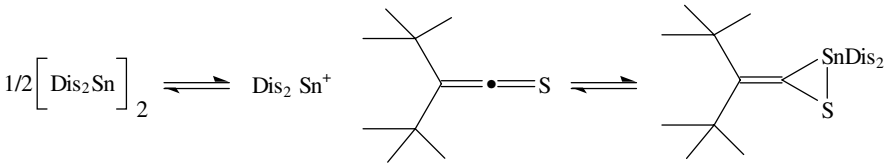
Germylenes can be generated either thermally or photochemically[438] and, apart from thioketones, they have been reacted with thioketenes to afford initially

3-alkylidenethiagermiranes **110**, which undergo further insertion of germylenes yielding thiadigermetanes **111** as the final products[439] (equation 125).



(125)

The most common precursors for generating germylenes are the corresponding germanorbornadienes **109** which decompose by thermolysis or photolysis. A related reaction is the stannylene addition to a C=S bond, where the final product is highly dependent upon a fine balance between the steric and electronic factors of the thiocarbonyl compounds involved. Thus, in the case of thioketenes the reaction with stannylene **112** yields first the corresponding thiastannirane **113** which is air- and moisture-sensitive. In contrast, on treatment of **112** with thioketones only five-membered dithiastannolanes were isolated[440] (equation 126). A compound similar to **113**, but more stable, was obtained by addition of $(R_F)_2Sn$, where R_F is 2,4,6-tris(trifluoromethyl)phenyl, to di-*t*-butylthioketene[441].



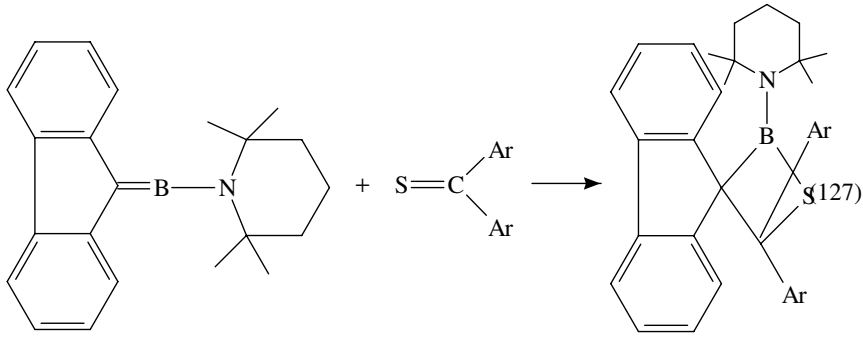
Dis = $CH(SiMe_3)_2$

(126)

2. Thermal [2+2] cycloaddition

In recent years thermal [2+2] cycloadditions have been the subject of several theoretical studies, and in the case of the reaction of substituted thiobenzophenones with phenyllallene mechanistic and kinetic studies were also performed[442]. Linear free-energy correlations showed that the thione system is more sensitive to electron-donating than to electron-withdrawing substituents. Reactions with heteroatom bonds such as C=B and C=P have also been examined. Thus, thioketones react with borane **114** to give thiaboretanes **115**[443]

(equation 127).



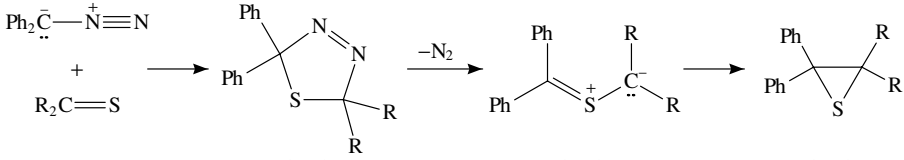
(127)

(114) Ar = 4-$ClC_6H_4^-$ **(115)**

The thio-Wittig reaction between thioaldehyde and phosphorus ylides yields initially a thiaphosphetane, which undergoes cycloreversion to a P=S bond[444].

3. [2+3] Cycloaddition

Together with Diels-Alder reactions, [2+3] cycloadditions are the most common strategies used both in the trapping of unstable thiocarbonyl species and in the synthesis of a wide variety of heterocyclic systems. The first examples of dipolar cycloadditions between diazoalkanes and thioketones date back to 1920[445,446], but it was not until Huisgen performed a systematic study, reviewed in 1984[447], that thiones reached broad recognition as versatile synthons. In 1989 Huisgen coined the term 'superdipolarophiles'[448] to emphasize the high reactivity of the C=S bond. Thus, 1,3-cycloadditions of diphenyldiazomethane to thioketones are much faster than those to α,β-unsaturated compounds and nitriles previously regarded as the fastest dipolarophiles[448]. The primary cycloadducts, 1,3,4-thiadiazolines **116**, extrude N_2 and furnish thiiranes **118** via the corresponding thiocarbonyl ylides **117** (equation 128), which are not isolable.

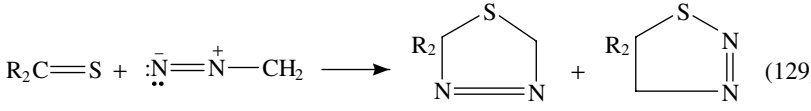


(116) **(117)** **(118)** (128)

A quantitative estimate of the high reactivity of thiones is given by the fact that the cycloadditions of thiobenzophenone *S*-methylide [formed *in situ* by extrusion of N_2 from intermediate **116** (R = Ph)] to thiofluorenone and thiobenzophenone proceed 7.8×10^7 and 1.15×10^6 times faster than that to methyl propiolate. Even thiofluorenone is 2.4 times more reactive than tetracyanoethylene (TCNE), the superb C=C dipolarophile[449].

The regiochemistry of this cycloaddition has been examined by Huisgen and is called 'thiophilic': a bond is created between sulfur and the carbon end of the dipole[450], although the opposite regiochemistry has been observed sometimes. For instance, diazomethane

adds in two directions to dialkyl ketones[451] and the ratio of the regioisomers depends on the size of the substituents and solvent polarity (equation 129).



(129)

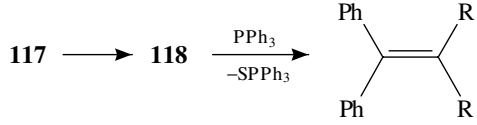
(119) **(120)**

Rising polarity of the solvent favors the production of 1,2,3-thiadiazolines **120** whereas increasing steric demand of the thione assists formation of the 1,3,4-isomer **119**.

The preference for the 1,2,3-thiadiazoline structure in more polar solvents is explained by the higher dipole moment (*ca* 5 D as compared to *ca* 2 D) of the transition structure[452]. Extensive *ab initio* calculations on the reaction of diazomethane with thioformaldehyde concluded that both regioisomers should be formed via concerted pathways[452], but some semiempirical methods (AM1, MNDO-PM3) suggest that the reaction takes place in a stepwise manner.

The mechanistic picture is more complicated because in reactions of aliphatic thiocarbonyl ylides, generated from sterically hindered thioketones and 2-diazopropane, evidence was found for the formation of zwitterionic intermediates[453]. These thiocarbonyl ylides are bases and can undergo addition of nucleophiles such as methanol. In the presence of tetrasubstituted acceptor olefins such as TCNE or a variety of dipolarophiles such as dimethyl fumarate, *N*-phenylmaleimide[454], zwitterionic intermediates can close to afford a five-membered thiolane ring or a seven-membered ketene imine ring, and can also undergo rotation to furnish cyclopropane and thione in an intramolecular nucleophilic substitution[453].

In equation 128 it is shown that thiocarbonyl ylide **117** may undergo a conrotatory electrocyclic reaction leading to thiirane **118**. Thiirane is the smallest sulfur heterocycle and the Munich group has thoroughly studied not only the construction of this system, but also its destruction[455], since the elimination of sulfur converts thiiranes into olefins **121** providing an important synthetic application for these molecules (equation 130).

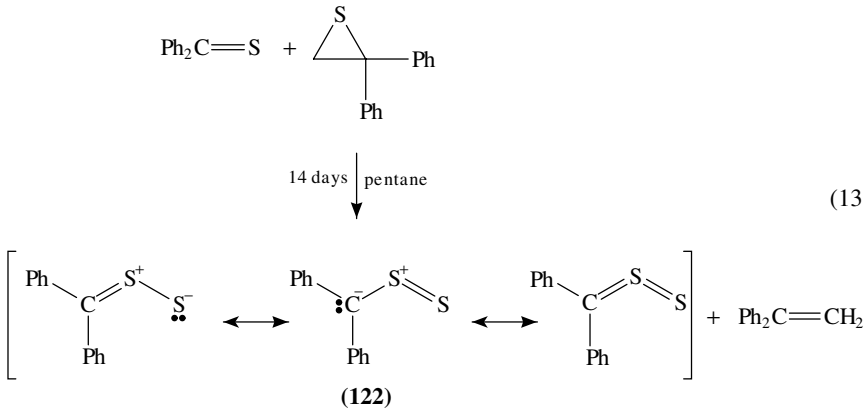


(130)

(121)

Barton and coworkers exploited this strategy in the preparation of overcrowded ethylenes[456]: usually the desulfurization of a thiirane is accomplished by one equivalent of tertiary phosphine, mainly triphenylphosphine. However, spontaneous loss of sulfur from thiiranes substituted by aryl or halogen has sporadically been reported. Huisgen has reviewed this subject[455] and performed many kinetic studies. He found that the desulfurization step can be accomplished by catalytic thiolates and also by thiobenzophenone or other thioketones, although in this case the reaction is slower (equation 131).

The thiirane donates sulfur to the thioketone, thus furnishing olefin and thiobenzophenone *S*-sulfide **(122)** which can be intercepted in 1,3-dipolar cycloadditions to activated acetylenes or thiones[455].



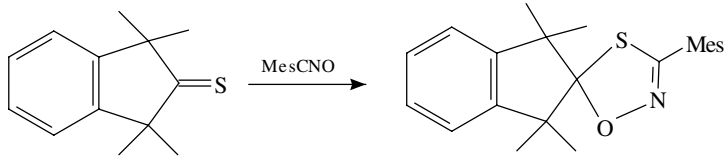
(131)

(122)

In addition to diazoalkanes, a large variety of dipolarophiles have been submitted to cycloaddition with thiocarbonyl compounds[226]. Reactions often occur at room temperature, are highly regioselective and can be classified after the nature of the 1,3-dipoles according to Sustmann's classification[457], where diphenyldiazomethane belongs to the category of nucleophilic 1,3-dipoles, whereas nitrones (azomethine oxides) are type II dipoles with a nucleophilic–electrophilic nature.

Very recently, Huisgen and Sustmann carried out both mechanistic[458] and theoretical[459] studies of the 1,3-dipolar cycloaddition of several nitrones with aliphatic thioketones finding that, again, thiones are superdipolarophiles *vs* nitrones[458]. In the *ab initio* calculations performed at different levels for the cycloaddition of the parent nitrone to thioformaldehyde, a CT orientation complex was found[459]. The perturbational analysis shows a strong $HOMO_{nitrone}$–$LUMO_{thioformaldehyde}$ interaction as the principal reason for the high thione reactivity.

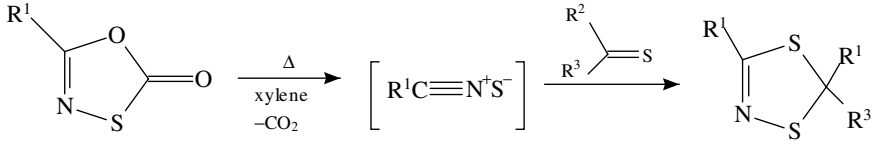
Nitrile oxides have also been used as dipoles, in particular mesitonitrile oxide (MesCNO) which was reacted with different thiones leading to the corresponding oxathiazoles[368,460] as shown in equation 132[460].



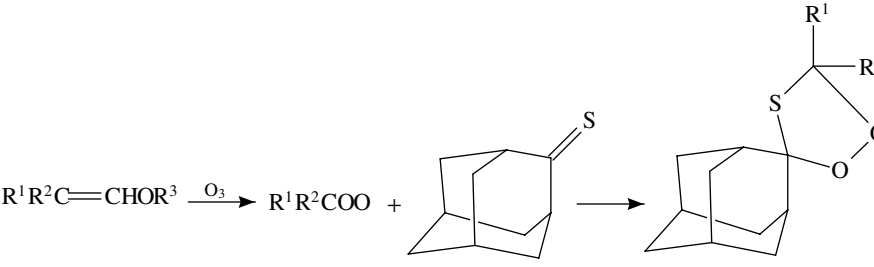
(132)

Examples of 1,3-dipolar cycloadditions of nitrile sulfides **(124)** onto thioketones have been reported[272] (equation 133). **124** were generated by thermal decomposition of 1,3,4-oxathiazol-2-ones **(123)** which, in turn, may be prepared bearing a wide variety of substituents R^1. Thermolyses were carried out in the presence of the dipolarophile which traps the transient nitrile sulfide, with the formation of 5*H*-1,4,2-dithiazoles **125**. Regioisomeric 1,2,3-dithiazole products were not observed.

In the case of carbonyl oxides **127**, generated by ozonolysis of vinyl ethers **126**, the addition to a number of thioketones affords thioozonides **128** in moderate yields[461] (equation 134), although sometimes oxidation to sulfines was observed.

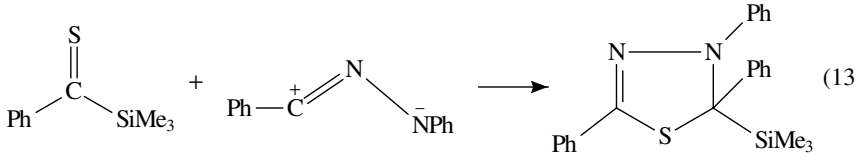


(123) **(124)** **(125)** (133)



(126) **(127)** **(128)** (134)

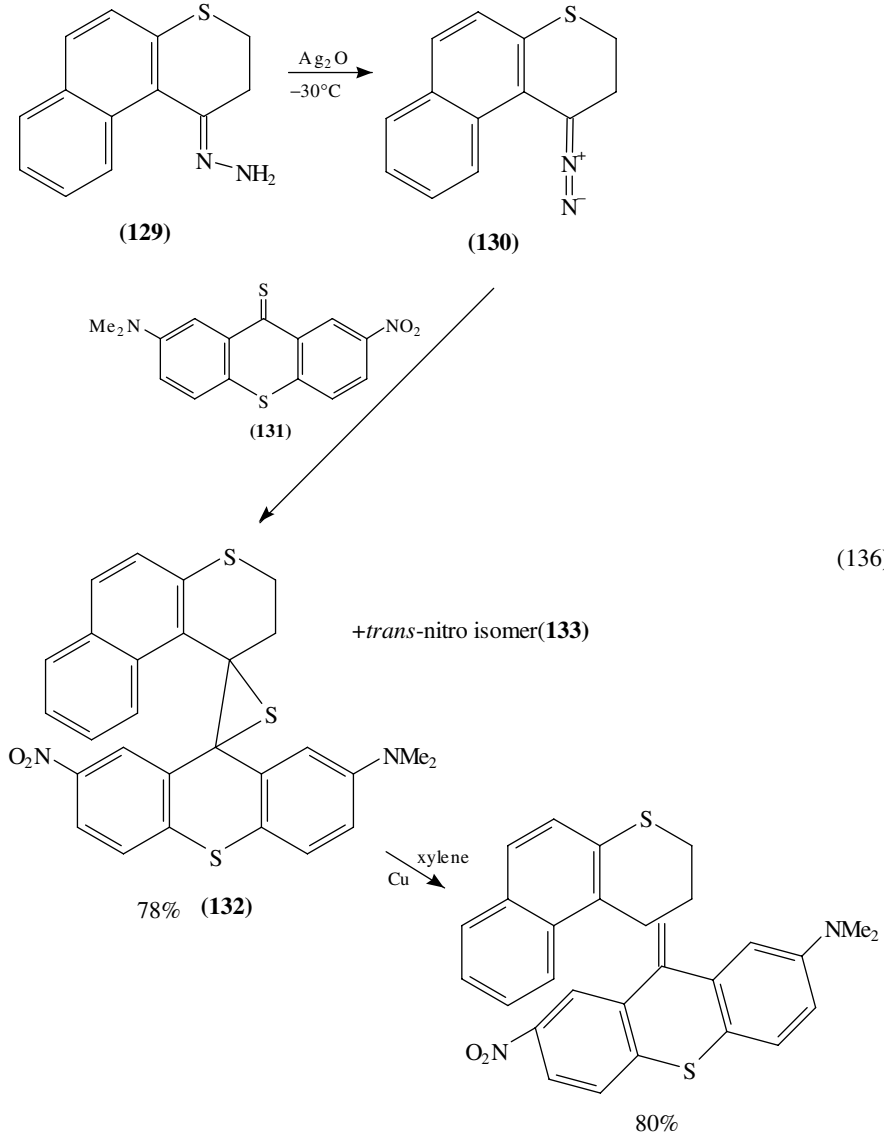
We have already mentioned the synthetic versatility of silyl thioketones[249] which is confirmed because they react with 1,3-dipoles (nitrile oxides, nitrile imines and nitrile ylides) to give regiospecifically silyl thiaheterocycles[462]. Equation 135 illustrates the reaction between phenyl trimethylsilyl thioketone and diphenyl nitrilimine.



(135)

The reactions with most synthetic applications are those between thioketones and diazo compounds which provide highly conjugated systems after extrusion of nitrogen[463]. As we mentioned earlier, another application consists of the preparation of sterically overcrowded ethylenes (equation 130): this strategy has been extensively studied by Feringa and collaborators[464–467] in the search for chiroptical molecular switches, which are organic materials for optical data storage[464]. Equation 136 illustrates the thioketone–diazo coupling method for the formation of the central double bond in thioxanthene systems[467]. Hydrazone **129** was oxidized to the corresponding diazo compound **130** and subsequent 1,3-dipolar cycloaddition with thioketone **131** was followed by extrusion of N_2 to provide the episulfides **132** and **133**. The latter were desulfurized to afford *cis* and *trans* isomers which were separated chromatographically[467].

Organosilicon compounds have also been reacted with thiocarbonyl ylides to afford a variety of heterocycles[468,469] and in Section III.F.5 we pointed out the 1,3-dipolar cycloaddition between *in situ* generated thioaldehydes and a pyrazolidinium ylide to produce a nuclear analogue of pyrazolidinone antibacterial agents[332]. Moreover, Vedejs has applied the dipolar cycloaddition between a thione, generated from a Norrish-type II fragmenta-



(136)

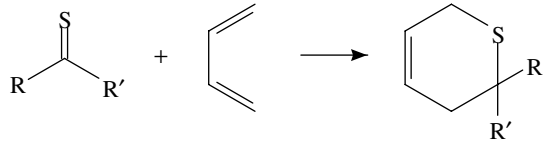
tion, and a nitronate as a key step in the preparation of the natural product methynolide[323] (Section III.E.2).

Finally, Isaacs has investigated the effect of high pressure on the 1,3-dipolar cycloaddition of thiones to diazoalkanes, finding that the reaction is strongly accelerated by pressure which is extremely important in the case of sterically hindered substrates[470].

4. [2 + 4] Cycloaddition

Diels-Alder chemistry has been reviewed by several authors[226,470–472].

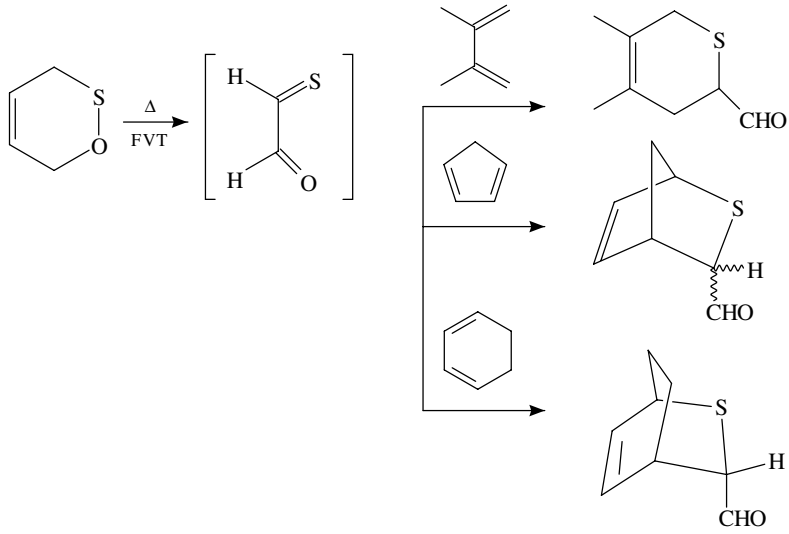
a. Thiocarbonyl compounds as dienophiles. Cycloaddition of a thiocarbonyl compound and a 1,3-diene affords a 5,6-dihydro-2*H*-thiapyran (equation 137).



(137)

Virtually all types of thiocarbonyl compounds have been found to react as heterodienophiles. In general, thiocarbonyl compounds are more reactive and versatile dienophiles than the corresponding carbonyl compounds. One major difference between the two types of dienophile is that a dihydrothiapyran formed from a thiocarbonyl group often has a tendency to undergo a thermal retro-Diels-Alder reaction, whereas the corresponding dihydropyran is less prone to do so[471]. This problem may be partly solved by using high pressure and Isaacs has studied the cycloaddition of thiobenzophenone with several dienes (e.g. isoprene, cyclopentadiene)[470]. The rate of Diels-Alder reactions is accelerated by high pressure because these reactions have a large negative volume of activation (the TS occupies a smaller volume than the reagents). High pressure can also prevent thermal decomposition which can accompany Diels-Alder reactions.

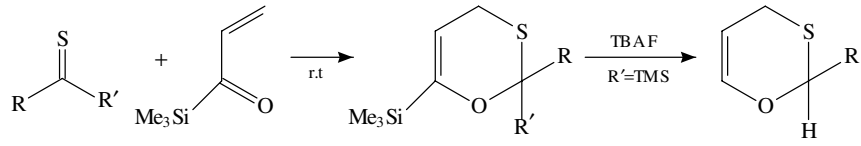
The competition C=O *vs* C=S in Diels-Alder reactions is represented in the case of thioxoethanal, generated by FVT, and which only reacts through the C=S bond when trapped with a variety of dienes[20,373,377] (equation 138). In the case of cyclic dienes, *endo* selectivity was observed and α-oxothiones behaved similarly[20,379] as well as α-oxosulfines[20,378].



(138)

Diels-Alder reactions of thioketones are well documented in the literature[471], however, since Schaumann published his review[1], advances have been recorded in the cycloadditions with thioaldehydes due, mainly, to the development of new synthetic methods (Section III) and techniques (FVT), and therefore the reactions with aldehydes will be highlighted[473].

Silyl thioketones act as synthetic equivalents of thioaldehydes by protodesilylation with TBAF[249,250], as shown in equation 23 (Section III.C.1). A related reaction is the heterocycloaddition of thiones with vinyltrimethylsilylketone, behaving as heterodiene[474], to afford 4*H*-1,3-oxathiins as shown in equation 139.



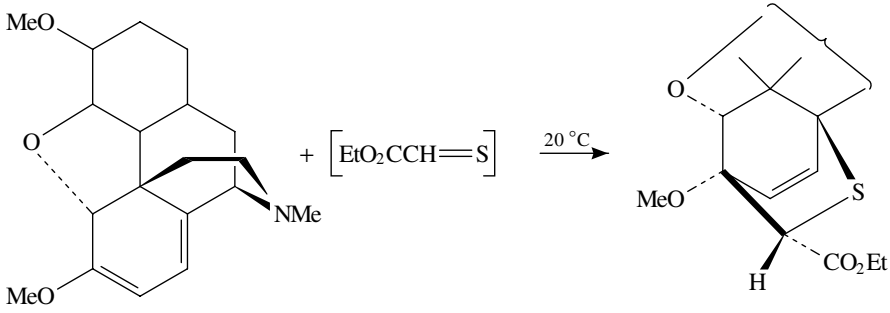
R = Aryl
R′ = Aryl, TMS

(139)

Very few mechanistic studies have appeared on this subject and Houk group has studied the hetero-Diels-Alder reaction between thioformaldehyde and butadiene[475], using *ab initio* calculations, to show that the reaction is concerted and nearly synchronous. In the case of unsymmetrical dienes, several rules are known to establish the regiochemistry of the cycloadducts[1,471].

The most frequently used dienes in the trapping of thioaldehydes have been cyclopentadiene, 2,3-dimethylbutadiene[369,370,238] and anthracene[351]. However, in recent years the applications of thioaldehydes in the synthesis of natural products have been reported mainly by the groups of Kirby, who has reviewed his contributions[224], and Vedejs, who generated thioaldehydes by cleavage of phenacyl sulfides and then allowed them to react with electron-rich dienes and ketene acetals, to give, after further transformations, azocine derivatives[476]. Also, cytochalasans were prepared by using transient thioaldehydes and 2-(*tert*-butyldimethylsilyloxy)-1,3-butadiene[322].

The groups of Kirby[224,340] and of Revesz[477] have studied the Diels-Alder reactions of thebaine **134** with ethyl thioxoacetate (equation 140) and other thioaldehydes, thus preparing several opiate antagonists.

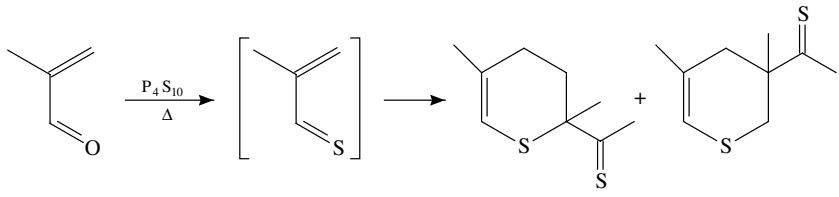


(134)

(140)

Stereochemical aspects have been covered by the groups of Turro and Le Noble, who propose hyperconjugation as a crucial factor in face selectivity during cycloaddition of 5-fluoroadamantane-2-thione[478].

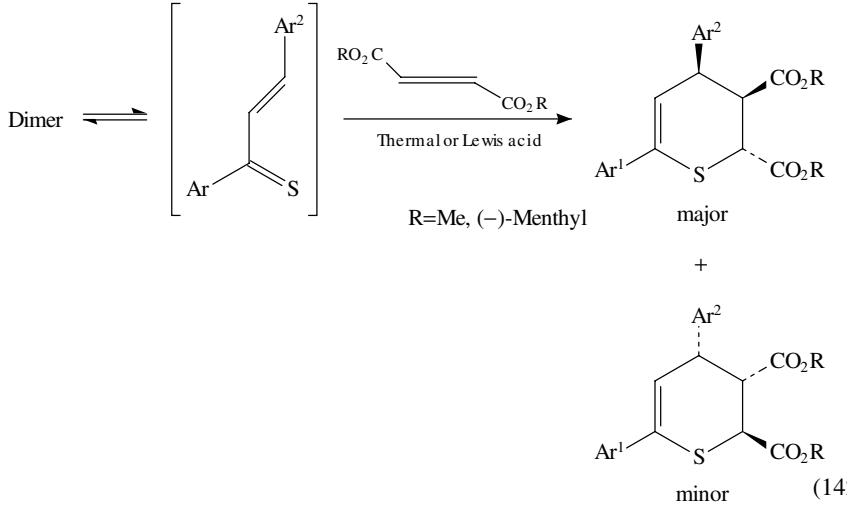
b. Thiocarbonyl compounds as dienes. α,β-Unsaturated thiocarbonyl compounds (1-thiabutadienes), although usually not stable at room temperature, have been employed in Diels-Alder reactions to prepare thiopyranyl systems[226,472]. Equation 141 shows the formation of thiometacrolein and its subsequent cycloaddition.



(141)

The parent compound, thioacrolein, affords similar cycloadducts which are present in garlic and show potent antithrombotic activity[479,480].

Mechanistic studies were performed for simple systems such as 1-thiabutadiene and ethylene[481], although dimerization and cycloaddition of thiochalcones have received more attention, including several calculations[482–484]. Nevertheless, more synthetic utility possesses the uses of Lewis acids as catalysts in hetero-Diels-Alder reactions (equation 142)[485,486] involving 1-thiabutadienes.

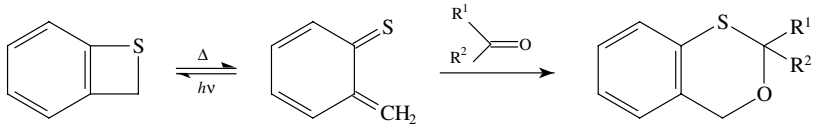


(142)

Among the Lewis acids investigated, $AlCl_3$ and $EtAlCl_2$ were found to accelerate remarkably the reaction even at low temperatures, the reaction being very slow in the absence of catalyst[486], and the asymmetric version has also been reported[485].

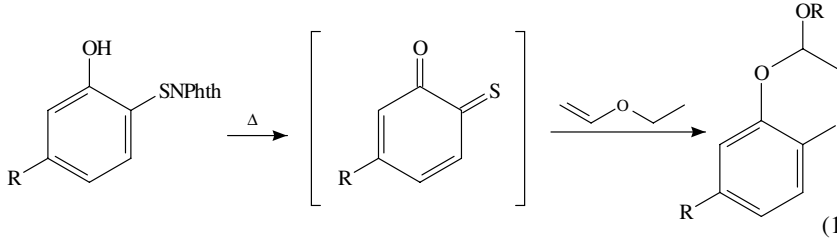
As described earlier *o*-thioquinonemethide can be generated by several routes[353], including thermal ring-opening of benzothietes **72** (Section III.F.3)[357–359], and by reaction with carbonyl compounds it yields benzoxathianes **135** as shown in equation 143[357].

The reaction of **69** with electron-deficient nitriles furnished 4*H*-1,3-benzothiazines[358] and a wide array of cumulenes were allowed to react with this intermediate[359]. On the other hand, the reaction with styrenes afforded a variety of benzothiapyrans[487].



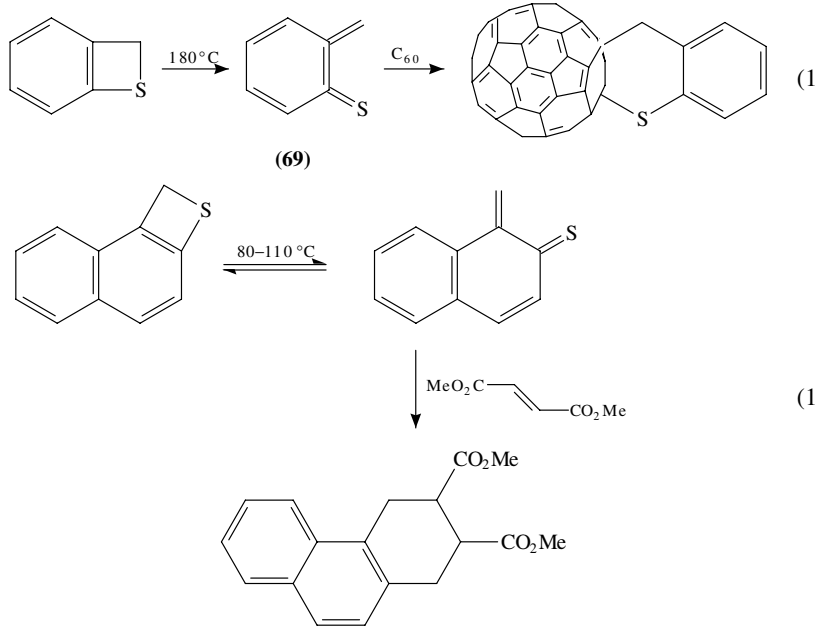
(72) **(69)** **(135)** (143)

o-Thioquinonemethide could also be generated from phthalimidesulfenyl chloride by S,N-cleavage (Section III.E.3) and, by reaction with ethyl vinyl ether, gave rise to a variety of 1,4-oxathianes[331] (equation 144).



(144)

Even derivatization of fullerene was achieved by reaction with *o*-thioquinonemethide **69**[360] (equation 145). Finally, naphthalene analogs of **69** have been discovered and applied in the preparation of angular systems[488] (equation 146).

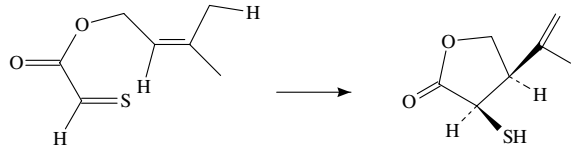


(69) (145) (146)

F. Other Pericyclic Reactions. Ene Reactions

Ene reactions of thiocarbonyl groups have experienced an intense growth in recent years and the intramolecular version, particularly in the hands of Kirby[224] and of Motoki, has become a useful tool in the synthesis of natural products.

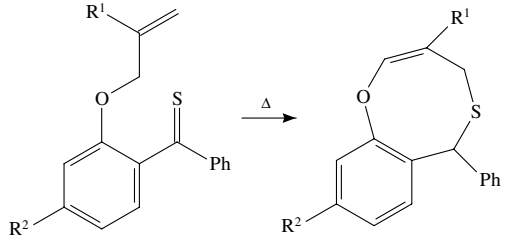
According to Motoki[489] and following known criteria established by Oppolzer and Snieckus[490], there are three different types of intramolecular ene reactions. Kirby pioneered type I[491] consisting of the intramolecular ene reaction of thioaldehydes to afford α-mercapto-γ lactones[347] **136** (equation 147). The *cis* stereochemistry supports a concerted mechanism.



(147)

(136)

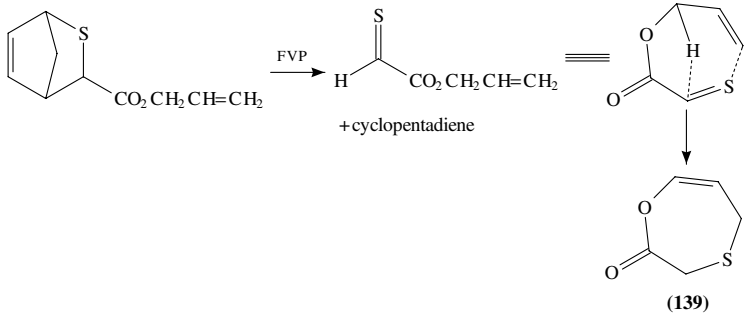
Type II intermolecular ene reaction of thioaldehydes was reported by Vedejs and coworkers[492] and already mentioned by Schaumann[1]. Type III has recently appeared and involves the formation of a C−S bond instead of a C−C bond, as in the case of type I. Type III intramolecular ene reaction has been reported for thioketones and for thioaldehydes. The group of Motoki[489] examined the thermal cyclization of *o*-(2-substituted allyloxy) thiobenzophenones **137** leading to 1,5-oxathiocine derivatives **138** (equation 148).



(148)

(137) **(138)**

The course of the reaction was largely influenced by the nature of the substituents and the chain length[493]. Finally, Kirby has also applied type III of intramolecular ene reaction of thioaldehydes for the preparation of macrocyclic thia-alkenolides[494,495] **139** (equation 149). The starting thioaldehydes were generated by FVT.



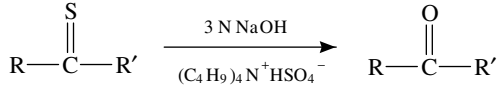
(149)

(139)

Thialactones **139** may undergo further transformations, namely for higher homologs, [3,3] sigmatropic rearrangements[495].

G. Desulfurization Reactions

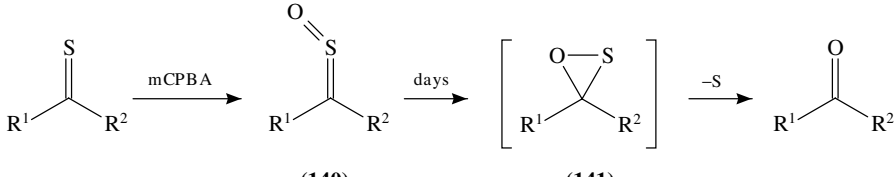
The S/O exchange represented by the direct transformation of a thiocarbonyl group into a carbonyl group has received scarce attention in the scientific literature, although some hydrolytic methods have been reported[432], such as the use of PT catalysts (equation 150) introduced by Alper and coworkers[496]. This method has broad scope and yields are usually high.



(150)

Another reagent which can effect the conversion of C=S into C=O is mercuric acetate under reflux[371].

An indirect strategy consisting of the slow decomposition of sulfines **140** into ketones has been investigated by Metzner[409,410] (equation 151).



(140) **(141)**

(151)

Sulfines are obtained by oxidation of thioketones and, after some days, elemental sulfur is formed and the corresponding ketones are produced quantitatively. A possible mechanism is the thermally allowed electrocyclization of sulfines to give an intermediate oxathiirane **141** which, upon sulfur extrusion, affords the corresponding ketones[409].

Finally, we have already mentioned (Section IV.D) that sodium telluride in aqueous media regenerated the original ketones from thioketones[434].

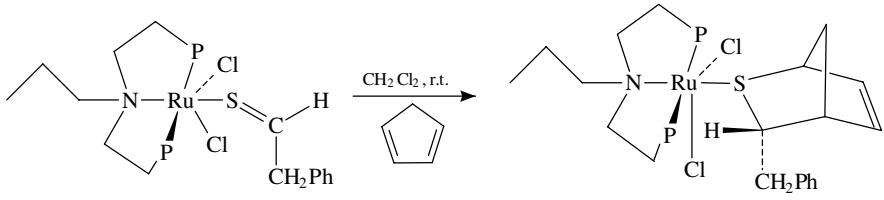
H. Synthetic Applications of Organometallics and Complexes

In Section III.K we have briefly summarized the major advances in the preparation of thiocarbonyl compounds stabilized by organometallics. The synthetic applications of this kind of reagents have experienced impressive growth in recent years and major contributions will be collected in this section, although the interested reader is referred to specialized Serials on this subject.

Organometallic thioketones behave as dienophiles in the reactions with cyclopentadiene[497] and also undergo attack by butyllithium to give mostly reaction at the thiocarbonyl sulfur. The organometallic moiety (ferrocenyl, Mn complex etc.) is inert under these reaction conditions[498].

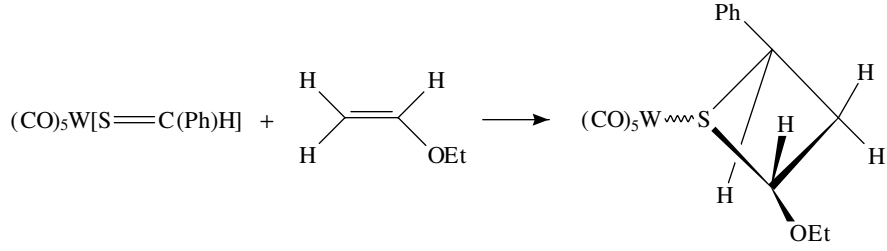
Ruthenium thiobenzaldehyde[499] or other thioaldehyde complexes undergo Diels-Alder cycloadditions yielding readily the corresponding adducts with cyclopentadiene[499–501] as shown in equation 152[500]. *Endo* stereoselectivity is observed and the adduct can be removed from the metal by simply heating a $CHCl_3$ solution of **142** under reflux. However, in the absence of a specific reagent for trapping the phenylethanethial, this spontaneously

oligomerizes. The addition of O-, S- and C- nucleophiles to ruthenium–thioaldehyde complexes has also been studied by Schenk's group[501].



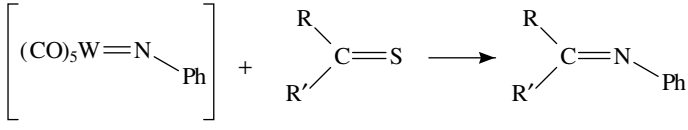
(142) (152)

More attention has been paid to tungsten complexes and Raubenheimer and coworkers[502] studied the reactions of carbene complexes such as $[W(CO)_5\ \{C(OEt)Ph\}]$ with a variety of electrophiles to give coordinated thioaldehydes. Fischer's group has reported many studies on the behavior of pentacarbonyltungsten-coordinated thiobenzaldehyde $[(CO)_5W\ \{S{=}C(Ph)H\}]$ with vinyl ethers[503] (equation 153) and alkynes[504].



(143) (153)

Regiospecific addition took place affording good yields of thietanes **143**[503] and, with alkynes, diene systems were formed[504]. Fischer has also described the reactions of thioketones with $(CO)_5W{=}NPh$ which undergo metathesis with these substrates to yield N-phenyl imines **144**[505] as shown in equation 154.

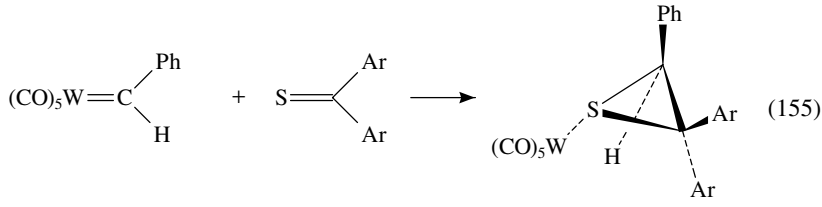


(154)

R = aryl, alkyl
R′= aryl, H

(144)

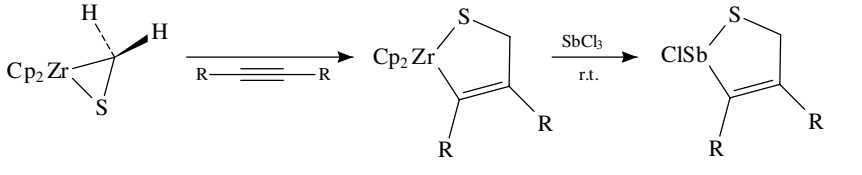
In a related reaction, the benzylidene complex $(CO)_5W{=}C(Ph)H$ reacted with several diaryl thioketones affording thiirane complexes **145**[506] (equation 155).



(155)

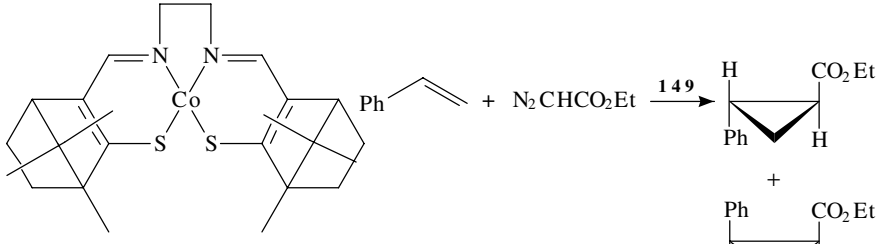
(145)

Only one isolated example of formation of thioketene and thioaldehyde dimolybdenum complexes has been reported[507], but in contrast, zirconocene thioacetaldehyde and thiobenzaldehyde complexes, introduced by Buchwald, have been the subject of several studies[508], including their application in the synthesis of novel antimony thiametallacycles **148**[509] (equation 156). Compound **146** was generated *in situ* and, after reaction with alkynes, gave rise to metallacycles **147** which, by treatment with $SbCl_3$, afforded **148**.



(146) **(147)** **(148)** (156)

Finally, several complexes of chiral β-thioxoketones have been prepared[510] and the cobalt complex **149** has found an interesting synthetic application as catalyst in asymmetric cyclopropanation reactions (equation 157)[511].



(149) (157)

Chemical yields were acceptable (50–60%) but, notably, enantioselectivity was very good (75%). The ee increased to 97% when 1-octene was used as olefin.

I. Quantitative Aspects of the Basicity of Thiocarbonyl and Carbonyl Compounds

The adiabatic ionization potentials of **5** and **6** are respectively 9.376 ± 0.003 and 10.874 ± 0.002 eV[75]. This helps explain why, in processes involving donor–acceptor interactions such as CT[512–516] and alkylation (formally similar to Menshutkin

reactions[517])[518,519], thiocarbonyl compounds are more reactive than their carbonyl homologues. Other factors come into play, notably the difference in the stabilities of the reaction products (in the case of the formation of covalent bonds), the size of the electronic 'lone pairs' in the case of hydrogen bonding and the polarizability of the heteroatoms in the case of electrostatic complexes with alkali metal ions[116]. These factors might lead to an inversion of the ranking of reactivities.

1. Proton and methyl cation basicities

The intrinsic basicity (i.e. the standard Gibbs energy change for reaction 158 in the gas phase) for a variety of compounds XC(=S)Y have been determined by means of Fourier Transform lon Cyclotron Resonance Spectroscopy (FT ICR) by the groups of Abboud[39] and of Gal[520].

$$BH^+(g) \longrightarrow B(g) + H^+(g) \qquad (158)$$

Table 16 summarizes these results together with data from other sources for the homologous carbonyl compounds. Other values are given elsewhere[39]. Figure 2 is a plot of GB (XCSY) vs GB (XCOY) obtained from the data given in Table 16.

As shown in this plot, the quality of the correlation is extremely good. The breadth of structural effects involved (72.1 and 59.1 kcal mol^{-1} for carbonyl and thiocarbonyl compounds, respectively) is possibly the largest ever reported for any linear free-energy relationship (LFER)[521]. It is known[88] that, in the gas phase, carbonyl compounds protonate on the carbonyl oxygen. The LFER shown above very strongly suggests[39] that the homologous thiocarbonyl compounds also have a constant basic center, namely the sulfur atom of the CS group. Theoretical calculations[39] confirm this contention.

The slope of the correlation equation (*ca* 0.80) reflects the fact that differential substituent effects are 20% smaller in the thiocarbonyl series. This notwithstanding, thiocarbonyl compounds are consistently more basic than their carbonyl homologs over the entire range of reactivity examined in this work.

TABLE 16. Gas-phase basicities (GB) for thiocarbonyl and carbonyl compounds

Substituents		GB (kcal mol^{-1})[a]	
X	Y	X(CO)Y[b]	X(CS)Y[b]
$N(CH_3)_2$	$N(CH_3)_2$	214.2	218.1
CH_3	$N(CH_3)_2$	209.0	213.7
$NHCH_3$	$NHCH_3$	208.3	213.2
1-$C_{10}H_{15}$	1-$C_{10}H_{15}$	205.5	209.4
H	$N(CH_3)_2$	203.8	208.0 (207.9)[c]
CH_3O	$N(CH_3)_2$	201.9	205.7
C-C_3H_5	C-C_3H_5	201.4	207.1
NH_2	NH_2	200.7[d]	205.1
t-C_4H_9	*t*-C_4H_9	198.4	202.2
camphor	thiocamphor	197.3	201.7
CH_3	OC_2H_5	191.4	197.0
H	H	162.3	177.0
F	F	142.1	159.0

[a] GB(NH_3) = 195.3.
[b] Values from Reference 39.
[c] Values from Reference 520.
[d] Values from Reference 536.

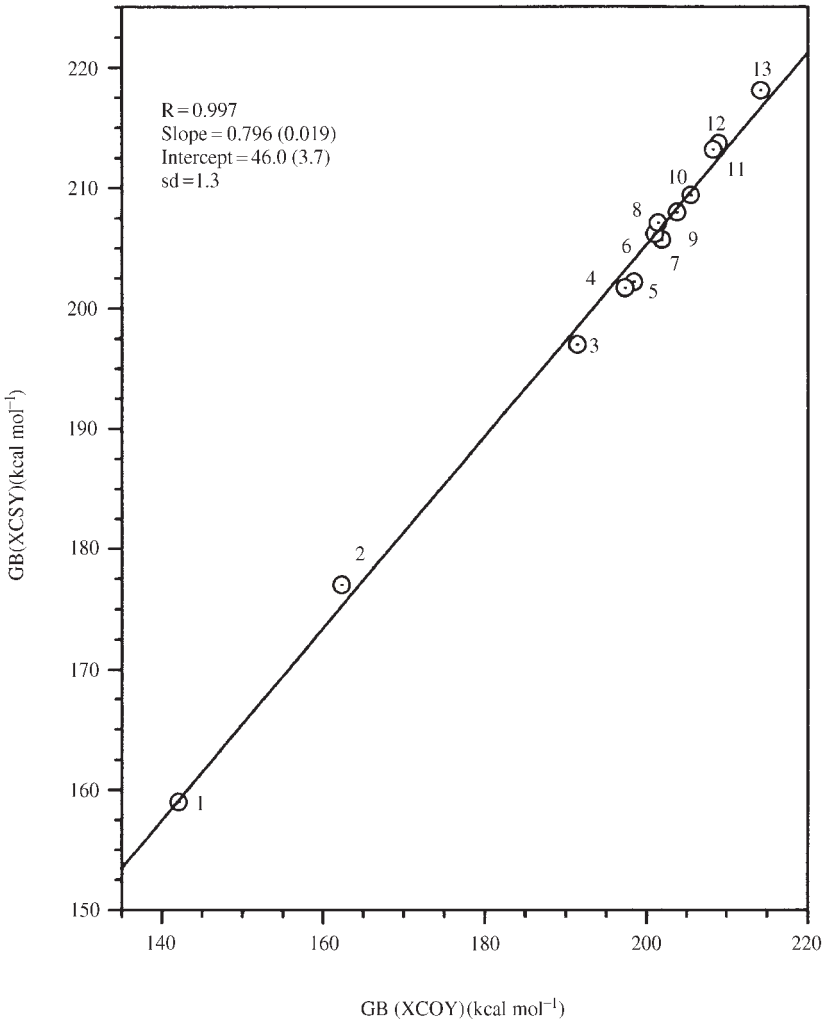
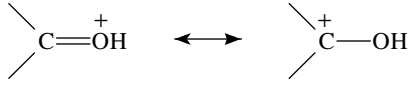


FIGURE 2. Relationship between the experimental gas-phase basicities of thiocarbonyl and carbonyl compounds

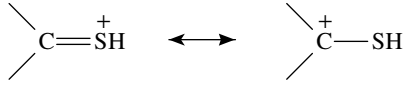
Experimental evidence indicates that most ketones, esters, amides and ureas also protonate on the carbonyl oxygen when in acidic solution[522,523] and the same holds for the homologous thiono compounds[524,525]. At variance with the gas-phase results, however, in the few instances in which a direct comparison of the pK_a values of the corresponding conjugated acids can be carried out[522,524] as in the case of the couples CH_3CONH_2/CH_3CSNH_2, $C_6H_5CONH_2/C_6H_5CSNH_2$ and ε-caprolactam/ε-thiocaprolactam, one finds that the tiocarbonyl compound is more basic by 1.5–2.0 pK units. This is likely a consequence of two facts: (i) the strong attenuation of polarizability effects in aqueous solution[526] (pK_a values are referred to a standard state of pure

water) and (ii) the poorer solvation of the protonated thiocarbonyl compounds in aqueous solution. This last point agrees with the hydrogen-bonding acidity of thiols being much smaller than that of alcohols[527] as well as with the values of the experimental solvation parameters, such as Olsen's ϕ[528] or Marziano–Cimino–Passerini's[529,530] or Cox–Yates[531,532] m^*. For the latter, it is found that $m^*(CS) > m^*(CO)$. The reader is referred to the important work by Bagno and Scorrano[533] on the physical meaning and derivation of these parameters. These authors pointed out[533] that, when the weaker base (as measured by the pK_a of the conjugate base) has a larger m^* value (as is the case here), the basicity gap narrows and eventually leads to a crossover as one moves from pure water to increasingly acidic solutions. This bridges smoothly the gap between the relative basicities of homologous carbonyl and thiocarbonyl compounds in the gas phase and in pure water. It is remarkable that, while it had been predicted[39] that — on the basis of the experimental data available in the gas phase and in solution for CH_3CONH_2 and CH_3CSNH_2 — the crossover should take place in a 50% weight solution of H_2SO_4, Bagno and coworkers[534] reported in an independent and parallel experimental study that the crossover for the cognate couple CH_3CONMe_2/CH_3CSNMe_2 takes place in a 48% solution of H_2SO_4. In Reference 39 the proton affinities PA (that is, the standard enthalpy changes for reaction 158) were computed theoretically at the MP2/6-31+G(d,p)//6-31G(d)+ZPE level. The calculated and experimental values of the proton affinities displayed an excellent correlation. Furthermore, this allowed the estimation of the proton affinities for a large number of thiocarbonyl compounds HCSX for which experimental data were not available. A treatment of these results by means of the Taft–Topsom[88,535] method in terms of the σ_α, σ_F and σ_{R+} parameters displayed excellent statistical quality and showed, as expected, that field and resonance effects oppose each other, as in the case of the carbonyl compounds[88]. As for the latter, polarizability contributions were found to be quite important.

The correlation portrayed in Figure 2 is deceiving, in that it suggests a great similarity between C=O and C=S compounds. Yet, O and S atoms widely differ in size and electronegativity[1]. This formal analogy originates in canonical structures such as **150b** and **151b** wherein the positive charge of the incoming proton is relayed to the sp^2 carbon through O and S.



(150a) **(150b)**

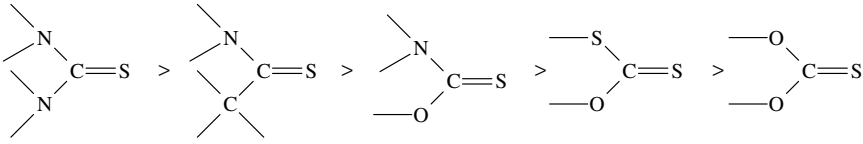


(151a) **(151b)**

Alcami and coworkers[116] have examined in detail the protonation of **5** and **6** and they found that the charge redistributions undergone upon protonation are very different. In the case of $\mathbf{6H^+}$, the net atomic charge on the oxygen is practically the same as in **6**. This is a consequence of the large electronegativity of oxygen: this atom overcomes the loss of 0.24 σ electrons with the gain of 0.24 π electrons. In the case of $\mathbf{5H^+}$, the more polarizable and less electronegative sulfur atom loses 0.7 σ electrons and recovers 0.18 π electrons only. In the cases of substituted compounds, the protonated heteroatoms become

again π-electron deficient and polarize the p–π system(s) of the substituents, if available. This helps to understand the comparable (albeit somewhat reduced in the case of CS) stabilizing effect of potential π electron-donor substituents in the two series of protonated compounds as well as the planarity of the amino groups in protonated amides/thioamides (a similar behavior has been reported for urea[536]). The π-interactions mentioned in the case of the neutral species are enhanced in the case of the protonated forms. The possible CT from the substituent to the electron-deficient carbon is less favorable the greater is the electronegativity of the substituent. As a result, for monosubstituted, protonated C=O and C=S compounds, the ranking of substituent effects on basicity is $NH_2 > OH > F$.

In the case of disubstitution, the ranking of substituent effects on the intrinsic basicities of C=S compounds, both measured or calculated[39], is as follows:



Arbelot, Chanon and coworkers have reported[518,519] kinetic data on the alkylation of thiocarbonyl bases, XCSY with MeI in Me_2CO at 25.0 °C, equation 159:

$$XC(=S)Y + MeI \longrightarrow [XC(SMe)]^+ + I^- \tag{159}$$

Representative values are given in Table 17.

A direct comparison of Gibbs energies of activation, $\Delta G^{\ddagger}$, and the corresponding gas-phase basicities is not yet possible, because their database is mostly built on cyclic compounds for which gas-phase data are not available. However, the trend of increasing $\Delta G^{\ddagger}$ with substitution α to the thiocarbonyl is exactly the same as decreasing intrinsic basicity given above. It has been shown[537] that 'extended' Brønsted equations can be obtained that link the gas-phase basicities of $N(sp^2)$ and $N(sp^3)$ bases with their nucleophilicities towards MeI in MeCN solution at 25.0 °C. The above points at the likelihood of this being also the case here. These experimental facts and inferences derived therefrom are further supported by G2(MP2) calculations of the methyl cation affinities MeA (i.e. the standard enthalpy change for reactions such as 160 in the gas phase):

$$[XC(=SMe)Y]^+(g) \longrightarrow XC(=S)Y(g) + Me^+(g) \tag{160}$$

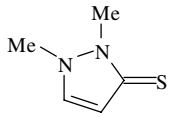
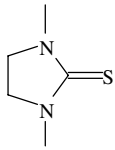
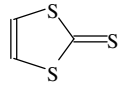
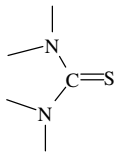
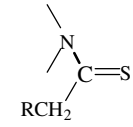
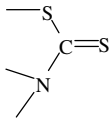
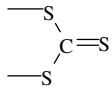
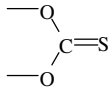
These calculations show that: (i) the methyl affinities (MeAs) of C=S compounds are consistently much higher (for X = H, 15 to 25 kcal mol^{-1} over the range Y = F to $Y = NH_2$) than those of the C=O homologs, and (ii) the sensitivity to substituent effects of the thiocarbonyls is *ca* 72% that of the carbonyls. Protonation and methylation therefore display the same pattern of structural effects (there is also a nearly perfect correlation between the PAs and MeAs for each family, although in all cases the PA exceeds the MeA by some 100 kcal mol^{-1}).

Arbelot and Chanon[518,519] have also reported a comprehensive series of semiempirical calculations that conclusively show the dependence of the kinetic reactivity in reaction 159 on the energy of the sulfur lone-pair orbitals.

2. Charge-transfer (CT) complexes

Suszka[538] has reported spectroscopic and thermodynamic data on the association of imidazole-2-thiones and *N*,*N*′-dialkylthioureas with SO_2 in a variety of solvents.

TABLE 17. Rate constants in $mol^{-1}\,s^{-1}$ for reaction 158 at 25.0 °C[518,519]

Compound	$k(mol^{-1}s^{-1})$
	4×10^{-1}
	3×10^{-3}
	6.5×10^{-6}
	1.5×10^{-3}
	5×10^{-4}
	1×10^{-5}
	5×10^{-7}
	9×10^{-9}

Complexes with diiodine have received much more attention. To our knowledge, the most complete database is that by Bouab and Esseffar[539], who have carried out a very thorough comparison of the thermodynamics of the 1 : 1 CT associations between a variety of C=S and C=O compounds in solution in *n*-heptane and other 'inert' solvents. Representative results are given in Table 18.

This table shows that complexes involving C=S have a much greater stability than those involving C=O. However, log K_c values for both families are linearly related to a

TABLE 18. Equilibrium constants K_c (in $l\,mol^{-1}$) for the formation of 1 : 1 CT complexes between I_2 and selected thiocarbonyl compounds in *n*-heptane at 25.0 °C[539]

Compound	K_c	
	X = O	X = S
$HC(=X)N(CH_3)_2$	6.4±0.6	1570±38
$CH_3C(=X)N(CH_3)_2$	15.0±0.4	1790±95
$ClC(=X)N(CH_3)_2$	0.70±0.08	14.5±1.5
$(C_2H_5O)_2$ C=X	0.62±0.07	7.0±0.8
Camphor/thiocamphor	2.50±0.15	110±9
$CH_3OC(=X)N(CH_3)_2$	3.80±0.55	155±12
$[(CH_3)_2N]_2$ C=X	14.3±0.9	$(1.01 \pm 0.10) \times 10^4$

good degree of precision. In this case, and at variance with protonation, the sensitivity of the stability constant to π-electron donation by the substituents is *ca* 60% higher for C=S than for C=O. This should follow from the increased electron demand in the case of the C=S...I=I complexes in which the extent of actual CT is more important.

UV-visible spectroscopic data for these systems also display a number of remarkable features. Thus, in the case of bulky thioamides and tetrasubstituted ureas, there are indications of the existence of two different 1 : 1 complexes. Their possible structures are presently being studied by means of high level *ab initio* calculations[540].

Freeman, Po and coworkers[541] have determined the X-ray structures of the crystalline 1 : 1 CT complexes of I_2 with imidazole-2-thione **(152)**, 1-methylimidazole-2-thione and 1,3-dimethylimidazole-2-thione. Devillanova and coworkers[542,543] have carried out similar studies on 1 : 1 complexes involving 5,5-dimethylimidazoline-2,4-dithione **(153)** and 5,5-dimethyl-2-oxoimidazolidin-4-one. In all cases, the S...I–I arrangement is essentially linear. The angles CSI are in the range 90–100°. The stability of the complexes of **152** and its derivatives is much higher than that of **153** as shown by the increase and decrease of the C–S and S...I bond lengths, respectively being more important in **152** and its derivatives. The thermodynamic stability of the complex of **153** substantially increases on going from CCl_4 to CH_2Cl_2 solutions. This confirms the substantial degree of CT involved in these complexes.

3. Hydrogen-bonding (HB) interactions

The diffusiveness of the electronic charge in the 'lone pairs' of sulfur leads to C=S compounds being substantially weaker HB bases than the homologous C=O derivatives. A number of cases in which the C=S group acts as a HB basic site in *intra*molecular interactions have been described earlier. The following deals with 1 : 1 *inter*molecular associations.

The problem of the quantitative ranking of HB basicities was treated simultaneously and independently by groups of Taft[544] and of Abboud[545]. Both took as a starting point the formation constants K_c pertaining to the 1 : 1 association between HB bases B and HB donors ('acids') H–A in 'inert' solvents such as cyclohexane and CCl_4 (reaction 161):

$$B + H{-}A \longrightarrow B \ldots H{-}A \qquad K_c \tag{161a}$$

Taft used $\log_{10} K_c$ for H–A = 4-fluorophenol to define the pK_{HB} scale of basicities through $pK_{HB} = \log_{10} K_c$. Abboud and Bellon used their own experimental data to define parameters quantitatively describing both HB acidity and basicity, $\log_{10} K_c$ being given by a bilinear form of these descriptors. Later on, this approach was applied by Abraham,

Abboud, Taft and collaborators[546] to define the α_2^H and β_2^H scales of HB acidities and basicities.

Quite generally, and for media ranging from the gas phase to CCl_4, it is known[547] that for thousands of (AH, B) systems, the bilinear equation 161b yields $\log_{10} K_c$ values with a satisfactory degree of precision:

$$\log_{10} K_c = a + b \cdot \alpha_2^H(\text{AH}) \cdot \beta_2^H(\text{B}) \tag{161b}$$

wherein a and b are constants.

Experimental data on the HB basicity of the compounds most relevant to this chapter are scarce. Abboud and colleagues[548] summarized the available data in 1988. They also determined new constants for the HB associations between 3,4-dinitrophenol and some thiocarbonyl compounds. Recently, Laurence and coworkers have published new results, particularly for thioamides and thioureas[549]. Some representative data are given in Table 19.

This table shows that: (i) C=S compounds are significantly weaker HB bases than their C=O homologs, a situation similar to that prevailing for S(sp^3) and O(sp^3) bases[548]. (ii) The dependence of β_2^H on substitution needs more data to be fully understood. Thus, it seems that for weakly basic compounds the sensitivity of C=O compounds to substituent effects is more important than that of C=S while for the most basic compounds, sensitivities are nearly the same. (iii) 2,4-bisdimethylamino-4-methyl-1-thia-3-azabutadiene **(154)** is the strongest thiocarbonyl HB base ever reported.

In cases of intermolecular HB the situation is convoluted. On the basis of the available α_2^H and β_2^H parameters we know that, for homologous series of monofunctional compounds, $\alpha_2^H(\text{OH}) > \alpha_2^H(\text{SH})$ and $\beta_2^H(\text{C=S}) > \beta_2^H(\text{C=O})$. The orders of magnitude are such, however, that the product $\alpha_2^H(\text{OH}) \cdot \beta_2^H(\text{C=S})$ is larger than the product $\alpha_2^H(\text{SH}) \cdot \beta_2^H(\text{C=O})$. On the basis of equation 161b this fact, alone, would tend to shift the equilibrium towards the enol form of thioxoketones and thioxoaldehydes Of course, other factors come into play (see Section II).

4. Lithium cation affinities

A wealth of thermodynamic data are available for reaction 162 in the gas phase.

$$\text{XC(=O)Y(g)} + \text{Li}^+\text{(g)} \longrightarrow [\text{XC(=O}\ldots\text{Li)Y}]^+\text{(g)} \tag{162}$$

TABLE 19. Hydrogen-bonding basicity parameters for selected thiocarbonyl and carbonyl compounds

Compound	β_2^H (C=S)	β_2^H (C=O)
Thiocamphor	0.31[a]	
Diethylketone		0.48[b]
Cyclohexanone		0.52[b]
$HC(=X)NMe_2$	0.46[a]	0.66[b]
$CH_3C(=X)NMe_2$	0.52[a]	0.73[b]
$MeOC(=X)NMe_2$	0.41[a]	
$MeSC(=X)NMe_2$	0.38[a]	
$Me_2NCH=N(C=X)NMe_2$	0.68[a]	
$Me_2NC(=X)NMe_2$	0.53[a]	0.74[b]

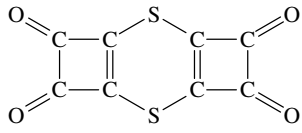
[a]From Reference 549.
[b]From Reference 546.

Such information is not yet available for C=S compounds, although Alcami and coworkers[116] and Speers and Laidig[550] have reported results of theoretical studies, which include a number of G2(MP2) calculations on both families of compounds[116]. They show that, while the binding of $Li^+(g)$ involves essentially electrostatic interactions in both cases, the structures and energetics of the Li^+ adducts of C=O and of C=S are profoundly different. At the MP2/ 6-31+G(d, p) level, for example, Li^+ is found along the C_2 symmetry axis of H_2CO and close to the oxygen atom. In the case of thioformaldehyde, Li^+ is located near the sulfur atom, but now the LiSC angle amounts to 107.5°. This indicates that in the first case the ion is located *between* the lone pairs of the oxygen, while in the second, it is *aligned with* one of the sulfur lone pairs. A detailed discussion of various other carbonyl and thiocarbonyl compounds is given[116]. From the thermodynamic point of view, the lithium cation affinities of thiocarbonyls are appreciably smaller than those of carbonyls, at variance with the behavior towards the proton.

J. Synthesis and Reactivity in a Mass Spectrometer

Over these last few years, a powerful technique, neutralization–reionization mass spectrometry (NRMS), has been developed that allows the generation and study of highly reactive species[20–22,551]. This technique has obviously not reached the 'preparative' scale of FVP but, nevertheless, it has led to some important discoveries. Typically, instruments of this sort are built around a multisector mass spectrometer[552]. Ions are generated by ionization of neutral species, ion dissociation or ion–molecule reactions[553]. These primary ions can be characterized by appropriate techniques such as collision-induced dissociation (CID)[554]. Then, they are selected and separated under the influence of electric and magnetic fields. The selected ions are neutralized (e.g. with metal vapor or Xe) in the first collision chamber and the remaining ions are ejected. The fast neutral beam thus obtained undergoes collisions with a target neutral gas, such as O_2, in the second collision chamber, this leading to a reionization process. The ions thus generated are mass-analyzed and identified.

An example is provided by thioxoethylenone, O=C=C=S. Its radical cation **(155)** can be generated[555] by electron impact (70 eV) on its precursor **(156)** (equation 163).



(163)

(156) **(155)**

In the first experiment, **155** thus generated was decomposed by collision. In the second one, the ion upon neutralization led to O=C=C=S which, in turn, was reionized and collision-decomposed. The MS obtained in both cases were essentially identical, showing the existence and stability (within the time scale of the experiment) of both O=C=C=S and **155**.

In the field of C=S chemistry this method has proven to be quite useful to generate and identify species such as: C=C=S[556], S=C=C=S[176] and S=C=C=C=C=S[556].

Later on, Schwarz and coworkers[557] have described the generation of both even- and odd-numbered polycarbon disulfides $S(C_n)S$ with $n = 2–6$.

Flammang, Wong, Wentrup and collaboration have reported the preparation and characterization of (methylimino)ethenethione, $CH_3N=C=C=S$ and iminoethenethione, HN=C=C=S[558], and of their oxygen homologues[559]. These compounds are stable on the microsecond time scale. They were also studied theoretically, at the G2(MP2) level.

V. COORDINATION CHEMISTRY

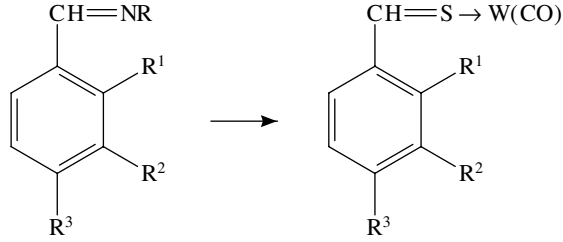
The versatility of sulfur as the heteroatom in hetero-organic ligands has been the source of the diversity of organosulfur ligands known today[30]. Since Schaumann's chapter[1], there have been several studies about coordination complexes involving thioketenes and thioaldehydes as ligands. For example, complexes of thioketenes with Mo[560], Os[561,562], W[563–565], Co[566], Fe[566,567], Ru[568], Ti[569] and of thioaldehydes with Mo[560], Re[570], Ti[571,572], W[502,573,574] and Ta[575] have been reported.

To obtain thioaldehyde complexes, Muraoka and coworkers[573] have synthesized a new reagent $[PPh_4][W(CO)_5SH]$ according reaction 164:

$$[NEt_4][W(CO)_5] \xrightarrow{i} [W(CO)_5(C_4H_8O)] \xrightarrow{ii} [PPh_4][W(CO)_5SH] \qquad (164)$$

Reagents and conditions: (i) $AgNO_3$–H_2O, THF, room temp., 30 s (*ca* 100%);
(ii) $[PPh_4]SH$–EtOH, THF,20 °C, 30 s(95%).

Aromatic thioaldehyde pentacarbonyltungsten(0) complexes were synthesized by treatment of *N*-phenyl or *N*-cyclohexyl imines of aryl aldehydes with $[PPh_4][W(CO)_5SH]$ in CH_2Cl_2 or C_6H_6 in the presence of $BF_3 \cdot OEt_2$ and $MeCO_2H$ (reaction 165):



(165)

Reagents and conditions: $[PPh_4][W(CO)_5SH]$, $BF_3 \cdot OEt_2$–$MeCO_2H$, C_6H_6 or CH_2Cl_2,room temp.

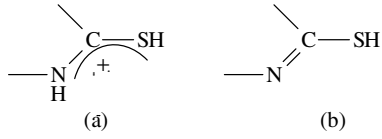
Similar pentacarbonyltungsten(0) complexes of heteroaromatic thioaldehydes, such as 2-thioformylfuran 2-thioformylthiophene, thioarylenals or thioaryldienals, were also synthesized[573].

Heterocyclic thiones have been extensively studied because of their facility to yield coordination complexes. All the ligands contain thione and occasionally thiol (mercapto) groups directly attached to the carbon atoms of heterocyclic molecules. They have been previously reviewed by Raper in 1985[576], and very recently the same author has reviewed[28] the copper complexes of heterocyclic thioamides and related ligands.

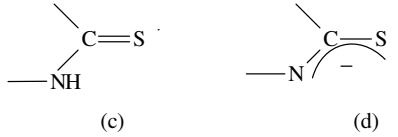
The combination of an exocyclic thione group and a heterocyclic molecule, which may contain nitrogen, oxygen, sulfur or a combination thereof, generates a group of molecules with considerable coordination potential.

An important factor in realizing such potential is that of prototropic tautomerism and, in particular, which tautomer is present in solution immediately prior to the formation of the metal–ligand bond[576]. A common feature of all nitrogen-containing heterocyclic thiones is thione **(157c)**–thiol **(157b)** tautomerism.

As already discussed above, the thione–thiol equilibrium is dependent on environmental factors with the thiol form favored in the gas phase and nonpolar solvents, and the thione form favored in the solid state and polar solvents.

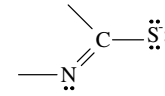


(a) (b)



(c) (d)

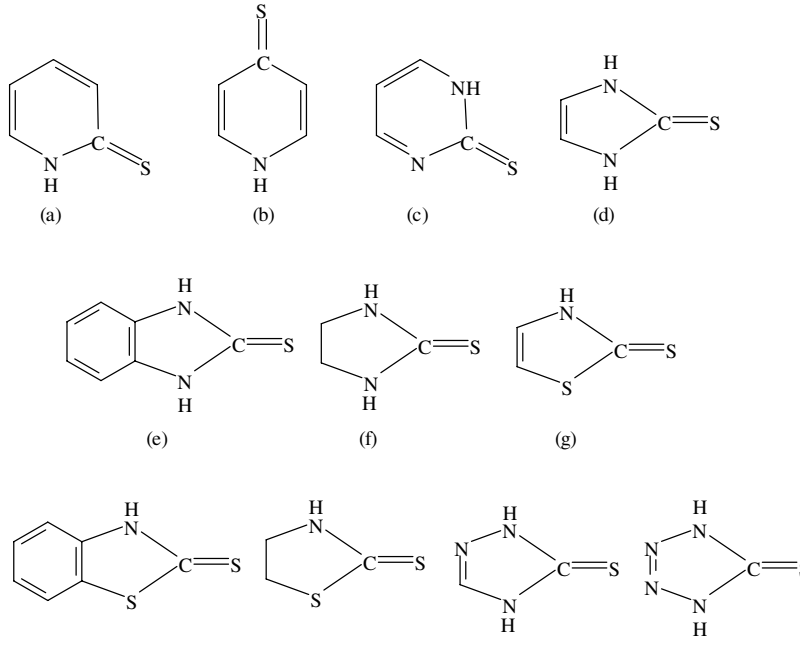
(157)



(158)

Deprotonation of heterocyclic 'thiones' **(157c)** produces the corresponding 'thionate' ion **(157d)** in which an electron pair on the heterocyclic trigonal nitrogen and three electron pairs on the thionate sulfur generate considerable coordination potential **(158)**.

Among the heterocyclic thiones, we present in Tables 20–25 the metal complexes of some of the thiocarbonyl ligands most widely used, which are represented in Figure 3. In these tables, data are given from 1988. In the case of copper, only complexes reported since Raper's review[28] are given.



(a) (b) (c) (d)

(e) (f) (g)

(h) (i) (j) (k)

FIGURE 3. Thiocarbonyl ligands involved in Tables 20–25: (a) pyridine-2-thione, (b) pyridine-4-thione, (c) pyrimidine-2-thione, (d) 1,3-imidazoline-2-thione, (e) benz-1,3-imidazoline-2-thione, (f) 1,3-imidazolidine-2-thione, (g) 1,3-thiazoline-2-thione, (h) benz-1,3-thiazoline-2-thione, (i) 1,3-thiazolidine-2-thione, (j) 1,2,4-triazoline-3(5)-thione, (k) 1,2,3,4-tetrazoline-5-thione

TABLE 20. Metal complexes of pyridine-thiones

Ligand(LH)	Metal	Ligand type	Stoichiometry metal : ligand	References
Pyridine-2-thione	Au(I)	L^-	1 : 2	577
			1 : 1	578
		LH	1 : 1	579, 580
			1 : 2	579
	Ag(I)	LH	1 : 1	581
	Cu(I)	LH	1 : 1	582–584
			1 : 2	585
	Os(II)	L^-	1 : 2	586
	Zn(II)	LH	1 : 2	587
	Ru(II)	L^-	1 : 2	588, 589
		LH	1 : 2	588
	Ni(II)	L^-	1 : 1	590
			1 : 2	591
	Fe(II)	LH	1 : 2	592
	Mn(II)	LH	1 : 4	593
	Cd(II)	LH	1 : 2	587
	W(II)	LH	1 : 1	594
		L^-	1 : 2	594
	Mo(II)	LH	1 : 1	594
		L^-	1 : 2	594
	Pd(II)	L^-	1 : 1; 3 : 2	595
	Fe(III)	LH	1 : 1; 1 : 3	596
	Co(III)	L^-	1 : 3	597
	Re	L^-	1 : 1	598
Pyridine-4-thione	Au(I)	LH	1 : 1	580
	Ag(I)	LH	1 : 1	581
	Ni(II)	L^-	1 : 1	590
1-Hydroxypyridine-2-thione	Cu(II)	L^-	1 : 1	599
			1 : 2	600
	Ru(II)	L^-	1 : 2	589
	Mn(II)	L^-	1 : 2	600
	Co(II)	L^-	1 : 2	600
	Ni(II)	L^-	1 : 2	600
	Zn(II)	L^-	1 : 2	600
	VO_2^+	L^-	1 : 2	600
	Mn(III)	L^-	1 : 3	601
	Cr(III)	L^-	1 : 3	600
	Fe(III)	L^-	1 : 3	600
6-*N*, *N*-Dimethylcarbamoyl-1-hydroxypyridine-2-thione	Zn(II)	L^-	1 : 2	602
6-*N*, *N*-Diethylcarbamoyl-1-hydroxypyridine-2-thione	Zn(II)	L^-	1 : 2	602
3-Hydroxy-6-methyl-pyridine-2-thione	Ni(II)	LH	1 : 2	603
	Cu(II)	LH	1 : 2	603
6-Methylpyridine-2-thione	Ru(II)	LH	1 : 2	588
		L^-	1 : 2	588
	Pd(II)	L^-	1 : 1	595
	Re	L^-	1 : 1	598

(*continued overleaf*)

TABLE 20. (*continued*)

Ligand(LH)	Metal	Ligand type	Stoichiometry metal : ligand	References
3-Trimethylsilylpyridine-2-thione	Cu(I)	L^-	1 : 1	604
	Ni(II)	L^-	1 : 2	604
	Zn(II)	L^-	1 : 2	604
	Cd(II)	L^-	1 : 2	604
		LH	1 : 1	605
6-Substituted-4-aryl-3-cyanopyridine-2-thiones	Ni(II)	L^-	1 : 2	606–608
	Zn(II)	L^-	1 : 2	606–608
	Co(II)	L^-	1 : 2	606, 608
	Cu(II)	L^-	1 : 2	606, 608

TABLE 21. Metal complexes of pyrimidine-thiones

Ligand(LH)	Metal	Ligand type	Stoichiometry metal : *ligand*	References
Pyrimidine-2-thione	Au(I)	L^-	1 : 2	577
			1 : 1	578
		LH	1 : 1; 1 : 2	579
	Ag(I)	LH	1 : 1	581
	Cu(I)	LH	1 : 1	582,609
	Zn(II)	L^-	1 : 2	610
	Cd(II)	L^-	1 : 2	610
	Ni(II)	L^-	1 : 1	590
			1 : 2	611
	Pd(II)	LH	1 : 1; 1 : 2	612
		L^-	1 : 1; 1 : 2	612
	Pt(III)	L^-	2 : 5	613
	Sn(IV)	L^-	1 : 2	614
		LH	1 : 2	614
4,6-Dimethylpyrimidine-2-thione	Cu(I)	L^-	1 : 1	615, 616
	Cd(II)	L^-	1 : 2	617
	Ni(II)	L^-	1 : 2	617
	Zn(II)	LH	1 : 2	618
	Re(III)	L^-	1 : 1	619
	Ru	LH	3 : 2	620
	OS	LH	3 : 2	620,621
	Re(V)	L^-	1 : 1	619
1-Phenyl-4,6-dimethylpyrimidine-2-thione	Ni(II)	LH	1 : 1; 1 : 2; 1 : 3	622
	Co(II)	LH	1 : 1; 1 : 2; 2 : 3	623
4-Hydroxy-6-methylpyrimidine-2-thione	Cu(I)	L^-	1 : 1	624
4,6-Diaminopyrimidine-2-thione	Co(III)	L^-	1 : 1; 1 : 2	625
2,4-Diaminopyrimidine-6-thione	Co(III)	L^-	1 : 1; 1 : 2	625

TABLE 22. Metal complexes of imidazoline-thiones

Ligand(LH)	Metal	Ligand type	Stoichiometry metal : ligand	References
1,3-Imidazoline-2-thione	Cu(I)	LH	1 : 1	584, 609
	Sn(IV)	LH	1 : 2	626, 627
	Fe(II)	LH	1 : 2	628
Methylimidazoline-2-thione	Cu(I)	LH	1 : 1	582
	Ag(I)	LH	1 : 1	581
	Fe(II)	LH	1 : 2	628
	Ni(II)	L^-	1 : 1	590
		LH	1 : 4	629
	Pb(II)	LH	1 : 3	630
	Sn(IV)	LH	1 : 1	631, 632
			1 : 4	633
1,3-Dimethylimidazoline-2-thione	Pb(II)	LH	1 : 2	634
	Cd(II)	LH	1 : 2	634
4,5-Diphenylimidazoline-2-thione	Ag(I)	LH	1 : 1	635
		L^-	1 : 1	635
Benz-1,3-imidazoline-2-thione	Cu(I)	LH	1 : 1	582–584, 609
	Cu(II)	LH	1 : 1	636
	Au(I)	L^-	1 : 2	577
	Ag(I)	LH	1 : 1	581
	Ni(II)	L^-	1 : 1	590
5-Methybenz-1,3-imidazoline-2-thione	Cu(I)	LH	1 : 1	584
5-Nitrobenz-1,3-imidazoline-2-thione	Cu(I)	LH	1 : 1	584
1,3-Imidazolidine-2-thione	Ag(I)	LH	1 : 1	637, 638
	Au(I)	LH	1 : 1	637, 639, 640
	Cu(II)	LH	1 : 1	636
	Pd(II)	LH	1 : 2	641
	Co(II)	LH	1 : 2	642
	Ni(II)	LH	1 : 2	642
	Zn(II)	LH	1 : 2	642
	Hg(II)	LH	1 : 2	643
	Bi(III)	LH	1 : 4	644
	Pt(IV)	LH	1 : 2	642
	VO^{2+}	LH	1 : 2	645
1-Methylimidazolidine-2-thione	Pd(II)	LH	1 : 1	641
	Te(II)	LH	1 : 3	646
	Hg(II)	LH	1 : 2	643
1-Ethylimidazolidine-2-thione	Cu(I)	LH	1 : 2	647
	Pd(II)	LH	1 : 1	641
	Hg(II)	LH	1 : 2	643
1-Propylimidazolidine-2-thione	Cu(I)	LH	1 : 2	647, 648
	Pd(II)	LH	1 : 1	641
	Hg(II)	LH	1 : 2	643

(*continued overleaf*)

TABLE 22. (*continued*)

Ligand(LH)	Metal	Ligand type	Stoichiometry metal : ligand	References
1-Isopropyl imidazolidine-2-thione	Cu(I)	LH	1 : 2	647
	Hg(II)	LH	1 : 2	643
	Au(I)	LH	1 : 1	637
	Ag(I)	LH	1 : 1	637
1,3-Dimethyl imidazolidine-2-thione	Hg(II)	LH	1 : 2	643
	VO^{2+}	LH	1 : 2	645
1,3-Diethyl imidazolidine-2-thione	Hg(II)	LH	1 : 2	643
1,3-Di-isopropyl imidazolidine-2-thione	Hg(II)	LH	1 : 2	643

TABLE 23. Metal complexes of thiazoline-thiones

Ligand(LH)	Metal	Ligand type	Stoichiometry metal : ligand	References
1,3-Thiazoline-2-thione	Cu(I)	LH	1 : 1	609
	Ni(II)	L^-	1 : 2	649, 650
	Pd(II)	LH	1 : 4	651, 652
			1 : 2	652
		L^-	1 : 2	653
	Pt(II)	LH	1 : 2; 1 : 4	652
		L^-	1 : 2	653
Benz-1,3-thiazoline-2-thione	Cu(I)	LH	1 : 1	584, 609
	Au(I)	LH	1 : 1; 1 : 2	579
	Ag(I)	LH	1 : 1	581
	Zn(II)	L^-	1 : 2	654, 655
	Cd(II)	L^-	1 : 2	654, 655
	Ni(II)	L^-	1 : 1	590
			1 : 2	649, 655
			1 : 3	656
	Pd(II)	LH	1 : 2; 1 : 4	652
		L^-	1 : 2	653
	Pt(II)	LH	1 : 2; 1 : 4	652
		L^-	1 : 2	653
	Sb(III)	L^-	1 : 1	657
1,3-Thiazolidine-2-thione	Cu(I)	LH	1 : 2	647
			1 : 1	582–584, 658
	Au(I)	LH	1 : 1; 1 : 2	579, 659
	Ag(I)	LH	1 : 1	581
	Zn(II)	LH	1 : 2	660
	Ni(II)	LH	1 : 1	661
		L^-	1 : 1	590
			1 : 2	649, 662
	Co(II)	LH	1 : 2	660
	Pd(II)	LH	1 : 2; 1 : 4	652
		L^-	1 : 2	653
	Pt(II)	LH	1 : 2; 1 : 4	652
		L^-	1 : 2	653
	Rh(II)	L^-	1 : 1; 1 : 2	663

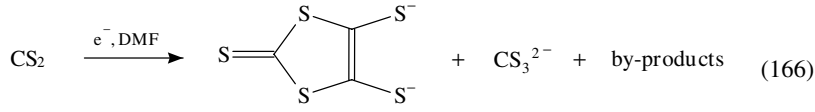
TABLE 24. Metal complexes of triazoline-thiones

Ligand(LH)	Metal	Ligand type	Stoichiometry metal : ligand	References
1,2,4-Triazoline-3(5)-thione	Pd(0)	LH	1 : 1	664
	Pt(0)	LH	1 : 1	664
	Co(II)	L^-	1 : 1	665
	Fe(II)	L^-	1 : 1	665
	Fe(III)	L^-	1 : 1; 1 : 2; 1 : 3	666
	Zr(IV)	LH	1 : 2	667
		L^-	1 : 4	667
1-Phenyltriazoline-3-thione	Fe(III)	L^-	1 : 1; 1 : 2; 1 : 3	666
5-Phenyltriazoline-3-thione	Fe(III)	L^-	1 : 1; 1 : 2; 1 : 3	666
5-Methyltriazoline-3-thione	Fe(III)	L^-	1 : 1; 1 : 2; 1 : 3	666
3-(4-Pyridyl)-4-phenyltriazoline-5-thione	Pd(0)	LH	1 : 1	668
	Pt(0)	LH	1 : 1; 1 : 2	668
	Rh(I)	L^-	1 : 1	668
	Ag(I)	LH	1 : 1	669
	Co(II)	LH	1 : 2	669
	Cu(II)	LH	1 : 1	669
	Pd(II)	LH	1 : 1	669
	Hg(II)	LH; L^-	1 : 1	669
	Zr(IV)	LH	1 : 1; 1 : 2; 1 : 4	667
	ZrO^{2+}	LH	1 : 1; 1 : 4	667
4-Amino-3-hydrazinotriazoline-5-thione	Pd(0)	LH	1 : 1	670
	Pt(0)	LH	1 : 3	670
	Rh(I)	L^-	1 : 1	670
	Co(II)	L^-	1 : 2	670
	Ni(II)	L^-	1 : 2	670
	Zr(IV)	LH	1 : 2; 1 : 4	670
		L^-	1 : 3′	670
	ZrO^{2+}	LH	1 : 3; 1 : 4	670
4-Amino-1,4-dihydro-3-methyl-triazoline-5-thione	Cu(II)	LH	1 : 1; 2 : 1	671
2,6-Dimethyl-5-oxotriazoline-3-thione	Ni(II)	L^-	1 : 1	590
4-Amino-triazoline-5-thione	Ni(II)	LH	1 : 1; 1 : 2; 1 : 3	672
	Co(II)	LH	1 : 1; 1 : 2; 1 : 3	672
4-Amino-3-methyltriazoline-5-thione	Ni(II)	LH	1 : 1; 1 : 2; 1 : 3	672
	Co(II)	LH	1 : 1; 1 : 2; 1 : 3	672
	Hg(II)	L^-	1 : 1	673
	Zr(IV)	LH	1 : 1; 1 : 2	667
	ZrO^{2+}	LH	1 : 3; 1 : 4	667
	Hf(IV)	L^-	1 : 1; 1 : 3	674
4-Amino-3-ethyltriazoline-5-thione	Ni(II)	LH	1 : 1; 1 : 2; 1 : 3	672
	Co(II)	LH	1 : 1; 1 : 2; 1 : 3	672
	Hf(IV)	L^-	1 : 1; 1 : 3	674
4-Amino-3-propyltriazoline-5-thione	Hf(IV)	L^-	1 : 1; 1 : 3	674

TABLE 25. Metal complexes of tetrazoline-thiones

Ligand(LH)	Metal	Ligand type	Stoichiometry metal : ligand	References
1-Phenyl-1,2,3,4-tetrazoline-5-thione	Cu(I)	LH	1 : 1	675
		L^-	1 : 1	676
	Sb(III)	LH	1 : 1	677
	Bi(III)	LH	1 : 1	677
	Ir(III)	LH	1 : 2	678
	Hf(IV)	L^-	1 : 1; 1 : 3	674
	Sn(IV)	L^-	1 : 1	679
	ZrO^{2+}	LH	1 : 4	680
	Zr(IV)	LH	1 : 1	680
	VO^{2+}	LH	1 : 1	680
	VO_2^+	LH	1 : 2	680
	MoO_2^{2+}	LH	1 : 2	680
	WO_2^{2+}	LH	1 : 2	680
	Nb(V)	L^-	1 : 1; 1 : 2	680
	Ta(V)	L^-	1 : 5	680
1-*p*-Tolyltetrazoline-5-thione	Sb(III)	LH	1 : 1	677
	Bi(III)	LH	1 : 1	677
	VO_2^+	LH	1 : 2	680
1-*m*-Tolyltetrazoline-5-thione	Sb(III)	LH	1 : 1	677
	Bi(III)	LH	1 : 1	677
	Ir(III)	LH	1 : 1; 1 : 2	678
	Nb(V)	LH	1 : 4	680
	Ta(V)	LH	1 : 5	680
1-*o*-Tolyltetrazoline-5-thione	Ir(III)	LH	1 : 2	678
	Hf(IV)	L^-	1 : 1; 1 : 3	674
1-*p*-Chlorophenyl tetrazoline-5-thione	Sb(III)	LH	1 : 1	677
	Bi(III)	LH	1 : 1	677
	MoO_2^{2+}	LH	1 : 2	680
	Hf(IV)	L^-	1 : 1; 1 : 3	674
1-*p*-Methoxyphenyl tetrazoline-5-thione	Hf(IV)	L^-	1 : 1; 1 : 3	674

A very important ion related to thiocarbonyl compounds is the 1,3-dithiole-2-thione-4,5-dithiolate (isotrithione-dithiolate, dmit) **(159)**, introduced by Steimecke and coworkers[681] in 1975. It is formed as the main product by chemical (with sodium or potassium)[681,682] or electrochemical reduction[683] of CS_2 in DMF (reaction 166).



(166)

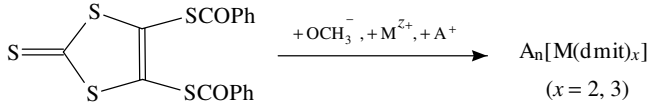
(159)

Nowadays, transition metal chelates of dmit are studied worldwide by numerous research groups. This is stimulated by those properties of the dmit chelates which favor electrical conductivity in molecular metals, e.g. planarity with delocalized π-electrons as well as open-shell character (dithiolene behavior)[29].

The first molecular inorganic superconductor, [TTF][Ni(dmit)$_2$]$_2$ (TTF = tetrathiafulvalene), was obtained in 1986 by Cassoux and collaborators[24,684–686].

There are reviews[24–27,29] on the chemistry of dmit and we present here some of the articles published since Olk's review[29].

The first metal chelates of dmit were reported by Steimecke and coworkers in 1975[681]. The general method applied to synthesize dmit chelates is the solvolysis of the dibenzoyl compound, $(PhCO)_2$ dmit **(160)**, by methanolic potassium or sodium methanolate followed by an *in situ* reaction of the generated dithiolate with the corresponding metal salt[681] (reaction 167).



(167)

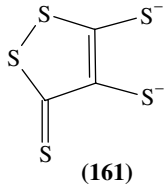
(160)

The anionic complexes formed can be isolated as crystalline salts using suitable large cations.

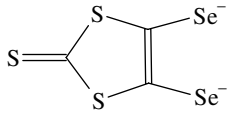
Numerous dmit chelates have been synthesized following that route. Although dmit chelates of common metal ions are known, considerable interest has been focused on those of d^8 ions (nickel triad). Nickel chelates are listed in Tables 26 and 27. Table 28 summarizes all other salts of bis-chelates of dmit, including the other two elements of nickel triad, palladium and platinum.

There are some studies about neutral mixed-ligand chelates of dmit in which there is interligand CT, while the dithiolene properties are maintained. These chelates are considered to be suitable for studies of both solid-state conductivity and spectral properties in solution[29]. Examples are the neutral mixed-ligand dmit chelates, [M(dmit)L], with L = (cyclopentadiene)$_2$ and M = Ti[744,745], Zr[744], Hf[744], V[744] and Nb[746]. There are also some recent studies about tris-chelates of dmit, with the metals Re[742], W[747,748] Mo[747–749] and *Cu*[750,751].

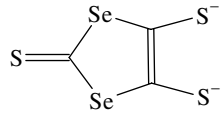
Other complexes of thiocarbonyl compounds related to dmit, such as 1,2-dithiole-3-thione-4,5-dithiolate (dmt, **161**)[741,744,752], 1,3-dithiole-2-thione-4,5-diselenolate (dsit, **162**)[687,753–758] or 1,3-thiaselenole-2-thione-4,5-dithiolate (dmits, **163**)[699] have been described.



(161)



(162)



(163)

TABLE 26. Chelate salts of general formula A_n [Ni(dmit)$_2$]

A	*n*	References
Me_4N	$\leqslant 2$	687
	n	688
	0.5	689, 690
Me_3NH	*n*	688
	0.5	691, 692
$Me_{4-y}NH_y$ ($y = 0$–3)	*n*	693
	1	694, 695
Me_2Et_2N	1	696
	0.5	689, 697, 698
Bu_4N	1,2	699
$Me_3N(CH_2)_4NMe_3$	0.2	700
Imidazolium	0.5	701
1,2,3-Trimethylimidazolium	1	702
Guanidinium	0.5	703
1,1-Dimethylguanidinium	0.5	703
N, *N*-Dimethylmorpholinium	1	704
N, *N*-Dimethylpyrrolidinium	1	704
	0.5	705, 706
N, *N*-Dimethylpiperidinium	0.5	705
N-Methylquinolinium	1	707
N-Octadecylpyridinium	2	708
S-Methyl-1,3-dithianium	1	704
	0.5	706
Tetraphenyldithiapyranylidine	1	709

TABLE 27. Chelate salts with π-donors of general formula A_n[Ni(dmit)$_2$]

A	*n*	References
TTF[a]	0.5	690, 710–715
TTF tetrathiol derivatives	1	716
EDT-TTF[b]	1	717, 718
TBT-TTF[c]	1	719
BPDT-TSF[d]	0.5; 1	720
OMTSF[e]	1	721
Cp_2Co	0–2	722
$(MeCp)_2Fe$	1	723

[a]TTF = tetrathiafulvalene.
[b]EDT-TTF = ethylenedithiotetrathiafulvalene.
[c]TBT-TTF = tetrabenzylthiotetrathiafulvalene.
[d]BPDT-TSF = bis(propylenedithio)tetraselenafulvalene.
[e]OMTSF = bis(tetramethylene)tetraselenafulvalene.

TABLE 28. Chelate salts of general formula $A_n[M(dmit)_2]$

M	n	A	References
Cu	1,2	CpFe(PhMe)	723
	1	TTF tetrathiol derivatives	716
	2	Bu_4N	699
Cu/Pd	2	Bu_4N	724
Pd	0.5	Me_2Et_2N	697, 725
	$\leqslant 2$	Me_4N	687
	0.5	Me_4N	690, 725, 726
	n	$Me_{4-y}NH_y (y = 0-3)$	693
	1	$Me_{4-y}NH_y (y = 0-3)$	695
	0.5	octadecylpyridinium	727
	0.5	TTF	690, 710
	0.67, 1	EDT-TTF	728
	0.5	Me_4As	726, 729
	0.5	Cs	729, 730
	2	Bu_4N	699
	1	$(MeCp)_2Fe$	723
	1,2	CpFe(PhMe)	723
Pt	0.5	Me_4N	731
	$\leqslant 2$	Me_4N	687
	1	$Me_{4-y}NH_y (y = 0-3)$	695
	n	$Me_{4-y}NH_y (y = 0-3)$	693
	0.33	Me_3NH	693, 732
	1	EDT-TTF	693
	0.5	octadecylpyridinium	727
	1	$(MeCp)_2Fe$	723
Au	1	$(Ph_3P)_2N$	733
	0.5	octadecylpyridinium	727
	1	Bu_4N	699, 734
	1	tridecylmethylammonium	735, 736
	1	$Me_{4-y}NH_y$ $(y = 0–3)$	694, 695
	1	$(Me_5Cp)_2Fe$	737
Sb	1	Et_4N	738
	1	1,4-dimethylpyridinium	738
Mn	2	Me_4N	739
Zn	1	TTF tetrathiol derivatives	716
	1	TBT-TTF	740
	2	Bu_4N	699
Cd	2	Bu_4N	699
Hg	2	Bu_4N	699
Se	2	PPN[a], Ph_4As, Me_3Te	741
Te	2	PPN[a], Me_3Te, Cp_2Co	741
ReO	1	Ph_4P	742
Fe	1	Bu_4N	743
Co	1,2	CpFe(PhMe)	723

[a]PPN = bis(triphenylphosphine)iminium

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CHAPTER **24**

Advances in the metathesis of olefins

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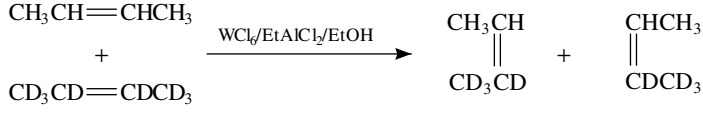
I. ABBREVIATIONS

ADMET	acyclic diene metathesis
COSY	correlation spectroscopy
CTA	chain transfer agent
DBC	double bond cleavage
HT	head–tail
MO	molecular orbital
MWD	molecular weight distribution
RCM	ring-closing metathesis
ROMP	ring-opening metathesis polymerization
SAXS	small-angle X-ray scattering
TBC	triple bond cleavage
TEM	transmission electron microscopy
ZNP	Ziegler–Natta polymerization

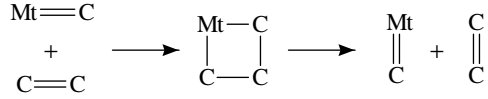
II. INTRODUCTION

The olefin metathesis reaction was so named by Calderon[1] in 1967 following the discovery that it involved the total cleavage of the C=C bond and the apparent exchange of alkylidene moieties between two alkene molecules (equation 1).



(1)

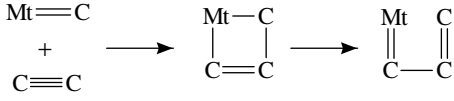
Such reactions are chain reactions catalysed by compounds of many of the transition elements, particularly Ti, Nb, Mo, Ru, Ta, W, Re, Os and Ir, and occasionally V, Co and Rh. A cocatalyst such as $EtAlCl_2$ or Me_4Sn is often, though not always, required. It was first postulated[2] in 1971 and later proved beyond doubt that both the initiating and propagating species of the chain reaction were metal carbene complexes, the initiation and propagation reactions being two-step processes, represented by the framework in equation 2, involving the intermediate formation of a metallacyclobutane complex. (Mt denotes the transition metal centre; M will later denote monomer.)



(2)

Over the past 15 years the understanding of the mechanism of these reactions has been greatly enhanced through the preparation of metal carbene complexes, particularly of Mo, W and Ru, that are both electronically unsaturated (<18e) and coordinatively unsaturated (usually <6 ligands), and which can act directly as initiators of olefin metathesis reactions. The intermediate metallacyclobutane complexes can also occasionally be observed. Furthermore, certain metallacyclobutane complexes can be used as initiators.

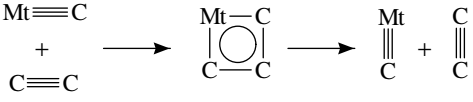
With cycloalkenes the metathesis reaction leads to long-chain unsaturated polymers together with unsaturated cyclic oligomers formed by intramolecular metathesis reactions of the propagating species. These are termed ring-opening metathesis polymerizations (ROMP). Dienes can undergo either intramolecular metathesis with ring closure, or intermolecular metathesis leading to a high polymer with the elimination of a small olefin (a type of condensation polymerization). The intramolecular reaction dominates when it is thermodynamically favoured (at low substrate concentration, and/or with conformational restrictions to bring the two double bonds into close proximity). Such ring-closing metathesis (RCM) reactions have proved of great synthetic value. Alkynes are also polymerized by olefin metathesis catalysts and it is now established that here too the reactions are propagated by metal carbene complexes. Equation 3 shows the framework for the addition of the first molecule of alkyne to the metal carbene initiating species, with the intermediate formation of a metallacyclobutene complex.



(3)

The alkyne thus behaves as a quasi-cycloalkene, two of the three C≡C bonds being broken in the propagation step.

Alkynes can also undergo total metathesis, with cleavage of all three C≡C bonds, catalysed by metal carbyne complexes at room temperature and proceeding through metallacyclobutadiene intermediates as indicated by the framework in equation 4[3–6].

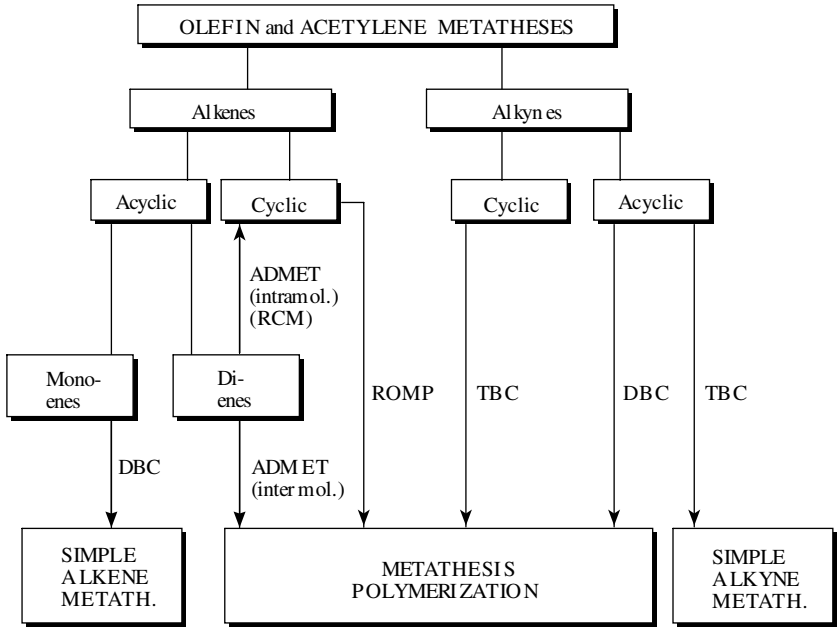


(4)

For a cycloalkyne the product is a ring-opened polymer containing C≡C bonds; cyclic oligomers can also be formed[7,8].

Scheme 1 summarizes the interrelationships of the various types of olefin and acetylene metathesis reaction that are observed for single substrates. When there are two substrates present then so-called cross-metathesis reactions occur, for example between ethene and a higher olefin (ethenolysis), or between a cycloalkene and an acyclic olefin (which acts as a chain transfer agent and reduces the molecular weight of the polymer formed), or between two cycloalkenes (giving a copolymer). With metal carbene complexes as initiators one can often obtain 'living' systems (free from termination reactions) allowing the preparation of well-defined homopolymers or block copolymers of very narrow molecular weight distribution ($M_w/M_n < 1.1$). Cross-metathesis reactions can also occur between alkenes and alkynes, and the intramolecular metathesis reactions of enynes and dienynes can sometimes provide a valuable step in a synthetic strategy.

Before passing to more detailed considerations it should be noted that the reactions of metal carbenes are part of a much wider family of [2 + 2] reactions between multiply-bonded compounds in which one of the reactants involves an Mt=X bond. Equation 5



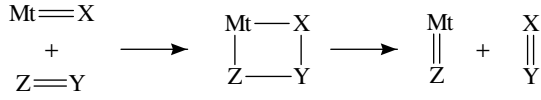
SCHEME 1. Types of alkene and alkyne metathesis reactions. **DBC**, double bond cleavage; **TBC**, triple bond cleavage; **ADMET**, acyclic diene metathesis; **RCM** ring-closing metathesis; **ROMP** ring-opening metathesis polymerization

TABLE 1. Some types of observed [2 + 2] reactions involving metal atoms attached to double bonds (other than those involved in olefin metathesis); cf. equation 5

Multiple bonds[a]		Type of compound	Notes	References
Mt···X	Y···Z	containing Y···Z		
Ti=C	C=O	ketone		9
Mo=C	C=O	aldehyde		10
		β- or γ-hydroxyketone	*b*	11
W=C	C=O	ketone, aldehyde		11–13
W=C	C=N	carbodiimide		14
		imine		15
W=P	P=P	diphosphene		16
Os=C	S=O	sulphur dioxide	*c*	17
Ta=C	C≡O	carbonyl complex	*d*	18
Zr=N	C=N	imine		19
W=N	C=N	carbodiimide		14
Zr=N	C≡C	alkyne	*e*	19

[a] The products correspond to the formation of an initial metallacycle $\overline{\text{MtXYZ}}$.
[b] The hydroxyl group is essential for the reaction to succeed.
[c] Reaction stops at the metallacycle.
[d] Product formed by rearrangement rather than cleavage of the metallacycle.
[e] Product is an unsaturated metallacycle.

indicates the reacting framework and Table 1 gives some examples.



(5)

There are similar [2 + 2] reactions involving W≡X and Mo≡X bonds[20–25].

For a recent comprehensive account of the subject, see the book by Ivin and Mol[26], which updates an earlier book[27]. An extensive collection of papers concerning metathesis catalysts may be found in the proceedings of a NATO Advanced Study Institute[28].

III. CATALYSTS, INTERMEDIATES, INITIATOR EFFICIENCIES

A. First-generation Catalysts (Non-carbene Catalysts)

The first metathesis catalysts were discovered by chance, arising out of observations on (i) the heterogeneously catalysed reactions of olefins using MoO_3 supported on Al_2O_3[29–31], and on (ii) the attempted Ziegler–Natta polymerizations of cycloalkenes using $TiCl_4/LiAlH_4$, $MoCl_5/Et_3Al$, or WCl_6/Et_3Al[32,33]. The Calderon catalyst $WCl_6/EtOH/EtAlCl_2$ (1/1/4) was later found to be extremely effective for both ROMP of cycloalkenes[34] and metathesis of acyclic alkenes[1]. The EtOH converts some of the chloride ligands at the tungsten centre to ethoxy ligands thereby making the system more active; see Schrock[35] for a recent discussion of the role of OR ligands in olefin metathesis reactions.

The Calderon catalyst has two disadvantages: (i) the Lewis acids in the system are liable to cause double-bond shift reactions, and (ii) it is vulnerable to destruction by polar groups in the substrate. These problems were overcome by using R_4Sn (R = Me, Bu, Ph) in place of $EtAlCl_2$ as cocatalyst with WCl_6; the metathesis of unsaturated esters such as methyl oleate can then be achieved[36]. In the system $WCl_6/(^{13}CH_3)_4$ Sn one can observe the initiating metal carbene species by both ^1H and ^{13}C NMR, but the initiation efficiency for the ROMP of norbornene is low (<0.7%) and the propagating species cannot be detected[37].

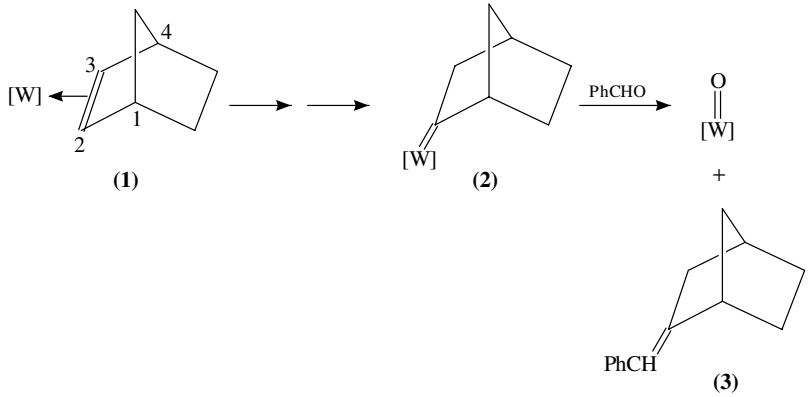
When there is no cocatalyst the initiating metal carbene complex must result from a reaction between the catalyst and the substrate olefin. In the case of Re_2O_7/Al_2O_3 (activated at 550 °C) its interaction with but-2-ene to form $[Re]{=}CHCH_3$ can be clearly demonstrated by the so-called 'chemical counting' method. After removing the excess but-2-ene by evacuation the catalyst is treated with ethene. This reacts with $[Re]{=}CHCH_3$ to form propene, the amount corresponding to about 1.8% of the total Re in the catalyst[38]. At low Re content (<3% Re_2O_7) the activity of this catalyst is extremely low, but rises very rapidly as the Re content is increased (>7%). The explanation for this behaviour is based on an examination of the surface OH groups by FTIR. At low loadings ReO_4^- ions have reacted mainly with the basic surface alumina OH groups during deposition of the rhenium compound, while at higher loadings the neutral and more acidic OH groups have also reacted, the latter resulting in the most active sites[39]. Similar behaviour is observed for MoO_3/Al_2O_3[40].

R_4Sn or R_4Pb causes a spectacular improvement of the catalytic performance of Re_2O_7/Al_2O_3, raising the rate of propene metathesis by 10–100 and also making possible the metathesis of functionalized alkenes where previously no reaction was observed[41–43]. When R = Me some methane is produced, suggesting that the reaction $[Re](CH_3)_2 \rightarrow [Re]{=}CH_2 + CH_4$ is involved in the production of the initiating species.

The active centres generated in this way appear to be different from those present in the unpromoted catalyst[44,45].

Another example of enhancement of catalytic activity of a heterogeneous catalyst by appropriate pretreatment of the catalyst is observed with MoO_3/SiO_2 and $MoO_3/SiO_2-Al_2O_3$. Best results for the metathesis of propene are obtained if the calcined catalyst is first photoreduced in CO at room temperature, using a mercury lamp or laser ($\lambda = 308$ nm), and then exposing the catalyst to cyclopropane followed by heating at 350 °C. Molybdenum carbenes are formed, as shown by both IR and UV/vis spectra[46,47], and are assumed to result from the sequence of reactions shown in Scheme 2[48–50]. A small proportion (<5%) of the molybdacyclopropane complexes yields propene by reductive elimination at 350 °C. The reaction of methylcyclopropane yields both $[Mo]=CH_2$ and $[Mo]=CHCH_3$[51,52].

The nature of the initiating complex can sometimes be deduced from the product of its reaction with a carbene trap. For example, the seven-coordinate, 18e complex $WCl_2(CO)_3(AsPh_3)_2$ catalyses the ROMP of norbornene in benzene at 80 °C, presumably through loss of a CO ligand followed by coordination of the norbornene, and rearrangement to a tungsten carbene complex which then propagates the ROMP. In the presence of benzaldehyde as carbene trap, polymerization is inhibited and the main product is 2-benzylidenenorbornane **3**. One may therefore conclude that its precursor **2**, produced by a 2,3-hydrogen shift in the tungsten–olefin complex **1**, is the initiating tungsten carbene complex[53].

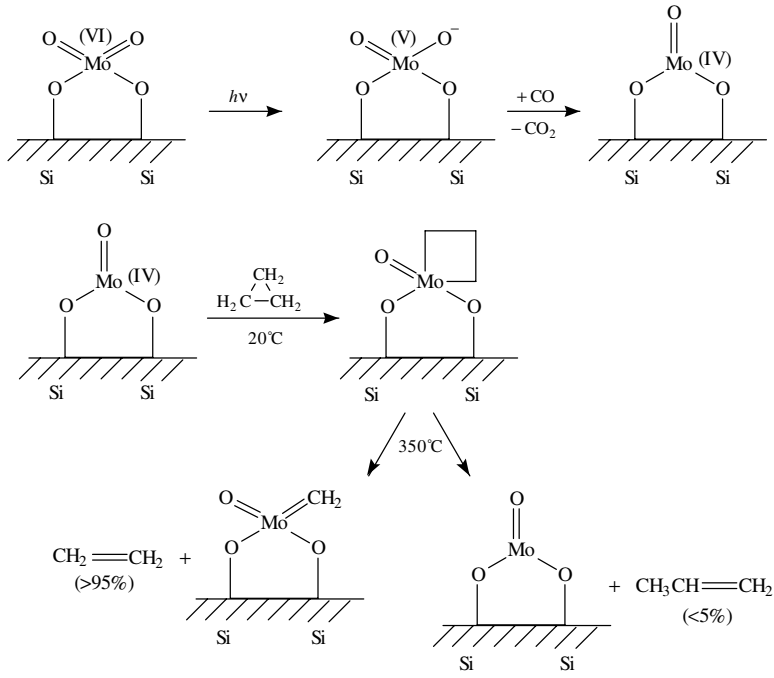


Among the more novel non-carbene metathesis catalysts recently reported are the following.

(1) The organoisopolymolybdate $[(C_{13}H_{27})_3NH]_4[Mo_8O_{26}]$ is soluble in *endo*-dicyclopentadiene and, with Et_2AlCl as cocatalyst, can be used to effect smooth ROMP without added solvent. This is a considerable advantage when using the reaction–injection moulding technique[54].

(2) $WOCl_3(OAr)$, $WOCl_2(OAr)_2$ or $WOCl(OAr)_3$ in conjunction with R_3SnH are reported to be very effective for the ROMP of dicyclopentadiene, the activity increasing with the electron-withdrawing power of the OAr ligand[55]; also for the metathesis of pent-2-ene when brought onto a support[56,57]. The related imido complexes, $W(=NAr)(Cl)_{4-x}(OAr)_x$ are also effective[58].

(3) Cobalt neodecanoate or acetylacetonate in combination with R_3Al (R = Et, *i*-Bu) in heptane at 20 °C initiates the ROMP of norbornene, giving an 80% yield of an all-*cis* polymer in 3 days. This is the first report of a cobalt-based metathesis catalyst[59].



SCHEME 2. Generation of molybdenum carbenes by the reaction of cyclopropane with Mo(IV)/SiO_2

(4) Metal carbenes have long been proposed as intermediates in the reactions of diazoalkanes; see Schwab and coworkers[60] for references extending back to 1952. A recent example in olefin metathesis is $Ru(H_2O)_6(OTs)_2$ the activity of which is enhanced by the addition of ethyl diazoacetate to the extent that it will then bring about the ROMP of less strained monomers such as cyclopentene and cyclooctene[61]. Likewise $RuCl_2$(*p*-cymene)(PCy_3), when treated with Me_3SiCHN_2, gives a very active catalyst for promoting the ROMP of functionalized norbornenes and cyclooctenes (Cy = cyclohexyl); both the initiating species [Ru]=$CHSiMe_3$ and the propagating species can be detected by NMR[62]. Unassisted non-carbene compounds of ruthenium, such as $RuCl_3$, do not generally catalyse the ROMP of low-strain cycloalkenes because of the difficulty of generating the initial metal carbene complex by reaction with the substrate.

(5) An extensive series of molybdenum nitrosyl complexes have been prepared which are very active in the presence of a cocatalyst, e.g. $[Mo(NO)_2(OEt)_2]$/$EtAlCl_2$[63–73].

(6) The polystyrene-bonded complexes Pol−CH_2−(η^5-C_5H_4)−$W(CO)_3$R (R = H, Cl, Me), when activated by *i*-$BuAlCl_2$, are reported to be highly active for the metathesis of internal olefins, though accompanied by double-bond migration reactions[74].

(7) Three reports have appeared recently in which it is claimed that catalysts not containing a transition metal can bring about metathesis; first, that magnesium chloride can effect the ROMP of norbornene and other strained monomers[75]; second, that Al_2O_3/Me_4Sn brings about the metathesis of propene, hex-1-ene and pent-2-ene[76]; third, that SiO_2 alone, activated by evacuation at high temperature, catalyses the metathesis of deuterated ethene with propene under photoirradiation[77]. The mechanisms of these reactions need further investigation.

The first-generation catalysts are still preferred for many synthetic or commercial applications, e.g. RCM reactions using *trans*-$WOCl_2(OAr)_2/Et_4Pb$ (1/2) where Ar = 2, 6-dibromophenyl[78]. However, the metal carbene catalysts provide much more detail about the mechanism and are being used increasingly for synthetic applications.

B. Second-generation Catalysts (Carbene Catalysts)

1. Fischer complexes (18e)

Among the first 18-electron (18e) Fischer-type metal carbene complexes to be used as part of an olefin metathesis catalyst system were W[=C(OMe)Et](CO)$_5$ with Bu_4NCl (for pent-1-ene)[79], and W[=C(OEt)Bu](CO)$_5$ with $TiCl_4$ (for cyclopentene)[80]. These complexes may also be activated thermally, e.g. for the polymerization of alkynes[81], or photochemically, e.g. for the ROMP of cycloocta-1,5-diene[82]. The essential requirement is that a vacancy be created at the metal centre to allow the substrate to enter the coordination sphere. Occasionally the substrate may itself be able to displace one of the CO ligands.

2. Complexes with less than 18e around the metal centre

Much more effective are metal carbene complexes that are both electron-deficient (<18e) and coordinatively unsaturated (usually with 4 or 5 ligands). Since 1980 a large number of these have been prepared, thanks to the pioneering work of the groups of Schrock, Osborn, Grubbs and Basset. The main examples are listed in Table 2. Some but not all can bring about the metathesis of pent-2-ene and low-strained cycloalkenes. For molybdenum and tungsten carbenes the activity of the initiator can be much enhanced by the use of electron-withdrawing ligands, making the metal centre more attractive towards the olefinic substrate. Thus for the family of complexes related to **7**, in which the alkoxy ligands are progressively substituted, the reactivity increases in the order $OCMe_3 < OCMe_2(CF_3) < OCMe(CF_3)_2 < OC(CF_3)_3$. The analogous tungsten complexes are more reactive but more prone to side reactions[87]. With **10** the reactivity is greatly enhanced by the presence of an equivalent of $GaBr_3$ which essentially removes a bromide ion to form an ion-pair. Mo and W complexes that are sufficiently electron-deficient are capable of bringing about the metathesis of pent-2-ene, whereas the less electron-deficient complexes can only cause the metathesis of strained olefins such as norbornene. On the other hand, with the ruthenium carbene complexes **18** and **19** it is the one with the better σ-donating alkylphosphine ligands (PCy_3) that is the more active and able to metathesize pent-2-ene. This has been explained in terms of the increased stability conferred on the intermediate metallacyclobutane by the better σ-donor, the metal centre being formally Ru(IV)[110].

The isolation of the ruthenium carbene complexes of the type **20** represents a major step forward for olefin metathesis. Not only are these complexes easy to prepare but they are stable to air and water, unlike the molybdenum and tungsten carbene complexes which must be handled in a dry box. Furthermore, they are highly efficient initiators. Thus for the ROMP of norbornene (M) initiated by Ru(=CHC_6H_4X-*p*)(Cl)$_2$(PPh_3)$_2$ the ratio of the initiation to propagation rate constants k_i/k_p ranges from 9 for X = H to 1.2 for X = Cl in C_6D_6 at 17 °C. This means that for $[M]_0/[Ru]_0 = 20$, the initiator is all converted to propagating species at a very early stage in the reaction, i.e. the initiator is 100% efficient. In this respect they are better than **18** and **19** which are 20–1000 times less active[60,91]. The one-pot synthesis of Ru(=CHPh)(Cl)$_2$(PCy_3)$_2$ is shown in equation 6. The second stage must be carried out immediately after the first. The product is obtained as a purple

TABLE 2. Examples of metal carbene complexes with a count of less than 18 electrons and their effectiveness as initiators of olefin metathesis[a]

Complex[b]	Metathesis reactivity		References
	pent-2-ene	norbornene	
4 Nb(=CHCMe$_3$)(Cl)(OCMe$_3$)$_2$(PMe$_3$)	yes		92
5 Ta(=CHCMe$_3$)(OAr)$_3$(THF)	yes[c]	yes[d]	93,94
6 Ta(=CHCMe$_3$)(TIPT)$_3$	no	yes[e]	93,94
7 Mo(=CHCMe$_2$R)(=NAr)(OCMe$_3$)$_2$ (R = Me, Ph)	no	yes	95
8 Mo(=CHCMe$_2$R)(=NAr)[OCMe(CF$_3$)$_2$]$_2$ (R = Me, Ph)	yes[f]	yes	87,96,97
9 W(=CHCMe$_3$)(O)(Cl)$_2$(PEt$_3$)	yes		98
10 W(=CHCMe$_3$)(Br)$_2$(ONp)$_2$	no[g]	yes[h]	99,100
11 W(=CHCMe$_3$)(Cl)(Np)(OAr′)$_2$(O-*i*-Pr$_2$)	yes	yes	83
12 [W]=CHCMe$_3$[i]	yes	yes	101
13 W[=CHC$_6$H$_4$(OMe)-2](=NAr″)[OCMe(CF$_3$)$_2$]$_2$	yes	yes	102
14 W(=CHSiMe$_3$)(=NPh)(CH$_2$SiMe$_3$)L[j]	no	yes	103,104
15 Re(=CHCMe$_3$)(≡CCMe$_3$)[OCMe(CF$_3$)$_2$]$_2$	yes[k]	yes	105
16 Re(=CHCMe$_3$)(≡CCMe$_3$)(CH$_2$CMe$_3$)(OTf)L[l]	yes		106
17 Re(=CHCH=CPh$_2$)(O)[OCMe(CF$_3$)$_2$]$_3$(THF)	yes[m]		107
18 Ru(=CHCH=CPh$_2$)(Cl)$_2$(PPh$_3$)$_2$[n]	no	yes	108,109
19 Ru(=CHCH=CPh$_2$)(Cl)$_2$(PCy$_3$)$_2$[n]	yes[p]	yes	110,111
20 Ru(=CHR)(Cl)$_2$(PR′$_3$)$_2$; R′ = PPh$_3$, PCy$_3$; R = H, Me, Et, Ph, *p*-ClC$_6$H$_4$		yes	60,91

[a] For synthetic routes to metal carbene complexes see elsewhere[60,83–91].
[b] The W counterparts of **7** and **8** are denoted as **7W** and **8W**, respectively, in the text. Ar, C$_6$H$_3$-*i*-Pr$_2$-2,6; Ar′, C$_6$H$_3$-Ph$_2$-2,6; Ar″, C$_6$H$_3$-Me$_2$-2,6; TIPT, S−C$_6$H$_2$-*i*-Pr$_3$-2,4,6; Np, CH$_2$CMe$_3$; Cy, cyclohexyl; OTf, triflate.
[c] Short-lived.
[d] At 50 °C, via isolable metallacyclobutane complex.
[e] Reaction inhibited in THF.
[f] Also active for terminal olefins.
[g] Becomes very active in the presence of a Lewis acid such as AlBr$_3$ or GaBr$_3$, which removes a bromide ion from the complex.
[h] Becomes much more active in the presence of GaBr$_3$.
[i] See text.
[j] L is a ligand such as 8-quinolinolate containing a nitrogen chelated to the tungsten.
[k] Much retarded in THF.
[l] L = MeCN; short-lived (<1 h).
[m] When activated by GaBr$_3$.
[n] Mixture of isomers in which the phosphine ligands are either *cis* (20%) or *trans* (80%).
[p] Rate dependent on solvent: CD$_2$Cl$_2$ > C$_6$D$_6$ > THF-d_8 (relative rates 103:26:11, respectively).

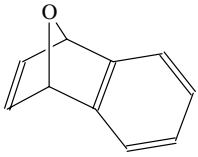
microcrystalline solid by precipitation in methanol (99% yield).

$$\mathrm{RuCl_2(PPh_3)_3} \xrightarrow[\substack{-78\,^\circ\mathrm{C\ to\ }-50\,^\circ\mathrm{C}\\ 3\text{–}5\ \mathrm{min}}]{\substack{2.0\ \mathrm{equiv\ PhCHN_2}\\ \mathrm{pentane}}} \xrightarrow[\substack{-50\,^\circ\mathrm{C\ to\ }20\,^\circ\mathrm{C}\\ 30\ \mathrm{min}}]{\substack{2.2\ \mathrm{equiv\ PCy_3}\\ \mathrm{CH_2Cl_2}}} \mathrm{Ru(=CHPh)(Cl)_2(PCy_3)_2} \qquad (6)$$

3. Detection of propagating metallacyclobutane complexes

When catalysts of the type **10**/GaBr$_3$ are used to initiate the ROMP of norbornene derivatives at low temperature (−50 °C) the intermediate *transoid* metallacyclobutane complexes (the precursors to the formation of *trans* double bonds) may be observed. The corresponding *cisoid* complexes are not stable enough to be detected. No metallacyclobutane complexes are observed in the absence of GaBr$_3$[100,112–114].

Intermediate molybdacyclobutane complexes have also been detected in the reactions of **7** with **21–24**[115]. Only in the case of **21** is the ultimate product a long-chain polymer, but in all cases one may observe, at 0–60 °C, a clean first-order rearrangement of the initial metallacyclobutane complex to the first metal carbene adduct, consisting of an equilibrium mixture of *syn* and *anti* rotamers in the ratio 9:1 (see below). Except in the case of **21**, the metal carbene complexes do not survive for very long. For **21**, however, ROMP is propagated, and distinct ^{1}H NMR signals are seen for the longer-chain metal carbene complexes in both *syn* and *anti* forms.



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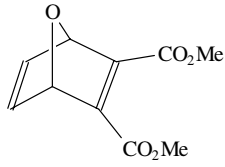

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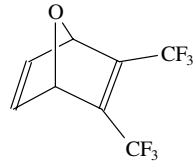

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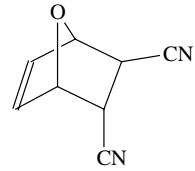
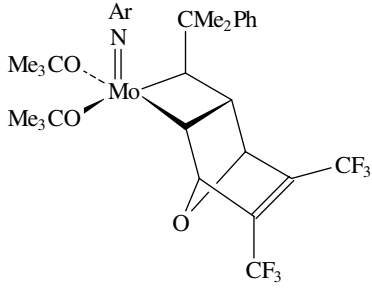


(24)

In some cases the metallacyclobutane complexes can be isolated and their crystal structure determined. Thus, for **25** the geometry about the molybdenum atom is square-pyramidal (with NAr at the apex), the CMe_2Ph substituent is *trans* to the norbornene ring with the phenyl group directed towards this ring and the MoC_3 ring is planar. The distance between Mo and O (3.32 Å) indicates that there is no significant bonding between them. In the reaction of **24** the ^{1}H NMR spectrum shows that two square-pyramidal *transoid* metallacycles are formed, in one of which the cyano group closest to CMe_2Ph is in the *endo* position (65%), see **26**, while in the other (not shown) it is in the *exo* position (35%).



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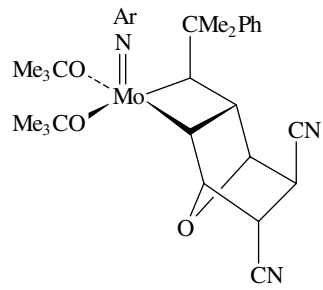


(26)

The half-life for the rearrangement of **25** to the metal carbene adduct in C_6D_6 at 35 °C is 22 h, with an activation energy of 97 kJ mol^{-1}. When the substituent is CMe_3 in place of CMe_2Ph the rate constant of rearrangement increases five-fold. The rate goes up by another order of magnitude if the CF_3 groups are replaced by CO_2Me, and by yet another order of magnitude for the rearrangement of the metallacyclobutane derived from **21** (half-life *ca* 1 h at 0 °C). The stabilization brought about by the CF_3 groups is attributed to their inductive effect. Replacement of the Me_3CO ligands by Et_3CO ligands reduces the rate of rearrangement of the metallacyclobutane (R = Ph) derived from **22** by a factor of six[115].

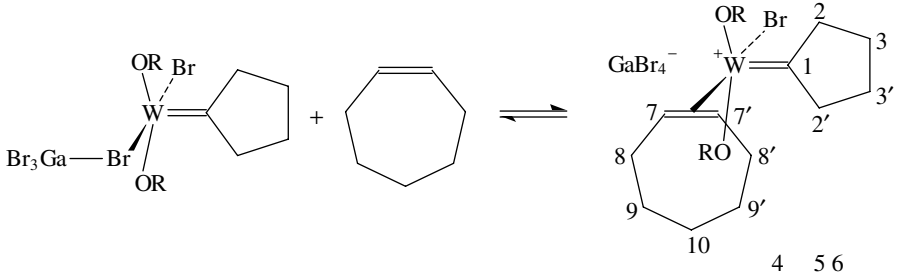
Square-pyramidal metallacycles are not observable at 25 °C upon adding 7-oxa-norbornadiene derivatives to $Mo(=CHMe_2R)(=NAr)(OCMe_2CF_3)_2$ except as a transient

red colour, rapidly changing to the characteristic orange colour of the living carbene complexes. However, the metallacycles can be observed at low temperature[115].

4. Detection of propagating metal–carbene–olefin complexes

It has generally been assumed that in olefin metathesis reactions the olefin first coordinates to the metal carbene complex, en route to the formation of the intermediate metallacyclobutane complex, and that after cleavage of this intermediate the newly formed double bond is temporarily coordinated to the metal centre. A number of stable metal–carbene–olefin complexes are known; see elsewhere[116,117] for earlier references. They are mostly stabilized by chelation of the olefin and/or by heteroatom substituents on the carbene, although some have been prepared which enjoy neither of these modes of stabilization[118,119].

The only direct evidence for the presence of metal–carbene–olefin intermediates in catalytic metathesis systems comes from a study of the interaction of the tungsten cyclopentylidene complex **27** with cycloalkenes such as cycloheptene **28** in CD_2Cl_2. When these are mixed at $-96\,^{\circ}C$ and the temperature raised to between -53 and $-28\,^{\circ}C$, no polymerization occurs but the ^{13}C NMR spectrum contains additional resonances which may be assigned to the metal–carbene–olefin complex **29**. The line intensities show that the equilibrium 7 moves to the right as the temperature is lowered[120].



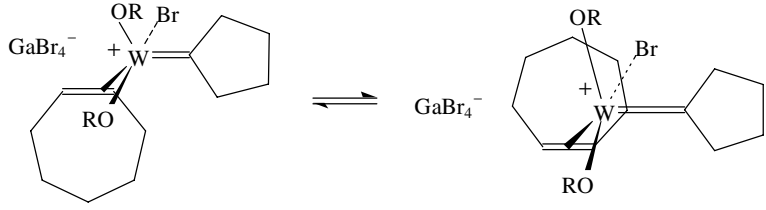
(**27**) OR = OCH_2CMe_3 (**28**) (**29**) OR = OCH_2CMe_3 (7)

The nature of **29** is established by the presence at $-73\,^{\circ}C$ of a signal at δ 355.3 ($^1J_{WC}$ = 142 Hz), which is assigned to the carbene carbon (C-1) of the cyclopentylidene unit, and of two signals at δ 124.4 and 107.8 ($^1J_{CH}$ = 165 Hz) corresponding to two non-equivalent olefinic carbons, upfield from the olefinic carbon signal of **28** at δ 132.4 ($^1J_{CH}$ = 154 Hz). The assumption that $GaBr_4^-$ has left the coordination sphere of tungsten to yield a cationic complex is based on the large low-field shift of the alkylidene carbon and on the substantial decrease of $^1J_{WC}$, which suggest that the tungsten centre is significantly more electron-deficient in **29** than in **27** (δ 335.6 and $^1J_{WC}$ = 169 Hz). The olefin occupies an apical site of the trigonal–bipyramidal geometry with its C=C axis aligned with the W=C axis and with its 'plane' parallel to that of the cyclopentylidene ligand. This particular conformation is the one that would most easily lead to a metallacyclobutane.

The ^1H NMR spectra are in keeping with this interpretation, showing that the two hydrogens of each β-methylene group of the cyclopentylidene ligand, as well as those of the neopentoxy methylene groups, are non-equivalent. However, the two signals for the olefinic hydrogens give only one multiplet at δ 5.64 which is little shifted from the corresponding signal (δ 5.76) in **28**. Such small changes, compared with those for non-alkylidene d^2 olefin complexes, tend to show that the complex **29** should be viewed as a

d^0 metal complex in which the olefin is bound mainly through donation of its π electrons into an empty orbital of tungsten. A weak additional interaction of the π^* orbital with the π electrons of the W=C bond may, however, be at the origin of the parallel configuration and of the substantial barrier to rotation (see below).

The equilibrium constant for the formation of **29**, determined from the NMR spectrum at $-38\,^{\circ}C$, is 4.5 M^{-1}; the temperature variation gives $\Delta H^{\circ} = -57\ kJ\,mol^{-1}$ and $\Delta S^{\circ} = -230\ J\,K^{-1}\,mol^{-1}$. Raising the temperature to $-33\,^{\circ}C$ leads to the coalescence of the olefinic carbon signals C-7/C-7′ (δ 124.4, 107.8), reversible on cooling. Likewise the pairs of peaks for C-3/C-3′ and C-5/C-5′ coalesce to singlets at -58 and $-63\,^{\circ}C$ respectively, while the two AB (2H) patterns due to the pairs of geminal protons attached to C-2 and C-2′ simplify to a single AB (4H) pattern above $-48\,^{\circ}C$, and the same applies to the two AB patterns due to the two $-OCH_2-$ groups. Consideration of the splittings as a function of coalecence temperature shows that they result from a single intramolecular dynamic process with an energy barrier of 44 $kJ\,mol^{-1}$. In this process, equilibration of the two neopentoxo ligands and of the two sides of both cycloheptene and cyclopentylidene ligands occurs, leaving their CH_2 protons non-equivalent. This can only be reconciled with the occurrence in **29** of olefin ligand rotation about the tungsten–olefin axis (equation 8). Such rotational barriers with one rotamer favoured at low temperature could clearly be of importance in determining the stereochemistry of propagation reactions in olefin metathesis.



(8)

When the temperature is raised above $-18\,^{\circ}C$, the ROMP of cycloheptene begins to occur, indicating that **29** can be considered as a true intermediate in this system. No further intermediates are, however, detected and hardly any of the initiator is consumed showing that propagation is very much faster than initiation.

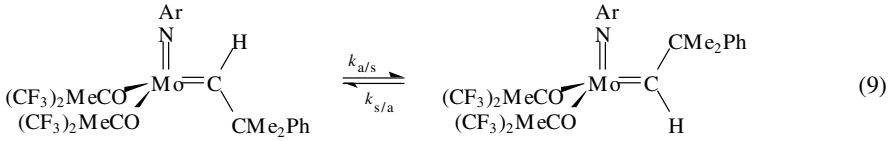
Similar observations have been made on replacing bromo ligands by chloro ligands, cyclopentylidene by cyclohexylidene or cycloheptene by cyclooctene. However, when one bromo ligand is replaced by neopentoxo, or cyclopentylidene by neopentylidene, no intermediate can be detected, even though the ROMP of **28** occurs at $-33\,^{\circ}C$. No interaction is found between **27** and cyclohexene, and no ROMP occurs, suggesting that ring-strain relief is involved in the formation of the cycloalkene adducts as well as in their actual ROMP. Replacing the cyclopentylidene ligand by *n*-pentylidene leads to a metallacyclobutane complex as the main observable intermediate and the ROMP of **28** starts at even lower temperature ($-53\,^{\circ}C$), this behaviour being similar to that for norbornene and its derivatives, probably arising from further ring-strain relief on conversion of the metal–carbene–olefin complex into the metallacyclobutane[120].

These results show that subtle changes in the nature of the metal carbene initiator or of the substrate can lead to important modifications in the relative energy levels of the three types of intermediates involved in catalytic olefin metathesis reactions.

5. Structures; barriers to rotation about Mt=C

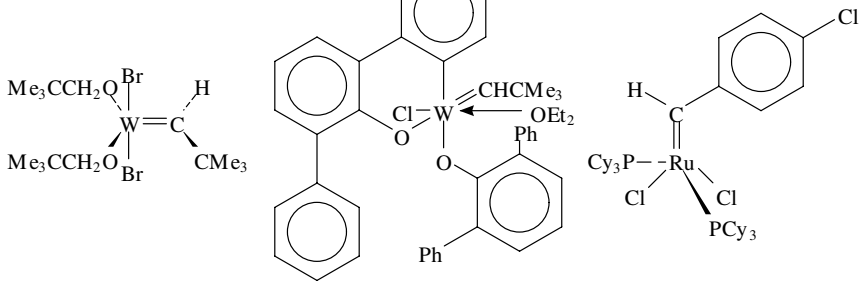
The structures of **8**, **10**, **12** and **20a** (R = *p*-ClC_6H_4, R′ = PCy_3) are known. The geometries around the metal centres are approximately tetrahedral (12e),

trigonal–bipyramidal (12e), octahedral (14e) and square–pyramidal (16e), respectively.



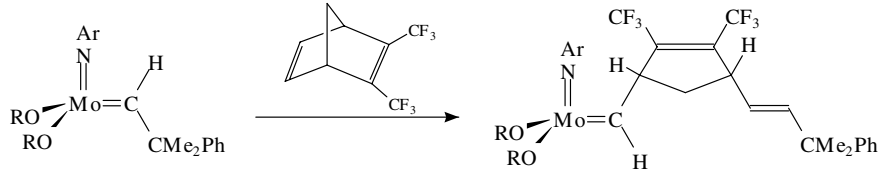
(9)

(8a) *anti* $K = k_{a/s}/k_{s/a}$ **(8b)** *syn*



(10) **(12)** **(20a)**

As indicated, the complex **8** exists in two forms, **8a** (*anti*) and **8b**) (*syn*), in equilibrium (equation 9). The *syn* rotamer is the dominant form in toluene at 25 °C ($K = k_{a/s}/k_{s/a} = 1450$); the *anti* form is difficult to detect in routine NMR spectra. However, the equilibrium can be displaced by UV-irradiation (366 nm) of the solution for several hours at −80 °C to yield a mixture containing about 33% of the *anti* rotamer as determined from the H_α resonances: *syn*, δ 12.11, $J_{CH} = 120.3$ Hz; *anti*, δ 13.30, $J_{CH} = 153.3$ Hz. On adding 0.33 equiv of 2,3-bis(trifluoromethyl)norbornadiene to this solution and running the spectrum again at −80 °C it is found that the *anti* rotamer has been completely consumed, giving the *syn* first-addition product (equation 10), while the *syn* rotamer has scarcely reacted at all. It is estimated that the *anti* rotamer is at least 100 times more reactive than the *syn* rotamer[121,122]. The possibility of the presence of different active species having different reactivities must clearly be borne in mind in other metathesis systems and may be of profound importance for the mechanism of formation and structure of the product. The new C=C double bond formed in reaction 10 is *trans* as shown by the value of 15.4 Hz for J_{HH}. Further irradiation of the reaction mixture (containing 0.67 equiv of *syn* initiator and 0.33 equiv of *syn* first-addition product) results in the isomerization of some of each to the *anti* isomers. In THF the coordination of the solvent alters the position of equilibrium ($K = 23$ for **8** at 25 °C) and reduces the rate of attainment of equilibrium, but qualitatively the same effects are observed as in toluene.



anti initiator *syn* first-addition product (10)

While certain ethers, such as THF and DME, may be strongly bound and have a moderate or strong retarding effect on metathesis, as for **6, 15** and **19**, other solvents may be less strongly bound and have no serious effect on the rate of metathesis, as for **11** and **12** where the loosely bound ether in the octahedral complex is readily displaced by the substrate.

In the complex **10** the neopentoxy ligands are non-equivalent and no rotation of the carbene ligand can be observed below the decomposition temperature (>150 °C)[123], corresponding to a barrier ($\Delta G^{\ddagger}$) of >96 kJ mol^{-1}. In the complex **20a** the structure is close to square-pyramidal, the bond angles being Cl−Ru−Cl 167.6°; P−Ru−P 161.1°; Cl−Ru−P 87.2°, 90.8°, 91.5° and 86.5°; P−Ru=C 97.5° and 101.2°; Cl−Ru=C 88.7° and 103.7°. The aryl ligand is only slightly twisted out of the $Cl_2Ru{=}C$ plane[60].

The ease with which the geometry of the metal carbene complexes can adjust to accommodate the incoming olefin may be an important factor in determining the rate and stereoselectivity in a given metathesis reaction[124].

C. Initiator Efficiencies

Initiation	$I + M \longrightarrow P_1$	k_i
Propagation	$P_n + M \longrightarrow P_{n+1}$	k_p

When the initiator (I) is very efficient, e.g. $k_p/k_i < 0.3$, and an excess of monomer (M) is used, the initiator disappears according to a near-first-order law before much monomer has been consumed. Once it is all used up the monomer disappears exactly according to a first-order law since the concentration of living propagating species (P) is now constant and equal to the original concentration of initiator. Hence, provided that both initiator and monomer concentrations can be followed, say by ^{1}H NMR, both k_i and k_p may be determined[60].

On the other hand, if the initiator is not very efficient, e.g. $k_p/k_i > 3$, the monomer may be used up before the initiator. An expression for k_p/k_i in terms of the fraction of initiator remaining can be obtained by dividing the rate of reaction of the monomer by that of the initiator, substituting $[P] = [I]_0 - [I]$, and integrating between the limits $[M] = [M]_0$ and 0, and $[I] = [I]_0$ and $[I]_\infty$, where $[I]_\infty$ is the final concentration of initiator. This leads first to equation 11 and, after integration, to equation 12.

$$d[M]/d[I] = 1 + (k_p/k_i)([P]/[I]) = [1 - (k_p/k_i)] + (k_p/k_i)([I]_0/[I]) \quad (11)$$

$$k_p/k_i = \{([M]_0/[I]_0) + ([I]_\infty/[I]_0 - 1\}/\{\ln([I]_0/[I]_\infty) + ([I]_\infty/[I]_0) - 1\} \quad (12)$$

In order to determine values of k_p/k_i experimentally from this relationship, presented graphically in Figure 1, it is best to adjust $[M]_0/[I]_0$ so that the measured value of $[I]_\infty/[I]_0$ is in the middle range, preferably near 0.5. When P_1 and P_n ($n > 1$) give separate signals in the NMR spectrum, as is often the case, k_p/k_i can be determined directly from the value of $[I]/[P_1]$ at the maximum concentration of $[P_1]$, since at this point the rate of formation of P_1, ($k_i[I][M]$), is equal to its rate of disappearance ($k_p[P_1][M]$). Some values are collected in Table 3. In most cases $k_p > k_i$, presumably because the substituent on the carbene ligand of the initiator offers more steric hindrance to the reacting monomer than the substituent on the carbene ligand of the propagating species.

D. Theoretical Treatments

Extended Hückel MO calculations on $Ti(=CH_2)L_2$, where L = H, Cl, Cp, have shown that the completely planar molecule is easily distorted into a flattish pyramid with Ti at the

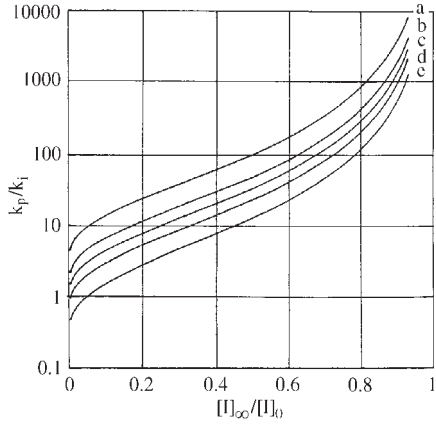


FIGURE 1. Relationship between k_p/k_i and $[I]/[I]_0$ when $[M]_0/[I]_0$ is (a) 20, (b) 10, (c) 7, (d) 5 or (e) 3; see equation 12. Reprinted with permission from Ref. 129. Copyright (1995) American Chemical Society

TABLE 3. k_p/k_i values determined mainly from equation 12[a]

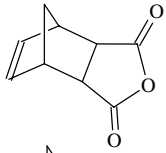
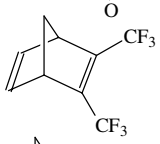
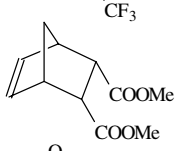
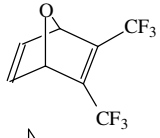
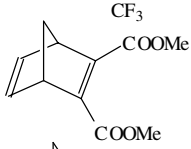
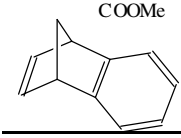
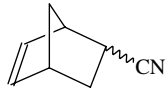
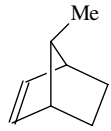
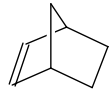
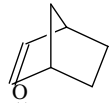
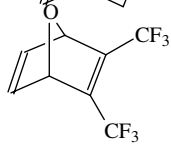
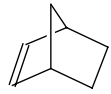
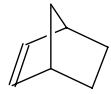
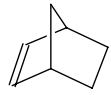
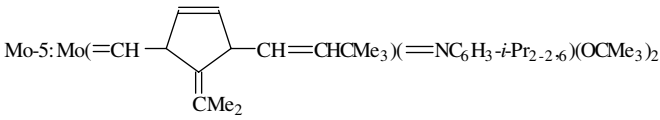
Monomer	Catalyst[b]	Solvent	k_p/k_i	Reference
	W-1	CD_2Cl_2	0.26	125
	Mo-1	C_6D_6	0.72	126
	W-1	CD_2Cl_2	1.0	127
	Mo-2	$C_6D_5CD_3$	2.4	115
	Mo-1	C_6D_6	3	126
	Mo-1	$C_6D_5CD_3$	7	10

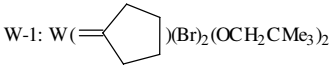
TABLE 3. (*continued*)

Monomer	Catalyst[b]	Solvent	k_p/k_i	Reference
	Mo-1	$C_6D_5CD_3$	7	126
	Mo-1	C_6D_6	9	128
	Mo-1	C_6D_6	12	126
	Mo-3	$C_6D_5CD_3$	30	129
	Mo-4	$C_6D_5CD_3$	40	115
	Mo-5	C_6D_6	270	10
	Ru-1 Ru-2	CD_2Cl_2/C_6D_6 CH_2Cl_2	v. large 170	110 60
	Ru-3	CH_2Cl_2	0.1–0.8[c]	60,91

[a] Ambient temperature.

[b] Mo-1: Mo(=CHCMe$_3$)(=NC$_6$H$_3$-*i*-Pr$_2$-2,6)(OCMe$_3$)$_2$
Mo-2: Mo(=CHCMe$_2$Ph)(=NC$_6$H$_3$-*i*-Pr$_2$-2,6) (OCMe$_2$CF$_3$)$_2$
Mo-3: Mo(=CHCMe$_2$Ph)(=NC$_6$H$_3$-*i*-Pr$_2$-2,6) (OCMe$_3$)$_2$
Mo-4: Mo(=CHCMe$_2$Ph)(=NC$_6$H$_3$-*i*-Pr$_2$-2,6) [OCMe(CF$_3$)$_2$]$_2$





Ru-1: Ru(=CHCH=CPh$_2$)(Cl)$_2$(PCy$_3$)$_2$; (Cy = cyclohexyl)
Ru-2: Ru(=CHCH=CPh$_2$)(Cl)$_2$(PPh$_3$)$_2$
Ru-3: Ru(=CHC$_6$H$_4$X-*p*)(Cl)$_2$(PPh$_3$)$_2$

[c] *p*-X in Ru-3 (k_p/k_i values): H (0.11), F (0.21), Me (0.34), NMe$_2$ (0.38), OMe (0.38), NO$_2$ (0.43), Cl (0.83).

apex, ready to receive the incoming donor olefin[130]. Similarly, SCF-Xα-SW calculations on Mo(=CH_2)(=NH)($OMe)_2$ show that the reaction with ethene at the COO face to form the metallacyclobutane is facilitated by twisting the =CH_2 ligand about the Mo=C bond[131].

Structural parameters and other data have been calculated by *ab initio* MO methods for various other models of the intermediates in the olefin metathesis reaction, for example Mo(=CH_2)(CH_3)(Cl)($OAlH_3$)[132]; Mo(=CH_2)$(Cl)_4$[133–135]; Mt(=CH_2)(=O)$(Cl)_2$ where Mt = Mo, W[136,137]; Mt(=CHR)(=NH)$(OH)_2$ where Mt = Mo, W[137]; Mo(=CH_2)(X)$(L)_2$ where X = O, NH and L = Cl, OMe, OCF_3[138]; Mo(=CH_2)(=NH)$(OR)_2$ where R = H, Me[131]; and W(=CR^1R^2)Cl_4[139]. These MO treatments mostly involve model compounds somewhat removed from real life. Nevertheless, they reveal factors and trends which are likely to be valid in real situations. The more recent force field (METMOD) treatments deal with actual metal carbene initiators and the intermediates derived therefrom and give remarkably accurate predictions of geometry, rotational barriers etc[140–143].

On the question of the transitory existence of metal–carbene–olefin intermediates, for which there is kinetic evidence in one system[144] and spectroscopic evidence in another (see Section III.B.4)[120], MO calculations do not reveal a potential-energy-well intermediate between the reactants Ti(=CH_2)$(Cl)_2$ + CH_2=CH_2 and the product metallacyclobutane, although the metal–carbene–olefin configuration does have an intermediate energy in the overall exothermic reaction[134,145]; similarly for the reaction of Mo(=CH_2)$(Cl)_4$ with CH_2=CH_2[133].

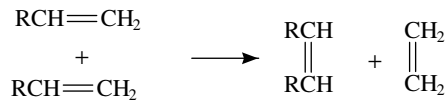
The interconversion of metal–carbene–olefin complexes with corresponding metallacycles are formally $2_\pi + 2_\pi$ processes. It might have been expected, from the Woodward–Hoffmann and other rules (see elsewhere[146,147] for summaries), that these would have large activation barriers. Yet they generally proceed with remarkable facility. The reason, as determined from a detailed consideration of the reaction of Ti(=CH_2)$(Cl)_2$ with CH_2=CH_2, is that the participation of a 3d orbital allows the Pauli principle constraints to be satisfied in a unique way that avoids the unfavourable transition-state bonding interactions that are usually the source of the high barrier[137,146].

The unsubstituted metallacyclobutane formed from Ti(=CH_2)$(Cl)_2$ + CH_2=CH_2 is calculated to have a planar but easily puckered ring. Even a substituent in the 2-position (opposite to Ti which is numbered 4) is known to cause very little puckering[124]. However, in 1,3-disubstituted tungstacyclobutanes, extended Hückel calculations show that the ring has a puckered *ee* configuration, as required by the interpretation of the *cis/trans* stereoselectivity in the metathesis reactions of alk-2-enes[148] (see Section IV).

IV. ACYCLIC MONOENES NOT CONTAINING FUNCTIONAL GROUPS

With terminal alkenes, degenerate metathesis (equation 13), competes with productive metathesis (equation 14), to an extent which depends very much on the catalyst.

(13)



(14)

Isotopic labelling experiments have demonstrated that for the reaction of propene on MoO_x/TiO_2 or on photoreduced MoO_3/TiO_2 the chain carrier for the degenerate metathesis is [Mo]=CHMe rather than [Mo]=CH_2[149–151]. As a general rule in olefin metathesis a substituted carbene is less reactive than an unsubstituted carbene, and so the former tends to build up to a higher steady state.

With proper choice of catalyst, high yields for reaction 14 can be obtained with all terminal olefins. When propene is passed over $Re_2O_7/Al_2O_3/Et_4Sn$ at 20 °C/1.5 bar, equilibrium conversion can be achieved with 100% selectivity at a throughput of 25 $dm^3\ h^{-1}$ (g catalyst)$^{-1}$[44]. The reaction of propene on a catalyst made from $Mo(CO)_6/Al_2O_3$ is somewhat stereoselective at 25 °C. In the early stages the product but-2-ene has a *cis/trans* ratio of 67/33, but this very quickly moves towards the equilibrium ratio of 24/76 as a result of secondary metathesis[152].

With liquid olefins the product ethene can be allowed to escape so enhancing the yield. For the substrates RCH=CH_2 one can obtain yields of RCH=CHR as follows: pent-1-ene 64% (using $WCl_6/Et_2O/Bu_4Sn$ in $CHCl_3$)[153], 3-methylbut-1-ene 58%[153], vinylcyclopropane 65%[154], hex-1-ene 99% (using catalyst **8**, R = Ph)[97], oct-1-ene 86% (by refluxing through a column of Re_2O_7/Al_2O_3)[153], dec-1-ene 77%[153], styrene 95% [using Mo(=$CHCMe_2Ph$)(=NC_6H_3-Me_2-2,6)($OCMe_2CF_3)_2$][97], allylbenzene 77%[153]. All these reactions occur with good selectivity.

Alkenes of the type RCH=CHR readily undergo *cis/trans* isomerization in the presence of metathesis catalysts. With unsymmetrical alkenes $R^1CH{=}CHR^2$ interest centres on the stereoselectivity. In the case of *cis*-pent-2-ene catalysed by **12** in chlorobenzene at 25 °C the reaction is highly stereoselective giving initially 99% *cis*-but-2-ene and 100% *cis*-hex-3-ene. Similarly, starting from *trans*-pent-2-ene the initial products are 99.6% *trans*-but-2-ene and 99.6% *trans*-hex-3-ene; *trans/cis* isomerization only begins to occur as the but-2-ene approaches its equilibrium proportion of 25%[101]. Such high selectivity can be explained in terms of a puckered metallacyclobutane intermediate (see Section III.D) in which the interaction of the substituents (Me or Et) in the 1,3-positions is the dominant factor (the metal is numbered 4)[26,27]. In the metathesis of pent-2-ene with other catalysts the initial *trans* content of the hex-3-ene is always higher than that of the but-2-ene regardless of whether one starts from the *cis* or *trans* reactant; see Ivin[26] for a summary. This may be taken as evidence of an effect of the substituent at the 2-position, a 2-ethyl group exercising a stronger influence than a 2-methyl group. Where this exists it favours the 1,2-aa and -ee structures, accounting for the *trans* bias in the hex-3-ene relative to but-2-ene. This effect becomes completely dominant in the metathesis of 4-methylpent-2-ene (*i*-PrCH=CHMe) where the product 2,5-dimethylhex-3-ene (*i*-PrCH=CH-*i*-Pr) is entirely *trans* for the reaction of both *cis*-and *trans*-substrates[155]. In line with these arguments the *trans* content of the products increases with the size of R^1 and R^2 in the $Re_2O_7/CsNO_3/Al_2O_3$-catalysed metathesis of linear olefins (C_5–C_9). The general order of reactivity on this catalyst is alk-2-ene > alk-3-ene > alk-4-ene > alk-1-ene[156].

The metathesis of 1,1-disubstituted alkenes is not so easy to achieve because the equilibrium lies on the side of the reactant. However, if the ethene is allowed to escape the reaction can proceed in certain cases, e.g. for 2-methylbut-1-ene[157,158], 2-methylpent-1-ene and 2-methylhept-1-ene[159]; also for methylenecyclobutane[160,161], but surprisingly not for methylenecyclopropane nor for methylenecyclopentane[154]. Methylenecyclohexane will exchange with W(=$CHCMe_2Ph$)(=NAr)[$OCMe(CF_3]_2]_2$ to give CH_2=$CHCMe_2Ph$ but the reaction does not proceed further[162]. It will also exchange methylene groups with isobutene in the presence of a Ti-based catalyst[163,164]. For a number of 1,1-disubstituted alkenes metathesis catalysts first bring about conversion to isomers which then undergo cross-metathesis with the remaining substrate[161,165,166].

The metathesis of some trisubstituted ethenes has recently been reported. The reaction of ethylidenecyclobutane over Re_2O_7/Al_2O_3 at 35 °C gives 30% dicyclobutylidene in 4 h, but if promoted with Bu_4Sn the yield is increased to 75%[154,167]. 2-Methylbut-2-ene undergoes metathesis in the presence of **8** (R = Ph), equation 15, reaching equilibrium (16% conversion) in 1 week or less. All attempts at bringing about the metathesis of trisubstituted ethenes containing an alkyl group larger than methyl have failed with this catalyst[162].

$$2Me_2C{=}CHMe \overset{\mathbf{8}}{\rightleftharpoons} Me_2C{=}CMe_2 + MeCH{=}CHMe \qquad (15)$$

With the catalyst $Re_2O_7/CsNO_3/Al_2O_3$ at 20–70 °C 2-methylpent-2-ene ($Me_2C{=}CHEt$) undergoes slow isomerization to 2-methylpent-1-ene ($MePrC{=}CH_2$) which then rapidly cross-metathesizes with the starting olefin to yield 4-methylhept-3-ene (MePrC=CHEt) with 75% selectivity. Small amounts of the self-metathesis products, $Me_2C{=}CMe_2$ and EtCH=CHEt, are also formed. Similar behaviour is observed with 2-methylhex-1-ene ($Me_2C{=}CHPr$) and 3-methylpent-2-ene (EtMeC=CHMe)[166].

The simplest example of a cross-metathesis reaction is that between ethene and but-2-ene; the equilibrium mixture then consists of a mixture of four compounds, counting both *cis* and *trans* isomers. For the reaction of $R^1CH{=}CHR^2$ and $R^3CH{=}CHR^4$, with R^1, R^2, R^3, R^4 all different, twenty different compounds will be present in the equilibrium mixture. If cross-metathesis reactions are to be used for synthetic purposes it is usually possible to simplify the situation by choosing at least one symmetrical olefin ($R^3 = R^4$) or one with R^4 = H and by taking one olefin in excess. Some examples are the following.

(1) The reaction of isobutene with hexa-1,5-diene catalysed by $Re_2O_7/Al_2O_3/Bu_4Sn$ at 40 °C gives >20% yield of 6-methylhepta-1,5-diene, an intermediate in the synthesis of vitamins and carotenoids[168].

(2) The reaction of isobutene with higher terminal alkenes or symmetrical internal alkenes catalysed by $Re_2O_7/Al_2O_3/Me_4Sn$ leads to 2-methylalk-2-enes with conversions of 70–80%[169].

(3) In the presence of $Mo(CO)_6/ZrCl_4/h\nu$, pent-1-ene undergoes substantial isomerization to pent-2-ene which then cross-metathesizes with pent-1-ene without itself undergoing appreciable self-metathesis. In the reaction of pent-1-ene with 4-methylpent-2-ene, the cross-products, hex-2-ene and 2-methylhept-3-ene, predominate over the products of self-metathesis[170].

(4) Cross-metathesis of hex-1-ene with a four-fold excess of tetradec-7-ene, catalysed by $WCl_6/Et_2O/Bu_4Sn$ at 50 °C, results in a 90% conversion of hex-1-ene and a selectivity of 90% for the cross-metathesis product dodec-5-ene[153].

(5) 3,3-Dimethylbut-1-ene (neohexene), which is inactive to self-metathesis, undergoes cross-metathesis with internal alkenes to high conversion when catalysed by $WCl_6/Et_2O/Bu_4Sn$[153].

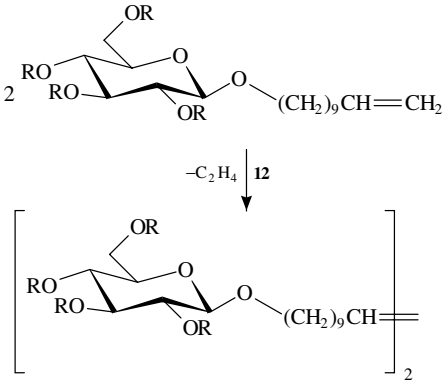
(6) Cross-metathesis of equimolar amounts of styrene with symmetrical alkenes occurs on Re_2O_7/Al_2O_3 at 50 °C. 85–90% of the styrene is converted to 1-phenylalk-1-enes and only 10% to the self-metathesis product stilbene[171]. Likewise, the reaction of styrene with 0.5 equiv oct-1-ene catalysed by **8** gives >85% of the cross-metathesis product (>95% *trans*) and <4% of the self-metathesis product of oct-1-ene[172].

(7) A number of insect sex pheromones are long-chain internal olefins or their epoxides and can be prepared via metathesis reactions, for example the reaction of dec-1-ene with pentadec-1-ene to give tricos-9-ene, the *cis* isomer of which is a sex pheromone of the housefly (*Musca domestica*)[173,174]; see also Küpper and Streck[175,176].

V. ACYCLIC MONOENES CONTAINING FUNCTIONAL GROUPS

This area has been well reviewed by Mol[177]. By suitable choice of catalyst almost any functional group may be tolerated in the substrate, but there must usually be one or more CH_2 groups between the double bond and a functional group for productive metathesis to take place. From Table 1 it may be seen which functional groups are liable to react with particular Mt=C bonds and therefore to be avoided in the substrates used with catalysts based on these metals. Table 1 does not include any reactions involving Ru=C bonds; in fact they do not react with the various Y=Z or Y≡Z functions listed. Ru-based catalysts therefore offer the widest scope for the metathesis of unsaturated compounds containing functional groups. Catalyst **19** will even bring about the metathesis of 200 equiv of oleic acid at 20° in 20 h[178].

Olefinic compounds containing OH or NH_2 groups destroy W- or Mo-based catalysts but metathesis is possible if these groups are first protected. For example, ω-unsaturated glucosides bearing protecting groups R will react in the presence of **12** to give boloamphiphiles (equation 16). For R = acetyl a yield of 64% is obtained at 80 °C, while for R = *t*-$BuMe_2Si$ the yield is 92% at 65 °C[179]. Equation 17 is an example of the metathesis of a protected amine (60% yield after 8 h)[180].



(16)

$$2Me_3CO(CO)NHCH_2CH{=}CH_2 \xrightarrow[-C_2H_4]{\mathbf{8}} [Me_3CO(CO)NHCH_2CH{=}]_2 \qquad (17)$$

Perhaps surprising at first sight is the fact that the metathesis of diallylphenyl phosphane can be carried out using **12** as catalyst (equation 18.) The tungsten centre in **12** is evidently too crowded to allow its deactivation by coordination of the phosphorus atom but not so crowded as to prevent the coordination and subsequent reaction of the double bond[181].

$$2Ph_2PCH_2CH{=}CH_2 \xrightarrow[\substack{\text{PhCl, } 80\,^{\circ}\text{C, } 12\text{h}\\ -C_2H_4}]{5\text{ mol\% }\mathbf{12}} [Ph_2PCH_2CH{=}]_2 \qquad (18)$$

Where there is no spacer group between the C=C bond and the functional group, productive self-metathesis does not occur, but cross-metathesis reactions with other olefins are still possible. Recent impressive examples of this are the cross-metathesis reactions of acrylonitrile (equation 19). The reaction occurs with a wide variety of R groups. For 15 different compounds the yield of the new nitrile after 3 h at room temperature is 40–90%, with the *cis* isomer always strongly preferred (75–90%). Only minor amounts of $RCH_2CH{=}CHCH_2R$ are formed, and no NCCH=CHCN[182]. The fact that acrylonitrile

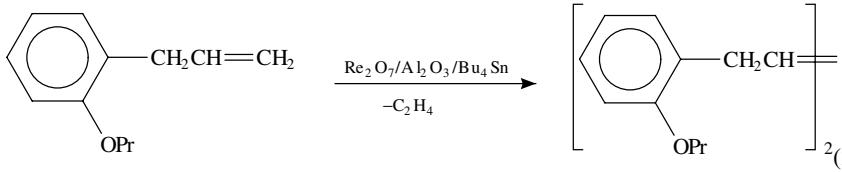
itself does not undergo metathesis must be due to the inability of [Mt]=CHCN to react with CH_2=CHCN in a productive manner, though the degenerate reaction may well occur.

$$\begin{matrix} CH_2{=}CHCN \\ + \\ CH_2{=}CHCH_2R \end{matrix} \xrightarrow[CH_2Cl_2]{8} \begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} + \begin{matrix} CHCN \\ \| \\ CHCH_2R \end{matrix} \qquad (19)$$

The results of some cross-metathesis experiments for a series of nitriles CH_2=$CH(CH_2)_nCN$ reacting with *cis*-hept-3-ene are summarized in Table 4. No cross-metathesis occurs with acrylonitrile ($n = 0$). For $n = 1, 2, 5, 8, 9$ cross-metathesis products are formed in substantial amount, but for $n = 3, 4$ very little reaction occurs, an effect which is attributed to intramolecular coordination of the nitrile group to the metal centre in [Mt]=$CH(CH_2)_nCN$ ($n = 3, 4$), thereby reducing its metathesis activity or causing its destruction. With $n \geqslant 5$ the nitrile group has little influence on the reaction and its self-metathesis is preferred over that of hept-3-ene, whereas the reverse is true for $n = 1, 2$.

For small values of n the ability of nitriles to undergo self-metathesis depends on the catalyst. Thus for $n = 1$ (allyl cyanide) WCl_6/Me_4Sn gives only very low yields[183], but WCl_6/1,1,3,3-tetramethylsilane-1,3-disilacyclobutane (1/2) with 50 equiv of substrate gives a 53% yield after 10 h at 60 °C (selectivity 82%)[184]. For $n \geqslant 2$ good yields are obtained with $Re_2O_7/Al_2O_3/Me_4Sn$ catalysts (selectivity >98%), and for $n \geqslant 5$ also with WCl_6/Me_4Sn[183].

The behaviour of unsaturated ethers follows a similar pattern. Thus for *cis*-$RO(CH_2)_nCH{=}CH(CH_2)_nOR$ with $n = 1$, R = *t*-$BuMe_2Si$ or Me, no *cis/trans* isomerization is observed in the presence of W(=CHC_6H_4-OMe-2)(=NPh)([OCMe$(CF_3)_2]_2$, but for $n = 2$ isomerization occurs quite readily[185]. The metathesis of *o*-allylphenyl propyl ether (equation 20) occurs at 22 °C with high yield (95% selectivity)[186]. *cis*-Propenyl ethyl ether and butyl vinyl ether have no CH_2 spacers between the C=C and ether functions and do not undergo self-metathesis, but they are able to cross-metathesize (equation 21) to give the monoether products only[188].



(20)

TABLE 4. The metathesis of CH_2=$CH(CH_2)_nCN$ with *cis*-hept-3-ene catalysed by $WC1_6/Me_4Sn$ at 100 °C (nitrile/heptene/W/Sn = 10/10/1/2)[183,187]

n	Cometathesis conversion (mol%)	Self-metathesis conversion (mol%)	
		cis-hept-3-ene	nitrile
0	0	42	0
1	42	28	0
2	59	30	4
3	12	4	2
4	2	0	0
5	47	9	26
8	42	7	46
9	46	5	40

$$\begin{matrix} MeCH{=}CHOEt \\ + \\ BuOCH{=}CH_2 \end{matrix} \xrightarrow{Cr[=C(OMe)Ph](CO)_5} \begin{matrix} MeCH \\ \| \\ BuOCH \end{matrix} + \begin{matrix} CHOEt \\ \| \\ CH_2 \end{matrix} \qquad (21)$$

In the presence of **12**, allyl methyl sulphide undergoes self-metathesis leading to $MeSCH_2CH{=}CHCH_2SMe$ (90% *trans*), and cometathesis with *cis*-but-2-ene leading to $MeCH{=}CHCH_2SMe$ (75% *trans*)[189].

Vinyl chloride, like acrylonitrile, is not able to self-metathesize but will cross-metathesize with simple alkenes[190,191]. Both allyl chloride and allyl bromide will undergo metathesis on $Re_2O_7/Al_2O_3/R_4Sn$ with good conversion and high selectivity[192,193].

Not surprisingly the metathesis of 10-nonadecen-2-one fails with W-based catalysts that will cause the metathesis of methyl oleate[194]; cf. Table 1. The metathesis of allyl acetone succeeds with $Re_2O_7/Al_2O_3/R_4Sn$ as catalyst[193] and the activity is increased by a factor of 10 if the support is pretreated with triethyl borate[192]. Improved yields (50%) can be obtained by first protecting the keto group by reaction with Me_3SiCl in the presence of Et_3N in DMF to give the silylenol ether, or by reaction with ethane-1,2-diol to give the 1,3-dioxolane derivative[195].

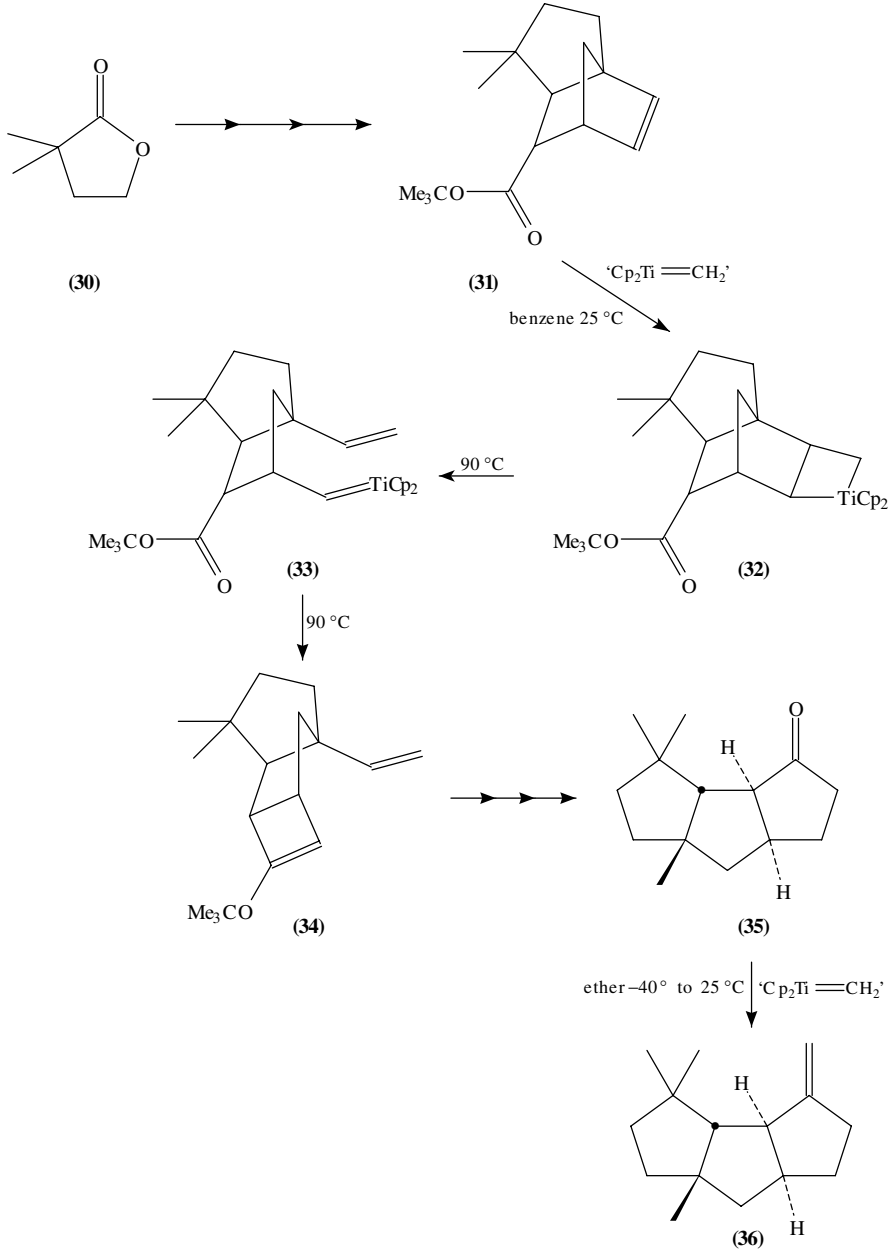
The metathesis of unsaturated esters, e.g. $CH_2{=}CH(CH_2)_nCOOR$ ($n \geqslant 1$), can be brought about by a variety of catalysts such as (i) WCl_6/Me_4Sn, where it is best to add the ester before the Me_4Sn[196,197], (ii) Re_2O_7-based catalysts which are active at 20 °C, are highly selective and easily recovered[198], and (iii) MoO_3/SiO_2 which has been photoreduced in CO and subsequently treated with cyclopropane[199,200]; also by carbene complexes of W[83,101,201], of Mo[97,202] and of Ru[178].

Vinyltrimethylsilane is reported to give good yields of the metathesis product $Me_3SiCH{=}CHSiMe_3$ with a number of ruthenium catalysts, e.g. $Ru_3(CO)_{12}/HSiPh_3$ in benzene at 80 °C (75% yield of *trans* isomer)[203] and $Ru(H)(Cl)(CO)(PPh_3)_3$ [38% yield of *trans/cis* (44/56) product]. With $Ru(SiMe_3)(Cl)(CO)(PPh_3)_2$ as catalyst there are indications of a competing reaction in which the C=C bond of the substrate inserts into a Ru−Si bond[204]. $RuCl_2(PPh_3)_2$ is also an effective metathesis catalyst not only for vinyltrimethylsilane but also for derivatives in which some of the methyl groups have been replaced by phenyl[205] or by alkoxy groups[204,206−208]. The metathesis of allylsilane derivatives proceeds readily on $WOCl_4$[209] and on $Re_2O_7/Al_2O_3/R_4Sn$[210−212].

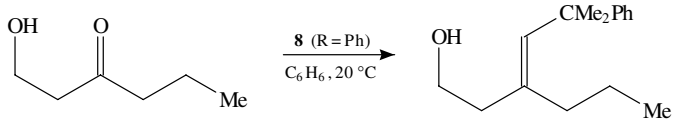
VI. THE CARBONYL−OLEFINATION REACTION

Before considering ring-closing metathesis (RCM) it is convenient to discuss the carbonyl−olefination reaction because this is sometimes an important adjunct to RCM. This reaction, e.g. equation 22, is like a Wittig reaction in which the Mt=C bond takes the place of a P=C bond. It is important both as a means of effecting clean termination of living ROMP reactions when initiated with Ti, Mo or W complexes, and as a convenient means of converting C=O groups into olefinic groups. While ketones can be used to terminate living Ti and W carbenes, they do not react so readily with Mo carbenes, except when carrying a β- or γ-hydroxy substituent, in which case the reaction becomes very stereoselective; e.g. $E/Z > 99/1$ for the product of reaction 23 in benzene at 20 °C. This effect is thought to be caused by coordination of the hydroxy substituent to the metal centre in the intermediate metallacycle[11].

$$[Mt]{=}CHR + R^1R^2C{=}O \longrightarrow [Mt]{=}O + RCH{=}CR^1R^2 \qquad (22)$$



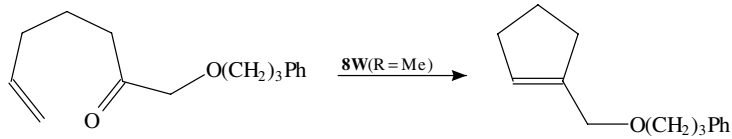
SCHEME 3. Synthesis of (±)-$\Delta^{9(12)}$-capnellene involving metathesis reactions **31** → **33**, **33** → **34**, and **35** → **36** facilitated by the Tebbe reagent '$Cp_2Ti{=}CH_2$'



(23)

The analogous reaction, using the tungsten analogue **8W** of the molybdenum complex **8** in toluene, is stereoselective at $-78\,^{\circ}C$ ($E/Z > 99/1$), but less so at $20\,^{\circ}C$ ($E/Z = 89/11$). The stereoselectivity is not so high when the HO group is replaced by $PhCH_2O$ or MeCOO, or if the HO group occupies the α- or γ-positions. This suggests that the hydroxyl group is the only Lewis base functionality that is small enough or basic enough to coordinate strongly to the highly sterically hindered metal centre[11]. In passing it should be noted that living ruthenium carbene complexes are unreactive towards both aldehydes and ketones but can be terminated by stoichiometric metathesis with ethyl vinyl ether[109] and other strained or functionalized olefins[213].

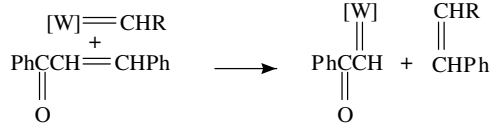
The complex **8W** (R = Me) can also be used in a stoichiometric metathesis sequence to effect the ring closure of unsaturated ketones so as to form 1-substituted cyclopentenes, cyclohexenes and cycloheptenes in good yield, e.g. equation 24. The C=C bond reacts first to give $[W]{=}CH(CH_2)_3CO(CH_2)O(CH_2)_3Ph$, which then undergoes an internal carbonyl–olefination reaction[13].



(24)

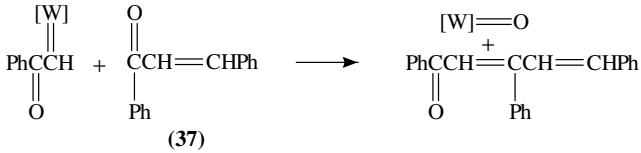
The same strategy has been used in the total synthesis of (±)-$\Delta^{9(12)}$-capnellene **(36)** from dimethyl-γ-butyrolactone **(30)**, the key steps of which are shown in Scheme 3. The Tebbe reagent is used to cleave the C=C bond in **31** to give **33** via **32**, immediately followed by the carbonyl–olefination reaction to give **34**. This is then transformed to **35** by standard procedures and finally converted to **36**, again using the Tebbe reagent. This synthesis of **36** is the first to achieve the formation of all four asymmetric centres in a single step. The overall yield is 20%[214,215].

The WCl_6-assisted condensation polymerization of conjugated ketones such as benzylideneacetophenone **(37)** proceeds through the formation of oligomeric ketones $PhCO(CH{=}CPh)_nCH{=}CHPh$ which can be detected (n = 1–6) in the early stages of the reaction[216]; see also elsewhere[217–222]. By analogy with reaction 24 it is likely that the polymerization proceeds via alternate metathesis reactions of the C=C and C=O bonds with tungsten carbene species formed from the reactants (equations 25 and 26).



(25)

(37)



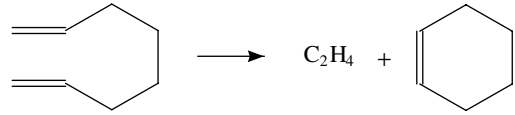
(26)

(37)

VII. ACYCLIC DIENE METATHESIS (ADMET)

Dienes can undergo olefin metathesis reactions of two types: (i) intermolecular and (ii) intramolecular, as illustrated by the reactions of hexa-1,5-diene and octa-1,7-diene, equations 27 and 28, respectively.

$$2CH_2{=}CH(CH_2)_2CH{=}CH_2 \longrightarrow [CH_2{=}CH(CH_2)_2CH{=}]_2 + C_2H_4 \qquad (27)$$



$$C_2H_4 \quad + \qquad (28)$$

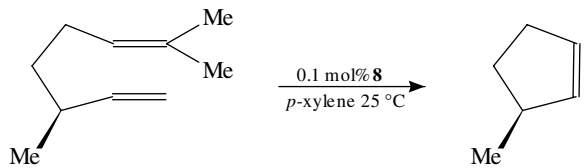
The linear product of reaction 27 can undergo further metathesis condensation reactions, eventually leading to high polymer. This is known as ADMET (*a*cyclic *d*iene *met*athesis) polymerization, to be discussed in Section VIIB. Ring-closing metathesis reactions (RCM), such as reaction 28, occur with great readiness whenever the product is a 6-membered ring. They are also often favoured for the production of 5-, 7- and 8-membered rings, depending on the nature, number and location of any substituents. The formation of much larger rings can also be achieved by imposing conformational restraints on the bonds lying between the two C=C bonds; examples are given later. Whether polymer or cyclic compound is formed from any given diene is usually determined by thermodynamic rather than kinetic factors. When the standard free energy of polymerization of the cyclic compound is close to zero, a high concentration of substrate will favour polymer formation, while low concentration will favour the formation of the cyclic compound. For a discussion of the thermodynamics of polymerization of cyclic compounds, see Ivin[223].

A. Ring-Closing Metathesis (RCM)

This reaction has become a powerful tool for the synthesis of numerous cyclic compounds including many which are biologically active; see the recent reviews by Schmalz[224] and Grubbs[225]. Here we shall give examples of various classes of compound which undergo this reaction or can be made in this way.

1. Hydrocarbons

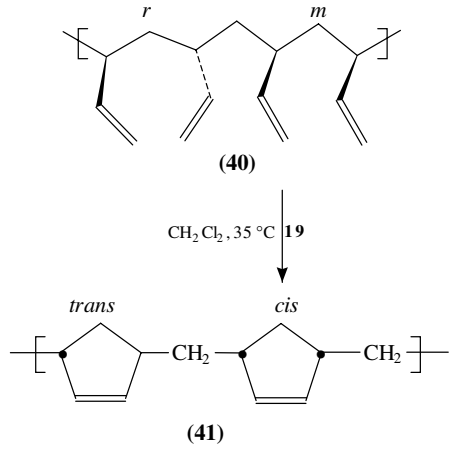
The RCM of (+)-β-citronellene (**38**, 2,6-dimethylocta-2,7-diene) in toluene (0.75 M), induced by **8**, proceeds quantitatively at 20 °C to yield isomerically pure (*S*)-3-methylcyclopentene **(39)**; see equation 29[226]. The same result can be achieved with *trans*-$WOCl_2(OC_6H_3\text{-}Br_2\text{-}2,6)_2/Et_4Pb$ as catalyst[78]. This is a remarkable improvement on the previous, very difficult synthesis of this compound. In concentrated solution in toluene (5 M), **39** undergoes ROMP when initiated by **8** at −30 °C[226]. (*S*)-4-methylcyclohexene can be made in a similar way, as can 3,3-dimethylcyclohexene and 2-methylcyclohexene[78].



(29)

(38) **(39)**

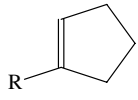
RCM is also possible between pairs of double bonds contained in the side chains of polymers, for example atactic 1,2-polybutadiene **(40)**; see equation 30. The reaction proceeds to 90% conversion in 30 min and then much more slowly to 97% conversion in 200 min. The first stage corresponds to the random reaction of adjacent double bonds in the chain, leaving 13.5% of isolated vinyl groups. These react more slowly by secondary metathesis with the double bonds in the neighbouring cyclopentene rings, thereby causing the vinyl group in effect to move along the chain until it meets another isolated vinyl group with which it can undergo RCM. The product **(41)** contains two types of repeat unit, *trans* and *cis*, according to whether the reacting dyad was *r* or *m*, giving rise to distinct olefinic ^{1}H NMR signals[227a].



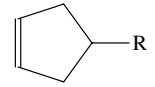
(30)

2. Ethers and sulphides

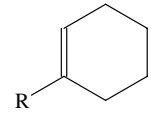
Some side-chain and ring ethers that have been prepared by RCM are shown below. Latterly the carbene catalysts, particularly **19** and **8**, have been used to obtain these compounds in high yields (mostly 70–95%). Re_2O_7-based catalysts or *trans*-$WOCl_2(OAr)_2/Et_4Pb$ are also quite effective.



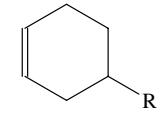
R = $PhCH_2O$ [1]



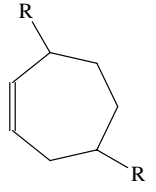
R = *t*-$BuMe_2SiO$ [2-4]
R = *i*-Pr_3SiOCH_2 [4]



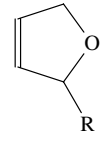
R = $PhCH_2O$ [1]



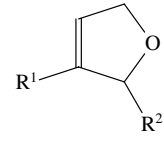
R = $PhCH_2O$ [2]



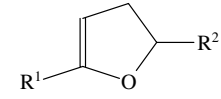
R = $PhCH_2O$ [5]



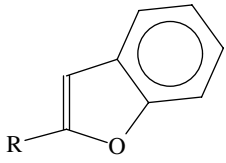
R = H [6,11]
R = C_7H_{15} [4]
R = Ph [3,7]



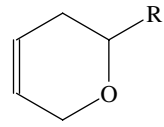
R^1 = Me
R^2 = Ph [7]



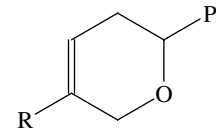
R^1 = $PhCH_2$
R^2 = Ph[1]



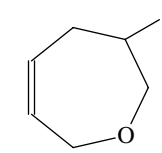
R = Pr [1]
R = $PhCH_2$ [1]



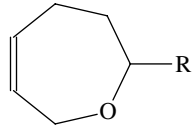
R = H [3,8]
R = Me [8]
R = Ph [3,7,8]



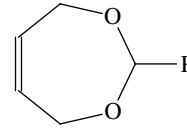
R = Me [7]
R = $PhCH_2$ [1]



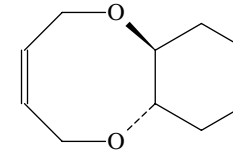
R = Ph [9]



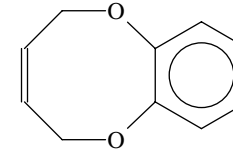
R = Ph [7]



R = Ph [7]
R = $PhCH_2$ [3]



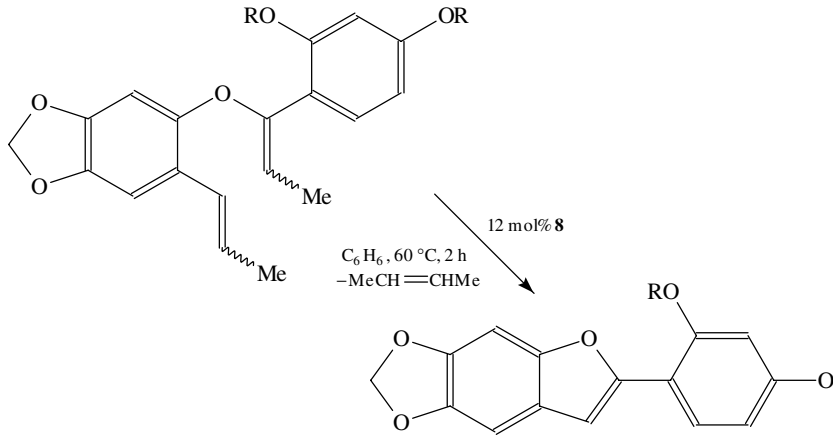
[10]



[10]

Refs. [1][228], [2][13], [3][227b], [4][78], [5][227c], [6][227d], [7][251], [8][227e], [9][227f], [10][238], [11][262]

If the precursor dienes have vinyl end-groups, ethene is eliminated in the metathesis reaction, but it is sometimes advantageous to use a precursor with one or two propenyl end-groups, eliminating propene or but-2-ene in the metathesis reaction. An example is shown in equation 31, the final stage in the synthesis of the protected precursor (**42**) of *Sophora* compound I, the antifungal phytoalexine isolated from the aerial part of *Sophora tomentosa* L[228].



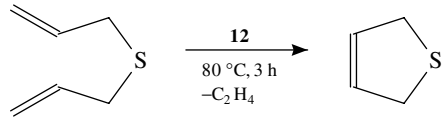
(31)

(**42**) R = CH_2Ph, yield 85%

Substituted unsaturated pyrans prepared by RCM using **19** as catalyst can be immediately submitted to zirconium-catalysed kinetic resolution of the racemic product at 70 °C. This provides a new route to medicinally important agents containing 6-membered cyclic ethers. A one-pot synthesis can give 63% conversion with >99% enantiomeric purity[229].

The complex **12** catalyses the RCM of di- and tri-substituted ω-unsaturated protected glucose and glucosamine derivatives yielding bicyclic carbohydrate-based compounds containing 12- and 14-atom rings[230].

Diallyl sulphide also undergoes RCM in the presence of **12** at 50–80 °C to give 2,5-dihydrothiophene **(43)** in up to 88% yield (equation 32). The reaction can be conducted without the use of a solvent[189].

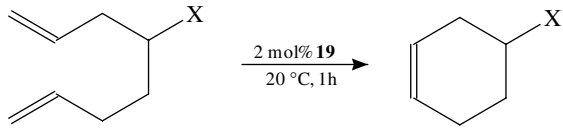


(32)

(43)

3. Alcohols, aldehydes, acids, esters and ketones

The ruthenium carbene catalyst **19** is capable of effecting RCM of dienes bearing alcohol, aldehyde or carboxylic acid functions, with remarkably high yields (equation 33).

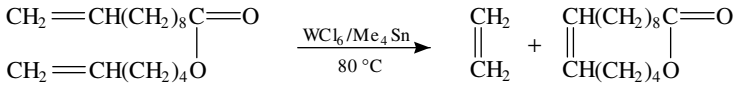


X	Yield
CH_2OH	88%
CHO	82%
COOH	87%

(33)

The cyclopentene ester derivatives **44** and **45** are both readily obtained by the RCM of diallyl precursors using W-based catalysts[78,231]. Likewise, the 16-membered unsaturated lactone **46** can be made according to equation 34[232]. Tsuji[233] gives a similar example.

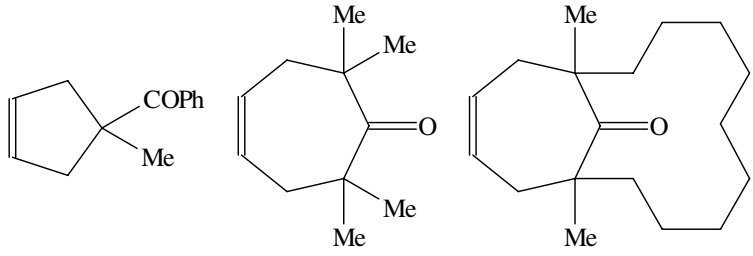
(44) **(45)**



(34)

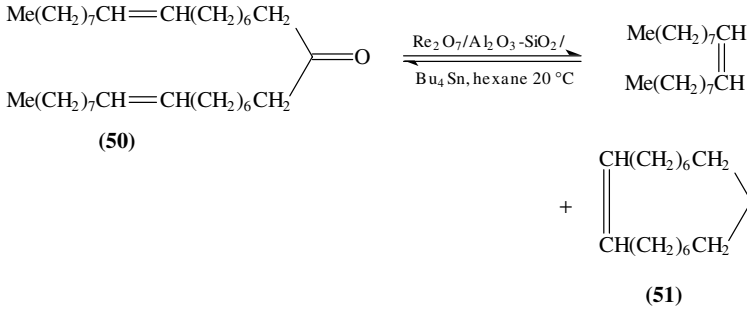
(46)

The ketones **47–49** can be made in good yield (55–95%) by RCM of the appropriate diallyl compounds using **8** as catalyst[234]. If the spacing between the two C=C bonds in the reactant is increased to ten bonds, then ADMET polymerization is the preferred reaction at normal concentrations. However, by working at 10^{-3} M it is possible to favour the RCM of oleon **(50)**, equation 35, to give civetone **(51)** (musk odour) with a yield of up to 14%[235]. This method of preparation of **51** has the advantage that the metathesis reaction



(47) **(48)** **(49)**

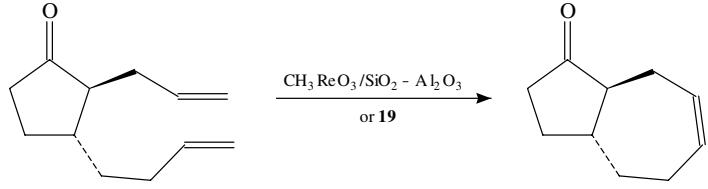
can be carried out at room temperature and the catalyst is re-usable after regeneration.



(50) (35)

(51)

The synthesis of some hydroazulenes such as **51a** by reaction 35a, catalysed by $CH_3ReO_3/SiO_2-Al_2O_3$[236], or better still by **19**[237], has been reported. Such ring systems occur in many natural products of pharmacological interest.

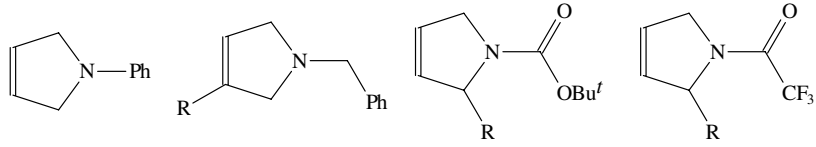


(35a)

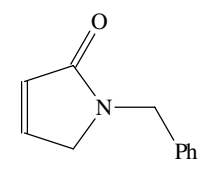
(51a)

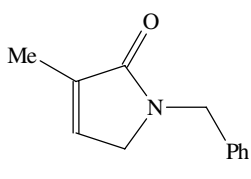
4. Rings containing N

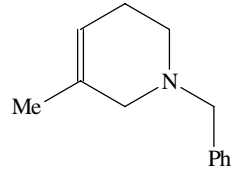
Many 5-, 6-, 7- and 8-membered ring compounds containing nitrogen in the ring have been prepared by RCM using the same catalysts as for the ethers; see Section VII.A.2. Some examples are given below.

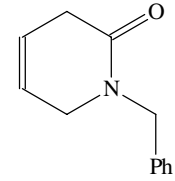


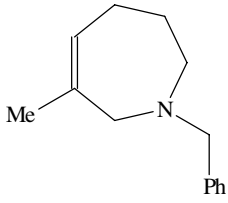
[1] R = H, Me [2] R = H, CH_2OH [3,4] [2,3,5]

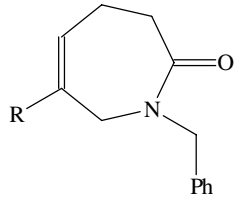

[3]


[2,3]


[2]

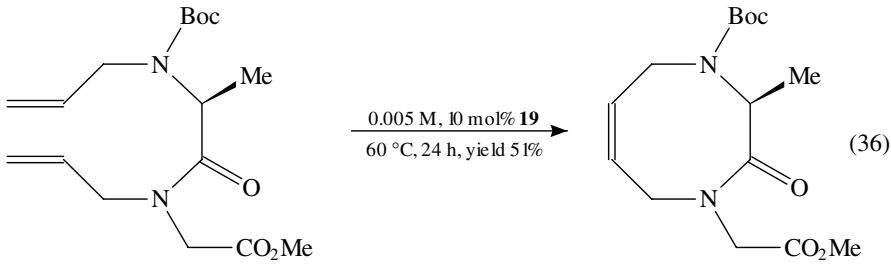

[3]


[2]


R = H, Me [2,3]

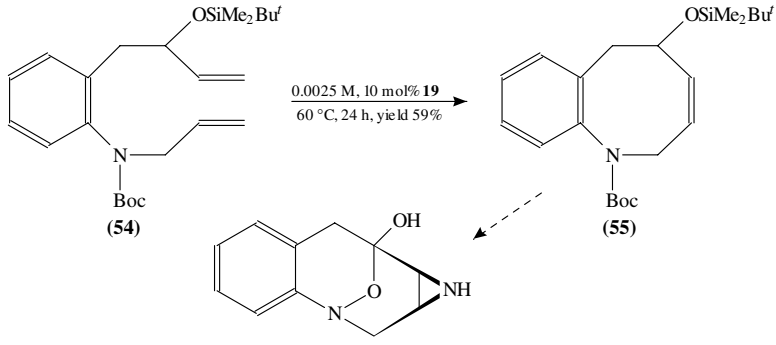
Refs. [1][261], [2][227f], [3][227b], [4][227g], [5][78]

The bis(*N*-allyl) dipeptide **52** gives a 51% yield of the cyclic dipeptide **53** under the conditions shown in equation 36, whereas an analogous *N*,*O*-bis(allyl) ester fails to undergo RCM[238]. This illustrates that the success or failure of RCM of such acyclic dienes depends critically upon the preferred conformations about the seven intervening bonds and upon the potential strain energy in the 8-membered ring to be formed. A number of factors may favour a rotamer which is conformationally and energetically disposed towards RCM, leading to the formation of 8-membered or larger rings. Such factors are (i) peptide linkages, which have a significant rotational barrier, as in **52**; (ii) an attached ring which prevents rotation about one of the bonds, as in **54**, equation 37; (iii) hydrogen bonds, particularly in polypeptides; see below. First it may be noted that **55** can be converted to **56**, which is the core fragment of the anti-cancer agent FR-900482[238,239].

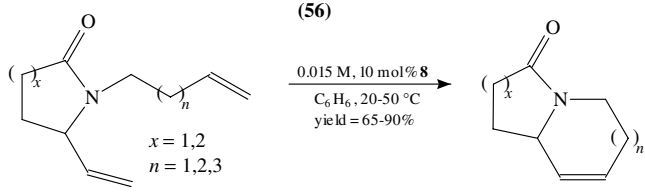


(52) (53) (36)

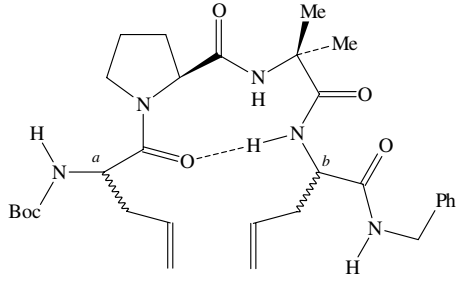
The preparation of fused nitrogen heterocycles such as pyrrolizidines, indolizidines, quinolizidines, pyrrolidinoazocines and piperidinoazocines by the RCM of appropriate dienes (equation 38), is another case where presence of a ring assists the RCM reaction. However, when $n = 7$ (with $x = 1$), the C=C bonds, separated by 11 single bonds, are too far apart for RCM to occur. Applications of this general strategy are in prospect for the formation of fused nitrogen heterocyclic systems in problems of alkaloid synthesis[240].



(37)

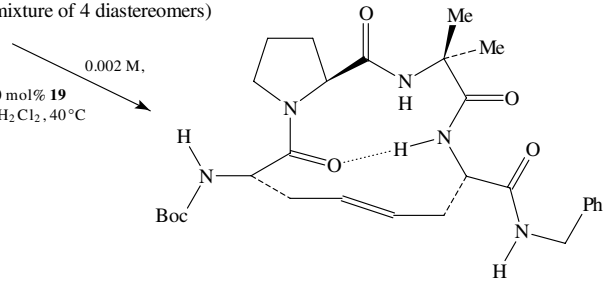


(38)



(57) (mixture of 4 diastereomers)

(39)

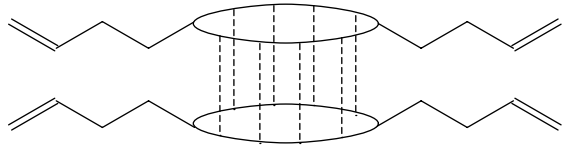


(*S*, *S*, *S*)-**(58)** formed from one diastereomer

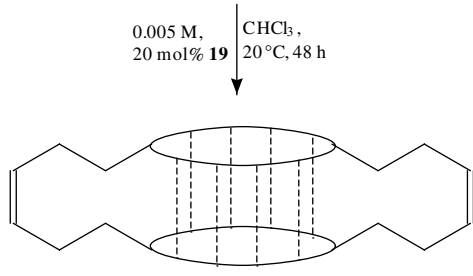
A remarkable case of RCM assisted by conformational restraint is that shown in equation 39. This involves a substrate in which the two double bonds are separated by 13 single bonds only one of which forms part of a ring, but in which an additional constraint is imposed by the hydrogen bond. When a mixture of the four stereoisomers denoted by **57** is treated with catalyst **19** under the conditions indicated, only one of the isomers undergoes RCM to give (*S*,*S*,*S*)-**58**, showing that in this case the configuration

with respect to the chiral centres *a* and *b* is also crucial. The yield is 60% with respect to the (*S*,*S*,*S*)-reactant[241].

An even more remarkable case of RCM in a hydrogen-bonded system is shown in equation 40. The eight-residue cyclic polypeptide *cyclo*[-L-Phe-D-^{Me}NAla-L-Hag-D-^{Me}NAla)$_2$-], containing two L-homoallylglycine (Hag) residues, self-assembles to form two interconverting hydrogen-bonded dimers, one of which is represented by **59** and contains two pairs of double bonds in sufficiently close proximity that each pair undergoes RCM in the presence of **19** to give **60** with a conversion of 65% (mixture of *cc*, *ct* and *tt* isomers). Such a strategy may be useful in stabilizing kinetically labile α-helical and β-sheet peptide secondary structures[242].



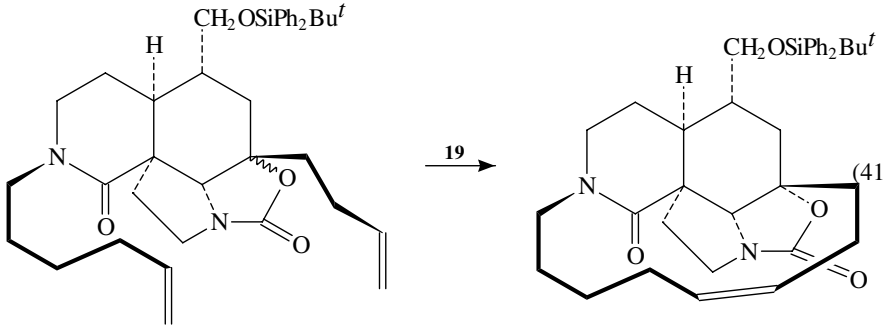
(59)



(40)

(60)

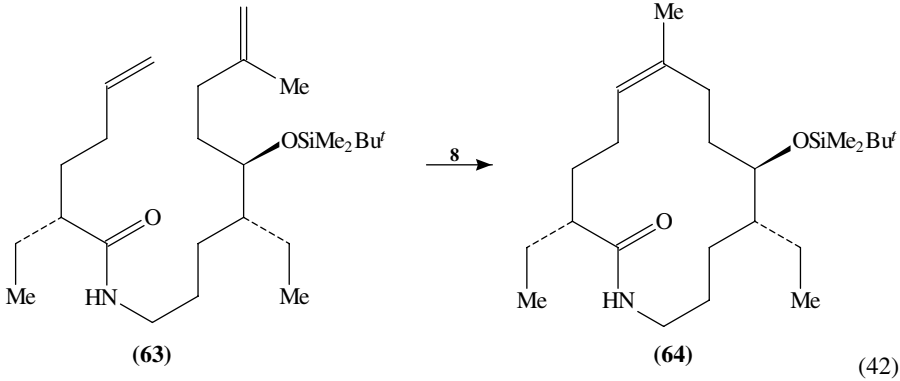
Another case of long-range RCM is shown in equation 41. In **61** the C=C bonds are separated by 12 single bonds, four of which are restrained by ring systems. The product, **62**, is an intermediate in the synthesis of manzamine A (a novel anti-tumour alkaloid)[243]; also see Martin[244].



(41)

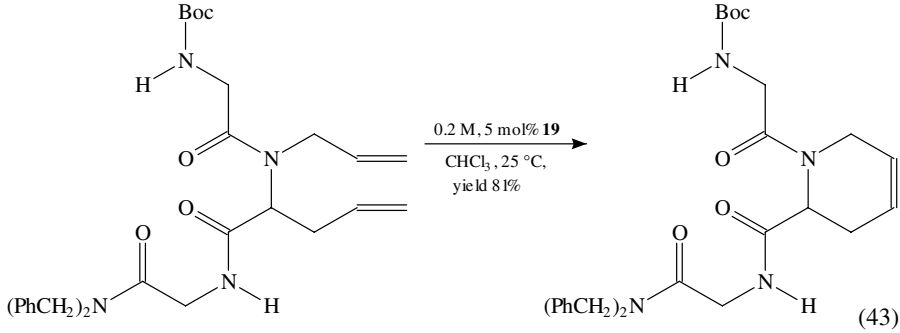
(61) **(62)**

The synthesis of compound **64** from **63** by reaction 42 is notable in that there are 13 single bonds between the reacting double bonds, and only a single peptide link to provide a measure of conformational restraint. A 60% yield of a single stereoisomer (>98% *Z*) is achieved when carried out in 0.01 M solution in THF, using 25 mol% **8** as catalyst. After hydrogenation and removal of the silyl protecting group one obtains a direct relative of the anti-fungal agent Sch 38516 (fluvirucin B_1)[245].



(42)

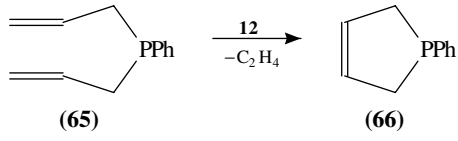
Finally, one should again note that with catalyst **19** one can carry out RCM on compounds containing unprotected peptidic structures, as illustrated by equation 43[241].



(43)

5. Rings containing P

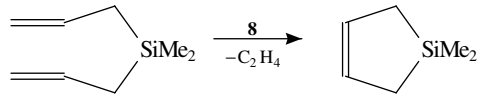
Diallylphenyl phosphane **(65)** undergoes RCM when heated at 80 °C with 5 mol% of **12** in chlorobenzene for 24 h, giving a 95% yield of the corresponding phospholene derivative **(66)**; see equation 44. The reaction is considerably faster than the intermolecular metathesis of allyldiphenyl phosphane with the same catalyst[181,246].



(44)

6. Rings containing Si, Ge and Sn

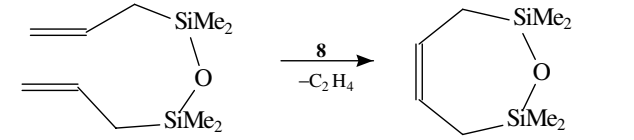
The metathesis of dimethyldiallylsilane **(67)** is a case where there is a delicate balance between the intramolecular and intermolecular processes. The balance may be swung either way by adjusting the substrate concentration. The yield of cyclic 'monomer' **(68)**, equation 45, varies from 28% to 90% according to the catalyst and conditions[209,247,248]. When the reaction is carried out in solution with **8** as catalyst, the three cyclic dimers of **68** (*cc*, *ct* and *tt*) are also formed (78% *cc*), at an overall concentration which exceeds that of **68** itself[247]. Reactions analogous to equation 45 have been reported for $(CH_2{=}CHCH_2)_2GeMe_2$[249] and $(CH_2{=}CHCH_2)_2SnBu_2$[248], but with the formation of other products.



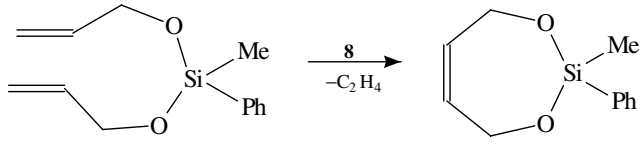
(45)

(67) **(68)**

Good yields of product are obtained for reactions 46 (100%)[234,250] and 47 (71%)[251].



(46)



(47)

B. ADMET Polymerization

The ability of hexa-1,5-diene to undergo multiple condensation reactions in the presence of a WCl_6-based catalyst, with the elimination of ethene and the formation of a series of linear oligomers, was first reported by the group of Dall'Asta[252] in 1973. The preparation of high polymers by this route was pioneered by Wagener and coworkers[254] using first **8W** and more recently **8** itself. These carbene catalysts have the advantage over the earlier catalysts of being Lewis-acid-free and of giving much longer-lived propagating systems. The molecular weight of the polymer increases as the reaction proceeds, its final value being determined by the initial ratio of substrate to initiator and by the initiation efficiency. Table 5 lists most of the dienes which have been shown to undergo ADMET polymerization over the last 6 years.

For the diallyl compounds the final product is an equilibrium mixture of the cyclic species formed by RCM and the linear polymer, as illustrated in Figure 2 for diallyl ether as reactant. In this case the double bonds in the polymer are nearly all *trans*. More usually the double bonds formed in ADMET polymers are 65–85% *trans*; an example is shown in Figure 3.

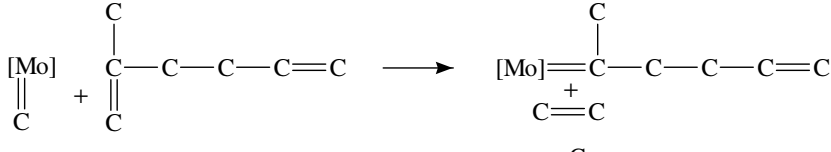
Isopropenyl groups are relatively unreactive towards metathesis. 2,5-dimethylhexa-1,5-diene, with an isopropenyl group at both ends, does not react at all in the presence of either **8** or **8W**. However, while 2-methylhexa-1,5-diene reacts only at the vinyl end in the

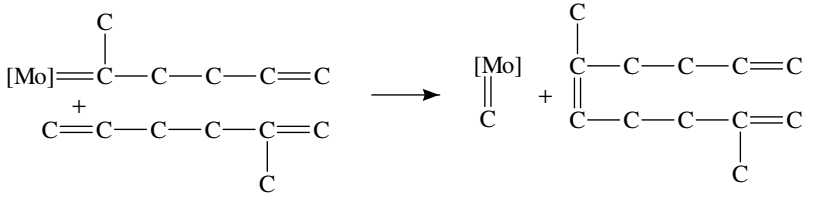
TABLE 5. Substrates susceptible to ADMET polymerization

Substrate	Catalyst	Polymer DP	Reference
$(CH_2{=}CHCH_2)_2$	**8W**[a]	>500	254
	W-1[b]		255
$CH_2{=}C(Me)(CH_2)_2CH{=}CH_2$	**8**	[c]	162
p-$CH_2{=}CHC_6H_4CH{=}CH_2$	**W-2**[d]	2–720	256
$[CH_2{=}CH(CH_2)_3]_2$	**8W**	*ca* 1000	254
	8	130	257
$CH_2{=}CH(CH_2)_2C(Me){=}CH_2{=}CH(CH_2)_2CH$	**8**	*ca* 110	258
$[CH_2{=}CH(CH_2)_3\ CMe_2]_2CO$	**8**		234
$(CH_2{=}CHCH_2)_2\ SiMe_2$ (neat)	**8W**, **8**	100	247
$(CH_2{=}CHCH_2)_2SiPh_2$ (neat)	**8**	20	247
$(CH_2{=}CHCH_2)_2SiMeCl$ (neat)	**8**	oligomer[e]	259
$(CH_2{=}CHCH_2SiMe_2CH_2)_2$	**8W**	240	260
p-$C_6H_4(SiMe_2CH_2CH{=}CH_2)_2$	**8W**	6	260
$[CH_2{=}CH(CH_2)_2]_2NPh$	**8**	45	261
$(CH_2{=}CHCH_2)_2O$ (neat)	**8**	10[f]	262
$[CH_2{=}CH(CH_2)_3]_2O$	**8**	140	263
$[CH_2{=}CH(CH_2)_4]_2O$	**8**	100	263
$CH_2{=}CH(CH_2)_2COO(CH_2)_4CH{=}CH_2$	**8**	101	264
p-$C_6H_4[COO(CH_2)_xCH{=}CH_2]_2$ ($x = 2$–4)	**8**	22–45	264
$[CH_2{=}CH(CH_2)_8COOCH_2]_2$	**8W**	15	265
$[CH_2{=}CH(CH_2)_xO]_2CO$ ($x = 2$–4)	**8**	51–58	266
p-$[CH_2{=}CH(CH_2)_2OCOOC_6H_4]_2CMe_2$	**8**	40	266
$[CH_2{=}CH(CH_2)_3SiMe_2]_2O$	**8**	128	250
$(CH_2{=}CHCH_2SiMe_2O)_2SiMe_2$	**8**	55	250

[a] The tungsten analogue of **8**.
[b] $WCl_6/Me_4Sn/PrOAc$ with 5-acetoxypent-1-ene as chain transfer agent.
[c] 1,4-Polyisoprene with $Z/E = 35/65$.
[d] $W(=CHC_6H_4\text{-}OMe\text{-}2)(=NC_6H_3\text{-}Me_2\text{-}2,6)[OCMe(CF_3)_2]_2$ (thf).
[e] 55% linear oligomer +38% cyclic 'monomer'.
[f] 37% polymer +63% cyclic 'monomer'; see Figure 2.

presence of **8W**, to give the 'dimer', the molybdenum complex **8** is much more active and the end product is perfectly head-tail 1,4-polyisoprene ($Z/E = 35/65$). This is presumably formed by alternate reactions of the types represented by equations 48 and 49[162].


(48)


(49)

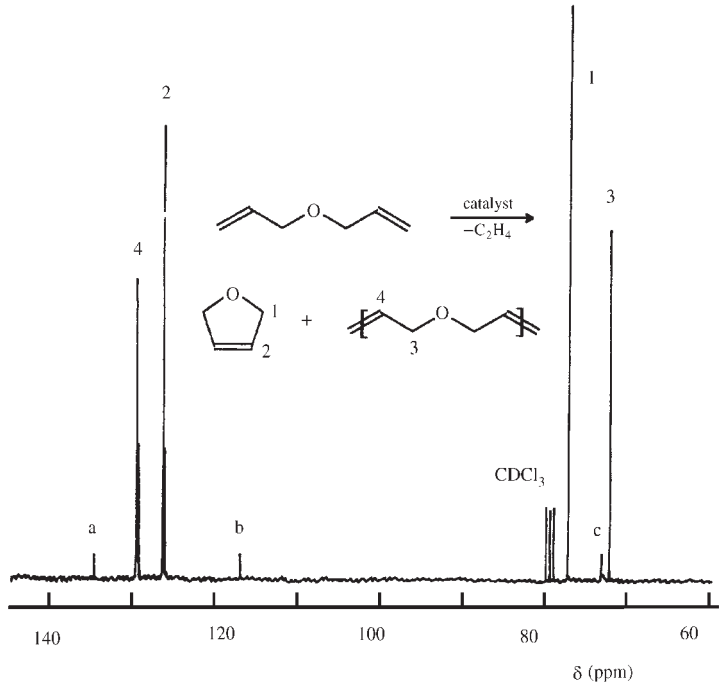


FIGURE 2. 50 MHz ^{13}C NMR spectrum of the equilibrium products of metathesis reactions of diallyl ether catalysed by **8** (R = Me). Peaks 1 and 2: 2,5-dihydrofuran. Peaks 3 and 4: linear polymer (*ca* 100% *trans*). Peaks a, b and c: end-group carbons, a $-CH_2CH{=}CH_2$, b $-CH_2CH{=}CH_2$ and c $-CH_2CH{=}CH_2$. Solvent $CDCl_3$. Reproduced by permission of Hüthig & Wepf Publishers, Zug, Switzerland, from Ref. 262

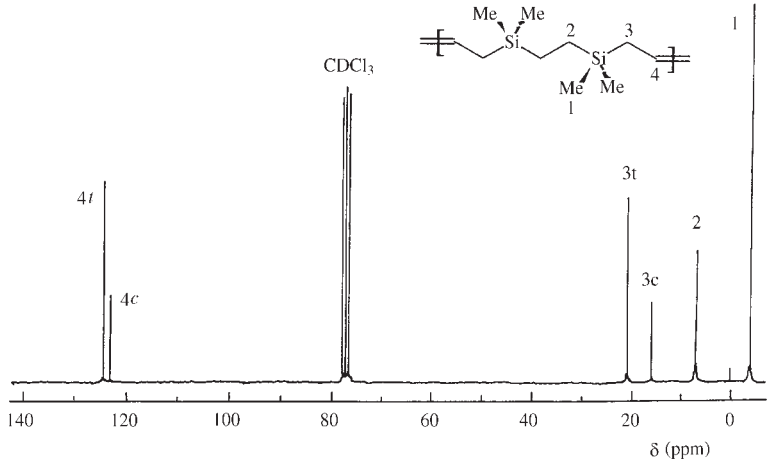


FIGURE 3. 50 MHz ^{13}C NMR spectrum of the 81% *trans* polymer obtained by the ADMET polymerization of 4,4,7,7-tetramethyl-4,7-disiladeca-1,9-diene. Reprinted with permission from Ref. 260. Copyright (1991) American Chemical Society

C. ADMET Copolymerization

Hexa-1,5-diene and deca-1,9-diene react together in the presence of **8W** to form a copolymer containing [=$CH(CH_2)_2CH$=] and [=$CH(CH_2)_6CH$=] units, M_1 and M_2 respectively. In the ^{13}C NMR spectrum of the copolymer, the olefinic carbons in the M_1M_2 junctions are clearly resolved from those in the M_1M_1 and M_2M_2 junctions and the intensities show that M_1 and M_2 units are distributed at random along the chains[253]. Copolymers have likewise been obtained in the reactions of deca-1,9-diene with α,ω-dienes containing keto[234], ether[263], ester[264], thio[267] and ferrocene[268] groups. Copolymers can also be formed by placing a homopolymer derived from one diene in contact with the second diene in the presence of a metathesis catalyst. The double bonds in the polymer chain readily undergo secondary metathesis reactions with the second diene, leading to the formation of a copolymer.

Sometimes it is possible to make a copolymer from deca-1,9-diene and a second diene that will not itself undergo ADMET polymerization, for example with divinyldimethylsilane[260] or with *p*-dipropenylbenzene[269]. In other cases the second diene refuses to copolymerize but instead undergoes RCM; this is so with $(CH_2{=}CHCH_2CMe_2)_2CO$ as the second diene[234].

VIII. RING-OPENING METATHESIS POLYMERIZATION (ROMP) OF CYCLOALKENES

A. General Aspects

1. Ring–chain equilibria

It is well known that in many cases of ROMP a series of cyclic oligomers is produced as well as linear polymer. If the catalyst is long-lived an equilibrium is eventually reached between the various cyclic species and the linear polymer. This may take some time to achieve. Thus, with cyclooctadiene as substrate the most abundant cyclic oligomeric species initially formed is $(C_4H_6)_4$, but this eventually gives way to $(C_4H_6)_3$ as a result of secondary metathesis reactions[270]. Sometimes the cyclic dimers are strongly favoured, as in the case of **68** (see Section VII.A.6) and cycloheptene[271–273]. The concentrations of the higher cyclic oligomers decrease with increasing ring size and provide a good test of the theory of ring–chain equilibria developed by Jacobson and Stockmayer[274]. Although the original theory gives the correct form of dependence of equilibrium constant K_x on ring size x, the calculated values of K_x are too high; but when the theory is refined by the use of the rotational-isomeric-states model (with no adjustable parameters) the calculated values are in satisfactory agreement with experiment for rings containing more than about 30 atoms[275]. The discrepancy between theory and experiment for smaller rings is due to the failure of the assumption that the rings are unstrained. Their strain energy has been estimated by means of a Monte Carlo configurational search using molecular mechanics (MM3), leading to much better agreement between the calculated and experimental values of K_x for rings of all sizes[276].

Strictly speaking, the value of K_x depends not only on x but also on the *cis/trans* ratio in the polymer and in the cyclic oligomer. However, the theory predicts that, in the range 20–90% *trans*, the effect will be very small[275].

2. Use of transfer agents; telechelic polymers

Alk-1-enes are the preferred transfer agents when it is desired to reduce the molecular weight (MW) of polymers produced by ROMP in non-living systems. The transfer

constants are rather small and it is usually necessary to employ a fairly high concentration of transfer agent if a substantial reduction of MW is required, say to make the polymer easier to dissolve or to improve the resolution of its NMR spectrum. End groups derived from the transfer agent can be detected and identified[277–279]. Polymers with functional end-groups at both ends (telechelic polymers) can be prepared by the use of appropriate unsaturated transfer agents, preferably the more reactive *cis* isomers; for example diesters[280], bis(silyl) ethers[281], borane derivatives[282] or protected diols[185].

With living systems the MW of the polymer can be reduced by increasing $[I]_0$, but this requires the use of large amounts of initiator. The same result can be achieved at low $[I]_0$ by inclusion of a good transfer agent[283].

The determination of transfer constants (k_{tr}/k_p) in living systems is not as straightforward as in non-living systems. A detailed consideration of the problem has been given[129]. The following serves to illustrate some of the complications that can be encountered. First suppose that $k_{tr} \ll k_p \approx k_i$. If the concentration of the transfer agent is not very high the ROMP will proceed initially as though the transfer agent were not present and a living polymer will be formed with a number average degree of polymerization DP_n equal to $[M]_0/[I]_0$. In time the transfer agent will react with the living polymer to give dead polymer of the same DP, and a new carbene species. Addition of a fresh batch of monomer would allow the process to be repeated and, provided that the initiation efficiency for the new carbene species was high, the second batch of polymer would again have a narrow molecular weight distribution (MWD). Such conditions are realized in practice with **7** (R = Me) as initiator, styrene (30 equiv) as transfer agent and norbornene added in eight successive batches of 80 equiv at 40 min intervals. The GPC of the total product shows a main peak (95% of the whole) with $M_w/M_n = 1.07$. When the monomer is 2,3-bis(trifluoromethyl)norbornadiene the product consists only of low-molecular-weight oligomers. This is because k_p is much smaller and the transfer constant therefore much larger than for norbornene, so that the chains have no chance to grow to their full length before suffering reaction with the transfer agent[283].

A different situation exists when the transfer constant is high and the amount of transfer agent used is such that it is all consumed before polymerization is complete. The remaining monomer will then polymerize in the absence of transfer agent and give rise to a fraction with a much higher MW than that of the initially formed polymer. The product will thus have a bimodal MWD. There may also be some cyclic oligomers formed by the backbiting reaction. The most reliable method of measuring the transfer rate constant k_{tr} in such a system is to observe directly by NMR the rate of removal of chain transfer agent (CTA) by reaction with the propagating species. In this way the reaction of $CH_2{=}CHCMe_3$ with the propagating species in the ROMP of norbornene initiated by **7** (R = Ph) is found to have $k_{tr} = 3 \times 10^{-5}$ M^{-1} s^{-1} at 22 °C compared with $k_p = 17$ M^{-1} S^{-1}. Once the rate constants are known the relative amounts of reagents in the reaction can be optimized to secure the required MW and MWD. It will be evident that the slopes of (Mayo) plots of $1/(DP_n)$ against $[CTA]/[M]_0$ do not provide a reliable method of determining k_{tr}/k_p in living systems unless care is taken to obviate the aforementioned pitfalls[129].

3. Cis/trans blockiness

The distribution of the *cis* and *trans* double bonds in a given polymer chain may be expressed in terms of the ratios $r_t = (tt)/(tc)$ and $r_c = (cc)/(ct)$. If the probability of formation of a *cis* double bond is independent of the configuration of the previous double bond, the distribution will be random (Bernoullian) and characterized by a single parameter $r_t = 1/r_c$. This is the case for polymers of norbornene with less than 35% *cis* content, but for polymers with more than 50% *cis* content the distribution is generally somewhat

blocky, with $r_t r_c$ reaching values of 8 or more in some cases. This pattern of behaviour is found not only for the ROMP of norbornene[284–286] but also for its derivatives, and for cyclopentene[287,288]. A very significant observation is that r_t seldom falls below unity even when the *cis* content is high. This means that at high *cis* content the *trans* double bonds tend to occur in pairs and are not to be found singly in the chain. To explain both the blockiness and the *tt* pair phenomenon it is necessary to postulate the presence of three kinetically distinct propagating species when the *cis* content is high. Detailed analysis of the proportions of double-bond triads in polynorbornene samples shows that the propagating species which have just formed a *cis* double bond (P_c) all have the same selectivity, but those which have just formed a *trans* double bond have different selectivity according to whether the last but one double bond formed was *cis* (P_{tc}) or *trans* (P_{tt})[285]. It has been argued that P_{tc} and P_{tt} differ essentially in their ligand geometry as a result of the disrotatory modes of cleavage of the metallacyclobutane precursors. P_{tt} and P_c may differ more in the extent of crowding of the metal site by the polymer chain itself, which may or may not involve coordination of double bonds to the metal centre[289]. The *cis* content tends to fall and the blockiness to disappear as the monomer concentration is reduced[290] or as the temperature is raised. This would suggest that, given time, the two species P_{tc} and P_{tt} become kinetically identical through relaxation to a species with common ligand geometry represented by P_t. Polymers of cyclooctene do not exhibit *cis/trans* blockiness, showing that lengthening of the repeat unit tends to eliminate the kinetic distinction between P_t and P_c[291–293].

4. Head–tail bias

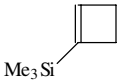
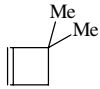
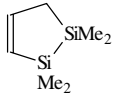
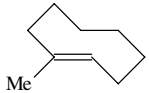
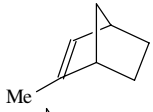
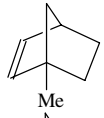
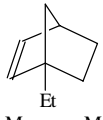
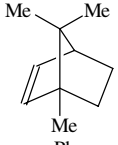
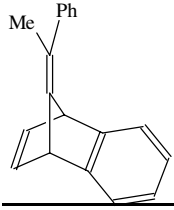
The extent of HT bias in the polymers of substituted cycloalkenes is very dependent on (i) the location and nature of the substituent(s), and (ii) the catalyst. Monomers with a substituent at the double bond generally give strongly biased polymers with most catalysts. For example, 1-methylcyclobutene with $W(=CPh_2)(CO)_5$ gives an 85% *cis* polymer with HH : HT : TT = 1 : 8 : 1[294]. The presence of one or two substituents at the α-position results in fully biased polymers with some but not all catalysts. When the substituent(s) are further removed from the double bond there is usually very little HT bias in the polymer.

Some examples of monomers giving polymers with a completely regular HT structure are shown in Table 6. In most cases the polymers are either high-*cis* or high-*trans* and then have exceptionally simple ^{13}C NMR spectra; (Figure 4). A few, however, are of intermediate *cis* content.

With the polymers of 1-methylnorbornene there is a remarkable variation of HT bias with catalyst. Thus $RuCl_3$ at 60 °C gives an unbiased all-*trans* polymer (HH : HT : TT = 1 : 2 : 1), whereas $IrCl_3$ at 75 ° gives a strongly biased high-*trans* polymer, the extent of bias increasing with dilution of the monomer. $OsCl_3$ at 60 °C gives a polymer containing 16% *cis* double bonds which occur only in HT dyads, and 84% *trans* double bonds which occur mainly in HT dyads (HH : HT : TT = 1 : 11.3 : 1). Catalysts such as WCl_6/R_4Sn (R = Me, Bu) at 20 °C give polymers with 40–70% *cis* double bonds, but containing absolutely no *cis* HH structures. Figure 5 shows the olefinic region of the ^{13}C NMR spectrum for a polymer of this kind, having a modest overall bias. Note that (*trans* HH) = (*trans* TT) + (*cis* TT), and that (*cis* HH) is not present. Models indicate that the formation of a *cis* HH structure would be extremely difficult[303].

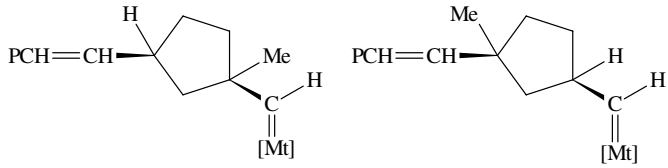
The magnitude of the HT bias is clearly determined by both polar and steric effects and may also be governed to some extent by relaxation processes between propagation steps. In living systems the head species P_H **(69)** is generally present in higher concentration than the tail species P_T **(70)**[307]. It is likely that in most, but not all, cases of total HT

TABLE 6. Systems giving fully HT-biased polymers

Monomer	Catalyst	Temp. (°C)	σ_c[a]	Reference
	$W(=CPh_2)(CO)_5$	40	1.0	295
	$Mo(=CHCMe_2Ph)(=NAr)(OCMe_2CF_3)_2$	20	1.0	296
	$Mo(=CHCMe_2Ph)(=NAr)(OCMe_3)_2$	20	0.0	297
	$Mo(=CHCMe_3)(=NAr)(OCMe_3)_2$	20	0.0	298
	$Cr(=CPh_2)(CO)_5$	40	0.5	299
	$Mo(=CHCMe_2Ph)(=NAr)[OCMe(CF_3)_2]_2$	25	0.03	300
	$W(=CPh_2)(CO)_5$	50	0.24	301
	$W(=CPh_2)(CO)_5$	40	~0.4	295
	$ReCl_5$	20	1.0	302,303
	$IrCl_3$	75	0.09	304
	$Mo(=CHCMe_2Ph)(=NAr)[OCMe(CF_3)_2]_2$	20	0.00	305
	$Mo(=CHCMe_3)(=NAr)(OCMe_3)_2$	20	0.00	306

[a] σ_c is the fraction of *cis* double bonds in the polymer.

bias the propagation proceeds through the head species. The increase in HT bias with increasing dilution observed in some cases may be interpreted in terms of two distinct P_H (or P_T) species: an unrelaxed form of higher energy which is less H/T discriminating, and a relaxed form of lower energy which is more H/T discriminating.



P_H **(69)** P_T **(70)**

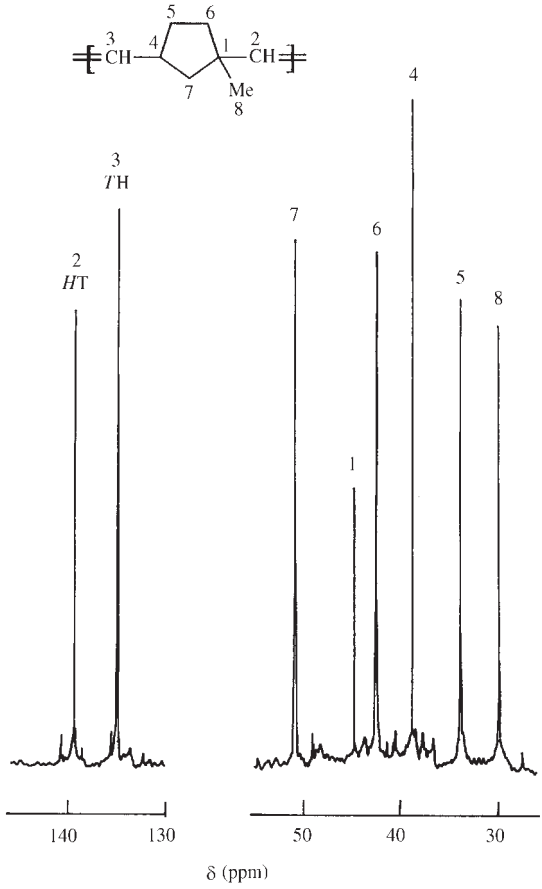


FIGURE 4. 62.8 MHz ^{13}C NMR spectrum of an all-*cis*, all-HT polymer of 1-methylnorbornene. Catalyst: $ReCl_5$[302,303]. Reproduced by permission of the Society of Chemical Industry

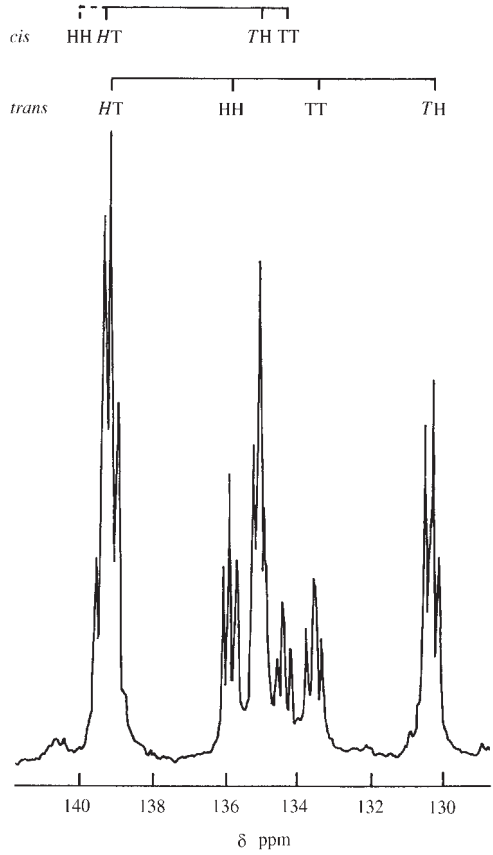


FIGURE 5. 62.8 MHz ^{13}C NMR spectrum (olefinic region) of a 48% *cis* polymer of 1-methylnorbornene. Catalyst: $Mo_2(OAc)_4/EtAlCl_2$. (HT + TH)/(HH + TT) = 2.8. The fine structure arises from double-bond triads, e.g. *cct, ccc, tct, tcc*[302]. Reproduced by permission of the Society of Chemical Industry

5. Tacticity

Tacticities have been determined for polymers of derivatives of cyclopentene, norbornene, norbornadiene and 7-oxanorbornene. Three methods have been used: (i) by polymerizing single enantiomers of 5- or 5,5- or *endo,exo*-5,6-substituted norbornene derivatives and determining whether the polymers have an HT (*m*) or HH/TT (*r*) structure, or both (*m* and *r*); (ii) by polymerizing 5,6-disubstituted norbornene derivatives in which the *substituents* contain a chiral centre of a single handedness and determining whether the olefinic protons in the polymer are coupled (*m*) or not (*r*); (iii) by polymerizing prochiral monomers and arguing by analogy with the results on closely related chiral monomers. The first method requires some assumptions about the magnitude of ^{13}C NMR substitution parameters, but the second method is absolute. The third method should be safe if applied with caution.

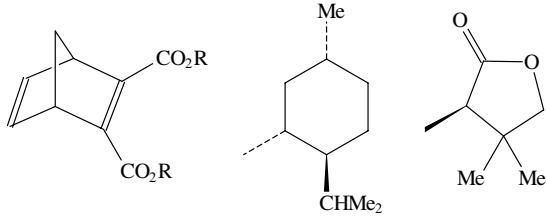
Tacticity determinations by the first method have been carried out using enantiomers of the following derivatives of norborn-2-ene: 1-methyl-[302,308], *exo*-5-methyl-[309,310],

5,5-dimethyl-[311,312], *endo,exo*-5,6-dimethyl-[313,314], 1,7,7-trimethyl-[305], *endo*-5-methoxymethyl-[315], *endo*-5-acetate[316,317], *endo,exo*-5,6-dimethoxymethyl[313], and *endo,exo*-5,6-dicarbomethoxy-[313]; and the following derivatives of 7-oxanorborn-2-ene: *exo*-5-methoxymethyl-[318] and *endo*-5-methoxymethyl-[319].

The extremely slow ROMP of 1,7,7-trimethylnorbornene is initiated by **8** (R = Ph) to give an all-*trans*, all-HT polymer which is necessarily isotactic when made from a single enantiomer. It is atactic when made from racemic monomer showing that the two enantiomers then add randomly to the growing chain[305].

All resonances in the ^{13}C NMR spectra of all-HT polymers of racemic 1-methylnorbornene are insensitive to tacticity, but C-6 in the spectrum of the *hydrogenated* polymer does show *m/r* splitting (0.05 ppm) when the precursor is made with $OsCl_3$ as catalyst. The downfield component (39.12 ppm) is dominant when the experiment is repeated with partially resolved monomer and is therefore assigned to *m* dyads. The upfield component (39.07ppm) is the only peak observed in the spectrum of the hydrogenated all-*cis*, all-HT polymer made from *racemic* monomer with $ReCl_5$ as catalyst, and it may be concluded that this is a syndiotactic alternating copolymer of the two enantiomers. This structure is forced on the polymer by the steric exclusion of *cis* HH structures[302,308]; also see Couturier and coworkers[101].

The second method for determining tacticities is essentially an extension of the first, the only difference being that the chiral centre is placed in the side chain(s) of a monomer that would otherwise be prochiral. Thus the chiral diesters **71** and **72** have been prepared and polymerized using several molybdenum carbene initiators. The protons H^2 and H^3 attached to C^2 and C^3 are now non-equivalent both in the monomer and polymer **(73)**. In an *m* dyad the double bonds (*cis* or *trans*) will all be of the type $-C^2H^2=C^3H^3-$ so that if the chemical shift difference is not too small, the signal for H-2,3 will be an AB quartet, split further by coupling to the adjacent ring protons. On the other hand, in a fully syndiotactic polymer the double bonds in the *r* dyads will be alternately of the types $-C^2H^2=C^2H^2-$ and $-C^3H^3=C^3H^3-$ and there will be no coupling between H-2 and H-3. The $^1H-^1H$ correlation spectrum (COSY) of the all-*trans* polymer of **71** made with **74** as initiator, Figure 6(a), shows clearly that the olefinic protons of the *trans* double bond are not coupled (δ 5.568 and 5.534), and that the polymer is therefore fully syndiotactic. Note also that the couplings to the adjacent protons, H-1 and H-4, are not resolved. In the ^{13}C NMR spectrum the C-1 and C-4 signals are just resolved (δ 46.7 and 46.8), while C-7, being always situated within an *rr* triad, gives a single peak at δ 37.5. For the all-*cis* polymer of **71** made with **75** as initiator the ^{13}C NMR spectrum gives a single set of peaks as expected for a tactic polymer. Its COSY spectrum, Figure 6(b), shows that the H-2 and H-3 protons (δ 5.51 and 5.37) *are* coupled and that the dyads are therefore isotactic (*m*). In this case there is some observable coupling to H-1 and H-4 and on irradiation of these protons the signal collapses to the expected AB quartet with a coupling constant of 10 Hz characteristic of *cis* C=C.



(71, 72) **(71)** R = (−)-menthyl **(72)** R = (−)-pantalactonyl

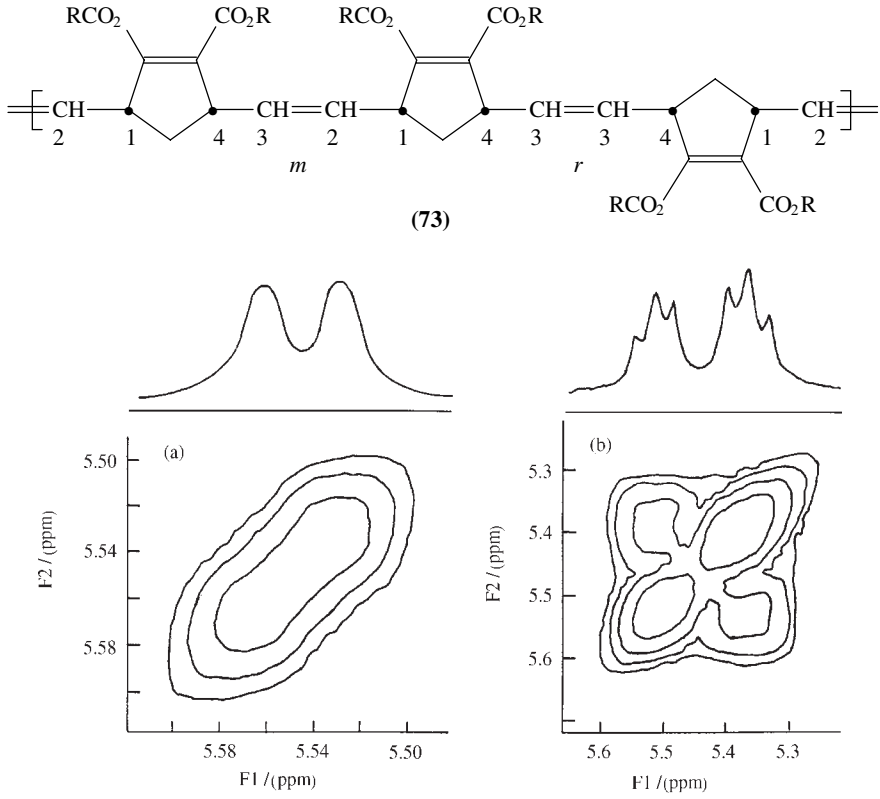


FIGURE 6. $^{1}H-^{1}H$ COSY spectra of the olefinic protons H-2,3 for (a) syndiotactic *trans* polymer of **71** initiated by **74**, and (b) isotactic *cis* polymer of **71** initiated by **75**. Reprinted with permission from Ref. 313. Copyright (1994) American Chemical Society

The third method of determining tacticities may be illustrated by reference to the polymers of *anti*-7-methylnorbornene. The ^{13}C NMR spectra of all-*trans* and high-*cis* polymers are shown in Figures 7 and 8. The first is clearly atactic, all carbons except C-7 being sensitive to tacticity. The assignments are based on a comparison with the spectrum of a polymer made with $W(CO)_3$ (mesitylene)/$EtAlCl_2$/*exo*-2,3-epoxynorbornane as catalyst and the assumption that, as in the polymer of 5,5-dimethylnorbornene made with this catalyst, the *trans* double bonds are always associated with *m* dyads. Likewise the high-*cis* polymer made with $ReCl_5$ as catalyst is assumed to be syndiotactic as for the polymer of 5,5-dimethylnorbornene made with this catalyst. The spectrum of the hydrogenated atactic polymer shows larger *m*/*r* splittings than in the spectrum of its precursor, although C-7 remains insensitive to tacticity. The hydrogenated syndiotactic polymer gives essentially a single set of lines, as expected[320].

Tacticities in polymers of prochiral monomers made with various catalysts have been determined in this way for the following: *anti*-7-methylnorbornene[128,320–322], *syn*-7-methylnorbornene[128,322], *endo,endo*-5,6-dimethylnorbornene[323], spiro(norbornene-7,1′-cyclopropane)[324] and 5,6-bis(trifluoromethyl)norbornadiene[325], and the hydrogenated polymers of 4-methylcyclopentene[326] and *exo, exo*-5,6-dimethylnorbornene[323].

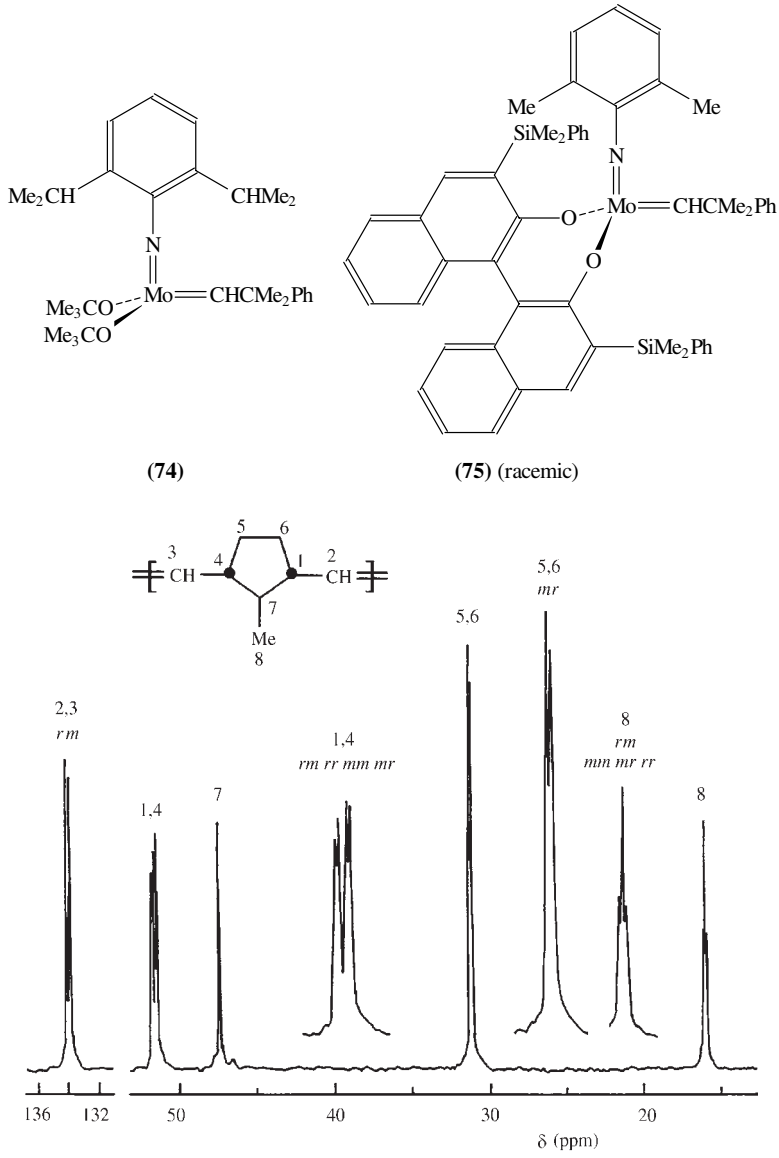


FIGURE 7. ^{13}C NMR spectrum of an all-*trans* polymer of *anti*-7-methylnorbornene. Catalyst: $RuCl_3$ at 60 °C[320]. Reproduced by permission of Elsevier Science from Ref. 320

Three broad types of tacticity may be distinguished in polymers made by ROMP: (i) fully tactic polymers which may be divided into the first four groups c/r, c/m, t/m, t/r listed in Table 7, and a fifth group in which the polymer has intermediate *cis* content but in which only c/r and t/m structures are found; (ii) completely atactic polymers, which may be of any *cis* content; and (iii) polymers of intermediate tacticity.

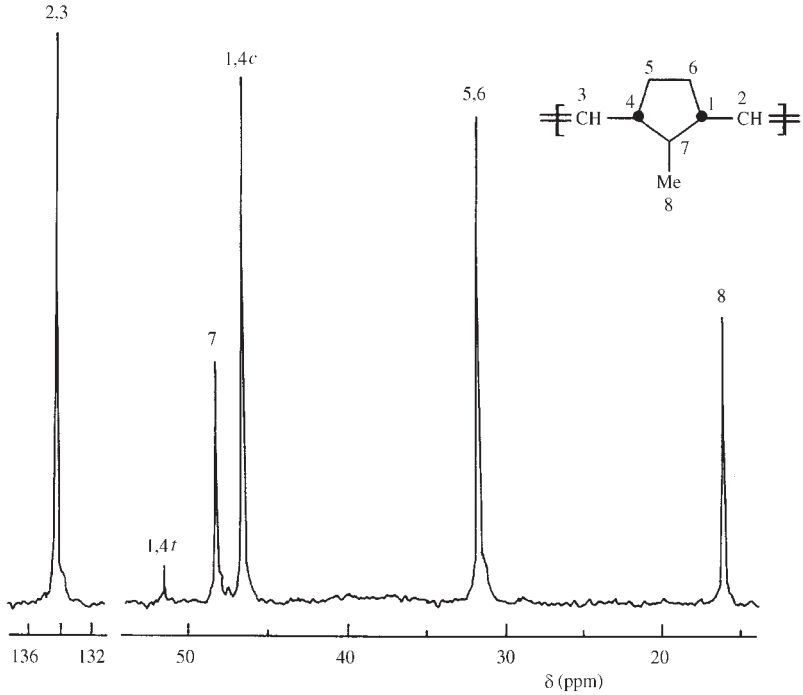


FIGURE 8. ^{13}C NMR spectrum of a 90%-*cis* polymer of *anti*-7-methylnorbornene. Catalyst: $ReCl_5$. Reproduced by permission of Elsevier Science from Ref. 320

A given catalyst does not always result in polymer of a given type of tacticity: it can vary with the monomer, temperature and dilution. This is to be expected if second-order propagation processes are competing with first-order epimerization or relaxation processes involving a reorganization of the ligand geometry around the metal centre of the propagating species. The catalyst systems WCl_6/R_4Sn provide good examples of the way in which a change of conditions can give rise to a substantial change in tacticity. Thus the polymer of 5,5-DMNBE is fully tactic (c/r, t/m) when the cocatalyst is Bu_4Sn at 20 °C, but if it is changed to Ph_4Sn, or the temperature is raised to 100 °C, or the monomer changed to *anti*-7-MNBE, the polymer formed is atactic or nearly so[311].

As in Ziegler–Natta polymerization, steric control of the propagation step may involve either the interaction of the monomer with a chiral metal centre (enantiomorphic sites model), or the interaction of the monomer with the chiral centres in the repeating unit(s) adjacent to the metal centre (chain-end model). (The relationship to Ziegler–Natta polymerization will be considered further in Section VIII.C.3.)

In the enantiomorphic sites model the propagating species may have left- or right-handed forms (P_l or P_r), say with octahedral symmetry about the metal centre Mt, and one position vacant for the acceptance of monomer. Assuming that norbornene presents its less hindered *exo* face to the metal centre and that the Mt=C and C=C double bonds approach each other in parallel alignment, it is readily shown that the formation of a *cis* double bond in the propagation step results in a metal carbene complex in which the chirality of the metal centre is *opposite* to that in the reacting complex[27]. This means that, provided that P_l and P_r retain their chiral identity between propagation steps, the

TABLE 7. Some limiting cases of tactic polymers made by ROMP

Monomer[a]	Catalyst[b]	σ_c^c	Predominant structure				Reference
			c/r	*c/m*	*t/m*	*t/r*	
5,5-DMNBE	$ReCl_5$	~1.0	√				312
	W-4	~1.0	√				327
anti-7MNBE	$ReCl_5$	~1.0	√				320
(±)-1-MNBE	$ReCl_5$	1.0	√				302
7-MNBD	$OsCl_3$	0.97[d]	√				328
MOMONBE	W-1	0.97	√				319
endo,exo-							
5,6-DMNBE	Mo-1	0.85		√			314
5,6-$(CO_2R^*)_2$NBD	Mo-2	0.99		√			313
5,5-DMNBE[e]	W-2	0.15			√		329
MOMONBE	Ru-1	0.04			√		319
(+)-1-MNBE	$OsCl_3$	0.0			√		302
(−)-1,7,7-TMNBE	Mo-3	0.0			√		305
5,6-$(CO_2R^*)_2$NBD	Mo-4	0.06				√	313
anti-7-MNBE	W-2	0.45	√		√		320
5,5-DMNBE	W-3	0.61	√		√		311

[a]MNBE, methylnorbornene; DMNBE, dimethylnorbornene; TMNBE, trimethylnorbornene; MNBD, methylnorbornadiene; MOMONBD, *endo*-5-methoxymethyl-7-oxanorborn-2-ene; $(CO_2R^*)_2$NBD, dicarboalkoxynorbornadiene [R^* = (−)-menthyl].

[b]W-1, $W(=CHCMe_3)(=NAr)[OCMe(CF_3)_2]_2$ (Ar = 2,6-diisopropylphenyl); W-2, $W(CO)_3$ (mesitylene)/$EtAlCl_2$/*exo*-2,3-epoxynorbornane; W-3, $WCl_6/Bu_4Sn/20\,^{\circ}C$; W-4, $W(=NC_6H_3\text{-}Me_2\text{-}2,6)(Cl)_3(OArO)(OEt_2)/Et_2AlCl$; Mo-1, $Mo(=CHCMe_3)(=NAr)[OCMe(CF_3)_2]_2$; Mo-2, $Mo(=CHCMe_2Ph)(=NAr)[OC(CF_3)_3]_2$; Mo-3, $Mo(=CHCMe_2Ph)(=NAr)[OCMe(CF_3)_2]_2$; Mo-4, $Mo(=CHCMe_2Ph)(=NAr)[OCMe_3]_2$; Ru-1, $[RuCl(\mu\text{-}Cl)(\eta^3{:}\eta^3\text{-}C_{10}H_{16})]_2$ ($C_{10}H_{16}$ = 2, 7-dimethyloctadienediyl).

[c]Fraction of double bonds with *cis* configuration.

[d]Mainly *anti* repeating units. [e][M] = 0.4 M.

enchained rings in an all-*cis* polymer will have alternating configurations, i.e. the polymer will be syndiotactic (*c/r*). At the other extreme, an all-*trans* polymer will be isotactic (*t/m*) and, if P_l, and P_r propagate independently, the result will be a racemic mixture of polymer molecules.

When the propagating metal carbene complex does not have a predetermined vacant ligand position, but is instead trigonal–bipyramidal or tetrahedral, it may still behave like the octahedral model provided that the ligands other than the carbene offer an asymmetric environment which controls the direction of approach of the monomer. If this is not the case there will not be a favoured direction of approach unless the chain-end effect comes into play.

Barriers to rotation about Mt=C have been measured by observation of NMR coalescence temperatures[123,330,331]. In some cases these are sufficiently high that epimerization by rotation about Mt=C is unlikely to be important, but in other cases such a process may be as fast as or faster than the propagation step. More detailed considerations show that when both *cis* and *trans* double bonds are formed in accordance with the enantiomorphic sites model then the *cis* junctions will always be associated with *r* dyads, and *trans* junctions with *m* dyads[27,332]. This model thus correctly predicts the observed tacticities in the first, third and fifth groups of results listed in Table 7. Cases of intermediate tacticity can also be interpreted in terms of this model if it is modified to include partial epimerization of P_l and P_r between propagation steps.

This leaves the second (*c/m*) and fourth (*t/r*) groups in Table 7 to be explained in a different way. In these cases it must be the stereochemistry of the polymer chain itself that

is controlling the mode of addition of the next monomer unit. We have already seen that in the formation of high-*cis* polymers of norbornene the *c/t* selectivity depends not only on the configuration of the previously formed double bond but, when this is *trans*, also on the one before that. It is therefore very reasonable to expect that in high-*cis* polymers made using carbene initiators with symmetrical tetrahedral ligand geometry, any *m* selectivity must arise through the influence of the configuration of the previously added monomer unit or units. While one cannot argue in the same way for high-*trans* polymers, where the *c/t* selectivity is generally independent of the configuration of the previously formed double bond, nevertheless the *m/r* selectivity with such initiators may still be sensitive to the configuration of the previously added unit, so accounting for the comparatively rare case of predominantly *t/r* structure (Table 7).

B. Monocyclic Alkenes

In this section are summarized some of the recent findings for monocyclic alkenes of various ring sizes.

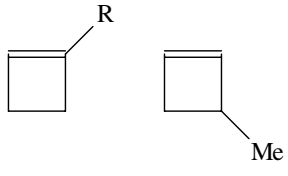
1. Four-membered rings

The ROMP of cyclobutene initiated by **7W** (R = Me) gives a polymer with a relatively broad MWD ($M_w/M_n > 2$). This is because propagation is much faster than initiation and only a very small fraction of initiator is consumed (k_p/k_i *ca* 1000 at −60 °C). If PMe_3 is added to the system an equilibrium is established between free PMe_3 and PMe_3 bound to both initiating and propagating species. However, the binding to the propagating species at 25 °C (K *ca* 10^5 M^{-1}) is much stronger than to the initiating species (K *ca* 500 M^{-1}) because it is sterically less hindered; and in the presence of sufficient PMe_3 (10 equiv) the propagation reaction is slowed down relative to initiation to such an extent that all the initiator is consumed and the MWD becomes very narrow ($M_w/M_n = 1.03$). The reaction then shows well-defined kinetics and all the characteristics of an ideal living system. Similar results are obtained when the reaction is initiated with the corresponding molybdenum carbene complex **7**. The polymers may be hydrogenated to give very well defined samples of polyethene[333,334].

Of the cyclobutene derivatives **76–87** all except **87** undergo clean ROMP. The polymer of **87**, obtained in low yield using WCl_6/Me_4Sn as catalyst, is a black insoluble powder of reduced chlorine content, caused by loss of HCl and development of conjugation[335].

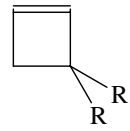
Polymers of **76** generally have a high proportion of *cis* double bonds but with varying degrees of HT bias[296,336]. The initiator Mo(=CHCMe$_2$Ph) (=NC$_6$H$_3$-*i*-Pr$_2$-2,6) (OCMe$_2$CF$_3$)$_2$ is the only one to give an all-*cis*, all-HT, polymer, identical with natural rubber, *cis*-1,4-polyisoprene. This remarkable result clearly stems from a fine balance between the electrophilicity of the metal centre, and the steric interactions during the approach of the monomer to the initiator. Very little of the initiator is consumed and the propagating species cannot be detected by ^{1}H NMR, indicating a high value of k_p/k_i. The yield of polymer is 78% (MW *ca* 20,000), but the MWD is inevitably broad ($M_w/M_n = 2.5$). Propagation can be slowed down relative to initiation by addition of 10 equiv of PPh_2Me to the initiator. About half the initiator is then consumed during polymerization and the carbene proton in the propagating species can be detected as a triplet, corresponding to the tail species [Mo]=CHCH$_2$CH$_2$C(Me)=CHP$_n$ (δ 13.2, $J = 6.3$ Hz)[296].

The behaviour of 3-methylcyclobutene **(78)** with various catalysts resembles that of cyclobutene. With **7** as initiator the propagating species gives a ^{1}H NMR spectrum

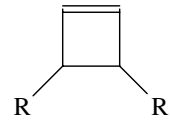


(76) R = Me
(77) R = $SiMe_3$

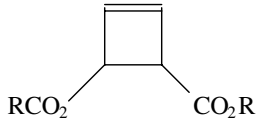
(78)



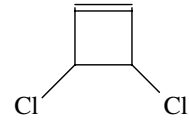
(79) R = Me
(80) R = Pr



(81) R = $CHMe_2$
(82) R = CH_2OMe
(83) R = CH_2OCH_2Ph



(84) R = Me
(85) R = Et
(86) R = CH_2Ph



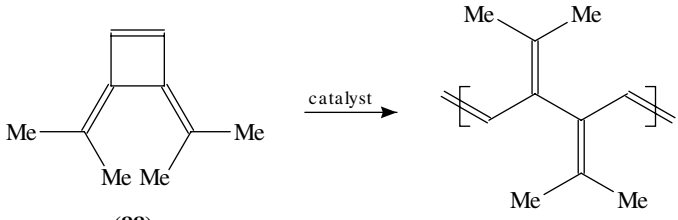
(87)

containing two carbene proton doublets (δ 11.95, J = 6.6 Hz; δ 11.50, J = 9.5 Hz), assigned to the *anti* and *syn* rotamers of the head species [Mo]=CHCHMeCH_2CH=CHP in which the polymer chain P′ in [Mo]=CHP′ points away from (*anti*) or towards (*syn*) the (=NAr) ligand. This polymer contains 84% *cis* double bonds and the methyl substituents are randomly oriented with respect to both *cis* and *trans* double bonds[298]. In contrast 3,3-dimethylcyclobutene **(79)** with the same initiator gives the 'tail' propagating species [Mo]=$CHCH_2CMe_2$CH=CHP, characterized by a carbene proton triplet (δ 8.53, J = 5.9 Hz), and an all-*trans*, all-HT polymer[298]. Likewise the ROMP of 3,3-dipropylcyclobutene **(80)** initiated by **74** also gives an all-*trans*, all-HT polymer. The ^{13}C NMR spectrum of the hydrogenated polymer contains four signals from methylene carbons confirming that it has an all-HT structure. On the other hand, the initiator **8** (R = Ph) gives a largely *cis* HT polymer, and catalysts such as WCl_6/Et_3Al give polymers which are neither stereospecific nor regiospecific[297].

The monomers **82–86** all give living polymers when initiated by **7** and related complexes. The ROMP of **85** shows well behaved second-order kinetics in C_6D_6 at 25 °C. The rate constant is about 10 times lower than for the reaction of 5,6-dicarbomethoxynorbornadiene, no doubt due to the greater deactivating effect of the COOR groups in **85**. Polymers of **84** and **85** have 45–93% *cis* content depending on the initiator[337].

The ROMP of **88** can be effected using [Ti(=CH_2)Cp_2] sources as catalyst[338], also with $WOCl_4/EtAlCl_2$ in chlorobenzene at −78 °C, admitting the monomer as a gas[339] (equation 50). The polymer forms as a transparent highly soluble material that becomes conductive (10^{-3} ohm^{-1} cm^{-1}) when doped with iodine. The undoped polymer shows a single absorption peak at 278 nm (ε = 20,000 M^{-1} cm^{-1} per triene unit), the position of which shows that the π-system of the polymer chain is segregated into triene segments. This is the result of steric interactions that force the polymer backbone into a non-planar conformation.

For work on **77** and **81** see Katz and Shippey[340] and Brunthaler and coworkers[335], respectively.



(88) (50)

2. Five-membered rings

Among the more recently used catalyst systems for the ROMP of cyclopentene the following are of particular interest.

(i) $W(=CHCMe_3)(=NAr)(OCMe_3)_2$ **(7W)** (0.04 M in benzene) will polymerize 50 equiv of cyclopentene to give an equilibrium mixture containing about 5% monomer (0.1 M) at −60 °C and about 95% monomer (1.9 M) at 60 °C. The monomer may be stripped completely from the living polymer by continuous evacuation, reforming the original initiator. In order to make a polymer of narrow MWD ($M_w/M_n = 1.08$) with this system it is necessary to work at −40 °C and to terminate the reaction after 1 h so as to forestall the tendency towards a thermodynamic distribution[341,342]. Star polymers can be made by terminating such a living polymer with a polyfunctional aldehyde[343].

(ii) Tetraphenylporphyrinatotungsten tetrachloride/tetraisobutylaluminooxane (1/2) polymerizes cyclopentene (4.8 M) in toluene to give a 20% *cis* polymer with a surprisingly narrow MWD ($M_w/M_n = 1.2$)[344]. The polymer formed initially using $(C_{17}H_{35}COO)_2MoCl_3/Et_2AlCl$ as catalyst also has a narrow MWD[345]. These too may be living systems.

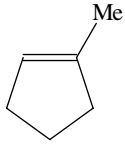
(iii) The ruthenium carbene complex **19**, containing the electron-rich ligand PCy_3, brings about the ROMP of cyclopentene, the propagating species being quite stable and detectable by ^1H NMR[110]. Certain other ruthenium complexes are effective in the presence of diazoesters[61,346].

In poly(1-pentenylene) the chemical shifts of the α-carbons are about 0.5 ppm upfield from those in the polymers of the other cycloalkenes, an effect which is attributed to a higher proportion of *gauche* conformations about the CH_2-CH_2 bonds arising from the influence of the γ-olefinic carbons[347].

The cyclopentene derivatives **89**[348], **92**[349] and **93**[350] do not appear to undergo ROMP, probably because their free energy of polymerization is positive. However, the fact that 1% of **89** can completely inhibit the polymerization of **90** and **91** indicates that it is likely to add preferentially to the active site forming the head carbene complex, [W](=$CMeCH_2CH_2CH_2CH$=CHR), which is then unable to add any of these three monomers. It should be capable of copolymerization with norbornene.

Individual enantiomers of **90** have been prepared by RCM (Section VII.A.1) and polymerized by **8** (R = Ph) at −30 °C to give a 52% yield of a 74% *trans* polymer[226]. Likewise **91**, with the same initiator at −55 °C, gives a 51% yield of 60% *cis* polymer, with a blocky *cis/trans* distribution ($r_t r_c = 6.3$); the ^{13}C NMR spectrum of the hydrogenated polymer shows it to be atactic[326].

The ring-opened polymer of norbornadiene consists of 3,5-disubstituted cyclopentene units **(94)**. When the concentration of these units is kept below 0.2 M the polymer remains soluble, but above this concentration, in the presence of WCl_6/Me_4Sn (1/2), it gels. This is caused by cross-linking, brought about by the ROMP of the enchained cyclopentene



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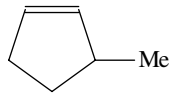
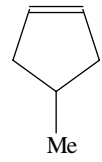
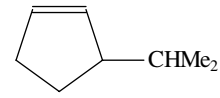


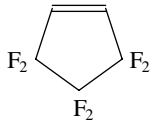
(90)



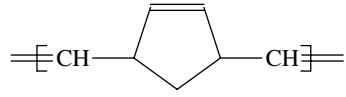
(91)



(92)



(93)



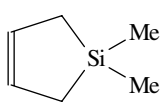
(94)

rings. This process is reversed by dilution[351]. The opening of the second double bond, leading to cross-linking of the polymer, is thus thermodynamically allowed above a critical concentration, as for the ROMP of cyclopentene itself. From the slight variation of this critical concentration with temperature (−40 to 18 °C) one obtains $\Delta H^\circ = -4.6$ kJ mol^{-1} and $\Delta S^\circ = -2.9$ J K^{-1} mol^{-1} (standard state 1 M) for the opening of the second double bond[352].

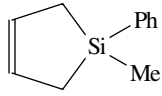
Four disubstituted 1-silacyclopent-3-enes (**95–98**) have been studied; also **99**. When polymerized in bulk, using **8** (R = Ph) as initiator, **96** and **97** give high polymer (M_n *ca* 40, 000)[247,353], as does **99** (M_n *ca* 10, 000)[300], but **95** gives low polymer (M_n *ca* 4000) not only with this initiator but also with the catalyst systems WCl_6/*i*-Bu_3Al/Na_2O_2[354], Re_2O_7/Al_2O_3/Bu_4Sn[355] and WCl_6/Me_4Sn[247]. WCl_6/Ph_4Sn is also an effective catalyst for the ROMP of **97** and **98** provided that a small amount of cyclopentene or cyclohexene is present to assist initiation[356,357]. WCl_6/Me_4Sn (and WCl_6/Ph_4Sn) gives a high-*cis* polymer of **97**, whereas **8** gives a polymer with only 45% *cis* double bonds. The corresponding polymers of **96** contain 80% and 25% *cis* double bonds, respectively. The former has a ^{29}Si NMR spectrum (in $CDCl_3$) with three signals at δ –4.31(*cc*), −4.44(*ct*) and −5.18(*tt*) in the ratio 72:20:8, corresponding to a blocky *cis/trans* distribution ($r_t r_c$ *ca* 5.5); the latter has a random distribution ($r_t r_c$ *ca* 1). These polymers all have a broad MWD ($M_w/M_n \geqslant 2$). The polymer of **98** initiated by WCl_6/Ph_4Sn has 84% *cis* double bonds and both the ^{29}Si and benzylic ^{13}C NMR signals are sensitive to *cc*, *ct*, *tt* dyads[357].

When **97** is sufficiently dilute its polymerization is no longer thermodynamically allowed, but, in the presence of **8**, a mixture of cyclic dimers, *cc* (84%), *ct* (14%) and *tt* (2%), is readily formed, in equilibrium with the monomer. The *cc* dimer has been isolated and its crystal structure determined[247]. These cyclic dimers can also be made by metathesis degradation of the polymers or by ADMET of diallyldiphenylsilane (Section VII.A.6).

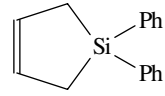
The ROMP of neat **99** is remarkable in that it proceeds to 96% conversion in 18 h at 25 °C to yield an all-HT, 97% *trans* polymer. Dilution of the living polymer with benzene causes neither reversion to monomer nor backbiting to form cyclic oligomers. The driving force for polymerization in this case derives from the relief of torsional strain in the monomer caused by interaction between eclipsed methyl groups on the adjacent silicon atoms[300].



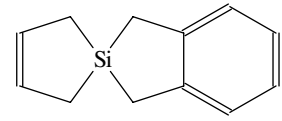
(95)



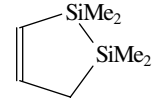
(96)



(97)



(98)



(99)

3. Six-membered rings

It is well known that the failure of cyclohexene to form long-chain polymer by ROMP is due to the greater thermodynamic stability of the monomer. However, if a 5 M solution of cyclohexene in toluene is added to a WCl_6/Me_4Sn solution at 25 °C and then cooled to −77 °C, 12% of the cyclohexene is consumed; it is regenerated on warming to 25 °C. If cold wet acetone is added to the reaction mixture at −77 °C, the products are found by GC to consist of oligomers containing 2–6 monomer units. The number of peaks indicates that several *cis/trans* isomers of the various oligomers are present, with *cis* double bonds preferred. Exposure of the mixture of oligomers to fresh catalyst brings about reversion to cyclohexene.

If norbornene is added to a mixture of WCl_6/Me_4Sn/cyclohexene (1/2.4/5) in toluene at 25 °C, 5% of the cyclohexene is consumed and incorporated into the polymer of norbornene, as shown by the presence of 7.5% 1,6-hexanediol in the products obtained by ozonolysis of this polymer followed by reduction with $LiAlH_4$. If the copolymer is allowed to stand overnight in the presence of the catalyst at 25 °C the cyclohexene units are split out, with 99% recovery of the original cyclohexene.

These two pieces of evidence show that cyclohexene can add to metal carbene complexes to some extent, but that at low temperature backbiting to give oligomers is preferred to propagation, while at room temperature the product of addition can be trapped, at least for a time, by reaction with norbornene[358].

There is also some indirect evidence for the interaction of cyclohexene with catalyst systems. First, the presence of cyclohexene assists the formation of the initiating species in the WCl_6/Ph_4Sn-catalysed ROMP of **28**[356]. Secondly, the presence of cyclohexene increases the rate of ROMP of cycloocta-1,5-diene catalysed by WCl_6/Me_4Sn at 25 °C by 30%, without itself being consumed[359]. However, there is no NMR spectroscopic evidence that $W[=\overline{C(CH_2)_3CH_2}](Br)_2(OCH_2CMe_3)_2/GaBr_3$ can interact with cyclohexene although it does so with cycloheptene and cyclooctene. Ring-strain relief is therefore of some importance in the formation of these cycloalkene adducts[120].

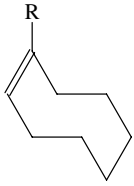
The formation of polymers containing $[=CH(CH_2)_4CH=]$, units is possible through the ROMP of an appropriate cyclic diene, such as cycloocta-1,3-diene, or by a double-bond shift reaction of a polymer such as poly(1-pentenylene). Such units can be eliminated as cyclohexene so long as metathesis activity is present in the system[360]. The ROMP of 2,3-dihydropyran, initiated by $Mo(CO)_6/CBr_4/h\nu$, has been reported[361].

4. Seven-membered rings

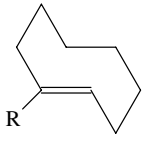
The ROMP of cycloheptene can lead mainly to dimer or to high polymer depending on the conditions. The equilibrium monomer concentration is temperature-dependent[271].

When a 30% solution in hexane is refluxed in a Soxhlet apparatus through a fixed bed of Re_2O_7/Al_2O_3, preferably pre-treated with Me_4Sn, a 68% yield of cyclic dimers is obtained, the proportions being close to the equilibrium values: *tt* 88%, *tc* 9%, *cc* 3%[272,273]. Metal carbene complexes give 20–50% *cis* polymers[120,271,347].

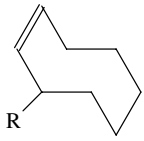
5. Eight-membered rings



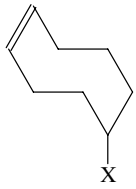
(100) R = H
(101) R = Me



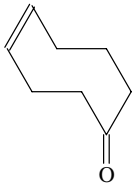
(102) R = H
(103) R = Me



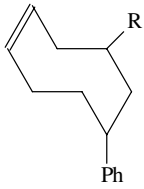
(104) R = Me
(105) R = Ph



(106) X = Me, **(107)** X = Cl,
(108) X = Br, **(109)** X = CO_2Me,
(110) X = CO_2SiMe_3, **(111)** X = OH,
(112) X = OAc,
(113) X = O.CO.CMe(=CH_2),
(114) X = I, **(115)** X = SR′,
(116) X = BEt_2, **(117)** X = CN



(118)

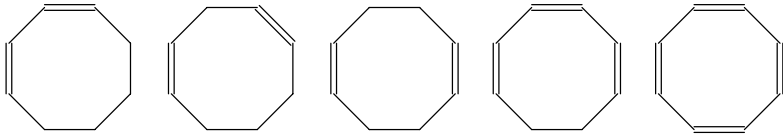


(119) R = Me
(120) R = Ph

Cis- and *trans*-cyclooctene, **100** and **102** respectively, and their derivatives **103–107**, all undergo ROMP[295]; also **108**[62,362], **109** and **110**[62], **111–113**[362], **114**[363], **115**[364], **116**[365], **118**[362], **119** and **120**[366,367]. Only **101**[295] and **117**[362] fail to polymerize, perhaps due to unfavourable choice of catalyst and conditions. The *trans* monomer **102** gives a 43% *cis* polymer very rapidly in the presence of $MoCl_2(PPh_3)_2(NO)_2/EtAlCl_2$[368] and is polymerizable by **18**[110]. With a catalyst of type **10** secondary metathesis reactions of the double bonds in the polymer of **100** cause the *cis* content to fall from 75% to 25% as the reaction proceeds[271].

The 5-substituted cyclooctenes (**106–116**, **118**) generally give unbiased polymers, the substituent being too far away from the reaction site to influence the direction of addition of monomer. This is particularly clearly seen in the ^{13}C NMR spectrum of the polymer of **118**, made using **19** as initiator, the olefinic region consisting of two well-defined symmetrical quartets (1:1:1:1) attributable to *cis* and *trans* olefinic carbons within HH, HT, TH, TT structures[362].

For the ROMP of the 5-alkylthiocyclooctenes (**115**), with R′ = Et, Bu, Hex, *c*-Hex, *t*-Bu, initiated by **12**, the most reactive monomers are those with branched alkyl substituents on the sulphur atom; for R′ = *t*-Bu, reaction is 95% complete in about 10 min. The variations in rate are likely to be connected with the strength of coordination of the sulphur atoms in the monomer and/or the propagating species to the tungsten centre. Coordination of the monomer to the metal centre through the sulphur atom will be impeded when R′ is *t*-Bu or *c*-Hex, allowing a higher equilibrium concentration of the precursor complex that leads to addition of monomer. For R′ = Bu the rate of polymerization is proportional to both monomer and initiator concentrations[189,364].



(121) **(122)** **(123)** **(124)** **(125)**

All the unsubstituted cyclooctapolyenes **121–125** undergo ROMP with the usual catalysts but, if the reactions of **121**, **124** and **125** are carried out in dilute solution, C_6 ring compounds are eliminated by backbiting reactions, while **122** and **123** form cyclic oligomers. Thus with **8W** (see Table 2) in dilute solution **121** yields cyclohexene. This suggests that the preferred mode of addition is that to give $[W]{=}CH(CH_2)_4CH{=}CHCH{=}CHCMe_3$ rather than $[W]{=}CHCH{=}CH(CH_2)_4CH{=}CHCMe_3$ since the former can eliminate cyclohexene immediately. With the same catalyst in dilute solution **124** yields some cyclohexa-1,3-diene and **125** gives a 75% yield of benzene[360]; also see elsewhere[369–371].

There are numerous studies of the ROMP of **123** of which the most recent have involved the use of molybdenum carbene[347] and ruthenium carbene catalysts[60,110]. Most catalysts give initially a polymer of at least 80% *cis* content, since one of the *cis* double bonds is pre-formed.

The ROMP of cyclooctatetraene (COT, **125**) to give polyacetylene was first reported in 1985[372,373] with $W[OCH(CH_2Cl)_2]_nCl_{6-n}/Et_2AlCl$ ($n = 2$ or 3) as catalyst at 20 °C. When the reaction is conducted in toluene the yield of black insoluble polymer is only 6%, but if the monomer is condensed onto a solid layer of catalyst a yield of up to 40% polymer is obtained. In the former case there is a much greater tendency towards formation of oligomers, amongst which the cyclic products of backbiting reactions, $(CH{=}CH)_n$, $n = 5–8$, can be identified by MS. The nature of the polyacetylene formed by the second method depends on the initial Al/W ratio. When Al/W is 1 the polymer is formed as a blue-black film containing 84% *cis* double bonds, but when Al/W is 2 the film is golden and contains only 39% *cis* double bonds. A 50% yield of polymer can also be obtained from neat monomer with $WCl_6/BuC{\equiv}CH$ as catalyst[348]. Better control over this reaction can be achieved using **8W** as catalyst[360]. Dissolution of catalyst in neat **125** produces, within a few seconds at room temperature, a high-quality lustrous silver film with smooth surface morphology. When first prepared, its CP-MAS ^{13}C NMR spectrum shows two olefinic peaks: a stronger peak at 126.4 ppm (*cis*) and a weaker peak at 132.2 ppm (*trans*). On heating the sample the spectrum changes, giving a main peak at 135.9 ppm (*trans*) and an upfield shoulder (*cis*). The chemical shift of the *trans* olefinic carbons are known to be sensitive to the configuration of the surrounding double bonds. Heating thus induces *cis/trans* isomerization to produce long segments of *trans–transoid* structure within the polymer chains. When doped by exposure to iodine the polymer acquires a conductivity greater than 100 $ohm^{-1}\,cm^{-1}$. Linear copolymers of varying conjugation length can be produced by the inclusion of a second monomer such as **123** during the preparation of the film, allowing a wide range of conductivities in the doped copolymers[374].

Ring-opened polymers have been made from monosubstituted cyclooctatetraenes (RCOT) with the following substituents R: Br[360], Me, *i*-Pr, Bu, *s*-Bu, *t*-Bu, neopentyl, 2-ethylhexyl, octyl, octadecyl, cyclopropyl, cyclopentyl, phenyl, methoxy and *t*-butoxy[375–377], $SiMe_3$[378,379] and the chiral substituents CHMeCHMe(OMe), $CHMeCHMe(OSiMe_2CMe_3)$ and $CH_2CHMe(OSiMe_2CMe_3)$[380]. The initiators **8W** and **13** are both very effective, but even with pure monomer some backbiting reaction occurs in competition with propagation, giving rise to 7–16% C_6H_5R. No benzene is detected, showing that ring-opening does not occur at the substituted double bond. Ring-opening

may, however, occur at any of the other three double bonds, so that the product is a polyacetylene having substituents placed on average on every fourth or fifth double bond (elimination of C_6H_5R will tend to decrease the frequency), but never on adjacent double bonds, unlike the polymers of substituted acetylenes; see Section X.C.

The initially formed polymers have a high *cis* content and, except when R is Me, are generally soluble in tetrahydrofuran, chloroform and benzene (M_n *ca* 10^4–10^6). On standing at room temperature the solutions slowly change colour, and a new absorption maximum appears at longer wavelengths. This change is fastest for the polymers with straight-chain substituents and slowest for those with branched substituents. It is accelerated by exposure to light and is due to *cis/trans* isomerization; see Figure 9. Long sequences of *trans* double bonds allow a much greater degree of conjugation, giving rise to a low-energy $\pi \rightarrow \pi^*$ electronic absorption. For monomers with straight-chain or alkoxide substituents the predominantly *trans* polymer comes out of solution as it is formed. In contrast, polymers containing a secondary or tertiary substituent adjacent to the backbone remain soluble in the mainly-*trans* form. Effective conjugation lengths of up to 30 double bonds have been observed for these soluble polymers.

For the polymer of *s*-BuCOT in benzene *cis/trans* isomerization can be monitored by the change of absorbance at 560 nm. The reaction is first-order, with a half-life of about 27 min at 65 °C and an activation energy of 89 kJ mol^{-1}. However, the isomerization of the trisubstituted *cis* double bond proceeds only part way. Its reaction can be followed separately by means of ^{1}H NMR spectra, the methine signal of the side groups being sensitive not only to the configuration of the nearest double bond but also that of the next-nearest double bond: *tt* 2.75, *tc* 2.51, *cc* 2.12 ppm. At equilibrium the preference for the *cis* configuration means that the proportion of long *trans* sequences is small. During the isomerization process the absorption spectra exhibit an isosbestic point at 400 nm, which is consistent with a mechanism involving multiple isomerization of the *cis* double bonds in one chain by a cooperative motion.

When R = *t*-Bu the polymer is freely soluble and yellow-orange in colour (λ_{max} = 432 nm after isomerization); it also remains an insulator in the presence of iodine.

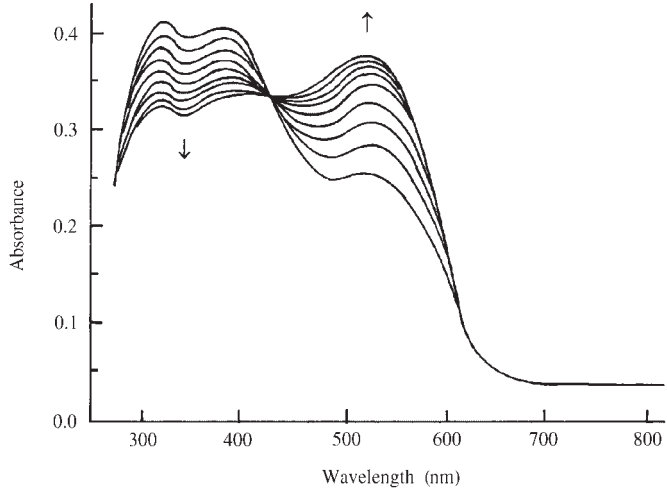


FIGURE 9. Absorption spectra of polymer of trimethylsilylcyclooctatetraene in CCl_4 (10^{-6} M) obtained between eight periods of photolysis (10 s each). Reprinted with permission from Ref. 378. Copyright (1989) American Chemical Society

This indicates a very low effective conjugation length even after isomerization. This is attributed to a twist in the polymer chains, caused by the bulky *t*-Bu groups. This effect is much less for the polymers with other R groups and their films can be made conducting by doping with iodine[375]. For the polymers bearing chiral substituents, the backbone $\pi \rightarrow \pi^*$ transition shows substantial circular dichroism, the magnitude of which is characteristic of a disymmetric chromophore. The chiral side groups thus twist the main chain predominantly in one sense rather than just perturbing that chromophore electronically[380].

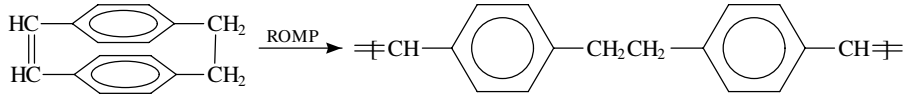
The possible application of these materials to form surface barrier solar cells, and to make conductor/insulator/conductor sandwiches by sequential polymerization of different monomers has been explored[376,379,381].

6. Larger rings

The ROMP of *cis*-cyclodecene and cyclododecene by metal carbene complexes gives high-*trans* polymers[347]. Methyl 3,7-cyclodecadienecarboxylate has been successfully polymerized by ring-opening using $WCl_4(OC_6H_3\text{-}Ph_2\text{-}2,6)_2/Et_4Pb$ as catalyst at 60 °C. ^{13}C NMR spectra show that the monomer consists of either the *cis,trans* or the *trans,cis* isomer; also that the polymer has a very regular structure[382].

9-Phenyl-1,5-cyclododecadiene undergoes ROMP in the presence of $WCl_4(OC_6H_3\text{-}Cl_2\text{-}2,6)_2/Et_4Pb$ in PhCl at 80 °C; 98% yield in 2 h[383].

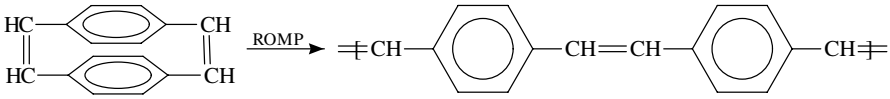
[2.2]Paracyclophan-1-ene **(126)** can be regarded as a 12-membered ring but its rigid structure is akin to that of cyclobutene. The ROMP of **126** is initiated by **8** (R = Ph) in toluene, giving a living polymer with a carbene proton singlet at 12.84 ppm, the intensity of which increases as the reaction proceeds slowly to completion (18 h). The polymer **(127)** has 98% *cis* double bonds, but on irradiation or exposure to catalytic amounts of iodine the double bonds undergo *cis/trans* isomerization and the polymer comes out of solution. Many other Mo- and W-based catalysts are also effective but give insoluble polymer, presumably because of a high *trans* content. A solution of the high-*cis* polymer fluoresces when excited by irradiation at 330 nm. The initial spectrum displays a weak emission at about 370 nm attributed to 2% of *trans*-stilbene segments originally present in the chains. With continued irradiation (2 min) there is an increase in the emission from this band as more *trans* double bonds are generated, and a new emission appears at 445–500 nm. After further irradiation, this intense red-shifted luminescence becomes the predominant feature before the polymer precipitates. In a statistical copolymer of 9% of **126** and 91% of norbornene, the units of **127** are isolated between norbornene units, and the fluorescence spectrum is confined to the shorter-wavelength region with a maximum around 360 nm[384].



(126) **(127)**

Similar results have been obtained for a derivative of **126** in which one of the CH_2 hydrogens is substituted by $OSiMe_2CMe_3$. The polymer is unbiased but differs from that made from **126** in that after isomerization to a high-*trans* polymer it remains soluble in organic solvents. The silyl group in the polymer can be removed by treatment with Bu_4NF to give the hydroxy analogue, which can then be dehydrated thermally at 105 °C or catalytically (HCl) at 25 °C to give poly(*p*-phenylenevinylene)[385,386].

The ROMP of [2.2]paracyclophane-1,9-diene **(128)** yields poly(*p*-phenylenevinylene) **(129)** as an insoluble yellow fluorescent powder. Soluble copolymers can be made by the ROMP of **128** in the presence of an excess of cyclopentene[387], cycloocta-1,5-diene[388] or cyclooctene[389]. The UV/vis absorption spectra of the copolymers with cyclooctene show separate peaks for sequences of one, two and three *p*-phenylene-vinylene units at 290, 345 and about 390 nm respectively, with a Bernoullian distribution. The formation of the odd members of this series must involve dissection of the two halves of the original monomer units by secondary metathesis reactions.



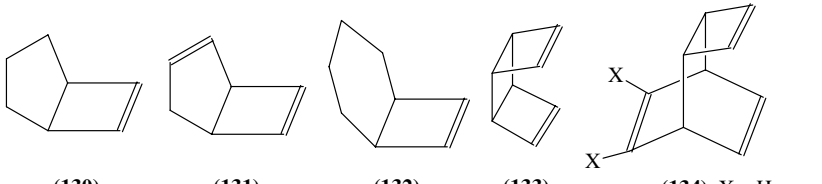
(128) **(129)**

Attempts to bring about the ROMP of ferrocenophanes, in which the two cyclopentadienyl rings are linked by a divinylene group, have met with limited success. Soluble oligomers ($M_n = 1700$) are obtained using a tungsten carbene complex as catalyst. Soluble polymers, probably of higher MW, can be obtained by placing a methoxy group on the carbon adjacent to a Cp ring or by copolymerizing with *s*-butylcyclooctatetraene[390].

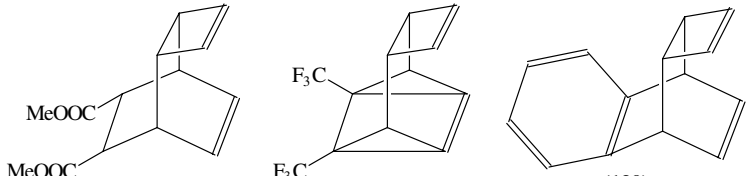
C. Polycyclic Alkenes

1. Monomers containing a fused cyclobutene ring

The ROMP of the following compounds has been reported: **130**[109,391], **131**[392], **132**[392,393], **133**[394], **134**[395,396], **135**[396,397], **136**[341,395,396,398–404], **137**[397], **138**[405,406], **139**[395,407], **140**[395], **141–143**[337]. In all cases the reactive double bond is that in the C_4 ring. The repeat units in the polymer have an *erythro* structure corresponding to the *cis* relationship of the bonds which attach the cyclobutene ring to the rest of the ring system in the monomer.



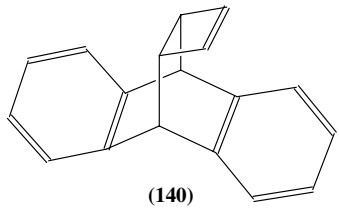
(130) **(131)** **(132)** **(133)** **(134)** X = H
(135) X = COOMe
(136) X = CF_3



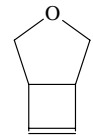
(137) **(138)** **(139)**

When **18** in CH_2Cl_2 is added to 20 equiv of **130** at 40 °C all the initiator I is consumed and ROMP proceeds at a rate proportional to both [I] and [M], with an apparent k_p of

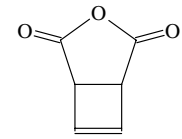
0.183 M^{-1} min^{-1}. The ^1H NMR spectrum shows the presence of three propagating species in equilibrium, of which one is probably the main propagating species. One has two PPh_3 ligands, while the other two are presumed to have one such ligand; the ^{31}P NMR spectrum shows two signals. This system exhibits all the characteristics of a living polymerization and gives a polymer with 58% *cis* double bonds. On adding **8** to a mixture of norbornene and **130**, all the **130** reacts first and then the norbornene so that a block copolymer is formed. The same result may be achieved by adding norbornene to the system after all the **130** has been consumed[109].



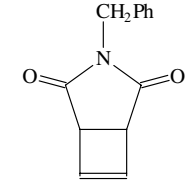
(140)



(141)

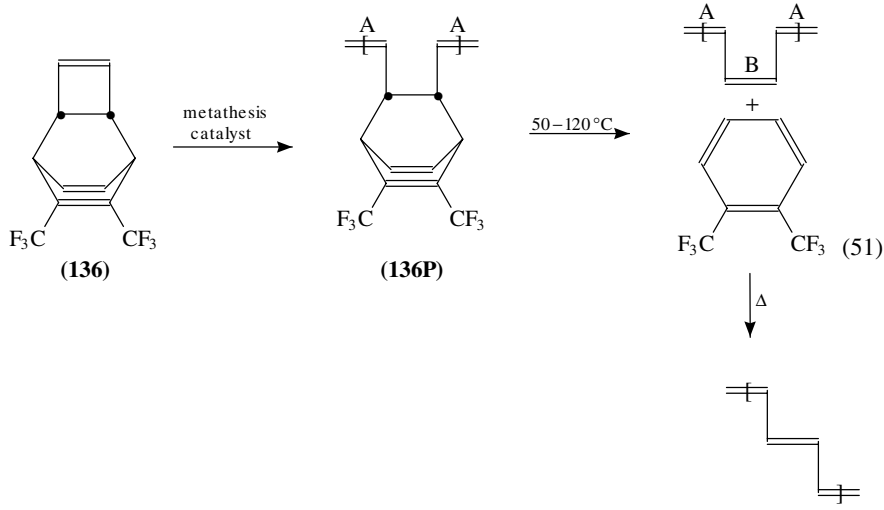


(142)



(143)

The ring-opened polymers of **134**, **139**, **140**, **135**, **136** (and **138**) undergo a retro-Diels-Alder reaction, either at room temperature or on heating to 120 °C, with the elimination of benzene, naphthalene, anthracene, dimethyl phthalate and 1,2-bis(trifluoromethyl)benzene respectively, and the formation of polyacetylene, as illustrated for **136** in sequence 51. The elimination reaction is accompanied by a change of colour from yellow to deep red as longer polyenes are formed. The polymer **136P** is moderately stable at 20 °C with a half-life of 20 h[395]. This is long enough for films to be made and stressed uniaxially, and then converted to highly-oriented non-fibrous crystalline films of polyacetylene[398].



(136) **(136P)** (51)

The polymer of **138** is more stable than that of **136** but its conversion to polyacetylene is much more exothermic and not so easily controlled[406]. The double bonds B formed in the retro-Diels-Alder reaction are initially *cis*, as may be some of the double bonds A formed in the metathesis reaction, but these quickly isomerize to *trans* above 100 °C. In a DSC

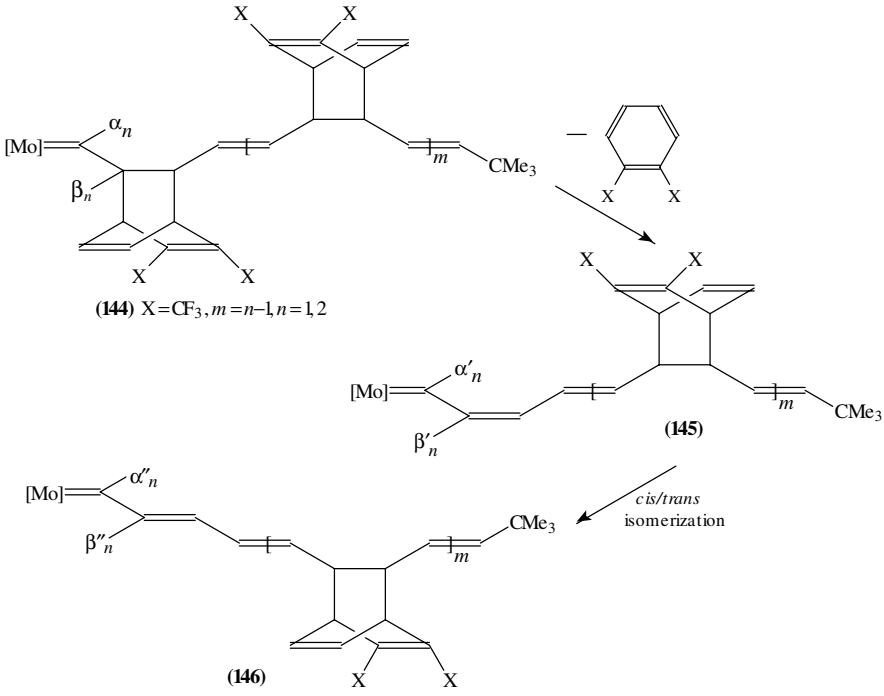
trace of **136P** the exotherm associated with this isomerization process can be detected at a higher temperature (110 °C) than that of the retro-Diels-Alder reaction (70 °C), but not in the case of the polymer of **138** where the former is merged with the latter (110 °C). The order of stability of the polymers is **134P** < **136P** < **135P** < **138P** ≈ **139P** < **140P**. The last two are quite stable at room temperature and must be heated to 100–200 °C to effect their conversion to polyacetylene.

A closer insight into these reactions, particularly with monomer **136**, has been gained through the use of **7** as initiator[396], and its W analogue **7W**[401], the chains being terminated by reaction with Me_3CCHO, $Me_3CCH{=}CHCHO$ or $C_7H_{15}CHO$, either before or after the retro-Diels-Alder reaction has occurred. When polyacetylene made in this way is passed through a column of silica gel under nitrogen at −40 °C one can isolate homologues containing up to 13 double bonds. Reaction of the tungsten carbene initiator with **136** gives a *trans* double bond, as also does the reaction of Me_3CCHO with the living end, while the propagation reaction gives 75% *trans* double bonds. On the other hand, the initially formed double bond from the retro-Diels-Alder reaction is always *cis*. Such a procedure therefore yields a series of polyenes with $(2n + 1)$ double bonds in which initially the most abundant components are those having alternate *trans* and *cis* double bonds: $(tc)_n t$. If instead the living ends are terminated by reaction with $Me_3CCH{=}CHCHO$ a series of polyenes with an even number of double bonds is obtained, but the termination reaction is not stereospecific. Termination with 0.5 equiv of an unsaturated dialdehyde such as OHCCH=CHCH=CHCH=CHCHO can also be used as a means of joining two chains together and extending the polyene sequence, but solubility and stability problems limit the usefulness of this procedure[396].

With **7** (R = Me) as initiator the various stages of reaction may be followed very closely by ^{1}H NMR. The spectrum taken 20 min after mixing equivalent proportions of monomer and initiator shows two main carbene proton doublets ($J_{\alpha\beta} = 6$ Hz) at 11.21 and 11.09 ppm as well as the singlet from residual initiator at 11.24 ppm. The doublets are assigned to the protons α_n in the products **(144)** of addition of one and two molecules of **136** respectively. Already in this spectrum may be seen small doublets ($J_{\alpha\beta} = 11$ Hz) at 12.63 and 12.48 ppm assigned to the corresponding protons α'_n in the products of the retro-Diels-Alder reaction, which occurs most readily at the unit adjacent to molybdenum **(145)**. As the reaction proceeds these signals strengthen at the expense of the α_n protons, as also do those around 8 ppm (β'_n in **145**). In **145** the newly formed double bond is *cis*. On heating to 50 °C for 90 min the *cis* double bonds are largely converted to *trans* giving rise to new carbene proton doublets at 11.96 and 11.85 ppm (α''_n in **146**) and a new signal for the β''_n protons.

In **144–146** the alkylidene ligand lies in the N/Mo/C plane and may be oriented so that the growing chain points either toward the nitrogen atom in the imido ligand (*syn* rotamer) or away from the nitrogen atom in the imido ligand (*anti* rotamer). The *syn* rotamer predominates in each case but the *anti* rotamers are also detectable for **145** and **146**. The carbene proton signals from the species corresponding to $n \geqslant 3$ are also resolved[396]. The rate constant for **144** → **145** at 25 °C is 1.06×10^{-2} min^{-1} while that for **145** → **146** is 1.80×10^{-3} min^{-1}, some six times smaller. These rate constants are independent of solvent (C_6D_6 and THF-d_8). When reaction is initiated by the tungsten complex the rate constants are somewhat smaller; also the rate of the retro-Diels-Alder reaction for the unit adjacent to the tungsten centre in the analogue of **144** is about ten times faster than for the unit that is further away[401].

The ROMP of **136** may be used as the first stage in the preparation of polyacetylene molecules with mesogenic (liquid-crystalline) functional groups at the chain ends: the ROMP of **136** is initiated by a molybdenum carbene complex and the living ends terminated by reaction with a substituted benzaldehyde bearing a mesogenic group, followed



by heating to effect the retro-Diels–Alder reaction[408]. In a similar manner block copolymers, containing ring-opened units of **139**, can be prepared and then heated to 220 °C to eliminate naphthalene, so yielding copolymers containing polyacetylene blocks[407].

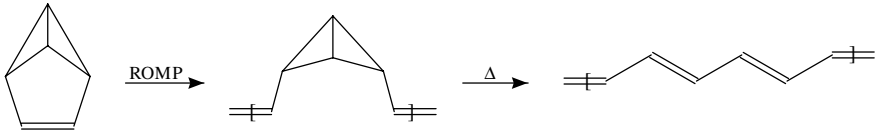
If it is desired to introduce a controlled proportion of cross-links during the ROMP, say, of cyclooctene, one may use a small proportion of *syn*-tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene, **133**, as cross-linking agent, with catalysis by WCl_6/Me_4Sn. Both the double bonds in **133** react completely and, if sufficient **133** has been used, the cyclobutane rings which form the cross-links give rise to observable signals at 41.2 ppm in the ^{13}C NMR spectrum and 3.5 ppm in the ^{1}H NMR spectrum[394]. The physical properties of polyacetylenes prepared in these various ways have been closely studied[402,403,406].

Monomers that contain (i) a cyclobutene ring substituted at the olefinic carbons by COOMe or CF_3, and (ii) a norbornene ring system, undergo ROMP by preferential opening of the norbornene ring[409].

2. Benzvalene and deltacyclene

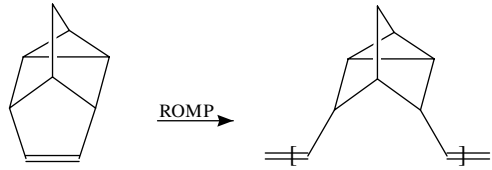
The ROMP of benzvalene **(147)**, equation 52, proceeds smoothly using tungsten carbene initiators, and films of the polymer **(147P)** can be cast directly from the reaction mixture[410,411]. The polymer has a tendency to cross-link and to decompose spontaneously once isolated in dry form, so is best handled in solution, especially as the decomposition can be explosive. The DSC thermogram of the polymer shows an exotherm at 153 °C, attributed mainly to isomerization to polyacetylene **(148)**, and a second exotherm at 308 °C, of unknown origin. The polymer **147P** made using **7W** (R = Me) as initiator has a very simple three-line ^{13}C NMR spectrum but it is not known whether the structure

is all-*cis* or all-*trans*. Polymers made with other initiators give spectra of greater complexity, probably due to partial isomerization to **148**. For clean conversion of **147P** to **148** it is best to treat freshly cast films with a 5% solution of $HgCl_2$ in THF. The films turn red within seconds, to blue-green over the next 30 s, and finally to a black, silvery, shiny film within 2–3 min.



(147) **(147P)** **(148)** (52)

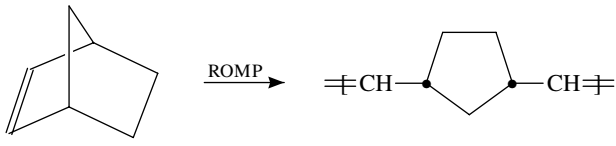
The ROMP of deltacyclene **(149)**, equation 53, leads to polymers **(149P)** of high MW, with a range of *cis* content depending on the catalyst: 27–35% for **7** (R = Ph), 60–70% for $RuCl_3$/60 °C, 70% for WCl_6/Ph_4Sn and 100% for $ReCl_5$[412–414]. The all-*cis* polymer can be fully epoxidized using dimethyldioxirane; with *cis/trans* polymers only the *cis* double bonds are epoxidized[413].



(149) **(149P)** (53)

3. Norbornene

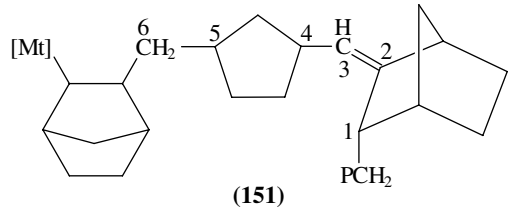
The original discovery of the ring-opening polymerization of norbornene (equation 54) was made using $TiCl_4/LiAl(C_7H_{15})_4$ as catalyst in an attempt to carry out Ziegler–Natta polymerization (ZNP) of this monomer[32]. Since then the relationship between ZNP and ROMP has been a matter for considerable speculation[415–418]. In many cases the same catalyst system can induce ZNP of one olefin and ROMP of another. For example, WCl_6/Bu_4Sn (1/10) in hydrocarbon solvents initiates ZNP of ethene[419] but ROMP of cyclopentene[420]. When these two olefins are reacted together with this catalyst only the two homopolymers are formed, indicating the presence of metal alkyl complexes propagating ZNP and metal carbene complexes independently propagating ROMP. Evidence for an equilibrium between a tungsten(IV) methyl complex and a tungsten(VI) methylene hydride complex (equation 55) was first provided by Cooper and Green[421–423]. The question then arises as to whether systems can be found where such species are in sufficiently rapid equilibrium for polymers to be formed containing both types of repeat unit in the same chain.



(150) **(150P)** (54)

$$[Mt]{-}CH_2P \rightleftharpoons [Mt]{=}CHP \quad (H \text{ on } [Mt]) \tag{55}$$

Consider, for example, the reaction of a metal alkyl complex $[Mt]-CH_2P$ with norbornene (NBE) by the following sequence of events: (i) insertion of one molecule of NBE into the Mt−C bond, (ii) migration of an α-hydrogen to the metal, (iii) addition of one molecule of NBE by metathesis with the Mt=C bond, (iii) migration of the hydrogen atom on the metal back to the α-carbon so as to re-form the Mt−C bond, (iv) insertion of a further molecule of NBE into the Mt−C bond. The resulting structure **151** will contain two characteristic features at the junctions between the two types of unit, namely an olefinic carbon with no attached hydrogens (C-2) and a CH_2 group between the rings (C-6).



(151)

Two catalysts have been found which, under limited conditions, give polymers containing both these features. With $Mo(CO)_5(py)/EtAlCl_2/R_4NCl$ as catalyst the polymer made at 26 °C has 100% ring-opened units, but when made at 110 °C, only 31% such units; and with $ReCl(CO)_5/EtAlCl_2$ as catalyst the polymer made at 100 °C contains 98.6% ring-opened units, falling to 5.1% when made at 110 °C and zero when made at 132 °C (i.e. 100% ZNP). These figures are based on the olefinic to aliphatic proton intensity ratio in the ^1H NMR spectra which is not in itself proof that the two types of unit are present in the same chain, but the fact that the GPC of the polymer exhibits a single, relatively narrow peak is a strong indication that this is so. The conclusive evidence is as follows[424]. (i) The ^{13}C NMR spectra show four resonances in the olefinic region (131.8, 132.3, 132.5 and 132.8 ppm) which disappear in the DEPT spectrum, showing that these carbons do not carry hydrogens and can therefore be assigned to C-2. The fine structure can be attributed to the four stereomers arising from the two possible configurations about C-3 (*E* and *Z*) and about C-1 (*endo* and *exo*). (ii) The product of ozonolysis of the polymer gives a resonance at 218.4 ppm consistent with the presence of an aliphatic ketone similar to that in norcamphor (216 ppm). (iii) When 2,3-dideuterionorbornene is used in place of NBE the hydrogens on C-6 in **151** are replaced by deuterium; C-6 can then be found in the $^{13}C-\{^2H\}$ INEPT spectrum at 27 ppm.

Although most catalysts for the polymerization of NBE and other cycloalkenes give mainly ZNP or ROMP[59], quite a number are known where the IR spectrum or the olefin/aliphatic proton ratio indicates a mixed product[27]. If subjected to examination along the above lines some of these might be found to have both types of unit in the same chain. Similar questions arise in the reactions of acyclic olefins on heterogeneous supported oxide and other catalysts, where olefin metathesis is often in competition with polymerization or homologation reactions. An IR study of the polymerization of ethene on a sulphate-containing TiO_2 (anatase) sample shows evidence of an alkylidene surface end-group of the polymer, and for substantial perturbation of CH_2 groups of the polymer chain by interaction with the oxide surface[425]. However, for most Mo-based catalysts the evidence from isotopic labelling and selective poisoning experiments is that the different types of reaction proceed independently at distinct catalyst sites[426–429].

In the rest of this section we report results on some of the more recently used catalysts for the ROMP of NBE, taken in Group order.

A number of titanacyclobutane complexes act as initiators of living ROMP of NBE[321,430,431]. Such initiators can be used to make block copolymers[432] and adapted to the production of star-shaped polymers[433]. The living ends can be terminated with benzophenone to yield a $Ph_2C=$ end-group[9] or with terephthalaldehyde to yield a $=CHC_6H_4$-(CHO)-4 end-group[434].

Tantalum carbene complexes such as **5** and $Ta(=CHCMe_3)(S-C_6H_2$-*i*-Pr_3-2,4,6)$_3$(py) are effective, provided the conditions are such as to allow the coordinated base (THF or py) to give way to monomer (M). In the first example the initially formed tantalacyclobutane complex has been isolated and shown to have a trigonal–bipyramidal structure, and to polymerize NBE at a rate that is independent of [M]. In this case the rearrangement of the intermediate tantalacyclobutane complex, to form the tantalum carbene complex, controls the rate of polymerization. In contrast, in the second example the rate is first-order in monomer; here the reaction of the tantalum carbene complex with the monomer is the slower step. In both cases the polymer, after termination by reaction with benzaldehyde, is nearly monodisperse[93,94].

Molybdenum carbene complexes like **7** are very effective for the ROMP of NBE[341] and can be manipulated (i) with chain transfer agents such as penta-1,3-diene and styrene to reduce the MW without sacrificing the narrow distribution[283], (ii) with norbornadiene dimer to produce star polymers and star-block copolymers[126] and (iii) with substituted benzaldehydes as terminating agents, to give polymers with a variety of functionalized end-groups[435]; also to make other block copolymers[407]. The ROMP of NBE in THF initiated by **7** (R = Ph) is first-order in both monomer and initiator; $k_p = 4.3\ \text{M}^{-1}\,\text{s}^{-1}$ at 20 °C, $\Delta H_p^{\ddagger} = 43\ \text{kJ mol}^{-1}$, $\Delta S_p^{\ddagger} = -84\ \text{J K}^{-1}\ \text{mol}^{-1}$[436]. With the same initiator in toluene at 22 °C, and using $Me_3CCH{=}CH_2$ as transfer agent, $k_p = 17\ \text{M}^{-1}\,\text{s}^{-1}$ and $k_{tr} = 3 \times 10^{-5}\ \text{M}^{-1}\,\text{s}^{-1}$[129]. A molybdenum carbene complex with a tridentate ligand [tris(pyrazolyl)borate] is effective in the presence of $AlCl_3$[437].

An interesting heterogeneous catalyst has been obtained by adding one drop of 1.8 M $EtAlCl_2$ in toluene to a crystal (20 mg) of $(Bu_4N)_2(Mo_6O_{19})$; its surface colour changes from yellow to dark brown, corresponding to Mo(VI) → Mo(V) → Mo(IV). If a solution of NBE in toluene is added after 30 s there is instant polymerization to a gel, which is partially soluble in chloroform and contains 33% *cis* double bonds. On removing the crystal from the polymer with forceps its surface colour is restored by atmospheric oxidation and it can be used to repeat the process without loss of activity. Similar results are obtained with related tungstates[438,439].

A variety of tungsten carbene catalysts has been used having (i) all monodentate ligands, of which two may be alkoxy or aryloxy[100,102,112–114,307,341,440–442], or (ii) one bidentate ligand[101,103,104,443,444] or (iii) one tridentate ligand[445]. With $W[=C(OMe)Ph](CO)_5$ there is evidence that one permanent ligand in the propagating species is derived from the original carbene ligand[446].

Re_2O_7/Al_2O_3 gives an all-*cis* polymer, but when pretreated with Me_4Sn gives a polymer with comparable proportions of *cis* and *trans* double bonds showing that a different active species must then be involved[45]. One rhenium carbene complex is reported to be active[105].

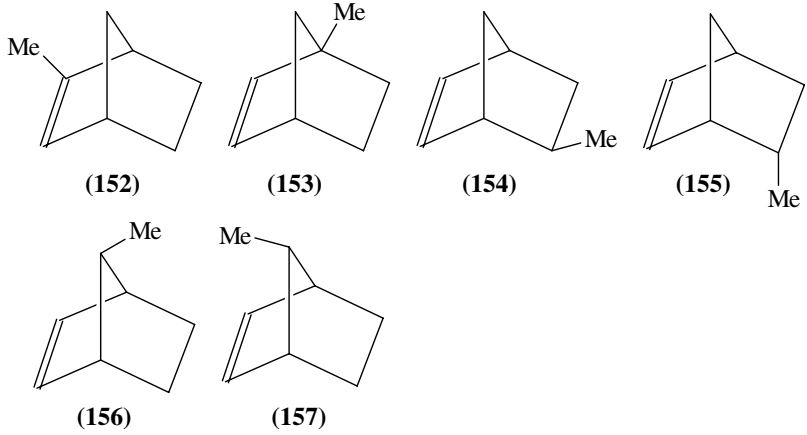
The hydrate of $Ru(OTs)_2$ is effective at 50 °C both in protic solvents giving high-*trans* polymers[61,447], and in supercritical carbon dioxide to give a high-*cis* polymer[448]. Arene complexes of this salt are very active when exposed to UV radiation[449]. $RuCl_2(PPh_3)_2(py)_2$ and related complexes are active even at 20 °C in the presence of oxygen[450]. The monomer first undergoes catalytic epoxidation, followed by formation

of an oxaruthenacyclobutane complex which can then generate the propagating carbene complex. Catalysis by OsO_4 at 60 °C probably operates in a similar fashion[451]. Ethyl diazoacetate enhances the activity of ruthenium compounds for the ROMP of NBE[346]. The complex **19** polymerizes 142 equiv of NBE in CD_2Cl_2/C_6D_6 (1/4) at room temperature in less than a minute, giving a polymer with 86% *trans* double bonds, but very little of the initiator is used and the polymer has a broad MWD[110]. The complex **18** is somewhat less active and gives a living system; the carbene proton in the propagating species appears at 17.79 ppm in the ^1H NMR spectrum[108]. These complexes are also active when supported on polystyrene[452]. The complexes $Ru(=CHR)(Cl)_2(PPh_3)_2$ (R = Me, Et, Ph) are much more efficient ($k_i/k_p = 9$ when R = Ph compared with 0.006 for **18** and give polymers with very narrow MWD ($M_w/M_n = 1.04$)[60,91].

Dienes can have a significant effect on the course of reaction by coordinating to the metal centre. Thus isoprene (6×10^{-4} M) can completely suppress the formation of cyclic oligomers during the ROMP of NBE catalysed by WCl_6/Me_4Sn[453]. In the absence of isoprene, 40% of the product consists of oligomers containing from 2 to 14 monomer units, as detected by GPC[454]. Again, $RuCl_3$ which has been pretreated with DCPD gives a 95% *cis* polymer of NBE[289], whereas $RuCl_3$ alone gives a 5% *cis* polymer. For $OsCl_3$, the effect is somewhat smaller, 85% *cis* and 29% *cis* respectively, while with $IrCl_3$, the difference is very small, 43% and 36% *cis* respectively[285,289]. The ability of the doubly coordinated diene molecule to influence the relative ease of approach of the monomer to form *cis* and *trans* double bonds is thus a sensitive function of the nature of the metal. A similar effect is observed with certain bis(allyl)ruthenium(IV) complexes as catalysts which give polymers of NBE containing 30–90% *cis* double bonds[455,456].

NMR spectra of the polymers of NBE are insensitive to ring tacticity but their fully hydrogenated derivatives show fine structure when the spectra are run under the most favourable conditions[457].

4. Monosubstituted alkylnorbornenes



(152) **(153)** **(154)** **(155)** **(156)** **(157)**

The ROMP of (±)-2-methylnorbornene (2-MNBE). **(152)** gives an all-HT polymer (Table 6). The HT bias in polymers of (±)-1-MNBE **(153)** depends markedly on the catalyst, probably reflecting the polarity of the Mt=C bond[101,302–304,308,321,441,442,458],

whereas (±)-*exo*-5-MNBE **(154)** and (±)-*endo*-5-MNBE **(155)** give virtually unbiased polymers[310,459]. As normally made 7-MNBE is a 50 : 50 mixture of the *anti*- and *syn*-isomers, **156** and **157** respectively. When this mixture is treated with WCl_6/Me_4Sn the *anti*-isomer is selectively polymerized and the *syn*-isomer can be recovered from the final reaction mixture in good yield[320,460]. The *syn*-methyl group, being close to the double bond, hinders the approach of the *exo* face of the monomer. More active initiators, such as **7, 10** and $W(CO)_3$(mesitylene)/$EtAlCl_2$/epoxide, are less discriminating, and although the *anti*-isomer still reacts preferentially at the beginning of reaction, the *syn*-isomer reacts later to give its own distinctive propagating species, detectable by ^1H NMR; the product is then a block or tapered-block copolymer of the two isomers[128,307,320,322].

5. Norbornenes with a 5-(Si-containing) substituent

The ROMP of norbornenes with the following substituents (*endo/exo* mixtures) has been reported[91,461–465]: $SiMe_3$, $SiMe_2(CH_2SiMe_3)$, $SiMe_2$[$(CH_2)_3$-9-carbazolyl], $CH_2Si(Me)(CH_2CH_2CH_2)$, $SiMeCl_2$, $SiCl_3$, $Si(OMe)_3$ and $Si(OEt)_3$. For the ROMP of the $Si(OR)_3$ monomers it is best to use Lewis-acid-free catalysts such as $RuCl_2(PPh_3)_3$ at 60 °C[464] or a molybdenum carbene complex[95]. The $SiMe_3$-containing polymer has considerably enhanced permeability and diffusion coefficients for light gases, compared with polynorbornene[463]. The polymer containing carbazolyl groups can form charge transfer complexes with acceptors such as 2,4,7-trinitro-9-fluorenone[464].

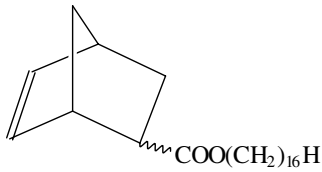
6. Norbornenes with a 5-(COOR) substituent

Monomers in this category fall into three groups: (i) those with small substituents, giving polymers which may be thermoplastic[466]; (ii) those with substituents of intermediate size and of such a character that the polymers can have liquid-crystalline or other interesting properties; and (iii) macromonomers in which a polymer is terminated by a norbornenyl group and which can be used to make graft copolymers by ROMP. Except where stated the monomers are *endo/exo* mixtures.

The first group of monomers includes those with the following substituents: *endo*-COOMe **(158)**, *endo*-COOEt, *exo*-COOMe **(159)**, *exo*-COOEt and $COOC_6H_2Br_3$. All types of metathesis catalyst are effective[467], including metal carbene complexes[127] and $RuCl_2(PR_3)$(*p*-cymene)/$Me_3SiCH_2N_2$[62]. The ^{13}C NMR spectra indicate that the substituents are randomly oriented in the polymers. The ethyl ester polymers can also be produced by heating the carboxylic acid monomer with $IrCl_3$ in ethanol[467].

The reaction of **158** with a tungsten cyclopentylidene initiator has been followed in CD_2Cl_2 at 27 °C by ^1H NMR. The initiator is all consumed in 15 min and the monomer (3 equiv) in about an hour. The head and tail propagating species give separate carbene proton signals, and the head species formed by addition of one unit of monomer may be distinguished from the head species containing more than one monomer unit. The final concentration of head species is nearly twice that of the tail species, indicating a somewhat lower overall reactivity of the head species in the propagation steps. With **159** as monomer the spectra of the head and tail propagating species are indistiguishable, although the first addition product gives a distinct spectrum[127].

In the second group some monomers (**160–162**) have been polymerized by $RuCl_3$[468], and others in a more controlled fashion by **7** or related complexes: **163**[469,470], **164**[471], **165–167**[472,473]. Both **160** and its polymer form monolayers, but the polymer exhibits a higher collapse pressure and reduced collapse area compared with the monomer. The



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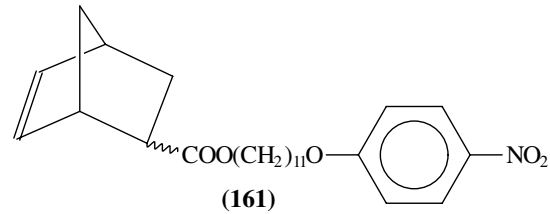

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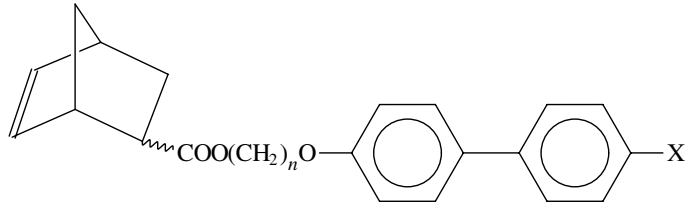
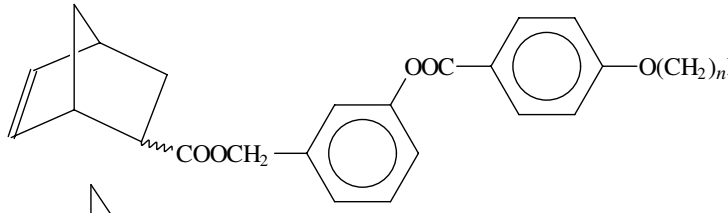
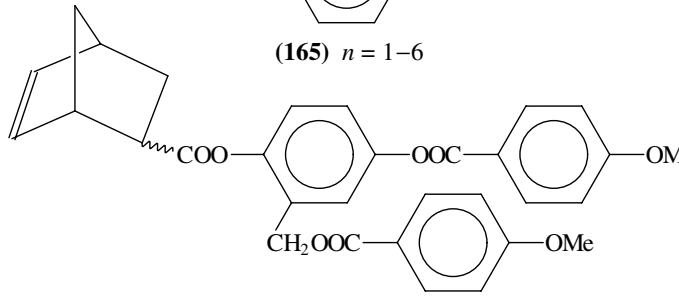


(162) X = NO_2, n = 11
(163) X = OMe, n = 2–12
(164) X = CN, n = 3–12



(165) n = 1–6



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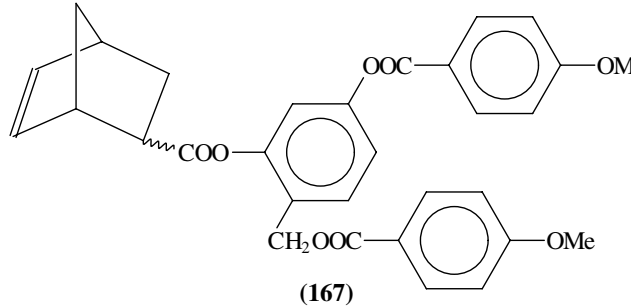
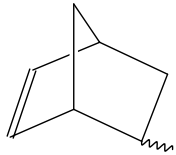


(167)

hexadecyl chains must evidently be able to pack more closely in the monolayer of polymer. The polymers of **161** and **162** do not form well-defined monolayers.

With **163** and **164** not only has the spacer length n been varied, but a series of polymers of narrow MWD ($M_w/M_n = 1.05–1.28$, DP = 5–100) has been prepared in high yield through the use of living systems. The polymers of **163** ($n = 2–8$) exhibit an enantiotropic nematic mesophase. The glass transition and isotropization temperatures increase with increasing MW and reach a limit at about 30–50 repeat units (30 °C and 90 °C respectively for $n = 8$). With longer spacers ($n = 9–12$) some side-chain crystallization is observed in the lower-molecular-weight materials (DP = 10–20), along with a nematic or smectic mesophase, but this is suppressed at higher MW (DP = 50–100). The polymer of **164** ($n = 3$) is amorphous whereas with longer spacers ($n = 4–12$) the polymers display enantiotropic nematic mesophases that are independent of MW, and no side-chain crystallization is observed. Similar results have been obtained with the polymers of **165–167**. The phase behaviour becomes independent of MW at about 25 repeat units and the transition temperatures decrease with increasing n in the polymers of **165**. The polymer backbone in fact has little effect on the transition temperatures of laterally attached side-chain liquid-crystalline polymers displaying nematic mesophases, even when the chemical structures of the backbones are substantially different, as with polynorbornenes vs polyacrylates. This result is consistent with the proposal that mesogens jacket the extended polymer chain[472]. Monomers containing a long 5-substituent and bearing a methacrylate end-group have also been prepared and polymerized to give products with potential electro-optic applications[474].

The third group in this category is exemplified by the macromonomer **168** which can be made by first initiating the anionic polymerization of styrene with *s*-BuLi, end-capping with ethylene oxide and then reacting with norborn-2-ene-5-carbonyl chloride[475]. It can then be copolymerized with norbornene using WCl_6/Me_4Sn as catalyst to give poly(norbornene-*graft*-styrene) copolymers. The ROMP of the macromonomer itself ($M_n = 2700–11{,}000$) proceeds to high conversion only when initiated by a molybdenum carbene complex, yielding comb-like polymers of high MW. The solution behaviour of these polymacromonomers is very dependent on both the MW of the monomer, which governs the length of the polystyrene side-chains, and that of the final polymer[476].



(168) $COOCH_2CH_2[CH(C_6H_5)CH_2]_nCHEtMe$

7. Norbornenes with a 5-(OCOR) substituent

Monomers of this kind, with R = Me **(169)**, Pr **(170)**, Ph **(171)**, readily undergo ROMP with all types of catalyst[83,316,317,477–479]. $W(=CHCMe_3)Cl(CH_2CMe_3)(OAr)_2(O\text{-}i\text{-}Pr_2)$ induces complete polymerization of (±)-*endo*-**169** in 10 s at 25 °C[83]. With (−)-*endo*-**169** initiated by **7** (R = Ph) a 30% *cis* polymer is formed which is nearly atactic with respect to both *cis*- and *trans*-centred ring dyads, but when initiated by **8** (R = Ph) the polymer has a much higher *cis* content (87%) and the *cis*-centred dyads are biased towards isotactic, as shown by the inequality, TH > TT, of the olefinic signals in the ^{13}C NMR spectrum[316]. The 87% *cis* polymer has nearly twice the specific rotation of the 30% *cis* polymer. The enantiomers of *endo*-**170** and *endo*-**171** likewise give optically active polymers[317].

8. Norbornenes with 5-substituents containing OH or OR

Norbornenes with the following 5-substituents (X) undergo ROMP: X = $HOCH_2$[480]; X = MeO[481]; X = $MeOCH_2$[315] and a derivative in which the methyl group is replaced by 6-*N*-carbazoylhexyl (the carbazole units in the side chains of the polymer can be oxidatively coupled to form dicarbazyls)[482]; X = *endo*-$MeO(CH_2)_2$, which has been used to make block copolymers offering potential for binding zinc and cadmium compounds through the oxygen donors[483]; X = $MeOC_6H_4C_6H_4O(CH_2)_5$, yielding polymers (M_n = 31–130 × 10^3) that show an isotropic/smectic transition at about 70 °C on cooling[484].

9. Norbornenes with 5-substituents containing CN or halogen

Norbornenes with the following 5-substituents (X) undergo ROMP: X = CN[83,126,477,485–487] (optical discs can be made from the polymer, having a heat distortion temperature of 145 °C)[466,488,489]; X = CF_3 **(171a)** giving polymer with M_w/M_n = 1.09[490]; X = $BrCF_2CF_2$[485]; X = perfluoroalkyl[491]; X = Cl[465]; X = $ClCH_2$[465,492].

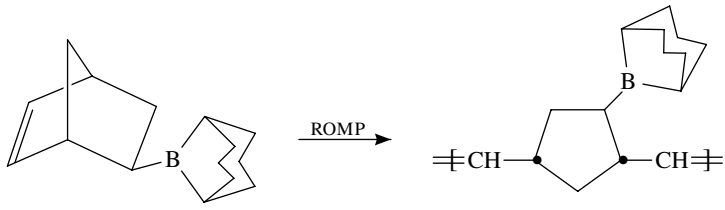
In ROMP it is sometimes found that the GPC of the product shows two peaks: a main peak and a much smaller peak at twice the MW of the main peak; for example, in the ROMP of *exo*-dicyclopentadiene[432]. The reason for this was first elucidated in the living polymerization of *endo/exo*-**171a** initiated by **7** (R = Me). If, after the monomer has polymerized, a trace of oxygen is present there is premature termination of some of the living ends to form an aldeyde end-group, which in turn terminates a second chain, to which it becomes attached. If benzaldehyde is then added, the main portion of the living ends react to give a benzylidene end-group. The GPC of the product shows the aforementioned two peaks if an RI detector is used, but only the main peak if a UV detector, set to detect absorption by the aromatic ring, is used[493].

10. Other 5-substituted norbornenes

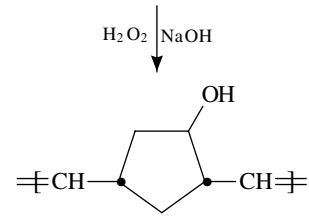
A series of glycomonomers represented as NBE-*exo*-5-CONH(glu)R_4 has been prepared by the reaction of norborn-2-ene-*exo*-5-carbonyl chloride with glucosamine hydrochloride; R = H or a protecting group (COMe, COPh or $SiEt_3$). These monomers all undergo ROMP when initiated by **19** in benzene at 50 °C. The reaction of the unprotected monomer proceeds quantitatively when carried out in aqueous emulsion but the polymer is rather insoluble in all solvents, unlike the polymers of the protected monomers. In principle this range of monomers can be extended to include those attached to biologically relevant carbohydrates via flexible extenders[494].

The monomer **172** can be made by hydroboration of norborna-2,5-diene with 9-borabicyclononane (9-BBN) using excess of diene. It undergoes ROMP to yield a polymer **173** which can be readily oxidized to the hydroxy derivative **174**. **174** is insoluble in water and common organic solvents, but soluble in mixed solvents such as $CDCl_3/CD_3OD$. The *cis* content varies with the catalyst: 93% with **8W** (R = Me), 48% with WCl_6/Me_4Sn and 26% with **7W**. The high-*cis* polymer has a relatively simple spectrum, with two main pairs of equally intense olefinic lines: δ 135.36 (TH), 134.00 (TT), 133.24 (HH), 131.88 (HT), indicating a random orientation of the substituents. The corresponding signals for the *trans*-centred dyads may be seen in the spectra of the polymers obtained with the other two catalysts, but with fine structure caused by *tt/tc* splitting: δ 134.42 (TH), 132.90 (TT), 132.05 (HH), 130.78 (HT)[495].

The hydrophilic (OH) groups in these otherwise hydrophobic polymers allow the formation of stable monolayers at an air/water interface. The high-*cis* polymer occupies 38 $Å^2$/monomer unit which is much larger than the 9 $Å^2$/monomer unit occupied by the



(172) **(173)**



(174)

74% *trans* polymer, suggesting that the *cis* polymer is rather rigid and lies stretched on the water surface with most of its OH groups at the interface. The T_g values for these polymers are in the range 118–140 °C, much higher than those for polymers of norbornene (5 °C)[495,496].

Hydrogenation of polymers of substituted norbornenes is frequently a valuable aid to the determination of structural detail and is best carried out using diimide (NH=NH) generated *in situ* by the decomposition of *p*-toluenesulphonohydrazide in xylene at 120 °C. This procedure works well and selectively even in the presence of groups such as COOMe and PPh_2[497].

11. 5,5-Disubstituted norbornenes

Some systems which have been recently studied are summarized in Table 8. Polymers of the racemic monomers show little sign of HT bias for any value of the *cis* double-bond

TABLE 8. ROMP of some 5,5-disubstituted norbornenes (substituents *exo*-X, *endo*-Y)

X	Y	Catalyst system	Reference
CH_3	CH_3	[W](=$CHCMe_3$)[a]	307
		[W](=$CHCMe_3$)[b]	442
		W(=Z)$(Cl)_2$(OArO)(THF)[c]	498
		W(=Z)$(Cl)_3$(OArO)(OEt_2)[c]	327
$COOCH_3$	CH_3	Various	467
CH_2Cl	CH_2Cl	Various	492
Spiro compounds[d]		W-based	499

[a] W(=$CHCMe_3$)$(Br)_2(OCH_2CMe_3)_2/GaBr_3$; the head propagating species is present in higher concentration than the tail species and is thus the less reactive.
[b] Seven different complexes.
[c] X = O or NC_6H_3-Me_2-2,6; cocatalyst Et_2AlCl. The *cis* content of the polymer varies from 41 to 100% depending on the nature of the chelating diolate ligand.
[d] Norborn-2-ene-5-spiro-3′-*exo*-succinic anhydride, and norborn-2-ene-5-spiro-3′-*exo*-N-phenylsuccinimide and derivatives.

content. Detailed tacticity studies have been made on the 5,5-dimethyl compound (see Section VIIIA.5). The high-*cis* syndiotactic polymer has a higher T_g (106 °C) than the atactic polymer (47 °C)[498].

12. 5,6-Disubstituted norbornenes

Monomers in this category can be divided into three groups: (i) those in which the two substituents are the same: some recently studied systems are listed in Table 9; (ii) those in which the substituents are different; and (iii) those in which the substituents form part of a ring system.

TABLE 9. ROMP of 5,6-disubstituted norbornenes (both substituents the same)

R	Isomers[a]			Catalyst type[b]	Reference
CH_3	*xx*		*nn*	WC	307
	xx	*xn*	*nn*	A,B	323
			nn	WC	113, 114
	xx			WC	442
		(+)*xn*		MoC	313,314
COOMe			*nn*	MoC	500
			nn	MoC	341
			nn	WC	467
	xx	*xn*		MoC	485
	xx	*xn*	*nn*	WC	127
		(+)*xn*		MoC	313
COOEt		*xn*		B	468
$COO(CH_2)_{12}H$	*xx*			B	501
$COOCH_2(CF_2)_6F$	*xx*			B	501
$COOSiMe_3$		*xn*		MoC	502
$COO(CH_2)_nOC_6H_4C_6H_4CN$[c]		*xn*		MoC	503
$COOCHMeCH_2(sty)_nBu$[d]		*xn*		MoC	504
COO(pte)[e]		*xn*		MoC	505
OCOMe	*xx*			MoC	485, 506
			nn	MoC	407
O(CO)OMe	*xx*			MoC	507,508
O(CS)SMe	*xx*			MoC	507,508
CH_2OMe		*xn*		MoC	483
		xn		MoC	502
		(+)*xn*		MoC	313
CH_2SMe		*xn*		MoC	483
CH_2Cl	*xx*[f]		*nn*	A	509
$(CF_2)_nF$ ($n = 4,6,8$)					491
CH_2NHCMe_3		*xn*		MoC	510
$CH_2NHSiMe_3$		*xn*		MoC	510
PPh_3		*xn*		MoC	511

[a] *xx*, *xn*, *nn* denote *exo,exo-*, *exo,endo-*, *endo,endo-* respectively; (+) denotes enantiomer.

[b] A: $TiCl_4$-, $MoCl_5$-, WCl_6- or $ReCl_5$-based, or similar; B: Ru-, Os- or Ir-based; MtC: metal carbene complexes (Mo=C or W=C).

[c] $n = 2$–12; both monomer and polymer show liquid-crystalline phases.

[d] sty = styrene, $n = 4$–9; gives well-defined comb graft copolymers, containing an average of 4, 7 or 9 styrene units in the side chains.

[e] pte = phenothiazin-10-ylethyl.

[f] Monomer assumed to be mainly *xx*.

The metal carbene complex initiators generally give living polymerizations. The carbene proton doublet from the first propagating carbene complex is often resolved (about 0.02 ppm downfield) from that of the longer-chain species, e.g. for R = COOMe. The intermediate *transoid* metallacyclobutane species can sometimes be detected at low temperature, but not the corresponding *cisoid* species. With R = Me (*endo,endo*) the first *transoid* metallacyclobutane complex formed by reaction with **10** + $GaBr_3$ is particularly stable at −38 °C. It can be produced in 70% yield and its rearrangement followed at higher temperatures. Diastereoisomers (precursors of *m* and *r* dyads) in the subsequently formed metallacyclobutanes can also be distinguished[113,114].

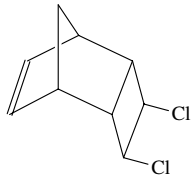
Absolute tacticities have been determined for polymers of *exo,endo*-monomers with R = Me, COOMe and CH_2OMe, using single enantiomers[313]. Depending on the initiator one can obtain a high-*trans* atactic polymer or a high-*cis* isotactic polymer. Polymers of racemic *exo,endo*-monomers and of the prochiral *exo,exo*- and *endo,endo*-monomers sometimes show *m*/*r* splittings in the ^{13}C NMR spectra of both their high-*trans* and high-*cis* polymers and more clearly in the spectra of their fully hydrogenated products[323].

The reactions of the monomers with R = COOMe proceed with measurable speed in CD_2Cl_2 at 25 °C when initiated with a tungsten cyclopentylidene complex. For the *endo,endo*-isomer the initiation and propagation rate constants are about the same: 5.0×10^{-3} M^{-1} s^{-1}[127]. The monomer with R = $COOSiMe_3$ has been used to make amphiphilic star-block copolymers in which the trimethylsilyl esters have been converted to carboxylic acids. The monomer with R = COO(pte) has been used to make block copolymers with norbornene, end-capped by reaction with 1-pyrenecarboxaldehyde. Fluorescence emission from the pyrene end-groups is quenched by electron transfer from the phenothiazine group to the excited singlet state of the pyrene group, to an extent which depends on the structure of the copolymer, in particular on the closeness of the two groups in the chain. The polymer made from the monomer with R = OCOMe (*exo,exo*) is a white powder that can be cast from toluene as a flexible transparent film. On heating at 300 °C the film becomes red-black and insoluble, two equivalents of acetic acid being lost. Similar behaviour is observed with related polymers[407,506].

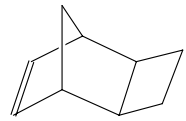
The polymers made from the monomers with R = CH_2OMe or CH_2SMe form chelation complexes with Zn or Cd compounds; likewise for R = PPh_3, with Au or Ag compounds; and polymers can be made from monomers in which R = CH_2NHCMe_3 or $CH_2NHSiMe_3$ are already chelated to Sn or Pb compounds. Such monomers (M_1) can be used in living systems to make diblock copolymers with methyltetracyclododecene or norbornene (M_2) in which the morphology (lamellar, cylindrical or spherical) can be readily revealed by transmission electron microscopy. The metal component in the M_1 blocks can be reacted in various ways without too much effect on the morphology. Thus, Pb and Zn components can be converted to the sulphides by exposure to H_2S, while Ag and Au components can be decomposed to the metal at 150 °C resulting in small clusters of metal atoms which reside largely within the original microdomains (20–100 Å for Ag, 15–40 Å for Au). Further development along these lines can be expected to produce interesting new materials, consisting as they do of conducting or semi-conducting nanoclusters within a non-conducting matrix[510–512].

An example of the second group of monomers is *trans*-5-carbomethoxy-6-ferrocenylnorborn-2-ene. Fluorescence quenching studies have been made on its polymers[505,513].

Recent examples of the third group of monomers include compounds **175**[514], **176**[409,515], **177**, **178**[409], **179**[515], **180**[409], **181**[516], **182**[517], **183**[517], **184**[518], **185**[519], **186**[520,521], **187**[522–525], **188**[526], **189**[517], **190**[125,501], **191**[485], **192**[526], **193**[527], **194**[528], **195**[485,529,530], **196**[530], **197**[485,531], **198**[532]. The dicyclopentadienes are discussed in Section VIII.C.16.



(175)



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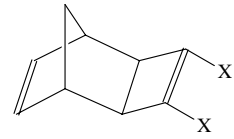
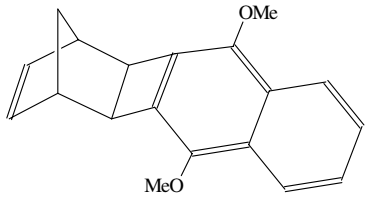
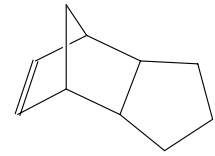


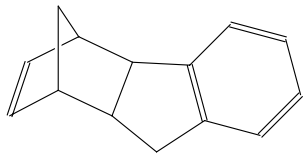
(177) X = CF_3
(178) X = CO_2Me
(179) X = CN



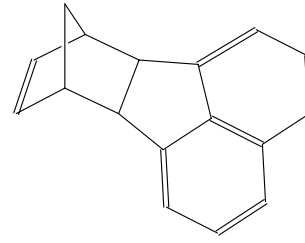
(180)



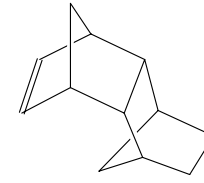
(181) (*endo* and *exo*)



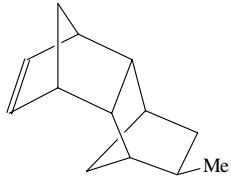
(182)



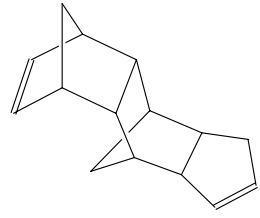
(183)



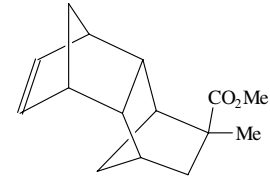
(184)



(185) (main isomer)



(186)

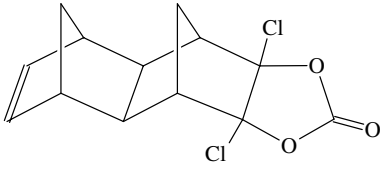


(187)

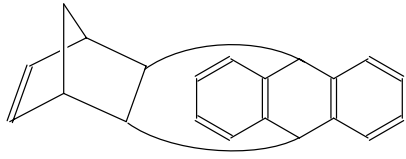
The ROMPs of **177** and **178** proceed through the opening of the norbornene ring and not the sterically hindered cyclobutene ring. The same is probably true of **179** which gives an insoluble polymer; also of **180**.

In much of the early work the monomers used were mixtures of isomers. For example, *endo,anti*-**175** as prepared contains minor amounts of the *exo,syn*-isomer, a smaller amount of the *endo,syn*-isomer, but no *exo,anti*-isomer. Again, **185** is the main isomer (66%) in a mixture with seven others of which only one is present in a significant amount (33%). In general the *endo*-isomers are less reactive than the *exo*-isomers, no doubt because of the greater degree of steric hindrance when the *endo*-isomer approaches the propagating complex. However, *endo*-isomers that are unreactive with A- or B-type catalysts, as defined in Table 9, have sometimes been found to react slowly when placed in contact with a metal carbene initiator. For example, when 3.2 equiv of *exo*-**190**, containing some

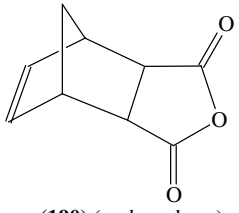
of the *endo*-isomer, are mixed with $W[=\overline{C(CH_2)_3CH_2}](OCH_2CMe_3)_2Br_2$ in CD_2Cl_2 at 25 °C, the *exo*-monomer reacts first to give the propagating species P_1 which then adds further *exo*-monomer to give P_n ($n > 1$). P_1 and P_n ($n > 1$) are distinguished by their $(OCH_2CMe_3)_2$ NMR signals at δ 4.44, 4.39 and 4.46, 4.41 respectively, the two neopentoxy ligands being non-equivalent in each case. The concentration of P_1 passes through a maximum after about 10 min and then declines as it is replaced by P_n. The ratio of concentrations of P_1 and initiator at this maximum gives the ratio of initiation to propagation rate constants, k_i/k_p, as 3.8. Once the initiator has all been consumed, the concentration of propagating species is constant and the remaining monomer disappears with a half-life of 74 min, corresponding to $k_p = 3.15 \times 10^{-3}$ M^{-1} s^{-1}. The carbene proton signals for P_1 and P_n are not resolved; both give a doublet at δ 11.245. Towards the end of the reaction, when the *exo*-monomer peaks have practically disappeared, a second carbene proton doublet appears in very low intensity at δ 11.59 and other weak peaks appear in the upfield part of the spectrum. On addition of pure *endo*-isomer to the reaction mixture, in amount similar to that of the original *exo*-isomer, the weak doublet at δ 11.59 grows at the expense of the *exo*-P_n doublet at δ 11.245, until after 3 h it represents 70% of the tungsten carbene proton signal. The fall in concentration of the *endo*-monomer is also several times that of the new carbene proton species, indicating that more than one molecule of



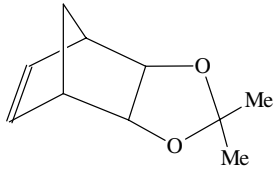
(188)



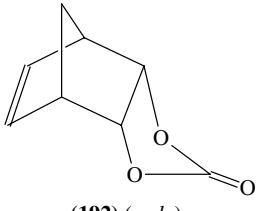
(189)



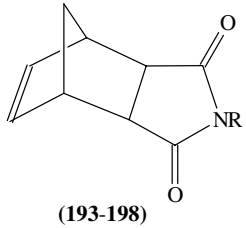
(190) (*endo* and *exo*)



(191) (*exo*)



(192) (*endo*)



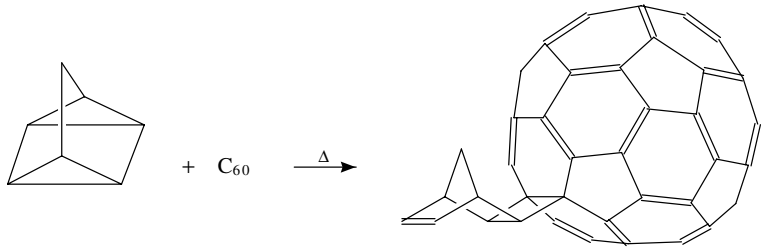
(193-198)
(*endo* and *exo*)

(193) R = H, **(194)** R = Me, **(195)** R = Ph,
(196) R = C_6H_4X (*o*, *m*, *p*; X = F, Cl, Br, I),
(197) R = C_6F_5, **(198)** R = *CHMeCO$_2$Me
(optically active and racemic monomers)

endo-monomer has added to the chain[125]. Likewise *endo*-**190** cannot be homopolymerized by the relatively short-lived WCl_6/Me_4Sn catalyst but can be incorporated into a copolymer with norbornene. Polymers of *exo*-**190** are readily converted to diester or half-ester derivatives by reaction with alcohols. It is also possible to carry out ROMP of *exo*-**190** and esterification in one operation using $RuCl_3$ or $OsCl_3$ at 70 °C as catalyst[501]. The polymer of *exo*-**191** is readily converted to the diol derivative by hydrolysis with aqueous trifluoroacetic acid[485].

The ROMP of *endo*-**195** gives a 15% yield of a low-molecular-weight product. In contrast the ROMP of *exo*-**195** proceeds to high conversion with the formation of high-molecular-weight polymers[529]. The 7-isopropylidene derivative of *exo*-**195** gives a high-*trans* polymer with $RuCl_3$[533]. The T_g values of the polymers of *exo*-**196** vary with the substituent X: from 199 °C (X = *m*-I) to 270 °C (X = *o*-Br)[530,534]. The ROMP of *exo*-**197** catalysed by $MoCl_5/Me_4Sn$ at 60 °C gives a high yield of high-*trans* polymer. *Endo*-**197** fails to homopolymerize but can be copolymerized to some extent with its *exo*-isomer[531].

Potentially the most interesting polymers in the third group are those of **198**, made by reacting **190** with (+)- or (−)-alanine methyl ester, and thus containing a chiral substituent. The chirality and molecular recognition capacity of the resulting polymers might ultimately be useful as a template for controlling the architecture of other polymers formed in their presence. Both *endo*-**198** and *exo*-**198** readily undergo ROMP to give high-*trans*, optically active polymers of narrow MWD[532]. The synthesis of numerous monomers related to **198** has been reported[535].



(56)

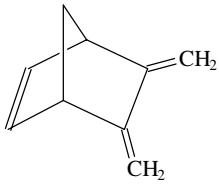
(199) **(200)**

The fullerene monomer **(200)**, made by the cycloaddition of quadricyclane **(199)** to C_{60} (equation 56), can be copolymerized with an excess of norbornene in the presence of **8** (R = Me) to yield a high-molecular-weight, soluble, film-forming copolymer (86% *cis*), containing 1% of C_{60} derivative and exhibiting electronic and electrochemical properties which are typical of the carbon cluster[536].

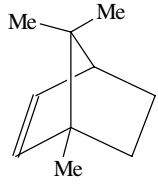
13. Other polysubstituted norbornenes

Various polymerizable polysubstituted norbornenes have been reported, among them **201**[537], **202**[305], **203**[324,538], **204**[350], **205**[539], **206**[485]; also see elsewhere[526,540,541].

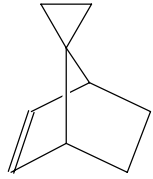
1,7,7-Trimethylnorbornene **(202)** was originally thought to be unpolymerizable[320] but it yields to initiator **8** (R = Ph). In CD_2Cl_2 at 20 °C the head alkylidene adduct P_{1H}, in which the C=C bond is *trans*, is formed after a few hours, reaching a maximum of more than half the original initiator concentration, and then declines very slowly as more monomer adds to P_{1H} to give an all-*trans*, all-HT polymer. The first-order rate constant for the decay of initiator in the presence of excess monomer M shows a complex dependence on [M], tending towards first-order at low [M] and zero-order at high [M].



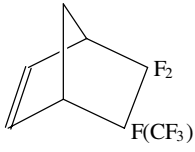
(201)



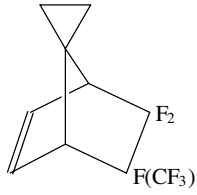
(202)



(203)



(204)



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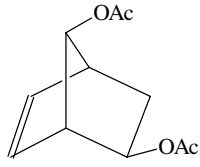


(206)

This is interpreted in terms of a mechanism involving an equilibrium between the *syn* and *anti* rotamers of the initiator, in which the conversion of the dominant *syn* rotamer into the minor *anti* rotamer is rate-determining at high [M], with $k = 6.1 \times 10^{-5}$ s^{-1}, while at low [M] the addition of M to the *anti* rotamer becomes rate-determining[305]. The value of k agrees well with the value determined directly in toluene by photochemical displacement of the equilibrium between the rotamers[121,122]. The tacticity of this polymer is mentioned in Section VIII.A.5.

The spiro compound **203** is more readily polymerizable than *syn*-7-methylnorbornene **(157)**; the cyclopropyl group evidently offers less steric hindrance than the *syn*-methyl group in the propagation reaction. The pattern of the fine structure of the ^{13}C NMR spectrum of the high-*trans* polymers of **203** is similar to that of the high-*trans* polymers of *anti*-7-methylnorbornene **(156)** and *m*/*r* assignments can be made on this basis[324].

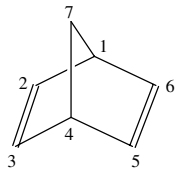
For **205** (55% *exo*-CF_3, 45% *endo*-CF_3) the *exo*-isomer is more reactive so that if polymerization is incomplete, the residual monomer is enriched in the other isomer[539]. Polymers of **206** have a narrow MWD if initiated by **7** in THF. The polymer has a T_g of 110 °C and decomposes at 300 °C losing two molecules of acetic acid per repeat unit. It is also readily hydrolysed to the polydiol, which is soluble in $CF_3COOH/CHCl_3$ and degrades with loss of water at 300 °C[485].

14. Norbornadiene and its monosubstituted derivatives

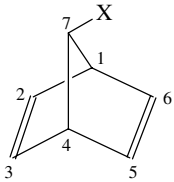
Monomers in this category that undergo ROMP are **207**[103,278,328,542,543], **208**[328], **210**[544], **211**[545], **212**[546] and **213**[547]. For ease of comparison between these monomers and those derived from norbornene we shall adopt the numbering system shown below, with $C^2{=}C^3$ always unsubstituted. This sometimes differs from the IUPAC numbering system.

Where one (or both) of the 5,6-positions are substituted, ROMP invariably occurs only by cleavage of the unsubstituted double bond. For monomers substituted at the 7-position only **(208–210)**, less active catalysts favour cleavage of the less hindered $C^2{=}C^3$ double bond but more active catalysts show little discrimination between $C^2{=}C^3$ and $C^5{=}C^6$.

With norbornadiene **(207)** the first double bond to react can open in one of four ways, as for norbornene, to give either a *cis* or *trans* double bond, located within an *m* or *r* ring

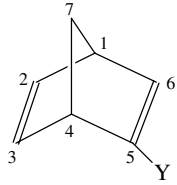


(207)



(208) X = Me
(209) X = Ph
(210) X = $OCMe_3$

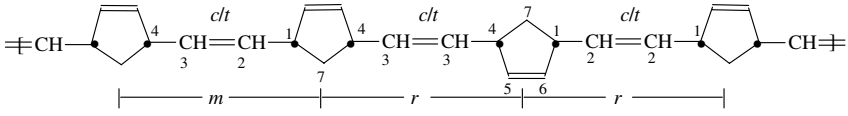
(208–210)



(211) Y = $SiMe_3$
(212) Y = $SiHMe_2$
(213) Y = CF_3

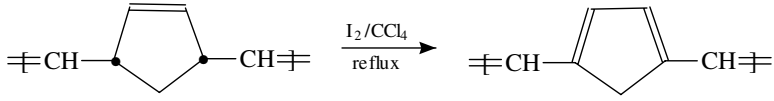
(211–213)

dyad. Polymers have been produced in which the *cis* contents of the double bonds between the rings range from 90% ($OsCl_3$ catalyst) to 37% ($MoCl_5/Bu_4Sn$ catalyst). Provided that $[M]_0 < 0.2$ M and hex-1-ene is used as chain transfer agent (40% of $[M]_0$), the polymers are soluble, allowing well-resolved ^{13}C and ^1H NMR spectra to be obtained which can be fully assigned in terms of the structures represented in **207P**[103,278]. However, if the concentration of $C^5{=}C^6$ bonds in the polymer solution exceeds 0.2 M, this double bond also opens with the formation of a cross-linked polymer; see Section VIII.B.2.



(207P)

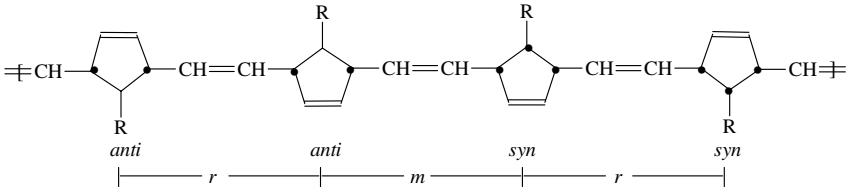
Several other features are worthy of note in the ROMP of norbornadiene. First, $OsCl_3$ gives a polymer with a much higher *cis* content (90%) than for the ROMP of norbornene (40%); and $RuCl_3$ fails to give any polymer at all, yet with norbornene it gives a high-*trans* polymer. These differences are ascribed to the di-*endo* chelation of one molecule of norbornadiene to the metal carbene centre, acting as a spectator ligand. For $OsCl_3$ the resultant crowding of the reaction site favours the approach of the monomer leading to the formation of a *cis* double bond, while for $RuCl_3$ the crowding is such as to prevent reaction altogether. Secondly, like the polymers of norbornene, the high-*cis* polymers of norbornadiene tend to have a blocky *cis/trans* distribution[278]. Thirdly, the polymer may be dehydrogenated to give a black lustrous rigid solid which is strongly paramagnetic ($g = 2.0027$) and may be presumed to contain some units of the type shown in equation 57[543].



(57)

Like **207**, the 7-substituted norbornadienes **208–210** give high-*cis* polymers with $OsCl_3$, containing 7%, 11% and 30% *syn* units respectively[328,544,548]. With **8** as initiator both **208** and **210** give high-*cis* polymers containing approximately 50% *syn* units[549]. Some of the possible dyad sequences are illustrated in **214**. The higher proportion of *syn* units when the substituent is *t*-butoxy suggests that the lone pairs of electrons on the oxygen atom may assist the approach of the monomer to the $C^5{=}C^6$ double bond on the *exo* face. This might happen through simultaneous coordination of the metal centre to the oxygen atom and the *syn* double bond (*syn–exo* chelation)[328].

Polymers of **208** can be made with *cis* contents ranging from 97% ($OsCl_3$ catalyst) to 20% ($MoCl_5/Me_4Sn/Et_2O$ catalyst); a somewhat narrower range (80–33%) is observed for polymers of **209**. The ^{13}C NMR spectra of the polymers of **208**, containing mainly



(214)

anti units, show a similar *c/t* and *m/r* splitting pattern to that observed in the spectra of polymers of **156**. Tacticity assignments have been made by comparing the spectra of the fully hydrogenated polymers of **208** and **209** with those of **156**. $ReCl_5$ gives an 80% *cis* polymer of **208** in which the *cis*-centred dyads are *r* and the *trans*-centred dyads are *m*. Very high syndiotacticity is also observed in the 97% *cis* polymer made with $OsCl_3$ as catalyst. In contrast, the 42% *cis* polymer made with WCl_6/Me_4Sn as catalyst is essentially atactic. $RuCl_3$ is ineffective for **208** and **209**, as for **207**[328].

Monomers **211–213** are all readily polymerized by WCl_6/Me_4Sn to give unbiased, approximately 50% *cis*, polymers[545–547]. A 95% *cis* unbiased polymer of **213** is obtained with **8** (R = Ph) as initiator[490].

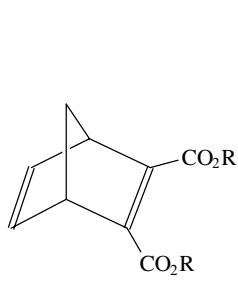
15. Polysubstituted norbornadienes

The 5,6-dicarboxylic chiral esters (**71**, **72**) have already been mentioned in connection with the determination of tacticity; see Section VIIIA.5. Other polysubstituted norbornadienes, not containing fused aromatic rings, which undergo ROMP are **215**[10,126,325,550], **217**[551], **218**[551], **219**[10,325,552–555], **220**[539], **221**[551], **222**[121,550,551] but not **216**[10].

Polymers formed by ROMP of **219** range from all-*trans* (polymer A), made with **7** (R = Me or Ph) as initiator, to all-*cis* made with **8** (R = Ph) or **223** as initiator, (polymers B and C respectively)[10,550]. The ^{13}C NMR spectrum of the all-*trans* polymer A gives single lines for C-2,3 (133.50), C-1,4 (49.80) and C-7 (37.20 ppm). However, while the all-*cis* polymer C gives a single C-7 line at δ 38.38, the all-*cis* polymer B gives three lines: at δ 38.38, 37.61 and 36.44, in order of diminishing intensity. This fine structure can only be due to *m/r* splitting. Polymer C is therefore fully tactic, while polymer B is partially tactic in the same direction (74/26), but one cannot say whether the bias is towards *m* or *r*. Nor can one be sure that polymer A is tactic since no all-*trans* polymers have been made which show fine structure for C-7 (or any other carbon). The fact that the *trans* polymer is semi-crystalline with a melting point at 200 °C, and can be fibred and cold-drawn, lends support to the belief that it is in fact highly tactic[325,554]. The *trans* polymer of **219** also has an unusually high relaxed dielectric constant which accords with a predominantly syndiotactic structure, but the relatively low value for the *cis* polymer can be interpreted in terms of either a syndiotactic structure[557] or an isotactic structure[313].

A marked temperature dependence of the *cis* content of the polymer formed from **219** using **224** as initiator in THF (100% at −35 °C, 24% at 60 °C) has been interpreted in terms of an equilibrium between *syn* and *anti* rotamers, with *cis* C=C formed mainly by addition to the THF-free *syn* rotamer, and *trans* C=C formed mainly by addition to the THF-free *anti* rotamer[556]; cf Section III.B.5.

The reaction of **219** with **7** (R = Me) proceeds mainly *via* the less abundant but much more reactive *anti* rotamer of the initiating and propagating species. The first four propagating species may be distiguished in the ^1H NMR spectrum; for the longer chains the *anti* and *syn* rotamers are just resolved, in the ratio of 1:6. The corresponding ^{13}C



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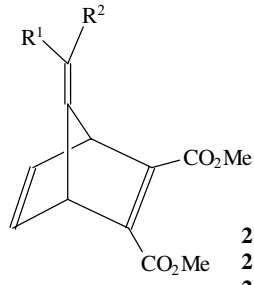
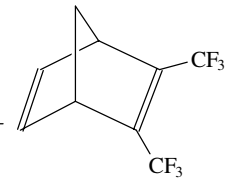


(216–218)

	R^1	R^2
216	Me	Me
217	Me	Ph
218	Ph	Ph



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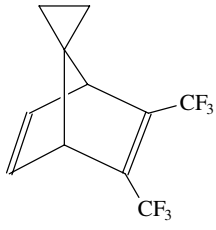

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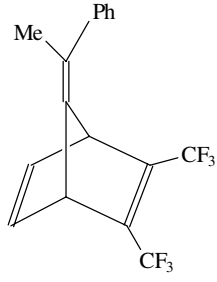

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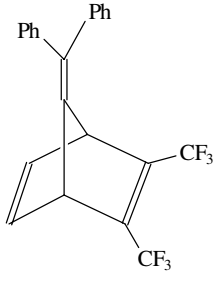

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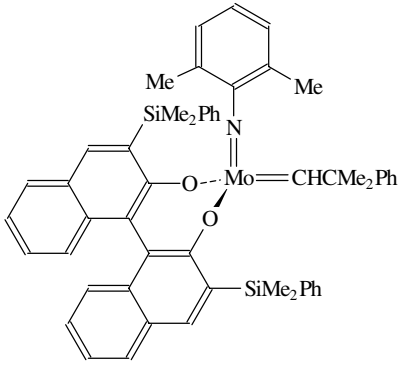
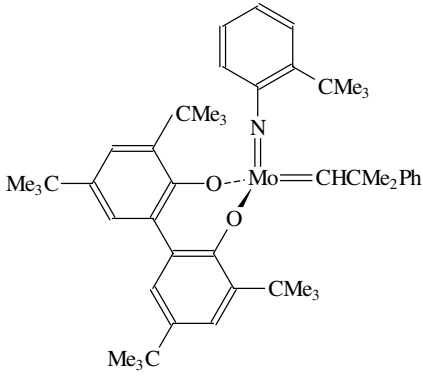


(223) (racemic)



(224)

NMR signals are also resolved: δ 253.1 and 252.6. In benzene at 22 °C, $k_p/k_i = 0.72$ and $k_p = 0.057\ M^{-1}\ s^{-1}$. The reactivity of **219** is some 30 times less than that of **215** (R = Me). This may be ascribed mainly to a lower electron density at the unsubstituted double bond in **219**[10,96].

The ROMP of **219** initiated by a mixture of **7** (R = Ph) and **8** (R = Ph) in trifluorotoluene might have been expected to give a mixture of all-*trans* and all-*cis* polymer. Instead the *cis* and *trans* double bonds are distributed throughout the chains, as shown by the C-7 fine structure[557]. This is because the alkoxy ligands in **7** and **8** undergo rapid exchange to form an equilibrium mixture with the complex containing one of each type of alkoxy ligand, the rates of exchange of alkoxy ligands being much faster than the rates

of addition of monomer. A polymer of any desired *cis* content can thus be prepared from **219** by mixing with appropriate proportions of the two initiators[555].

The ROMP of **215** (R = Me) initiated by **7** (R = Me) in C_6D_6 gives a mainly *trans* (*ca* 95%) polymer, with $M_w/M_n = 1.06$. The initiator is fairly quickly consumed when there is an excess of monomer ($k_p/k_i = 3$)[10,325,490].

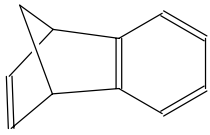
The all-*cis* polymers in the series **215** (R = Me, Et, *i*-Pr, *t*-Bu), initiated by **8** (R = Ph) in toluene, have an isotactic bias (78, 84, 81, 97% *m* dyads, respectively), as judged by the C-7 fine structure, assuming that the line order is the same in each case[556]. A remarkable observation has been made for the system **72/223**. The GPC of the polymer ($M_n = 28,200$) shows two sharp peaks each of which has M_w/M_n *ca* 1.06, and taken together, 1.13. This has been attributed to the fact that the initiator is a 1:1 mixture of non-interconvertible enantiomers and that highly regular all-*cis* isotactic chains grow separately from each enantiomeric metal site. The chirality at the metal site, interacting with the chiral monomer, controls the rate of propagation, while the chirality of the chain 'end', i.e. the previously added monomer unit, independently controls the stereochemistry of the next monomer addition. This effect is not observed with **71** as monomer, where the rates of propagation at the two types of site are presumably not sufficiently different[313].

The ROMP of the dicyano analogue of **219**, also the tricyclic monomer having $[CH_2C(CN)_2C(CN)_2CH_2]$ attached to the 5,6-positions, can be initiated by **7** (R = Me), the latter giving a 97% *trans* polymer[515].

The ROMP of **220** proceeds readily in the presence of WCl_6/Ph_4Sn at 70 °C to give an 80% *trans* polymer[539]. The ROMP of the bicyclofulvene derivatives **217**, **218**, **221** and **222** is catalysed by $MoCl_5/Ph_4Sn$ at 70 °C to give high-molecular-weight products[551]. Surprisingly **216** is not polymerized by **7** (R = Me) although it adds one molecule slowly at 25 °C to give the molybdenum carbene adduct. Although the adduct will not add **216** it will add norbornene ($k_p/k_i = 270$). Both ^1H and ^{13}C NMR spectra indicate that only one rotamer is present in the solution of the adduct. An X-ray study shows that in the crystal the molecule is in the form of the *syn* rotamer and this is presumably also the dominant form in solution. The rate of reaction of **7** (R = Me) with **216** ($k = 1.3 \times 10^{-3}$ M^{-1} s^{-1} at 22 °C) is some 500 times smaller than its rate of reaction with **215** as is to be expected for reaction at the *exo* face[10].

The norbornadiene derivatives that have fused aromatic rings **(225–234)** all undergo ROMP readily at 20 °C in chlorobenzene by opening of the unsubstituted double bond of the norbornadiene ring system: **225**[10,432,548,558], **226**[432], **227–228**[559], **232–234**[560], **229–231**[306,508]. This was first demonstrated for **225** using WCl_6/Ph_4Sn (1/2) as catalyst and later for **227**, **228**, **232–234** using WCl_6/Me_4Sn. The *cis* contents are mostly 40–50% and are somewhat lower with $MoCl_5/Me_4Sn$ as catalyst, becoming as low as 4% for **234**. The polymer of **228** is insoluble and has not been characterized. The complex **7** (R = Me) effects smooth and rapid ROMP of 100 equiv of **225** in toluene ($k_p/k_i = 7$) to give a 24% *cis* polymer with $M_w/M_n = 1.05$[10]. With $Cp_2\overline{TiCH_2CMe_2CH_2}$ as initiator for the ROMP of **225** and **226** in toluene the polymer comes out of solution after the addition of only 9 units of monomer[432].

The most remarkable results for this group of monomers are those obtained with the fulvene derivatives **229–231**. Their ROMP is initiated by both **7** (R = Me) and **8** (R = Me) in toluene at 20 °C, the latter giving the faster reaction. For each initiator the rate decreases in going from **229** to **230** to **231** i.e. as the bulk of the substituents becomes larger. Surprisingly the *cis* content of each polymer is independent of the catalyst: 20% for **229**, 0% for **230** and 100% for **231**. The NMR spectra of the polymers of **230** are in keeping with an all-HT structure[306].



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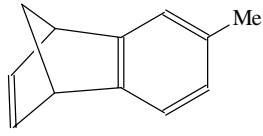

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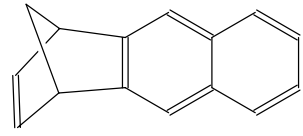

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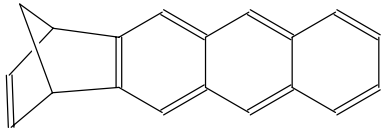

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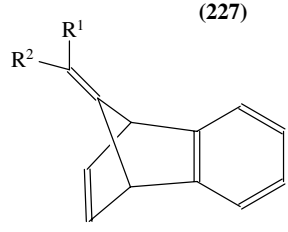
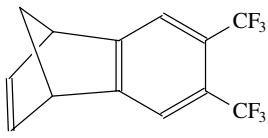


(229) $R^1 = R^2 = Me$
(230) $R^1 = Me$, $R^2 = Ph$
(231) $R^1 = R^2 = Ph$



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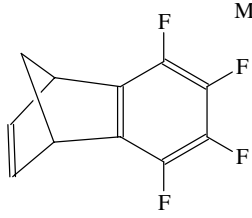

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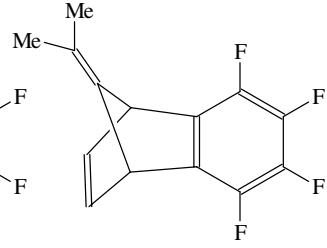


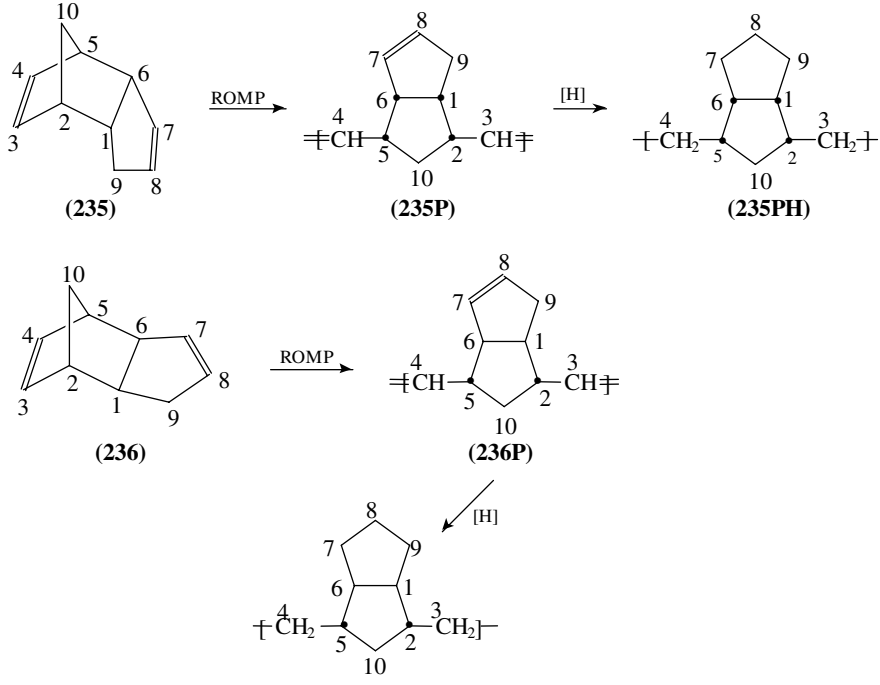
(234)

All the above polymers containing fused aromatic rings are susceptible to photoxidation but remain stable at low temperature in the absence of air and light. They can also be dehydrogenated to yield conjugated polymers.

16. Dicyclopentadienes

The ROMP of the common *endo* isomer **235** was first reported in the late sixties. Since then numerous other catalysts have been shown to be effective. More recently reported catalysts include titanacyclobutane complexes[432,434,561], $IrCl_3$ and $RuCl_3$[516], $ReCl_5$[516,562], various $WCl_n(OR)_{6-n}$ compounds[55,563–566], the robust complex $Mo(=NC_6H_3\text{-}i\text{-}Pr_2\text{-}2,6)(=NCMe_3)(CH_2CMe_3)_2$ in conjunction with a phenolic activator[567], and various polymetallates[54]. Since the eighties the ROMP of **235** has been developed into a commercial process for the production of quite large objects (300 kg) by reaction injection moulding. The *exo*-isomer **236** also readily undergoes ROMP.

In many cases the polymer formed is only partially soluble in organic solvents, but sometimes it is fully soluble, particularly if $[M]_0$ is not too high, or if a chain transfer agent has been used to restrict the MW. Insolubility of the polymer indicates a certain degree of cross-linking and the question arises as to how this comes about, in particular whether the double bonds in the rings of **235P** and **236P** can also open by metathesis. The opening of these double bonds, situated in a disubstituted cyclopentene ring, is thermodynamically much less favourable than the opening of the double bond in the norbornene ring system. However, there is good evidence that there is a critical concentration above which these



(235) **(235P)** **(235PH)**

(236) **(236P)**

(236PH)

double bonds do in fact undergo the metathesis reaction thereby giving rise to cross-links. The best documented case is that of the ROMP of **236** initiated by various tungsten or molybdenum carbene complexes, I. For $[I]_0 = 0.005$ M in toluene at 70 °C and $[M]_0$ up to 1.0 M the polymer is completely soluble and the polymerization living ($M_w/M_n = 1.14$); but with neat monomer (7 M) the product consists of about 50% insoluble polymer, 25% soluble polymer and 25% unreacted monomer. If the soluble polymer is isolated, dissolved in fresh initiator solution and gradually concentrated by evaporation, up to 35% insoluble material is obtained. On the other hand, if the insoluble polymer is treated with fresh initiator solution for 36 h, 70% goes into solution and this soluble product is identical with the original soluble fraction[561]. The opening and closing of the second double bond is thus reversible and the behaviour is parallel to that observed for the polymer of norbornadiene; see Section VIII.B.2. For the ROMP of **235** catalysed by $ReCl_5/Me_4Sn$ in CCl_4 at 50 °C the critical concentration for the opening of the second double bond appears to be close to that of the neat monomer as judged by the change of viscosity as the reaction proceeds; but at 60 °C the critical concentration appears to be not much greater than 0.3 M[562]. Cross-linking may also occur by cationic reactions through the second double bond, especially for those catalyst systems known to generate acidic species. Such cross-linking would not be subject to a critical concentration effect and would not be reversible.

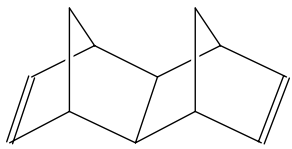
The aforesaid $ReCl_5/Me_4Sn$-catalysed ROMP of **235** (3 M in CCl_4) is notable in that within a few minutes the main part of the monomer is transformed into oligomers (presumably cyclic), while the formation of high polymer begins slowly and reaches an

asymptotic value corresponding to 50% conversion of monomer after 4 h. The concentration of oligomers passes through a maximum and reaches an ultimate equilibrium value corresponding to 30% of the original monomer[562].

With a titanacyclobutane complex as initiator the rate of polymerization is independent of [M] and therefore governed by the rate of opening of the titanacyclobutane chain carrier[432]. The comparative stability of the metallacyclobutane bearing an *endo* substituent is a feature which is also found in the ROMP of other substituted norbornenes; see Section VIII.C.12. In contrast, the rate of ROMP of **235** induced by $ReCl_5/Me_4Sn$ (1/1.5) is first-order in both catalyst and monomer and here the addition of monomer to the metal carbene complex must be rate-determining[562].

The *cis* content of the $C^3{=}C^4$ bonds in **235P** can be varied from 19% using $IrCl_3$ as catalyst to 100% using $RuCl_3$ or $ReCl_5$ as catalyst. The high *cis* content with $RuCl_3$ is attributed to the ability of the monomer to provide a chelated spectator ligand in which both double bonds are coordinated to the metal centre, favouring the approach of the reacting monomer molecule which leads first to the formation of a *cisoid* metallacyclobutane complex and then to a *cis* double bond. This effect is not found with the *exo*-isomer because the two double bonds cannot coordinate simultaneously to the metal centre. In this case $RuCl_3$ gives a 10% *cis* polymer **236P** while $ReCl_5$ still gives a 100% *cis* polymer. The ^{13}C NMR spectra of **235P**, **236P** and their fully hydrogenated products **235PH** and **236PH** show that the repeating units are randomly oriented in the chains. Tacticity splittings (*m*/*r*) are observed for C-3 and C-4 in high-*trans* **235P**, for C-2,5 in **235PH** and for C-2,5, C-3,4 and C-10 in **236PH**. Most of the polymers appear to be atactic except for those made with $ReCl_5$[516].

Compounds of the type **237** and **238**, having two double bonds of equal reactivity, have been used to assist cross-linking during the ROMP of **235**[568]. Star-block copolymers can also be made through the controlled use of **238**[126]. For other polycyclic compounds containing two double bonds (but only one reactive) see elsewhere[520,521].



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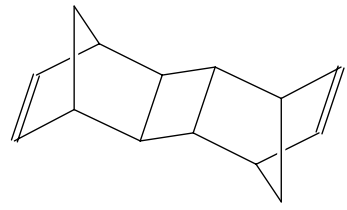
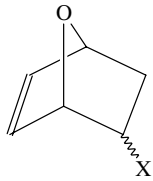


(238)

17. Bicyclo[2.2.1] compounds containing heteroatoms in the ring system

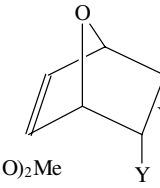
7-Oxanorbornene and its derivatives, **239–266**, have been intensively studied over the past few years, the polymers being potential complexing agents for metal ions. All are capable of ROMP if the catalyst is properly chosen: **239**[319]; **240**, **259**, **260**,[318]; **241**[318,569]; **242**[318,319]; **243**, **255**[501]; **244**[570]; **245**, **246**, **263**[115]; **247**[571,572]; **248**[279,318,319,570–577]; **249**, **250**, **257**, **261**, **262**[572]; **251**[578]; **252**[449]; **253**[62,449,578–582]; **254**[449]; **256**[583]; **258**[572,576]; **264**[572,576,584,585]; **265**[584]; and **266**[586,587].

Most of the work has been done with $RuCl_3$, $OsCl_3$ or $IrCl_3$ as catalysts at 50–80 °C in water, aqueous emulsion, an aromatic solvent, or mixtures of an alcohol and water. Tungsten or molybdenum carbene complexes in toluene are effective at 20 °C with monomers that do not contain hydroxyl groups. Thus **8W** (R = Me) gives polymers of very high



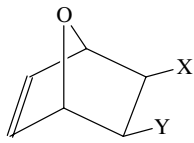
(239) X = H
(240) X = Me
(241) X = CH_2OH
(242) X = *endo*-CH_2OMe
(243) X = *exo*-$COO(CH_2CH_2O)_2Me$

(239–243)



(244) Y = CH_2OMe
(245) Y = OCOMe
(246) Y = $OC(=CH_2)Me$

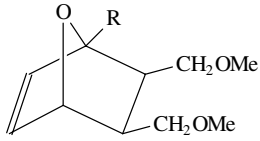
(244–246)



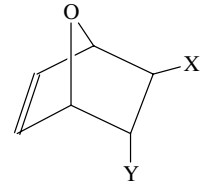
(247) X = Y = CH_2OH
(248) X = Y = CH_2OMe
(249) X = Y = CH_2OCOMe
(250) X = Y = CH_2OSiMe_3
(251) X = Y = COOH
(252) X = Y = COOMe

(253) X = Y = $COOCH_2Ph$
(254) X = Y = $COO(CH_2)_6H$
(255) X = Y = $COO(CH_2)_{16}H$
(256) X = Y = OCH_2OMe
(257) X = CH_2OH, Y = CH_2OMe
(258) X = COOMe, Y = COOH

(247–258)

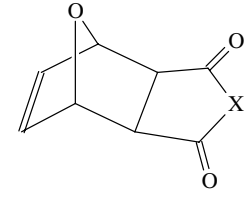


(259) R = Me
(260) R = Et



(261) X = Y = CH_2OMe
(262) X = Y = CH_2OCOMe
(263) X = Y = CN

(261–263)



(264) X = O
(265) X = NH
(266) X = NMe

(264–266)

cis content with **239**, **242** and **248**, while **7** (R = Me) gives a living polymer (60% *cis*) of **245**. However, **7** (R = Ph) with **263** gives only a 2:1 mixture of the two initial *transoid* metallacyclobutane square-pyramidal complexes (in which the cyano group nearest to the metal is in either the *endo* or *exo* position). The more powerful initiator $Mo(=CHCMe_2Ph)(=NAr)(OCMe_2CF_3)_2$ brings about the formation of a living polymer of **263**, having $T_g = 193\,^{\circ}C$ and decomposing above 240 °C.

The high-*cis* polymer of **242** (see above), when made from enantiomeric monomer, has a mainly HH, TT structure and is therefore largely syndiotactic. On the other hand, the 96% *trans* polymer made from enantiomeric monomer with $[RuCl(\mu\text{-}Cl)(\eta^3{:}\eta^3\text{-}C_{10}H_{16})]_2$ as catalyst ($C_{10}H_{16}$ = 2,7-dimethyloctadienediyl) has an HT structure and is therefore essentially isotactic. These tacticities are as predicted from the pseudo-octahedral model if the ligands are not labile and one site is available for coordination of monomer[319]; see Section VIII.A.5.

With $RuCl_3$ as catalyst the *cis* content of the polymer is often markedly dependent on the solvent, for example with **248**[318], **252**[581] and **261**[572]. Another feature of catalysis by $RuCl_3$ is that polymerization is generally preceded by an induction period (IP) during which the concentration of propagating ruthenium carbene species is building up to a stationary state. The length of the IP is very dependent on the solvent. Thus with **247** in chlorobenzene/ethanol at 55 °C it is 2–3 days, but in water it is only about 30 min; and if the same solution is used to initiate the ROMP of further batches of monomer the IP drops to 10 s. There is good evidence that initiation proceeds through an Ru(II) π-complex with the monomer[89,571].

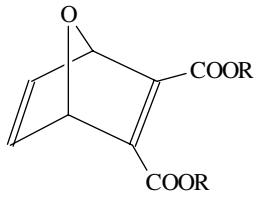
Derivatives of acyclic olefins can be used as chain transfer agents in these polymerizations. The most effective are those with a terminal double bond. For example, in the ROMP of **248** catalysed by $[Ru(H_2O)_6](OTs)_2$ the transfer constant (k_{tr}/k_p) for $CH_2{=}CHCH_2CH_2OH$ is 0.21. The size of the polymer particles produced by emulsion polymerization of **248**, using $RuCl_3$ with a non-ionic surfactant, is of the order of 0.03 μm[577].

In many cases side reactions are liable to occur during the ROMP of these monomers, for example esterification and *trans*-esterification when the ROMP of carboxylic acids, anhydrides or esters are carried out in solvents containing alcohols; or hydrolysis when carried out in water[572,576,579]. Retro-Diels-Alder reactions can also be a problem. Thus, although **266** is cleanly polymerized to high conversion by $[Ru(H_2O)_6](OTs)_2$ under mild conditions (55 °C), its *endo*-isomer fails to polymerize because the retro-Diels-Alder reaction produces *N*-methylmaleimide which complexes with the catalyst and puts it out of action. The *exo*-*N*-phenyl analogue is likewise unable to polymerize[587].

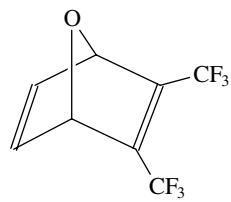
Much interest centres on whether these polyfuran derivatives can behave like crown ethers. The polymer of **248** does in fact coordinate alkali metal ions. The flexible binding cavities formed by this polymer also allow it to complex preferentially with large polyaromatic cationic dyes such as methylene blue and rhodamine 6G[318]. Analogues of **248**, in which the methyl groups are replaced by $(CH_2)_mCH_3$ ($m = 9$, 13, 15, 17, 19, 21), also undergo ROMP when heated with $RuCl_3$ in ethanol. For $m = 15$ the polymer has much the same value of $[\eta]$ in toluene as in THF indicating similar hydrodynamic behaviour of the polymer molecules in the two solvents, and therefore most probably a coil rather than helical conformation, contrary to previous suggestions[588].

The synthesis of an agglutination inhibitor by aqueous ROMP has been successfully accomplished. Cell-surface oligosaccharides have been implicated as key participants in many intercellular recognition events, and the ROMP of suitable monomers with carbohydrate substituents offers a means of obtaining polymers of potential recognition capacity. A diester of **251** has been prepared in which the ester groups are $COO(CH_2)_2$(glu), where (glu) is an α-glucose substituent attached *via* a C–glycoside linkage. The polymer, made using $RuCl_3$ in water as catalyst, is soluble in water and is 2000 times as effective as the monomer in inhibiting erythrocyte agglutination by concanavalin A (Con A, a carbohydrate-binding protein). The application of ROMP to the synthesis of these polyglycomers offers new opportunities for the design of materials for modulation of cell adhesion, immobilization of particular cell types and study of multivalency in extracellular interactions[589].

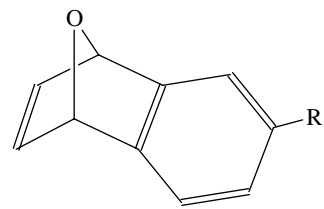
The ROMP of the 7-oxanorbornadiene derivatives **267–272** has been reported: **267**[115,584,590–592]; **268**, **269**[591]; **270**, **271**[115,449]; **272**[449].



(267) R = Me
(268) R = Et
(269) R = Pr

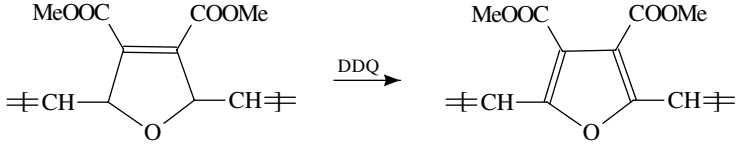


(270)



(271) R = H
(272) R = Me

$RuCl_3$ in PhCl/EtOH at 100 °C gives a 93% *trans* polymer of **267**, while $MoCl_5/Me_4Sn/Et_2O$ gives a 90% *cis* polymer. Only the unsubstituted double bond is broken, not the 1,4-epoxide ring. The high-*trans* polymer **267P** is readily dehydrogenated by refluxing in benzene with a stoichiometric amount of dichlorodicyanobenzoquinone (DDQ) to afford the soluble, purple-red (λ_{max} = 460 nm), conjugated polyene **273**, having an estimated conjugation length of 10 double bonds (equation 58). This material is moderately paramagnetic and gives a symmetrical ESR signal with $g = 2.0027$. The high-*cis* polymer is less readily dehydrogenated and gives a red product solution, but UV-irradiation of this solution causes the colour to change quickly to purple-red as a result of *cis* → *trans* isomerization. These polymers are readily hydrolysed to the corresponding polymers of the disodium carboxylate, the UV/vis spectra of which are dependent on the *cis* content, pH, state (solution or film) and sample history. This is to be attributed to the dependence of the conjugation length on these variables[592]. The dehydrogenation reaction succeeds only for polymers in which the enchained 5-membered rings are already unsaturated; it does not work for the analogous polymer of **252**.



(58)

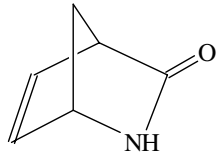
(267P) **(273)**

Unlike the ROMP of **252**, that of **267** catalysed by $RuCl_3$ in PhCl proceeds without an induction period. In the series of esters, **267–269**, the rate declines with increasing bulk of the ester group while the *cis* content of the polymer goes up from 15 to 22 to 26%. The presence of the 7-oxa group enhances the reactivity[591].

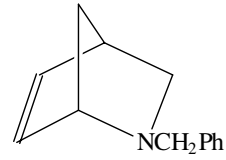
The monomers **267**, **270** and **271** react with **7** (R = Me) to give the relatively stable *transoid* metallacyclobutanes. That derived from **270** is the most stable. X-ray studies show that it is square-pyramidal with the 7-oxa atom 3.33 Å from the Mo centre, too great a distance for bonding. The comparative stability of the metallacycles formed from these monomers is therefore ascribed mainly to inductive effects. The metallacycle formed from **270** opens slowly ($k = 4.2 \times 10^{-5}$ s^{-1} at 35 °C in benzene) to yield two distinct metal carbene complexes, in a constant 9:1 ratio, with carbene proton resonances at δ 11.233 and 11.072, assigned to the *syn* and *anti* rotamers respectively, at equilibrium. For the reaction of **271** initiated by **7** (R = Me), the molybdenum carbene complex formed by the rapid rearrangement of the initial metallacyclobutane (60% conversion in 1 h at 0 °C) adds further monomer to yield long-chain living polymer ($M_w/M_n = 1.06$). The ROMPs of both **267** and **270** can be better achieved by initiation with the more active $Mo(=CHCMe_2Ph)(=NAr)(OCMe_2CF_3)_2$ in CH_2Cl_2; $k_p/k_i = 2.4$ for **270**[115].

Competition experiments show that **270** reacts more than 50 times faster with **7** (R = Ph) than does its norbornadiene analogue **(219)**. The oxygen in the 7-position enhances the activity presumably by assisting the initial coordination of the monomer to the molybdenum centre, although it is released once the metallacycle has formed. Further competition experiments have shown that **270** also reacts about 30 times faster than norbornene with **7** (R = Me), but that when norbornene does react, the resulting metal carbene adds norbornene much more readily than **270**. When a molecule of **270** does manage to add to the growing chain to form the metallacycle, further addition of monomer is effectively halted[115].

The ROMP of **274** is catalysed by WCl_6/Et_3Al (1/4) in PhCl at 60 °C (34% yield). The ^{13}C NMR spectrum of the polymer in $CDCl_3$ shows only one line for each carbon, which indicates that the polymer is certainly all-HT with one dominant double-bond configuration[593]. The ROMP of **275** using a W-based catalyst at 70 °C gives an 11% yield of soluble polymer, $M_n = 5240$, but if the benzyl group is replaced by methyl it fails to polymerize[499].



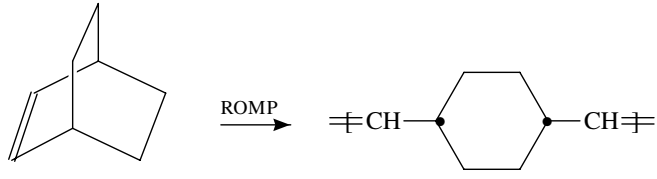
(274)



(275)

18. Miscellaneous

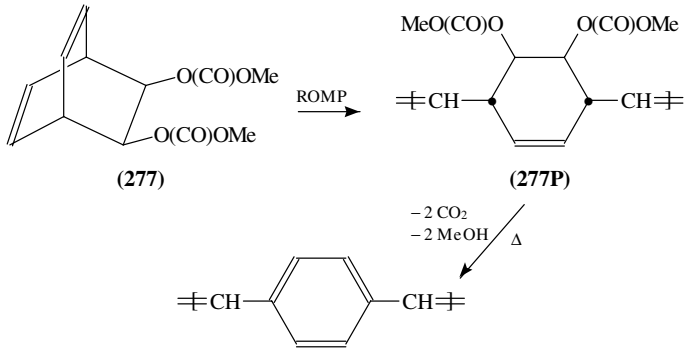
The ROMP of bicyclo[2.2.2]oct-2-ene **276** (equation 59) requires attack on the steric equivalent of the *endo* face of norbornene. ROMP can in fact be brought about in chlorobenzene at 20 °C by $W(CO)_3$(mesitylene)/$EtAlCl_2$/2,3-epoxynorbornane containing a trace of norbornene and Me_4Sn. The ^{13}C NMR spectrum of the polymer is entirely consistent with the ring-opened structure **276P**. The double bonds are 34% *cis* and the *c/t* distribution is somewhat blocky. The main chain bonds attached to the rings must necessarily have a formal *cis* relationship, as in the monomer. For a chair configuration this corresponds to an axial/equatorial relationship. The absence of *a/e* fine structure in the ^{13}C NMR spectrum shows that either there is rapid *ae* ↔ *ea* interconversion or that the rings exist in an intermediate twist-boat conformation[594].



(59)

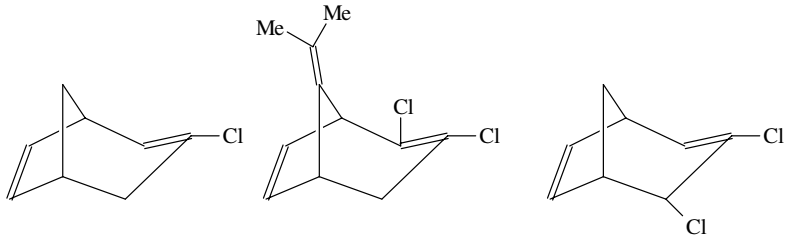
(276) **(276P)**

The ROMP of **277** proceeds readily at 25 °C in CD_2Cl_2 when initiated by Mo(=CHCMe$_2$Ph)(=NC$_6$H$_3$-*i*-Pr$_2$-2,6)(OCMe$_2$CF$_3$)$_2$, giving a living polymer which can be terminated by capping with benzaldehyde (equation 60). The carbene proton of the propagating species exhibits a doublet at δ 12.69. The reaction proceeds much more slowly in THF. In both solvents propagation is somewhat faster than initiation. Approximately equal proportions of *cis* and *trans* bonds occur between the rings in **277P**. Reaction is presumed to occur on the face of the monomer that does not bear substituents, but whether the opening of one double bond is preferred over the other is not clear. On heating a film of **277P** to 280 °C under a flow of argon it loses carbon dioxide and methanol to afford a yellow film of poly(1,4-phenylenevinylene) **(278)**. The pyrolysis temperature can be reduced to 80 °C by the addition of catalytic amounts of tri-*n*-octylamine[595].

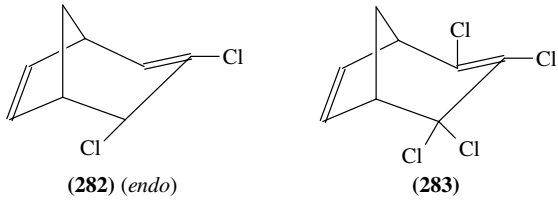


(277) **(277P)** **(278)** (60)

The bicyclo[3.2.1] compounds **279–283** have a structure derived from cyclopentene and contain a second double bond in the three-atom bridge. Only **279–281** undergo ROMP, catalysed by WCl_6/Me_4Sn or $MoCl_5/Me_4Sn$. The failure of **282** and **283** to polymerize is not due to any poisoning of the catalyst since it remains capable of polymerizing norbornene. Rather it is to be attributed to the adverse effect of the *endo* chlorine substituent[514].



(279) **(280)** **(281)** (*exo*)



(282) (*endo*) **(283)**

IX. COPOLYMERIZATION

There are several ways of using the olefin metathesis reaction to generate copolymers. Occasional reference has been made earlier to the formation of copolymers. Here we give further illustrations. For the ADMET copolymerization of linear dienes, see Section VII.C.

A. Direct Metathesis Copolymerization

In the ^{13}C NMR spectrum of a statistical copolymer of monomers M_1 and M_2 four groups of olefinic peaks may be seen, corresponding to M_1M_1 and M_2M_2 dyads, and

the two types of olefinic carbon in an M_1M_2 dyad, designated M_1M_2 and M_2M_1 and necessarily equal in number. Provided that the copolymer is made at low conversion the reactivity ratios r_1 and r_2 can be determined directly from such a spectrum, knowing the feed composition. Experimentally no distinction can be made between M_1M_2 and M_2M_1 dyads formed in the cross-propagation reactions $P_1 + M_2 \rightarrow P_2$ and $P_2 + M_1 \rightarrow P_1$ respectively. Detailed studies have shown that the copolymer composition formed from a given feed, and hence r_1 and r_2 for a given pair of monomers, are markedly dependent not only on the catalyst system but sometimes on the method of mixing. Thus, for cyclopentene (M_1)/norbornene (M_2) with various catalysts, r_1 values vary from 0.07 to 0.62 and r_2 values from 2.6 to 70. The copolymers are often compositionally blocky (e.g. $r_1r_2 = 3$ for WCl_6/Bu_4Sn catalysis), but sometimes the distribution of monomer units is close to ideal (Bernoullian), with $(M_1M_1) : (M_1M_2) : (M_2M_2) = x^2 : 2x(1-x) : (1-x)^2$, where x is the fraction of M_1 units in the copolymer. This is the case for WCl_6/Ph_4Sn catalysis[596]. Statistical copolymers of cyclopentene and norbornene can also be obtained using $Ru(OTs)_2(OH_2)_6$ as catalyst but only homopolymer of M_2 is obtained with **18** as catalyst (Table 2). However, with **19** as catalyst a copolymer is again obtained[597].

There are many factors determining the overall composition of copolymers made in this way and the experimental reactivity ratios can only be regarded as overall average values. To represent the propagating species as P_1 and P_2, according to whether the last unit added was M_1 or M_2, may clearly be an oversimplification. Apart from the fact that any given catalyst system may generate more than one type of initiating species, we have the possibility that each of these may exist in more than one conformation and/or configuration in which the previously formed double bond may or may not be coordinated to the metal site at the moment of reaction with the next monomer molecule. Penultimate unit effects, including the configuration of the previous double bond, may also influence the reactivity, and the reversible nature of the propagation reaction may also sometimes have to be taken into account, particularly for the addition of cyclopentene (M_1) to the propagating species P_1 above 0 °C. Some of these factors have been discussed by Efimov[598,599].

Some apparent reactivity ratios for various pairs of monomers have been summarized[27]. Broadly speaking, reactivities of monomers towards a given propagating species lie in the order: cyclobutene derivatives > norbornene and its 5-substituted derivatives > cyclopentene and larger rings. Thus, for the reaction of 5-norbornen-2-yl acetate (M_1) with cyclooctene (M_2), catalysed by WCl_6/Me_4Sn, $r_1 = 1/r_2 = 132$, whereas for its reaction with norbornene (M_2) or with dicyclopentadiene (M_2), $r_1 \approx r_2 \approx 1$[479,600]. Likewise the reactivity ratios for the copolymerization of norbornadiene and norbornene, catalysed by $OsCl_3$, are close to unity[278], as also are those for the copolymerization of cyclooctatetraene and cycloocta-1,5-diene, catalysed by **8W** (R = Me)[360]. Deltacyclene **(149)** is 2.4 times as reactive as norbornene when catalysed by $RuCl_3$[601]. Alternating copolymers, corresponding to $r_1 = r_2 = 0$, have not been found in ROMP except in the special case of the alternating copolymerization of the enantiomers of 1-methylnorbornene, catalysed by $ReCl_5$ to give an all-*cis*, all-HT polymer; see Section VIII.A.5.

In a living system, if M_1 is much more reactive than M_2 and polymerization is allowed to proceed to completion, the end-product is a tapered block copolymer, in which only the middle section contains units of both monomers, e.g. with *anti*-7-methylnorbornene (M_1)/*syn*-7-methylnorbornene (M_2), see Section VIII.C.4; also with norbornene (M_1)/cyclooctatetraene (M_2), catalysed by **8W** (R = Me)[360]. In the extreme case the cross-propagation reactions may be so slight that the product is indistinguishable from a perfect block copolymer, e.g. with bicyclo[3.2.0]hept-2-ene (M_1)/norbornene (M_2) catalysed by **18**[109,597], or with *anti*-7-methylnorbornene (M_1)/*syn*-7-methylnorbornene (M_2), catalysed by **7** (R = Me)[128]. The successive polymerization of the two monomers can be readily followed by ^1H NMR.

For 5- or 5,6-substituted norbornenes the *exo*-isomer is usually rather more reactive than the *endo*-isomer. An extreme case is provided by the *exo*- and *endo*-isomers of **190** where the *exo*-isomer polymerizes first, followed much more slowly by the *endo*-isomer; see Section VIII.C.12. In other cases the *endo*-isomer will not polymerize but will copolymerize to some extent with its *exo*-isomer, as with the isomers of **197**[531]. Other examples of this kind, where M_2 will not homopolymerize using a particular catalyst, are the copolymerization of norbornene (M_1), (i) with cyclopentene (M_2), catalysed by $Ru(OTs)_2(OH_2)_6$[597], (ii) with **192**, catalysed by WCl_6/Me_4Sn[526] and (iii) with cyclohexene (M_2), catalysed by WCl_6/Me_4Sn[358,359].

Some other recently reported metathesis copolymerizations are the following. (1) Norbornene (M_1) has been copolymerized with a number of its derivatives and with 7-oxanorbornene derivatives (M_2), using $RuCl_3$ and other catalysts. The monomers are of comparable reactivity ($r_1 = 0.5–2.6$) and the behaviour close to ideal ($r_1 r_2 = 0.9–2.2$)[602,603]. (2) In the ROMP of cyclooctadiene (M_1) with 4,7-dihydro-2-phenyl-1,3-dioxepin (M_2) catalysed by $Ru(=CHR)(Cl)_2(PCy_3)_2$, where R is $CH=CPh_2$ or Ph, M_2 is about half as reactive as M_1. By using a small proportion of M_2 one can produce a polymer of M_1 containing occasional M_2 units which may be broken by hydrolysis to yield 1,4-hydroxytelechelic polybutadiene (M_w/M_n *ca* 1.2)[604]. (3) The metathesis copolymerization of the cyclobutene derivative, **136**, with norbornene or cyclopentene (M_2) gives copolymers that are readily converted into acetylene copolymers by elimination of 1,2-bis(trifluoro)benzene from the M_1 units, but the compositional sequence distribution in these copolymers is difficult to establish[605].

Secondary metathesis reactions are sometimes encountered during metathesis copolymerization, leading to a reshuffling of the units in the chain and eventually to a random distribution; for example in the copolymerization of **248** and **258** using $RuCl_3$ as catalyst, statistical copolymers are produced no matter whether the monomers are mixed initially or added sequentially[576]. See also the copolymers of **128**; Section VIII.B.6.

B. Block Copolymers by Sequential Addition of Monomers to Living Systems

Early attempts at making block copolymers using first-generation catalysts met with limited success[372]. The big advance in this area came with the development of the well-defined metal carbene initiators. The first indication that these would provide a practical method of making long-chain block copolymers was the observation that the propagating tungsten carbene species P_1 derived from monomer M_1 (norbornene) could be readily converted, by dosing with a second monomer M_2 (*endo*-5-methylnorbornene), to the propagating species P_2, and then back again to P_1 by a further addition of M_1[307]. This was followed by qualitative observations of the appropriate increases in MW after each addition of monomer[606] and by more quantitative studies that showed that block copolymers could be made with a narrow MWD (PDI < 1.1), even from norbornene derivatives containing ester groups[500]. These observations have since been extended to a host of other systems, mostly involving norbornene[334,384,407,432,500,510,513,601,606–614], or methyltetracyclododecene[483,510–512,615,616] as one of the monomers. The latter has the advantage of producing block copolymers that are more easily microtomed to a thickness of 300–400 Å for study by transmission electron microscopy (TEM)[615].

In the formation of block copolymers by sequential addition of monomers it generally does not matter which monomer is polymerized first, and diblock or multiblock copolymers of narrow MWD and of any desired sequence length are readily prepared. Termination is usually effected by reaction of the living ends with aldehydes; ketones can be used for terminating titanacyclobutane ends, while unsaturated ethers are used for terminating ruthenium carbene complexes.

If the two components of the copolymer are of similar polarity, there is no observable phase separation within the block copolymer and DSC shows a single glass transition temperature T_g. When there is a larger difference in polarity, microphase separation can be detected by a variety of techniques. The simplest test is to look for the two T_g peaks of the separate amorphous phases[490]. SAXS (small-angle X-ray scattering) can also be used, but most impressive is TEM, especially for metal-containing block copolymers; see Section VIII.C.12. The morphology of Si-containing block copolymers can also be observed by TEM. As the proportion of M_2 units in the block copolymer decreases, the morphology changes in the usual way from lamellar to cylindrical to spherical and all three can be observed in the same system[611].

The M_2 units in the block copolymers from cyclobutene derivatives such as **136** and **139** readily eliminate an aromatic ring compound on heating, giving $M_{2'}$ units, =CHCH=CHCH=, equivalent to two acetylene units. $M_{2'}M_1M_{2'}$ triblocks made in this way can be doped with WF_6 and their morphology studied by SEM. They can also be surface-etched by metathesis degradation so as to enhance the spherical domains of M_1 units[613]. The reverse type of triblock, $M_1M_{2'}M_1$, can also be made, in which the average number of double bonds in the centre block can be closely controlled. Comparison with $M_1M_{2'}$ diblocks having the same number of $M_{2'}$ units shows that the triblocks are restricted in the extent to which their double bonds can be brought into conjugation by twisting of the polyene chain, whereas in diblocks the polyene chains are more mobile and more readily brought into conjugation[610].

Amphiphilic star-block copolymers can be prepared by adding a polycyclic diene such as **238** to a living diblock copolymer made by sequential ROMP of (i) the monomer in Table 9 with R = $COOSiMe_3$, and (ii) norbornene. The trimethylsilyl ester groups are then converted to carboxylic acids by soaking the cast film of the polymer in water for 2–3 days to give a product with a hydrophobic core of polynorbornene and a hydrophilic outer layer[126,502].

C. Block Copolymers by Modification of Homopolymers

If the ROMP of norbornene is initiated with a titanacyclobutane complex, the resulting living polymer chains may be coupled by reaction with half an equivalent of a polymer containing keto end-groups, so as to give an ABA triblock copolymer. This has been done using poly(oxy-2,6-dimethyl-1,4-phenylene) to provide block B, the phenolic hydroxyl end-groups in this polymer being first reacted with 4-fluorobenzophenone in the presence of K_2CO_3 to give the required keto end-groups. A copolymer formed in this way with three equal blocks shows only a single T_g (70 °C) compared with 36 °C and 90 °C for A and B, respectively; thus there is no phase separation in this triblock material, even though A and B are not miscible. However, with *exo*-dicyclopentadiene in place of norbornene, the triblock does show microphase separation[617]. A variation on this principle has been used to make well-defined ABA triblock copolymers where A consists of units of **185** and B is a pre-determined number (9, 10, 11 or 12) of [=CHCH=] units[396,618,619].

Block copolymers can also be made by transformation of the propagating species after polymerization of the first monomer. The following are some examples:

(1) If a mixture of *anti*- and *syn*-7-methylnorbornene (M_1 and M_2 respectively) is treated with W[=$\overline{C(CH_2)_3CH_2}$](Br)$_2$(OCH_2CMe_3)$_2$, M_1 is selectively polymerized. If an equivalent of $GaBr_3$ is now added, converting [W]–Br into $[W]^+$ $GaBr_4^-$, the metal carbene becomes much more active allowing M_2 to add to the living ends. However, propagation is much faster than initiation at this second stage and the product is a mixture of block copolymer and homopolymer of M_1[322].

(2) When a mixture of norbornene (M_1) and 5-acetoxy-1-cyclooctene (M_2) is treated with **18** (Table 2) in CH_2Cl_2, M_1 is selectively polymerized in less than 3 h. If 4 equiv of PCy_3 are now added, the PPh_3 ligands are displaced, giving a more active system and allowing M_2 to add to the chains, resulting in an increase in MW. The reaction must be terminated quickly, otherwise secondary metathesis reactions occur, converting the initial block copolymer into a random copolymer[597].

(3) A titanacyclobutane carrier for the living ROMP of norbornene can be converted, by reaction with methanol, into an alkyl titanocene methoxide complex which can then be used in conjunction with $EtAlCl_2$ to propagate the ZNP of ethene, so forming a block copolymer of norbornene and ethene[620].

(4) If the living ROMP of norbornene is terminated with a 9-fold excess of terephthalaldehyde, the chains formed carry an aldehyde end-group which, when activated by $ZnCl_2$, can be used to initiate the aldol-group-transfer polymerization of *tert*-butyldimethylsilyl vinyl ether[621].

(5) Living anionic polymerization of styrene can be initiated by butyllithium in cyclohexane. If a solution of WCl_6 in cyclohexane is added to such a living polymer solution (MW = 61, 000, W/Li = 1/4) and then exposed to gaseous acetylene, the latter reacts to give a soluble product for which the GPC gives two peaks, one corresponding to the original polystyrene and the other, MW > 200, 000, consisting of a block copolymer of styrene and acetylene. It seems likely that the reaction of the living anionic polystyrene with WCl_6 converts it partially into a living tungsten carbene complex which propagates the metathesis polymerization of acetylene[622]. Similar results have been obtained using cyclopentene in place of acetylene[623].

(6) The ADMET polymerization of 1,4-divinylbenzene gives rise to linear oligomers containing up to 20 units from which the dimer, trimer and tetramer can be readily isolated and then cross-metathesized with polybutadiene using a tungsten carbene initiator. The UV/vis spectrum of the product shows that the oligomer sequence remains intact in the resulting copolymer[624].

D. Comb and Graft Copolymers

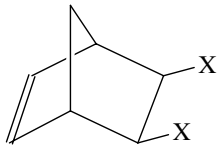
1. Comb copolymers

These are homopolymers that have short regular side chains and are akin to graft copolymers. They can be produced by the ROMP of such monomers as **284**[501], **285**[504] and **286**[470,471].

The polymers of **284** are hydrogels and can take up a moderate amount of water. The ROMP of **285** only proceeds to completion if the polystyrene side chains are kept reasonably short ($n = 4$, 7 or 9). Polymers of monomers such as **286** exhibit a nematic or smectic mesophase resulting from side-chain crystallization. Isotropization temperatures increase with increasing MW, becoming constant at about 30–50 repeat units. Side-chain crystallization tends to be suppressed as the MW increases.

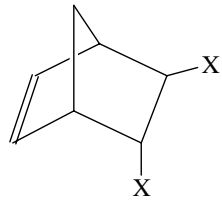
2. Copolymers with short grafts

These can be made by copolymerizing two monomers, one of which contains a side chain such as C_{10} or C_{12}, e.g. the copolymerization of norbornene dicarboxylic esters with 5-decylnorborn-2-ene. Alternatively, the homopolymer of the diester can first be hydrolysed to the acid form and then partially reacted with 1-dodecylamine. The viscosity



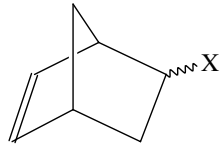
$X = CO_2(CH_2)_{11}CH_3$

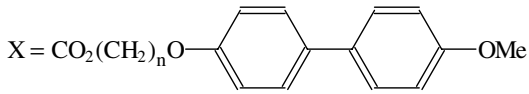
(284)



$X = CO_2CHMeCH_2[CHPhCH_2]_nCHEtMe$

(285) $n = 4–9$





(286) $n = 2–8$; *exo*/*endo* = 1/3

of aqueous solutions of such hydrophobically modified polymers increases sharply with increase in concentration as a result of intermolecular association[582].

3. Copolymers with long grafts

Three examples may be cited. First, the macromonomer ω-norbornenylstyrene has been made by reacting a living anionic polystyrene with ethylene oxide to give a hydroxyl end-group which is then reacted with norborn-5-ene-2-carbonyl chloride. The macromonomer so formed can be copolymerized with norbornene using WCl_6/Me_4Sn as catalyst. The resulting copolymer contains 3–16 polystyrene grafts per chain of 500 units and gives clear films, showing that the microdomains are smaller than the wavelength of visible light[475].

Another macromonomer has been made by reacting the terminal hydroxyl groups of poly(oxy-2,6-dimethyl-1,4-phenylene) (MW = 2000–7000) with norborn-5-ene-2-carbonyl chloride. When this macromonomer is reacted with the $5\text{-}COO(CH_2CH_2O)_3CH_3$ derivative of norbornene, using $RuCl_3$ as catalyst, copolymers of MW up to 250,000 are obtained which contain about 2% of the macromonomer units. If the macromonomer contains only *exo*-substituted end-groups, it is more reactive than when it contains 55% *exo* and 45% *endo* end-groups[625].

Thirdly, if living polynorbornene (A) having titanacyclobutane ends is terminated with a short-chain polyether ketone (B) containing about 3 keto groups per chain, a triblock copolymer ABA is formed, with a single graft of A emanating from the B block[617].

E. Copolymers by ROMP in Conjunction with Radical Reactions

The ROMP of cyclooctene-5-methacrylate and its copolymerization with cyclooctadiene is catalysed by **19** in the presence of *p*-methoxyphenol as radical inhibitor. The double

bonds in the methacrylate groups are inert towards metathesis. After chain transfer with ethyl vinyl ether to release the polymer from the ruthenium centre, it can be cross-linked by radical polymerization through the methacrylate side chains[626].

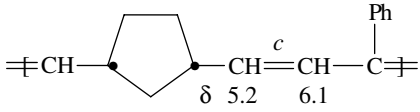
The simultaneous ROMP of norbornene or dicyclopentadiene on the one hand, and the radical polymerization of styrene or methyl methacrylate on the other, gives a polymer blend[627].

X. POLYMERIZATION OF ACETYLENES BY OLEFIN METATHESIS CATALYSTS

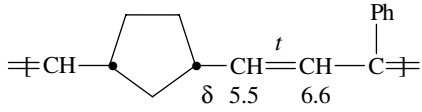
A. Proof of Mechanism

The most direct proof of the metal carbene mechanism of polymerization of acetylenes by olefin metathesis catalysts (equation 3) comes from the use of electron-deficient (<18e) metal carbene complexes as initiators. Thus **7W** (R = Me) initiates the polymerization of acetylene itself, and triblock copolymers can be made by successive addition of norbornene, acetylene and norbornene to the initiator. Provided that the centre block contains not more than 10 units of acetylene, such triblock copolymers have narrow MWD ($M_w/M_n < 1.1$), characteristic of a living system[628]. Again, Ta(=CHCMe$_3$)(DIPP)$_3$(THF), where DIPP = 2,6-diisopropylphenoxide, reacts with 1 equiv of MeC≡CMe to give a THF-free metallacyclobutene complex, which on addition of pyridine yields a vinylalkylidene complex by opening of the metallacyclobutene ring. This can then be used to initiate the polymerization of up to 200 equiv of MeC≡CMe to give a living polymer which, after termination with benzaldehyde, is found to have a very narrow MWD ($M_w/M_n < 1.05$)[629]. Likewise Mo(=CHCMe$_2$Ph)(=*N*-adamantyl)[OCH(CF$_3$)$_2$]$_2$(2,4-lutidine) initiates the living polymerization of HC≡CC$_6$H$_4$(SiMe$_3$)-2 to give a polymer with MW proportional to the amount of monomer consumed and with $M_w/M_n = 1.05$[630].

Further evidence comes from the structure of statistical copolymers of cycloalkenes (M_1) with acetylenes (M_2) in which the M_1M_2 junctions are present in sufficient proportion to be detectable by NMR. For example, a copolymer of cyclooctene and 2,4-dichlorophenylacetylene, containing 15% of M_1 units, has been prepared using WCl$_4$[OCH(CH$_2$Cl)$_2$]$_2$/Et$_2$AlCl as catalyst. The reactivity ratios are such that these units are nearly all flanked by M_2 units, and the olefinic protons of the M_1 units give a signal at δ 5.62, somewhat shifted from that for the olefinic protons in the homopolymer of M_1 (δ 5.3)[631]. This is direct proof that acetylenes can add to propagating metal carbene complexes. Another example is the copolymerization of norbornene (M_1) with phenylacetylene (M_2) using WCl$_6$ as catalyst in toluene at 30 °C. The reactivity ratios, $r_1 = 0.20$, $r_2 = 7.0$, show that both types of propagating metal carbene complex P_1 and P_2 (in which the previous units added were M_1 and M_2 respectively) prefer to add M_2 rather than M_1. In the ^{1}H–^{1}H COSY NMR spectrum of the copolymer there are two correlations for the M_1M_2 olefinic protons, one at the intersection of δ 5.2 and 6.1, the other at the intersection of δ 5.5 and 6.6. These are assigned to the protons in the *cis* and *trans* M_1M_2 dyads **287** and **288**. The presence of these peaks proves that the product is a statistical copolymer and not a mixture of homopolymers[632,633].

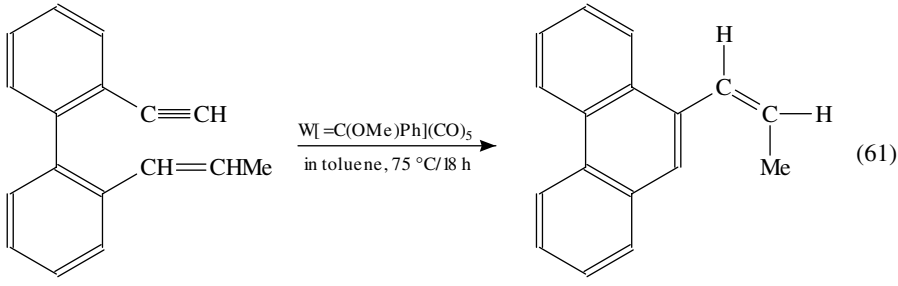


(287)



(288)

A further confirmation of the metal carbene mechanism is provided by enyne intramolecular metathesis reactions such as that depicted in equation 61. The C≡C bond in the substrate becomes the single bond attaching the alkenyl group to the phenanthrene ring system[634,635].



(61)

(289) **(290)**

B. Metathesis Polymerization of Acetylene

Since 1985 a number of typical olefin metathesis catalysts have been found to induce the polymerization of acetylene[636–641]. In most cases the polyacetylene formed is a black intractable material, insoluble in all solvents, and having a high *trans* content. However the initiator **7** (R = Me), in the presence of quinuclidine, provides much better control, allowing the preparation of soluble polymers containing up to 9 monomer units. The quinuclidine forms stronger complexes with the propagating species than with the initiating species, thereby slowing down propagation relative to initiation. The living ends may be terminated in a controlled way by cleavage with pivaldehyde. In the HPLC of such polymers, both the all-*trans* oligomers ($n = 3$–9) and those containing one or more *cis* double bonds are resolved[396,628].

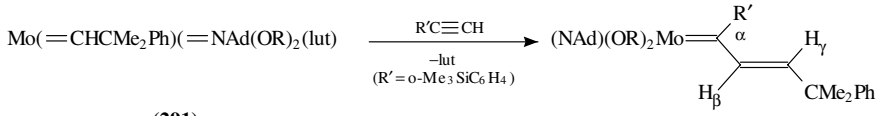
C. Metathesis Polymerization of Monosubstituted Acetylenes

Monosubstituted acetylenes are polymerized by most metathesis catalysts. The halides $NbCl_5$, $TaCl_5$, $MoCl_5$, WCl_6 can be used without a cocatalyst because acetylenes themselves react readily with the halide to generate an initiating metal carbene complex. The product may be linear polymer only (MW = 10^3–10^6), cyclic oligomers only or a mixture of linear polymer and cyclic trimers[642]. The linear polymers generally have an all-HT structure[295]. Backbiting to give cyclic trimers is markedly reduced or totally eliminated by the presence of bulky groups either on the metal centre or on the monomer. For example, HC≡CBu/$TaCl_5$ (or $NbCl_5$)[643] and HC≡CCH($SiMe_3$)R/$TaCl_5$[644] give only cyclic trimers, whereas HC≡CCMe_3/$TaCl_5$[645] and HC≡CCMe_3/Nb(OC_6H_3-Me_2-2,6)Cl_4(THF)/*t*-BuMgCl[646] give high polymer (MW *ca* 10^6).

The catalyst system $MoOCl_4$/Bu_4Sn/EtOH (1/1/1) is remarkable in that it is not only active in toluene at −30 °C, but it gives a 97% *cis* living polymer of CH≡CCMe_3, though the catalyst efficiency is only about 2%[647].

Much work has been carried out on phenylacetylene and its derivatives[631,648–674]. Of particular interest are the *ortho*-substituted phenyl derivatives because, unlike their *meta* and *para* isomers, they generally give living systems when initiated by $MoOCl_4$/Bu_4Sn/EtOH (1/1/1), allowing the preparation of block copolymers. This is the

case for phenylacetylenes with the following *ortho*-substituents: Me, $CHMe_2$, $GeMe_3$, Cl, Br, CF_3[672,675–678], $SiMe_3$[678] and also for (2,3,5,6-tetrafluoro-4-butyl-phenyl)acetylene[679]. As with $HC{\equiv}CCMe_3$[647], the steric hindrance offered by the substituents close to the metal centre in the propagating species is evidently a decisive factor in giving a living system with this catalyst. Even more instructive is the behaviour of the *o*-$SiMe_3$ monomer with $Mo(=CHCMe_2Ph)(=N\text{-adamantyl})(OR)_2$(base) initiators, in which the first step is represented by equation 62[630].



(291) **(292)** (62)

With initiator **291** [OR = $OCH(CF_3)_2$, lut = 2,4-lutidine, Ad = adamantyl], the first insertion product is **292**, in which the phenyl substituent is attached to the α-carbon (head structure), the double bond is *trans* ($J_{\beta\gamma}$ = 15.6 Hz) and the metal centre is base-free. The monomer is thus able to displace the lutidine ligand in **291** and then react, but the lutidine is unable to coordinate to **292** where less space is available. When further monomer is added the MW of the polymer formed is directly proportional to the amount of monomer consumed, and $M_w/M_n = 1.04$ when $M_n = 13,900$. Initiators with bulkier alkoxy or imido ligands either do not react or fail to show the characteristics of a living system. The key to success with this monomer is therefore to use a metal carbene complex with relatively small ligands. For the shorter-chain polymers (DP < 25) the absorption spectrum initially shows two maxima separated by about 50 nm but on standing gives largely the red-shifted form; this change is attributed to *cis* → *trans* isomerization. The living polymerizations of ethynylferrocene and ethynylruthenocene are also readily initiated[680].

The polymers of the more highly substituted acetylenes RC≡CH can generally be prepared with higher MW than for those of the less highly substituted acetylenes. They are usually colourless or yellow, amorphous, readily soluble and non-conducting, in sharp contrast to polyacetylene itself, which is black, insoluble and semi-conducting, showing metallic conduction when doped. This is because the substituents force the main chains to take up twisted, non-conjugated, conformations.

D. Metathesis Polymerization of Disubstituted Acetylenes

$W(CO)_6$ in hexane is effective as a photochemical initiator of polymerization of non-functionalized disubstituted acetylenes, such as MeC≡CMe, only if 1% of a monosubstituted acetylene is added. Polymerization then begins after an induction period of 30 min during which time a steady concentration of an active metal carbene complex is presumably generated. In contrast, initiation by $Mt(CO)_6/h\nu/CCl_4$ (Mt = Mo, W) is effective for the polymerization of PhC≡CCl without the use of a cocatalyst, and gives high polymer (M_w *ca* 10^6). Reaction continues in the dark after an initial irradiation period during which time the initiating species $[Mt]{=}CCl_2$ is thought to be generated[681,682]. $SnCl_4$/toluene can be used in place of CCl_4[683].

Terminal olefins such as vinyltrimethylsilane can act as chain transfer agents in the polymerization of MeC≡CPh catalysed by $NbCl_5/Bu_4Sn$ or of $ClC{\equiv}CC_6H_{13}$ or ClC≡CPh

catalysed by $MoCl_5/Bu_4Sn$. The end groups derived from the transfer agent can be detected when the MW is sufficiently low[684,685].

With WCl_6 or $MoCl_5$ as catalyst it is generally necessary to use a cocatalyst such as Ph_4Sn, unlike the situation with monosubstituted acetylenes, where the substrate acts as its own cocatalyst. With $NbCl_5$ and $TaCl_5$ a cocatalyst is not always necessary, though its use may affect the course of the reaction. For example, for the $TaCl_5$-catalysed polymerization of MeC≡CPh in toluene at 80 °C, the conversion reaches 100% in 6 h, but the polymer then degrades rapidly to oligomer[686,687]. With $TaCl_5/Ph_4Sn$ (1/1) under the same conditions the reaction is complete in 1 h and the MW of the polymer remains stable for at least 24 h; one may suppose that bulky ligands attached to the tantalum centre then prevent secondary metathesis reactions of the double bonds in the polymer chain. Similar observations have been made with $PhC{\equiv}CC_6H_4X$-4 as monomer, where X = H[688], CMe_3 etc.[689,690] and $SiMe_3$[691,692]. The structure of the monomer can be a crucial factor with these catalysts. Thus MeC≡CBu is polymerized by both $MoCl_5/Ph_4Sn$ and WCl_6/Ph_4Sn in toluene at 30 °C[681], but the more sterically hindered $MeC{\equiv}CCHMe_2$ is polymerized only by WCl_6/Ph_4Sn at 60 °C[682].

The catalyst system $MoOCl_4/Bu_4Sn/EtOH$ (2/2/1) is remarkable in that it gives living polymers of RC≡CCl (R=Bu, Hex) having narrow MWDs (M_w/M_n = 1.1–1.4), just as it does with certain monosubstituted acetylenes (Section X.C). With $MoOCl_4$ or $MoOCl_4/Bu_4Sn$ as catalyst the MW of the polymer increases with conversion, but the polymers have a broader MWD indicating the occurrence of secondary metathesis reactions[686,693]. The role of EtOH in the three-component catalyst system is probably to replace one of the chloride ligands by an ethoxy ligand in the propagating metal carbene species thereby making it less prone to undergo termination or secondary metathesis reactions[677]. The ^{13}C NMR spectra of these polymers are as expected for a regular HT structure[694].

These polymers are generally white and have intrinsic viscosities which are sometimes nearly proportional to the MW, for example the polymer of EtC≡CPh[695]. This indicates that the polymer molecules have a fairly rigid but twisted backbone with very little conjugation of the double bonds, unlike polyacetylene and polymers of *linear* monosubstituted acetylenes[682].

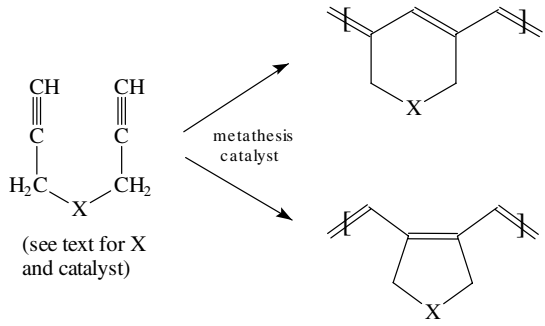
Further details may be found in the reviews of Masuda and coworkers[696,697] and of Breslow[698].

E. Metathesis Polymerization of Diynes; Cyclopolymerization

The monomer $HC{\equiv}C{-}C{\equiv}CX$ (X=$SiMe_3$) is readily polymerized by WCl_6/Ph_4Sn (1/1) in toluene at 40 °C to give a soluble polymer (M_n *ca* 10^4) which, when cast as a film and exposed to a mercury lamp for a few seconds, becomes completely insoluble[699]. The initial reaction is probably metathesis polymerization through the C≡CX bond, while the subsequent cross-linking by irradiation occurs through the other triple bond. Other 1,3-diynes (X=alkyl, phenyl, carbazolyl etc.) can be polymerized in this way. The polymerization of $PhC{\equiv}C{-}C{\equiv}CCH_2OH$ by $NbCl_5/Bu_4Sn$ in toluene at 80 °C gives an 80% yield of soluble polymer (M_w = 3200), which on heating under vacuum to 800 °C is converted to a graphite-like structure which has a high conductivity even in the absence of dopant. The first stage is thought to involve preferential metathesis polymerization through the $C{\equiv}CCH_2OH$ bond[700].

The metathesis polymerization of diynes having four single bonds between the triple bonds (dipropargyl compounds) yields cyclopolymers. The structural units may contain a cyclohexene ring (equation 63) or a cyclopentene ring (equation 64) with the possibility

of both in the same chain (see below).

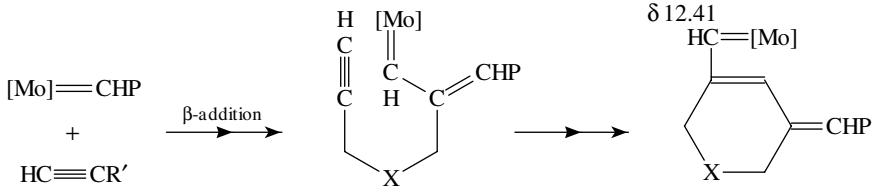


(63)

(64)

This reaction occurs with a wide variety of diynes in which X may be CPh_2[701], $C(CO_2R)_2$[702–705], C<(CO.O)$_2$ > CMe_2[706], $C[CO_2CH_2(CF_2)_5CF_2H]_2$[707], C[$CO_2(CH_2)_6$ N-carbazolyl]$_2$[708], CHOH[709], CPh(OH)[710a], $C(OPh)_2$[710b], CMe(OSiMe$_2$ CMe_3)[707], CHY or CY_2 where Y is a mesogenic group[711,712], $CHCO_2(CH_2)_2O_2CC_6H_3$-$(NO_2)_2$-3,5[713], C[$PO(OEt)_2$]$_2$ and $C(CO_2Et)[PO(OEt)_2]$[714], NY where Y is a mesogenic group[715–718], $N^+R_2Z^-$ where R = hexyl, Z = Br, BPh_4, tos[719,720], O[721,722], S, SO or SO_2[723–725], SiR_2 where R = Me, Ph[726,727], GeR_2 where R = Me, Ph[728]. When the monomer contains a mesogenic group, both the monomer and the cyclopolymer exhibit liquid-crystalline properties.

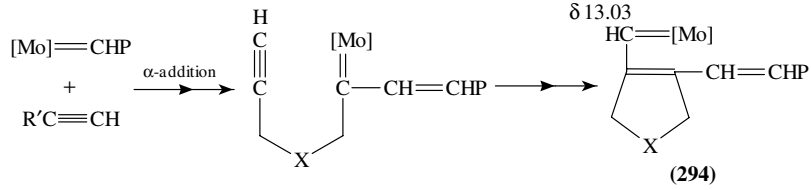
^{1}H and ^{13}C NMR spectra confirm the disappearance of triple bonds and the formation of double bonds during these reactions. Up to 1994 it was generally assumed that the rings formed were mainly 6-membered, but for X = $C(CO_2R)_2$ there is good evidence that 5-membered rings are also formed[705]. Thus, on addition of the initiator **8** (Table 2) to the monomer with R = Et, the carbene proton resonance of the initiator (δ 12.14) is replaced by resonances at δ 12.41 and 13.03, assigned to the carbene protons of living **293** and **294**, respectively (equations 65 and 66). Furthermore, in the ^{13}C NMR spectrum of the polymer, there are two distinct carbonyl signals (δ 170.8, 172.0) and two groups of quaternary carbon signals (δ 54–55, 57–58), the latter being assigned to 6- and 5-membered rings respectively by comparison with the spectra of model compounds. For the 5-membered rings the δ 57–58 signal shows fine structure that may be attributed to the influence of the ring structure in the adjacent units. On changing the initiator, the solvent, or the ester group in the monomer, there is some variation in the proportions of 5- and 6-membered rings formed (80/20–21/79), but the extremes are not reached.



P = polymer chain
R′ = $CH_2XCH_2C{\equiv}CH$
X = $C(CO_2Et)_2$

(293)

(65)



(66)

Such reactions clearly involve two successive types of propagation step: (i) double-bond exchange between Mt=C and the first C≡C of the monomer, and (ii) rapid intramolecular cyclization by double-bond exchange between Mt=C and the second C≡C of the monomer. If the first step occurs by β-addition (with the substituent β to the metal centre), the subsequent intramolecular reaction is likely to yield a 6-membered ring (equation 65), whereas if it occurs by α-addition the subsequent reaction is more likely to yield a 5-membered ring (equation 66). This observation is somewhat surprising because simple monosubstituted acetylenes, containing one C≡C bond, appear to polymerize only by α-addition to give an all-HT structure (Section X.C). It is therefore unexpected that a monosubstituted acetylene in a diyne can add in both directions. Further work is needed to establish whether the result with X = $C(CO_2R)_2$ is the exception rather than the rule. Preliminary reports indicate that when X possesses one extremely bulky substituent (X = $CHCH_2OSiPh_2Bu^t$), the resulting polymer has mostly one type of ring structure[713]. Sterically demanding substituents (preferably two) on X certainly encourage the second, intramolecular, step and reduce the proportion of residual pendant C≡C groups in the polymer which, if they subsequently react with each other, can give rise to a component with double the MW of the main product.

The use of molybdenum carbene initiators, and suitably substituted benzaldehydes as terminating agents, allows the preparation of cyclopolymers having electron-donating or electron-attracting groups at one or both ends of the chains. When the chains are sufficiently short, say DP = 5, and the two end-groups are the same, the absorption maximum for the 'push–push' polymer is at a rather longer wavelength than in the corresponding 'pull–pull' polymer, but when the DP is 20 or more the chain length exceeds the effective conjugation length and the end groups have comparatively little effect[705].

Copolymerization of the diynes having X = $C(CO_2Et)_2$ and X = $C[CO_2(CH_2)_6$ *N*-carbazolyl$]_2$ gives a conductive copolymer[729]. The cyclopolymerization of $RC{\equiv}CCH_2OCH_2C{\equiv}CH$ (R = Me, $SiMe_3$) gives insoluble polymers; but their copolymers with diethyl dipropargylmalonate are soluble[730]. Tripropargylammonium bromide gives a conjugated polymeric salt having two cyclic recurring units per monomer unit[731]. Tetrapropargylammonium bromide gives a cross-linked cyclopolymer[732].

Of the first-generation catalysts, those based on $MoCl_5$ are the most effective, either with a cocatalyst such as $EtAlCl_2$ or Bu_4Sn, or alone, at 60–90 °C in the usual solvents. Molybdenum carbene complexes give living systems, allowing the preparation of block copolymers of 1,4-diynes with norbornadiene derivatives[705]. The polymers are generally soluble and highly coloured, with MW = 10^3–10^5, and become conducting when doped with iodine. The diynes $HC{\equiv}C(CH_2)_nC{\equiv}CH$ (n = 2, 4, 6, 8) have also been polymerized. For n = 2, using $NbCl_5$ as catalyst, the product is mainly trimer, but for n = 6 or 8, a polymer with a highly branched structure appears to be formed[733].

F. Copolymerization of Acetylenes

Acetylenes copolymerize with each other and with cycloalkenes under the influence of olefin metathesis catalysts. With non-living systems it is possible to make statistical

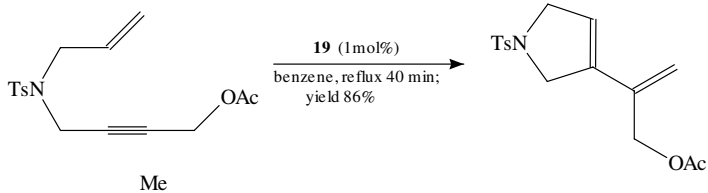
copolymers by adding the monomer mixture to the catalyst system. Copolymers of acetylene with phenylacetylene can be made with $MoCl_5$ as catalyst, containing 0–81.7 mol% acetylene units. The UV/vis absorption band moves to longer wavelengths as the proportion of acetylene in the copolymer increases, the absorption maximum at 508 nm corresponding to an average of 9–10 conjugated double bonds[734].

The Hammett parameters for these copolymerizations indicate that the chain carrier is electrophilic, i.e. the carbene carbon bears a net positive charge, with the counterbalancing negative charge spread to some extent over the chloride ligands. The product of the two reactivity ratios is sometimes considerably larger than 1.0, e.g. 13 in the case of $HC{\equiv}CC_6H_4CF_3$-2/norbornene, and 30 for $HC{\equiv}CC_6H_3$-$(CF_3)_2$-2,5/norbornene[735,736]. The copolymers in these cases are thus very blocky, which appears to be due to the presence of the 2-CF_3 group. Occasionally, as in the copolymerization of phenylacetylene and cyclopentene, the product of the reactivity ratios is so great that the cross-propagation reactions scarcely occur and the product is essentially a mixture of the two homopolymers[632].

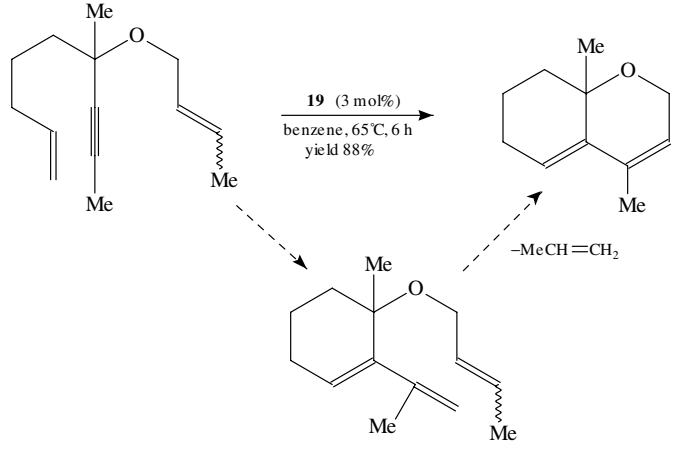
When the propagating species are long-lived it is possible to make block copolymers of controlled chain length by sequential addition of monomers, for example with $ClC{\equiv}CC_4H_9$/$ClC{\equiv}CC_{14}H_{29}$[686,693] and with acetylene/norbornene[396,628].

XI. INTRAMOLECULAR METATHESIS REACTIONS OF ENYNES AND DIENYNES

Enyne intramolecular metathesis reactions, of the type shown in equation 61, can be very useful in organic synthesis. A number of such reactions, catalysed by tungsten or chromium carbene complexes, have been reported[634,635,737–740]. The ruthenium carbene catalysts **18–20** (Table 2) are likely to be increasingly used for this purpose because of their stability, ease of handling and good yields, as in the synthesis of various 5-, 6- and 7-membered heterocycles, e.g. equation 67[741].



(67)



(68)

This catalyst also effects the ring-closing metathesis of many acyclic dienynes to form fused bicyclic rings, containing 5-, 6- and 7-membered rings, e.g. equation 68. The reaction may be assumed to take place in two stages as indicated by the dashed arrows: (i) intramolecular metathesis of the alkyne with the sterically less hindered double bond, followed by (ii) metathesis with the remaining exocyclic double bond[742].

Many natural products contain fused bicyclic structures and the dienyne metathesis reaction may well open up new and more efficient routes for their synthesis.

XII. METATHESIS REACTIONS OF ALKYNES INVOLVING TOTAL CLEAVAGE OF THE C≡C BOND

A. Acyclic Alkynes

The metathesis of internal acetylenes was first observed in 1968 using WO_3/SiO_2 at 350 °C as catalyst[743]. The most active and most selective MoO_3/SiO_2 catalysts are prepared by contacting SiO_2 with $(\pi\text{-allyl})_4Mo$ and then oxidizing the surface. Proof of triple-bond cleavage in such reactions was obtained by isotopic labelling experiments, e.g. equation 69[744–746].

$$2C_3H_7C{\equiv}C^{14}CH_3 \rightleftharpoons C_3H_7C{\equiv}CC_3H_7 + {}^{14}CH_3C{\equiv}C^{14}CH_3 \qquad (69)$$

The reaction of internal acetylenes $R^1C{\equiv}CR^2$ leads to a near 1:2:1 equilibrium mixture of $R^1C{\equiv}CR^1$, $R^1C{\equiv}CR^2$ and $R^2C{\equiv}CR^2$. In the cross-metathesis of PhC≡CEt with PrC≡CMe the equilibrium mixture contains the expected eight compounds PhC≡CPh, EtC≡CEt, PrC≡CPr, MeC≡CMe, PhC≡CPr, EtC≡CMe, PhC≡CMe and PrC≡CEt, as well as the reactants. However, the initial rate of production of PrC≡CPr and EtC≡CEt is more than three times that of PrC≡CEt[746].

Reactions of this type proceed via metal *carbyne* complexes (equation 4). The most direct evidence is that such complexes (Mt = Mo, W, Re) can act as initiators for the metathesis of $R^1C{\equiv}CR^2$[3,6], and of RC≡CH in the initial stages[747], and for the ROMP of cycloalkynes[7,8]. Metallacyclobutadienes have been prepared[748,749] and some can act as initiators of acetylene metathesis[750,751]; and their ready formation as intermediates can be expected on theoretical grounds[752–754].

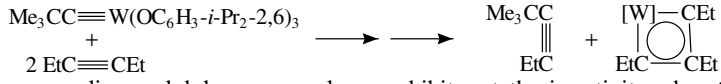
The ability of metal carbyne complexes of the type $Mt(\equiv CCMe_3)(OR)_3$ to metathesize internal acetylenes by a chain mechanism depends on a delicate balance between electronic and steric factors, otherwise reaction either stops after the first step, or gives other products[755] or does not proceed at all. The reaction of $W(\equiv CCMe_3)(OCMe_3)_3$ with PrC≡CEt produces an equilibrium mixture of PrC≡CEt, PrC≡CPr, and EtC≡CEt in less than 1 min at 25 °C and the ^{13}C NMR spectrum of the products indicates the presence of the three $W(\equiv CR)(OCMe_3)_3$ species, where R = Et, Pr and CMe_3[3]. Reaction 70 is an apparent single-step reaction but there is in fact an on-going degenerate exchange of the reactant with the product metal carbyne complex.

$$\begin{matrix} Me_3CC{\equiv}W(OCMe_3)_3 \\ + \\ EtC{\equiv}CPh \end{matrix} \longrightarrow \begin{matrix} Me_3CC \\ \| \\ EtC \end{matrix} + \begin{matrix} W(OCMe_3)_3 \\ \| \\ CPh \end{matrix} \qquad (70)$$

A potential side reaction is the formation of a metallatetrahedrane complex by tautomerization of the metallacyclobutadiene intermediate or by its direct formation from the reactants[756].

In reaction 71 the products are (i) $EtC{\equiv}CCMe_3$, resulting from the metathesis reaction, and (ii) a metallacyclobutadiene complex, produced by addition of a second molecule of

the acetylene to the initially formed carbyne complex. This metallacyclobutadiene complex is able to initiate the metathesis of EtC≡CPr and PrC≡CBu, and must therefore be in equilibrium with its dissociation products. It exchanges carbyne moieties with $C_2D_5C{\equiv}CC_2D_5$ at a rate that is independent of the substrate concentration; the dissociation of the metallacyclobutadiene complex into the metal carbyne complex is therefore rate-controlling[750]. However, when the OR ligands of the complex are $OCH(CF_3)_2$ instead of OC_6H_3-*i*-Pr_2-2,6 the rate of exchange with $C_2D_5C{\equiv}CC_2D_5$ is first order in substrate, indicating an associative mechanism[757].



(71)

The corresponding molybdenum complexes exhibit metathesis activity when OR is an electron-withdrawing ligand such as $OCMe_2CF_3$, $OCMe(CF_3)_2$ or $OC(CF_3)_3$[758], but not when OR is $OCMe_3$, $OCHMe_2$ or OCH_2CMe_3. In the last case EtC≡CPr is polymerized rather than metathesized, showing that the metal carbyne is then readily converted to a metal carbene complex which initiates polymerization[750]. The role of the alkoxide or phenoxide ligands in these reactions has been reviewed by Schrock[35].

The rhenium carbyne complex $Re(\equiv CCMe_3)(=NAr)(OR)_2$ is active for metathesis of internal acetylenes when OR is $OCMe(CF_3)_2$, but not when OR is $OCMe_2CF_3$, $OCMe_3$ or OC_6H_3-*i*-Pr_2-2,6[5,6]. The complex $W(\equiv CMe)(Cl)(PMe_3)_4$ undergoes stoichiometric metathesis with PhC≡CPh but the product PhC≡CMe remains coordinated to the metal centre[759].

The remarkable cocatalytic effect of certain phenols for the metathesis of internal acetylenes by molybdenum compounds such as $Mo(CO)_6$ was discovered in 1974[760]. Some systems are even active at room temperature. Thus $MoO_2(acac)_2/Et_3Al/PhOH$ and $MoO(OPh)_4/Et_3Al/PhOH$ cause metathesis of BuC≡CPr at 30 °C[4]. When the substrate itself bears a phenolic group, as in 4-HO−C_6H_4C≡CMe, it acts as its own cocatalyst with $Mo(CO)_6$ and gives a 78% yield of metathesis product on heating in toluene. If the 4-HO group is replaced by 4-MeO metathesis will only occur if a phenol is added. If 4-HO is replaced by 2-HO then metathesis gives way to the formation of cyclic trimer[761].

The mode of action of the phenolic cocatalysts is not fully understood. One suggestion, based on the identification of the initial products, is that the reaction is propagated by a metal *carbene* complex, the necessary rearrangement of the intermediate metallacyclobutene complex being facilitated by transfer of a proton from the phenol, a different proton being subsequently reclaimed by the phenoxide ion[762]. It is also possible that the reaction involves the replacement of carbonyl ligands by phenoxo ligands; the fact that metal carbyne complexes that initiate acetylene metathesis usually bear three RO ligands (R = aryl or alkyl) points in this direction; see above.

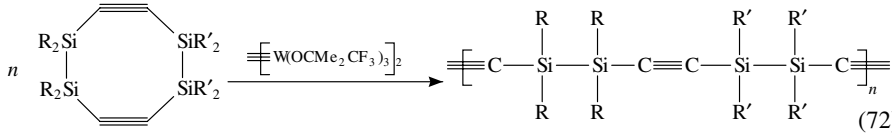
Catalysts such as $Mo(CO)_6$/MeCN also bring about the metathesis of hept-2-yne, but not of hept-1-yne; instead oligomers are formed from the latter[763].

B. ROMP of Cycloalkynes

The ROMP of cyclooctyne is initiated by $Mo(\equiv CPr)(OCMe_3)_3$[7]. The methyl protons in the propyl group of the initiator give a triplet at δ 0.74. On addition of 15 equiv of cyclooctyne this signal is replaced by a triplet at δ 0.92 assigned to the same protons in the propagating species, to which it has been completely converted. Another triplet (δ 3.02), due to the methylene protons nearest to the metal centre in the living propagating species, replaces the triplet (δ 2.95) due to $[Mo]{\equiv}CCH_2CH_2CH_3$ in the initiator. The ^{13}C NMR spectrum of the polymer exhibits a sharp resonance at δ 80.4, characteristic of C≡C in the chain and quite distinct from that for C≡C in cyclooctyne (δ 94.5).

Another initiator for this polymerization is $(Me_3CO)_3W{\equiv}W(OCMe_3)_3$, but analysis of the products by MS shows that they are macrocyclic oligomers. Their ring-size distribution, as determined by GPC, conforms to the Jacobson–Stockmayer relationship. It is evident that with the tungsten catalyst there is strong competition between the backbiting and propagation reactions. The molybdenum carbyne catalyst is less reactive and gives mainly linear polymer if the reaction is quenched with an excess of phenylacetylene within 2 min of addition of the monomer; but if the quenching is delayed for 15 min only cyclic species are subsequently isolated. When the backbiting reaction occurs at the end of the chain the initiator is regenerated. A small proportion of initiator is therefore present when the system reaches equilibrium. For example, when the initial ratio of cyclooctyne to $Mo(\equiv CPr)(OCMe_3)_3$ is 10, the equilibrium mixture contains 5% of the original initiator; this proportion becomes smaller if the original ratio of monomer to initiator is increased. The rest of the initiator ends up as very short chain living polymer. The equilibrium concentration of cyclooctyne is too small to measure, but a significant proportion of cyclic dimer (cyclohexadeca-1,9-diyne) is formed[7].

The ROMP of tetrasilacycloocta-3,7-diynes can also be initiated by W≡C or W≡W complexes of the above type (equation 72). When $R = R' = Me$, addition of 3 equiv of monomer to 1 equiv of $[{\equiv}W(OCMe_2CF_3)_3]_2$ results in complete consumption of monomer over 3 h at 25 °C to yield a partially soluble polymer. Relatively little of the catalyst is used so that propagation must be much faster than initiation. When $R = R' = Et$ there is no reaction with this catalyst. Hence when $R = Me$ and $R' = Et$ one may predict that there will be a strong preference for the reaction to proceed via the metallacyclobutadiene complex in which the bulkier $SiEt_2$ substituent is always placed away from the sterically congested metal. This leads one to expect that the polymer will have an all-HT structure and therefore only two ^{29}Si NMR signals, as indeed is observed. This is in contrast to the anionically produced ring-opened polymer which has additional signals from HH and TT structures. The monomer with $R = R' = Et$ can be polymerized using the more active catalyst $W(\equiv CMe)(OCMe_2CF_3)_3$[8].



(72)

C. Acyclic Diynes

The acyclic diyne metathesis polymerization of dodeca-2,10-diyne is catalysed by $W(\equiv CEt)(OCMe_3)_3$; see equation 73. But-2-yne is eliminated and the product is an off-white insoluble powder with the same T_m as the polymer prepared from cyclooctyne (Section XII.B)[7].

$$n\ MeC{\equiv}C(CH_2)_6C{\equiv}CMe \xrightarrow{[W]{\equiv}CEt} MeC{\equiv}[C(CH_2)_6C]_n{\equiv}CMe + (n\text{-}1)\ MeC{\equiv}CMe \quad (73)$$

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CHAPTER **25**

Biological activity of organic compounds elicited by the introduction of double bonds

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I. INTRODUCTION

Many aspects of the characteristics of the double-bonded functional groups have been reviewed in an impressive series of treatises, published over a period of more than 30 years. These reviews cover mostly the physicochemical aspects of double bonds: electrophilic additions to carbon–carbon double bonds[1], directing and activating effects of doubly bonded groups[2] etc.

The review 'Double bonds from a biochemical perspective'[3] summarizes the importance of the biochemical reactions of selected groups of physiologically active unsaturated compounds, e.g. those that react with the amino groups of amino acids, polyunsaturated fatty acids and vitamin A.

II. COMPARISON OF TOXICITY OF SATURATED AND UNSATURATED COMPOUNDS

The purpose of the present paper is to compare the toxicity and pharmacology of saturated compounds with their unsaturated analogs (wherever possible) and to list some important, physiologically active substances, bearing one or more double bonds.

TABLE 1. Hydrocarbons

Saturated	Toxicity	Unsaturated	Toxicity
Ethane[5]	narcotic in high concn.	Ethylene[6]	950,000 ppm[a]
Propane[7]	narcotic in high concn.	Propylene[4]	asphyxiant
Butane[8]	narcotic in high concn.	1-Butene[9]	asphyxiant
		1,3-Butadiene[10]	250,000 ppm[b]
		Isoprene[11]	0.144 mg/l[c]
Cyclopentane[12]	38,000 ppm[a]	Cyclopentene[13]	2.14 g/kg[d]
Cyclohexane[14]	0.06–0.07 mg/l[a]	Cyclohexene[15]	300 ppm[e]
Ethylbenzene[16]	5.46 g/kg[d]	Styrene[17]	0.09 g/kg[f]
Propylbenzene[18]	6.04 g/kg[d]	Allylbenzene[19]	3.6 g/kg[d]
Diethylbenzene[20]	1.2 g/kg[d]	Divinylbenzene[19]	4.04 g/kg[d]

[a]LC (lethal concentration) for mice in air.
[b]LC for rabbits in air.
[c]LD_{50} for mice in air.
[d]LD_{50} for rats (oral).
[e]Permissible exposure limit.
[f]LD_{50} for mice (iv).

TABLE 2. Halides

Saturated	Toxicity	Unsaturated	Toxicity
Ethyl chloride[21] (irritating, topical anaesthetic)	0.18 g/l[a]	Vinyl chloride[22]	47,660 ppm[a]
1,2-Dichloroethane[13]	0.97 g/kg[b]	1,2-Dichloroethene(trans)[23]	1.28 g/kg[b]
1,1,2-Trichloroethane[13]	0.84 g/kg[b]	1,1,2-Trichloroethane[13]	7.33 g/kg[b]
1-Propyl chloride[24]	$LD_{100} > 3$ g/kg[c]	Allyl chloride[25]	0.7 g/kg[b]
Isopropyl chloride[24]	potent anaesthetic		
1,2-Dichloropropane[13]	2.2 g/kg[b]	2,3-Dichloro-1-propene[16]	0.39 g/kg[b]
1-Butyl chloride[26]	2.67 g/kg[b]	1-Chloro-2-butene[27]	irritating
Ethyl bromide[28]	16,200 ppm (1 h)[a]	Vinyl bromide[24]	0.5 g/kg[b]
1,2-Dibromoethane[29]	0.22 g/kg[c]	1,2-Dibromoethene[30]	0.117 g/kg[b]

[a]LC (lethal concentration) for mice in air.
[b]LD_{50} for rats (oral).
[c]LD_{50} for mice (ip).

As E. E. Sandmeyer stated, 'in general, diunsaturation increases the toxicity'[4]. This is also true, although with some exceptions, for mono-unsaturation.

The toxicity evaluations of the various compounds were carried out on various animals. The most common test was the LD_{50} (the dose needed to produce the death of 50% of all tested animals) orally in rats. Cases where other animals or other conditions were applied, will be so noted.

Tables 1–9 present a listing of various groups of saturated compounds and of their analogs, bearing a double bond. Table 9 includes several hydroxy and keto derivatives (RCHOH vs RC=O).

As a rule the unsaturated analogs are more toxic. There are some exceptions: diethylbenzene[20] and divinylbenzene[19] (Table 1), 1,1,2-trichloroethane[13] and 1,1,2-trichloroethylene[13] (Table 2), 2-propanol[25] and acetone[16] (Table 9) etc.

TABLE 3. Alcohols

Saturated	Toxicity	Unsaturated	Toxicity
Ethanol[31]	10.6 g/kg[a]		
1-Propanol[26]	1.87 g/kg[a]	Allyl alcohol[25]	0.064 g/kg[a]
2-Propanol[25]	5.8 g/kg[a]		
1-Butanol[32]	4.36 g/kg[a]		
2-Butanol[26]	6.48 g/kg[a]	Crotyl alcohol[16]	0.79 g/kg[a]

[a] LD_{50} for rats (oral).

TABLE 4. Aldehydes and ketones

Saturated	Toxicity[a]	Unsaturated	Toxicity[a]
Propionaldehyde[32]	1.4 g/kg	Acrolein[32]	0.046 g/kg
Butyraldehyde[32]	5.89 g/kg	Crotonaldehyde[33]	0.3 g/kg
Methyl ethyl ketone[16]	5.52 g/kg	Methyl vinyl ketone[34]	0.035 g/kg

[a] LD_{50} for rats (oral).

TABLE 5. Acids

Saturated	Toxicity	Unsaturated	Toxicity
Propionic acid[16]	4.29 g/kg[a]	Acrylic acid[16]	2.59 g/kg[a]
Butyric acid[26]	8.79 g/kg[a]	Crotonic acid[33]	1.0 g/kg[a]
Valeric acid[35]	1.29 g/kg[b]	2-Methyl-2-butenoic acid	
Isovaleric acid[35]	1.12 g/kg[b]	*cis*[36], *trans*[37] (found in plants)	
Stearic acid[35]	0.022 g/kg[b]	Oleic acid[35]	0.23 g/kg[b]

[a] LD_{50} for rats (oral).
[b] LD_{50} for mice (iv).

TABLE 6. Esters

Saturated	Toxicity[a]	Unsaturated	Toxicity[a]
Ethyl formate[38]	4.3 g/kg	Vinyl formate[38]	2.82 g/kg
Propyl formate[38]	3.98 g/kg	Allyl formate[38]	0.124 g/kg
Ethyl acetate[38]	5.6 g/kg	Vinyl acetate[38]	2.92 g/kg
n-Propyl acetate[38]	9.37 g/kg	Allyl acetate[38]	0.142 g/kg
Isopropyl acetate[38]	3.0 g/kg	Isopropenyl acetate[38]	3.0 g/kg
n-Propyl butyrate[38]	15.0 g/kg	Allyl butyrate[38]	0.25 g/kg
Ethyl benzoate[26]	6.48 g/kg	Vinyl benzoate[38]	3.25 g/kg
Diethyl succinate[32]	8.53 g/kg	Diethyl fumarate[16]	1.78 g/kg

[a]LD_{50} for rats (oral).

TABLE 7. Amines

Saturated	Toxicity[a]	Unsaturated	Toxicity[a]
1-Propylamine[16]	0.57 g/kg	1-Allylamine[39]	0.106 g/kg
Isopropylamine[32]	0.52 g/kg		
Dipropylamine[16]	0.93 g/kg	Diallylamine[16]	0.65 g/kg
Diisopropylamine[26]	0.77 g/kg		
Tripropylamine[39]	0.096 g/kg	Triallylamine[39]	1.31 g/kg

[a]LD_{50} for rats (oral).

TABLE 8. Ethers

Saturated	Toxicity	Unsaturated	Toxicity
Diethyl ether[40]	2.53 g/kg[b]	Ethyl vinyl ether[13]	6.22 g/kg[b]
		Divinyl ether[41]	51,233 ppm[a]
Allyl ethyl ether[26]	14.53 g/kg[b]	Allyl vinyl ether[40]	0.55 g/kg[b]
Di-*n*-propyl ether[42]		Diallyl ether[40]	0.26 g/kg[b]

[a]LC (lethal concentration) for mice in air.
[b]LD_{50} for rats (oral).

TABLE 9. Alcohols vs keto compounds

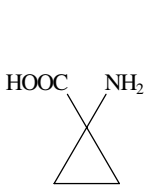
Saturated	Toxicity[a]	Unsaturated	Toxicity[a]
Ethanol[31]	10.6 g/kg	Acetaldehyde[32]	1.93 g/kg
1-Propanol[26]	1.87 g/kg	Propionaldehyde[32]	1.4 g/kg
2-Propanol[25]	5.8 g/kg	Acetone[16]	8.43 g/kg
1-Butanol[32]	4.36 g/kg	Butyraldehyde[32]	5.89 g/kg
2-Butanol[26]	6.48 g/kg	2-Butanone[16]	5.52 g/kg
Cyclohexanol[16]	1.98 g/kg	Cyclohexanone[13]	1.53 g/kg
Benzyl alcohol[32]	3.1 g/kg	Benzaldehyde[18]	1.3 g/kg
Phenethyl alcohol[18]	1.79 g/kg	Acetophenone[25]	0.9 g/kg

[a]LD_{50} for rats (oral).

III. UNSATURATED COMPOUNDS OF PHARMACOLOGICAL INTEREST

A significant number of unsaturated compounds are biologically active and known as drugs, agricultural materials etc.

Ethylene[6] ($CH_2{=}CH_2$, Table 1) has been found to exert major effects on plant growth and development[43]. The ethylene precursor in plants is 1-aminocyclopropane-1-carboxylic acid[44] **(1)**. Much attention is given to the carcinogenic[45,46] 1,3-butadiene[10] ($CH_2{=}CH{-}CH{=}CH_2$, Table 1), an important starting material for synthetic rubbers. Its carcinogenicity is due to the action of its metabolites, the butadiene oxides[46–48]. Its 2-methyl analog, isoprene[10] ($CH_2{=}CMe{-}CH{=}CH_2$, Table 1), is also carcinogenic[49]. Interestingly, isoprene is produced in nature by Gram-negative and Gram-positive bacteria[50].



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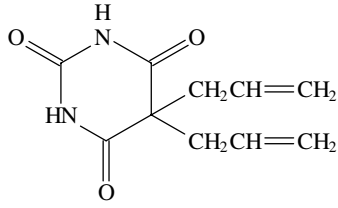

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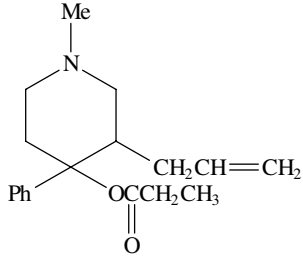
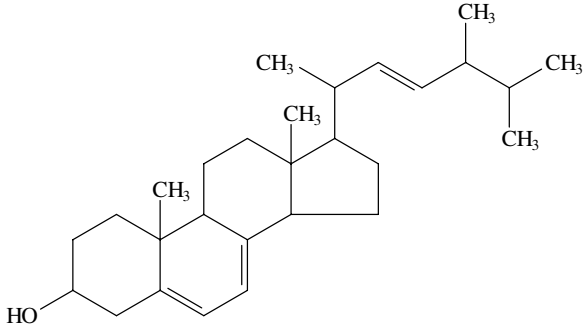


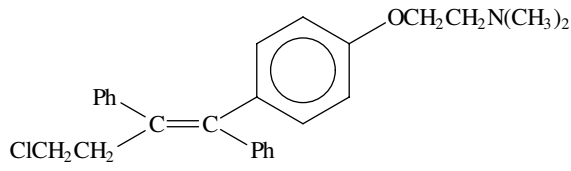
(3)

Other examples include allicin[51], $CH_2{=}CHCH_2S(O)CH_2CH{=}CH_2$, which is an antibacterial; allyl substituted substances like allobarbital **(2)**[52] are sedatives; allylprodine **(3)**[53] is a narcotic analgesic; ergosterol **(4)**[54] is an antirachitic vitamin; toremiphene **(5)**[55] is an antineoplastic; undecylenic acid ($CH_2{=}CH(CH_2)_8COOH$)[56] is an antifungal; hexalure **(6)**[57] and muscalure **(7)**[58] are insect attractants.

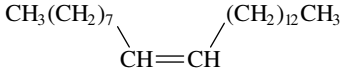


(4)

Prostaglandins[59], like prostaglandin E_2 **(8)**, are implicated in many physiological and pharmacological functions of living organisms. Another very interesting group of naturally occurring polyunsaturated compounds are retinoids **(9)** that include vitamin A (**9**, $X{=}CH_2OH$, $Y{=}H$). All these are involved in many essential physiological processes, e.g. vision, reproduction etc. Recently they were found to inhibit carcinogenesis. Their activity is summarized in a number of books and reviews[60,61].



(5)



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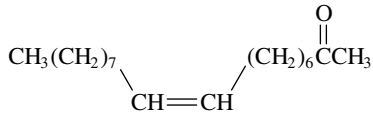

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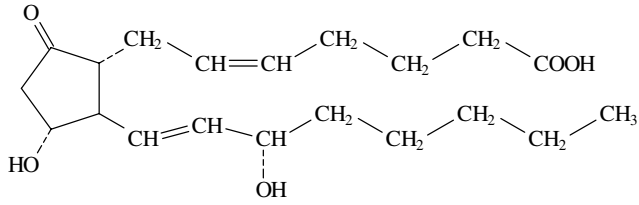
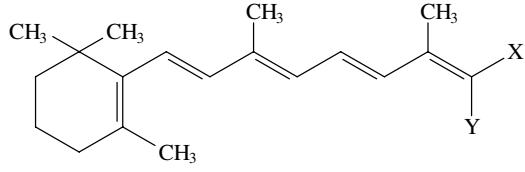


(8)



(9)

The presence of double-bonded fatty acids in proteins and their isomerization was found to help some bacteria to adapt to ambient temperature changes[62]. The alteration of C=C bonds in liposomes plays a role in protection against radiation-induced damage[63].

IV. DETECTION AND LOCALIZATION OF DOUBLE BONDS

There are numerous methods for detection and localization of double bond(s) in polyunsaturated compounds[64]. Recent papers mention derivatization and further detection, usually by GC/MS. The reagents used are 2,2-dimethyl-2-aminoethanol ($Me_2C(NH_2)CH_2OH$) for conversion to oxazolines in nearly quantitative yield[65], oxidation with potassium permanganate[66], ozonization[67] and reduction with hydrazine and subsequent reaction with dimethyl disulfide[68].

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CHAPTER **26**

N-Oxidative transformations of C=N groups as means of toxification and detoxification

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I. INTRODUCTION

The presence of a C=N functionality in xenobiotics, including drugs, is not uncommon as this constituent can occur in aliphatic, alicyclic, aromatic and heteroaromatic structures. Parli and coworkers were the first to report on the biological N-oxygenation of 2,4,6-trimethylacetophenone imine by rat and rabbit liver microsomal fractions to yield a stable oxime[1]. Similarly, amidines, a class of strongly basic imines, have been shown to undergo N-oxidative transformation to the corresponding amidoximes[2]. Subsequent studies with diarylimines indicated that microsomal oxygenation may lead to the formation of diarylnitrones[3]. Administration of bromazepam, a cyclic imine, to dogs has been found to result in nitrone production as a minor urinary pathway[4]. Interest in the role of oximes and nitrones in drug metabolism was enhanced upon the discovery of the occurrence of these N-oxy compounds as intermediates in the hepatic turnover of amphetamines[5,6] eliciting stimulant actions in the central nervous system. Pyridine, bearing a C=N group as part of a heteroaromatic nucleus, is an industrial chemical used as a solvent and as an intermediate in the synthesis of pharmaceuticals, paints and insecticides and has been detected to be metabolically converted to the N-oxide by various animal species[7], as is also the case with some aromatic diazines[8,9].

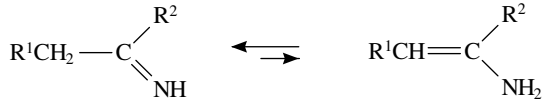
Particular accounts on the biochemistry and pharmacology of N-oxygenation of endogenous and exogenous compounds containing C=N group(s) have not been previously given. The present chapter thus undertakes to collate available data on this subject. Moreover, this compilation of information is hoped to focus attention on this specific area of nitrogen oxidation and promote research in this field.

II. CHEMICAL ASPECTS OF THE N-OXYGENATION OF THE C=N FUNCTIONALITY

A. Types of C=N Functionalities Prone to N-Oxygenation and Chemical Characteristics of the N-Oxygenated Products

Table 1 summarizes the prototypes of C=N functionalities susceptible to N-oxygenation in biological systems. Formation of imines from amines means a transition of the nitrogen electrons from sp^3 to sp^2 hybridization with a concomitant lowering of the basicity[10], the oxidation state of the constituent nitrogen in the imino group[11] being defined as −3. Basically, there exists an imine–enamine tautomerism, the equilibrium being largely shifted toward the imine structure (equation 1). Comprehensive studies on the metabolism

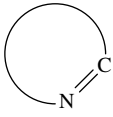
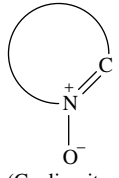
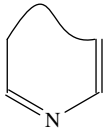
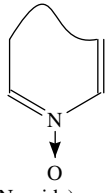
of imines have been frequently hampered by the fact that simple imines are readily hydrolyzed to ketones in the presence of moisture or dilute acids[12]. However, using a series of sterically hindered imines resisting hydrolysis, N-oxidative turnover could be successfully assessed[1,13]. Similarly, amidines and guanidines, representing strong bases containing double-bonded nitrogen atoms, are stabilized by resonance upon protonation to permit metabolic investigation[2,14].



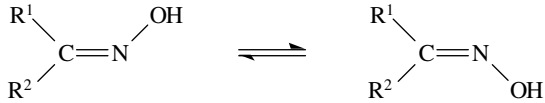
(1)

Oxidation of imine, amidine and guanidine nitrogens yields oximes, oxidative attack at the nitrogen centers in alkyl-, aryl- or cyclic imines affords nitrones. The oxidation state of nitrogen in these functions[11] is defined as −1. Both oximes and nitrones exist as a mixture of two geometric isomers, *Z* and *E*, previously termed *syn* and *anti*, respectively

TABLE 1. Prototypes of C=N functionalities prone to metabolic N-oxygenation

Type of compound	N-Oxygenated product	Model compounds studied	Reference
RCH=NH (Aldimine)	RCH=NOH (Aldoxime)	Butyraldimine	179
$RC(R^1)$=NH (Ketimine)	$RC(R^1)$=NOH (Ketoxime)	Acetophenone imines	1,13,85
$RC(NH_2)$=NH (Amidine)	$RC(NH_2)$=NOH (Amidoxime)	Benzamidines Pentamidine	2,47–50,86 51
$RNHC(NH_2)$=NH (Guanidine)	$RNHC(NH_2)$=NOH (Guanidoxime)	Debrisoquine	52
$RCH=N-R^1$ (N-Substituted imine)	$RCH=\overset{+}{N}(O^-)-R^1$ (Nitrone)	Diarylimines	3,31
 (Cyclic imine)	 (Cyclic nitrone)	Bromazepam Methaqualone	4 43,89
 (Heteroaromatic amine)	 (N-oxide)	Quinolines Pyridines Pyrimidines Purines Pyridazines Pyrazines Triazines	7,18,28,32,41,62,96 15,28,104 8,16,105,106 64,65,107 9,108 9 109

(equations 2 and 3). Under normal conditions, some nitrones are reasonably stable, while others are susceptible to nucleophilic attack and hydrolyze to give primary hydroxylamines and electrophilic aldehydes. Hydrolysis is acid catalyzed, but also occurs at a perceptible rate in neutral solutions at ambient temperature. Nitrones with an aryl substituent at the α-carbon are more resistant to hydrolysis owing to the presence of a double bond in conjugation with an aromatic ring. N-Alkylnitrones generally hydrolyze readily; however, stability increases with the size of the N-alkyl group.



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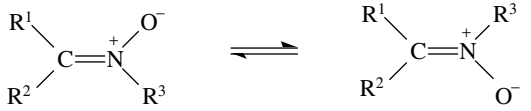


(3)

The class of heteroaromatic amines known to undergo biological N-oxygenation includes pyridine ($pK_a = 5.2$), quinoline ($pK_a = 4.85$), isoquinoline ($pK_a = 5.14$), pyridazine ($pK_a = 2.33$), pyrimidine ($pK_a = 1.3$) and pyrazine ($pK_a = 0.6$) structures[7,9,15,16]. As is evident, basicity of these compounds is highly divergent. N-Oxygenation of the heterocyclic ring systems produces the corresponding N-oxides, a reaction requiring the participation of the lone pair of electrons on the vulnerable nitrogen in the bonding orbital linking the nitrogen and oxygen atom; this process is associated with a change in the oxidation state of the nitrogen from -3 to -1. N-Oxide formation results in a considerable decrease in the pK_a of the amines[15]. Because of resonance stabilization, heteroaromatic N-oxides are chemically more stable and less sensitive to heat as compared with other classes of N-oxides[16,17]. Since no completely uncharged Lewis structure may be written for N-oxides, both the oxygen and nitrogen have octet configuration and bear $(-)$ and $(+)$ formal charges, respectively. When metabolically formed, the polarity of heteroaromatic N-oxides thus strongly favors their urinary excretion[18]. N-Oxide formation, therefore, has been considered a route of detoxication of foreign compounds[11].

B. Methods for the Detection of Oximes, Nitrones and N-Oxides

The detection of products derived from the N-oxygenation of C=N functionalities presents many problems, which illustrate difficulties that are associated with the isolation, identification and quantification of small amounts of water-soluble metabolites. Spectrophotometric methods[19] as well as differential pulse polarographic techniques[20] previously used to determine oximes, nitrones and N-oxides frequently lack sensitivity and/or specificity. Improved analytical methods for the quantification of these N-oxy compounds include chromatographic techniques taking into account the chemical peculiarities of the individual N-oxygenated C=N functionalities. These procedures usually require the chemical synthesis of authentic material for comparison with data obtained with the isolated metabolites, and also for the construction of calibration curves.

1. Paper and thin-layer chromatographic (TLC) methods

TLC has been found to be useful in the separation of 4-hydroxyphenylacetaldoxime generated from L-tyrosine in *E.coli* cell cultures[21]. This method has been also employed to

detect small amounts of isomeric acetaldoximes formed from SKF 40652A, a secondary phenylethylamine[22]; visualization of the N-oxygenated material was achieved by treatment after development of the chromatograms with specific chromogenic reagents or inspection under UV light. Using TLC as an analytical means, oximes were recognized to be metabolites of promazine and chlorpromazine[23]. This technique also permitted detection of oximes isolated from incubation media containing a series of substituted acetophenone imines[13]. Moreover, TLC served to analyze amidoximes produced from ring-substituted benzamidines[2]. Similarly, this method was apt to identify small amounts of nitrones formed from N-substituted amphetamines[24,25] or 4-substituted N-benzylanilines[26].

Multiple TLC systems have been developed taking advantage of a variety of polar solvents for the separation and identification of N-oxides derived from heteroaromatic amines, such as ring-substituted pyridines, quinolines, isoquinolines and quinoxalines[18,27–29]. However, these studies were unable to describe a chromogenic reagent generally applicable to the detection of the N-oxide function in the heterocycles examined. Ascending paper chromatography[30] along with TLC was also used to identify N-oxide metabolites originating from organic compounds containing a pyridyl nucleus[31,32]. Finally, TLC has proved to be useful in the separation of N-oxides arising from metabolic transformation of pyridazines, pyrimidines and pyrazines[8,9]. Identification of trace amounts of metabolites was often aided by the application of radiolabeled compounds[21,32] permitting autoradiography of the TLC plates.

2. Gas–liquid chromatographic (GLC) methods

GLC techniques, frequently combined with mass-spectral analysis to confirm the structures of the separated metabolites, have been applied to the detection of aldoximes and ketoximes generated from phenothiazines[23], acetophenone imines[1,13], phenylethylamines[5,22,33–37] and the phenoxyaminopropane compound mexiletine[38]. Quantification of these products by direct GLC has not always been possible because of their thermolability. This made necessary the development of methods permitting conversion of the substances to heat-stable derivatives, as was achieved by treatment with trimethylsilylating or trifluoroacetylating agents[5,22,23,33–35,37].

Direct GLC has also been used to separate synthetic or metabolically formed nitrones derived from N-substituted phenylethylamines[6,24,25,36,39]. As certain ring-substituted pyridines are thermostable and sufficiently volatile, Gorrod and Damani succeeded to establish procedures for direct GLC analysis of some pyridine N-oxides[18,40,41]. It has to be noted that N-oxides derived from the bispyridyl compound metyrapone undergo catalytic deoxygenation on the glass column during GLC separation to yield a single peak corresponding to that of metyrapone[42]. Similar observations were made with methaqualone N-oxide, a quinazolinone derivative[43]. Instable heteroaromatic N-oxides thus were quantitated after reduction by $TiCl_3$ to their parent amines[43,44].

3. High-performance liquid chromatographic (HPLC) methods

HPLC techniques have proved to be a major advance in direct analysis in a nondestructive manner of compounds bearing an N-oxygenated C=N functionality. Reverse-phase HPLC has been used for the separation of aldoximes[45], ketoximes[46], amidoximes[14,47–52] and nitrones[3,26,53–55]. This method also served to identify N-oxides derived from pyridines[7,29,31,56–63], pyrimidines[8,9,16], pyrazines[9], pyridazines[9] and purines[64,65]; the latter class of heteroaromatic N-oxides was analyzed on cationic exchange columns.

4. Nonchromatographic methods

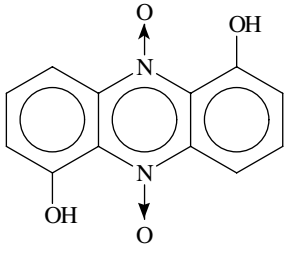
In many instances, oximes[13,22,23], nitrones[24,25,36] and N-oxides[9,18,29] isolated by the chromatographic procedures decribed above have been subjected to mass-spectral analysis to verify their chemical nature. The majority of oximes derived from phenylethylamines produced spectra with fairly abundant molecular ions. Oximes with a benzyl group gave a base peak at *m/z* 91 for this portion of the molecule. Diagnostic ion peaks were generally observed at $(M - 17)^+$ and $(M - 33)^+$. Nitrones produced from N-substituted amphetamines displayed weak molecular ion peaks and a diagnostic peak corresponding to $(M - R)^+$, where *R* is the mass of the N-alkyl group minus 14. N-Oxides arising from oxygenation of pyridines displayed a molecular ion peak in each case and a diagnostic $(M - 16)^+$ ion peak corresponding to the loss of an oxygen atom. An $(M - 17)^+$ peak was shown to be due to the loss of oxygen followed by the loss of H. Similarly, a series of quinoline and isoquinoline N-oxides gave relatively weak $(M - 16)^+$ ion peaks. The subject has been reviewed by Cowan[66].

Alternatively, oximes[13,23], nitrones[3,24,39,55] and N-oxides[30] have been identified by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy. In addition, $^{15}N - NMR$ techniques have been made available for the structural analysis of amidoximes and guanidoximes[50,52]. Owing to the spin of 1/2 of the ^{15}N nucleus, this nitrogen isotope is suitable for high-resolution experiments although its natural abundance of 0.37% causes but a very small magnetogyric ratio. This difficulty can be met by application of the pulse Fourier transform method. Despite this, there is a relative large requirement for material naturally abundant in ^{15}N to obtain spectra of good quality. Spectroscopic data obtained in this way exhibited chemical shifts for imine-type nitrogens in the middle-deshielded region of 380–150 ppm and coupling constants in the range of 60–80 Hz. For details, reference should be made to a recent account by Clement and Kämpchen[67].

III. OCCURRENCE OF N-OXYGENATED C=N FUNCTIONALITIES IN NATURAL AND SYNTHETIC COMPOUNDS AND BIOLOGICAL ACTIVITY

A. Occurrence in Microorganisms and Plants

Iodinine **(1)**, the pigment of *Chromobacterium iodinum*, was the first discovery of a heteroaromatic N-oxide[68]. The compound exhibits close structural relationship to myxin **(2)**, which possesses antibacterial activity[69]. Other naturally occurring di-N-oxides include the antibiotics pullcheriminic acid **(3)** and mycelianamide **(4)** isolated from various bacterial strains[70]. Further, aspargillic acid **(5)**, purified from *Aspergillus flavus*, and emimycin **(6)** represent pyrazine N-oxides characterized by antibacterial potency[15,71]. Mycobactin P **(7)** has been obtained from *Mycobacterium phlei* and is a potent growth factor for



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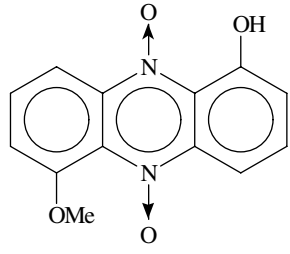

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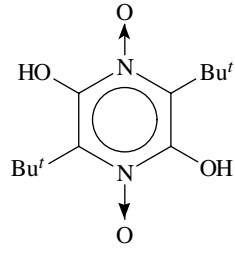

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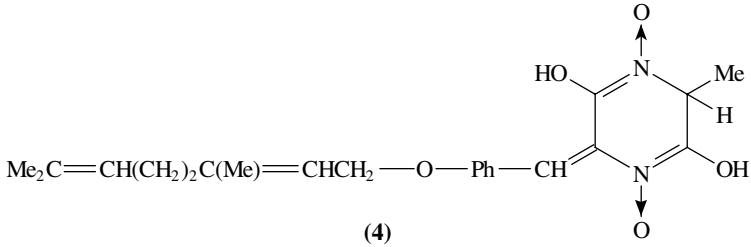

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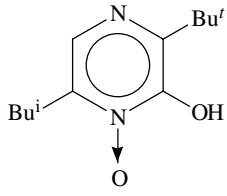

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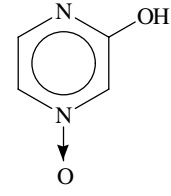

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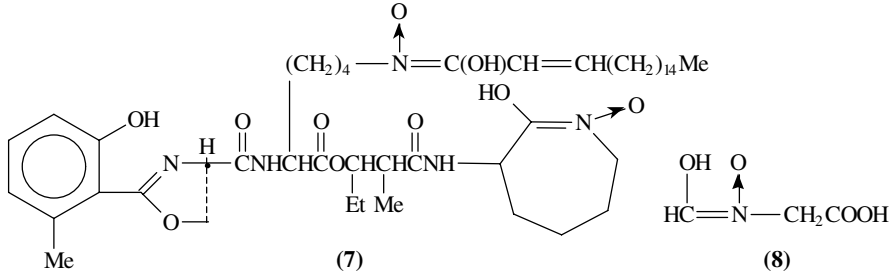
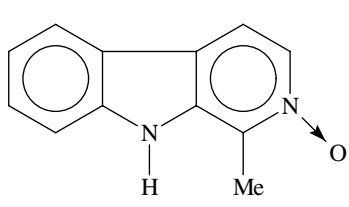


(7) **(8)**

Mycobacterium johnei[72]. Hadacidin **(8)** is produced by several *Penicillia*; its antitumor activity has been related to its antagonism to aspartic acid in adenylate synthesis[73].

N-Oxygenated C=N functionalities also occur in plants. Thus, harman N-oxide (harmanine, **9**) is the main alkaloid in all parts of *Calligonium minimum*[74]. The trunk bark of *Aspidosperma nigricans* contains the unstable olivacine N-oxide **(10)**[74]. Orellanine **(11)** has been isolated from the toadstool *Cortinarius orellanus*[75]. The substance is heat-stable and exerts considerable nephrotoxicity.



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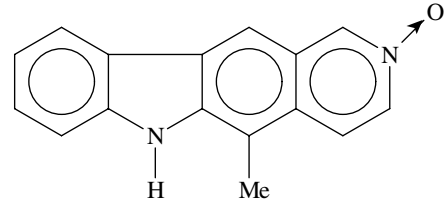

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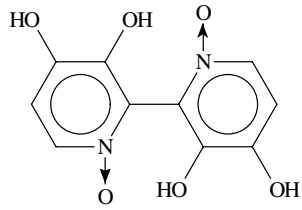
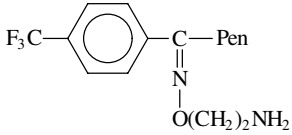


(11)

B. Occurrence in Synthetic Compounds

Although a broad spectrum of pharmaceuticals containing an N-oxygenated C=N functionality has been tested for pharmacological activity, only a few types of compounds proved useful in modern therapy.

The ketoxime derivative fluvoxamine **(12)** is a newer antidepressant thought to potentiate the action of 5-hydroxytryptamine[76]. Oxacillin **(13)**, cefuroxime **(14)** as well as the monobactam aztreonam **(15)** represent potent antibacterial agents of the beta-lactam type[77]. The aldoxime pralidoxime **(16)** and a number of *bis*-quarternary oximes, such as obidoxime **(17)**, can be used as reactivators of the phosphorylated esteratic site of acetylcholinesterase that occurs in the presence of organophosphate inhibitors[78,79].



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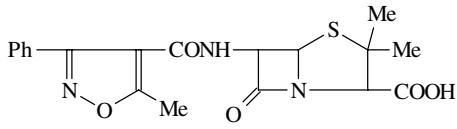

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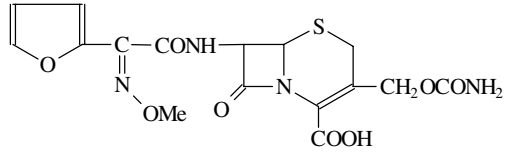

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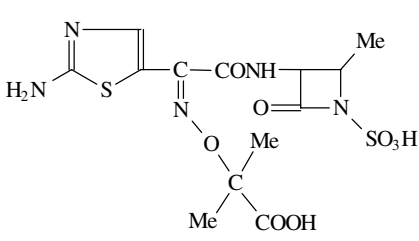

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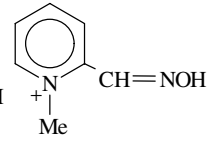

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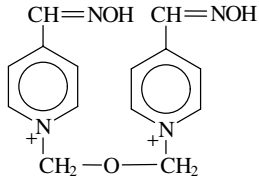
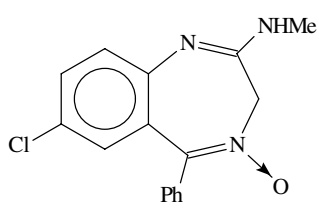


(17)

Similarly, the category of N-oxides comprises compounds of considerable pharmacological interest. Chlordiazepoxide **(18)** possesses potent antidepressant, sedative, anticonvulsant and muscle relaxant properties[80]. Minoxidil **(19)** is an antihypertensive of the vasodilatator type. Ciclopirox **(20)** shows antifungal activity[81].



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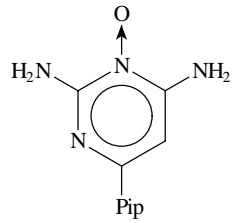

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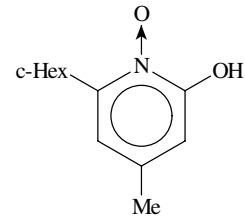
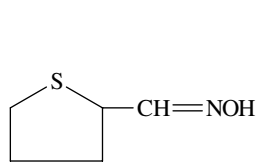


(20)

Within the class of N-oxy compounds designed for experimental use, the tremorogenic action of *Z*-thiophene-2-aldoxime **(21)** has been extensively studied[82]. Tremor is preceded by hyperpnoea and increased locomotor activity. Animals exhibit concurrent behavioral depression and ptosis. Nitroquinoline N-oxide **(22)** is a potent carcinogen, in which the N−O function appears to be essential to carcinogenic activity; conversion to the proximate carcinogen requires reduction of the nitro group to yield 4-hydroxylaminoquinoline N-oxide[83]. Similarly, some purine N-oxides have been demonstrated to induce malignant tumors[84].



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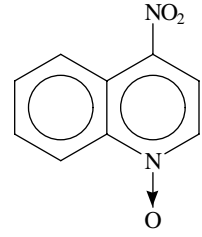


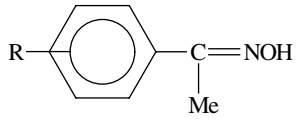
(22)

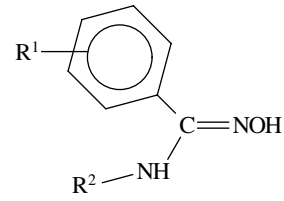
IV. METABOLIC IN VIVO AND IN VITRO FORMATION OF N-OXYGENATED C=N FUNCTIONALITIES

A. Formation of Oximes

Conversion of acetophenone imines to the corresponding ketoximes **(23)** has been studied both *in vivo* and *in vitro*. Thus, small amounts of 2,4,6-trimethylacetophenone oxime were found to be excreted in the urine of male rats dosed with the parent imine[1]. The oxime was also detected to arise from N-oxygenation of 2,4,6-trimethylacetophenone imine in aerobic incubation mixtures containing rat or rabbit liver microsomal fraction fortified with NADPH[1]. These observations were extended to other chemically stable substituted acetophenone imines, and it was shown that hepatic microsomal preparations from various mammalian species catalyzed biotransformation to differing extents, rates of isomeric oxime formation increasing in the order ferret < guinea-pig < mouse < rat < hamster < rabbit[13,85].

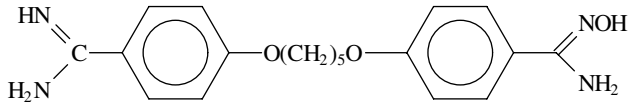
Incubation of benzamidine and its ring-substituted congeners with 9000 *g* supernatant fraction from rabbit liver[2,47,49] yielded the corresponding benzamidoximes **(24a)**. The antiprotozoal drug pentamidine, which can be regarded a diamidine, has been found to undergo N-oxidative transformation to the monoamidoxime **(25)** in human and rabbit liver





(23) **(24)**

(a) $R^1 = H$, Me, CN, Cl; $R^2 = H$
(b) $R^1 = H$; R^2 = Me, *t*-Bu, Ph



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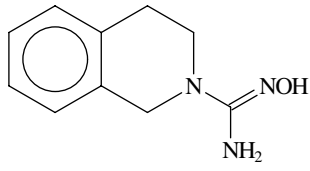
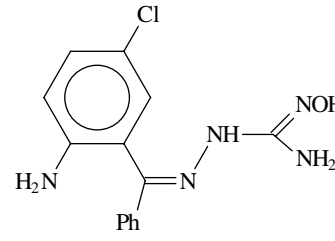


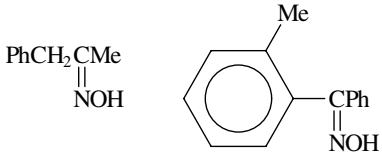


(26) **(27)**

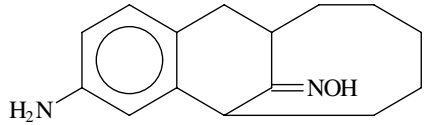
microsomal suspensions[51]. Similarly, amidoximes **(24b)** could be isolated from incubates of N-monosubstituted benzamidines with hepatic preparations from the rabbit[50,86]. The latter system was about 3 times as effective as rat liver microsomes in N-oxygenating debrisoquine[52], a guanidine derivative, to give the corresponding guanidoxime **(26)**. NADPH-dependent enzyme sources from rat and rabbit liver also served to convert the aminoguanidine group of 2-amino-5-chloro-benzophenone amidinohydrazone[14], an antiarrhythmic agent, to the oxime **(27)**.

Moreover, oximes have been recognized to arise from oxidative attack at the nitrogen center of primary arylalkylamines. Thus, phenylacetone oxime **(28)** was detected in reaction media containing amphetamine and rabbit liver preparations[5,33,34]. Analogously, (2,4,6-trimethylphenyl)ethylamine[37] gave the corresponding acetophenone oxime **(23)**. Using washed hepatic microsomes from rabbits, hamsters and guinea-pigs, Gorrod and Raman succeeded to demonstrate the formation of a mixture of isomeric ketoximes **(29)** from *o*-methylbenzhydrylamine[87]. Extracts of urine specimens obtained from rats dosed with dezocine, a bridged aminotetralin derivative, have been shown to contain small amounts of a ketoxime **(30)** metabolite[88].

Incubation of certain secondary[22] and tertiary[23] alkylamines with rabbit liver preparations has been reported to yield aldoximes upon N-oxygenation.



(28) **(29)**

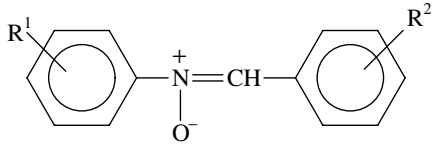


(30)

Apart from mammalian tissue preparations, microbial systems also appear to be active in the metabolic conversion of arylalkylamines to oximes. Thus, incubation broths of the fungus *Cunninghamella bainieri* supplemented with amphetamine have been detected to contain phenylacetone oxime **(28)** as one of the major metabolites[36].

B. Formation of Nitrones

Using male hamster hepatic microsomes, Gorrod and Ulgen were able to demonstrate the formation of diarylnitrones **(31)** from certain diarylimines[3]. Metabolic studies on the cyclic imine bromazepam have shown that the corresponding nitrone **(32)** is excreted in trace amounts by dogs, but not by mice, rats or man[4]. Similarly, the cyclic imino nitrogen in methaqualone affords a nitrone (**33**), which has been found to be the second most abundant urinary metabolite in healthy addults[43,89].



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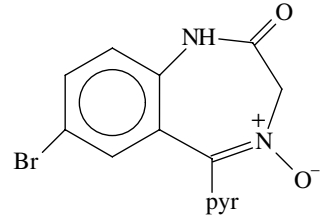

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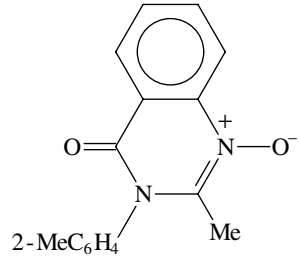
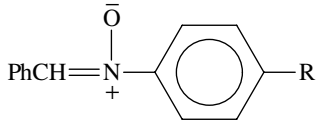


(33)

Moreover, biotransformation of secondary arylalkylamines also affords nitrones. Thus, N-oxygenation of a series of 4-substituted *N*-benzylanilines in liver microsomal preparations from various animal species has been detected to be a minor pathway of metabolism, usually generating α,*N*-diphenylnitrones **(34)** in a species-dependent manner[26]. Nitrone formation was most abundant in liver, kidney and lung[53]. There was a clear sex difference

in nitrone production using rat tissue, while no difference was evident when using mouse microsomes[53]. Several N-substituted phenylethylamines, such as *N*-methyl-, *N*-ethyl-, *N*-propyl- and *N*-benzylamphetamine as well as benzphetamine have been recognized to give nitrones of the general structure **35** as urinary or *in vitro* metabolites after incubation with rat, guinea-pig and rabbit liver tissue or fungal cell systems[6,24,25,36,39,54]. *N*-(1-Phenyl) cyclobutylphenyl nitrone **(36)**, existing in the *trans* configuration about the imine bond, has been isolated from reaction mixtures containing rat liver microsomal fraction fortified with *N*-(1-phenylcyclobutyl)benzylamine[55].



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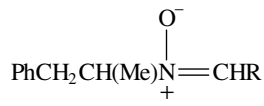

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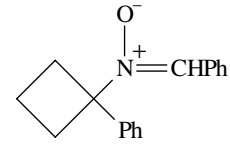
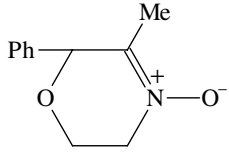


(36)

Heterocyclic secondary amines, such as phenmetrazine or (−)-anabasine, a minor tobacco alkaloid, undergo metabolic attack at the amino groups to finally yield nitrones **37** and **38**, respectively, when incubated with tissue preparations from various mammals[90,91].



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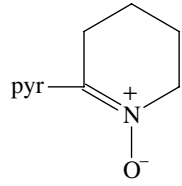

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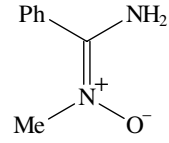
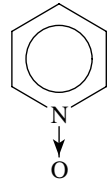


(39)

Incorporation of *N*-methylbenzamidine in hepatic microsomes from rabbits affords the tautomeric α-aminonitrone **39**, a completely new type of metabolite[50].

C. Formation of N-Oxides

N-Oxygenation of heteroaromatic amines to yield N-oxides is a well-established metabolic route. The pyridyl nitrogen is a likely target for electrophilic enzymatic oxidation because of its relatively high electronegativity and its unshared pair of electrons. Indeed, urinary excretion of pyridine N-oxide **(40)** has been observed after intraperitoneal administration of pyridine to mice, hamsters, rats, guinea-pigs, rabbits, cats and man[7,18,57];



(40)

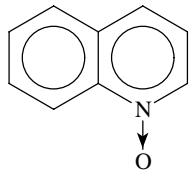
the N-oxide accounted for up to 40% of the administered dose in some species[18]. In studies on the *in vitro* N-oxidative transformation of pyridine, **40** was isolated from hepatocytes and subcellular fractions from the livers and lungs of various mammals incubated with the parent amine[28,29,41,56,58–60,92,93].

Similarly, a series of N-oxides derived from simple 3-substituted pyridines as model compounds, bearing substituents such as −Me, −Et, −Cl, −Br, −F or −CN, were identified as urinary[18] or *in vitro*[28,41,92] metabolites. 3-Acetylpyridine has been reported to afford 1-(3-pyridyl N-oxide)ethanol as a principal metabolic product in the rat[94], while 3-benzoylpyridine undergoes hepatic conversion to 3-hydroxybenzoyl pyridine N-oxide[95]; there are strong differences in the urinary metabolic profile between rat and dog. The urinary excretion of nicotinamide N-oxide in mice and rats has been confirmed after the animals were given nicotinamide[96,97], and the presence of this pyridyl N-oxide has been recognized in mouse liver, kidney, muscle, intestine, lung and heart tissue upon the administration of radioactive nicotinamide[98]. Similarly, nicotinamide and isonicotinamide N-oxides were detected in liver microsomes from rats and rabbits incubated in the presence of the heteroaromatic parent amines[28,56]. *N*,*N*-Diethylnicotinamide (nikethamide), a strong central nervous stimulant, has been shown to be oxygenated at the pyridyl nitrogen to yield the corresponding N-oxide in hepatic and pulmonary microsomes from various mammalian species[28]. This oxy product has a much lower toxicity than the parent drug. The pyridyl moiety of cotinine is prone to N-oxygenation both *in vivo*[99] and *in vitro*[28]. In the presence of mouse or rat hepatic microsomal enzymes, 2-methyl-1,2-bis (3-pyridyl)propane-1-one (metyrapone), a drug used as a diagnostic tool for the determination of residual pituitary function, is converted to a mixture of two isomeric metyrapone mono-N-oxides[31,42,61]. The urinary metabolic profile of the heterocycle has been studied following intraperitoneal administration, and marked species and sex differences in the excretion of the two metyrapone mono-N-oxides have been found[100]. However, quantitative analysis has revealed that two metyrapol mono-N-oxides, formed after keto reduction, are the major metabolic products, together accounting for about 75% of the administered dose[101]. Rats and humans treated with radioactive 1-methyl-3-(3-pyridyl)-5-(2-hydroxymethylphenyl)-1*H*-1,2,4-triazole, a hypnotic, were found to excrete a high percentage of total radioactivity in the form of the pyridyl N-oxide[32]. Similarly, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a potent pulmonary carcinogen, undergoes oxygenation at the pyridyl nitrogen in human kidney cells[62]. The NNK N-oxide exhibits significantly less tumorigenic activity as compared with the parent amine, and is, therefore, regarded as a detoxification product[102].

Examples of the N-oxygenation of 4-substituted pyridines are given by 2-phenyl-1,3-di(4-pyridyl)-2-propanol and 4,4′-bipyridyl, two potent metabolic inhibitors. The former prochiral compound afforded a levorotatory chiral pyridyl N-oxide excreted in the urine upon the administration to rats, dogs and humans, which was also detected after *in vitro* incubation of the parent amine in subcellular fractions from rat liver[30]. Using the $TiCl_3$ reduction technique, N-oxide production has been reported to constitute the major pathway in the metabolic transformation of 4,4′-bipyridyl[15]. The xanthine oxidase inhibitor 3,5-di(4-pyridyl)-1,2,4-triazole undergoes oxygenation at one pyridyl nitrogen, the resulting N-oxide being excreted in the bile[103].

Small amounts of the benzopyridines quinoline and isoquinoline are excreted as their N-oxides **(41)** by guinea-pigs and are also formed by guinea-pig and rabbit hepatic microsomes[15,28]. Moreover, the antimalarial agent chloroquine affords an N-oxide as a metabolite of the quinoline ring system[104].

The two nitrogens in the pyrimidine structure are also likely candidates for enzymatic oxygenation. Indeed, the antibacterial agent 2,4-diamino-5-(3,4,5-trimethoxybenzyl)



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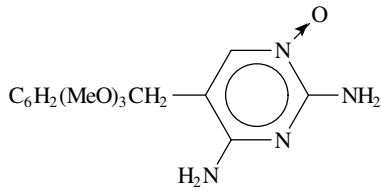

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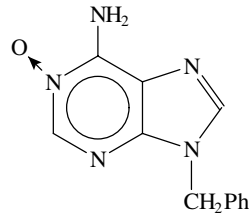
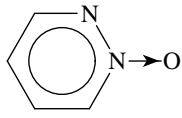


(43)

pyrimidine (trimethoprim) affords small amounts of its 1-N-oxide **(42)** and 3-N-oxide as urinary metabolites in rats, dogs and humans[105]. A species variation in the relative proportions of the isomeric N-oxides of trimethoprim formed has been reported: whereas man excretes about equal amounts of each isomer, rats and dogs excrete predominantly the 1-N-oxide and 3-N-oxide, respectively[105]. N-oxygenation *in vitro* of trimethoprim has also been documented using washed hepatic microsomal preparations from rats, hamsters, mice and guinea-pigs[16]. The antimalarial agent pyrimethamine, another 5-substituted 2,4-diaminopyrimidine, has been shown to be excreted in rat urine mainly as the 3-N-oxide[106]. A series of 6-substituted analogues has been demonstrated to yield 3-N-oxides in liver microsomal fractions from various animal species without evidence of 1-N-oxide formation[8].

In experiments with various 9-substituted adenines, the 1-N-oxide **(43)** derived from 9-benzyladenine has been found to be the major metabolite in dog liver microsomes, while 9-benzhydryladenine underwent N-oxygenation at the 1-position to considerably lower extent[65]. Studies with the two purines conducted with hepatic preparations from other species revealed increasing rates of 1-N-oxide formation in the order guinea-pig < rat < rabbit < mouse < hamster[64,65]. Similarly, the anticoccidial agent aprinocid, a halogenated congener of 9-benzyladenine, is converted to an active 1-N-oxide by liver microsomes from the chicken and dog[107].



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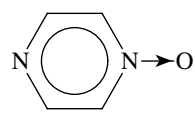

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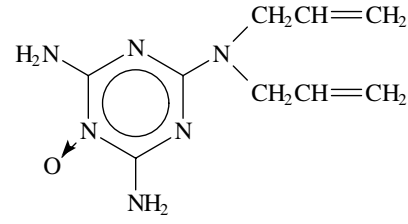


(46)

Electrophilic attack at one nitrogen in pyridazine and the herbicide 3-(2′-methylphenoxy)pyridazine (credazine) has been recognized to produce pyridazine N-oxide **(44)** and the analogous credazine N-oxide when the aromatic diazines were incubated with liver microsomes from various sources[9,108]. Marked species differences in the ability to convert pyridazine to its mono-N-oxide have been observed[9]. The same holds true for the microsomal formation of pyrazine N-oxide **(45)** from pyrazine[9]. The only reported N-oxygenation of a triazine ring appears to be for the vasodilatator *N*, *N*-diallylmelamine[109], which has been demonstrated to undergo a unique bioactivation in rats and dogs to the highly hypotensive nuclear 5-N-oxide **(46)**.

V. ENZYMOLOGY OF THE FORMATION OF N-OXYGENATED C=N FUNCTIONALITIES

In experiments with subcellular tissue fractions, microsomal preparations have been detected to be abundant in N-oxygenating activity giving rise to the formation of oximes[1,5,29,51], nitrones[3,6,26,53] and heteroaromatic N-oxides[15,16,28,65]; these reactions invariably required the presence of oxygen and NADPH as the electron donor. Using ^{18}O, Parli and coworkers were able to demonstrate that the oxygen atom inserted into 2,4,6-trimethylacetophenone imine to yield the corresponding oxime derived from molecular oxygen and not from water[1]. Similarly, complete incorporation of ^{18}O into acetophenone oximes generated from amphetamines in microsomal incubates was observed by Beckett and Bélanger[110]. These findings permitted the conclusion that N-oxygenation of C=N functionalities bears characteristics typical of a monooxygenation reaction[111].

Basically, two major microsomal systems can be envisaged to mediate oxygenation of nitrogen functionalities in organic molecules. One of them, the cytochrome P-450-dependent monooxygenase (P-450; EC 1.14.14.1), has been classified into 22 mammalian subfamilies based on deduced amino-acid sequence identities, each representing a cluster of tightly linked genes[112]. While NADPH-cytochrome P-450 reductase (EC 1.6.2.4) and phospholipid have long been recognized to be essential in electron transfer to the hemoprotein[113], the role of microsomal cytochrome b_5 as a redox component is more complex[114]. The catalytic function of the diverse P-450 isozymes is the two-electron reduction of molecular oxygen to form water and a reactive oxygen species, which serves for insertion into substrate[115]. The multisubstrate flavin-containing monooxygenase (FMO; EC 1.14.13.8), comprising a single gene family composed of five genes[116], provides another significant route for the NADPH- and oxygen-dependent attack at nucleophilic centers in nitrogenous structures[117]. However, both types of monooxygenases operate at distinct catalytic mechanisms: while nitrogen oxygenation mediated by P-450 proceeds via the initial formation of a radical species[118], the flavin 4*a*-hydroperoxide intermediate of the FMO waits in a ready position to oxygenate vulnerable nitrogens in a concerted ionic reaction[119].

The relative contribution, in intact microsomal preparations, of the two monooxygenases to the formation of N-oxygenated C=N functionalities has been frequently assessed by measurements in the presence and absence of selective enzyme inhibitors or positive effectors. These observations were supplemented by studies using highly purified native or recombinant proteins in reconstituted systems.

A. Enzymology of Oxime Formation

Oxime formation can occur by various mechanisms. One possibility is the direct oxygenation of imino groups. The stoichiometry of this process is given in equation 4, where $R^2 = H$ (or alkyl) to yield either aldoximes or ketoximes.

$$R^1C(=NH)R^2 + O_2 + NADPH + H^+ \longrightarrow R^1C(=NOH)R^2 + NADP^+ + H_2O \quad (4)$$

Closer inspection of oxime formation from the stable 2,4,6-trimethylacetophenone imine revealed the N-oxygenating activity to be sensitive to the presence of prototypic inhibitors of the P-450 system, such as carbon monoxide, SKF 525A and DPEA[1].

N-Oxidative turnover was enhanced by pretreatment of the experimental animals with the P-450 inducer phenobarbital, whereas administration of 3-methylcholanthrene left reaction rates unaffected[1]. These early observations were extended to other acetophenone imines, and, using diagnostic modifiers, the formation of **23** was established to involve the obligatory participation of P-450[13,85]. N-Oxygenating capacity of microsomal P-450 was found to decrease with increasing number of methyl substituents in the ring structure of the various acetophenone imines, while the *E*/*Z* ratio of the isomeric oximes produced was augmented[13]. Generally, there was a preference for the formation of the *E* isomers, as is consistent with the lower steric hindrance associated with this configuration. Despite this, the relative proportion of the more sterically hindered *Z* isomers was not constant, but varied with the animal species examined[13]. These findings might hint at the involvement of distinct P-450 isozymes in acetophenone imine N-oxygenation.

Introduction of $R^2 = NH_2$ into the structure of the parent imine presented in equation 4 yields an amidine, which can be subject to N-oxygenation. Thus, a series of benzamidines have been detected to undergo conversion to benzamidoximes **(24a)**, and this process appears to be catalyzed by P-450, as evidenced by susceptibility of the microsomal turnover to CO or SKF 525A and the inability of highly purified hog liver FMO

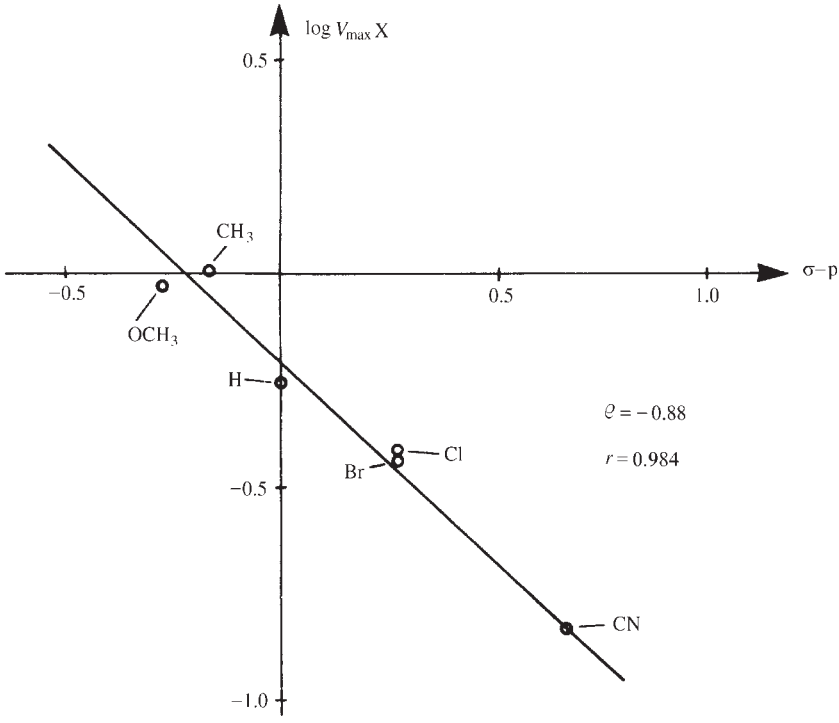
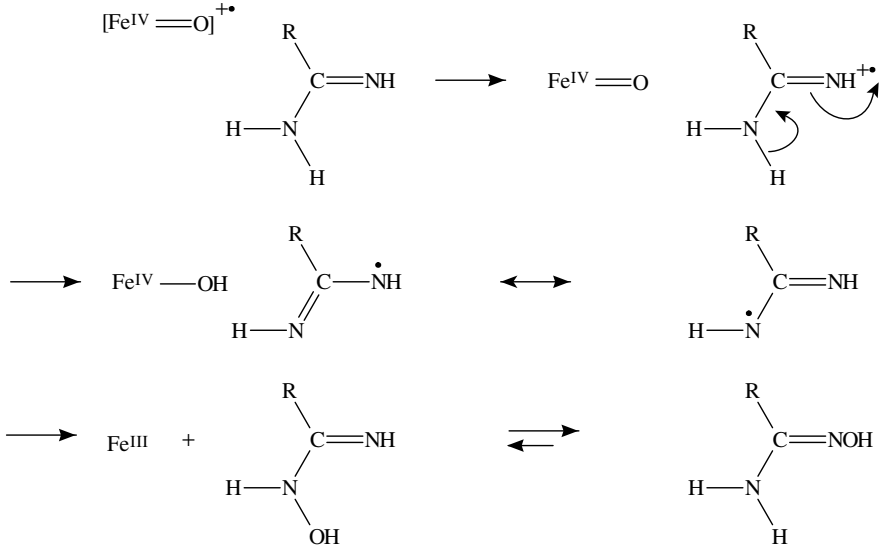


FIGURE 1. Correlation between $\log V_{max}$ and the Hammett σ_p constant for NADPH-sustained N-oxygenation of a series of *para*-substituted benzamidines by rabbit liver supernatant fraction. (Data taken from Ref. 47, with permission)

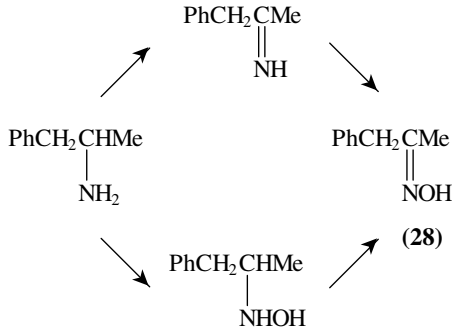
to mediate benzamidoxime formation to an appreciable exent[2,49]; neither superoxide nor H_2O_2 are directly involved in N-oxygenation of the amidine nitrogen[49]. Moreover, N-oxidative transformation of benzamidine is blocked by antibody against NADPH-cytochrome P-450 reductase[86]. Studies with a series of *para*-substituted benzamidines have disclosed a correlation between maximum rates of N-oxygenation and the Hammett σ_p constants[47,86]. Generally, the presence of electron-donating substituents on the aromatic ring increased reaction rates, whereas electron-withdrawing substituents decreased them. From the slope of the line depicted in Figure 1, a reaction constant of $\rho = -0.88$ could be taken, the negative sign of the value lending support to the notion of a radical mechanism operative in P-450-catalyzed N-oxygenation[47,86], as outlined in Scheme 1. Here, the putative oxene species takes up an electron to produce a cation radical, which is stabilized by proton abstraction and exists in a mesomeric state. The latter species undergoes hydroxylation to yield hydroxyamidine, which tautomerizes to furnish the amidoxime. Unequivocal proof of the participation of P-450 in benzamidoxime formation has been provided by experiments with reconstituted systems consisting of hemoprotein and NADPH-cytochrome P-450 reductase embedded in a phospholipid matrix. Using this technique, the constitutive rabbit liver P-450 2C3 and its variants 6βH and 6βL were shown to N-oxygenate benzamidine[48] with a turnover number of 0.63 min^{-1}. This isozyme also accounts for the metabolic conversion of *N*-methylbenzamidine[50], pentamidine[51], debrisoquine[52] and some aminoguanidines[14] to the N-oxy products **24b**, **25**, **26** and **27**, respectively.



SCHEME 1

It has to be pointed out that imines do not only serve as substrates for the N-oxygenase(s) when added exogenously to assay mixtures, but are also acted upon by these enzymes when metabolically formed from primary amines. Thus, it is interesting to note that benzylmethyl ketimine has been proposed as an intermediate in microsomal

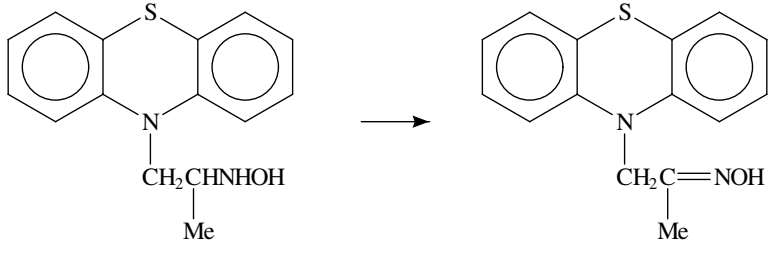
amphetamine metabolism assumed to undergo, in turn, oxygenation to yield phenylacetone oxime[34,110,120] (equation 5).



(5)

A second possibility for metabolic oxime formation comes from biotransformation of aliphatic primary hydroxylamines bearing at least one α-hydrogen[87]. Indeed, **28** was identified in rat and rabbit liver microsomal incubates of *N*-hydroxyamphetamine[33,35,121]. Oxime formation was NADPH/O_2-dependent, but did not appear to involve H_2O_2 or superoxide[35,121]. The *R*(−) N-hydroxy enantiomer was converted at a faster rate than the *S*(+) form[33]. It has to be mentioned that **28** has not been unequivocally accepted as a product generated by enzymatic catalysis: based on chemical stability studies, **28** has been contended to arise from chemical oxidation of *N*-hydroxyamphetamine during the analytical workup procedure[122]. However, the quantitative difference in conversion between the *N*-hydroxyamphetamine enantiomers as well as the inability of boiled enzyme to produce substantial amounts of oxime have been advocated to prove the enzymatic nature of the process[33]. The latter has been shown to be a P-450-independent reaction, since oxime formation from the hydroxylamine precursor was insensitive to the presence of CO, SKF 525A or DPEA and was unaffected by pretreatment of the animals with phenobarbital[35,121]. This finding is in accord with the observation that highly purified FMO can catalyze oxidation of primary alkylhydroxylamines to oximes[123], as illustrated in equation 6. Thus, FMO1 from hog liver brings about oxidation of *N*-hydroxydidesmethylpromethazine[124] to the corresponding oxime **(47)** with $K_m = 160\ \mu M$ and a k_{cat} value of 34 (equation 7). Similarly, cDNA-expressed human FMO3 forms oximes from a series of aliphatic primary hydroxylamines possessing chromophores[125].

$$RNHOH + Enz\text{-}FAD \cdot OOH \longrightarrow R{=}NOH + Enz\text{-}FAD \cdot OH + H_2O \quad (6)$$

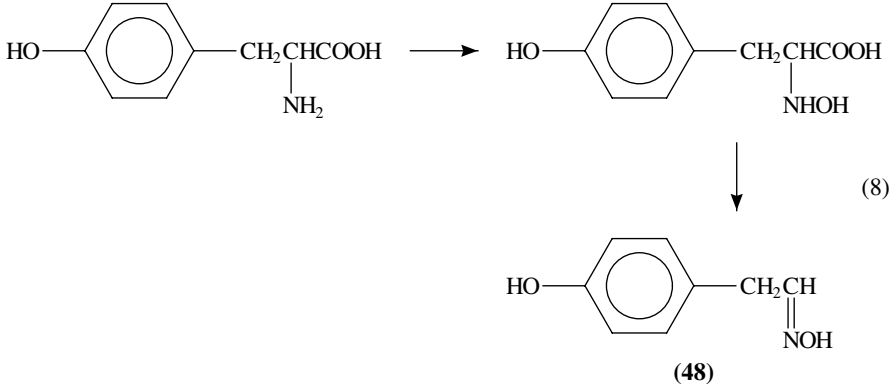


(47)

(7)

Oximes have been isolated along with primary hydroxylamines from incubation mixtures containing arylalkylamines[22,33,87,126] and related compounds[23]. This fostered the notion that, for example, oxime formation from amphetamine might proceed via a hydroxylamine as an alternative intermediate to imine[34] (equation 5). Another possibility was offered by assuming dehydration of an α,*N*-dihydroxyamphetamine metabolite to give the oxime[34]. In a study on the biotransformation of a number of α-substituted amphetamines, oxime levels were found to be highest with the α-Me compound and substantially lower with amines bearing α-Et, α-Pr^i or α-Bu^t substituents[126].

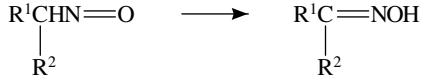
Apart from mammalian systems, hydroxylamine/oxime interconversion also occurs in higher plants. Microsomal fractions prepared from etiolated seedlings of *Sorghum bicolor* catalyze the transformation of the amino acid *L*-tyrosine to the cyanogenic glucoside dhurrin, *N*-hydroxytyrosine and *p*-hydroxyphenylacetaldoxime **(48)** being key intermediates in biosynthesis[127]. Cytochrome P-450 79 (P-450$_{TYR}$) has been demonstrated to account for metabolism of *L*-tyrosine all the way to the aldoxime with K_m = 140 μM and a turnover number of 200 min^{-1}, the dehydration and decarboxylation steps apparently being nonenzymatic reactions[21,45] (equation 8).



(8)

(48)

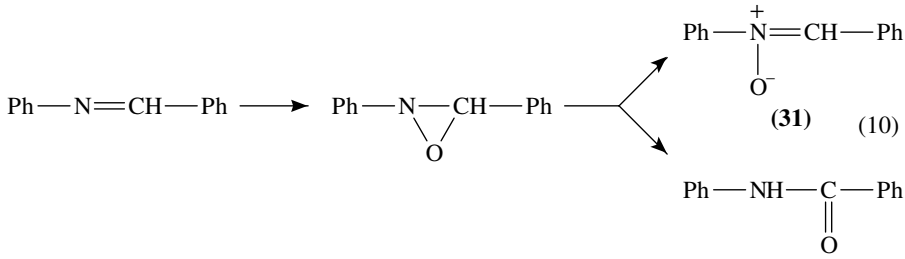
A third pathway for oxime formation is given by tautomerization of nitroso compounds possessing an α-hydrogen (equation 9). Such a process involves an intramolecular redox reaction, in which the nitrogen undergoes a formal two-electron reduction, while the α-carbon is oxidized. Kinetic analysis of this conversion, as performed with a set of α-substituted 2-nitroso-1-phenylethane compounds, has revealed sensitivity toward both the bulkiness of the substituents and the initial concentration of the nitroso dimers[128]. For instance, tautomerization of 2-nitroso-1-phenylpropane to **28** has been proposed to play a role in the metabolism of methamphetamine by fortified rat liver tissue[129].



(9)

B. Enzymology of Nitrone Formation

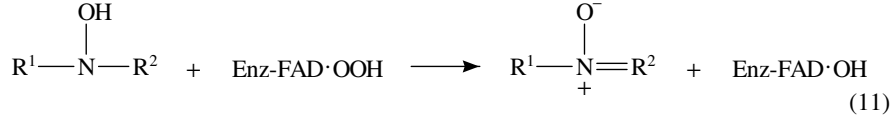
Diarylnitrone **(31)** formation from N-substituted, diaromatic imines has been recognized to require the presence of NADPH/O_2, and has been proposed to proceed via the intermediacy of an oxaziridine[3] possibly arising from reaction of the parent imines with the putative P-450 $[FeO]^{3+}$ species in analogy to the oxidation of olefins[118]. Ring cleavage of the oxaziridine then yields nitrone or amide (equation 10).



(10)

Moreover, secondary hydroxylamines, generated by N-oxygenation of secondary amine compounds, can afford nitrones after oxidative attack. In this way, a series of N-substituted amphetamines has been found to produce the corresponding nitrones **(35)** in liver preparations fortified with NADPH[6,24,25,54,110,129,130]. When *N*-hydroxy-*N*-methylamphetamine was used as the substrate, considerably more nitrone was formed in the presence of liver supernatant containing NADPH than with supernatant or cofactor alone[129]; on the other hand, appreciable quantities of nitrone were obtained, when *N*-hydroxy-*N*-propylamphetamine was incubated in mixtures containing supernatant but no cofactor, or boiled supernatant with NADPH[130]. These findings clearly indicate that both enzymatic and nonenzymatic processes are operative in the oxidative transformation of the hydroxylamines to the nitrones. While there was only a small enantiomeric preference, during nitrone formation, for the *S*- and *R*-isomers of *N*-benzylamphetamine[6,131], *R*(−)-*N*-propylamphetamine strongly favored nitrone production in liver supernatant[130]; no correlation between nitrone and P-450 levels could be established[130].

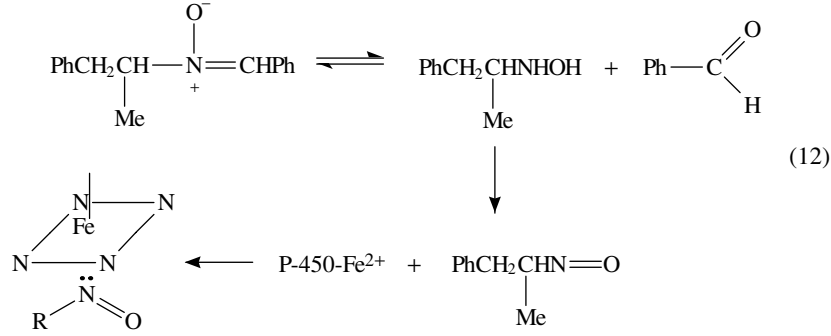
Similarly, hamster hepatic preparations convert *N*-benzyl-4-chloroaniline[53] to a mixture of intermediary hydroxylamine and stable α,*N*-diphenylnitrone **(34)** end product with K_m values ranging from 300 to 420 μM. Velocity of nitrone formation from *N*-benzylaniline is enhanced when the pH of the reaction medium is raised from 7.4 to 8.5 and is diminished by the presence of methimazole[53,132], as is typical of a FMO-catalyzed process[133]. Indeed, the flavin-containing monooxygenase has been reported to metabolize secondary hydroxylamines, such as *N*-methyl-*N*-benzylhydroxylamine[19,134], *N*-methyl-*N*-benzhydrylhydroxylamine[19] or *N*-hydroxynorzimeldine[135], to the corresponding nitrones, as illustrated by the general equation 11. Reactions probably proceed via unstable hydroxylamine N-oxides, which readily dehydrate to yield nitrones, asymmetric secondary hydroxylamines affording two isomeric N-oxy products[134]. FMO-dependent hydroxylamine oxidase activity requires the presence of NADPH and oxygen; cofactor cannot be replaced with H_2O_2[19].



(11)

However, with certain secondary hydroxylamines, P-450, too, can catalyze transformation to nitrones. Thus, incubation of *N*,*N*-(1-phenylcyclobutyl)benzyl hydroxylamine with P-450 2B1 in the presence of NADPH-cytochrome P-450 reductase and NADPH has been demonstrated to trigger nitrone **36** formation with $K_m = 48$ μM by direct oxidation of the N-hydroxy compound; exogenous catalase did not change the amount of product generated[55].

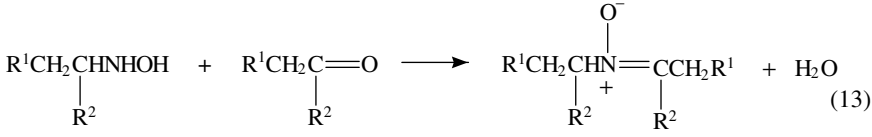
Nitrones, such as *N*-methylene-1-phenyl-2-propylamine N-oxide or *N*-benzylidene-1-phenyl-2-propylamine N-oxide, have been found to produce so-called metabolic-intermediate (MI) spectral complexes with phenobarbital-inducible P-450 characterized by Soret bands positioned around 455 nm[54,136,137]; the presence of NADPH/O_2 was a prerequisite for adduct formation (Figure 2). Comparative studies on the correlation between MI complex formation and dealkylation of N-substituted phenylalkylamines suggested that the nitrones themselves were unlikely to represent the ultimate ligands, but rather served to release, upon their hydrolysis, primary hydroxylamines as precursors to the corresponding nitroso compounds presumed to bind to the heme iron of P-450[136,137]. A representative sequence of events for this process is given in equation 12. Iron chelation by the nitroso functionality affords a tight, quasi-irreversible complex associated with severe inhibition of P-450 activity[138].



(12)

It seems noteworthy that, apart from the P-450 system, other hemoproteins also appear to be active in the production of nitrones from secondary hydroxylamines. Thus, in the presence of O_2, hemoglobin brings about diarylnitrone **(31)** formation from *N*-benzylphenylhydroxylamine, presumably by a peroxidative mechanism[139].

In addition to the pathways described above, nitrones can derive from condensation of a primary hydroxylamine with an aldehyde or ketone[140]. Under simulated biological conditions, Beckett and coworkers were able to demonstrate that primary hydroxylamines metabolically formed from amphetamine, mexiletine or norfenfluramine readily combined with ketones produced by metabolic deamination of the primary amines[141]. Reactions can be formulated according to equation 13, where R^1 = aryl, alkyl or aralkyl, and R^2 = alkyl or H.



(13)

Moreover, nitrones can be generated from N-hydroxy products during extraction into an organic solvent, such as diethyl ether. The latter contains acetaldehyde as an impurity even after careful distillation. Indeed, nitrones arising as artifacts from the reaction of primary hydroxylamines, metabolically derived from methamphetamine and chlorpromazine, with acetaldehyde upon sample treatment with ether have been identified[23,39]. Acetone is frequently used as one of the components of the solvent systems applied for TLC analysis.

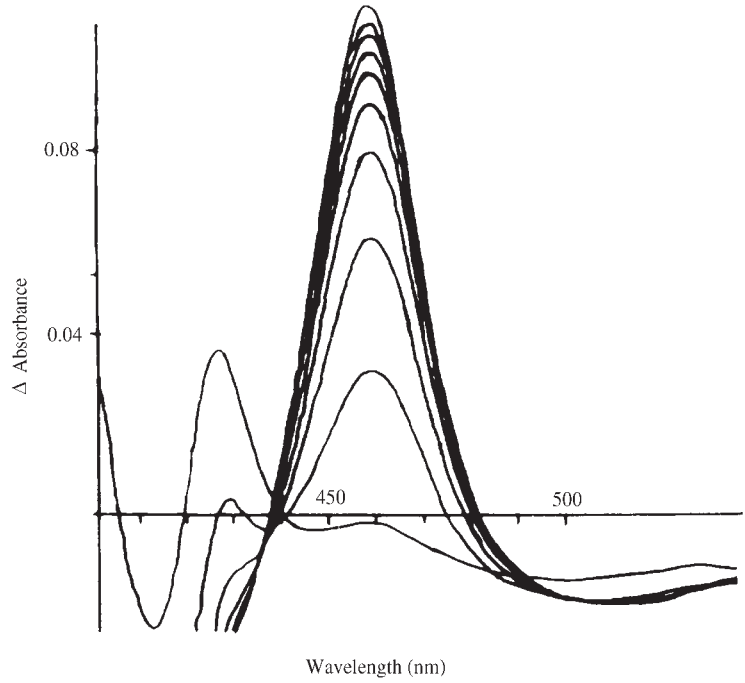
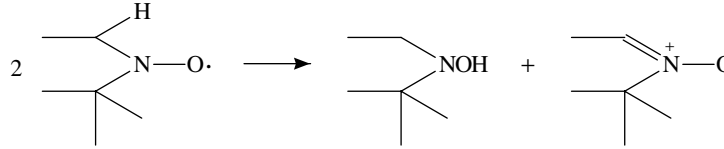


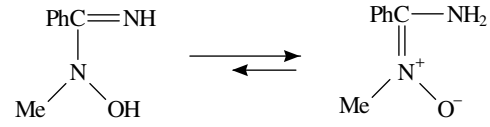
FIGURE 2. Difference spectrum produced during NADPH/O_2-dependent rat liver microsomal metabolism of *N*-methylene-1-phenyl-2-propylamine N-oxide. The time interval between each scan is about 40 s. (Data taken from Ref. 136, with permission)

The presence of small amounts of this agent converts primary hydroxylamines completely to their nitrones[141].

Further possibilities for nonenzymatic nitrone formation include the disproportionation of nitroxides in cases where the nitroxyl functionality is attached to an α-carbon bearing at least one hydrogen[142] (equation 14), or the rearrangement of certain N-hydroxy compounds to the thermodynamically more stable tautomeric forms, as has been observed for the formation of α-aminonitrone from *N*-hydroxy-*N*-methylbenzamidine[50] (equation 15).



(14)

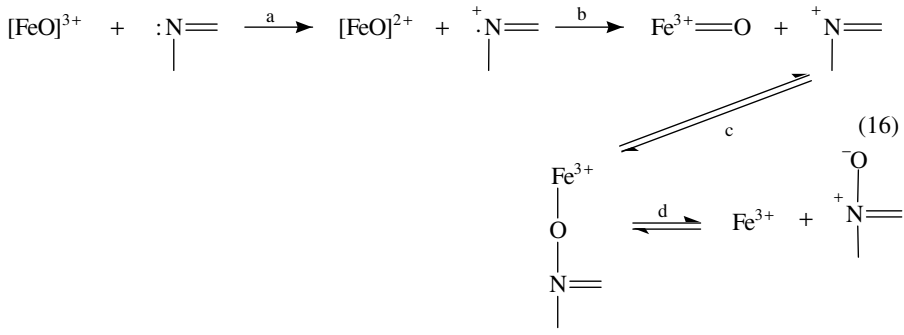


(15)

(39)

C. Enzymology of N-Oxide Formation

N-Oxygenation of heterocyclic aromatic amines to yield N-oxides appears to be a domain of the P-450 system, as the 4*a*-hydroperoxyflavin intermediate of the FMO has been recognized to be a not sufficiently strong oxidant to attack the nitrogen in this type of amines[123]. This view is consistent with the inability of highly purified FMO from rabbit liver to catalyze the formation of N-oxide **40** from pyridine[29], while sensitivity of hepatic microsomal N-oxygenation of the base and some simple 3-substituted derivatives to the presence of CO, metyrapone, SKF 525A, *n*-octylamine and ethyl isocyanide suggests involvement in this process of P-450[58,59,92,143]. In accord with this, any treatment of microsomes causing destruction of P-450 also gives rise to a fall in pyridine N-oxygenase activity[92]. Moreover, immunochemical titration of microsomal fractions with antibody against NADPH-cytochrome P-450 reductase has been shown to inhibit pyridine N-oxide production, lending further support to a pivotal role of P-450 in catalysis[59]. The putative reaction sequence is presented in equation 16. A key step in heteroatom oxygenation is electron abstraction (a) to yield an aminium radical[118]. Electron transfer from this species (b) gives a cation/Fe^{3+}=O pair that generates an Fe(III)−N-oxide adduct (c). Indeed, N-oxidative turnover of pyridine by hepatic microsomes from phenobarbital-pretreated rabbits is associated with the gradual formation of a 442-nm-absorbing metabolic-intermediate spectral complex having the oxygen atom of the polar N−O function coordinated to the heme iron[29]. This adduct decays to release stable N-oxide and ferric pigment (d).



(16)

Special attention has been drawn to the effects of selective P-450 inducers on the N-oxygenation of pyridines. Thus, pretreatment of animals with phenobarbital has been reported to result in a 3- to 13-fold increase in rates of N-oxide formation, while 3-methylcholanthrene left activities unaffected[92]. In rabbit hepatic microsomes, the barbiturate increased the level of immunoreactive P-450 4B, a low-affinity isoform (K_m = 949 μM) accounting for 80% of total pyridine N-oxide production at high amine concentration[60]. Pyridine administration to rats and rabbits substantially elevated the P-450 2E1 content of liver microsomes, whereas expression of P-450 4B was only marginally enhanced[59,60]. The former isozyme was recognized to represent a high-affinity pyridine N-oxygenase (K_m = 81 μM)[60].

Comparative studies[60,93] with highly purified cytochromes P-450 1A2, 2B4 and 2E1 recombined with NADPH-cytochrome P-450 reductase and phospholipid revealed that the latter hemoprotein species catalyzed conversion of pyridine to its N-oxide with the largest turnover number (*ca* 5 min^{-1}). It is interesting to note that P-450-enriched fractions,

obtained from crude extracts of *Streptomyces griseus*, have been found to effect NADPH-driven N-oxygenation of pyridine when complemented with ferredoxin and NADPH-ferredoxin reductase from spinach[144].

Participation of P-450 in the microsomal pyridyl N-oxygenation pathway has been further inferred for compounds such as cotinine[145], metyrapone[42] and 2-phenyl-1,3-di(4-pyridyl)-2-propanol[30] from results obtained with diagnostic inhibitors or inducers. Cytochrome P-450 2B1, either heterologously expressed in human Ad293 kidney cells[62] or highly purified from phenobarbital-induced rat liver[63], preferentially attacks the pyridyl nitrogen in the pulmonary carcinogen NNK with $K_m = 131$ μM and a turnover number of about 0.3 min^{-1}. Similarly, P-450 appears to be involved in the production of N-oxides from some benzopyridines, such as quinoline **(41)** or isoquinoline[146].

Detailed work has been devoted to the elucidation of factors governing N-oxygenation of amino azaheterocycles. To this end, a series of substituted 2,4-diaminopyrimidines and 6-aminopurines was subjected to metabolic analysis[8,16,64,65,147,148]. Generally, P-450

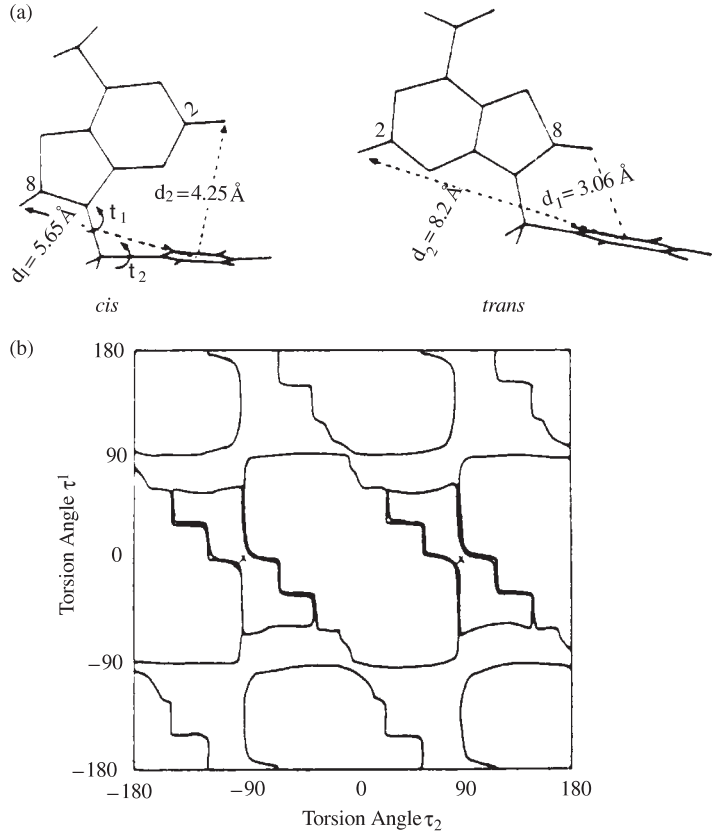
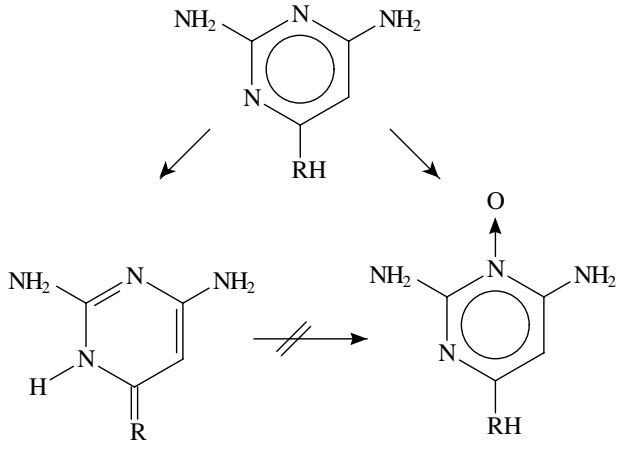


FIGURE 3. Graphic displays of the *cis* and *trans* conformations of 9-benzyladenine (a) and variation of the potential energy of the azaheterocycle as a function of the torsion angles τ_1 and τ_2 (b). Contours are shown at intervals of 1 kcal mol^{-1} with the lowest energy level (−17.6 kcal mol^{-1}) indicated by the symbol (x). (Data taken from Ref. 148, with permission)

was found to be responsible for oxidative attack at the vulnerable *endo*-nitrogens in these compounds to yield N-oxides (**42**, **43**), as evidenced by blockage of this process by the presence of modifiers such as CO, SKF 525A, DPEA, metyrapone and *n*-octylamine[8,16,148]. The stimulatory action of pretreatment of animals with phenobarbital on N-oxide formation from the heterocycles was taken as an indication of the preponderant involvement of barbiturate-inducible P-450 isoform(s) in catalysis[8,16,148]. This type of isozyme is known to accommodate within its active site nonplanar nitrogenous compounds characterized by large depth, small area-to-depth ratio and flexibility in conformation[149]. Such a favorable geometry appears to be afforded by some 9-substituted adenines. Calculation of the potential energies as a function of bond rotations relating the 9-substituents with the ring system revealed 9-benzyl- and 9-benzhydryladenine to be low-energy conformers (Figure 3) most likely existing in the *trans*-form in solution[65]. Using ^{1}H-NMR spectral techniques, it could be seen that the phenyl rings in those structures were close to the 8-H protons, exposing $N_{(1)}$ to permit 1-N-oxide **(43)** formation[65]. The N-oxy products, once formed, have been proposed to be stabilized by hydrogen bonding with the *exo*-amino group[64]. These findings were interpreted to provide evidence of the importance of stereochemistry in controlling N-oxygenation of these compounds.

Experiments with 5,6-substituted 2,4-diaminopyrimidines (pyrimethamine, metoprine) showed that N-oxygenation occurred at the ring nitrogens leading to the formation of both 1- and 3-N-oxides[8]. The failure to form any 1-N-oxide from 6-monosubstituted azaheterocycles obviously could not be due to steric hindrance by the substituent at the 6-position. In this case, amine–imine tautomerism has been proposed to be a determinant of the site of biological N-oxygenation[148,150], as illustrated by equation 17. Some correlation appears to exist between binding interaction of amino azaheterocycles with P-450 and susceptibility to N-oxygenation. Thus, the N-oxide forming 2,4-diamino-6-piperidinopyrimidine[8] has been demonstrated to generate a marked low-spin adduct with ferric P-450[148] characterized by a Soret band centered around 420 nm, while its 3-N-oxide derivative **(19)** elicited a 438-nm-absorbing spectral species[151] with $K_d = 2.4$ μM.



(17)

Electron density at a particular *endo*-nitrogen and lipophilicity are other factors which may have an influence on the N-oxygenation of pyrimidines and purines by the P-450 system[64,65,147,148].

VI. FURTHER TRANSFORMATIONS OF N-OXYGENATED C=N FUNCTIONALITIES

A. Enzymatic Processes

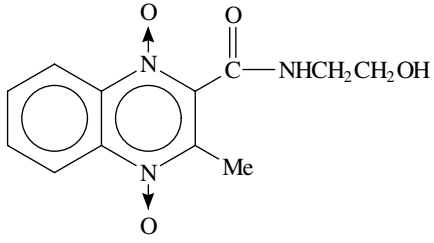
1. Reductions

Among other options, N-oxygenated C=N functionalities can undergo enzymatic reduction. Thus, acetophenone oxime **(23)** has been found to be reduced under anaerobic conditions to the corresponding hydroxylamine by microsomes fortified with NADPH. The reductive process was sensitive to O_2, but insensitive to CO and exhibited substantial species differences: rat liver homogenates reduced the oxime only to the level of the hydroxylamine, while liver preparations from guinea-pigs, mice and hamsters converted it to the amine[152,153]. Similarly, rabbit and human liver microsomes have been reported to reduce the amidoxime **25** derived from pentamidine to the parent compound with $K_m = 8.8\ \mu M$; NADH was the preferred cofactor, and lowering the pH from 7.4 to 6.3 gave rise to a pronounced increase in the rate of reductive transformation, whereas the alternative substrate *N*-methylhydroxylamine was inhibitory[51]. The enzyme involved appeared to be identical with that responsible for the reduction of oximes **24**, **26** and **27** originating from the N-oxygenation of benzamidines[154], guanidines[52] and aminoguanidines[14], and seemed to correspond to the NADH-dependent reductase system previously purified from liver microsomes[19,155].

Although heteroaromatic N-oxides are more stable metabolically than other types of N-oxides, there is ample evidence from experimental data that reduction does occur to a certain extent. When radiolabeled pyridine N-oxide **(40)** was administered intravenously to rats, almost 95% of the dose was recovered unchanged in the urine. However, after oral dosing, only 50% of the urinary radioactivity corresponded to the N-oxide, suggesting that the heteroaromatic N-oxide had been subject to reduction by the gut microflora[156]. This finding is in agreement with *in vitro* studies demonstrating the reduction of some pyridyl N-oxides by mammalian tissues. Thus, Chaykin and Bloch were the first to show nicotinamide N-oxide reduction by pig liver homogenates[157]. The same group succeeded to solubilize an enzyme from hog liver that reduced nicotinamide N-oxide to the parent amine. The reductase was a metalloflavoprotein and exhibited dependence on NADH[158]. This enzyme had properties similar to those of xanthine oxidase (XOD; EC 1.1.3.22), and XOD purified from milk was indeed able to catalyze the reduction of nicotinamide N-oxide; the reaction was inhibited by cyanide and oxygen[159] and proceeded by direct transfer of the oxygen atom from nicotinamide N-oxide to xanthine[160]. In later experiments, evidence was provided that aldehyde oxidase (EC 1.2.3.1), supplemented with its electron donor, also functions as a major liver enzyme responsible for the reduction of nicotinamide N-oxide to nicotinamide[161]. It is interesting that the cytosolic aldehyde oxidase can mediate NAD(P)H-sustained nicotinamide N-oxide reduction when combined with the microsomal NADPH-cytochrome c(P-450) reductase (EC 1.6.2.4) redox protein[162]. Similarly, nicotinic acid N-oxide has been found to be reduced *in vivo* after an oral or intravenous dose to rats, and this activity was associated with the hepatic cytoplasm[163].

Oral administration of **42** to rats resulted in extensive reduction to trimethoprim[106]. The 1,4-di-N-oxide olaquindox **(49)**, a substance used as a growth promotor in cattle breeding, pig husbandry and poultry farming, has been shown to be converted to a limited extent to the 4-mono-N-oxide in rats[164], and compound **46** was readily reduced to *N*,*N*-diallylmelamine both *in vivo* and *in vitro*[109]. The anerobic reduction, in the presence of xanthine oxidase, of a series of purine N-oxides, such as adenine 1-N-oxide or guanine

3-N-oxide, has been pointed out by Stöhrer and Brown[165]. This metabolic step is considered a detoxification mechanism[166] for this class of azaheterocycles, many of which exert oncogenic actions[84].



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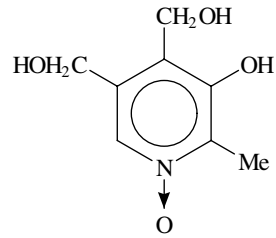

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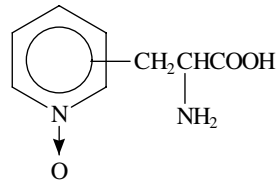
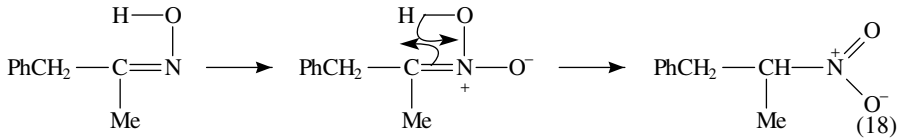


(51)

Microbial reduction of heteroaromatic N-oxides has also been reported. Thus, pyridine N-oxide **(40)** is reduced to pyridine in fermenting sucrose solutions containing baker's yeast[167]. Similarly, the vitamin B_6 derivative pyridoxine N-oxide **(50)** has been demonstrated to undergo reduction in yeast incubates[168]. Resting cells of *Escherichia coli* transform nicotinic acid N-oxide to nicotinic acid[169]; it has been concluded that certain microbes can adaptively produce enzymes which reduce the N-oxide, so that the nicotinic acid formed can be utilized. Pyridylalanine N-oxides **(51)** block the growth of *Escherichia coli*, the 4-isomer being the most potent inhibitor[170]. This isomer is the most rapidly reduced to 4-pyridylalanine, the putative toxicant. Since *Lactobacillus arabinosus* does not bring about reduction of the isomeric N-oxides, this organism remains unaffected by their presence[170].

2. Oxidations

When 2,4,6-trimethylacetophenone oxime **(23)** was reacted with fortified rabbit liver supernatant, analysis of the extracts permitted the identification of the corresponding nitro derivative as a metabolite[37]. Similarly, incubation in the presence of NADPH/O_2 of phenylacetone oxime **(28)** with hepatic preparations from rabbits, mice, hamsters, guinea-pigs and rats yielded variable amounts of 2-nitro-1-phenylpropane[171]. Formation of the nitro compound **(52)** was almost absent in assay media containing no cofactor or heat-denaturated supernatant, suggesting enzymatic turnover of the oxime[172]. The potential reaction sequence has been proposed to include N-oxygenation followed by isomerization[172] (equation 18). The process is unlikely to be catalyzed by the FMO, since the 4*a*-hydroperoxyflavin does not attack oximes[123]. Matsumoto and Cho reasoned that oxidative activity might be associated with the cytosolic rather than with the microsomal liver fraction[35].



(18)

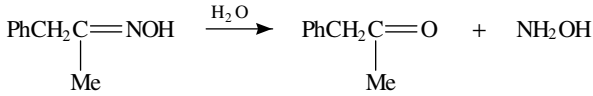
(52)

A novel pathway for oxidative transformation of oximes has been recently described. Thus, purified P-450 2C3 reconstituted with NADPH-cytochrome P-450 reductase and phospholipid has been found to convert the amidoxime derivative of pentamidine **(25)** to the corresponding amide and NO[51]. This isozyme also oxidized the guanidoxime **(26)** originating from N-oxygenation of debrisoquine to the urea derivative[52]. Reactions required the presence of NADPH/O_2 and appeared to involve both the oxygenase and peroxidase activity of P-450[51,52]. In accord with these findings, a series of aldoximes, ketoximes, amidoximes and guanidoximes were oxidized by liver microsomes from dexamethasone-treated rats with the formation of nitrogen oxides, and it was concluded that oxidative cleavage of the C=NOH bond is a general P-450 3A-mediated reaction[173] proceeding according to equation 19 (R^1, R^2 = H, alkyl, aryl, NH_2). This process has been considered to be analogous to the biosynthesis of NO by two-step oxidation of L-arginine, as promoted by NO synthases (NOS, EC 1.14.13.39), which are hemoproteins related to cytochromes P-450[174]. The second step in the catalytic cycle, oxidative denitration of the guanidoxime intermediate (N^{ω}-hydroxy-L-arginine) to release citrulline and nitric oxide, is likely to involve a Fe^{3+}-OO^- species[174] and is also brought about by the classical rat liver P-450[175]. Nitric oxide (endothelium-derived relaxing factor; EDRF) produced by the constitutive endothelial NOS inhibits adhesion of platelets and polymorphonuclear granulocytes to the endothelial surface and is an important factor in the maintenance and regulation of vascular tone[176]. It has to be mentioned that NO is capable of oxidizing guanidoximes to generate another potent, longer-lived, and as yet unidentified vasoactive agent, possibly HNO[177].

$$R^1R^2C = NOH \longrightarrow R^1R^2C = O + NO\ (NO_2^-, NO_3^-) \tag{19}$$

3. Deaminations

Results on the role of oximes in deamination reactions are ambiguous. Phenylacetone oxime **(28)** was reported by Hucker and coworkers[34] to be prone to enzymatic hydrolysis in rabbit liver supernatant to yield phenylacetone, the ketone being reduced to 1-phenylpropan-2-ol by the presence of microsomal oxidoreductases (equation 20). This mechanism requires incorporation of oxygen from water into the ketone. However, experiments with ^{18}O in the atmosphere revealed that the carbonyl group of phenylacetone formed in rabbit liver microsomal incubates contained either ^{18}O or ^{16}O, the presence of ^{16}O in the product obviously not arising from exchange of ketone ^{18}O with solvent[120]. These findings were interpreted to mean that, apart from the hydrolytic route, a significant proportion of phenylacetone had been formed via an oxidative pathway, postulated as involving loss of ammonia from a carbinolamine intermediate[120].



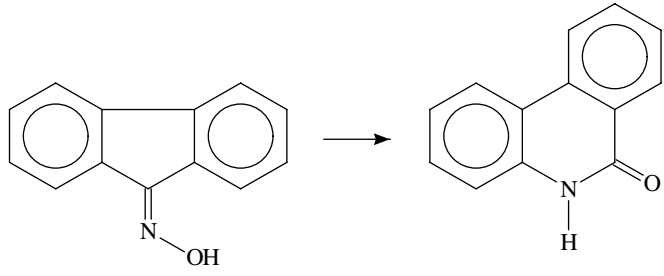
(20)

Reinvestigation of the metabolic turnover of **28** in fortified hepatic microsomes from rabbits showed that the oxime did not readily undergo hydrolysis to ketone[120]. Similarly, acetophenone oxime has been demonstrated to be fairly resistant toward hydrolytic transformation in anaerobic rat liver homogenates[152], while incubation of 2,4,6-trimethylacetophenone oxime **(23)** with rabbit liver preparations gave ketone and alcohol[37]. The stability toward hydrolysis of certain oximes on the one hand and the preponderant incorporation of ^{16}O into the ketone products on the other led to the proposal that ketone formation might proceed via hydrolysis of the corresponding imine intermediates to eliminate ammonia[87,120].

4. Isomerization and rearrangement reactions

As discussed previously, asymmetric oximes show geometric isomerism owing to restricted rotation about the C=N bond (equation 2). Investigations into the further metabolism of the *Z*-isomer of *o*-methylbenzophenone oxime, the predominant and more stable form of this N-oxy compound, in hamster hepatic microsomes disclosed conversion to the *E*-enantiomer, maximum transformation being dependent on the presence of NADPH, as was consistent with the participation in the isomerization process of microsomal enzyme(s)[178]. The extent of metabolic conversion of the *Z*- to the *E*-isomer was observed to vary with the species and sex of the animals used. The reaction was catalyzed by a number of organ homogenates, being maximal with lung and liver tissue. Microsomal isomerization was blocked by CO, SKF 525A and DPEA, indicating the involvement of P-450[178]. It was speculated that isomer interconversion took place via an α-hydroxy or a hydroxylamine intermediate.

Another interesting type of reaction is the oxime–amide rearrangement, as has been reported for the enzymatic transformation of fluorenone oxime to phenanthridinone[46] (equation 21). The process is catalyzed by NADPH-supported enzyme(s) located in the mitochondrial and microsomal fraction of rat liver, is insensitive to the presence of O_2 and CO, but is stimulated by phenobarbital administration to the animals. The reaction mechanism has been postulated to be analogous to the Beckmann principle, the enzyme serving as an acid catalyst[46]. Similarly, *n*-butyraldoxime has been found to undergo a Beckmann-type dehydration catalyzed by P-450 to form butyronitrile[179] (equation 22).



(21)

$$PrCH{=}NOH \xrightarrow{-H_2O} PrC{\equiv}N \qquad (22)$$

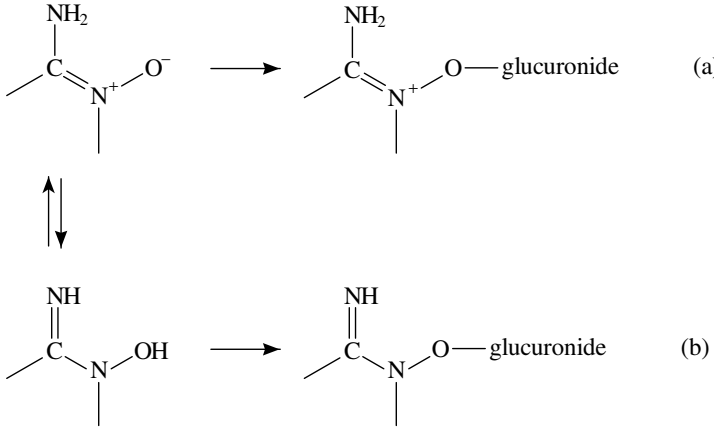
5. Conjugations

The OH-group in the *E*-configuration of acetophenone oximes has been proposed to be more accessible than that in the sterically hindered *Z*-conformers, and thus may be more

susceptible to conjugation to yield water-soluble products[85]. Indeed, treatment with sulfatase of urine from rabbits dosed with 2,6-dimethylacetophenone imine caused a drastic increase in the amount of free acetophenone oxime **(23)** extractable, the *E*-form being the preponderant isomer[85]. These results indicated that rabbits excreted a considerable proportion of the isomeric ketoxime as a sulfate conjugate. Similarly, incubation with β-glucuronidase or sulfatase of urine samples from rabbits administered amphetamine has been shown to be a prerequisite for detecting free phenylacetone oxime **(28)** as a metabolic derivative[34]. Moreover, evidence of the *in vivo* formation of conjugates from benzamidoximes **(24)** has been provided after hydrolytic cleavage[180]. Incubation of benzamidoxime with rabbit liver supernatant in the presence of uridine-5′-diphosphoglucuronic acid (UDPGA) gave rise to a fall in the level of extractable free oxime[86].

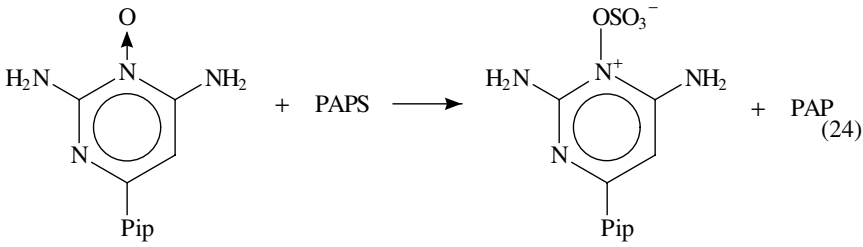
Until recently, N-oxides generated by oxygenation of aromatic heterocycles were regarded as metabolically stable, being excreted without further modification of the N−O functionality. However, data have accumulated suggesting the N-oxide oxygen in such compounds to be a potential target for conjugation. Studies on the metabolic profiles of pyrimethamine and metoprine indeed showed that β-glucuronidase treatment of urine from rats dosed with the diaminopyrimidines resulted in an increase in free 1- or 3-N-oxides, respectively, indicating that the N-oxides were at least partially transformed to glucuronic acid conjugates[106]. Similarly, the N-oxide drug minoxidil **(19)** has been found to be subject to glucuronidation, especially in monkeys and humans[181,182].

The structures of the N-O-glucuronides produced from diaminopyrimidine N-oxides have not been fully established. There exist two possibilities, one of them implicating direct reaction of glucuronic acid with the N-oxide oxygen (equation 23a). Alternatively, amine–imine tautomerism might afford an N-hydroxyimine configuration, followed by reaction of glucuronic acid with the N-hydroxy functionality (equation 23b). The latter mechanism has been favored by some investigators[182]. In this regard, it seems interesting that minoxidil can undergo sulfation directly at the N-oxide oxygen. The corresponding N-O-sulfate has been isolated from the bile of rats following intravenous administration of radiolabeled minoxidil[183] and appears to be an active metabolite, since pretreatment of the animals with 4-acetamidophenol, a possible scavenger of sulfate groups, markedly decreased the hypotensive action of minoxidil[183].



These findings were substantiated by *in vitro* experiments. Thus, rat liver cytosol has been detected to contain sulfotransferase (EC 2.8.2.1) activity which catalyzed

N−O-sulfation of minoxidil in the presence of adenosine-3′-phospho-5′-phosphosulfate (PAPS) (equation 24). The enzyme-synthetized product was identical to authentic N−O-sulfate with respect to chromatographic behavior and mass spectral characteristics and was split to minoxidil when treated with sulfatase[183]. The pH optimum for minoxidil N−O-sulfation was about 8.0. Enzyme activity in crude preparations was maintained for several months during storage at −76 °C, while activity of partially purified enzyme was lost under these conditions[183].



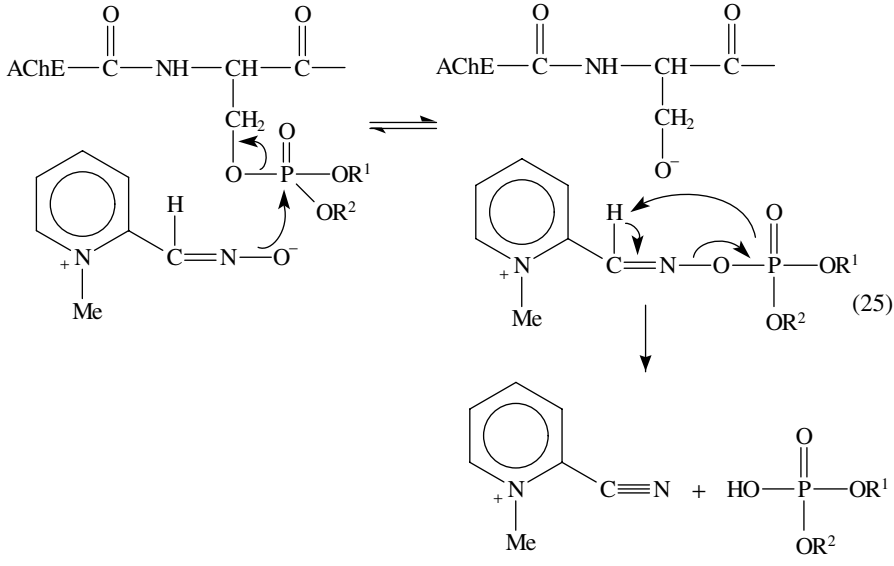
(19) (24)

Sulfotransferase activity is not restricted to minoxidil. The ability of other pyrimidine-, as well as pyridine-, triazine- and imidazole N-oxides to serve as substrates was investigated using soluble liver preparation and PAPS. The variety of structures studied indicated that heteroaromatic N-oxides are generally metabolized by sulfotransferases[183]. Presumably, all of the heterocycles tested were conjugated via their N-oxide oxygens.

B. Nonenzymatic Processes

1. Nucleophilic reactions

Oximes are known to exert nucleophilic attack at appropriate targets. An elegant example of this is offered by the oxime-induced reactivation of the phosphorylated esteratic site of acetylcholinesterase (AChE; EC 3.1.1.7). Quasi-irreversible phosphorylation of AChE is brought about by highly toxic organophosphorus compounds used as pesticides or chemical warfare agents (GV, sarin, soman, tabun)[184]. Successful regeneration of modified AChE has been reported using pralidoxime (PAM; **16**) as a reactivator. The restoration mechanism has been thought to include close apposition of the nucleophile to the attached phosphorus to permit attack, the oxime-phosphonate then being split off; the latter intermediate decays to release nitrile and organophosphate[185] (equation 25). It is interesting to note that the *Z*-isomer of pralidoxime was inactive, while the *E*-form proved to be a highly efficient reactivator. There was a spread of a factor 2 in reaction rate between the 2-, 3- and 4-substituted derivatives[185]. A number of *bis*-quarternary oximes, such as obidoxime (toxogonin; **17**), were subsequently shown to be even more potent reactivators and antidotes for nerve gas poisoning[186,187]. However, the failure of obidoxime to appreciably reactivate AChE blocked by soman[188] prompted the synthesis of new pyridinium oximes. Thus, a variety of asymmetric *bis*-pyridinium aldoximes **(53)**, referred to as H-oximes[189], have been shown to possess good antidotal properties, of which HI-6 is regarded as a promising compound against poisoning by soman, sarin and GV[189−192]. The oxime HLö7 closely resembles HI-6, but bears an additional aldoxime functionality at the 4-position **(54)** and appears to be the first broad-spectrum reactivator[193].



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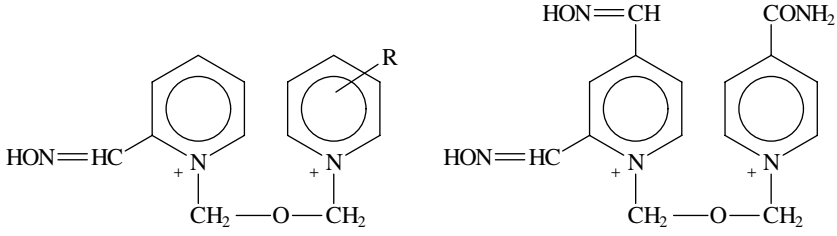


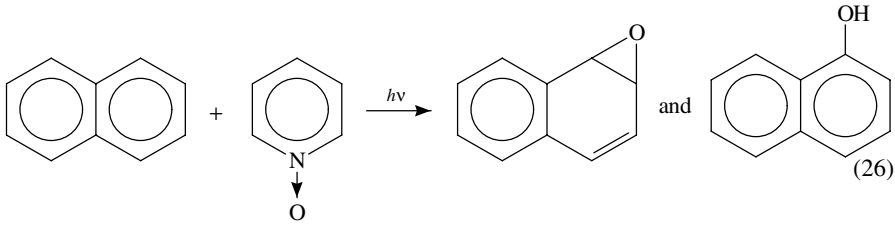
(53) **(54)**

Reactivity of phosphorylated AChE toward pralidoxime has been found also to vary with the nature of the phosphoryl group, increasing in the order di-Pr^{i}-<di-Et-<di-Me-phosphoryl-AChE. Moreover, phosphorylated AChE can undergo fairly rapid "aging", so that it becomes completely resistant to the action of oximes. This process is probably due to the loss of one alkyl or alkoxy group, leaving a much more stable monoalkyl- or monoalkoxyphosphorylated enzyme[194]. Phosphonates containing tertiary alkoxy groups are more prone to "aging" than their primary or secondary congeners[195].

2. Photochemical reactions

Photolysis of heteroaromatic N-oxides has proved to be useful as a mechanistic model for enzymatic oxygen atom transfer reactions. Thus, irradiation with UV light of solutions containing naphthalene and pyridine N-oxide **(40)** resulted in the production of 1,2-naphthalene oxide and naphthol (equation 26), suggesting the intermediacy of arene oxides during oxygenation of aromatic compounds[196]. This system also effected aliphatic hydroxylations as well as sulfoxidations, reactions typical of monooxygenases. Aromatic

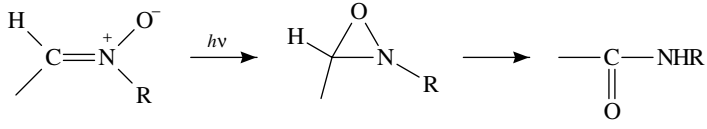
hydroxylations were also brought about when pyridazine N-oxide **(44)** or pyrazine N-oxide **(45)** served as the oxygen donors in the photolytic process[196].



(26)

(40)

Irradiation with UV light of nitrones has been observed to induce rearrangement to yield oxaziridines and amides[197] (equation 27). In this context, light exposure of the nitrones derived from the cyclic imino nitrogens in the methaqualone **(33)** and diazepam structure gave reactive oxaziridines, which were toxic to *Salmonella typhimurium* strain TA100[198,199]. Similarly, oxaziridine is the main product obtained upon irradiation of chlordiazepoxide **(18)**. The intermediate induces DNA damage in bacterial test systems, reacts with SH-groups in compounds such as glutathione[199] and is subject to irreversible binding to proteins[200]. Analogous light-induced transformation to a toxic oxaziridine has also been reported for the di-N-oxide olaquindox **(49)**, which elicits severe photoallergic reactions in animals and man[164,201]. Finally, oxaziridines can arise from the photolysis of purine N-oxides[84].



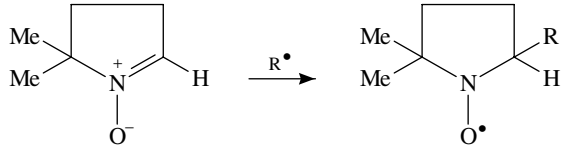
(27)

3. Radical reactions

Free radicals have been frequently recognized as being involved in the mechanism of toxicity of foreign compounds. However, many free radicals of biological interest are too reactive to permit direct observation. This difficulty can be overcome by using a diamagnetic organic molecule, such as a nitrone, to 'trap' the short-lived radical species and produce a more stable 'spin adduct'. The latter is a nitroxide radical, the magnetic moment exerted by its unpaired electron being easily detected by electron paramagnetic resonance (EPR) spectrometry[202,203].

Some more common nitrone spin traps are 5,5-dimethyl-1-pyrroline N-oxide (DMPO; **55**), α-phenyl-*tert*-butylnitrone (PBN; **56a**) and α-(4-pyridyl-1-oxide)-N-*tert*-butylnitrone (POBN; **56b**). As an example, the reaction of **55** with free radicals ($R^{\bullet}$) may be expressed as illustrated by equation 28. Spin adducts of this type will exhibit six-line EPR spectra with different hyperfine coupling constants for nitrogen and β-hydrogen[204]. However, identification of the parent radicals can be difficult with nitrone spin traps because adducts derived from different radicals often have very similar EPR spectra. Rates of trapping of oxygen-centered radicals ($O_2^{-\bullet}$, $HOO^{\bullet}$, $OH^{\bullet}$, $RO^{\bullet}$) by DMPO have been estimated to be within the order of 10^4 to 10^9 $M^{-1}\,s^{-1}$, but adduct formation with carbon-, nitrogen- and sulfur-centered radicals also proceeds at appreciable velocity[204]. Carefully designed

control experiments are essential if meaningful conclusion are to be drawn from spin-trapping data for putative oxygen-centered radicals. Thus, air or H_2O_2 oxidation of nitrones following their hydration or nucleophilic transformation has been described to be a source of artefactual nitroxide radical formation, as is oxidation of the spin traps by trace amounts of iron and other heavy metals. The subject has been reviewed by Finkelstein and associates[202].



(28)

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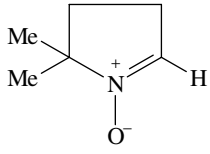

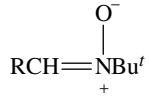

(a) R = Ph

(b) R = O$^-$—N$^+$

(55) **(56)**

VII. CONCLUSIONS

Compounds bearing N-oxygenated C=N functionalities exhibit interesting pharmacological and toxicological properties. Thus, some synthetic oximes exerting central nervous or antibacterial effects have been introduced as medicinal agents. Certain metabolically formed oximes, such as amid- and guanidoximes, may have genotoxic activities inducing DNA single-strand breaks. Moreover, nitrones can bind covalently to proteins, and some congeners, such as diarylnitrones, release arylhydroxylamines upon their hydrolysis, which are known to be quite toxic. Oxaziridine intermediates, proposed to be precursors in enzymatic nitrone production or to arise from photolysis of nitrones, may be expected to react with cellular macromolecules to induce mutagenic, carcinogenic, immunological and other toxic processes.

There is widespread occurrence of heteroaromatic N-oxides in nature; many of them possess antibiotic potency while others are growth factors in microorganisms. In some cases, synthetic heteroaromatic N-oxides exhibit pharmacological activity greater than the parent amines and are currently used as drugs. Usually, metabolic N-oxide formation from aromatic heterocycles is regarded as a detoxification or deactivation reaction, leading to the production of stable water-soluble metabolites that are readily eliminated in the urine. However, there are examples in the literature of synthetic carcinogenic heteroaromatic N-oxides.

N-oxygenated C=N functionalities may be subject to further metabolic transformation through various reactions, such as reduction, oxidation, deamination, rearrangement or conjugation. Reduction of oximes and heteroaromatic N-oxides *in vivo* undoubtedly diminishes their release from the liver, and redox cycling in the sense of N-oxygenation followed by limited reduction might act as a sort of 'metabolic buffer'. Oxidative cleavage of the C=NOH bond in certain amid- and guanidoximes to liberate NO may be related to their ability to lower blood pressure. Sulfation of vasoactive azaheteroaromatic N-oxides most likely infers interesting pharmacological properties. In addition to the enzymatic processes described, nitrones and heteroaromatic N-oxides may undergo disposition by

post-enzymatic mechanisms, such as photolysis to produce reactive intermediates that elicit severe phototoxic effects in parts of the body exposed to sunlight.

N-Oxidative biotransformation of C=N functionalities as well as secondary metabolism of the N-oxygenated products formed is brought about by a multiplicity of enzyme systems, including oxidoreductases (P-450; FMO; xanthine oxidase; aldehyde oxidase), hydrolases and transferases. The interplay in the diverse organs of animal species of the various catalysts, characterized by definite substrate specificities, is likely to control the mode and/or extent to which metabolic turnover occurs, and this may serve to rationalize differences in the particular response to the pharmacological or toxicological actions of certain organic compounds containing N-oxygenated C=N groups.

VIII. REFERENCES

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