Supplement A

The chemistry of

double-bonded functional groups

Volume 2

Part 1

THE CHEMISTRY OF FUNCTIONAL GROUPS

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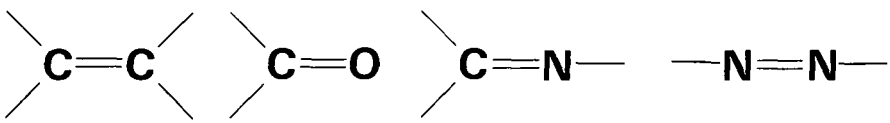

Supplement A
The chemistry of
double-bonded functional groups

Volume 2

Part 1

Edited by

SAUL PATAI

The Hebrew University, Jerusalem

1989

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Foreword

The first supplementary volume in The Chemistry of Functional Groups series was published in 1976. This included thirteen chapters in the form of essay-reviews complementing the original main volumes in the series on C=C, C=O, C=N and N=N double bonds. As then, in the present second Supplement A2, several of the authors were asked to write 'integrative' chapters, i.e. chapters which give a unified and comparative treatment of several double-bonded functional groups together. It is a great satisfaction to the Editor, that this aim has been achieved and indeed more than half of the chapters in the book are such 'integrative' ones, concentrated in the first part of the volume.

Other chapters deal with special subjects which for various reasons have not been treated in the original volumes or in Supplement A. Unfortunately, several chapters which were planned did not materialize. We hope that these omissions will be filled in future volumes of the Series, together with the presentation of novel developments in the various subjects at present being actively studied.

The literature coverage in most chapters is up to about the end of 1987 and in some cases even to the middle of 1988.

Jerusalem
March 1989

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 Editor set himself 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 or 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 single 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 author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, 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 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 and F). 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.

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

The publication of this series would never have been started, let alone continued, without the support of many persons in Israel and overseas, including colleagues, friends and family. The efficient and patient co-operation of staff members of the publisher also rendered me invaluable aid. My sincere thanks are due to all of them, especially to Professor Zvi Rappoport, who for many years shares the work and responsibility of the editing of this Series.

The Hebrew University
Jerusalem, ISRAEL

SAUL PATAI

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List of abbreviations used

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

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

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

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

The Chemistry of Double-bonded Functional Groups
Edited by S. Patai

CHAPTER 1

Complementary views on the homopolar double-bond structure

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I. INTRODUCTION

Ab initio quantum chemistry has now attained such a degree of sophistication and accuracy that for systems such as H_nXYH_m in their ground state, with X and Y normal elements, the numerical answers concerning geometry, energy and sometimes viabrational properties compare favourably with experiment[1]. For transient system of that size, such as, those involved in astrochemistry, quantum chemistry may be considered as a privileged and reliable tool[2]. In that situation, the ethylenic bond has received less attention during the last decade, while exotic multiple bonds involving heavier elements of group 14 were extensively studied by quantum chemists[3-10]. Such systems actually offered many surprises and unexpected behaviour, in particular concerning equilibrium structures.

The present review will concentrate on *homopolar double* bonds in column 14, and especially the CC and SiSi bonds, neglecting heteropolar bonds such as Si=C, to which 'a healthy rivalry between theory and experiment' has drawn attention for a while[11]. The classical picture of the double bond fitting ethylene does not hold when heavier elements are involved. Several electronic rationales of these structural changes have been proposed and will be reviewed herein, with special attention being paid to pictures based on *ab initio* calculations, including electronic correlation. Modern quantum chemistry devotes most of its efforts to the electronic correlation problem, i.e. to filling the gap between the best (Hartree–Fock) single determinational wave function and the exact one[12]. In the Hartree–Fock (HF) scheme the electrons move in the *mean* field and do not avoid each other sufficiently. Most chemists have now accepted and understood the molecular orbital (MO) picture, but they remain reluctant to proceed past this step and enter the world of correlated models. Efforts in that direction are usually presented as formal or computational procedures, a forest of approximations and acronyms without clear physical significance. This obscure status is due to a lack of care on the part of quantum chemists to clarify the physical content of electronic correlation and picture qualitatively and in an intuitive manner the correlated wave function. The first challenge of the present contribution is to translate such sophisticated descriptions into a tentatively more understandable language.

The electronic correlation problem is known to be more important and more complex for multiple bonds than for single bonds[12,13]. While textbooks usually introduce the configuration interaction problem on H_2, i.e. on the less correlated bond, they do not explain its effect on multiply bonded molecules. The more multiple the bond, the larger the correlation effects and the more difficult the quantum chemical treatment. The most dramatic failure of quantum chemistry until now, its shame and nightmare, is the sextuply bonded molecule Cr_2, for which *ab initio* calculations give a qualitatively irrelevant binding energy and bond length[14,15]. A clear picture of the electronic correlation in the double bond may help to understand the difficulties and limits encountered in systems where a number of bonds of various intensities are superimposed in the same region of space.

As a general thesis concerning electronic correlation in molecules, we have elsewhere formulated the following statement: 'Electronic correlation restores some preferences of

the constituent atoms or fragments to minimize their intrinsic energy within the constraint of maintaining some bonding through interatomic pairing of electrons'[13]. In some sense, the MO bond building introduces very disordered situations and a correlated wave function is needed to lower the weight of such high-energy contributions. This will be illustrated later on.

In Section II, the basic conceptual alternative regarding the double bond is introduced. This section also recalls some fundamental features of the atomic elements, XR_3 radicals and XR_2 diradicals of column 14, which will appear as a prerequisite background for further interpretations. Section III is devoted to the ground state of olefins including well-known structural and energetic problems. Sections IV and V deal with the valence excited states. In conclusion, a few comments on the radical cations are given in Section VI.

II. SOME UNAVOIDABLE BACKGROUND

A. Two Views on the Double Bond

1. A problematic π bond

There exist two different ways of looking at the double-bond problem. The first considers the σ bond as a normal σ bond, built from oriented hybrids, comparable to that occurring in saturated compounds, and then focuses attention on the π bond. This bond is actually built from parallel, weakly overlapping, π atomic orbitals (AO) and may be regarded as weaker, more correlated, more problematic, i.e. more sensitive and subject to dramatic effects. In that approach the A=B problem can be treated as a possibly diradical problem A'—'B, in other words as the interaction between two σ-bonded methyl or silyl groups. One then concentrates attention on two active electrons—the π electrons. It will be seen that this way of thinking map help to rationalize certain facts.

In that two-electron approach the π bond is isomorphic to the H_2 problem, and one may benefit from what is known about the simplest molecule. In particular, it will become possible to categorize the various states of these two valence electrons in the field of a qualitatively unchanged σ core: the π and π^* MOs built from p_π AOs correspond to the σ and σ^* MOs built from 1s AOs; the ground state is a neutral state in the sense of the valence bond (VB) theory, with an important admixture of ionic configurations, as in the $^1\Sigma_g^+$ ground state of H_2; the lowest excited state is a purely neutral triplet $\pi\pi^*$ state and corresponds to the $^3\Sigma_u^+$ state of H_2; the lowest valence singlet excited state is built from the $\pi\pi^*$ excitation and is purely ionic, as the $^1\Sigma_u^+$ state of H_2. The discussion on excited states will frequently refer to that isomorphism.

2. An interaction between carbenes

The other approach consists in regarding a double bond as the interaction between two carbene moieties A and B. In that approach the CH bonds are considered to be approximately invariant and attention is focused on *four* active electrons—the four electrons engaged in both the σ and π bonds. This approach is more sophisticated, since it treats the interplay between the two bonds occurring in the same region of space. In that approach, qualitative translation of a correlated wave function will proceed through a valence-bond-like decomposition of the wave function. However, that VB analysis will not be a strict VB decomposition which is expressed in terms of products of atomic orbitals. We will analyze in this work the molecular wave function in terms of products of states of the carbene fragments, the carbene being described through an MO picture of the CH bonds and lone pair or singly occupied orbitals. This point enlightens a basic hypothesis of interpretative quantum chemistry: the MO–VB opposition does not have to be retained as

an unquestionable border line, one may play with it. The MO approach privileges the delocalization, but localized MOs are better suited for local analysis. Conversely, one may work in terms of products of fragment wave functions described in terms of fragment MOs. We shall decompose both the Hartree–Fock Φ_0 and the correlated ψ wave functions of the A—B bond into linear combinations of antisymmetrized products of functions Φ_A^I and Φ_B^J on both fragments A and B:

$$\Phi_0 = \sum_{I,J} C_{IJ}^0 |\Phi_A^I \Phi_B^J| \quad \text{and} \quad \psi = \sum_{I,J} C_{IJ} |\Phi_A^I \Phi_B^J|$$

The functions Φ_A^I will concern either neutral or ionized (A^- or A^+) situations of the fragment A, and will correspond to ground or excited states of the fragment in various oxidation states. We expect that comparing the expansion of the HF determinant with the correlated one, i.e. comparing the values of C_{IJ} and C_{IJ}^0, will clarify the physical meaning of the electronic correlation.

In the case of the $H_2X{=}XH_2$ double bond, the fragments are XH_2 carbenes and the present contribution might be called 'the presence of carbenes in the double bond, and their effects'. The analysis will concern the main valence states of the double bond, namely the ground state and the lowest $\pi\pi^*$ triplet and singlet valence states.

B. Atomic Background. Carbon Versus Silicon

The carbon atom has a ^3P ground state, belonging to the s^2p^2 configuration. This means that the lowest single determinantal description of the carbon atom is, omitting the 1s atomic orbital,

$$\Phi_{^3P} = |2s\,\overline{2s}\,2p_x 2p_y| = |2s\,\overline{2s}\,2p_x 2p_z| = |2s\,\overline{2s}\,2p_y 2p_z|$$

The excited state of the same configuration is the ^1D state

$$\Phi_{^1D} = \frac{1}{\sqrt{2}}|2s\,\overline{2s}\,(2p_x\,\overline{2p_y} + 2p_y\,\overline{2p_x})|, \quad \text{or} \quad \Phi_{^1D} = \frac{1}{\sqrt{2}}|2s\,\overline{2s}\,(2p_x^2 - 2p_y^2)|$$

which lies 29 kcal mol^{-1} above the ground state. The ^1S state

$$\Phi_{^1S} = \frac{1}{\sqrt{3}}|2s\,\overline{2s}\,(2p_x^2 + 2p_y^2 + 2p_z^2)|$$

is by 62 kcal mol^{-1} higher in energy. The hierarchy within the configuration reflects Hund's rules: (1) the electrons prefer to be spread out among the degenerate atomic orbitals of the p open shell; and (2) they refer to have parallel spins.

The sp^3 configuration is important in organic chemistry, since in most molecules the carbon atom may be considered to be in that configuration. It involves several spectroscopic states. The lowest one is the ^5S quintet state, written in a single-determinantal form as

$$\Phi_{^5S} = |2s\,2p_x\,2p_y\,2p_z|$$

It lies 96 kcal mol^{-1} above the ground state. Notice that within its configuration it satisfies the above-mentioned Hund's rules. The excited states of that configuration involve a lower spin and/or double occupancy of some 2p atomic orbitals. They stand higher in energy at more than 80 kcal mol^{-1} above the ^5S state. For silicon the hierarchy is the same, with somewhat *smaller* energy differences, as shown in Table 1.

The ground state of C^+ is of $|2s\,\overline{2s}\,2p_x|$ ^2P character; the lowest excited state will be written $|2s\,2p_x\,2p_y|$ and will have three parallel spins. For the negative ion, C^-, the ground state will be written $|2s\,\overline{2s}\,2p_x\,2p_y\,2p_z|$ which again satisfies Hund's rules. The ionic

TABLE 1. Atomic energies for carbon and silicon

			C	Si
Monoelectronic energies[a] (in eV)		ε_s	−19.4	−14.8
		ε_p	−11.1	−7.6
Relative energies of states[b] (in kcal mol^{-1})				
neutral atom	s^2p^2	^3P	0	0
		^1D	29	18
		^1S	62	44
	sp^3	^5S	96	
		^3D	183	138
cation	s^2p	^2P	0	0
	sp^2	^4P	123	126
Ionization potential (in eV)		IP	11.3	8.1
Electron affinity (in eV)		EA	1.1	1.5
IP−EA (in eV)			10.1	6.7

[a]From Reference 16.
[b]From Reference 17.

structures $X^+ X^-$ are at lower energies for heavier elements than for carbon atom and one might expect that charge transfer and electronic delocalization should be easier in double bond containing heavy elements. It will be demonstrated that this is not true, since it is balanced by another factor of interatomic nature.

The energy required to promote the atoms from their s^2p^2 configuration (s^2p or s^2p^3 for the positive or negative ions) to the lowest sp^3 state (respectively sp^2 or sp^4) is larger in carbon than in silicon. This trend appears already from the difference between monoelectronic energies (see Table 1). Since the quadruple coordination of these elements is explained through the promotion to an sp^3 atomic state, the silicon should be more easily hybridized, more easily engaged into four bonds. Any chemist knows that, on going down along a column of the Periodic Table, the atoms tend to prefer to stay in their ground state configuration, i.e., for column 14, to keep an s^2p^2 character and to engage in two bonds only. For instance, $PbH_2 + H_2$ is more stable than PbH_4, and we shall see later that many differences between the C=C and Si=Si bonds may be related to the lesser tendency of the Si atom to hybridization. This seems to be in contradiction to the smaller energy difference between s and p electrons when one proceeds to heavier elements.

This paradox has been clarified by Kutzelnigg, who pointed out that the spatial characteristics of s and p orbitals play the key role in that tendency[18]. While for carbon atom the s and p AOs have the same spatial extent, for heavier elements the s AO is more concentrated around the nucleus than the p AOs (for heavy elements like Pb, relativistic effects reinforce this trend). Table 2 gives the mean radius $\langle r \rangle$, which is characteristic of the extent of the AO, and the overlap with the 1s AO of an hydrogen atom situated at a typical C—H or Si—H bond distance. Since the hopping integral, responsible for the electron delocalization from one AO p to the AO q of the neighbor atom, is roughly proportional to the overlap S_{pq}, the silicon atom will prefer to engage the p AOs in bonds rather than the s AO, while the carbon atom will accept stronger sp mixing.

Actually, the tendency to hybridize will result from competition between two opposite factors: (1) the energetic gap $\epsilon_s - \epsilon_p$ between the s and p orbitals, larger in carbon, and which favors a strong occupation of the s AO, or in other words which resists hybridization. This factor would make Si more easily hybridized than carbon; (2) the interatomic overlap, larger for p AOs in silicon, which favors a bond formation from

TABLE 2. Mean distances[a] to the nucleus of s and p electrons and overlaps[b] in typical XH bonds

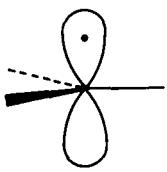
	C	Si
$\langle r \rangle_s$(Å)	0.84	1.16
$\langle r \rangle_p$(Å)	0.92	1.48
S_{sH}	0.50	0.38
S_{pH}	0.50	0.51

[a]From Reference 16.
[b]See Appendix.

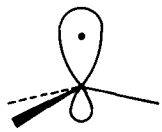
dominantly p hybrids in that atom. These remarks are now applied to the properties of the corresponding radicals and diradicals.

C. Methyl Versus Silyl Radicals

The methyl radical is planar in its ground-state equilibrium geometry, **1**. It is built from a ^5S promoted carbon atom, bearing three equivalent sp^2-hybridized orbitals which enter the CH bonds, and one pure π singly-occupied orbital. On the other hand, the silyl radical, **2**, is pyramidal[19–22] and may be considered as being built from four sp^3 hybrids, one of them bearing the unpaired electron. This difference will play a basic role in some interpretations of the characteristics of the C=C and Si=Si double bonds, and deserves some comment.



(1)



(2)

Let us start with an extended Hückel-type calculation[23], taking typical values of the atomic diagonal energies

$$\text{C} \quad \varepsilon_s = -21.4\,\text{eV}, \quad \varepsilon_p = -11.4\,\text{eV}$$

$$\text{Si} \quad \varepsilon_s = -17.5\,\text{eV}, \quad \varepsilon_p = -9.2\,\text{eV}$$

$$\text{H} \quad \varepsilon_s = -13.5\,\text{eV}$$

and using the Wolfberg–Helmholtz approximation

$$\beta_{pq} = kS_{pq}\left(\frac{\varepsilon_p + \varepsilon_q}{2}\right)$$

where S_{pq} is taken from Table 2. To simplify the diagonalization of the $(H - \varepsilon S)$ matrix, we first build directional hybrids. We then neglect (1) the overlap between the hydrogen atoms, (2) the overlap between hydrogen atoms and the hybrids which are not directed in their directions, and (3) the small Hamiltonian matrix elements between hybrids on the same atom. Then the problem splits into the definition of three bond orbitals and one

unpaired electron orbital. For the planar system these orbitals are

$$\varphi_{XH} = \lambda\left(\frac{1}{\sqrt{3}}s + \sqrt{\frac{2}{3}}p\right) + \mu h$$

$$\varphi_{\cdot} = p$$

where h is the 1s AO of the hydrogen atom. For a perfectly pyramidal sp^3 system they are

$$\varphi_{XH} = \lambda\left(\frac{1}{2}s + \frac{\sqrt{3}}{2}p\right) + \mu h$$

$$\varphi_{\cdot} = \frac{1}{2}s + \frac{\sqrt{3}}{2}p$$

Optimizing λ and μ by solving a 2×2 matrix gives the XH bond energies and unpaired-electron energies listed in Table 3.

This simple model, performed on a pocket calculator, actually predicts the preference of CH_3 to be planar and that of SiH_3 to be pyramidal. In order to see the roles of the $(\varepsilon_s - \varepsilon_p)$ separation and of the S_{pH}/S_{sH} ratio, we have calculated two fictitious systems. One is a pseudo-CH_3 in which $(\varepsilon_s - \varepsilon_p)$ is maintained equal to that of carbon, but where overlap integrals are those of the SiH bond; the other is a pseudo-SiH_3 in which the $\varepsilon_s - \varepsilon_p$ difference is that of silicon but where overlap integrals are those of the CH bond. In the first case (see Table 4) the planar structure remains more stable, but the resistance to pyramidalization is much weaker than in real CH_3. In the second case the planar structure becomes less stable than the pyramidal one (by 0.005 eV, not appearing in Table 4). It is therefore confirmed that the tendency to pyramidalization of SiH_3 is due to the difference between spatial extensions of the s and p atomic orbitals, in other words to the tendency of

TABLE 3. Bond energies in methyl and silyl radicals, as calculated with the simplified EHT-type model (in eV)

	CH_3		SiH_3	
	planar	pyramidal	planar	pyramidal
ε_{XH}	−18.8	−16.3	−16.4	−16.3
$\varepsilon_{\cdot}$	−11.4	−13.9	−9.2	−11.2
$\Sigma = 6\varepsilon_{XH} + \varepsilon_{\cdot}$	−124.4	−123.9	−108.7	−109.0

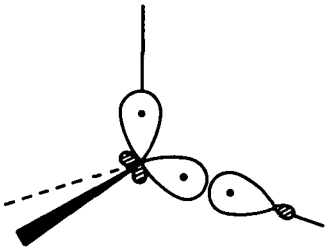
TABLE 4. Bond energies in the pseudo-$XH_3^{\cdot}$ systems (in eV)[a]

	'CH_3'		'SiH_3'	
	planar	pyramidal	planar	pyramidal
ε_{XH}	−18.4	−17.9	−17.0	−16.6
$\varepsilon_{\cdot}$	−11.4	−13.9	−9.2	−11.2
$\Sigma = 6\varepsilon_{XH} + \varepsilon_{\cdot}$	−121.7	−121.6	−111.0	−111.0

[a] The pseudo-methyl radical is calculated from $\varepsilon_{\cdot}$ and ε_p energies of carbon and S_{sH} and S_{pH} C—H overlaps of a typical Si—H bond. The pseudo-silyl radical corresponds to the actual ε_s and ε_p energies of silicon but with the S_{sH} and S_{pH} overlap fixed to those of a typical C—H bond.

Si to enhance the p content in bonding orbitals. A similar intepretation has been proposed by Janoschek[24].

One should, however, note that the planarity of methyl radicals is not universal. The substitution of hydrogenations by methyl groups induces a pyramidalization, despite the bulky character of the methyl groups, which should repel each other[25-27]. A tentative explanation of that phenomenon has been proposed by Dewar under the name of σ-conjugation[28]. Since there is a nonzero matrix element between two sp^3 hybrids on the same center, the three electrons borne by the unpaired atomic orbital and the two hybrids of an XC bond would enter some allylic-type conjugation when the molecule is pyramidal, **3**. Notice however that the pyramidalization lowers the delocalization between adjacent



(3)

(4)

XC bonds which is a butadiene-type conjugation, **4**, since the hopping integral is larger between sp^2 hybrids than between sp^3 ones

$$\langle (sp^3)|h|(sp^3)'\rangle = \tfrac{1}{4}(\varepsilon_s - \varepsilon_p)$$

$$\langle (sp^2)|h|(sp^2)'\rangle = \tfrac{1}{3}(\varepsilon_s - \varepsilon_p)$$

and the overall effect is not obvious.

D. Methylene Versus Silylene Diradicals

If one brings two hydrogen atoms onto a carbon atom in its s^2p^2 ground state ^3P, delocalization and bond building may take place between the 1s orbitals of the hydrogen atoms and 2p orbitals of the carbon atom. An $^1A_1$ state is created, with the wave function

$$\Phi_0 = |\sigma_1^2 \sigma_2^2 n_\sigma^2|$$

in which σ_1 and σ_2 are the molecular orbitals centered on the CH bonds and n_σ is essentially a lone pair of large s character, localized on the carbon atom. On the other hand, if one brings two hydrogen atoms onto a carbon atom in its sp^3-promoted ^5S state, one will obtain a $^3B_1$ state, the wave function of which will be

$$\Phi_0' = |\sigma_1'^2 \sigma_2'^2 n_\sigma' p_\pi|$$

where p_π is a pure $2p_z$ atomic orbital.

Applying our simplified EHT scheme (which reduces to 2×2 matrices) to various states of hybridization of the central atom gives the energies listed in Table 5. This model happens to predict quite correctly the order of magnitude of the observed angles for both states and both molecules. Again the SiH bonds take a stronger p character than do the CH bonds.

The energy ordering between the $^1A_1$ and $^3B_1$ states is not accessible if one omits the repulsion between the electrons. In the $^3B_1$ state, the two unpaired electrons do not occupy the same region of space and they repel less than two electrons which occupy the same lone pair in the $^1A_1$ state. Moreover, in the triplet state, the two electrons of the same spin avoid

TABLE 5. Energies of methylene and sylilene as calculated with the simplified EHT-type model (in eV)

Valence angle Hybridization		180° sp	120° sp^2	109° sp^3	90° p	
CH_2	singlet	−101.9	−104.8	−106.2	−105.9	(102°)[a]
	triplet	−101.9	−101.4	−101.2	−95.9	(134°)
SiH_2	singlet	−87.0	−90.1	−91.7	−93.9	(93)°
	triplet	−87.0	−87.4	−87.6	−85.8	(118°)

[a]The last column reports the actual experimental HXH angles[29,30].

each other, and an exchange integral brings an extra stabilization of the triplet. Calling J_{nn} and $J_{n\pi}$ the repulsion of two electrons occupying the same n_σ MO or the n_σ and the p_π MOs respectively,

$$J_{nn} = \left\langle nn \left| \frac{1}{r_{12}} \right| nn \right\rangle \quad \text{and} \quad J_{n\pi} = \left\langle n\pi \left| \frac{1}{r_{12}} \right| n\pi \right\rangle$$

$J_{nn} - J_{n\pi}$ happens to be larger in CH_2 than in SiH_2 due to the more concentrated character of the carbon atomic orbitals. This finally results in the well-known energy gap between the singlet and triplet states,

$$\Delta E_{ST} = E_T - E_S = -9 \text{ kcal mol}^{-1} \text{ in methylene}^{29}$$
$$= +18 \text{ kcal mol}^{-1} \text{ in silylene}^{30}$$

This difference will play a crucial role in the properties of the C=C and Si=Si double bonds. Notice that these gaps are not significantly larger in germylene and stannylene (22–23 kcal mol^{-1}) for which the HXH angles become very close to 90° in the singlet state (92°) and very close to 120° in the triplet state (119°)[31,32].

As in subsequent sections and referring to the alternative descriptions of the double bond, if one regards it as a weak π bond, largely of radical character, its properties will be interpreted in terms of the trends of the constitutive fragments (the XH_3 radicals), while if one regards it as a four-electron problem, i.e. as an interaction between XH_2 fragments, the properties of these building blocks will play the key role in the interpretation.

III. THE GROUND STATE OF OLEFINS AND HEAVIER ANALOGS

A. The Planar Double Bond

1. π-only description

As already mentioned, the π bond, being built from parallel p AOs which have a rather weak lateral overlap, should be weaker and more strongly correlated than a σ bond. A Hartree–Fock (HF) wave function for the valence part of an olefin may be written as

$$\Phi_0 = |\sigma_1^2 \sigma_2^2 \sigma_3^2 \sigma_4^2 \sigma_{CC}^2 \pi_{CC} \overline{\pi_{CC}}|$$

where σ_1 to σ_4 are the σ orbitals localizable on the C—H bonds and σ_{CC} and π_{CC} are the σ and π orbitals defined on the C=C bond. π_{CC} is the highest occupied MO, whereas the lowest empty MO will be, of course, the antibonding π^* MO. These molecular orbitals can be expressed as the simple sum or difference of the $2p_z$ atomic orbitals a and b centered on

each atom A and B:

$$\pi = \frac{1}{\sqrt{2}}\{a+b\} \tag{1}$$

$$\pi^* = \frac{1}{\sqrt{2}}\{a-b\} \tag{2}$$

The weakness of the π bond is clear if one notices a tendency to Hartree–Fock instability: A determinant Φ_0' in which the two π electrons of spin α and β prefer to occupy two distinct (albeit not very significantly) orbitals π' and π'',

$$\Phi_0' = |\sigma_1^2\sigma_2^2\sigma_3^2\sigma_4^2\sigma_{CC}^2\pi_{CC}'\overline{\pi_{CC}''}|$$

will be lower in energy than Φ_0:

$$\langle\Phi_0'|H|\Phi_0'\rangle < \langle\Phi_0|H|\Phi_0\rangle$$

The new π MOs may be expressed as

$$\pi' = a\cos\theta + b\sin\theta \quad \text{and} \quad \pi'' = a\sin\theta + b\cos\theta$$

with $\cos\theta > \sin\theta$, meaning the α electron has a larger amplitude on the left-side carbon atom A while the β electron has a larger amplitude on the right-side carbon atom B. This instability, of spin-density-wave type[33], appears in ethylene at its equilibrium geometry ($r_{CC} = 1.34$ Å). It remains weak for that distance, but increases rapidly for longer ones: at $r_{CC} = 1.40$ Å, the π spin density on each carbon atom is as large as 0.5.

The propensity towards HF instability is even more marked in disilene, where it starts at a silicon–silicon distance as short as 1.96 Å. For the restricted Hartree–Fock (RHF) planar geometry, corresponding to $r_{SiSi} = 2.12$ Å, the π spin density on each silicon atom is 0.9. The overlap between the corresponding π' and π'' orbitals is calculated at 0.8. Using a relation proposed by Fukutome[33], Teramae has thus inferred and quantified a diradical character which happens to remain small ($\sim 2\%$)[34].

The Hartree–Fock instability is always a symptom of prominent correlation effects. Since the two π electrons are strongly correlated, the wave function must be expressed with at least two configurations,

$$\psi = \lambda\Phi_0 - \mu\Phi_{(\pi\to\pi^*)^2} \tag{3}$$

where λ and μ are two variational parameters and the second determinant is obtained by emptying π and filling π^*. The best definition of ψ is given by a two-configuration MCSCF calculation. Now, let us develop equation 3 using expressions 1 and 2 for π and π^* and omitting the σ core, the explicit statement of which is no longer needed for the purpose:

$$\psi = \lambda|\pi\bar{\pi}| - \mu|\pi^*\overline{\pi^*}|$$

$$\psi = \frac{1}{\sqrt{2}}\{\lambda|(a+b)\overline{(a+b)}| - \mu|(a-b)\overline{(a-b)}|\}$$

$$\psi = \frac{1}{\sqrt{2}}\{\lambda+\mu)|a\bar{b}+b\bar{a}| + (\lambda-\mu)|a\bar{a}+b\bar{b}|\} \tag{4}$$

The wave function ψ thus appears as the sum of a neutral or diradical-type configuration

$$\Phi_N = \frac{1}{\sqrt{2}}|a\bar{b}+b\bar{a}|$$

and an ionic configuration

$$\Phi_I = \frac{1}{\sqrt{2}}|a\bar{a} + b\bar{b}| \tag{5}$$

the coefficients of which are $(\lambda + \mu)$ and $(\lambda - \mu)$ respectively:

$$\psi = (\lambda + \mu)\Phi_N + (\lambda - \mu)\Phi_I \tag{6}$$

This development is strictly valid with a minimal basis set of atomic orbitals in which the expression for π and π^* are as simple as those in equations 1 and 2. In real SCF calculations, the molecular orbitals have to be developed over larger basis sets in order to ensure reliable numerical results. Actually, throughout this work we shall illustrate the purposes by SCF or MCSCF calculations of wave functions expressed in double-zeta plus polarization (DZP) basis sets which are specified in the Appendix. Nevertheless, it is possible to relocalize the π and π^* orbitals expressed in a nonminimal basis set. This leads to two equivalent molecular orbitals a' and b', essentially located on each atom A and B respectively and which can be defined as simply as

$$a' = \frac{1}{\sqrt{2}}\{\pi + \pi^*\} \tag{7}$$

and

$$b' = \frac{1}{\sqrt{2}}\{\pi - \pi^*\} \tag{8}$$

The preceding development can now be achieved by using a' and b' instead of a and b, leading to coefficients for equation 6.

Such results are given in Figure 1, which shows the diradical and ionic character as a function of the interatomic distance for the C=C and Si=Si double bonds in ethylene and disilene. At the RHF equilibrium distances, the contents of the wave functions are not very different: The Si=Si π bond is found slightly more diradical like than the C=C one (73% vs 70%). At this level of description, the difference in nature between the Si=Si and C=C π bonds is therefore not prominent. Incidentally, it is noteworthy in Figure 1 that the propensity towards HF instability, which appears at 1.34 Å in ethylene and at 1.96 Å in disilene, occurs in both cases for the same content of the wave function.

Such a wave function is poor, however, and cannot insure a correct dissociation, since the σ bond is kept in a single determinantal picture through the σ^2_{CC} description. A correct description of the double bond as the bond length increases requires one to correlate at least the four electrons involved in the σ and π bonds.

2. $\sigma + \pi$ description

In this model, four electrons and four valence orbitals are considered, namely π, π^*, σ and σ^*, all located in the C—C region. Let us write a multiconfigurational wave function with all the configurations of the relevant symmetry built from these four MOs:

$$\psi = \sum_{I=1,6} C_I \Phi_I \tag{9}$$

The various configurations Φ_I defining this complete active space include the ground state configuration Φ_0, four doubly excited configurations Φ_D and the quadruply excited one

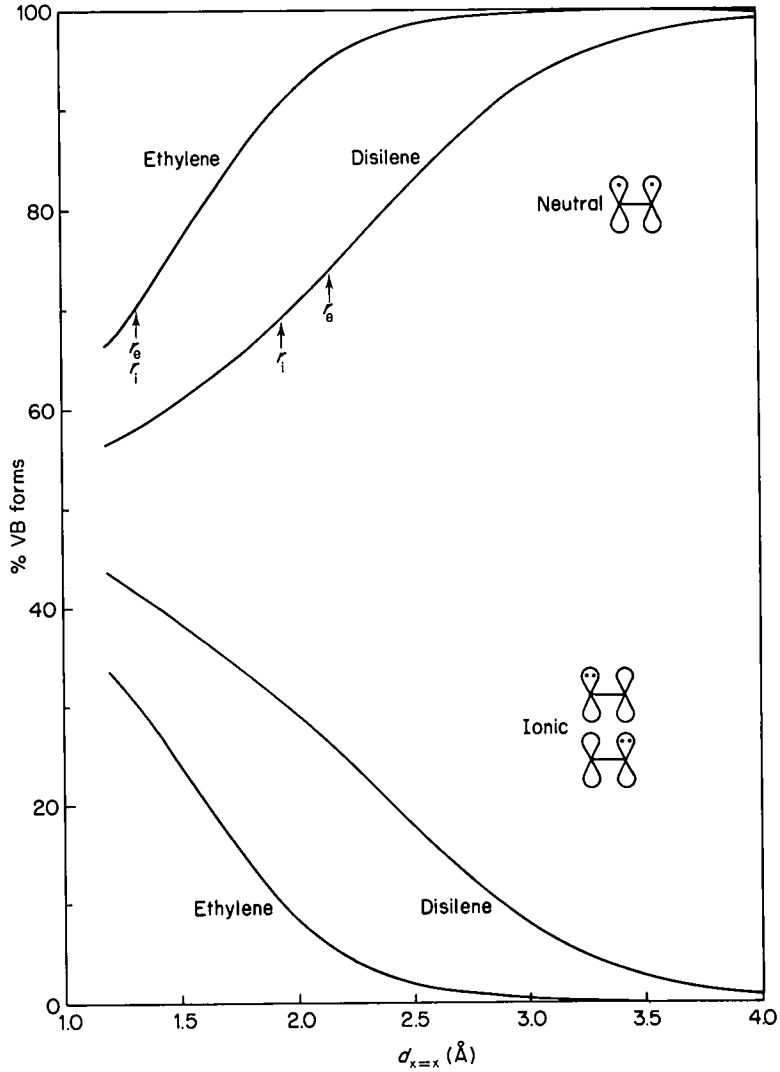


FIGURE 1. π-correlated treatment from the two-electron two-orbital MCSCF calculations: contribution of the two orthogonal valence-bond components as a function of C=C and Si=Si distances in ethylene and disilene; r_e indicates the RHF equilibrium distance and r_i indicates where the Hartree–Fock instability appears

Φ_Q. If we no longer consider explicitly the σ_{CH} core σ_1 to σ_4, these configurations become

$$\Phi_0 = |\sigma\bar{\sigma}\pi\bar{\pi}|$$

$$\Phi_{D\pi} = |\sigma\bar{\sigma}\pi^*\bar{\pi^*}|$$

$$\Phi_{D\sigma} = |\pi\bar{\pi}\sigma^*\bar{\sigma^*}|$$

$$\Phi_Q = |\pi^* \overline{\pi^*}\, \sigma^* \overline{\sigma^*}|$$

$$\Phi_{D\sigma\pi}(X2) = |\sigma\, \pi \overline{\pi^*}\, \overline{\sigma^*}| + \cdots \text{ (proper combinations insuring singlet character)}$$

(These two $\Phi_{D\sigma\pi}$ doubly excited singlets are linear combinations of the six open-shell determinants with a $|\sigma\pi\pi^*\sigma^*|$space part.) Performing a variational MCSCF calculation

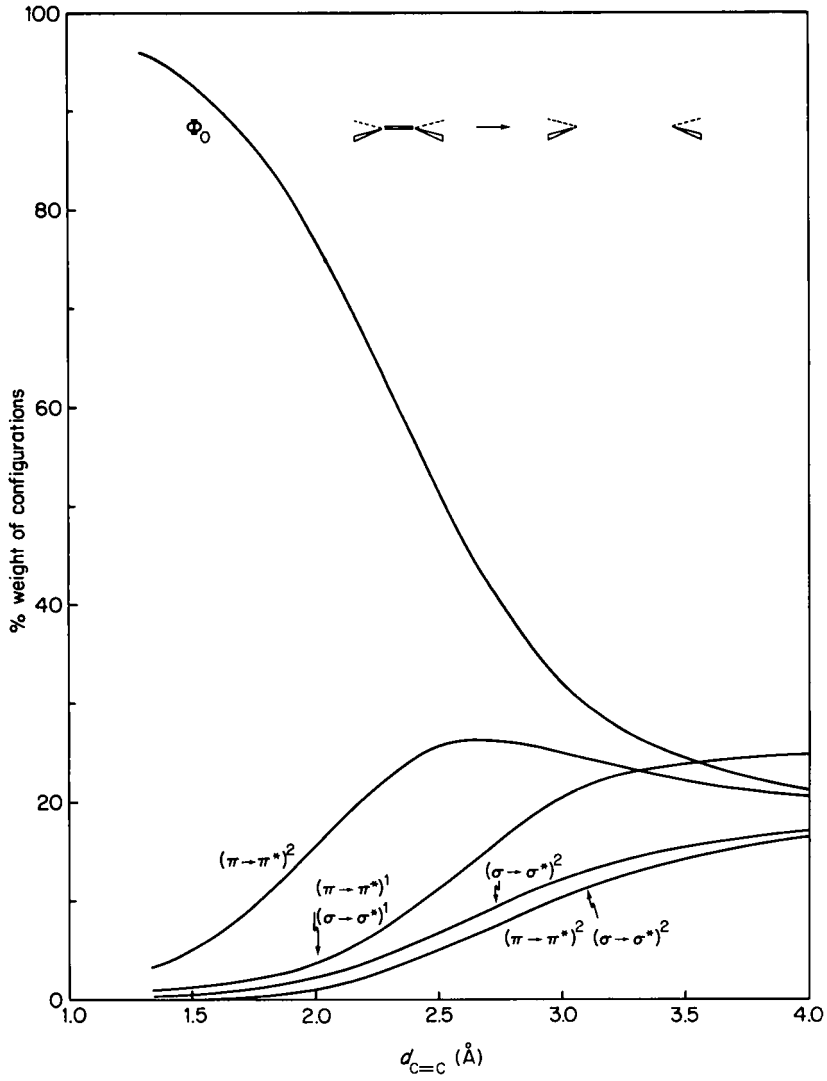


FIGURE 2. Dissociation of ethylene into two triplet ground-state methylenes: weights of the various symmetry-adapted configurations resulting from the four-electron four-orbital CAS–SCF calculations. The left-side limit of the curves corresponds to the equilibrium geometry

will optimize both the coefficients C_I of equation 9 and the content of the MO's σ, σ^*, π and π^*: This is called a four-electron four-orbital complete active space MCSCF calculation (CAS–MCSCF). Such a calculation allows one to correctly break the double bond into neutral XH_2 fragments, as shown on ethylene by Ruedenberg[35]. Of course, as the bond breaks, the weight of the excited configurations increases. This is illustrated in Figure 2, which shows how the weights of the various configurations reflect the order:

$$\pi \text{ correlation} > \sigma\pi \text{ correlation} > \sigma \text{ correlation}$$

A similar calculation may be performed on Si_2H_4, and at equilibrium distance the Si=Si double bond appears to be slightly more correlated than the C=C one, since the weight of the closed-shell ground-state determinant becomes 93% instead of 96%, the difference coming essentially from the $(\pi\pi^*)^2$ doubly excited configuration.

In order to clarify the physical content of the electronic correlation effect, let us translate it into a valence-bond language. To the localized π MOs defined earlier in equations 7 and 8 we add two localized σ orbitals which are centered, in the same way, on atoms A and B:

$$\sigma'_A = \frac{1}{\sqrt{2}}\{\sigma + \sigma^*\} \tag{10}$$

and

$$\sigma'_B = \frac{1}{\sqrt{2}}\{\sigma - \sigma^*\} \tag{11}$$

These are some kind of optimal orthogonal atomic orbitals. The full set σ'_A, σ'_B, a' and b' is not exactly the real set of n_σ and p_π orbitals of the two carbene fragments, but it is as close to it as possible. Accordingly, these localized orbitals will henceforth be labelled σ_1, π_1 (left-side methylene) and σ_2, π_2 (right-side methylene):

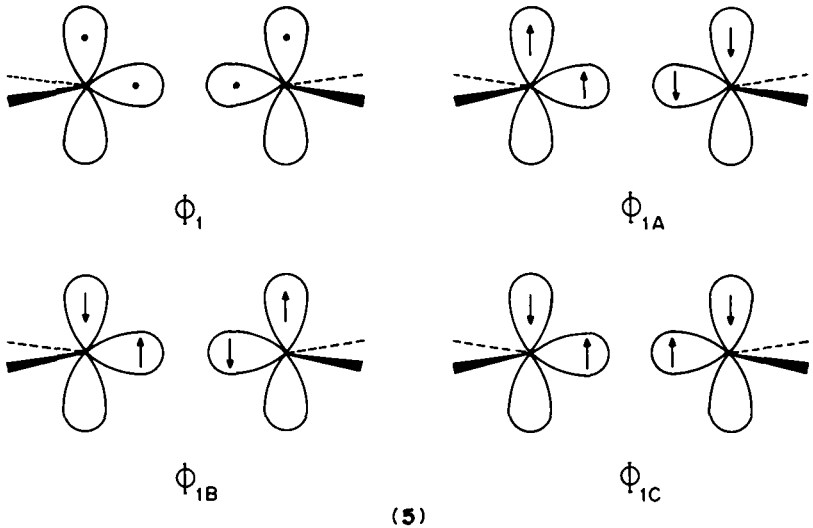
$$\{\sigma_1, \sigma_2, \pi_1, \pi_2\} \equiv \{\sigma'_A, \sigma'_B, a', b'\}$$

The problem is then reformulated on the basis of these equivalent localized MOs, i.e. in an orthogonal valence-bond (OVB) language. The new configurations, labelled Φ_1 to Φ_7, are listed and shown in detail in Table 6. They can be classified into neutral, singly-ionic and doubly-ionic configurations. The first neutral one, Φ_1, splits into three types of

TABLE 6. The valence-bond determinants for a planar double bond

Determinant	Configuration	Degeneracy	Nature	States of the fragments
Φ_{1A}	$n_1 \pi_1 \overline{n_2 \pi_2}$	2		$^3B_1$–$^3B_1$
Φ_{1B}	$n_1 \bar{\pi}_1 \overline{n_2 \pi_2}$	2		$^{1,3}B_1$–$^{1,3}B_1$
Φ_{1C}	$n_1 \bar{\pi}_1 n_2 \bar{\pi}_2$	2		$^{1,3}B_1$–$^{1,3}B_1$
Φ_1	$(n_1 \pi_1 n_2 \pi_2)$		neutral	
Φ_2	$n_1^2 \quad \pi_2^2$	2	neutral	$^1A_1$–$^1A_1^*$
Φ_3	$n_1^2 \quad n_2^2$	1	neutral	$^1A_1$–$^1A_1$
Φ_4	$\pi_1^2 \quad \pi_2^2$	1	neutral	$^1A_1^*$–$^1A_1^*$
Φ_5	$n_1^2 \pi_1 \pi_2$	4	ionic	$^2B_1$–$^2B_1$ (A^-–B^{+*})
Φ_6	$n_1 \pi_1^2 n_2$	4	ionic	$^2A_1$–$^2A_1$ (A^{-*}–B^+)
Φ_7	$n_1^2 \pi_1^2$	2	di-ionic	$^1A_1$–$^1A_1$ (A^{--}–B^{++})

determinants: Φ_{1A}, Φ_{1B} and Φ_{1C}, **5**. The three other neutral configurations are Φ_2, Φ_3 and Φ_4, **6**. They may be identified with the $^1A_1$ spectroscopic states of the fragments, since $^1A_1$ is mainly the n^2 configuration while $^1A_1^*$ is mainly the π^2 configuration, **7**. On the other hand, Φ_{1A} is a pairing of two $^3B_1$ fragments, **8**, while in Φ_{1B} and Φ_{1C} each fragment is a mixture of $^3B_1$ and $^1B_1$ configurations. Note that whereas Φ_{1A}, Φ_{1B} and Φ_2 bear two electrons of opposite spin in both the σ and π bonds, Φ_{1C}, Φ_3 and Φ_4 violate this basic rule of bond building since they have either zero or four electrons in the σ or π bond, or two electrons of the same spin in the σ and π bonds. Therefore they are expected to be little involved in the bond building.



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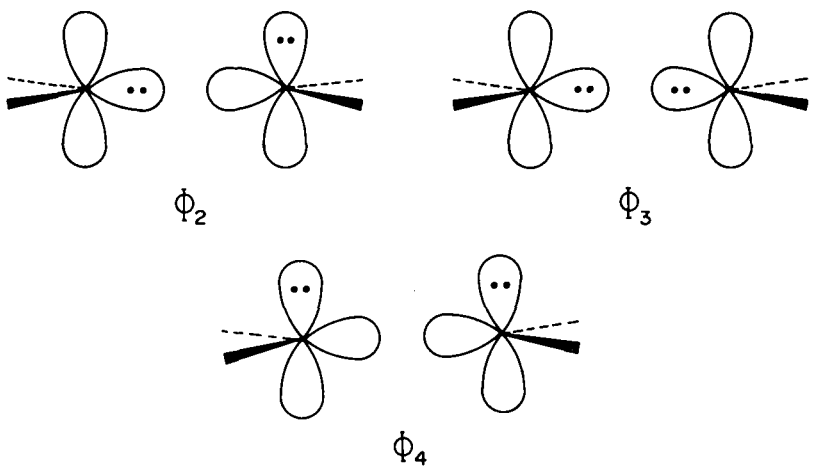

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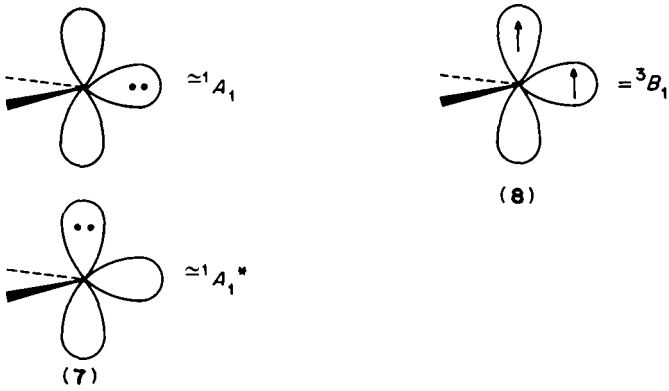
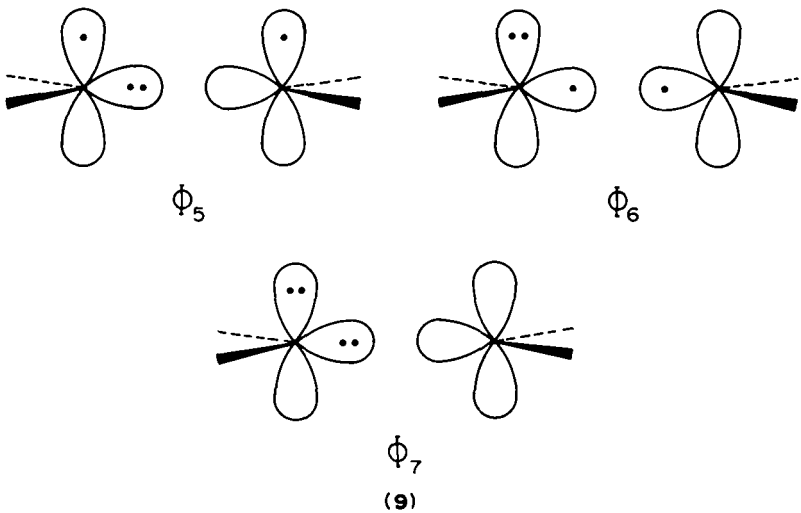


The two singly-ionic configurations are Φ_5 and Φ_6, **9**, in which the A^- and B^+ parts are in electronic states $^2B_1$–$^2B_1$ and $^2A_1$–$^2A_1$, respectively. Last, the sole doubly-ionic configuration will be labelled Φ_7, **9**. Of course, because the centers A and B are equivalent, the determinants will be twofold or fourfold degenerate, except Φ_3 and Φ_4 which are unique.



The SCF description gives equal coefficients on those components which have two $\alpha\beta$ electrons in both σ and π spaces, namely Φ_{1A}, Φ_{1B}, Φ_2, Φ_5, Φ_6 and Φ_7. In other words, it gives equal importance to neutral components of various physical contents, singly-ionic components and doubly-ionic components. This is of course unrealistic. The coefficients of the other configurations are zero. Note that Φ_3, a product of two $^1A_1$ singlet carbenes (and remember that many carbenes have a singlet ground state), is therefore not introduced at the SCF level.

The weights of these valence-bond forms in ethylene are given in Table 7 (column 3) at the equilibrium C=C distance and in Figure 3 as the C=C bond breaks. At the equilibrium geometry, Table 7 shows that:

(1) The neutral structures with one electron per AO, Φ_1, represent already 38% of the

TABLE 7. Distribution of the valence-bond forms calculated from MCSCF correlated wave functions, for planar ethylene and disilene at equilibrium geometry (in %)

	Uncorrelated[a]	Ethylene		Disilene	
		π correlated	$\sigma + \pi$ correlated	π correlated	$\sigma + \pi$ correlated
Φ_{1A}	12	18	21	19	24
Φ_{1B}	12	18	17	19	18
Φ_{1C}	0	0	0.1	0	0.5
Φ_1	25	35	38	38	43
Φ_2	12	7	11	6	10
Φ_3	0	0	0.02	0	0.2
Φ_4	0	0	0.01	0	0.02
Φ_5	25	35	29	38	30
Φ_6	25	15	18	12	15
Φ_7	12	7	4	6	3

[a]This column refers to the noncorrelated SCF description which, for symmetry reasons, leads to identical distributions for both molecules.

wave function. At the dissociation limit, they will bear entirely the wave function, as a consequence of the triplet ground state of methylene (see Figure 3).

(2) The σ charge-transfer, embodied in the singly-ionic form Φ_5, is much more important than its π counterpart, embodied in Φ_6. This confirms that a π bond is of a more diradical nature (more neutral, less delocalized) than a σ one.

(3) The neutral closed-shell VB form Φ_2 has a nonnegligible weight. Its importance is related to the correlation of the movements of σ and π electrons. When the π electrons are on the left-side atom, the σ electrons are pushed toward the right-side atoms, and *vice versa*.

(4) The doubly-ionic structure Φ_7 has a very small weight.

(5) The forms that violate the $\alpha\beta$ pairing of electrons in the two bonds, Φ_{1c}, Φ_3 and Φ_4, are almost negligible.

The ordering effect of the $(\sigma + \pi)$ electronic correlation further appears by comparing the weights of these VB components with those provided by a noncorrelated description (first column in Table 7)—which is by essence unique for any homopolar double bond—and those provided by the π-only correlated description (column 2 of Table 7) discussed in Section III.A.1. Correlation effects increase the neutral VB structures in ethylene from 37% (SCF) to 42% (two-electron MCSCF) and 49% (four-electron MCSCF). The $(\sigma + \pi)$ correlation treatment brings the specific increase of Φ_{1A}, which satisfies the atomic Hund's rule.

In disilene, the description is qualitatively the same at the equilibrium Si=Si distance, as also shown in Table 7. With respect to ethylene, the neutral VB structures Φ_1 have a larger weight, wheras the π charge-transfer contribution Φ_6 is weaker. When the Si=Si bond is lengthened (see Figure 4), a sudden change occurs in the wave function at $r = 3.37$ Å. The wave function, mainly described by the open-shell VB configurations Φ_1 at short distances, recovers there the closed-shell neutral structure Φ_3 which is the product of two SiH_2 fragments in their $^1A_1$ singlet ground state. The curve crossing occurs because the planar double-bond wave function, involving mainly Φ_{1A}, correlates orbitally with the $^3B_1$–$^3B_1$ asymptote which is a pairing of two excited triplet silylenes.

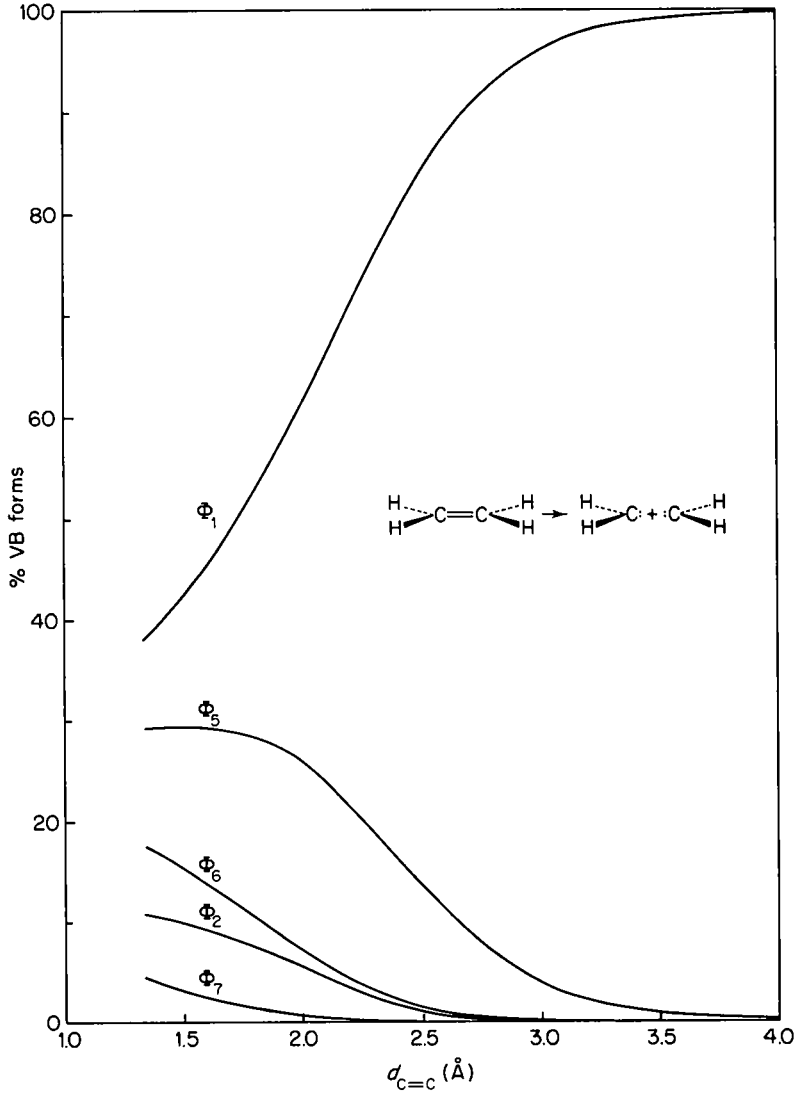


FIGURE 3. Dissociation of ethylene into two triplet ground-state methylenes: valence-bond decomposition of the four-electron four-orbital CAS–SCF wave function. See Table 6 and **5, 6, 9** for the definition of determinants. Only determinants which have significant contributions are plotted

B. The *trans*-Bent Distortion

Disilene and its heavier analogs, digermene and distannene, are not planar in their equilibrium geometry, but *trans* bent, **10**. Such a distortion of the double bond was first noted experimentally on distannene derivatives[36–38] and confirmed by theoretical

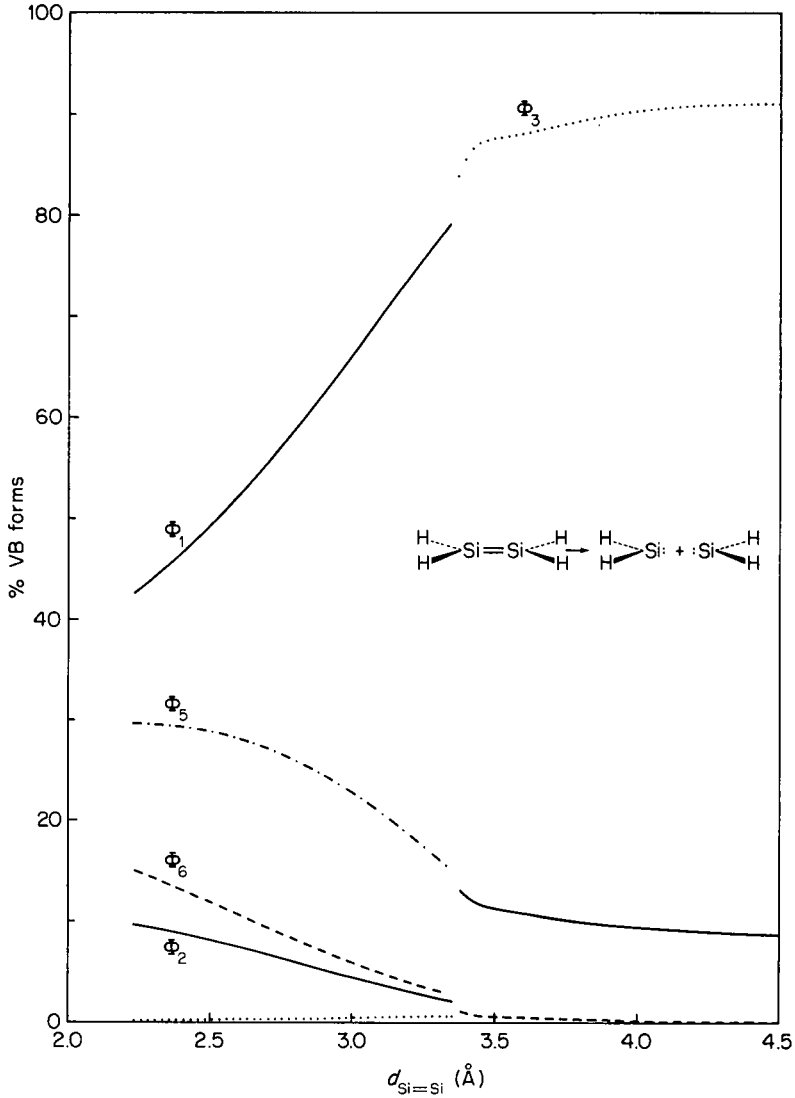
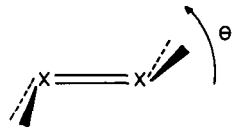


FIGURE 4. Dissociation of planar disilene into two singlet ground-state silylenes: valence-bond decomposition of the MCSCF wave function. Beyond the crossing at 3.37 Å, only the determinants Φ_2, Φ_3 and Φ_6 are involved, due to the n_σ^2 singlet nature of SiH_2

calculations on Sn_2H_4 and Ge_2H_4[38–42]. Later, the disilene molecule Si_2H_4 was explored by *ab initio* calculations using various basis sets and more or less extensive CI[43–46]. If correlation effects are described accurately enough, the disilene molecule is also found to be *trans* bent with a bending angle of 36° and a barrier to planarity of about 1–3 kcal mol^{-1}. Experimental geometries of disilene derivatives exhibit a wide range of nonplanar

distortions, in agreement with the flat potential surface calculated on disilene[44]. Several rationalizations for these bent geometries have been proposed which we would like to review here.



(10)

1. Available interpretations

a. A diradical π bond. The distortion in disilene may be explained by the diradical character of the Si=Si bond, manifested through the UHF instability[34]. Notice in that work that the diradical character increases weakly when pyramidalization takes place. If one proceeds beyond the UHF description and uses the two-electron two-configuration MCSCF calculation, which correlates the π bond, the weight of the neutral configuration goes from 75% for the planar structure to 79% when the pyramidalization angle is 40°. This shows undoubtedly some weakening of the π bond strength, and the energy lowering under pyramidalization must be attributed to the recovery of the pyramidal structure of the sylil radical[24]. In other words, one may assume that the Si—Si π bond is so weak (less conjugated) that it does not prevent the tendency of the $H_2Si^{\cdot}-$ groups to retain their intrinsic geometry. In this logic, the planar structure of ethylene is compulsory. As regards methylated ethylene, and keeping in mind the nonplanarity of the $(CH_3)_3C^{\cdot}$ radical, one must invoke the stronger character of the π CC bond to explain the planarity conservation.

This type of explanation has been applied to the nonplanarity of distannene by Dewar and coworkers, who refer to the above-mentioned interpretation of the nonplanarity of $SnH_3^{\cdot}$ radicals through 'σ-conjugative effects'[28,47].

b. Resonating ionic forms. In sharp contrast to the preceding rationale, Pauling has invoked ionic structures $H_2Sn^{+}\!\!-\!\!SnH_2^{-}$ to interpret the *trans* bending of distannene, through the pyramidalization of the XR_3^- group[48]. This model assumes that the gain of energy under the pyramidalization of the negative center is larger than the energy loss for the positive center. Anyway, it seems dubious to explain the phenomenon through ionic structures since these happen to play a lesser role when proceeding to heavier elements, despite the decrease of (IP − EA). Moreover, as previously mentioned, the weight of ionic configurations decreases under the *trans* bending at the two-electron two-configuration MCSCF level.

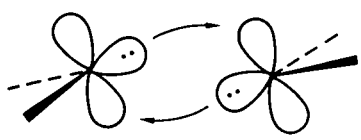
c. σ–π MO mixing. Extended Hückel calculations predict that digermene should exhibit a *trans*-bent distortion. One may therefore follow what happens in such a simple one-electron picture. The out-of-plane motion of the hydrogen atoms mixes the σ and π MOs but the *trans* bending retains a center of inversion, i.e. the g, u character. The bonding σ_g and π_u MOs mix with the antibonding π_g^* and σ_u^* MOs, respectively[49]. The first and stronger mixing concerns the interaction between π_u and σ_u^*, which are closer in energy. The energy distance between these two levels can be approximated by

$$\varepsilon_{\sigma_u^*} - \varepsilon_{\pi_u} = \frac{1}{2}E_{\sigma+\pi} - (\varepsilon_p - \varepsilon_s)$$

where $E_{\sigma+\pi}$ is the $\sigma + \pi$ bond energy while ε_s and ε_p are the monoelectronic energies of the

p_π and n_σ orbitals of the XH_2 group. The tentative stabilization under *trans* bending is therefore ruled by two opposing factors: (1) the stronger the bonds, the lesser the π–σ^* interaction; (2) the larger the quantity $\varepsilon_s - \varepsilon_p$, i.e. the larger the singlet–triplet separation ΔE_{ST} in the XH_2 diradical, the larger the π–σ^* interaction.

d. Effect of the n_σ^2–n_σ^2 neutral VB component. A *trans*-bent double bond may be pictured from two n_σ^2 ($^1A_1$) ground-state XH_2 fragments[36,39]. The *trans*-bent arrangement not only avoids excessive repulsion between the n_σ lone pairs, but also permits their delocalization toward the empty p_π Ao of the partner, **11**. The resulting MOs would be some dative bond MOs with unequal amplitudes on each center, **12**.



(11)

(12)

This rationale attributes a key role to the Φ_3 valence-bond component of the wave function. We have recently proposed a model to rationalize the various known examples of distorted multiple bonds[50]. These seem to occur whenever the fragments have a singlet n_σ^2 $^1A_1$-type ground state rather than a triplet $n_\sigma p_\pi$ $^3B_1$-type ground state. More precisely, the nonplanar distortion will take place if the sum of the $^1A_1 \rightarrow {}^3B_1$ singlet–triplet separation on each fragment, $\Sigma\Delta E_{ST}$, is large enough. A simple rule has been further proposed: the *trans*-bent distortion takes place when $\Sigma\Delta E_{ST}$ is larger than half a mean bond energy,

$$\Sigma\Delta E_{ST} > \frac{1}{2} E_{\sigma+\pi} \tag{12}$$

This relation, which is satisfied by all the presently known cases of distorted double bonds, has been obtained through a model of avoided crossing between two basic configurations: the $n_\sigma p_\pi$ $^3B_1$–$^3B_1$ configuration, leading to the classical planar $\sigma + \pi$ double bond, and the n_σ^2 $^1A_1$–$^1A_1$ configuration leading to the distorted double bond. We point out here that, as far as disilene is concerned, the n_σ^2 $^1A_1 - {}^1A_1$ valence-bond configuration actually plays a crucial role in stabilizing the distortion, but its influence does not extend beyond simple mixing and does not proceed through a crossing, as will be seen from detailed CAS–SCF calculations.

2. *Detailed valence-bond analyses*

Let us develop the preceding model and apply to the *trans*-bent bond the same kind of valence-bond analysis carried out for the planar bond in Section III.A.2. For such distorted geometries, we still have two bonding and two antibonding valence molecular orbitals φ_i in the C—C region, but the σ–π separation no longer holds. We cannot therefore localize two σ bonds and two π bonds through a simple sum or difference of the corresponding bonding and antibonding MOs as in equations 7, 8 and 10, 11. We can however project the n_1, π_1, n_2, π_2 orbital set of the separate carbene-type fragments onto that subspace φ_i, provided that the isolated fragments are kept in the exact conformation they possess in the molecule:

$$|n_1'> = \sum_{i=1,4} <n_1|\varphi_i> <\varphi_i|$$

TABLE 8. The four new valence-bond determinants which appear in the wave function when the double bond loses planarity

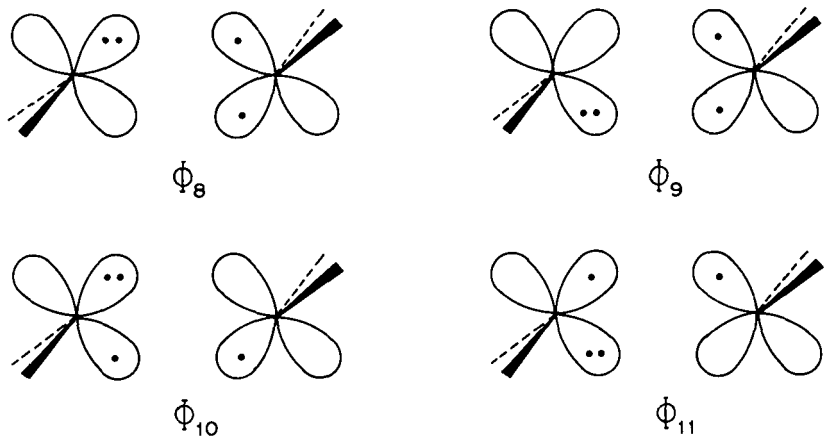
Determinant	Configuration	Degeneracy	Nature	States of the fragments
Φ_8	$n_1^2 n_2 \overline{\pi_2}$	4	neutral	$^1A_1$–$^1B_1$
Φ_9	$\pi_1^2 n_2 \overline{\pi_2}$	4	neutral	$^1A_1^*$–$^1B_1$
Φ_{10}	$n_1^2 \pi_1 \overline{n_2}$	4	ionic	$^2B_1$–$^2A_1$ (A^-–B^+)
Φ_{11}	$n_1 \pi_1^2 \overline{\pi_2}$	4	ionic	$^2A_1$–$^2B_1$ (A^{-*}–B^{+*})

After a proper orthogonalization of these projections

$$\{n_1'', \pi_1'', n_2'', \pi_2''\} = S^{-1/2}\{n_1', \pi_1', n_2', \pi_2'\}$$

one may reexpress the four-active-orbital CAS–MCSCF wave function in the basis of these equivalent localized MOs n_1'', n_2'', π_1'' and π_2''. In the OVB scheme, this set is as close to the real set of the separate fragments as can be obtained. This is why, again, we shall just label these orbitals n_1, π_1, n_2 and π_2, removing the double-prime index. It must be emphasized that for a planar geometry this procedure leads exactly to the same VB decomposition as was performed previously in Section III.A.2.

As soon as the bending occurs, four more configurations are involved, which were not present in the planar form for symmetry reasons. Two of them (Φ_8, Φ_9) are neutral and two of them (Φ_{10}, Φ_{11}) are ionic. These configurations are defined in Table 8 and depicted in **13**.



(13)

The weight of these eleven configurations along pyramidalization is given in Figures 5 and 6 for ethylene and Figures 7 and 8 for disilene. For clarity, we had to regroup the neutral and ionic VB forms on separate figures. Puting aside the differences between ethylene and disilene, let us first focus on what happens when the pyramidalization takes place. Those determinants with two electrons in n_1 or n_2 and two electrons in π_1 or π_2, namely Φ_1, Φ_2, Φ_5, Φ_6 and Φ_7, have their weights reduced. The determinants with three or four electrons in n_1 or n_2, namely Φ_3, Φ_8 and Φ_{10}, as well as those having three or four electrons in π_1 or π_2,

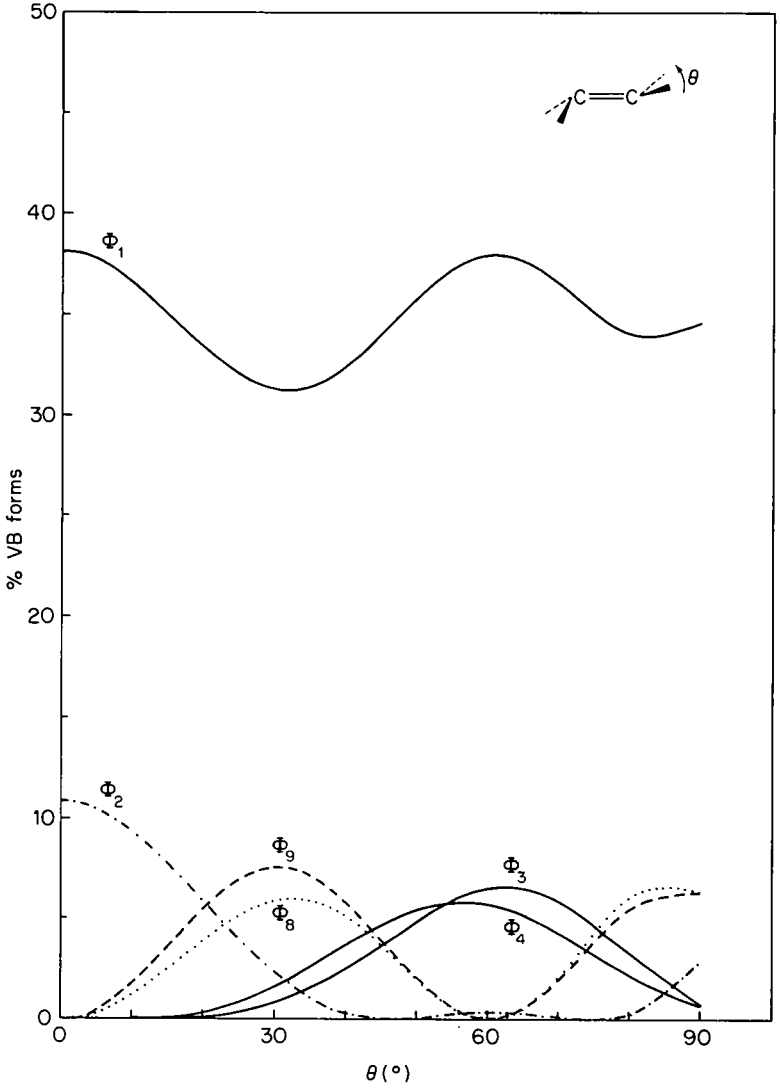


FIGURE 5. *Trans* bending of ethylene: valence-bond decomposition of the MCSCF wave function. Neutral forms. See Table 8 and **13** for the definition of Φ_8–Φ_{11}

namely Φ_4, Φ_9 and Φ_{11}, have their weights increased. These trends reflect the σ–π mixing. To make the tendencies more conspicuous, we have gathered the various contributions into three groups according to the n/π occupation:

$$n^2\pi^2 = \{\Phi_1, \Phi_2, \Phi_5, \Phi_6, \Phi_7\}$$

which are the only important ones in the planar form;

$$n^{3,4} = \{\Phi_3, \Phi_8, \Phi_{10}\}$$

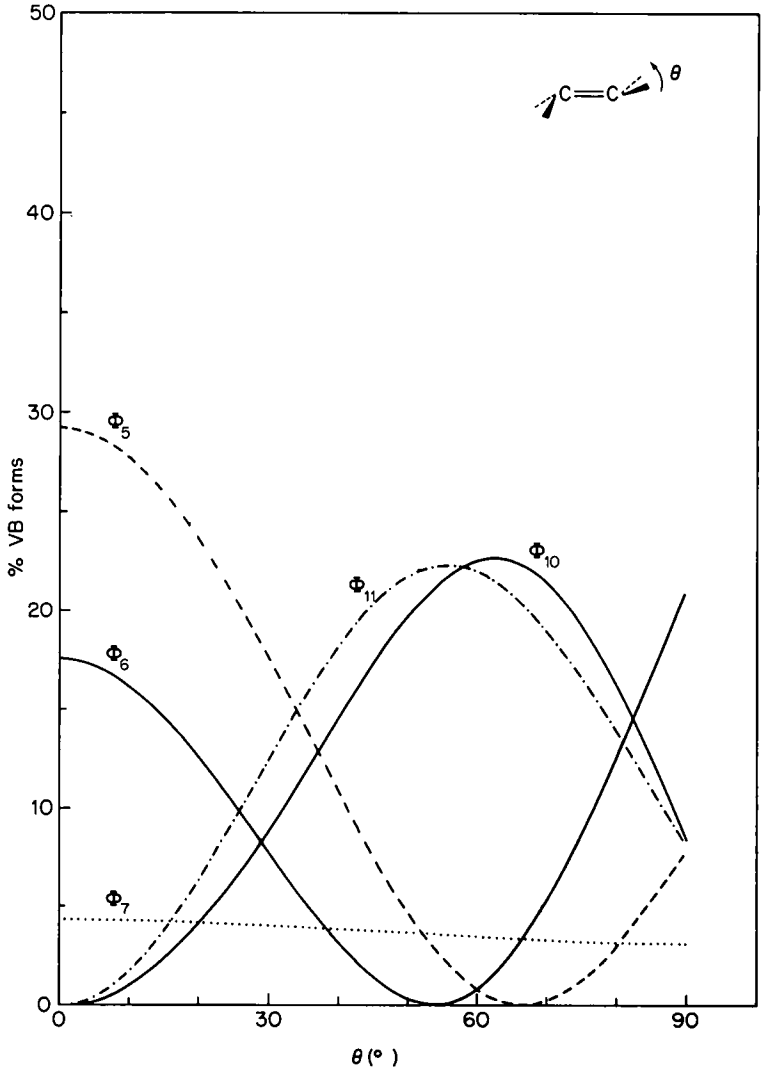


FIGURE 6. *Trans* bending of ethylene: valence-bond decomposition of the MCSCF wave function. Ionic forms

which increase the population in the n orbitals; and

$$\pi^{3,4} = \{\Phi_4, \Phi_9, \Phi_{11}\}$$

in which electrons are thrown from n to π orbitals. The weights of these three new sets along pyramidalization are plotted in Figures 9 and 10 for ethylene and disilene.

A striking difference between ethylene and disilene appears from these two figures. While in ethylene $n \rightarrow \pi$ and $\pi \rightarrow n$ electron jumps appear equally probable, in disilene the

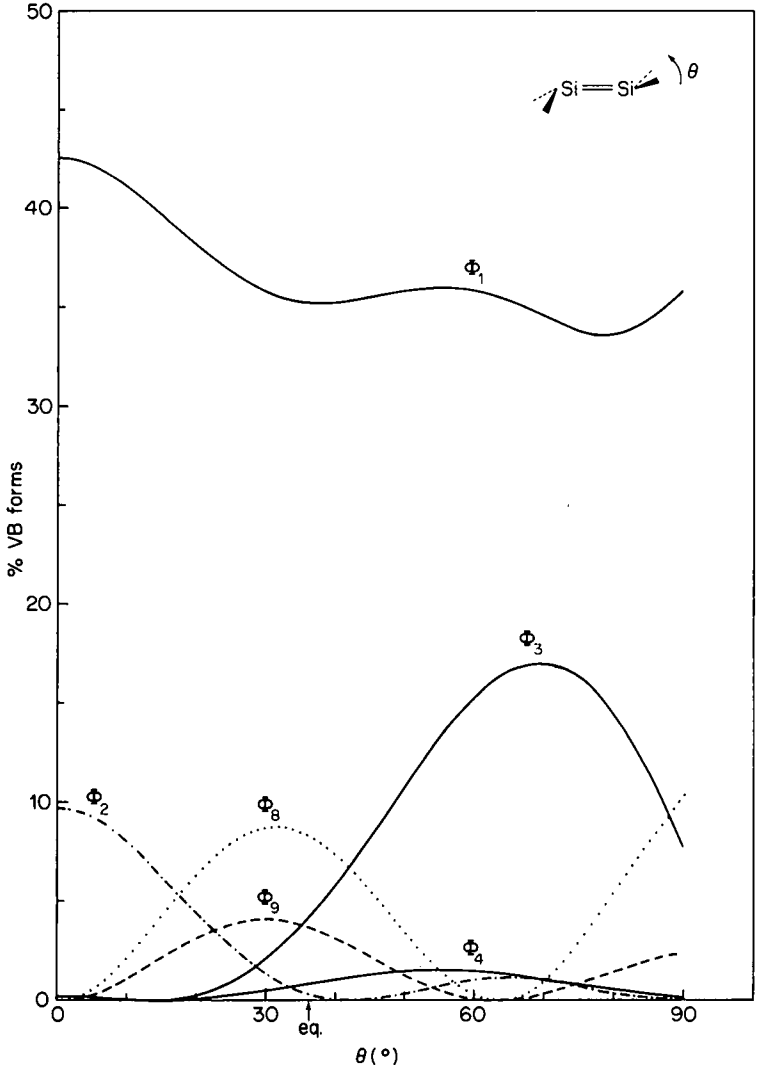


FIGURE 7. *Trans* bending of disilene: valence-bond decomposition of the MCSCF wave function. Neutral forms. The arrow indicates the equilibrium bending

$\pi \rightarrow$ n electron transfers largely prevail. This difference reflects the larger energy difference between n and π electrons. The tendency is even more marked in distannene, for which at equilibrium bending ($\theta \cong 50°$) the $n^{3,4}$ configurations become more important than the $n^2\pi^2$ configurations (see Figure 11).

These results confirm that the pyramidalization is linked to the tendency to occupy the n orbital, which in turn is linked to the large ΔE_{ST} gap in heavy XH_2 diradicals. One should note, however, that the neutral $n_\sigma^2 n_\sigma^2$ configuration Φ_3, which was supposed to become

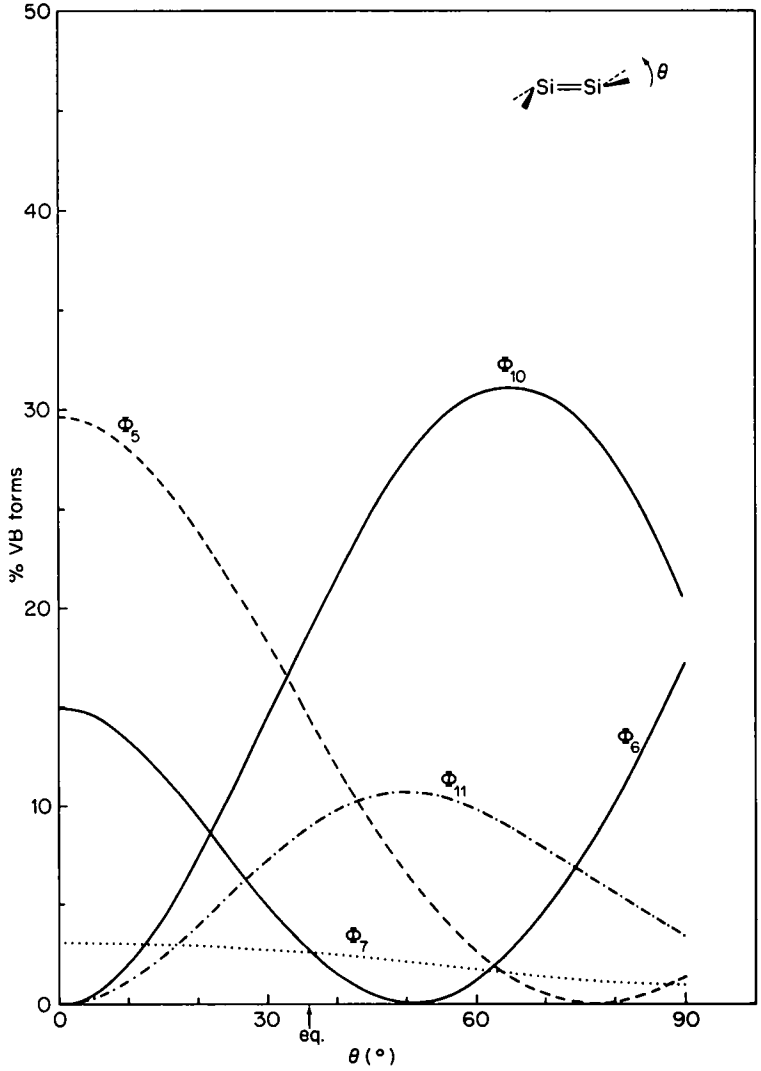


FIGURE 8. *Trans* bending of disilene: valence-bond decomposition of the MCSCF wave function. Ionic forms

dominant in the *trans*-bent form according to Reference 50, remains, in disilene, much less significant than the $n^2\pi^2$ configuration Φ_1 and the $n^3\pi^1$ singly ionic configuration Φ_{10}. The interpretation of the pyramidalization as being due to an avoided crossing between the n^4 and $n^2\pi^2$ configurations is confirmed only for distannene, at least if one relies on an orthogonal valence-bond analysis.

The CAS–SCF calculations give the correct behavior of the energy in the *trans* bending

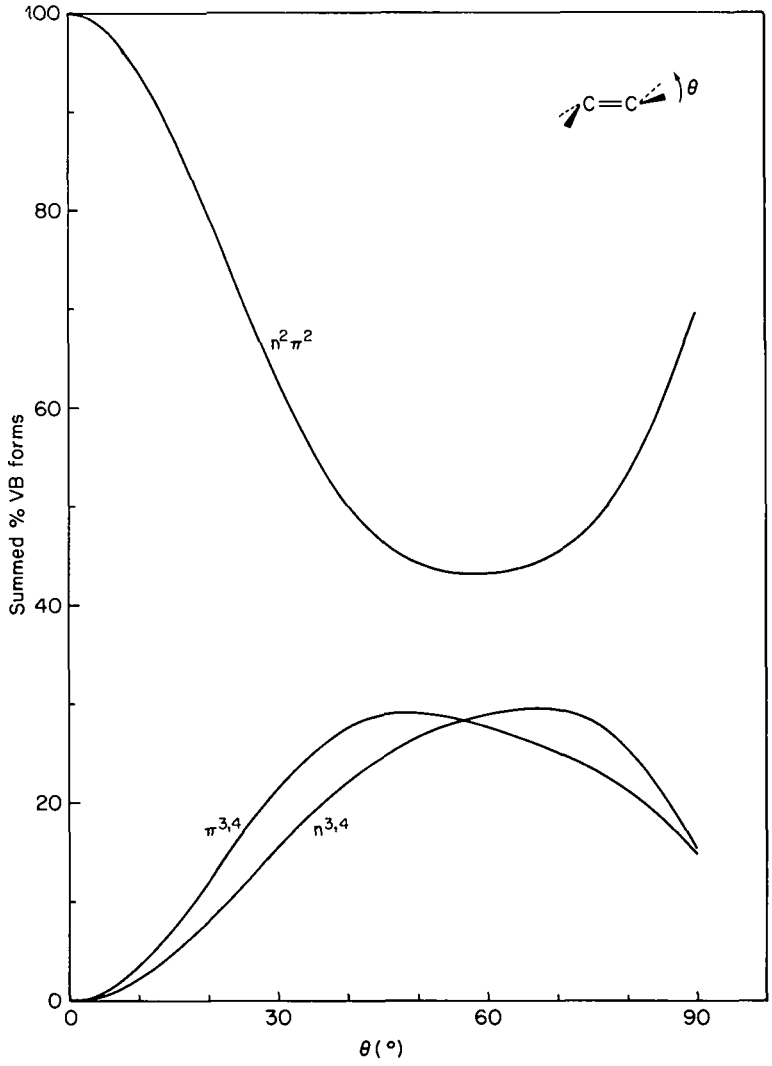


FIGURE 9. *Trans* bending of ethylene: valence-bond decomposition, collecting the determinants into three classes according to the n/π distribution of electrons

(see Figure 12, right part). The n^4 configuration actually plays an important role and is responsible for a large amount of the *trans* bending. Keeping this configuration Φ_3 out of the CAS–CI reduces the pyramidalization angle by a factor of 3 and the inversion barrier by a factor of 2. The n^2n^2 configuration therefore plays a quantitative role, despite its minor character in the wave function of disilene; this role is similar to that of the ionic configurations in the single-bond building.

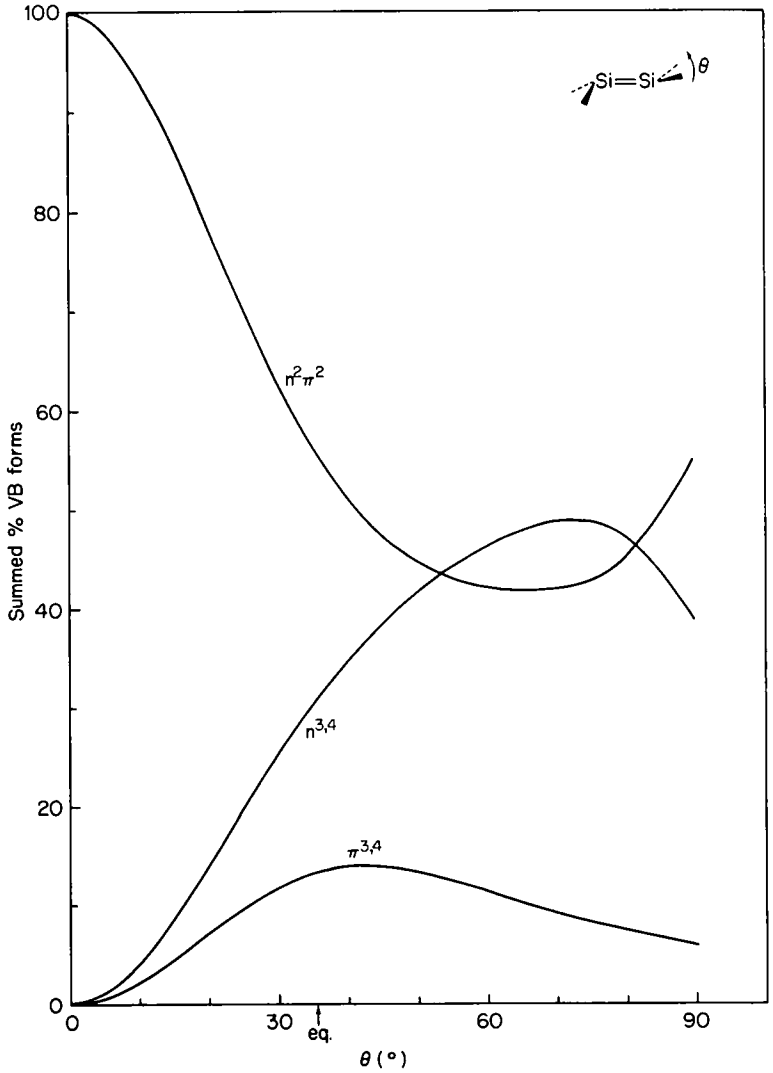


FIGURE 10. *Trans* bending of disilene: valence-bond decomposition, collecting the determinants into three classes according to the n/π distribution of electrons

C. *cis* Bending

In the model where the bending is induced by the preference of the XH_3 radical—say the silyl radical—for pyramidal geometry, one may expect that *cis* bending could lead to a secondary minimum. This is not observed. In Figure 12, left, the energy resulting from the four-electron four-orbital CAS–MCSCF calculation is plotted upon *cis* bending for ethylene, disilene and distannene. The *cis* deformation never appears to be favored even if

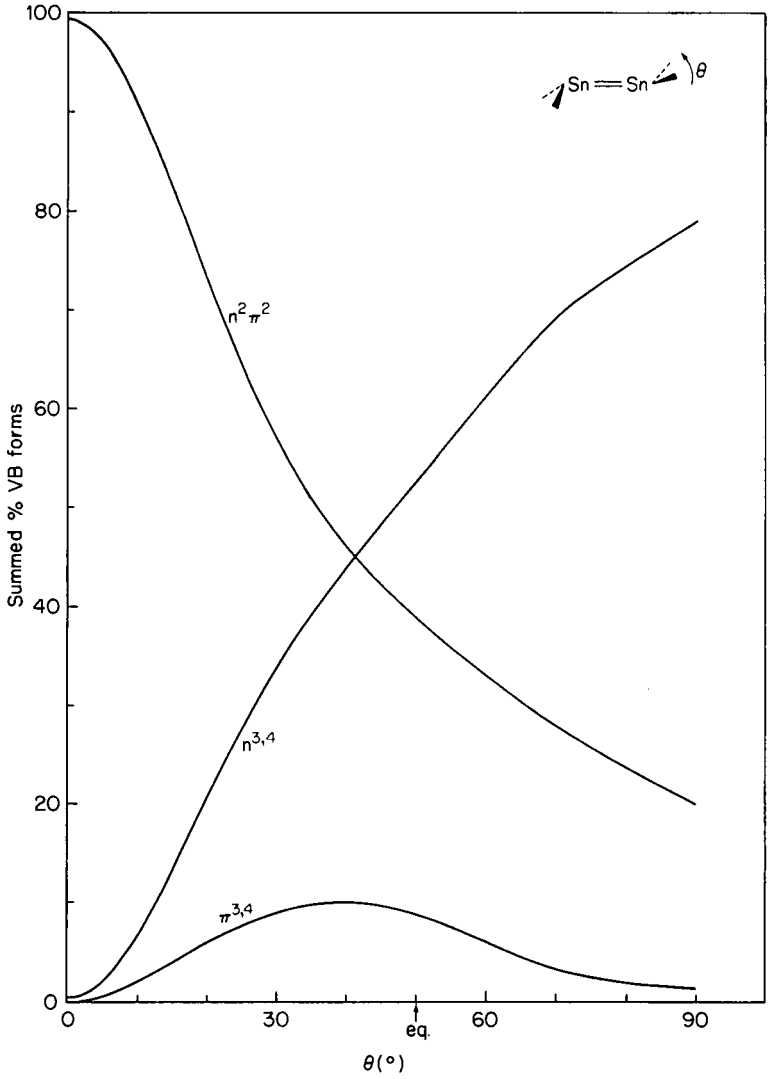


FIGURE 11. *Trans* bending of distannene: valence-bond decomposition, collecting the determinants into three classes according to the n/π destribution of electrons

the curve for distannene is rather flat near planarity. Two factors do not favor the *cis*-bent distortion:

(1) The repulsion between the XH bonds is much larger in *cis*-bent than in *trans*-bent geometries. The heavier the X element, the longer the X—X bond, which should reduce this effect, but on the other hand, the heavier the X element, the more polar the $X^+—{}^-H$ bond.

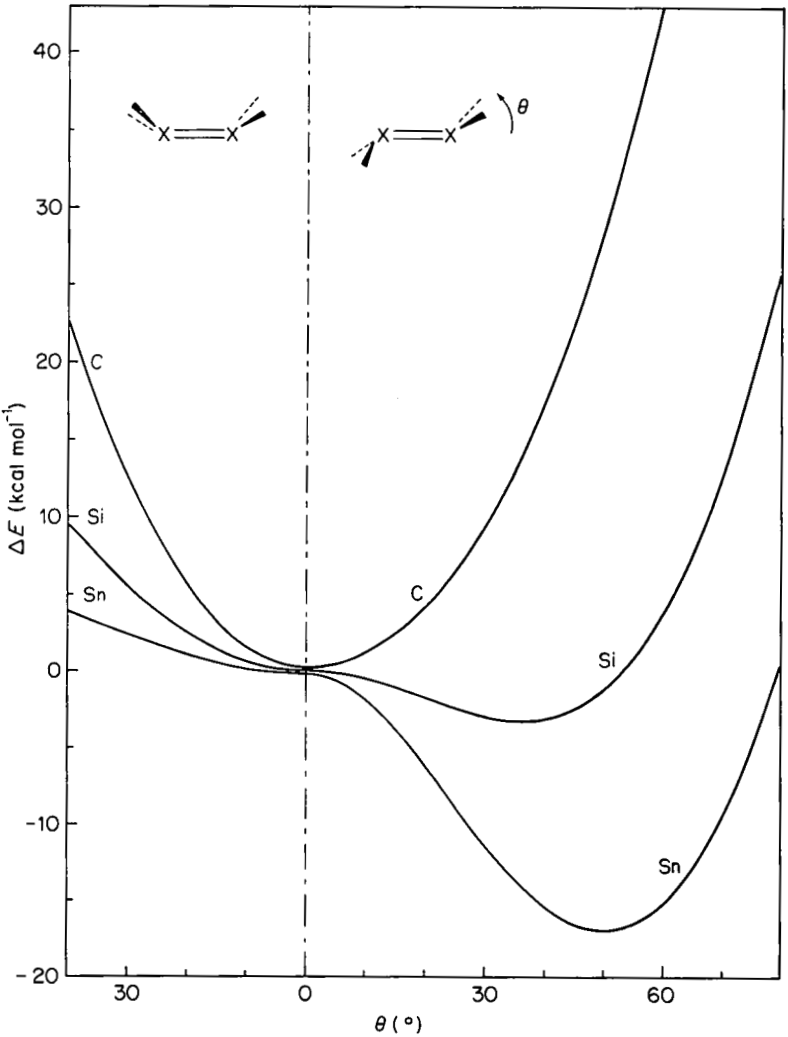
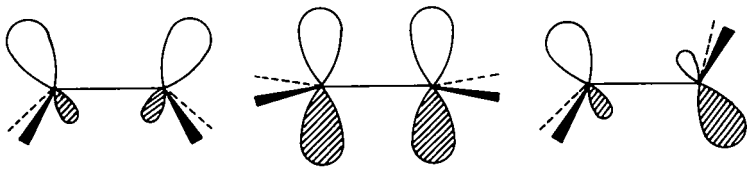


FIGURE 12. MCSCF-calculated energy upon *trans* bending (right) and *cis* bending (left) in ethylene, disilene and distannene

(2) The overlap, and therefore the electronic delocalization, between the two hybrids (or distorted π AOs) bearing the electrons of the 'π' bond is smaller for *cis* conformations than for *trans* conformations. This seems a bit counterintuitive, but it is quite in line with the well-documented problem of the $n_+ - n_-$ lone-pair splitting in hydrazine or diphosphine[51]. In these compounds, the $n_+ - n_-$ splitting, reflecting the extent of interaction between the two lone pairs, is larger for the *trans* than for the *cis* conformation. As an example **14** presents the overlap between two pure p AOs and two pure sp^3 hybrids on silicon for a Si–Si distance of 2.3 Å. The *trans* bending therefore keeps a larger electron delocalization, in other words a larger fraction of the π bond.

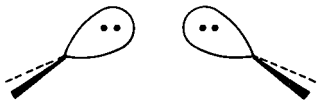


$S = 0.12$ $S = 0.20$ $S = 0.15$

(14)

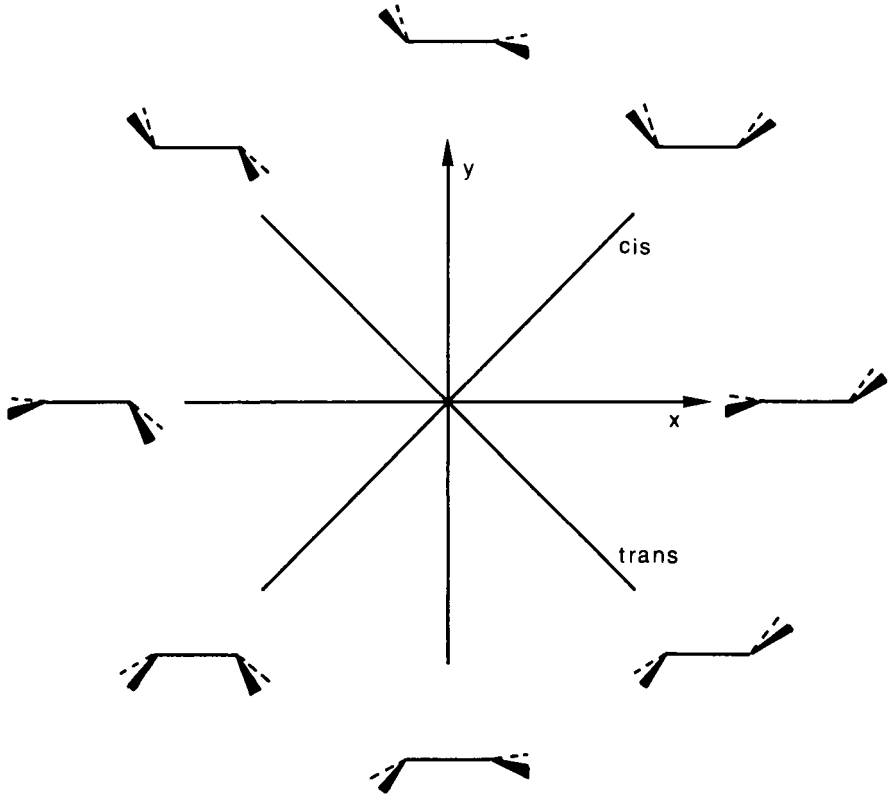
In the one-electron explanation of the bending, the *trans* bending takes place because of the π–σ^* mixing in the b_u symmetry and, to a lesser extent, the σ–π^* mixing in the a_g symmetry, the molecule having C_{2h} symmetry. Proceeding to the *cis* bending ensures C_{2v} symmetry. Now both occupied orbitals σ and π have the same a_1 symmetry and both empty orbitals π^* and σ^* have the same b_2 symmetry. The σ–π mixing of occupied orbitals does not bring any overall stabilization but rather an unfavorable four-electron repulsion scheme. Note that in transition metal-linked olefins, the well-known *cis*-bent deformation allows both stabilizing mixing of the σ and π occupied orbitals of the olefin with empty d orbitals or hybrid orbitals of the metal fragment, and similar stabilizing interaction between metal occupied orbitals and the olefin π^* and σ^* empty orbitals[49,52]. Therefore, one-electron arguments definitely rule out spontaneous *cis* bending of any isolated olefin.

The $\sigma \rightarrow \pi$ four-electron model explains the *trans* bending by a tendency of the XH_2 group to keep or restore their $n_\sigma^2\, {}^1A_1$ ground state. In this model it is easy to understand the reluctance to *cis* bending, since the two n_σ lone pairs would repel here much more than in the *trans* conformation, **15**. Turning back to the VB language, this means that the Φ_3 configuration (which corresponds to **15**) should be much higher in energy, thus stabilizing the ground state to a much lesser extent.



(15)

In Figure 12, left, the curvature of the energy curve is lowered when going from carbon to tin. For distannene only, a 10°-*cis* bending results in an energy loss of less than half the energy gain of the 10°-*trans* bending. For symmetry reasons in the partitioning of the Hessian matrix, it can be inferred that in such a case bending on a single side of the olefin should be favored with respect to the planar form, even if this does not correspond to any stationary point on the potential-energy surface. The problem can be demonstrated as follows. Let us draw the potential surface in which the x axis corresponds to bending on a single side of the olefin—say the right side—and the y axis corresponds to bending on the other side of the olefin—say the left side. As shown in **16**, the two bisector axes necessarily correspond to *trans* bending and *cis* bending at both sides of the olefin. If we choose as zero energy the energy of the planar form, for a molecule which *trans*-bent distorts, two cases can be observed according to whether the zero-energy contour line never crosses the x and y axes (**17**) or includes a part of these axes (**18**). This inclusion means that pyramidalization at a single side is favored with respect to the all-planar form. Actually, at the MCSCF level, 10° bending at a single center results in a 0.24 kcal mol^{-1} stabilization for distannene and a 0.07 kcal mol^{-1} destabilization for disilene. This suggests that, for digermene, the one-side-only bending should be rather flat on the potential-energy surface.



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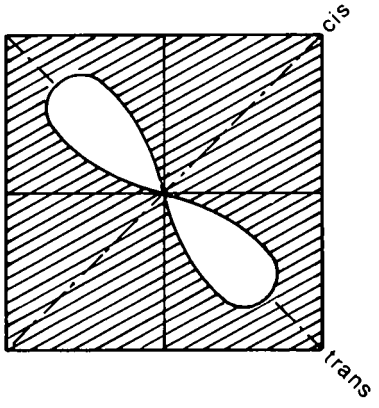

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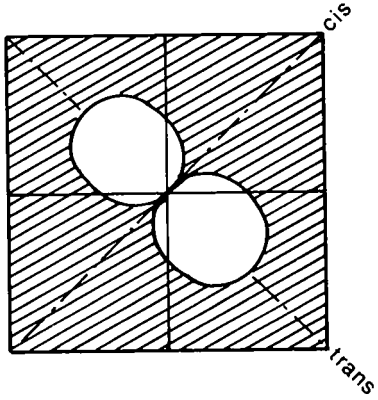


(18)

D. σ–π or Banana Bonds?

Once the σ and π orbitals have been defined, it is always possible to define two equivalent molecular orbitals

$$b_1 = \frac{1}{\sqrt{2}}(\sigma + \pi) \quad \text{and} \quad b_2 = \frac{1}{\sqrt{2}}(\sigma - \pi)$$

which look like banana bonds, one lying essentially above the plane of the molecule, the other below. A similar transformation will transform σ^* and π^* into antibonding banana bonds b_1^* and b_2^*, which both present a node in the plane of symmetry perpendicular to the CC bond. The ground state SCF wave function is invariant in the change $(\sigma, \pi) \rightarrow (b_1, b_2)$,

$$\Phi_0 = |\sigma\bar{\sigma}\pi\bar{\pi}| = |b_1\bar{b}_1 b_2\bar{b}_2|$$

since a determinant is invariant in linear combinations of its lines and columns. The latter formulation provides some support to an early proposal by Pauling and Slater[53,54], but at this stage the two descriptions are equivalent. Similarly, the four-electron four-orbital CAS–MCSCF wave function frequently used in this work is invariant in the transformation

$$(\sigma, \pi, \sigma^*, \pi^*) \rightarrow (b_1, b_2, b_1^*, b_2^*)$$

and the use of one set rather than another is a matter of convenience.

Recently, Palke claimed that double bonds *are* banana bonds[55]. His argument is based on a special type of wave function, namely a perfect pairing valence-bond wave function, where each electron pair consists of two different orbitals paired into a singlet. These orbitals, which are optimized, are nonorthogonal. The energy so obtained is slightly lower (by 7 kcal mol^{-1}) than that obtained from the so-called generalized valence-bond method, which requires strong orthogonality conditions between MOs of different pairs and leads to a $\sigma + \pi$ description. One cannot exaggerate the physical meaning of such a comparison, the validity of which is restricted to some type of simplified wave functions. Chemists should know that they may use either one picture or the other, as they may use in a more general way symmetry-adapted or localized MOs. They should never forget than one is not more true than the other, simply more convenient for a given purpose, since anyway there is *no* monoelectronic wave function in the exact wave function.

E. About the Energies

1. Double-bond strength

The simplest way to define a double-bond energy is to consider the energy of dissociation of $H_2X{=}XH_2$ into two H_2X fragments in their ground state. For ethylene, this dissociation energy D is found experimentally to be 172–179 kcal mol^{-1} [56,57]. We shall discuss later the possible partition of this quantity into σ and π increments. The Hartree–Fock approximation only gives 122 kcal mol^{-1}, which proves the energetic importance of the correlation effects in the double-bond problem. The four-electron CAS–SCF calculation which only introduces the internal correlation of the four electrons of the double bond gives 157 kcal mol^{-1}. The lacking 20 kcal mol^{-1} come from external correlation effects of these four electrons and from the instantaneous repolarizations of the σ electrons involved in the CH bonds in the fluctuating field created by the four electrons of the C=C bond, as shown by the success of the recently proposed Dissociation Consistent Configuration Interaction (DCCI) approximate method[57].

Ethylene adiabatically dissociates smoothly into two methylene groups in their $^3B_1$ ground state. In many substituted ethylenes, however, the constituent carbenes have a

$^1A_1$-type singlet ground state. As noticed by Carter and Goddard, the double-bond formation in these cases requires first a promotion of the carbenes to their $^3B_1$ excited state. Assuming a constant strength of the C=C double bond from the triplet asymptotes, we have

$$D(R_2C{=}CR'_2) = 172 \text{ kcal mol}^{-1} - \Delta E_{ST}(CR_2) - \Delta E_{ST}(CR'_2)$$

where ΔE_{ST} are the singlet → triplet transition energies of the singlet carbenes. This relation proved to work efficiently for a wide series of substituted olefins[56,58] and is in line with the simple rules proposed for the rationalization of the *trans*-bent distortions[50]. Note that it has also been used for estimating ΔE_{ST} from known dissociation energies[59].

The same consideration is valid for Si=Si or Si=C double bonds. Since SiH_2 has a $^1A_1$ singlet ground state ($\Delta E_{ST} = 18$ kcal mol^{-1}), the $H_2Si{=}SiH_2$ double-bond energy will be smaller by 36 kcal mol^{-1} than if built from triplet states. The experimental estimates are rather uncertain (72 kcal mol^{-1} is proposed as an upper limit)[60] while theoretical calculations give 64 kcal mol^{-1} (coupled-pair function, DZP basis set)[45], 70 kcal mol^{-1} (MP4 perturbation, DZP basis set)[61] and 63 kcal mol^{-1} (four-electron four-orbital MCSCF, DZd basis set, this work). The Hartree–Fock approximation gives 61 kcal mol^{-1} (DZd basis set, this work), which is 97% of the MCSCF value. This small difference does not mean that the internal correlation of the four valence electrons is negligible; it simply results from a cancellation between the large correlation effects in the $^1A_1$ singlet silylenes and in the double bond[62].

2. *$H_2X{=}XH_2$ versus $H_3X{-}XH$*

Ethylidene $H_3C{-}CH$, the carbene isomer of ethylene, lies in its $^3A''$ ground state quite high in energy above ethylene, by 67 kcal mol^{-1} according to MP4 calculations[63] (see other calculations in References 64 and 65). Absence of a barrier from ethylidene to ethylene has even been claimed[66]. The silicon analogs present a striking difference, since $H_2Si{=}SiH_2$ and $H_3Si{-}SiH$ are nearly degenerate in energy. The energy ordering of the two species has been the subject of a number of investigations[4,43,67–69]. Most recent and accurate calculations agree with a 6 kcal mol^{-1} energy difference in favor of disilene[46,63]. This near degeneracy between a double-bonded system and a divalent isomer is quite intriguing, but it may be rationalized by noting that, as explained in Section II.B, the silicon atom has stronger bonds when they are built from hybrids involving a large p content. In singlet silylsilylene the $H_3Si{-}Si{-}H$ angle is almost 90°, which means that the bond hybrids at the divalent silicon are almost pure p AOs while the lone pair is almost purely s, which is optimal. This energy gain is due to both the return of the atom to its ground state and the increase in the strength of the Si—Si and Si—H single bonds. It compensates the destruction of a π bond, which happens to remain rather weak as we shall discuss later. The germanium analogs present the same features: digermene has been calculated (at a CI level) to lie about 5 kcal mol^{-1} below singlet germylgermylene[39].

3. *Rotational barriers*

When the ethylenic bond is 90° twisted, the two p_π atomic orbitals are orthogonal: there is no delocalization between the electrons which they bear. The π bond may be considered to be broken and of a purely diradical character (or valence-bond neutral). The lack of π conjugation will lengthen the CC bond to between 1.47 Å (multireference second-order CI)[70] and 1.50 Å (MCSCF)[71] while the rotational barrier is calculated to be 61–65 kcal mol^{-1} [70,71], in agreement with an experimental value of 65 kcal mol^{-1} [72]. Of course, in the 90°-twisted conformation, hyperconjugation between a p_π electron and the

CH bonds of its neighbor group takes place and may slightly stabilize the structure. However, it seems reasonable to regard the rotational barrier as a measure of the π-bond strength.

For disilene, where π conjugation is insufficient to prevent pyramidalization of the silyl groups, the rotation is much more complex and the barrier occurs for a *gauche* conformation[71]. Lengthening of the SiSi bond is about 0.15 Å, which represent a *relative* lengthening smaller than that of ethylene (7% vs 12%). Since in a *gauche* conformation the two 'π' hybrids are not orthogonal, some π conjugation possibly remains and, in that case, the rotational barrier should give a lower bound to the π-bond energy. The rotational barrier is, however, in agreement with the π-bond energy estimated from hydrogenation energies, both calculated to be 23 kcal mol^{-1} [71].

4. σ/π relative strengths

The definition of additive systematics for bond energies is a desirable task, but involves many difficulties. The various possible approaches, from diatoms, from cohesive energies in the solids, from hydrogenation energies, from dissociation energies, etc., lead frequently to significant disagreements (see, for instance, the well-documented Appendix of Reference 18). The contradictions are not dramatic for CC bonds. For the CC σ bond, the cohesive energy of diamond (86 kcal mol^{-1})[73] and the dissociation energy of C_2H_6 into two CH_3 (88 kcal mol^{-1}) agree[74]. For the π bond, the estimates are quite disperse; they vary between 61 and 65 kcal mol^{-1} from rotational barriers up to 90 kcal mol^{-1} if one takes 179 kcal mol^{-1} for the double-bond dissociation energy, as suggested in Reference 57. The π/σ bond strength ratio for a C=C bond therefore ranges between 2/3 and 1.

For the Si=Si bonds, the dissociation of Si_2H_6 into two SiH_3 leads to a σ-bond energy of about 70 kcal mol^{-1}, according to both experiment[60] and theory[21], much larger than the value given by the cohesive energy of solid Si (54 kcal mol^{-1})[73]. The π-bond strength would be about 23 kcal mol^{-1} both from the rotational barrier in SiH_2=SiH_2 and from hydrogenation energies[71]. Notice however that the dissociation energy of Si_2H_4 into two SiH_2 groups is again of the order of magnitude of 70 kcal mol^{-1} (see Section III. E.1), which would suggest a vanishingly small π-bond energy if one takes the σ-bond energy value from the dissociation energy of disilane, and 16 kcal mol^{-1} if one accepts the σ-bond energy value taken from solids. In any case the π/σ bond strength ratio is much smaller for silicon than for carbon. This is a major phenomenon, the implications of which will be briefly mentioned in the Concluding Remarks.

IV. THE $\pi\pi^*$ TRIPLET STATE

The lowest excited state of ethylene is the $\pi\pi^*$ triplet state obtained by the jump of one electron from the π HOMO to the π^* LUMO. This state is neutral in the sense of the VB theory. The $S_z = 1$ component, associated with two parallel spins, can be expressed in the form

$$\Psi = |\pi\pi^*|$$

which decomposes to

$$\Psi = \tfrac{1}{2}|(a+b)(a-b)| \quad \text{or} \quad \Psi = \tfrac{1}{2}|aa + bb - ab + ba|$$

The Pauli principle will cancel the $|aa|$ and $|bb|$ terms. Since $|ba| = -|ab|$, Ψ reduces finally to

$$\Psi = -|ab|$$

For the $S_z = 0$ component, a similar development leads to

$$\Psi = \frac{1}{\sqrt{2}}|\pi\bar{\pi}^* - \pi^*\bar{\pi}|$$

$$\Psi = \frac{1}{\sqrt{2}}|\tfrac{1}{2}\{(a+b)\overline{(a-b)} - (a-b)\overline{(a+b)}\}|$$

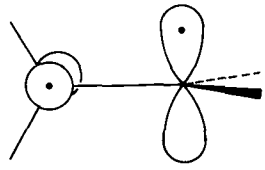
$$\Psi = \frac{1}{\sqrt{2}}|\tfrac{1}{2}\{a\bar{a} - a\bar{b} + b\bar{a} - b\bar{b} - a\bar{a} - a\bar{b} + b\bar{a} + b\bar{b}\}|$$

$$\Psi = -\frac{1}{\sqrt{2}}|a\bar{b} - b\bar{a}|$$

There is strictly no π-ionic VB component, i.e. no π-electronic delocalization in that state. Each atom always bears one π electron and only one—this is a true diradical.

The calculation of this excited state is not specially difficult, since it is less correlated than other states (such as the ground state) which are more ionic. Most calculations of the vertical transition energy[70,75–84] agree with the experimental value of about 98 kcal mol^{-1} [85–87]. Of course, because there is no longer π delocalization in the triplet state, the ground-state CC bond length is too short for that state. Keeping a planar conformation, the triplet state would lengthen the CC bond to 1.52 Å, which is close to a typical single bond length[70].

Even at that distance, the π electrons and the CH bonds of both groups are repelling. In this eclipsed conformation the two atomic orbitals occupied by electrons of parallel spins behave as doubly occupied bond orbitals. Accordingly the two methylene groups will rotate to a 90°-twisted conformation, **19**, ensuring a reduced p_π–p_π and CH—CH repulsion and a three-electron hyperconjugation between the singly occupied π orbital and the CH bonds of the opposite atom. In this conformation the C—C bond length reduces to 1.46 Å[65,70,88,89] and this is the real equilibrium geometry on the potential surface. As expected, it is almost the same as the geometry of the 90°-twisted ground state, which is the rotational transition state[70,71].



(19)

The energy of the relaxed triplet state is nearly degenerate with that of the 90°-twisted ground state, about 62–66 kcal mol^{-1} above the relaxed planar ground state. We should keep in mind that in their D_{2d} twisted geometries both states are purely neutral or diradical. The triplet state is so by its essence, as we have just seen, and the singlet ground state is so because in relation 4 (Section III.A.1) the ionic part cancels due to the orthogonality between a and b ($\lambda = \mu = \frac{1}{2}$). For the twisted geometries, the energy difference between these two states therefore becomes

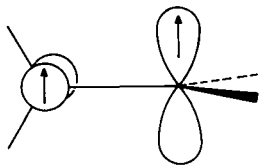
$$\Delta E = \langle\psi_{GS}|H|\psi_{GS}\rangle - \langle\psi_T|H|\psi_T\rangle$$

$$\Delta E = \tfrac{1}{2}\{\langle a\bar{b} + b\bar{a}|H|a\bar{b} + b\bar{a}\rangle - \langle a\bar{b} - b\bar{a}|H|a\bar{b} - b\bar{a}\rangle\}$$

$$\Delta E = \tfrac{1}{2}\{4\langle a\bar{b}|H|b\bar{a}\rangle\}$$

$$\Delta E = 2K_{ab}$$

where K_{ab} is the exchange integral between two orthogonal p_π AOs and so is small. Since these integrals are positive, the triplet state, **20**, is expected to lie *below* the ground state, **21**, as expected from Hund's rule. This result is not confirmed when the response of the σ electrons is included in schemes as simple as $(\sigma + \pi)$-CAS–MCSCF calculations (i.e. with an active space of four electrons and four orbitals) or UHF calculations, as well as in more extended correlated treatments. The triplet state is found to lie about 1 kcal mol^{-1} *above* the singlet ground state. The question has been clarified by Kollmar and Staemmler under the name of 'dynamic spin polarization'[90]. The σ electrons are spin polarized by the π electrons. Whereas the spin fields of the two electrons cancel in the triplet state, **22**, they add in the singlet state, **23**. The phenomenon is easy to understand if one thinks in terms of an electrostatic analogy, replacing α and β electrons by positive and negative charges and considering the electrostatic field in the centre of the bond.



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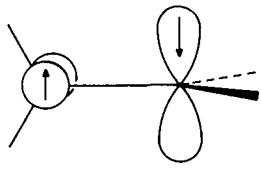

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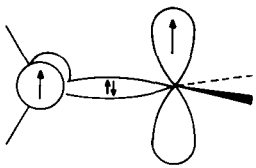

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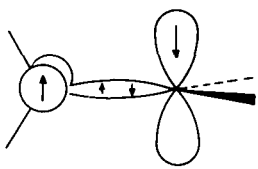
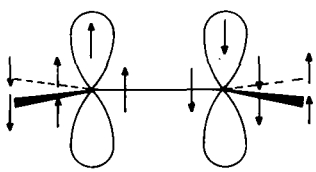


(23)

This is the simple reflection of the general tendency to antiferromagnetic spin waves in molecules. The VB configuration, which has the largest weight in a ground-state wave function, is a spin wave in which each atom is in the lowest state of its configuration (with parallel spins if it bears several electrons), **24**. In the triplet state, such a perfectly ordered spin wave cannot be drawn, since one of the carbon atoms has necessarily an $|S_z| = 1$ spin, **25**, i.e. it is of higher energy. The triplet state necessarily violates the tendency to build antiferromagnetic spin waves from atoms in the lowest state of their concerned electronic configuration—here sp^3. The same phenomenon accounts for the negative σ spin density found in the vicinity of a positive π spin density, as occurs in the methyl radical, **26**. In this



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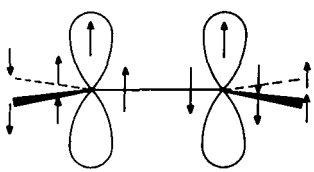


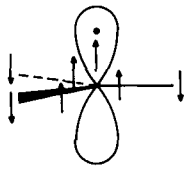
(25)

H C C H

^2S ^4S ^4S ^2S

$S_z = 2$ $S_z = -2$

$S_z = 2$ $S_z = -1$



(26)

case the σ bonds polarize in the static spin field of the π unpaired electron. This mechanism is exploited in the well-known McConnell relation[91].

For disilene, the $\pi\pi^*$ vertical excitation energy is smaller since the π bond is weaker. For the SCF-optimized planar geometry, the $\pi\pi^*$ triplet state is calculated to be 50 kcal mol^{-1} above the ground state. For the *trans*-bent MCSCF-optimized geometry, this value reduces to 34 kcal mol^{-1} (this work). The equilibrium geometry of triplet disilene has been calculated through four-electron four-orbital MCSCF calculations[71] and appeared to differ significantly from that of the singlet surface rotational saddle point. The energy of the triplet minimum would be 2 kcal mol^{-1} below the singlet rotational saddle point. This would restore Hund's rule and violate the preference for a spin-density wave, but one should notice that (1) the geometries being different it becomes difficult to make a direct comparison, and (2) the CI process performed in the energy calculation only includes a part of the dynamical spin polarization. Notice that another calculation (MP4 on an UHF geometry)[63] gives an energy difference of 20 kcal mol^{-1} between the singlet and triplet in their equilibrium geometry. In that calculation the SiSi distance in the triplet state is 2.32 Å, still 0.02 Å shorter than the single bond of disilane[7], showing the importance of a remaining hyperconjugation.

V. THE $\pi\pi^*$ SINGLET STATES

A. Valence-bond Content

While the triplet $\pi\pi^*$ excited state is neutral or diradical in the VB sense, the singlet $\pi\pi^*$ excited state is ionic or zwitterionic. The $\pi \rightarrow \pi^*$ HOMO–LUMO excitation leads to a $^1B_{1u}$ valence state. This is not actually the lowest singlet state of ethylene since several Rydberg states, in which one π electron is promoted to a diffuse orbital, lie below this valence state (see Section VI)[85–87]. This $\pi\pi^*$ singlet state, of $^1B_{1u}$ symmetry, is labelled V (for Valence) from the pioneering work of Mulliken[92]. Let us detail its VB content:

$$\psi_V = \frac{1}{\sqrt{2}}|\pi\overline{\pi^*} + \pi^*\bar{\pi}|$$

$$\psi_V = \frac{1}{\sqrt{2}}\{\tfrac{1}{2}|(a+b)\overline{(a-b)} + (a-b)\overline{(a+b)}|\}$$

$$\psi_V = \frac{1}{\sqrt{2}}\{|a\bar{a}| - |b\bar{b}|\} \tag{13}$$

This state therefore has a purely π ionic content without any covalent or neutral character, as also occurs for the $^1\Sigma_u^+$ excited state of H_2, which is in some sense isoelectronic to the π bond. The $\pi\pi^*$ singlet state is therefore a resonance between two zwitterions of opposite polarities $H_2X^- - {}^+XH_2$ and $H_2X^+ - {}^-XH_2$. In other words, the two π electrons jump simultaneously from one carbene to the other. Introducing left-hand and right-hand

localized determinants Φ_L and Φ_R given by

$$\Phi_L = \Phi_{A^-B^+} = |a\bar{a}| \quad \text{and} \quad \Phi_R = \Phi_{A^+B^-} = |b\bar{b}|$$

equation 13 becomes

$$\psi_V = \frac{1}{\sqrt{2}}(\Phi_L - \Phi_R) \tag{14}$$

and the energy of this state will be

$$E_V = \langle \psi_V | H | \psi_V \rangle$$
$$E_V = \tfrac{1}{2}\{\langle \Phi_L - \Phi_R | H | \Phi_L - \Phi_R \rangle\}$$
$$E_V = \langle \Phi_L | H | \Phi_L \rangle - \langle \Phi_L | H | \Phi_R \rangle \tag{15}$$

The second term in equation 15 represents the interaction between these two ionic forms.

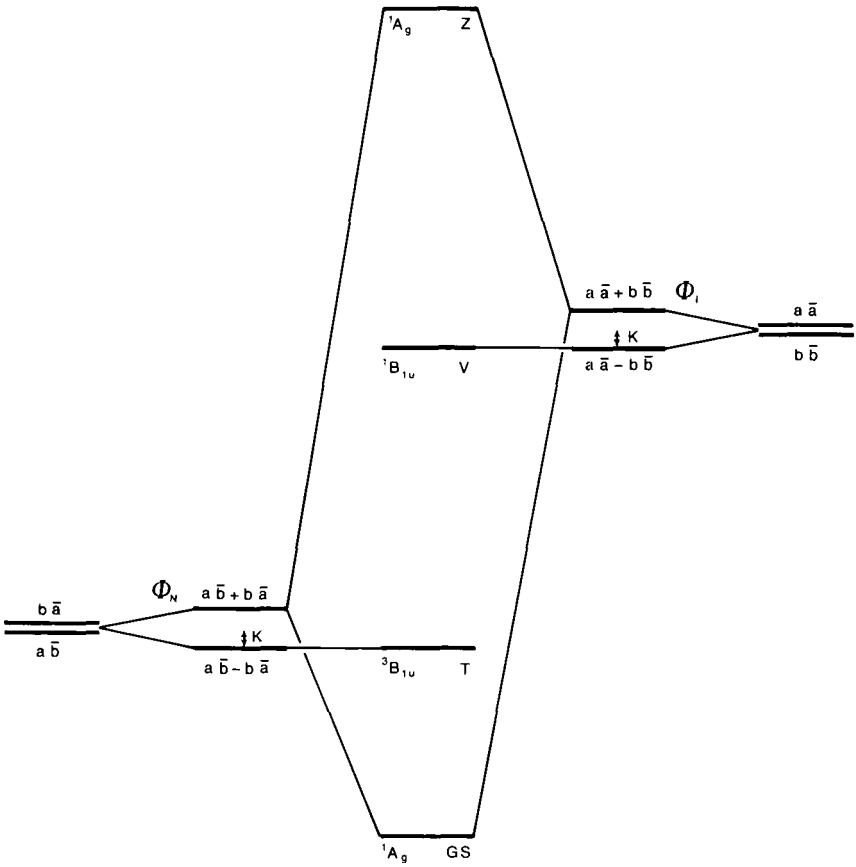


FIGURE 13. The content of the ground and valence $\pi\pi^*$ excited states of ethylene, as built from elemental π valence-bond forms

It decomposes further to

$$\langle \Phi_L | H | \Phi_R \rangle = \langle a\bar{a} | H | b\bar{b} \rangle$$

$$\langle \Phi_L | H | \Phi_R \rangle = \left\langle aa \left| \frac{1}{r_{12}} \right| bb \right\rangle = K_{ab}$$

which is a small bicentric exchange integral. For this reason the left–right electron jump (the resonance) does not contribute much energy—we shall remember this result subsequently.

Note that the symmetrical combination of Φ_L and Φ_R

$$\Phi_I = \frac{1}{\sqrt{2}}(\Phi_L + \Phi_R) \tag{16}$$

is nothing else than the ionic part of the ground-state wave function as defined in equation 5. The ground-state wave function can be seen as the neutral configuration Φ_N interacting with the ionic configuration Φ_I of the same symmetry. As in classical orbital interactions (see Figure 13), the ground state from Φ_N is pushed down in energy and the counterpart from Φ_I is pushed up in energy, creating a dominantly ionic state of $^1A_1$ symmetry labelled the Z state in the Mulliken terminology. In VB terms, ψ_z is expressed as the counterpart of equation 6:

$$\psi_z = (\lambda + \mu)\Phi_I - (\lambda - \mu)\Phi_N$$

In an MO picture, the Z state is the $(\pi \rightarrow \pi^*)^2$ doubly excited state. Taking into account the interaction with the ground-state determinant $|\pi\bar{\pi}|$, one may write

$$\psi_z = \lambda' |\pi^* \overline{\pi^*}| + \mu' |\pi\bar{\pi}|$$

This state is pushed to very high energies ($\cong 300\,\text{kcal mol}^{-1}$) above the ground state. Being of ^1A_g symmetry like the ground state, the transition between them is dipolarly forbidden, but we mention it since it will play an important role in the geometry relaxation of the V state.

B. Requisites for Accurate Computational Description

The transition to the singlet valence state is strongly allowed since the transition dipole moment from the ground state, governed by

$$\langle \psi_{GS} | \mathbf{r} | \psi_V \rangle = \sqrt{2} \langle \pi | \mathbf{r} | \pi^* \rangle$$

$$= \frac{1}{\sqrt{2}} \{ \langle a | \mathbf{r} | a \rangle - \langle b | \mathbf{r} | b \rangle \}$$

is proportional to the distance between the two carbon atoms and is directed along the C—C bond. Nevertheless, identification of the $\pi\pi^*$ transition was not easy for spectroscopists. Because the vertical transition is far from the adiabatic well (see below), the spectra are difficult to analyze and to interpret. The band is very broad, but one may accept a vertical transition energy of 176–180 kcal mol^{-1} [85–87]. Theoreticians were not more successful in the description of that state. A realistic estimate of the vertical transition energy in the region of 8 eV (200 kcal mol^{-1}) was only obtained when large basis sets and extensive CIs were included in the calculations[76–84]. This is a direct consequence of the ionic character of that state. The difficulties may be summarized as follows:

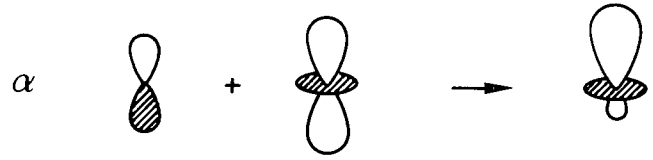
(1) Either in Φ_L or in Φ_R two electrons occupy the same p_π AO. They repel each other strongly. To avoid each other they will (i) make the p AO more diffuse, and diffuse

functions are actually necessary to represent this $\pi\pi^*$ singlet state, sometimes considered as of mixed valence–Rydberg character; the $\langle R^2 \rangle$ amplitude is actually about 17 Å^2 [84], half-way between the ground state and the Rydberg states; (ii) tend to minimize their repulsion by correlating their movement. When one electron (say α) is above the plane of the molecule, the other electron (say β) is preferably below the plane. This is called the angular correlation, which is obtained by mixing the $a\bar{a}$ product with a product of dz^2 orbitals $d\bar{d}$. The expression of the $a\bar{a}$ determinant is hence modified as

$$|a\bar{a}| \rightarrow |\overline{(\lambda a + \mu d)(\lambda a - \mu d)}| + |\overline{(\lambda a - \mu d)(\lambda a + \mu d)}|$$

$$|a\bar{a}| \rightarrow |\lambda^2 a\bar{a} - \mu^2 d\bar{d}|$$

The α electron occupies a distorted p AO with a larger upper lobe, **27**, and the β electron occupies a distorted p AO with a larger lower lobe, **28**. Actually, d atomic orbitals as polarization functions are crucial to represent satisfactorily such excited states. They play a larger part in the singlet excited state than in the ground state.



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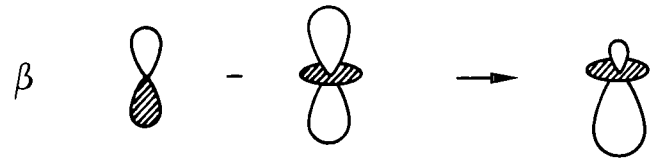
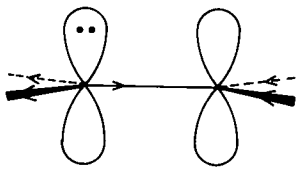


(28)

(2) The σ electrons react to the instantaneous field created by the π electrons. When the π electrons are on the left atom (A^-B^+), **29**, the σ electrons leave the A atom toward the other atoms, especially toward B^+, which is instantaneously electron deficient; the reverse is true when the π electrons are on the right atom, **30**. The electrons of the σ bond are



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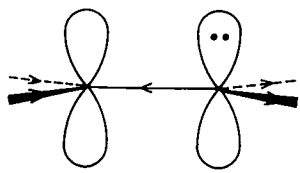


(30)

especially sollicitated since they are kept in the intense A^-B^+ (or A^+B^-) dipole, but the electrons of the CH bonds react as well. If one neglects this σ–π effect, keeping a frozen σ core or truncating the CI, one neglects a crucial mechanism which diminishes the $\pi\pi^*$ transition energy by as much as 30 kcal mol^{-1}. Chemists should remember that the treatment of ionic states (frequently obtained from HOMO–LUMO electron jumps) is more difficult than the treatment of neutral covalent states, even if these states are less intuitively described in an MO language as mixtures of single (HOMO − 1 → LUMO or HOMO → LUMO + 1) and double ($HOMO^2 \rightarrow LUMO^2$) excitations. The calculation of

the energy of ionic states requires larger basis sets and more extensive CI. This point, discussed in References 93 and 94, is valid for all conjugated molecules, aromatic or not. For instance, in the series of linear polyenes the ^1B_u state is always more difficult to locate correctly than the so-called 'hidden' state of ^1A_g symmetry, which is also of valence character but neutral, while ^1B_u is ionic.

A qualitative measure of the importance of the σ–π correlation effects may be found in a VB-like analysis of the four-electron four-orbital CAS–SCF wave function, analogous to that previously performed on the ground state. The VB configurations are the same as before. Starting from the single configuration of the $\pi\pi^*$ singlet state

$$\psi = \frac{1}{\sqrt{2}}|\sigma\bar{\sigma}(\pi\overline{\pi^*} + \pi^*\bar{\pi})|$$

one may easily obtain probabilities of 25% for neutral Φ_2, 50% for ionic Φ_6 and 25% for doubly ionic Φ_7. In the four-electron four-orbital CAS–SCF calculation, the weights of these configurations become 35%, 53% and 12%, respectively. Thus, introducing the σ–π correlation increases markedly the neutral component Φ_2, which may be regarded as built from one carbene in its singlet $^1A_1$ lowest state and one carbene in its singlet excited state of the same symmetry. The σ–π interaction restores some neutral (and closed-shell) character in a state which is purely ionic from the π-only point of view.

If only the two π electrons are correlated in both ^1A_g and $^1B_{1u}$, the vertical transition energy is calculated to be 234 kcal mol^{-1}. This value reduces to 225 kcal mol^{-1} in the four-electron four-orbital CAS–SCF calculation (this work), since the σ–π interaction is larger in the excited state. The effect is more pronounced when all σ electrons are involved. A second-order correction to the CAS–SCF wave function further lowers the vertical transition energy to 189 kcal mol^{-1}. This value is to be compared with theoretical results in the literature (175[83], 183[95], 186[84], 189[77,82] kcal mol^{-1}) and with the experimental result 179 kcal mol^{-1} [85–87].

C. Geometrical Relaxation

The $^1B_{1u}$ state is subject to complex conformational changes, as shown by an analysis of the vibrational structure[95]. Since the two components Φ_L and Φ_R in equation 14 only interact through a weak K_{ab} matrix element (the same occurring between the two components of the $S_z = 0$ triplet state), the left–right two-electron delocalization does not contribute much energy and cannot compensate both the preference of the σ CC bond to lengthen, and the repulsion between the CH bonds of the two carbenes. The first effect will lengthen the CC bond, while the second tends to induce twisting around the CC bond to stagger the CH groups.

It is quite arbitrary to hierarchize the two deformations, but the twisting is the most stabilizing one. If r_{CC} is maintained at 1.34 Å, the rotation diminishes the energy by 60 kcal mol (4-electron CAS–SCF) or 48 kcal/mol (second-order multireference perturbation, this work) (see also a similar value for a CC bond of 1.42 Å)[96].

It is useful to think about the physics of the ionic state in the 90°-twisted geometry. Here, the K_{ab} interaction between the two zwitterions Φ_L and Φ_R becomes vanishingly small since the two p_π AOs, located in perpendicular planes, have almost zero differential overlap. On the other hand, in this geometry, the in-phase combination Φ_I of ionic structures (equation 16) no longer interacts with the neutral singlet VB components, since

$$\tfrac{1}{2}\langle|a\bar{b}| + |b\bar{a}||H||a\bar{a}| + |b\bar{b}|\rangle = 2F_{ab}$$

is zero when the two $2p_\pi$ AOs are perpendicular. Then the Z ($^1A_1$) state becomes purely ionic and the Z and V states are very close in energy. In principle the Z state should lie

above the V state since

$$\langle \psi_Z | H | \psi_Z \rangle - \langle \psi_V | H | \psi_V \rangle = 2\langle \Phi_L | H | \Phi_R \rangle = 2K_{ab} > 0$$

Actually, extensive CI calculations predict that when the twisting angle exceeds 80°, the Z state is below the V state[96,97]. This is due again to the σ–π interaction, as occurred for the triplet state in the 90°-twisted conformation, for which σ spin polarization induced a violation of Hund's rule. Here again, a dynamic charge polarization of the σ electrons in the field of the fluctuating π electron pair is responsible for the counterintuitive energy order, as explained thoroughly elsewhere[98].

However, a further effect occurs in that region, where two strongly polar (zwitterionic) structures are weakly coupled. The situation of weak resonance between two strongly polar (and strongly polarized) situations, such as Φ_R and Φ_L, is known to lead generally to two effects related to symmetry breaking:

(1) One effect is purely internal to the theory; energy lowering is obtained by simply relaxing the partial wave function Φ_R (or Φ_L) and fitting the electronic distribution to the A^+B^-(or A^-B^+) field. This polarization of the electron cloud (and especially the σ MOs) changes Φ_R into Φ'_R and

$$\langle \Phi'_R | H | \Phi'_R \rangle \ll \langle \psi_V | H | \psi_V \rangle \quad \text{or} \quad \langle \psi_Z | H | \psi_Z \rangle$$

Similarly, opposite polarization of the σ MOs in the field of the π electrons in Φ_L leads to Φ'_L and

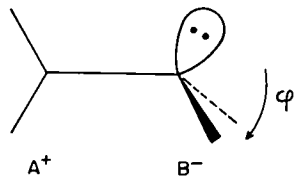
$$\langle \Phi'_L | H | \Phi'_L \rangle = \langle \Phi'_R | H | \Phi'_R \rangle$$

but the two polarized wave functions are no longer orthogonal,

$$\langle \Phi'_L | \Phi'_R \rangle \neq 0$$

Thus if one optimizes the single determinant Φ'_R, one obtains a much lower energy than by optimizing ψ_V or ψ_Z. In other words, a lesser energy is obtained by leaving the symmetry constraint and the left–right resonance and by allowing specific polarizations of one of the two resonating polar structures. The two nonorthogonal functions Φ'_L and Φ'_R may be used to obtain a good symmetry-adapted representation of the states by performing a nonorthogonal configuration interaction as shown nicely by Petsalakis and coworkers[99]. Symmetry breaking also occurs in our four-electron four-orbital MCSCF calculation; it lowers the energy by as much as 81 kcal mol^{-1}.

(2) The second effect is more physical; the HF or MCSCF instability may be regarded as the symptom of a physical tendency to leave the symmetry by an unsymmetrical distortion of the nuclear skeleton. Actually, it is clear that Φ'_R (A^+B^-) may be stabilized by a simple pyramidalization of the $-CH_2^-$ group (remember that CH_3^- is pyramidal). The resulting twisted–distorted geometry, **31**, corresponds to a real minimum on the potential-energy surface of both the V and Z states (since they are linked by a conical intersection for $\theta \cong 80°$, $\varphi = 0$). This phenomenon led to the discovery of the famous 'sudden' polarization effect[78,100–105]. The degree of suddenness of the polarization is questionable, but the existence of symmetry-broken polar minima is not an artifact and concerns the ^1B_u excited states of conjugate polyenes as well.



(31)

The extent of pyramidalization (φ in **31**) is controversial. CI calculations give $\varphi = 31°$ [78], $\varphi \geqslant 40°$ [96]. Optimization of the energy of the closed-shell single determinant Φ'_R lead to $\varphi = 65°$ (DZ basis set), and subsequent multireference CI maintained this value of the pyramidalization[106]. Using a DZd basis set, MCSCF or second-order multireference CI calculations also leads to the same pyramidalization of 64° (this work). Such a large pyramidalization does not contribute much energy (8 kcal mol^{-1}) and the lowest minimum of the set of V and Z potential surfaces finally lies at 131 kcal mol^{-1} above the ground-state minimum (this work). This calculated value and also other theoretical values (134 kcal mol^{-1} [78,96], 137 kcal mol^{-1} [84]) are in agreement with the adiabatic transition energy proposed from experiment (129–131 kcal mol^{-1})[84]. The zwitterionic nature of the singlet excited state in its minimum-energy conformation is further illustrated by the large calculated dipole moments: 3.4 D[107], 3.8 D[108], 4.0 D[96], 4.1 D[78] and 4.7 D[106].

In order to provide a physical picture for the wave function of the ionic excited state in its equilibrium geometry, its VB content has been calculated by the same procedure as used in Section III, i.e. by decomposing the four-electron four-orbital MCSCF function. The leading configurations are listed in Table 9; they are essentially as follows.

(1) For 34%: Φ_{10}, the product of CH_2^+ by CH_2^- both in their ground state ($n_1 n_2^2 \pi_2$). Note that this configuration had a zero coefficient for $\varphi = 0$ before symmetry breaking.

(2) For 22%: Φ_6, the product of CH_2^+ by CH_2^- in its excited state ($n_1 n_2 \pi_2^2$). This was the dominant configuration for $\varphi = 0$.

(3) For 16%: Φ_7, the doubly ionic configuration $CH_2^{+\,+} CH_2^{-\,-}$ ($n_2^2 \pi_2^2$).

(4) For 14%: Φ_8, neutral, with one methylene in its closed-shell singlet configuration, the other being open-shell ($n_1^2 n_2 \pi_2$).

(5) For 9%: Φ_3, where both methylenes are in their closed-shell singlet configuration ($n_1^2 n_2^2$).

Pyramidalization does not therefore change the dominantly ionic character of this state. Ten years ago we suggested that this state might be viewed as resulting from the interaction between two $^1A_1$ singlet methylenes (i.e. Φ_3)[106]. This component actually remains of minor importance. It seems more correct to say that the pyramidalization of the negative center allows a shift of the negative carbene from its excited $n_2 \pi_2^2$ configuration to its ground $n_2^2 \pi_2$ configuration, in other words from A^+-B^{-*} to A^+-B^-. We note that pyramidalization induces a similar phenomenon regarding the neutral configurations, since it favors two $^1A_1$ closed-shell methylenes (Φ_3) over Φ_2 which implies one excited $^1A_1$ closed-shell methylene. This is visualized in Figure 14, which exhibits the Φ_{10}/Φ_6 and Φ_3/Φ_2 reversal of importance upon pyramidalization.

TABLE 9. The valence-bond nature of ethylene in its ground state and $\pi\pi^*$ excited states (% VB forms)[a]

	Ground state		$\pi\pi^*$ triplet		$\pi\pi^*$ singlet		
	planar	twisted	planar	twisted	planar	twisted	pyramidal
Φ_1	38	56	56	56	—	—	—
Φ_2	11	—	—	—	35	29	4
Φ_3	0	—	—	—	—	—	9
Φ_5	29	44	44	44	0	0	—
Φ_6	18	—	0	—	53	55	22
Φ_7	4	—	—	—	12	16	16
Φ_8	—	—	—	—	—	—	14
Φ_{10}	—	—	—	—	—	—	34

[a] Determinants which have negligible contributions in all species are omitted for clarity.

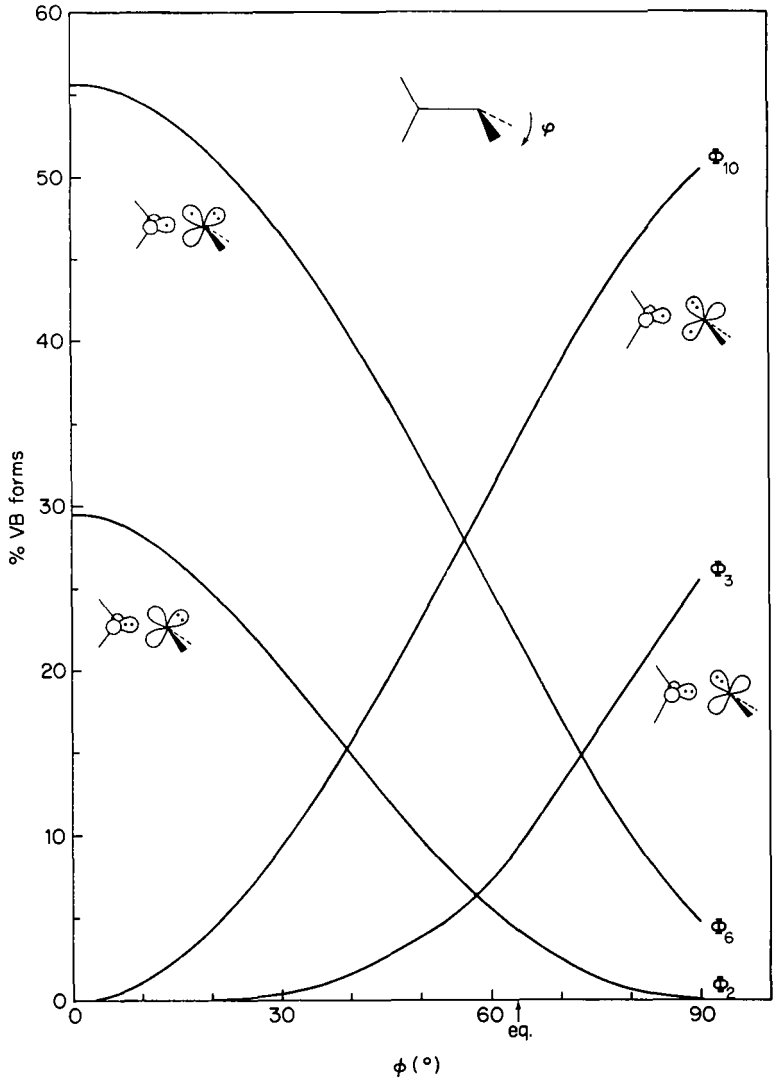


FIGURE 14. Pyramidalization of the twisted singlet $\pi\pi^*$ excited state of ethylene: main changes in the valence-bond decomposition. The arrow indicates the calculated equilibrium folding. The neutral Φ_2/Φ_3 crossing corresponds to primacy of A–B over A–B*. The ionic Φ_6/Φ_{10} crossing corresponds to primacy of A^+–B^- over A^+–B^-*

As expected here also the vertical excitation energy from ground state to $\pi\pi^*$ singlet excited state is lower in disilene than in ethylene. In the SCF-optimized planar geometry, the $\pi\pi^*$ singlet excited state of disilene lies 130 kcal/mol above its ground state. This value reduces to 117 kcal/mol for MCSCF-optimized trans-bent geometry (this work). Finally, let us mention the existence of two $\sigma \rightarrow \pi^*$ valence excited states of ethylene (of $^1B_{1g}$ and

$^1B_{2g}$ symmetry) in which the excitation starts from the b_{3g} or a_g σ MO. The valence character appears from the value of $\langle R^2 \rangle$ (8 Å^2 for both). The corresponding vertical transition energies have been located at 200 kcal mol^{-1} and 223 kcal mol^{-1}, respectively, in a calculation by Palmer and collaborators[84]. These authors noted that the $\pi\pi^*$ and $\sigma\pi^*$ valence states are fairly close in energy since they are all within 35 kcal mol^{-1}, whereas the energies of the corresponding $\sigma(b_{3g})$, $\sigma(a_g)$ and π orbitals, as known from the corresponding ionization potentials, are spread over a wider range of energy (92 kcal mol^{-1}). The narrowing of the electronic transitions with respect to the ionization potential spectrum can be traced to differential Coulomb operators $J_{\pi\pi^*} > J_{\sigma\pi^*}$ which relate transition energies ΔE to one-electron orbital energies $\Delta\varepsilon$ according to

$$\Delta E = \Delta\varepsilon - J + 2K$$

VI. RADICAL CATION AND RYDBERG STATES

In an early work, Mulliken had predicted that the radical cation of ethylene should be slightly twisted in its ground-state equilibrium geometry[109]. The singly occupied MO is the π orbital and, from a VB point of view, this state is a resonance between $CH_2^+ — {}^{\cdot}CH_2$ and $CH_2^{\cdot} \; {}^{+}CH_2$. Both $CH_2^{\cdot}$— and CH_2^+— keep an in-plane structure and the resonance integral is $F_{\pi\pi} = \langle a|F|b\rangle$. When a twist angle θ is introduced between the two CH_2 groups, this integral is diminished to $F_{\pi\pi}\cos\theta$ but some delocalization is introduced between the CH bonds and the half-empty π MO, which increases as $\sin^2\theta$. Notice that the twist also diminishes the repulsion between the CH bonds. Mulliken had proposed a twist of about 30°. This suggestion received two experimental confirmations: one concerns the $C_2H_4^+$ cation itself, for which the interpretation of vibronic effects in the photoelectron spectrum suggests a torsional angle of 25°[110]. The other experiment concerns the $^1B_{3u}$ Rydberg state (see below) for which the vibrational analysis also predicts a twist angle of 25°[111] (remember that the structures of Rydberg states are usually the same as those of the parent ion). A calculation of the Franck–Condon factors for the lowest ionization of ethylene gives a value of $\theta = 17°$ from a fit to experimental intensities of the photoelectron spectrum[112]. Other experiments suggest $\theta \cong 27°$ with a barrier of about 270 cm^{-1} (0.8 kcal mol^{-1})[113].

Most *ab initio* calculations gave planar equilibrium structures (see however Reference 114)[89,115,116]. The problem has been accurately studied using various basis sets and correlation treatments[117]. Correlation definitely favors the twisting, but more accurate calculations in larger basis sets would be needed to ascertain the structure since the torsional potential is very flat and the barrier is very weak (a few 100 cm^{-1} or tenths of kcal mol^{-1}). Increasing alkyl substitution would reduce the twisting according to semiempirical calculations[118]. The disilene radical cation $Si_2H_4^+$ has been calculated as well[46]. The molecule is found to be planar even from the most refined calculations (CISD, 6–31 G) which give a twisted $C_2H_4^+$. Note that the 0.1 Å lengthening of the Si=Si bond upon ionization of Si_2H_4 corresponds to the same *relative* lengthening (5%) as that occurring in ionization of C_2H_4.

Three Rydberg states lie below the first valence singlet excited V state. The lowest one, of $^1B_{3u}$ character, corresponds to a $\pi \rightarrow 3s$ excitation toward a diffuse, totally symmetrical MO. It lies at 164 kcal mol^{-1} above the ground state according to experimental measurement[85–87] and calculations (to within 2 kcal mol^{-1})[81–84]. The two other states, of $^1B_{2g}$ and $^1B_{1g}$ symmetries, result from $\pi \rightarrow 3p_z$ and $\pi \rightarrow 3p_y$ excitations toward diffuse 3p-type MOs. They are located around 180 kcal mol^{-1} according to experiments, and around 180–184 kcal mol^{-1} in all calculations[84]. The diffuseness of a state may be appreciated from the $R^2 = X^2 + Y^2 + Z^2$ operator taken on the electronic wave function. While for the ground state $\langle R^2 \rangle$ is close to 8 Å^2, the values are 22, 27 and 26 Å^2 for these three Rydberg states, respectively[84].

VII. CONCLUDING REMARKS

This survey was mainly restricted to homopolar bonds made of carbon and silicon. Obviously, all the trends evidenced above from the comparison between carbon and silicon would be even more pronounced when going down to the heavier group 14 elements, germanium, tin and lead. Some results have been given for tin (cf. Figures 11 and 12) but there are quite a few experimental and theoretical results on digermene[119-121], distannene[122] or even diplumbene systems, the latter requiring a proper inclusion of relativistic effects in the calculations[123]. Most of our conclusions remain valid for heteropolar double bonds as well. For such mixed systems $H_2X{=}YH_2$, we have predicted elsewhere the occurrence of *trans* bending when X, Y = Si, Ge, Sn[50]. Substitution of hydrogens by polar groups may induce large changes in the properties. Some of them may be rationalized by simply considering the singlet–triplet splittings of the R_2X divalent species, as shown for dissociation energies[56] and equilibrium structures[50]. Some substitutions may lead to a reorganisation in the molecular structure. Thus, lithium substitution will twist a C=C double bond[124] and perfluoro substitution will break a Si=Si or Ge=Ge double bond, giving doubly bridged structures[125,126].

One major lesson which emerges from this review is the importance of the interaction between the *four* electrons of the double bond. In noncorrelated pictures, this interaction is neglected or reduced to a static mean-field effect while it does play an important role in some distortions and in excitation energies. It is risky to describe the double bond as a weak π bond added to a normal σ bond. More adequate is the consistent description of the two bonds as a system of *four* strongly interacting electrons. On condition that a valence-bond decomposition is performed, the correlated description of these four electrons remains easy for the chemist to understand. Correlation simply reflects and restores the propensity of the fragments to move back to neutral situations and to satisfy their intrinsic electronic preferences. This tendency explains the crucial role of the singlet–triplet separation of the fragments. A 'standard' double bond is constructed from triplet carbenoids. If these happen to prefer strongly singlet configurations, the price to pay for reaching these triplet states may be too high, so that the carbenoids will be reluctant to build a normal double bond. Such fragments will rather try to find a compromise between electronic delocalization and their singlet ground-state preference—they will choose the *trans*-bending deal.

The weakness and problematic character of π bonds when carbon atoms are no longer involved is further illustrated by two near degeneracies: one between the thermodynamic stabilities of the two isomers $H_2X{=}XH_2$ and $H_3X{-}XH$, the other between the dissociation energies of the X—X single bond and the X=X double bond.

It is clear that the analysis, and in particular the VB picture, performed in the present work may be usefully applied to double bonds involving atoms of other columns. Special attention is drawn to the increasingly abundant literature on unsaturated systems involving group 15 atoms such as

$$\text{>Si=N<}^{127-130},\ \text{>Si=P<}^{131,132},\ \text{>Ge=N<}^{133,134},\ \text{>Ge=P<}^{122,135-137},$$
$$\text{>Sn=P<}^{138},\ \text{>P=P<}^{122,139-142},\ \text{>P=As<}^{143},\ \text{>P=Sb<}^{122}$$

Both in column 14 and in column 15, the double bond appears as an exception which only first-row atoms (C or N) commonly build[18]. Silicon and heavier elements are reluctant to form double bonds. This explains the striking difference between the small clusters of carbon and those of silicon. The former are linear or cyclic and π-bonded[144,145] while the latter have compact and hypervalent structures[146]. Increasing the size of the cluster will give π-bonded two-dimensional slabs for carbon (soccerball-shaped C_{60} 'buckminsterfullerene' or graphitene can be assimilated in such two-dimensional sys-

tems)[147-164] and again compact structures for silicon. Finally, the bulk structures also satisfy this trend since carbon crystallizes in graphite (π-bonded) (preferred over diamond by as little as half a kcal mol^{-1}, however) and silicon crystallizes only in a diamond lattice (σ-bonded). More generally, it is the ability of carbon atoms to enter versatile double or multiple bonds which is largely responsible for the wealth and diversity of organic compounds on which life could emerge and evolved the way we know.

VIII. APPENDIX

The overlaps listed in Table 2 were calculated from Slater orbitals with the following exponents, taken from atomic calculations[165] (except for hydrogen):

1s(H)	1.3
2s(C)	1.608
2p(C)	1.568
3s(Si)	1.634
3p(Si)	1.428

C–H and Si–H distances were fixed at 1.09 Å and 1.48 Å, respectively.

All SCF parts of the illustrating calculations were performed with the PSHONDO algorithm in which the core electrons are taken into account through an effective core potential[142]. The basis sets used are of double-zeta + d type (DZd) with the following exponents for the d functions:

η_d(C)	0.8
η_d(Si)	0.5
η_d(Sn)	0.2

The multireference CI calculations were performed using the CIPSI method[166].

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The Chemistry of Double-bonded Functional Groups
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CHAPTER **2**

Mass spectrometry of the double bond

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I. INTRODUCTION

It has been almost twenty years since the first chapter on the mass spectrometry of double bonds was included in *The Chemistry of Functional Groups Series*[1]. Since then mass spectrometry has made enormous progress and has established itself not only as a power-

ful instrumental method used in chemical analysis but as a scientific subject in its own right. Apart from a continuously growing number of books and textbooks, the wealth of research work carried out is sufficient to support no less than four monthly periodicals, *Organic Mass Spectrometry, Biomedical and Environmental Mass Spectrometry, International Journal of Mass Spectrometry and Ion Processes* and *Rapid Communications in Mass Spectrometry*. There is also a quarterly journal *Mass Spectrometry Reviews*, an annual *Specialist Periodical Reports, Mass Spectrometry* and a biannual *Analytical Chemistry Reviews*.

Mass spectrometry has found widespread applications in chemical, pharmaceutical, food and flavour industries, in forensic, toxicological and environmental residue analysis, in clinical, biochemical and pharmacological research as well as in research in synthetic, physical, physical organic and natural products chemistry.

The varied nature of samples from such different fields has imposed severe demands on the development of the instrumentation. Various techniques such as chemical ionization (CI), fast atom bombardment (FAB), mass analysed ion kinetic energy spectrometry (MIKES) or thermospray, which 20 years ago were known only to a few involved in mass spectrometry research and development, are nowadays used as routine sample analyses. However, only those techniques that are particularly useful in the interpretation of the mass spectra of compounds containing a double bond will be discussed here in detail.

This brings us to the question of how appropriate is the title of this chapter. It would be virtually impossible to cover all research in mass spectrometry, even in the past few years, that concerns compounds containing the double bond. Therefore the content of this chapter must be restricted to analogous fragmentation processes that are particularly associated with the presence of a double bond. Several chapters on some double-bonded functional groups, namely the C=O, C=N, N=N and N=O, have already appeared in this Series[2].

The ionization process in mass spectrometry is a unique process among other molecular spectrometric methods in that it involves irreversible chemical changes in the ions produced and naturally there have to be differences in the fragmentations and rearrangements that would be associated with the particular double-bonded groups. In this chapter the emphasis will be placed on the typical fragmentation processes associated with compounds containing double bonds and the C=C double bond in particular.

The information mainly requested from the mass spectrometrist by an organic chemist is to provide the relative molecular mass (therefore the molecular weight) and the exact elemental composition of the compound studied. Unfortunately, the majority of information in the mass spectrum concerning the structure is often ignored, since in the conventional mass spectrum the relationship between particular ions does not appear so clearly. There are many methods developed nowadays which are particularly useful in the structure elucidation, such as isotope labelling, metastable ion studies and derivatization. Those techniques concerned with double-bond fragmentation or rearrangements, or the double-bond location, will be treated here in more detail. The aim of this chapter is to provide the reader with information pertaining to the new potential that has been achieved in mass spectrometry and the advances in the interpretation of mass spectra. Some selected examples are provided for illustration, since again it is not possible to list them all.

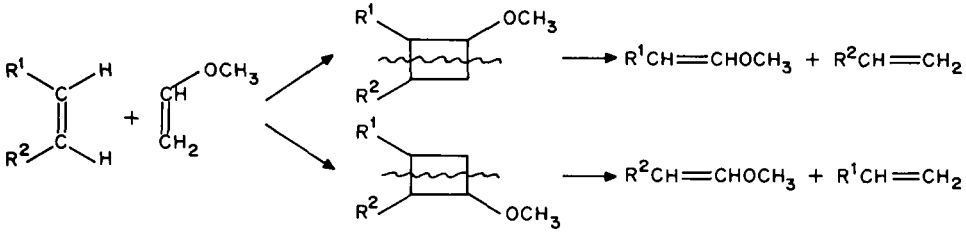
Finally, the literature covered is mainly that concerned with research and development carried out largely in the years 1978–1988.

II. TECHNIQUES DEVELOPED FOR MASS SPECTRAL STUDIES

A. Introduction

The relative molecular mass of the molecular ion is the most important piece of information in a mass spectrum. The need for other ionization techniques arose from the

nature of samples that would not exhibit a molecular ion using electron impact (EI). They were usually unvolatile, thermally unstable and contained polar functional groups. For these compounds the absence of the molecular ion was further complicated by extensive fragmentation in the low mass region which made the interpretation of the spectrum much more difficult. The development and the application of 'gentler ionization' methods increased enormously the range of samples that could be analysed by mass spectrometry. These techniques enhanced the molecular ion region and thus provided the desired information about the relative molecular mass (or the molecular weight), and further research has shown that the limited fragmentation observed could be useful for structure elucidation, e.g. for the location of the position of a double bond. In contrast, under electron impact the molecular ions may isomerize to a common structure or a mixture of structures and, from their fragmentation patterns which are very similar, it would be difficult to locate the exact position of the double bond.



SCHEME 1

For example, by using methyl vinyl ether as a chemical ionization reagent gas, it would be possible to determine the double-bond position without derivatization[3]. Methyl vinyl ether reacts with an olefin molecule under high pressure and produces a cyclic adduct complex (Scheme 1). This complex then dissociates and gives rise to fragments which are indicative of the double-bond position in the original molecule and which can be inferred from a single mass spectrum[4].

B. Chemical Ionization

Chemical ionization (CI) was developed in the early seventies from studies of ion–molecule reactions in the gas phase. The principle of this method is that a reagent gas is ionized by electron impact but at much higher source chamber pressure (usually 1–10 torr). Using methane as a reagent gas, three types of reaction take place in the ion source:

(a) EI ionization: $CH_4 + e \rightarrow CH_4^{+\cdot} + 2e$

(b) EI fragmentation: $CH_4^{+\cdot} \rightarrow CH_3^+ + H\cdot$

(c) Ion-molecule reaction: $CH_4^{+\cdot} + CH_4 \rightarrow CH_5^+ + CH_3^{\cdot}$

$CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2$

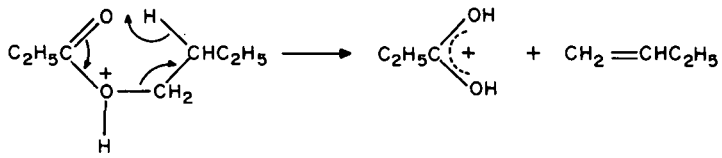
The CH_5^+ and $C_2H_5^+$ ions react with the neutral sample molecules which are ionized either by proton transfer or by a hydride abstraction. This is a much less energetic process than EI ionization:

(d) Proton transfer: $CH_5^+ + M \rightarrow MH^+ + CH_4$

(e) Hydride abstraction: $C_2H_5^+ + M \rightarrow (M-H)^+ + C_2H_6$

Thus in the CI mass spectra no molecular ion $[M]^{+\cdot}$ is observed, but so-called 'quasi-molecular' ions MH^+ or $(M-H)^+$ are quite abundant and the fragmentation is significantly reduced. CI can be used with additional selectivity by taking advantage of the relative proton affinities of reagent gas and analyte. The reagent gas will readily transfer a proton to compounds that are stronger bases[5]. In general, the protonation occurs at the most basic site of the molecule. However, for molecules with more than one basic site the question arises as to the site of protonation. For simple carboxylic acids and esters it has been established that they are protonated preferentially at the carbonyl oxygen[6], where the proton affinities are about $100\,kJ\,mol^{-1}$ lower than at the hydroxyl oxygen. Most CI protonation reactions would be under kinetic control and the kinetically favoured site might differ from the thermodynamically favoured one. For example, in the CI of halobenzenes significant protonation shows at the halogen even if the protonation of the aromatic ring is thermodynamically favoured[7]. The electron impact mass spectra of aliphatic nitro compounds generally do not exhibit a molecular ion $[M]^{+\cdot}$. The observed fragment ions are also non-specific and hence of limited analytical use. However, in CI the even-electron species $[M+H]^+$ can be expected to be more stable. In the series of aliphatic nitro compounds studied[8], the protonated ion $[M+H]^+$ was either the base peak or a very intense one in the CI spectra.

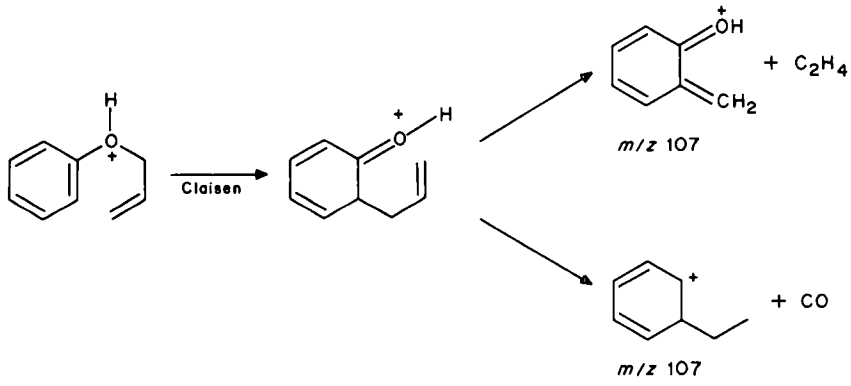
The CI technique is not only useful for the identification of the molecular ion but provides far greater opportunities than EI for preserving the stereochemical integrities of molecules, and the ensuing rearrangements of molecular parent ions. Many of the studies on rearrangements in CI have been supported by evidence such as isotopic labelling and metastable techniques. Various types of hydrogen and skeletal rearrangements have been reviewed[9]. A number of reactions involved in those different rearrangements could be rationalized by the assumption of a six-membered transition state. For example, $[M+H]^+$ ions of carboxylic esters undergo such rearrangement to form the corresponding alkenes and protonated carboxylic acids[10] (Scheme 2).



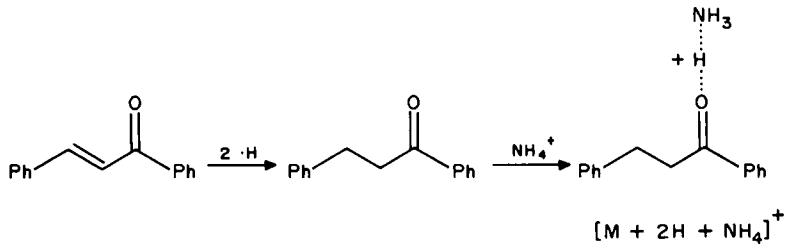
SCHEME 2

The protonated molecular ions of allyl phenyl ether undergo a Claisen rearrangement under the CI conditions which is analogous to reactions in solution. The rearranged ions undergo a fragmentation where the predominant loss is ethene, but the loss of CO also contributes to a certain extent (about 10%)[11] (Scheme 3). The evidence for the *ortho*-Claisen rearrangement was further supported by a low-pressure Fourier transform ion cyclotron resonance (FT-ICR) study[12].

It has been observed that under $CI(NH_3)$ conditions double bonds in some conjugated ketones, nitriles, acids and esters undergo a reduction reaction. A bimolecular reaction was proposed for the formation of $[M+2H+NH_4]^+$ ions in diethyl fumarate and diethyl mesaconate[13]. It has been demonstrated that the radical population in a CI source can be many times higher than the ion concentration[14]. This can lead to many otherwise unexpected reactions involving radicals, neutral molecules and ions. A mechanism for the reduction process forming the abundant $[M+2H+NH_4]^+$ ions has been proposed[15] (Scheme 4).



SCHEME 3



SCHEME 4

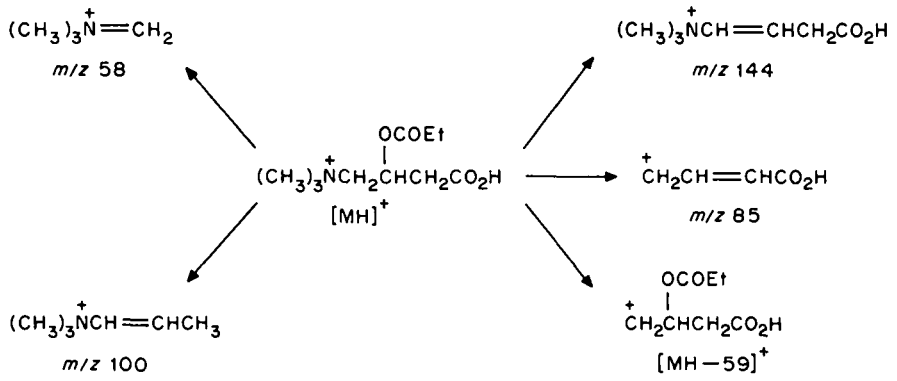
C. Fast Atom Bombardment

Fast atom bombardment (FAB) is an ionization method that has only recently come into common use in organic mass spectrometry, again as a result of the development of techniques for analyses of non-volatile or thermally labile compounds[16,17]. This has enabled mass spectral analyses of compounds of relative molecular masses as high as 1000 and above belonging to the category mentioned previously.

This technique employs a beam of fast neutral atoms, usually argon or xenon, to sputter ions from a sample. The sample is dispersed in a viscous liquid medium of low volatility, glycerol or thioglycerol being used extensively. The solubility of the sample in the matrix appears to be very important, although the process of ionization is not yet fully understood. The basic advantage of the liquid matrix is the time extension of the ion signal due to a replenishment of the surface population of the analyte.

FAB mass spectra are usually dominated by an intense $(M + H)^+$ ion with little fragmentation. Thus relative molecular mass data are provided but usually only very little structural information. In addition, the liquid matrix that is used can contribute to a relatively high background signal across the entire mass range.

However, specific structural information can be achieved by combining the FAB ion source with other techniques specifically associated with metastable ion studies. For example, the combination of FAB with linked scan at constant B/E ratio has enabled the identification of characteristic peaks of acylcarnitines $(CH_3)_3NCH_2CH(OCOR)CH_2COOH$ in metabolic diseases[18]. The mass spectra were



SCHEME 5

dominated by an $[M + H]^+$ ion and major fragment ions were observed at *m/z* 58, 85, 100, 144 and $[M - 59]^+$ (Scheme 5).

It has been demonstrated that FAB mass spectra allow a distinction to be made between geometrically isomeric dicarboxylic acids, such as maleic and fumaric acid and their methyl homologues. The most intense peak in the spectra corresponds to the $[M + H]^+$ ion. This ion, when originating from the *E* acids, fragments either by successive loss of water and carbon monoxide, or by elimination of carbon dioxide. In the case of the *Z* acids only elimination of water from the $[M + H]^+$ ion is observed to occur to a significant extent[19].

D. Metastable Ions

In the ion source, ions are formed in a series of competitive and consecutive fragmentations of the molecular ion. The task of structure elucidation from these fragment ions may be difficult since there is no indication of a particular fragmentation pathway. Information about some of the steps involved can be inferred from the study of metastable ions[20]. These are the fragment ions formed after leaving the ion source and therefore they have less kinetic energy than the primary ions formed in the source. When a parent ion m_1^+ decomposes to give a daughter ion m_2^+ in the field-free region, the product ion m_2^+ will have an apparent mass of m_2^2/m_1. In the conventional mass spectrum these metastable peaks are weak and are likely to be masked by the normal fragment peaks of higher intensity. Furthermore, a data system may not be easily programmed to identify them due to their broad shape, which is a consequence of an energy release in the form of the translational energy related to fragment separation.

The unimolecular decomposition reactions of ions can be confirmed by the appearance energies of metastable peaks. There is another useful inference that can be deduced from their shape as well, namely the amount of internal energy of the reactant converting into translation energy of the products[20].

E. Collisional Induced Dissociation

CID is a widely used technique that has been developed for studies of metastable transitions[21]. Introducing a small amount of a neutral gas such as helium into a collision

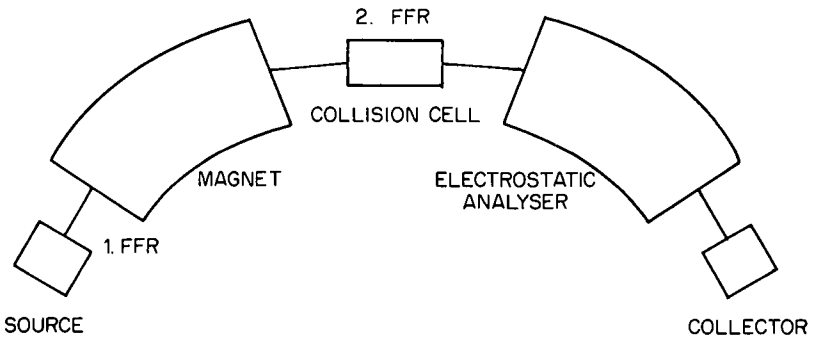
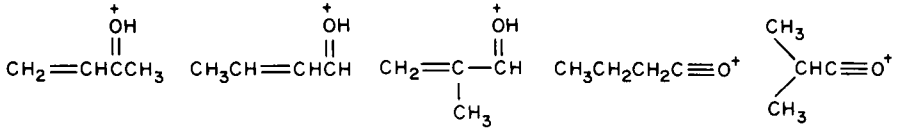


FIGURE 1. Schematic diagram of reverse geometry mass spectrometer

cell in a first or second field-free region (FFR) of the mass spectrometer causes the ions on their trajectory to collide with the gas (Figure 1).

Ion/neutral collisions occurring in the collision cell convert some of the kinetic energy of the ions into internal energy, which then may be randomized among the internal degrees of freedom of the ion[22]. Part of the translational energy of the ion is converted into electronic excitation energy resulting in a variety of fragmentation processes. The collision induced peaks are more intense than the metastable peaks and can be extremely valuable for structure elucidation. The CID spectra do not indicate any ions of m/z not seen in the EI mass spectrum. They provide the interconnections between these ions, point out the specific fragmentation pathways for the production of those ions and the possible further fragmentation of each ion. Most of the data in the literature indicate that CID fragmentation patterns depend generally on the ion structure. For example, it has been shown that the $[C_4H_7O]^+$ ion can have the five different structures shown below and that they can be characterized by their CID mass spectra[21].

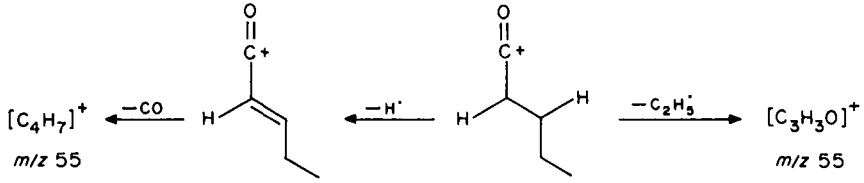


Mass analysis of the product ions is accomplished by one of the methods developed for studying metastable ions. The general approach involves a comparison between the CID spectrum of the species of the unknown structure with the spectra of the species of known or assumed structures. There are several techniques which involve the scanning of various sectors of the instrument in order to enhance a particular type of metastable fragmentation process[23].

F. Mass Analysed Ion Kinetic Energy Spectrometry (MIKES)

This method is applicable to a reversed geometry instrument where the ion m_1^+ selected by the magnet is then transmitted by the electric sector. In this case all daughter ions formed directly from this ion will be collected. MIKES spectra have the advantage, especially when a collision gas is used, that a more detailed fragmentation pathway can be constructed and can be very valuable for structure elucidation. This method has a number of other applications, such as the investigation of the properties of individual fragment

ions. For example, the *m/z* 55 of *n*-propylketene is formed from two isobaric ions[24]. The MIKES study has demonstrated that the loss of $C_2H_5^{\cdot}$ from the molecular ion accounts for about 85% of the main fragmentation, but that there is also a less important process which involves the consecutive losses of a hydrogen radical and of carbon monoxide (Scheme 6).



SCHEME 6

G. Linked Scans (*B/E*, B^2/E)

Another method of analysis of metastable peaks for reactions in the first field-free region is to use a scan of the magnetic field (B) and electric sector voltage (E) at a constant ratio with the accelerating voltage (V) remaining constant. Identification of the daughter ions m^+ formed from a selected parent ion m_1^+ is very useful in establishing molecular and ionic structure[25] and also in resolving mixtures without prior separation[26,27]. A B/E scan can provide a constant parent ion spectrum while a B^2/E scan can provide a constant daughter ion spectrum. It is more convenient to use a constant parent spectrum to analyse the fragmentation of a selected metastable ion since the fragmentations in the first field-free region show better resolution of peaks. The B/E linked scan spectrum is very similar to the MIKES spectrum. The MIKES spectrum can only be obtained using a reverse geometry instrument, whereas the B/E method is usually available on spectrometers of either geometry. The advantage for direct mixture analysis using instruments of conventional geometry over those of reversed geometry[28] is that daughter ions from fragmentation in the second field-free region are transmitted with the main beam for the conventional geometry instrument and therefore cannot obscure the peaks for the fragmentation in the first field-free region[29].

H. Tandem Mass Spectrometry (MS/MS)

Many of the 'soft' ionization techniques, such as CI, FD, FAB or thermospray, yield intense ions in the molecular region but generally few fragments. The structural information which may be directly obtained from such a mass spectrum is consequently limited. The large use of these ionization methods has therefore been oriented towards the development of spectrometers capable of two or more steps of mass analysis. These techniques are described by the term 'tandem' mass spectrometry. Basically they enable one to obtain the mass spectrum of a selected ion in the mass spectrum by the use of a combination of two or more mass analysers in series. Coupling mass spectrometers in tandem greatly enhances the specificity for both the analysis and structure determination of organic molecules. MS/MS can be a rapid procedure for analysis of complex mixtures[30,31], thus eliminating the necessity of a gas chromatograph, for the ion structure differentiation[32] and for metastable ion studies[33]. The process of a typical MS/MS experiment is shown schematically in Figure 2. After ionization the primary mass analysis is carried out in a mass filter (usually a quadrupole). The selected ions enter a collision region where they will undergo a secondary decomposition reaction. In the next stage a mass analysis of these secondary fragment ions is performed. Thus with MS/MS the

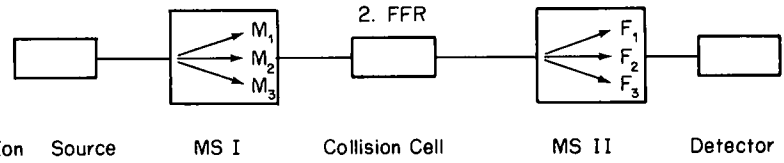


FIGURE 2. Schematic diagram of a tandem mass spectrometer

relative molecular mass can be obtained with the MS I and the structural information after a collisional activation is inferred from the MS II.

Almost every possible combination of magnetic (*B*), electrostatic (*E*) and quadrupole (*Q*) analysers has been used in tandem experiments and up to four mass analysers have been connected in tandem[33]. There has been rapid growth in the use of this type of mass spectrometry in the analytical applications. A detailed exploration of the influence of the instrument parameters on the fragmentation spectra has been carried out[34].

A combination of tandem techniques discussed above can be used in stereochemical studies. The effect of configuration of ethenedicarboxylic ethyl and methyl esters was studied with the aid of CI, CID and the triple quadrupole MS/MS. It was observed that the *cis* esters gave rise to very abundant $[MH - EtOH]^+$ and $[MH - EtOH - C_2H_4]^+$ ions, while the *trans* isomers exhibited abundant $[MH - C_2H_4]^+$ and $[MH - 2C_2H_4]^+$ ions[35]. Moreover, the configuration of the double bond in protonated diesters is retained under the CID conditions and the isomerization to common structures, which is a characteristic feature for the C=C double bond under EI, does not occur.

Another detailed study on nonan-4-one has been reported using a CID and a triple quadrupole mass spectrometer[36] which proves to be a potentially powerful system for structure elucidation. Over 400 fragmentation pathways have been elucidated, which could be a little on the excessive side for the necessary identification. Nevetherless it is an interesting demonstration of a powerful technique in modern mass spectrometry.

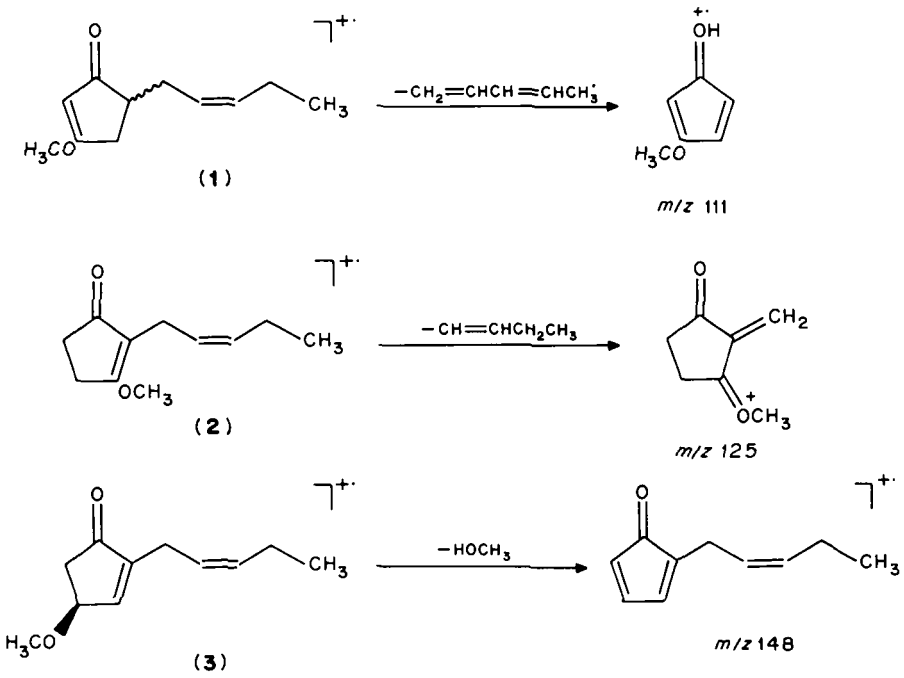
III. FRAGMENTATION PROCESSES ASSOCIATED WITH A DOUBLE BOND

A. Introduction

Mass spectrometry has established itself as one of the essential techniques for providing analytical information necessary for the identification of compounds. The relative molecular mass of the molecular ion determined with an accuracy of four or five decimal places is excellent confirmation of the elemental composition of a molecule. However, for its complete structural identification it is also important to understand the fragmentation pathways that are common to particular functional groups.

In general, fragment ions result from cleavages of vulnerable bonds in the structure. The stability of these ions depends on several factors, such as the inductive effect, the charge localization and the possibility of resonance forms. The fragmentation process is greatly influenced by the presence of a functional group or combination of several groups. The group with the most dominant factors would naturally have the greatest effect in the fragmentation process and in the formation of more stable positive ions.

As an example, the 3-alkoxy-2-cyclopentenones **1** and **2** and the 4-alkoxy-2-cyclopentenone **3**, which are important intermediates in the preparation of various natural products such as prostaglandins, contain three different types of double bond. Mass spectrometry has been shown to be a useful technique for their determination and for the location of functional groups in the molecule[37,38]. The main fragmentation in 5-substituted 3-methoxy-2-cyclopentanones (**1**) is associated with the α-cleavage together



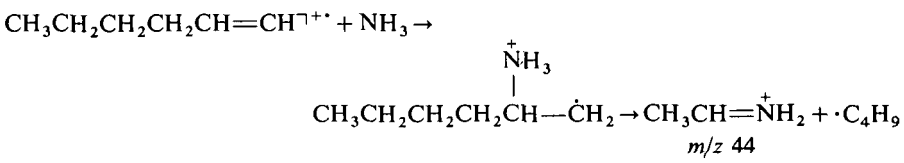
SCHEME 7

with hydrogen migration, thus forming an enol ion (Scheme 7), 2-Substituted 3-methoxy-2-cyclopentanones (**2**) show a substantial molecular ion and the main fragmentation corresponds to a simple β-cleavage of the side-chain. In the case of 4-methoxy-2-cyclopentenones (**3**) the molecular ion is very small (2–3%) but the $[M - CH_3OH]^{+\cdot}$ ion is significantly pronounced.

B. Ion–Molecule Complexes

A few unusual ion–molecule reactions have been observed under CI conditions. There have been several reports of the use of CI as a stereochemical probe in the analysis of organic molecules[39], where the adduct ions are the characteristic to be formed under such conditions. Moreover, additional unusual fragmentation processes were observed which are closely related to these adduct ions and which have not been found under the EI conditions.

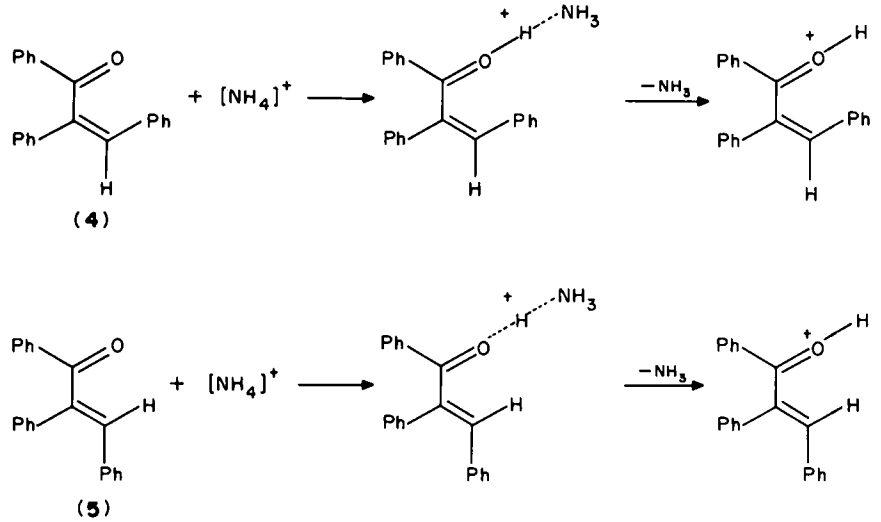
It has been reported that under NH_3 CI conditions, 1-alkenes form alkylamine type $[CH_3(CH_2)_{n-1}NH_2]^+$ ions[40,41] (Scheme 8). The reactive collisions results in addition of



SCHEME 8

NH_3 to the ionized double bond. A subsequent hydrogen transfer followed by an α-cleavage forms the ion *m/z* 44 $CH_3\overset{+}{C}H{=}NH_2$.

Stereospecific adduct ion formation has been observed in the CI mass spectra of certain *E*- and *Z*-1,2,3-triaryl-2-propen-1-ones[42]. The *Z* isomers **4** are found to give higher relative abundances of adduct ions $[MH]^+$ (63%) than the *E* isomers **5** (less than 10%). The $[MNH_4]^+$ ions are the base peaks in both cases of isomers. This adduct ion abundance is influenced markedly by ion source parameters and the $[MNH_4]^+/[MH]^+$ ratio is greater for the *Z* isomer as the source temperature is lowered or the source pressure is increased (Scheme 9).



SCHEME 9

Two different mechanisms have been proposed for the formation of ion–molecule complexes (equations 1 and 2)[43,44]. The first one bears a resemblance to E1 elimination in solution.

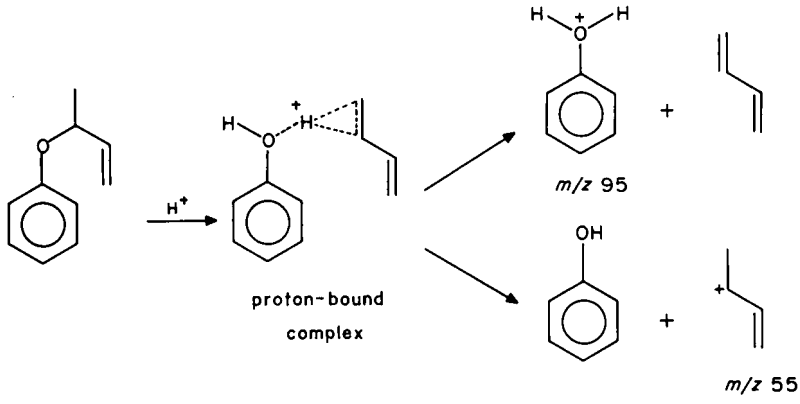
$$\text{Parent ion} \rightarrow \text{ion–molecule complex} \rightarrow \text{fragments} \quad (1)$$

$$\text{Parent ion} \rightarrow \text{tautomer (cyclic transition state)} \rightarrow \text{fragments} \quad (2)$$

Under CI conditions, the methyl substitution on the allyl group in phenyl allyl ether caused very significant changes in the fragmentation behaviour of the molecular protonated ions[44]. It can be assumed that some of the $[MH]^+$ ions exist as a proton-bound complex of phenol and the appropriate diene (Scheme 10).

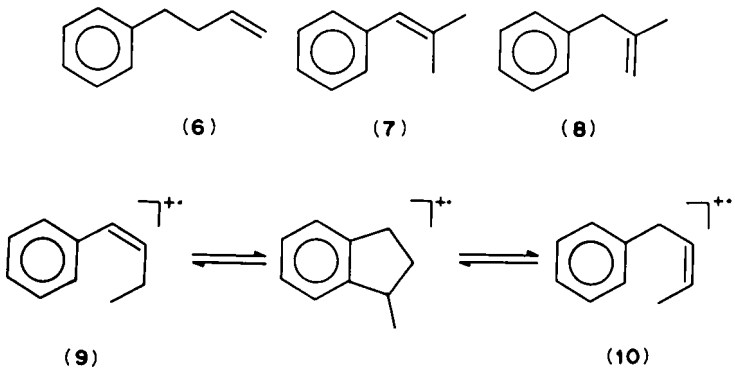
C. Isomerization of the Double Bond

It is well established that five- and six-membered cyclic compounds are the most stable among the isomers. The instability of small ring cyclic compounds is reflected by the ring strain[45]. The extent of isomerization of acyclic and cyclic gas-phase ions of composition $[C_{10}H_{12}]^{+\cdot}$ of several phenylbutenes **6–10** has been investigated by using a CID technique[46]. The ions formed from these olefins having a double bond in conjugation with the aromatic ring retain their initial structure to a significant extent. However, the ions



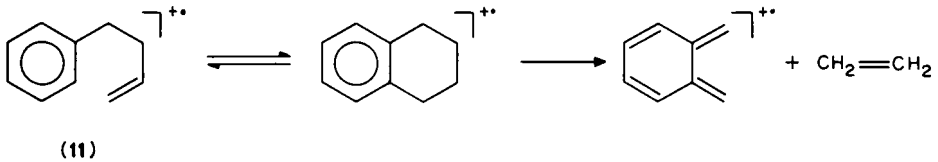
SCHEME 10

from the olefins where the double bond is out of conjugation with the aromatic ring rearrange preferentially to stable five- or six-membered cyclic ions. For example, 1-phenyl-1-butene (**9**) and 1-phenyl-2-butene (**10**) appear to isomerize into a common stable indane structure (Scheme 11).



SCHEME 11

The CAD spectrum of 4-phenyl-1-butene (**11**) shows the evidence of likely cyclization into a tetralin structure, which further undergoes a retro-Diels–Alder (RDA) rearrangement (Scheme 12). It appears that cyclization is a more favoured rearrangement for olefins where a methylene group is interposed between the phenyl ring and the double bond.

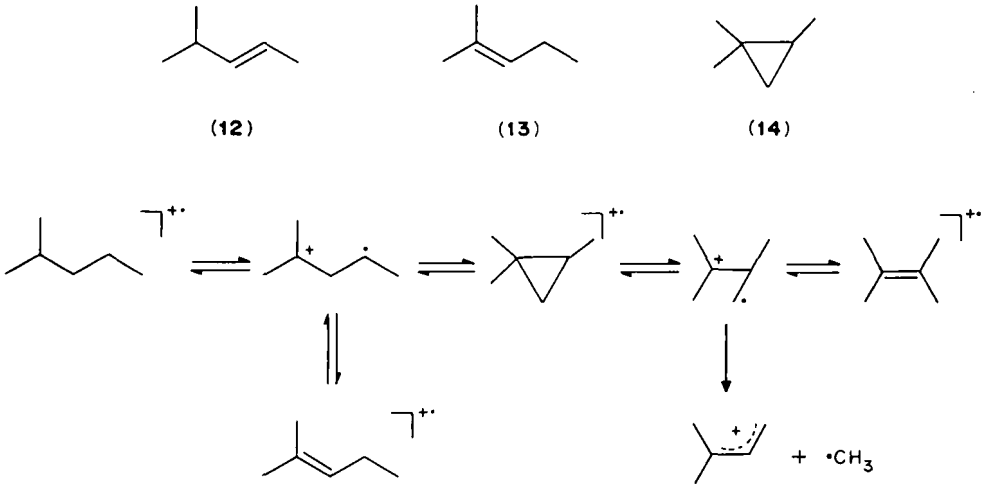


SCHEME 12

1. Rearrangement of olefinic molecular ions

The mechanisms of fragmentation of aliphatic hydrocarbon ions under electron impact is one of the complex problems in mass spectrometry. These ions show a considerable tendency to undergo isomerization prior to fragmentation which makes the interpretation of labelling results difficult in establishing the detailed mechanism of fragmentation.

A detailed study on specific rearrangements of the molecular ions of some $[C_6H_{12}]^{+\cdot}$ isomers with the use of isotope labelling and charge exchange has been reported[47]. The results suggest that 4-methyl-2-pentene (**12**) 2-methyl-2-pentene (**13**) and 1,1,2-trimethylcyclopropane (**14**) isomerize to a common structure or mixture of structures resembling a ring-opened form of the trimethylcyclopropane molecular ion prior to methyl loss in metastable ion decompositions (Scheme 13).



SCHEME 13

D. Low-energy Mass Spectra

The use of 70 eV ionizing energy has been selected largely due to the observation that the fragmentation patterns exhibited little dependence on the variation of the electron energy in this region and thus the mass spectra were easily reproducible. However, at this electron energy a wide range of internal energies imparted to the molecular ion results in several generations of fragment ions and consequently in complex mass spectra. This complexicity makes the structural assignment more difficult since the significant information is frequently hidden. The structurally informative ions are often the primary daughter ions which are usually formed in reactions of low critical energy, and there has been considerable interest in methods that simplify the mass spectra by emphasizing these primary ions. One possibility is to study the metastable ions produced by the fragmentation of the molecular ions in the field-free regions of the mass spectrometer[20]. However, because of the long life-time of the molecular ions, there is enough time for rearrangement with the result that the fragmentation reactions observed may not reflect the original structure of the molecule. An alternative approach has been to record mass spectra at low ionizing energy[48,49,50], thus emphasizing the primary fragmentation

reactions occurring in the ion source. Again, the use of low electron energies is associated with some difficulties. Firstly, the sensitivity is greatly reduced relative to ionization with 70 eV. Secondly, the mass spectrum becomes strongly dependent on the electron energy used and this has to be carefully controlled and calibrated.

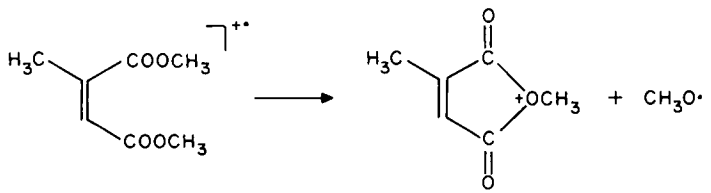
A low-energy charge exchange mass spectrometry provides yet another alternative for simple mass spectra with primary fragment ions[51]. This technique employs reagent gas systems such as $[CS_2]^{+\cdot}$, $[COS]^{+\cdot}$ and $[N_2O]^{+\cdot}$ in low-energy charge exchange chemical ionization. Under these conditions, simple primary ion mass spectra are produced which readily permit structure elucidation. In comparison with the low-energy spectra the sensitivity is greatly increased and mass spectra are, in general, less dependent on the instrument parameters. In several cases isomer differentiation is easier, but it may be necessary to employ a variety of reagent ions to determine which of them will give the most significant spectra.

E. Hydrogen Migration, Keto–Enol Tautomerism

The isomerization preceding the metastable decompositions of a number of $[C_6H_{12}O]^{+\cdot}$ ions are associated with a hydrogen transfer by three-, five- and six-membered ring rearrangements[52]. A study of a number of these compounds using deuterium labelling and CID metastable studies has demonstrated that six-membered ring transfers are generally preferred over competing five-membered ring hydrogen transfers. The 1,3-transfers are unfavourable in the case of enol tautomers where the products are of comparable stability. The factors which determine the isomerization of radical cations in the gas phase are the same as those which control the rearrangements of other reactive intermediates. It appears that the unimolecular decompositions in the mass spectrometer are similar to, and indeed they are controlled through, much the same energy effects as ordinary chemical reactions[53].

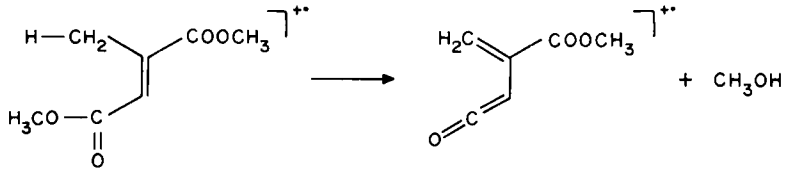
Stereospecific fragmentation has been demonstrated to be an important tool in the determination of the extent of retention of structural features of organic molecules upon ionization. The studies on dimethyl and diethyl mesaconates indicate that the double-bond geometry is retained to a large extent in α,β-unsaturated esters under EI conditions[54]. Dimethyl citraconate (**15**) gives rise to an abundant $[M - MeO]^+$ ion (Scheme 14a) while the geometrically isomeric mesaconate (**16**) mainly loses the alcohol. The results indicate that the elimination of alcohol from the molecular ions of mesaconates is partially preceded by a hydrogen transfer from the 2-methyl group to the ether oxygen atom of the ester group on the other side of the double bond (Scheme 14b). The importance of the second ester group has been established by a deuterium labelling.

Enol–keto tautomerism in gas-phase ions formed from suitable alcohol or keto precursors has been an extensively studied phenomenon. Heats of formation have proved to be valuable parameters in these investigations[55,56a]. In most of the studies reported,



(15) *m/z* 127 (100%)

SCHEME 14a



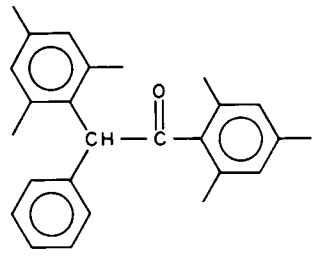
(16) *m/z* 126 (100%)

SCHEME 14b

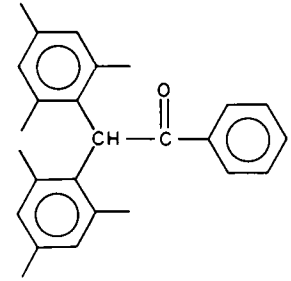
usually the enol tautomer has been produced as a fragment ion by dissociative ionization rather than as a parent ion by direct ionization. The most common route to enol ion production in the gas phase is discussed in the McLafferty rearrangement (Section III.F). In general the enol form appears to be more stable in the gas phase than the keto form by 42–146 kJ mol^{-1}[156b].

A comprehensive review on keto–enol tautomers and distonic ions of $[C_nH_{2n}O]^+$ structure with emphasis on the energetic aspects of the isomerization and dissociation reactions has been published[57].

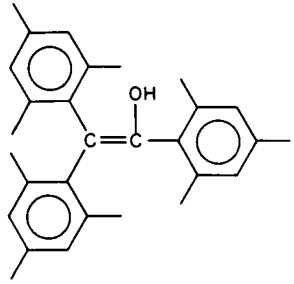
The two isomeric ketones, 1,2-dimesityl-2-phenylethanone (**17**) and 2,2-dimesityl-1-phenylethanone (**18**), and their stable isomeric enol forms **19** and **20**, have been synthesized for the purpose of studying the ionization reactions of both keto and enol forms directly in the gas phase[58] with the use of metastable ion studies. It was demonstrated that the enol ion is more stable than the keto ion by about 45–50 kJ mol^{-1}. Moreover, the enol ions are not freely interconverting to keto forms since their kinetic energy releases and their metastable peak shapes are different.



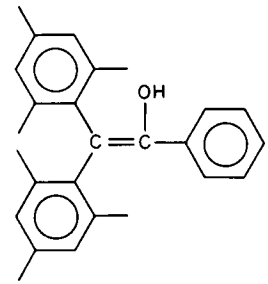
(17)



(18)



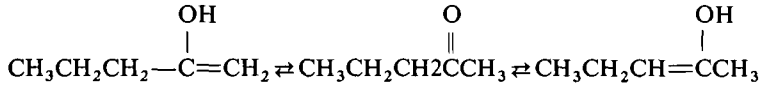
(19)



(20)

CID studies have shown that the 2-pentanone molecular ion fragments by the loss of the C(1) methyl and the C(5) methyl in the ratio 60:40. In this case the α-cleavage is the favourite process. For the enol ion the loss of methyl from the C(5) is clearly more favoured than the loss from the C(1) (ratio 70:30)[21].

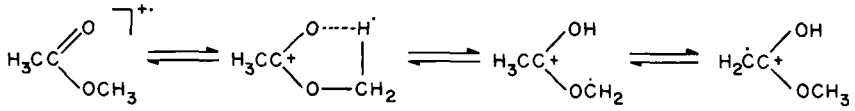
The ion source temperature has a strong effect on the CID spectra of 2-pentanone[59]. With temperature increase the ratio of enol to keto increases as well. This enol ion can exist in two possible isomeric forms (Scheme 15).



SCHEME 15

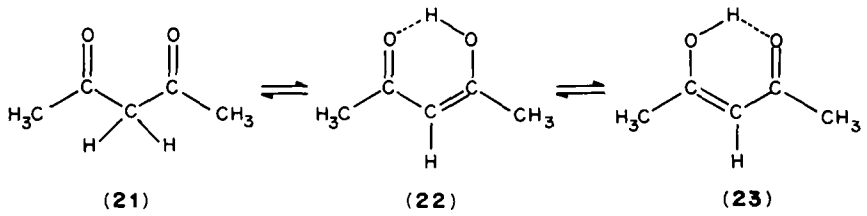
The enol form of ionized 2-pentanone is likely to be about 84 kJ mol^{-1} more stable than the keto form. Another factor that tends to increase the fraction of enolic ions is the difference in ionization energies, which for 2-pentanone is 9.4 eV, while for the enol form the estimated value from the heats of formation is 8.2 eV. This difference in ionization energy results in a higher probability for the ionization of the enol than the ketone.

An interesting study on methyl acetate and methyl propanoate has been undertaken using the isotopic substitution, time-resolved measurements and CID techniques[60]. It has been found that ionized methyl acetate rearranges largely into $CH_3C(OH)OCH_2$, whereas methyl propanoate isomerizes into $CH_2CH_2C(OH)OCH_3$. These two distonic ions appear to be thermodynamically fairly stable species. The enol form the ionized methyl acetate undergoes a rate-determining rearrangement from the keto to an enol form prior to a fragmentation. This results in a wider range of internal energies among enol ions decomposing in a field-free region (Scheme 16).



SCHEME 16

The diketo and ketoenol tautomers of aliphatic 1,3-diketones can easily be separated by gas chromatography. The mass spectra of tautomers of pentane-2,4-diones substituted at C(1) and C(3) and their fragmentation mechanisms have been investigated[61]. 1,3-diketones exist in an equilibrium mixture of tautomers, i.e. of the diketone **21** and the corresponding ketoenols **22** and **23** (Scheme 17).



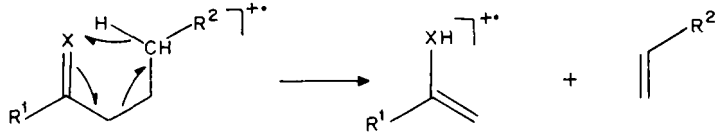
(21) **(22)** **(23)**

SCHEME 17

It has been shown that the molecular ions of the tautomers **21**, **22** and **23** are distinct stable species in the gas phase and do not tautomerize prior to decomposition in the ion source. The intensity of the molecular ion of **21** is small and decomposition by McLafferty rearrangement is favoured. The molecular ion for the ketoenols **22** and **23** is much more prominent due to greater stability of enol ions. The preferred fragmentations of these ions correspond to the loss of alkyl radical by α-cleavage and/or allylic cleavage. The differences in the mass spectrometric behaviour of the tautomeric ions are clearly linked to their ion structures. Moreover, quite a few isomers differing in the position of the substituent can also be distinguished by their mass spectra.

F. McLafferty Rearrangement

One of the most important rearrangements common to many types of double bonds is the McLafferty rearrangement. A comprehensive review of this topic has been presented[62]. The reaction actually was not first observed by McLafferty and a reference to a rearrangement applicable to this definition could be found in 1952 in a study of rearrangements in aliphatic acids[63]. However, McLafferty first recognized the importance of the cyclic transition state in his study of a series of aliphatic methyl esters[64]. This rearrangement, which is almost unique to mass spectrometry, is represented in Scheme 18. Its major requirements are the presence of a double bond and the availability of a γ-hydrogen for the transfer.



SCHEME 18

There have been numerous studies carried out on the McLafferty rearrangement of many compounds using various techniques. Some conclusive points can now be summarized:

(a) The McLafferty process is strictly six-centered and only α-, β- and γ- atoms are involved. Moreover, the hydrogen transferred has to come from the γ-position.

(b) This rearrangement is the most useful mass spectrometric diagnostic tool for the presence of the C=O group in a very wide variety of compounds, provided a γ-hydrogen is available for the transfer.

(c) Cleavage of the carbon–carbon bond yields an ionized enol and an olefin.

(d) The driving force for the reaction is the formation of the stable product ions.

(e) This rearrangement is not restricted to the—C=X group only. Other—Y=X groups such as —S=O, —P=O, —C=S, etc. can exhibit it as well. The double bond could equally be a part of an aromatic system.

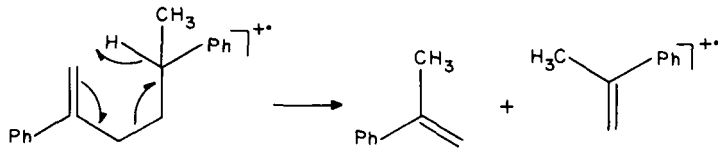
(f) The other atoms in the ring need not be carbons; they can be different combinations of C, O, N, S and P. However, there has to be a γ-hydrogen available for the transfer.

(e) H atoms on double bonds are not transferred; e.g. compounds with side-chains, where the γ-hydrogen is attached to a doubly-bonded atom, do not undergo the McLafferty rearrangement.

The transition state of the McLafferty rearrangement has been the subject of several theoretical studies, the question being asked whether this mechanism is a concerted or a stepwise process. Dougherty[65] employed perturbation molecular orbital (PMO) calcul-

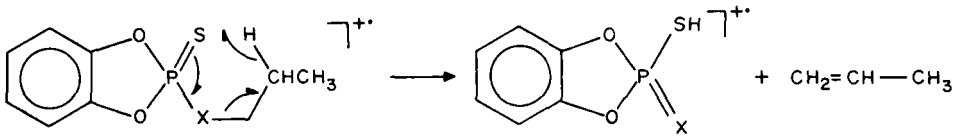
ations for the molecular ion of 1-pentene and proposed a concerted mechanism. However, in general, the accepted mechanism is considered to be a stepwise process[66], in which first the γ-hydrogen is transferred and then the α–β bond is cleaved.

Tureček and Hanuš[67] have investigated the mechanism experimentally by using 2,5-diphenylhexene (Scheme 19) and its deuterium labelled analogues. When this compound decomposes by a McLafferty rearrangement it produces two formally identical fragments—α-methylstyrene and its ion. The symmetrical charge distribution between both fragments indicates that they are formed with identical structures and in the same electronic states and thus support the proposed stepwise mechanism.



SCHEME 19

The McLafferty rearrangement ion is the base peak in the alkyl substituted 1,3,2-benzodioxaphospholes[68] (Scheme 20). In the case when X = O, the double bond between phosphorus and sulphur is transferred to oxygen with the fission of a C—O single bond and the migration of a hydrogen atom. Since the P=O double bond is more stable than that of P=S, the transfer of the double bond lowers the energy of the molecular ion and makes the rearrangement a more favourable process. When X = S, the rearrangement involves the transfer of the double bond from one sulphur to another and this process does not lower the energy of the molecular ion. Therefore other fragmentation processes will take precedence.



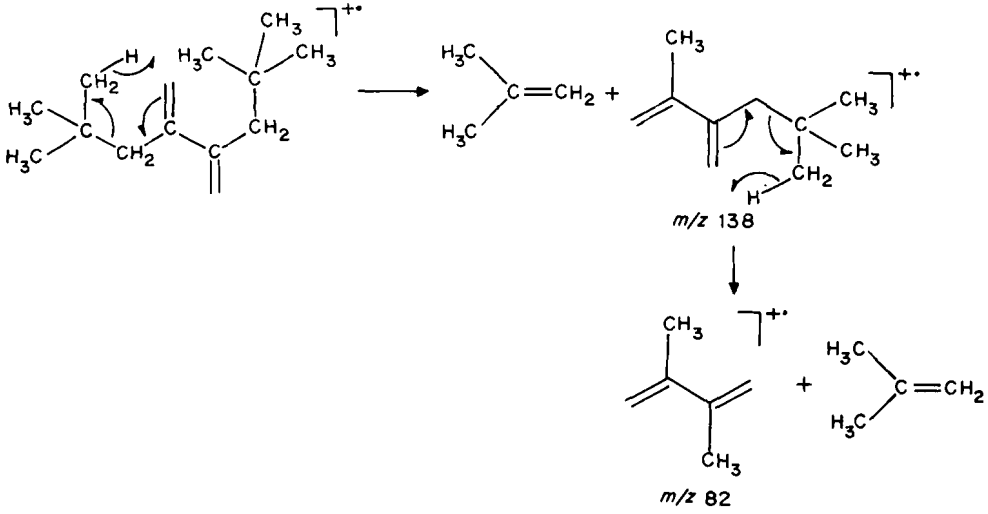
SCHEME 20

The major fragmentation ion in the 2,3-di-*t*-Bu-1,3-butadiene corresponds to a McLafferty rearrangement (Scheme 21), which gives *m/z* 138[69]. A second McLafferty rearrangement would yield the ion at *m/z* 82.

1. McLafferty reactions in even-electron ions

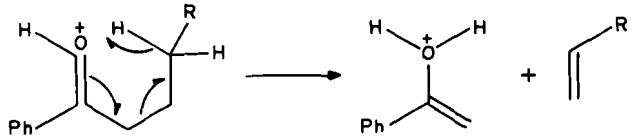
With the development of soft ionization techniques like CI which produce mainly even-electron primary ions such as $[M + H]^+$, it should be considered to what extent the accumulated knowledge about the radical ion behaviour can be applied to non-radical ions. The McLafferty rearrangement falls especially into this category, since it is very specific in the radical ion chemistry[70] and it provides a reliable argument in the mass spectrometric determination of structures. A strict set of requirements which has been discussed above must be met in order to justify a true McLafferty process. In particular, the specificity of the hydrogen transfer has to be experimentally verified.

It has been mentioned that the McLafferty rearrangement occurs in even-electron ions

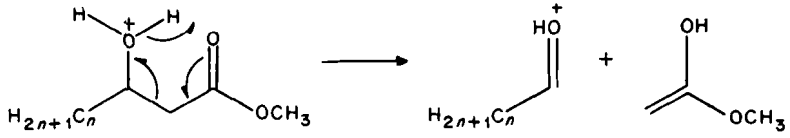


SCHEME 21

but this has not been investigated in great detail. However, in many cases the requirements for such a rearrangement were not satisfied. For example, the elimination of an olefin from protonated ketones and esters has been observed and supported by a metastable transition, but the hydrogen transfer in this case is non-specific[71,72] (Schemes 22 and 23).



SCHEME 22

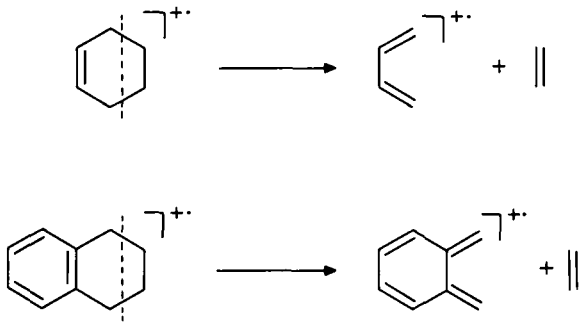


SCHEME 23

A six-centre transition state can be postulated for many fragmentation pathways of even-electron ions without the classification as a McLafferty process. A review on this topic[72] has concluded that the occurrence of McLafferty reactions in even-electron ions obtained by soft ionization does not appear to be very important, since under those conditions it is rather difficult to determine such a specific mechanism even by using isotope labelling and advanced metastable techniques.

G. Retro-Diels–Alder Rearrangement

The retro-Diels–Alder (RDA) reaction is one of the fundamental decompositions of organic ions in the gas phase[73–75]. Its significance in mass spectrometry was recognized many years ago by Biemann[76]. It is usually formulated as a retro-[4 + 2] process (Scheme 24). This reaction has been a subject of interest for many years and is very useful in structural elucidation of organic molecules containing a double bond in a six-membered ring.

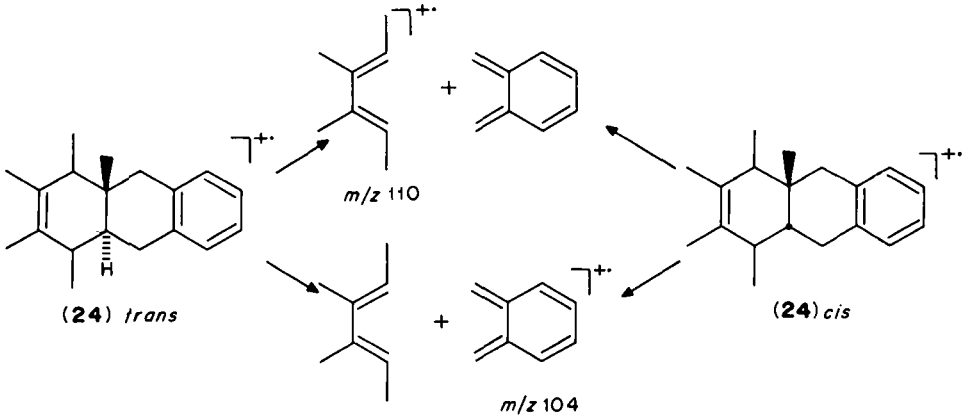


SCHEME 24

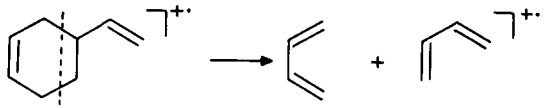
It has been observed that this type of reaction can distinguish between isomers by giving rise to most abundant ions predominantly in *cis* isomers[2a,b]. This RDA reaction is also a relatively high-energy process and, if more favourable possibilities exist in a molecule, the extent of the RDA decomposition is decreased. So if there are other functional groups present in the close vicinity, the relative contribution of this reaction is affected by their influence. The RDA reaction has been the subject of many studies concerning whether it occurs by a stepwise or concerted mechanism. From the studies involving the different techniques, such as isotope labelling, CA and kinetic release measurements, it has been concluded that the elimination of ethene from various substituted cyclohexenes is a stepwise mechanism[77]. However, the loss of ethene from the molecular ion of 1,2,3,4-tetrahydronaphthalene (tetralin) takes place by competing processes which are accompanied by extensive rearrangement. A detailed review on RDA reaction of tetralin and its derivatives has been published[78].

An interesting study has been reported on the RDA fragmentation of 1,2,3,4,9*a*-pentamethyl-1,4,4*a*,9,9*a*,10-hexahydroanthracene (**24**) in both its *cis* and *trans* isomers. This compound contains both a cyclohexene and a tetralin moiety. The *cis* isomer undergoes both RDA fragmentation giving rise to a most abundant ion *m/z* 110 (100%) by cleavage of the cyclohexene ring and to the less abundant ion *m/z* 104 (10%) which corresponds to the cleavage of the tetralin ring[79]. In the case of the *trans* isomer, the competing process is reversed and the *m/z* 104 ion is the most abundant (Scheme 25).

The electron-impact-induced RDA cleavage of 4-vinylcyclohexene and its substituents has been investigated with the help of deuterium labelling[80]. This compound gives rise to two identical fragments. It has been found that the diene ion containing the former vinyl group retains the charge preferentially and that the ionizing energy has no significant effect on the charge distribution. As the RDA cleavage requires an excess of internal energy in order to compete with other decompositions, the vinyl-containing ion could be formed in a variety of rotational states with lower ionization energy than the other fragment. This



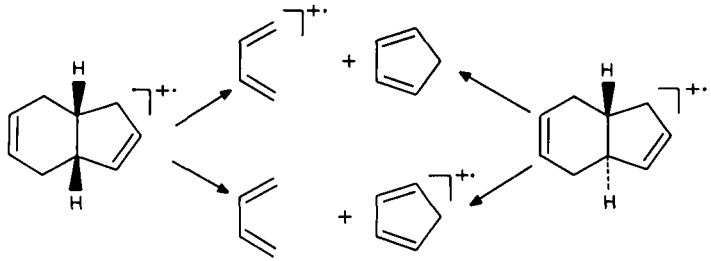
SCHEME 25



SCHEME 26

fragment would be produced in a planar conformation due to the ring (Scheme 26).

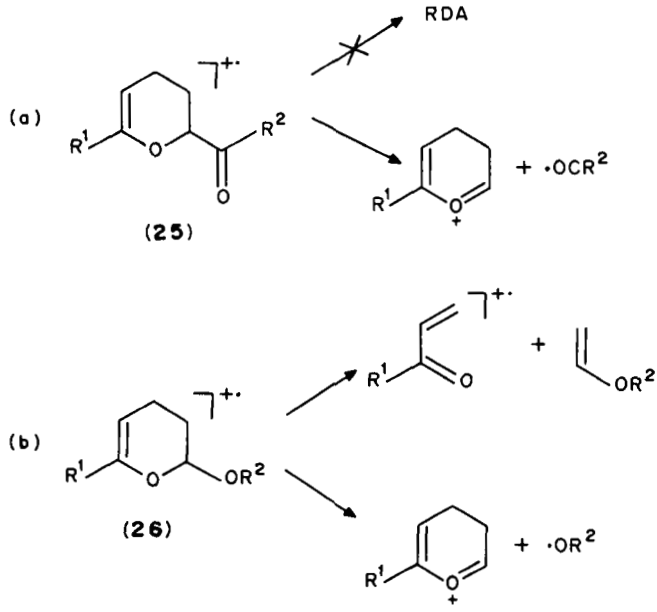
In polycyclic systems incorporating a cyclohexene unit the RDA reaction sometimes exerts remarkable stereospecificity, where the *cis* isomers decompose much more readily following the RDA reaction than do the corresponding *trans* isomers (Scheme 27)[81]. The EI and CID studies on bicyclo[4.3.0]nona-3,7-dienes together with theoretical calculations have supported the stepwise dissociation and it has been concluded that the different tendency of isomeric ions to decompose via the RDA process is due to the favourable stereoelectronic effect which promotes bond dissociation in the *cis* isomer.



SCHEME 27

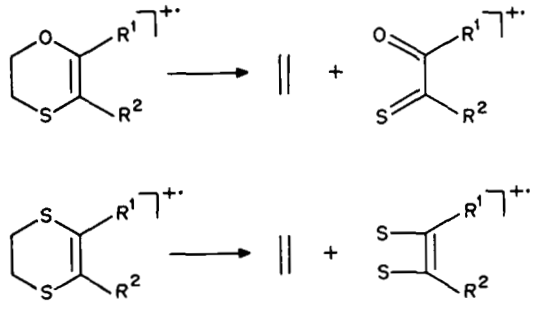
The RDA type of fragmentation occurs in heterocyclic compounds as well. The mass spectra of 2-substituted-2,3-dihydro-4*H*-pyrans showed a marked dependence on the nature of the substituent. In the case of carbonyl compounds **26**, energetically the most

favourable pathway is the α-cleavage. The RDA elimination and direct α-cleavage were found to be competitive in the ether series **26** (Scheme 28)[82].



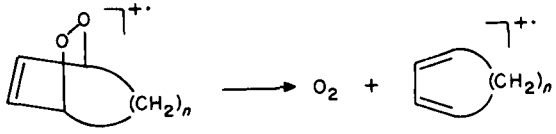
SCHEME 28

In the EI fragmentation of 2,3-disubstituted 5,6-dihydro-1,4-oxathiines[83] and 2, 3-disubstituted 5,6-dihydro-1,4-dithiines[84], the cleavage of the heterocyclic ring similar to the retro-Diels–Alder type of reaction is the major fragmentation process (Scheme 29) thus giving rise to substituted carbonyl and thiocarbonyl cations. The relative abundance of these ions depends on the nature of substituents R_1 and R_2. The presence of the two sulphur atoms in dihydro-1,4-dithiines results in more abundant molecular ions than in the case of the dihydro-1,4-oxathiine analogues. These types of compounds have been of interest mainly because of their potential use as fungicides.



SCHEME 29

Not only the monocyclic alkenes undergo the retro-RDA decompositions. It has been shown that also in heterocyclic compounds, e.g. dioxabicyclo[*n*.2.2]alkenes, this is the major fragmentation process[85], which produces dioxygen and 1,3-cycloalkadiene (Scheme 30). This process is further supported by the deuterium labelling and by the *B/E* linked-scan spectra, which are virtually identical to those of corresponding cycloalkadienes.



SCHEME 30

H. Location of a Double Bond by Mass Spectrometry

In general, determining the position of a double bond in compounds containing it has been a challenging problem in mass spectrometry for a long time[86]. A number of derivatives have been studied for the location of a double bond where the latter is derivatized and the fragments can reveal its position. However, the methods suggested are rather complex and are generally applicable only to a limited range of compounds[87].

It has been demonstrated that the double bond in alkenes could be located by chemical ionization (CI) with isobutane or nitrous oxide NO[88]. These reactant gases are not very suitable for short-chain alkenes, double-bond-branched or cycloalkenes. For these types of alkenes, the use of CH_3NH_2 as a reactant gas could provide an answer[89]. Isomers differing in their double bond position give distinguishable spectra which allow the identification even in short-chain compounds. Of interest is the observation that these odd-electron quasi-molecular ions appear to be essentially a low-energy species and that their fragmentation behaviour is influenced by extensive rearrangement processes. Thus these spectra resemble more likely the low-energy or MIKES spectra rather than the familiar 70 eV spectra.

The position of one double bond in long-chain alkenes[90] or in unsaturated fatty acids and their esters can be determined by CI using NO as a reagent gas[91]. Their mass spectra usually exhibit prominent peaks at $[M + NO]^+$, $[M + NO - H_2O]^+$ and $[M - H]^+$ which are usually more intense than $[M]^{+\cdot}$. Methyl esters are better suited for analysis since they show a less pronounced formation of unspecified hydrocarbon ions than free acids. The CI (NO) mass spectrum shows few peaks that are characteristic for the position of a double bond:

(a) 2-*n*-alkenoic acids (esters) exhibit a loss of ONOH (ONOR^2) from $[M + NO]^+$. The fragment ion $[R^1CO]^+$ is of significant abundance.

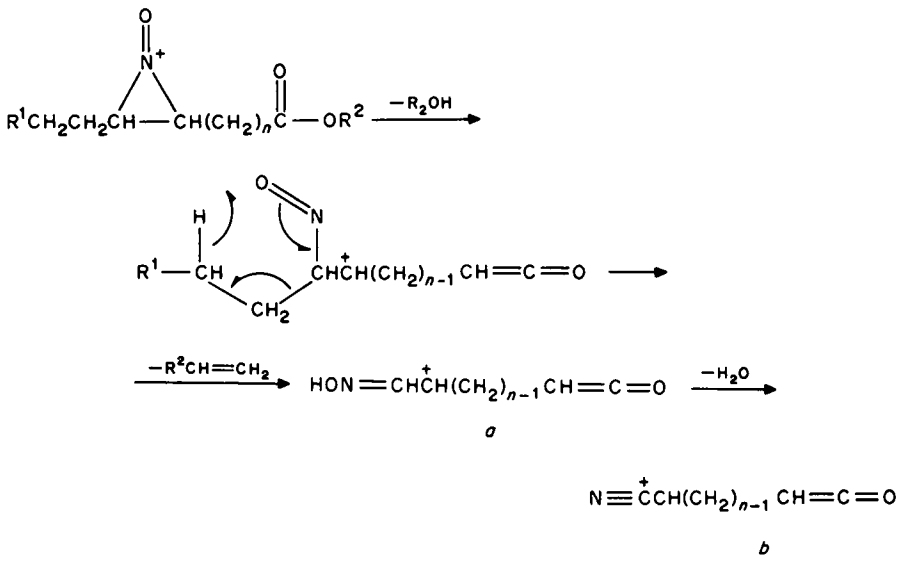
(b) 3-*n*-alkenoic acids (esters) show a fragment at *m/z* 104 (or *m/z* 118) with the formula $ON{-}CHCH_2COOH(R^2) + 2H$. These ions can be associated with a cleavage of the double bond and the transfer of two hydrogen atoms.

(c) 4-*n*-alkenoic acids (esters) do not show any ions initiated by an attack of NO^+ at the C=C double bond.

(d) For double bond positions at C(5) and beyond, there are two characteristic fragment ions, *a* and *b* (Scheme 31).

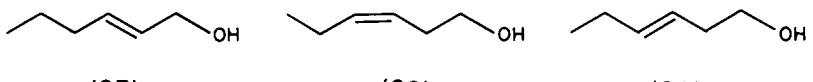
Methods used in mass spectrometry for the structural determination and analysis of fatty acids have recently been summarized in a detailed review[92].

The isobutane CI mass spectra of several hexen-1-ols (**27–31**) exhibit typical ions $[M + H - H_2O]^+$, $[M + C_4H_9 - H_2O]^+$ and $[M + H]^+$, but their intensities vary



SCHEME 31

significantly according to the position of the double bond[93]. In the case of *trans*-2-hexen-1-ol (**27**) the most intense ion corresponds to the $[M + H - H_2O]^+$ ion (63%) whereas the $[M + H]^+$ ion is negligible (about 1%). As the position of the double bond is shifted away from the hydroxy group, the $[M + H]^+$ ion becomes more prominent and is greater than 80% for 4-hexen-1-ol and 5-hexen-1-ol. Since the isobutane CI mass spectra of saturated acyclic alcohols contain essentially no $[M + H]^+$ ions[94], the $[M + H]^+$ ions observed for the unsaturated compounds result either from (a) protonation of the carbon–carbon double bond with significant internal solvation of the resulting carbocation by the hydroxyl group, or (b) protonation of the hydroxyl group with internal solvation of the OH_2^+ group by the double bond or followed by rapid intramolecular proton transfer from the protonated hydroxyl group to the carbon–carbon double bond.



(27) **(28)** **(29)**

(30) **(31)**

NO has been demonstrated to be very useful reagent gas in CI for the location of a double bond in aliphatic compounds[95]. The characteristic fragments observed in the CI(NO) spectra[96] have been found to be highly dependent on experimental parameters

(e.g. source temperature). The exact mass measurements are in agreement with the elemental composition, which means that under H migration an acyl ion $[CH_3(CH_2)_nC{=}O]^+$, where the CO carbon is associated with the position of the double bond, has been formed. However, the abundance of these acyl ions is very much dependent on the experimental conditions.

The recent development of FAB MS/MS techniques offers a positive advantage of a direct method of analysis of non-derivatized unsaturated acids. Free fatty acids dissolved in triethanolamine matrix yield in the FAB $[M-H]^+$ ions with no additional fragmentation[97,98]. If these ions are selected in tandem mass spectrometry and collisionally activated, they undergo highly specific elimination of H_2 and the C_nH_{2n+2} losses that begin at the alkyl terminus and progress along the alkyl chain. The presence of a double bond or a substituent disturbs this pattern and therefore its position could be determined from the mass spectrum.

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The Chemistry of Double-bonded Functional Groups
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CHAPTER 3

Nuclear magnetic resonance spectroscopy of C=C, C=O, C=N and N=N double bonds

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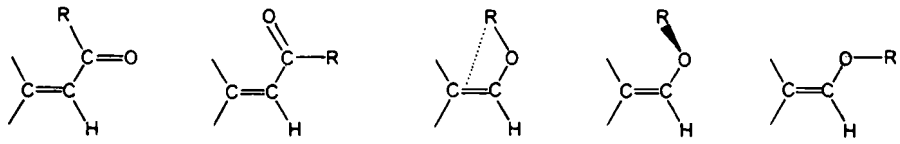
I. INTRODUCTION

Nuclear Magnetic Resonance (NMR) spectroscopy has over the last 20–30 years become *the* method of choice in structure elucidation of organic compounds. The technical progress has likewise made possible not only study of ^1H, ^{13}C and ^{15}N NMR but also ^{17}O nuclei can now be routinely investigated. This chapter will concentrate on the use of NMR to determine physico-chemical properties, conformational studies, hydrogen bonding, etc., whereas substitution patterns, e.g. *cis* vs. *trans* of olefins, are only included in special cases as this aspect is covered fully in a series of textbooks[1–3].

The functional groups are naturally discussed in connection with the compounds in which they occur. It is the aim to highlight some of the characteristic NMR features of the functional groups rather than to give an overview of the compounds. In order to do so the nuclei, being part of the functional groups, will naturally be in focus, but also nuclei away from the functional group are discussed if these are useful in the description of the character of the functional group.

II. C=C DOUBLE BONDS

The double-bond nature is clearly reflected in the ^1H chemical shift position, 4.5–6.5 ppm. Steric, electric field and electronic effects contribute to ^1H and ^{13}C chemical shifts. Furthermore, many substituents are anisotropic and a conformational change will likely lead to a change in the chemical shift. ^1H and ^{13}C may lead to information about most features concerning double bonds and in particular be helpful in structural studies. One of the intriguing features of double bonds is the possibility that substituents may have different conformations relative to the double bond (a feature not found in benzene derivatives) as exemplified in **1** and **2**.



(1) (2)

A multitude of coupling constants involving the ^{13}C and ^{1}H nuclei of the double bond as well as external nuclei provide likewise fundamental information about substitution patterns, bond angles, etc. The π-electron system makes possible extended coupling transmission across double bonds, but permits also interesting intramolecular non-bonded interactions as illustrated in **2A** ($R = CH_3$). The solution of the structural problems as described above will directly tell about the electronic properties of the double bond. Isotope effects on chemical shifts reflect the vibrational pattern of the molecules. Isotope effects due to deuterium or ^{13}C substitution thus provide useful structural information.

^{1}H chemical shifts have been discussed in this series[4] and will not be treated in detail.

A. ^{13}C Chemical Shifts

1. Range

^{13}C chemical shifts of C=C carbons fall in the range 100–160 ppm. The range is similar to that of aromatic compounds. Some typical values for simple vinylic compounds are given in Table 1 and References 1–5.

2. Chemical shift predictions

In simple substituted olefins values for ^{13}C chemical shifts of the olefinic carbons can be predicted using equation 1[6]:

$$\delta_C = \delta_0 + \sum_i Z_i \tag{1}$$

δ_0 denotes the chemical shift of the monosubstituted compounds $H_2C{=}CHX$ and Z_i takes values dependent on the i substituent and the position[7,8]. Additivity is assumed and is found for a number of simple substituents[9,10]. For certain types of substituents in crowded surroundings an extra term to account for pairwise interactions has to be added[11]:

$$\delta_C = \delta_0 + \sum_i Z_i + \sum_{i,j} Z_{i,j} \tag{2}$$

TABLE 1. Substituent parameters for olefins[a]

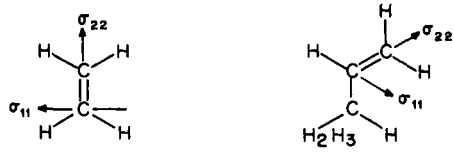
	$C_\beta—C_\alpha—X$	
Substituent	α	β
CR_3[b]	−10.6	+7.2
OR	+29	+2
$COCH_3$	+15	
COCH	+4	
CN	−16	
Cl	+3	−1
Br	−8	
I	−38	

[a]Data taken from References 5 and 6.
[b]R = alkyl.

Recently determined $Z_{i,j}$ values are given for carboxyl substituents[7], for nitrile and for methoxycarbonyl groups[12]. Equations 1 and 2 can be presented in different manners[1,13]. The need to have to include extra terms clearly weakens the approach. Couperous and colleagues[14] claimed that even for olefins no 'hard and fast' rules for shift predictions can be given and they provide instead chemical shifts for model compounds[14]. This is probably going too far. The standard parameters given in, e.g., Reference 1 can be extremely useful in many cases, but they are also likely to fall short in some cases. The inability to be able to predict shifts correctly is, however, useful information telling us that something unusual is in play[9]. One way of getting more profound information about the chemical shifts is to look into the dependence of not only the isotropic values known from high resolution studies in solution, but to study the influence on the shielding tensor elements.

3. ^{13}C Chemical shift tensors

Shielding tensors may be determined from single-crystal studies[15] or, since many simple olefins are not crystalline at room temperature, from matrix studies at low temperatures[16,17].



(3)

Tensor elements for a variety of small olefins are given in Table 2. The powder patterns obtained from matrix studies do not allow an association of the tensor elements with specific directions in the molecular framework. However, by use of doubly labelled ethene-^{13}C it is possible to associate σ_{22} with the C=C bond axis[18]. The upfield component σ_{33} is, based on theoretical arguments, along the normal to the molecular plane[19]. Thus, σ_{11}

TABLE 2. ^{13}C chemical shift tensor elements of olefinic carbon atoms[17a]

	σ_{11}	σ_{22}	σ_{33}	σ^b
Ethylene	234	120	24	126
trans-2-Butene	232	113	37	127
cis-2-Butene	232	119	22	124
trans-Cyclooctene	238	127	37[c]	
cis-Cyclooctene	240	123	28[c]	
Cycloheptene	245	126	27[c]	
Cyclohexene	236	123	23[c]	
Cyclopentene	235	118	39	131
Cyclobutene	244	138	30[c]	
Cyclopropene	239	79	5	108

[a] *In ppm relative to* Me_4Si.
[b] Average shift.
[c] ± 5 ppm.

lies in the molecular plane, but perpendicular to the C=C bond. The similarity of the components of the shielding tensors of Table 2 justify the assignments given[17]. However, minor rotations of the two in-plane shielding axes away from parallel and perpendicular axes may exist for molecules other than ethene (*vide infra*). In fact, such small rotations may be the best way of accounting for the minor variations in σ_{11} and σ_{22}[17].

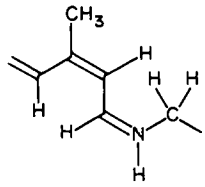
Theoretical calculations using the localized orbital/local origin method allow as estimation of the shielding tensor elements as well as a decomposition of the components of the shielding tensors of ethene (**3A**) and propene (**3B**). σ_{11} depends primarily on the π and σ electrons of the carbon–carbon bond. The small variation in σ_{11} signifies that the σ and π electronic structure of carbon–carbon double bonds in the ethylenes investigated must be similar[17]. σ_{22} involves the π electrons with the carbon's σ electrons external to the double bond. Changes in bond angles will change σ_{22} as seen in the series cyclohexene, cyclopentene, cyclobutene, cyclopropene and the data of Table 2 show also that σ_{22} is fairly constant for non-strained compounds.

σ_{33} involves only σ electrons of the double bond and the external bonds and is hence very similar to chemical shifts of aliphatic carbons.

For propene (**3B**), calculations give the following tensor components for $C_{(2)}$ and $C_{(3)}$ (in absolute LORG (=localised orbital/local origin) shieldings in ppm). $C_{(2)}$: $\sigma_{xx} = -31.8$, $\sigma_{yy} = 174.2$, $\sigma_{zz} = 12.6$, $\sigma_{xz} = -75.9$ and $\sigma_{zx} = -77.5$. $C_{(3)}$: $\sigma_{xx} = -5.5$, $\sigma_{yy} = 166.9$, $\sigma_{zz} = 56.7$, $\sigma_{xz} = -78.7$ and $\sigma_{zx} = -73.3$[20]. The off-diagonal elements are quite large and show antisymmetry, $\sigma_{xz} - \sigma_{zx} \neq 0$. This is in contradiction to Lynden-Bell, who predicts a very small antisymmetrical component of the shielding tensor[21]. The asymmetry of the shielding is quite large for the olefinic carbons. It is concluded that this is caused by local bond modifications[20].

Tensor elements of acrylamide[22] have also been determined and compared with those of dihydromuconic acid[23]. A comparison of the shielding tensors of C=C and C=O double bonds reveals dissimilarities.

Harbison and colleagues[24,25] investigated the shielding tensor of $C_{(14)}$ of the retinal Schiff base of dark adapted bacteriorhodopsin. This contains the partial structure of the 13-*cis*,15-*syn*-retinal Schiff base, part of which is shown in **4**. They found that 35% of the change in the isotropic shift, which is high field (low frequency) compared to the all-*trans* isomer, arises from a change in σ_{11} of the form shown in **4**. This is ascribed to a steric effect (γ-effect).



(**4**)

The better understanding of the shielding tensor components and their variation with bond-angle changes, steric strain, etc., is likely to lead to a better understanding of the isotropic chemical shifts measured in solution.

4. *Substituent effects*

The chemical shifts of olefinic carbons may be influenced by charge variation due to electronegative substituents. The charge may be due to both inductive, mesomeric and

electric field effects. Further, steric effects may be important. γ-effects have long been recognized.

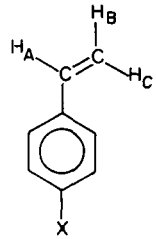
The polarization due either to electronegative substitutents or to charges may be far-reaching as demonstrated in fatty acids. The electric field effect is observable eight C—C bonds away from the polar groups[26] (for a discussion of electric field effects see Section III.A.5). In this case the electric field causes primarily a polarization of the isolated double bond. This case is straightforward. This is less so in compounds in which the double bond is part of a larger π-electron system.

Three different mechanisms may contribute in this case: (i) resonance effects, (ii) π polarization of the vinyl side-chain and (iii) through-space electric field effects.

The π polarization effects on ^1H chemical shifts are second-order effects, since the polarization of the double bond is caused by the electric field, and the polarization of the double bond leads to a change in charge at the olefine carbons. This change in the charge leads in turn to a change in the ^1H chemical shift. In case the double bond is part of a larger π-electron system, this effect becomes important.

In order to estimate the relative importance of the inductive, mesomeric and field effects, a two-parameter analysis is used. One set is the resonance (R) and field (F) parameters as suggested by Swain and Lupton[27]. A very suitable system is that of the 4-substituted styrenes used by Hamer, Peat and Reynolds[28–30].

^1H and ^{13}C chemical shift measurements complement each other in such investigations. Field effects polarize a C—H bond leading to partial positive and negative charges. The mesomeric effect of H_B and H_C is identical whereas the electric field effect depends on the



(5)

orientation of the C—H_B and C—H_C bond directions (5). This is clearly reflected in the F parameter in a Swain–Lupton analysis.

$$\delta H_B = 0.10\,F + 0.41\,R \tag{3}$$

$$\delta H_C = 0.17\,F + 0.42\,R \tag{4}$$

The substituent effects at the C_α and C_β carbons should be a help in determining the importance of the π-polarization effects.

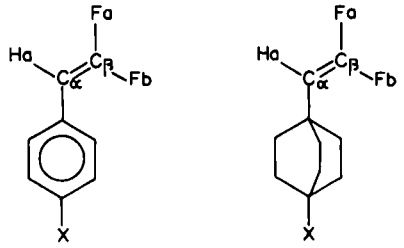
A dual substituent parameter (DSP) analysis yields

$$C_\alpha = -2.4\sigma_I - 0.4\sigma_R^0 \tag{5}$$

$$C_\beta = 5.0\sigma_I + 8.9\sigma_R^0 \tag{6}$$

These equations show that the chemical shift of C_β is much more strongly influenced by resonance effects than C_α. They also show different signs for ρ_I at C_α and C_β. π polarization is likely to cause this difference. According to Craik[31–34] such effects are unique to conjugated π-electron systems are not observed in simple non-conjugated alkenes. The difference lies in localized and extended polarizations as already described.

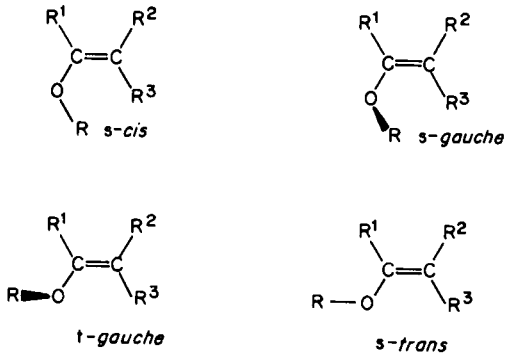
The ^1H chemical shifts of H_α and H_β of chalcones have likewise been correlated with F and R parameters[35] as well as with σ_I and σ_R^{32}. A similar approach can be used for the β-difluoro derivatives observing ^{19}F chemical shifts[36]. The internal shift difference between F_A and F_B should again solely reflect the difference in the electric field component along the two C—F bonds as the field-induced polarization and the resonance effects on the carbon π system will lead to equivalent π-electron density perturbations at both fluorine atoms and that these effects cancel when the differences are taken. The analysis shows that two effects are dominant, the field-induced π polarization of the π-electron system and the direct electrostatic field effect. Adcock and Kok refer to the latter effect as the electrostatic field effect acting on the π component of the C—F bond[37]. A DSP analysis of ^{19}F substituent chemical shifts of 4-substituted β,β'-difluorostyrenes (**6**) vs. σ_I (also referred to as σ_F^{37}) and σ_R^0 revealed that the resonance susceptibility parameters ρ_r for the two fluorines are slightly different. An analysis of 1,1-difluoro-2-(4-substituted-bicyclo[2.2.2]oct-1-yl)ethenes (**7**) gave a similar result[37].



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

5. *Conformations and correlations*

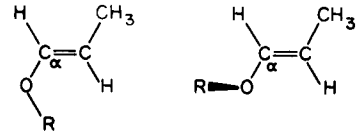
An interesting class of compounds is that of vinyl ethers, as the orientation of the OR bond may vary according to the nature of the R group. Structures **2** illustrate how chemical shift measurements in principle can help in solving this problem, but also the inherent difficulty in obtaining decisive information in such cases.



(**8**)

For cases in which $R^1 = R^2 = H$ and $R = CH_3$ or C_2H_5, the s-*cis* form is predominant (see **8**). As R, R^1 or R^3 increase in size, the answer is less certain. Taskinen[38] observed for **9** that the C_α carbon chemical shifts behave very similarly in the *E* and *Z* isomers, when R is

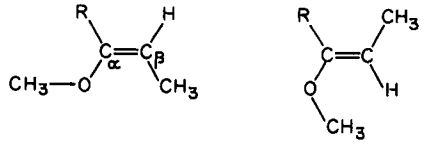
changing from CH_3 to $C(CH_3)_3$, whereas the chemical shift of the β carbon behaves irregularly when $R = C(CH_3)_3$.



(9)

Taskinen[38] assumes that this derivative is predominantly s-*trans*. The same assumption is made when $R^3 = CH_3$ (see **8**) irrespective of the size of R.

By varying the size of R and R^1, the ratios between *cis*, *trans* and *gauche* can thus be varied.



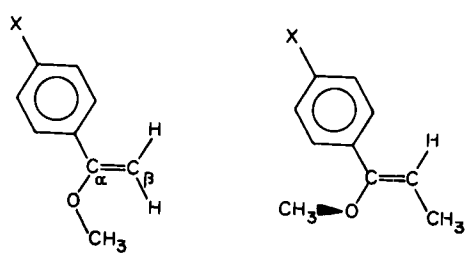
(A) (B)

(10)

The β carbon falls at 11–15 ppm to lower field (higher frequency) in **10A** than in **10B**. it also turns out that the chemical shift of the β carbon of **10B** can be plotted against chemical shifts of the structurally related alkenes. The slope is 0.79 and $r = 0.99$, whereas $R^1 = t$-butyl falls somewhat outside this line. The authors suggest that this is due to an increase in the *gauche*/s-*trans* ratio[40]. Taskinen on his side claims that the change at the β carbon is also due to steric effects of γ type rather than to a change in the conjugation of the —OR group[38,39].

Studies of substituted styrenes (**11**) provide another interesting system in which interaction between an aromatic system and a double bond can be studied. Dhami and Stothers[43] noticed that δC_B of *m*- and *p*-substituted styrenes show a correlation with the Hammett σ parameter. In *trans* β-alkoxystyrenes[41], $R^2 = Ph$ correlates δC_β with Taft E^{42} parameters[41]. Both Taskinen[39] and Huet[41] support the idea that the change in chemical shift of the C_β carbon is due to steric effects rather than to a diminution of resonance effects due to an increased amount of the *gauche* rotamer as suggested by Hatada and colleagues[40].

An extension to α-methoxystyrenes leads to the situation in which both the orientation of the aryl group and the —OR group may be important or even related.



(11)

Taskinen[44] correlates C_β chemical shifts to Hammett σ parameters. The reason that ρ decreases in the α-methoxystyrenes compared to styrene is ascribed to a polarization of the double bond caused by the OR group. Huet and coworkers[45] ascribe the effect to a twist of the phenyl ring. This view is supported by Webb and Yung[9].

The extreme high field shift of the β carbons of vinyl derivatives having OR and to a lesser degree SR substituents, coupled with the fact that substituents have small inductive effects, have enabled Kalabin and coworkers[46] to calculate the excess charge on the carbons in order to estimate the chemical reactivity. An extra electron density of 0.2 electrons is found in methyl vinyl ether. The value is 0.06 in the methyl vinyl sulphide. An investigation by Kajimoto and Fueno[47] in methyl butadienyl ether gave a much smaller extra electron density at the β carbon, demonstrating the delocalization in this system.

Additivity of chemical shifts was investigated in a large number of vinyl derivatives of sulphides, enamines and ethers[10]. The uncertainties are of the order of 1.5 to 3.2 ppm. This is not surprising, as no attempts are made to characterize the rotamers present and such rough additivity schemes are of little use.

The study by Kajimoto and Fueno[47] covers a number of *trans*-1-substituted-1,3-butadienes. An alternation in the effects at the carbon chemical shifts is observed.

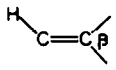
Another substituent type that can take up different conformations is the C(=O)X group in structure **1**. Loots and colleagues[48] have estimated both the σ- and π-electron density of α,β-unsaturated carbonyl compounds by first comparing the β-carbon chemical shifts with that of the corresponding alkene, obtaining a total charge density. 240 ppm/electron is used to convert chemical shift differences to charge. The σ charge density Z_β^σ is estimated by a comparison of the saturated ketone with the corresponding alkane

$$Z_\beta^1 = Z_\beta^\sigma + Z_\beta^\pi \tag{7}$$

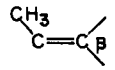
The method was applied to a series of α,β-unsaturated carbonyl derivatives such as acrylamide, acrylic acid, acrolein, 3-methylbut-3-en-2-one, methyl vinyl ketone, acetophenone, cyclohex-2-enone and others. The method seems to be suffering from the fact that the orientation of the C=O bond is not taken into account.

The present use of ^{13}C chemical shifts of double-bonded carbons is best characterized by its very qualitative nature. Very few quantitative relationships exist, and in those cases in which equations are used such as in DSP analysis the outcome is still to a large extent qualitative, as the coefficients cannot be directly be converted into quantitative physicochemical properties.

An example of a quantitative relationship is the correlation of the substituent effect of methyl group[49] on ^{13}C chemical shifts of the β-carbon in methyl-substituted alkenes (**12A**) compared to non-substituted alkenes (**12B**) with bond order (P_π)



(12A)



(12B)

$$\Delta\delta_\beta = \delta C_\beta^{(B)} - \delta C_\beta^{(A)} = 12.6 - 18.6 P_\pi \tag{8}$$

where P_π is the π-bond order.

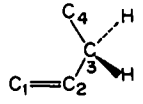
Equation 8 is no longer useful if interfering steric effects are present or, put more clearly, the β carbon must not bear a large substituent in a *cis* orientation to the methyl group.

Six-membered cyclic olefins make it possible to evaluate the factors influencing ^{13}C chemical shifts[50]. Studies of β-thioxoesters provide substituent effects of —SH and COOR groups[51]. Friedrich and coworkers[52] investigated cycloalkenyl silylenolethers and observed in 10-, 11- and 12- membered rings that the difference between the double-

bonded carbons is 43 ppm in the *E* isomer, whereas it is only 38 ppm in the *Z* isomer. The substituted carbon resonates 2 ppm to high field and the non-substituted one 3 ppm to lower field in the *E* isomer. Similar results are found for the ^{1}H chemical shifts. The double bond in the *E* isomer has a higher double-bond character according to IR spectra.

6. *Steric effects*

Steric effects may occur either directly due to changes in bond angles and bond lengths, or indirectly due to polarization of interacting bonds. Both Taskinen[39] and Huet[41] have claimed steric effects to be important in vinyl ethers. Steric effects are also very important in alkenes. Examples are given for *t*-butyl olefins[53]. de Haan and van de Ven[54] likewise noticed a larger deviation from additivity in tri- than in disubstituted ethylenes. de Haan and colleagues[55] suggest that the results of 1-substituted alkenes can be explained by a rehybridization as a result of small changes in bond angles. It is also proposed that the upfield shift of $C_{(2)}$ in the fragment **13** is caused by an interaction between the C-3, C-4 bond and the π orbital of $C_{(2)}$.



(13)

Steric effects are only treated sparingly as at present they are not fully understood. A detailed discussion also covering non-double-bonded carbons can be found in Reference 2.

7. *Torsion of double bonds*

The barrier to rotation in push-pull ethylenes can be measured both by ^{1}H and by ^{13}C NMR[56]. A large number of interesting structures have been investigated[56]. Sandstrom and Wennerbeck[57] found it difficult to correlate the barrier height of the torsion with substituent constants showing that the interaction between donor and acceptor groups is highly dependent on e.g. steric interactions in a non-additive way. It will hence not likely be easy to correlate ^{13}C chemical shifts directly with other properties of these molecules.

8. *Various observations*

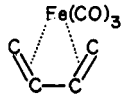
Substituted double-bonded carbons of several types have already been mentioned. These cover ethers, sulphides, styrenes, stilbenes, β-thioxoketones and ketones. In addition esters, ketones and nitriles[58], enamines and enaminones[59–63] and chalcones[64–66] can also be mentioned. Data for substituted allenes are also given[67–71]. References to older data are collected by Stothers[5] and by Levy and Nelson[72] whereas more recent data are given in Reference 2.

B. Coupling Constants

1. $^1J(C, C)$

One-bond carbon–carbon coupling constants fall in the range 40–104.5 Hz. The lower limit is set by the iron carbonyl complexes (**14**)[73] and the higher by the exocyclic double-bonded carbons of substituted heptafulvenes (**15**)[74]. The range is placed in a larger context in Reference 75. ^1J(C, C) are arranged according to hybridization in References 75–78. No

attempts are made to include couplings of the types such as ^1J(C-2, C-3) of butadiene in this review. Double bonds of aromatic systems such as ^1J(C-2, C-3) of indole are likewise not considered in Table 3 and readers are referred to References 2, 75–77.



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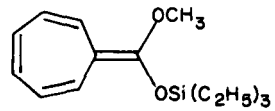
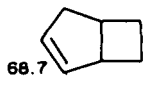


(15)

Carbon–carbon coupling constants are with the modern pulse techniques (INADEQUATE)[79,80], a quantity that can be measured routinely. This type of coupling reflects the basic properties of double bonds as shown below. They are at present not fully investigated. From the data given in Table 3 several trends emerge.

The one-bond carbon–carbon coupling constant of ethylene is 67 Hz[81]. Methyl substitution increases the value to 70 Hz[82] in propene. Disubstitution leads to a value ~ 72 Hz as observed in many bioenriched molecules (Table 3). The effects of ring formation cannot be fully elucidated. However, ^1J(C, C) of a four-membered ring is much smaller than those of a five- or six-membered ring. Ring strain caused by other rings or double bonds seems to be important judging from **16–21**.



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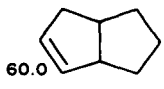

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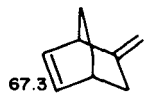

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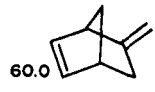

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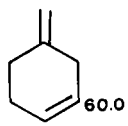

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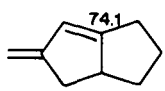
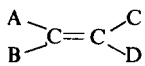


(21)[83]

TABLE 3. One-bond carbon–carbon coupling constants



	Ring[a] size	A B C D[b]	*i,j*	^1J(C-*i*, C-*j*)	Reference
Ethylene	0	H H H H	1,2	67.2	81
Propene	0	H H H C	1,2	70.0	82
2-Methylpropene	0	H H C C	1,2	72.6	82
2-Methyl-1-butene	0	H H C C	1,2	72.5	101
			1,2	70.9	139
2-Methyl-2-butene	0	C C C H	2,3	74.7	102
2-Methyl-2-pentene	0	C C C H	2,3	75.4	102
Penta-1,4-diene	0	H H H C	1,2	70	84
Hexa-1,4-diene	0	H H H C	1,2	70	84
			4,5	70	

(*continued*)

TABLE 3. (*continued*)

	Ring[a] size	A B C D[b]	*i,j*	^1J(C-*i*, C-*j*)	Reference
Hexa-1,5-diene	0	H H H C	1,2	70	84
Roquefortine	0	H H H C	24,25	70.0	141
4-Propyl-3-heptene	0	C C C H	3,4	73.1	103
Asplamomycin	0	C H C H	11,12	72.1	104
Capsidiol	0	C C H H	11,12	72	123
Lubimin[c]	0	C C H H	11,12	72	122
2,3-Germacrene diol[c]	0	C C H H	11,12	72	122
Penitrem A	0	C C H H	37,38	74.0	142
Rishitin	0	C C H H	11,12	72	147
Ovalicin	0	C H C C	10,11	74	151
1,1-Di-*t*-butylethylene	0	C C H H	1,2	70.8	87
1-Methoxybicyclo[3.2.0]-hepta-3,6-diene	4	C H C H	4,5	58.0	83
cis-Bicyclo[3.2.0]-hept-2-ene	5	C H C H	1,2	68.7	83
7,7-Dichloro-*cis*-bicyclo-[3.2.0]hept-2-en-6-one	5	C H C H	1,2	68.9	83
exo-4-Bromo-*cis*-bicyclo-[3.2.0]hept-2-ene	5	C H C H	1,2	67.8	83
exo-4-Bromo-7,7-dichloro-*cis*-bicyclo-[3.2.0]hept-2-en-6-one	5	C H C H	1,2	68.0	83
cis-Bicyclo[3.3.0]oct-2-ene	5	C H C H	1,2	60.0	83
1-Methylcyclopentene	5	C C C H	1,2	72.0	138
1-Methylcyclohexene	6	C C C H	1,2	73.6	103
Poriferasterol	6	C C C H	5,6	71.8	143
Methylenecyclohex-3-ene	6	H C H C	3,4	60.0	84
Ilicicolin H	6	C H C C	16,17	72.8	111
Methylursolate	6	H C C C	12,13	71–72	130
Methylenecyclopropane	3ex	H H C C	1,α	95.2	87
Methylenecyclobutene	4ex	H H C C	1,α	73.2	87
Methylenecyclopentane	5ex	H H C C	1,α	73.2	87
Kaurene	5ex	H H C C	16,17	73	126
2,3-Dihydro-1-methyl-eneindene	5ex	C C H H	1,8	73.9	85
Avenaciolide	5ex	C C H H	11,15	75	153
Methylenecyclohexane	6ex	H H C C	1,α	72.0	87
3,4-Dihydro(2*H*)-1-methylenenaphthalene	6ex	H H C C	1,9	72.6	85
Penitrem A	6ex	C C H H	11,33	74.2	142
Austin	6ex	H H C C	1′,2′	76	125
Methylenecyclohex-3-ene	6ex	C H H H	1,α	73	84
Methylenecycloheptane	7ex	H H C C	1,α	72.0	87
2,3,4,5-Tetrahydro-1-methylenebenzocycloheptene	7ex	H H C C	1,10	71.0	85
Methylenecyclooctane	8ex	H H C C	1,α	72.0	87
3,4,5,6-Tetrahydro(2*H*)-1-methylenebenzocyclooctene	8ex	H H C C	1,11	71.1	85
Butadiene	0	H H H C	1,2	68.8	91,73
2-Methylbutadiene	0	H H C C	1,2	70.9	139
		H C H H	3,4	69.2	139

(*continued*)

TABLE 3. (*continued*)

	Ring[a] size	A B C D[b]	*i,j*	^1J(C-*i*, C-*j*)	Reference
2,3-Dimethylbutadiene	0	H H C C	1,2	71.7	140
trans-Penta-1,3-diene	0	H C C H	1,2	74.4	84
trans-Hexa-2,4-diene	0	H H C C	2,3	71.9	84
trans-Hexa-1,3-diene	0	H H C H	1,2	70	84
			3,4	64.9	
cis,trans-Hexa-2,4-diene	0	C H C H	2,3	70.0	84
All-*trans*-retinal	0	C H C H	7,8	71.1	127
	0	C H C H	9,10	70.4	
	0	C H C H	11,12	69.8	
	6	C C C C	5,6	76.4	
Spiro[2,4]hepta-4,6-diene	5	C H C H	3,4	65.8	85
Cyclohexa-1,3-diene	6	H C H C	1,2	67.6	84
2-Phenylpropene	0	H H C C	1,2	72.4	139
Styrene	0	H C H H	α,β	70	86
t-Stilbene	0	H C H C	α,β	72.9	105,100
Tetraphenylethylene	0	C C C C	α,β	76.9	100
Tetra(*p*-bromophenyl)-ethylene	0	C C C C	α,β	77.4	100
Coniferyl alcohol	0	H C H C	α,β	72	121
7,8-Dihydrobenzopyrene-7,8-diol	0	H C H C	9,10	66.3	152
3-Methylenebicyclo-[3.3.0]oct-1-ene	5ex	C H H H	1,9	72.3	85
	5	C H C C	2,3	74.1	
3-Butene-2-one	0	H C H H	3,4	66.1	102
Acrylonitrile	0	C H H H	1,2	70.6	112
2-Methacrylonitrile	0	C C H H	2,3	73.8	82
2-Methacrylic acid	0	C C H H	2,3	70.5	82
2-Methacrylamide	0	C C H H	2,3	70.6	82
Methyl 2-methacrylate	0	C C H H	2,3	70.8	82
Fumaric acid	0	H C C H	1,2	70.2	137
Aspyrone	6	C C C H	2,3	68	132
Coumarin	6	C H C H	3,4	61.78	102
Cyclohex-2-enone	6	C C H C	2,3	62.2	102
Illuidin M	5	H C C C	8,9	65.1	121
Asperlactone	5	C C C H	3,4	68	131
2,3,4,4′-Tetrachlorocy-clobut-2-enone	4	C Cl C Cl	2,3	75.5	154
2-Chloropropene	0	C Cl H H	1,2	80.8	82
2,4,4′-Trichloro-3-butyl-oxycyclobut-2-enone	4	C Cl C O	2,3	77.1	154
5-Hydroxy-7-methoxy-9-methylchromone	6	C O H C	2,3	71	145
4,4′-Dichloro-3-ethoxy-cyclobut-2-enone	4	H C O C	2,3	66.5	154
Methyl vinyl ether	0	H H H O	1,2	78.6	149
Ethyl vinyl ether	0	H H H O	1,2	78.5	149
Propyl vinyl ether	0	H H H O	1,2	78.6	149
i-Propyl vinyl ether	0	H H H O	1,2	79.6	149
s-Butyl vinyl ether	0	H H H O	1,2	80.1	149
t-Butyl vinyl ether	0	H H H O	1,2	82.2	149
Benzyl vinyl ether	0	H H H O	1,2	79.2	149

(*continued*)

TABLE 3. (*continued*)

	Ring[a] size	A B C D[b]	*i,j*	^1J(C-*i*, C-*j*)	Reference
Divinyl ether	0	H H H O	1,2	81.2	149
Phenyl vinyl ether	0	H H H O	1,2	81.8	149
o-Methylphenyl vinyl ether	0	H H H O	1,2	81.0	149
m-Methylphenyl vinyl ether	0	H H H O	1,2	81.6	149
p-Methylphenyl vinyl ether	0	H H H O	1,2	81.4	149
2-Pyridyl vinyl ether	0	H H H O	1,2	80.9	149
3-Pyridyl vinyl ether	0	H H H O	1,2	81.4	149
Trimethylsilyl vinyl ether	0	H H H O	1,2	80.2	149
8-Quinolinyl vinyl ether	0	H H H O	1,2	82.0	149
Vinyl acetate	0	H H H O	1,2	82.5	149
Vinyl benzoate	0	H H H O	1,2	83.0	149
Vinyl furanoate	0	H H H O	1,2	82.5	149
Vinyl thiophenoate	0	H H H O	1,2	81.0	149
2,2′-Dimethyl-3-ethoxy-cyclobut-2-enone	4	C H C O	2,3	61.9	154
Isopropenyl acetate	0	H H O C	1,2	84.2	82
2-Ethoxypropene	0	H H O C	1,2	80.9	82
Ochrepilone	0	C C O H	1,2	78	110
Asclocinitine	6	H O C C	1,9	71.3	98
Colletotrichinin	6	C C C O	2′,3′	89	129
Citrinin	6	C C C O	7,8	63.6	99
		C C H O	1,8a	69.6	
Herqueichrysin triacetate	6	C C C O	4,5	66	115
Austidiol diacetate	6	H O C C	1,9	75.8	134
Secalonic acid A	6	C C C O	8,8a	70.9	109
Cochlioquinone B	6	C C C O	8,9	68.9	124
Aflatoxin B_1	5	C H O H	15,16	75	118
Sterigmatocystin	5	C H O H	16,17	76	117
Versicolorin A	5	H C H O	3′,4′	75	119
Austocystin D	5	H V H O	2,3	75.6	120
Penicillic acid	5	H C O C	5,6	74	104
Malonomicin	5	C C C O	2,3	65	146
Methyl *O*-methylmulticolate	5ex	C O C H	4,10	90	107
Geldanamycin	6	H C N C	19,20	70.4	136
Deoxtherqueinone diacetate	6	C O C O	8,9	85	115
Herqueinone	6	C O C O	8,9	42/44	116
Ascorbic acid	5	C C O O	2,3	91.8	96
Streptonigrin	6	O C N C	6,7	72/75[d]	135
8-*N*,*N*′-Dimethyl-8-oxyheptafulven	7ex	C C O N	7,8	88	74
8-*N*,*N*′-Dimethyl-8-tri-ethylsilyloxyheptafulvene	7ex	C C O N	7,8	97.4	74
8-Methoxy-8-triethyl-silyloxyheptafulvene	7ex	C C O O	7,8	104.5	74
Allene	0	H H C C	1,2	98.7	114
1,1-Dimethylallene	0	C C C C	1,2	99.5	148

[a] A zero indicates an acyclic compound. Numbers larger than 3 show the ring size and that both olefinic carbons are part of the ring. ex means that the double bond is exocyclic.
[b] Letters refer to the first atom of the substituent given in the order shown in the formula at the top of the table.
[c] Several other derivatives show identical coupling constants.
[d] The authors are unable to assign the coupling constants.

The change in ^1J(C, C) in the exocyclic case is very moderate for the four-, five- and six-membered ring[84]. In the benzannelated case ^1J decreases for the seven- and eight-membered rings. Buchanan and collaborators found a good correlation between %S orbital character and the one-bond couplings[85]. The dependence on %S character was first suggested by Frei and Bernstein for double-bonded carbons[86] based on a finding that the Fermi contact term dominates the one-bond coupling constant.

Günther and Herrig[87] found, for a variety of compounds which include olefins, a relationship:

$$^1J(C,C) = (598.3 \pm 36.5)S(i)^*S(j) - (3.5 \pm 3.6) \tag{9}$$

The original equation by Frei and Bernstein has also been reformulated by Maksic and colleagues[88] using the maximum overlap method:

$$^1J(C,C) = 1020.5a_{C1}^2 a_{C2}^2/(1 + S_{CC}^2) - 8.2 \tag{10}$$

a_{C1} being the bond overlap and s_{CC} being the bond order.

Kalinowski and coworkers[2] noticed that the %S character dependence is poorer for double- and triple-bonded carbons and suggested that π-bond order and other contributions to the coupling could play a role. Fukui, Tsuji and Miura[89] calculated the σ- and π-electron contributions and found for ethylene 67.2 and 15 Hz, respectively. Engelmann and coworkers[90] calculated both the σ and π contributions for all the terms, Fermi contact, spin dipole (SD) and orbital (OB), and obtained the following values: Fermi, 66.6 and 14.9; SD, 0.83 and 7.18; OB, -1.53 and 4.91, giving a total of 65.94 and 4.91 (σ contributions mentioned first), and a total of 70.85 Hz, which is in this case also slightly too high compared with the experimental result. It had been suggested long before these theoretical calculations were performed that ^1J(C, C) depends on π-bond order[91]. This was investigated by Gunther and Herrig[87]. They found for sp^3–sp^3, sp^3–sp^2 and sp^2–sp^2 hybridized carbons a correlation between ^1J(C, C) and bond length (R_{CC}) which is usually related to bond order:

$$^1J(C,C) = (-167.2 \pm 9.4)R_{CC} + (294.4 \pm 13.5) \tag{11}$$

but found another correlation for sp–sp, sp–sp^2 and sp–sp^3 hybridized carbons and concluded that a single parameter is not able to predict ^1J(C, C). A bond-order dependence has also been observed for aromatic compounds[92]. A comparison of couplings in 2,3-dimethyl-1,3-dienes with the corresponding substituted ethylene shows again a decrease in the diene. No such difference is, however, observed when comparing exocyclic mono- and dimethyl compounds[85].

a. Substituent effects. Conjugation with a carbonyl group leads, as seen for 3-butene-2-one and cyclohex-2-enone, to a decrease in ^1J. Conjugation with a carboxylic acid derivative leads to a slight increase, as seen in methacrylic acid and fumaric acid compared to ethylene. The conjugation in lactones gives rise to a variety of coupling constant values, as observed in aspyrone, coumarin and asperlactone. No trends can be established for this particular type of compound. Bartuska and Maciel[82] suggested that $-I^+$ substituents lead to an increase in ^1J(C, C). This fits the rough picture seen for oxygen substitution. ^1J(C, C) values of oxygen substituted double bonds do not only depend on the number of oxygen atoms, but also on the orientation of the oxygen lone-pair as demonstrated in vinyl ethers[93]. The orientational dependence is opposite to that observed for the one-bond carbon–hydrogen coupling (see Section II.B.4b).

b. Correlations. One-bond carbon–carbon coupling constants of vinyl derivatives correlate with electronegativity (E) as shown in equation 12:

$$^1J(C,C) = 14.4E + 33.1, \qquad r = 0.967, \quad n = 12 \tag{12}$$

The correlation is not perfect. Substituents that fall outside are typically OR and C(= O)X. ^1J of vinyl derivatives can be correlated to couplings of benzenes[93].

$$^1J(\mathrm{C,C})_{\mathrm{vinyl}} = 1.11\,^1J(\mathrm{C,C})_{\mathrm{phenyl}} + 5.21, \qquad r = 0.989, \quad n = 11 \tag{13}$$

The finding that ^1J(C, C) of phenyl groups can be used to predict one-bond couplings of vinyl derivatives makes the equation of Marriot and colleagues[94] very interesting. They found:

$$\Delta^1J(\mathrm{C,C}) = 53.9\sigma_x^2 + 0.3, \qquad r = 0.978, \quad n = 28 \tag{14}$$

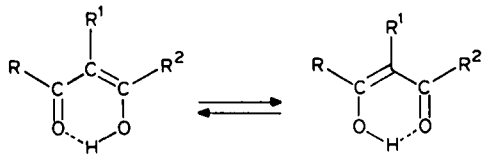
where ΔJ is the difference between benzene and vinyl derivatives, and σ_x is an electronegativity parameter based on atomic charges[95].

c. Applications. One bond carbon–carbon couplings across double bonds increase with the number of oxygen atoms directly attached, as discussed previously. Ascorbic acid is a typical example. The coupling constants in the diprotic form as shown in **22A** are ^1J(C-2, C-3) = 91.8 Hz and ^1J(C-1, C-2) = 84.9 Hz. When one equivalent of base is added, the two coupling constants are almost reversed in size. Berger[96] concluded that the **22B** form is the most likely structure for the anion. As the one-bond couplings depend on bond length, it seems as though these have also switched. A comparison with X-ray data of sodium ascorbate shows that the bond length of the $C_{(2)}$—$C_{(3)}$ bond increases and the bond length of the $C_{(1)}$—$C_{(2)}$ bond decreases in the anion compared to the protio form. However, the latter bond is still the longer in contrast to Berger's expectations. In view of what is seen in Table 3 and discussed above, ^1J(C-1, C-2) of the anion ought to be larger than ^1J(C-2, C-3) in the protio form assuming equal bond lengths, as the C-1, C-2 double bond of the former is carrying three oxygen atoms vs. two in the C-2, C-3 double bond of the latter. The fact that $^1J(\mathrm{C\text{-}2,C\text{-}3})_{\mathrm{A}} \sim {}^1J(\mathrm{C\text{-}1,C\text{-}2})_{\mathrm{B}}$ thus shows that the $C_{(1)}$—$C_{(2)}$ bond in the anion must be longer than the $C_{(2)}$—$C_{(3)}$ bond of the protio form (A), in good agreement with X-ray studies.

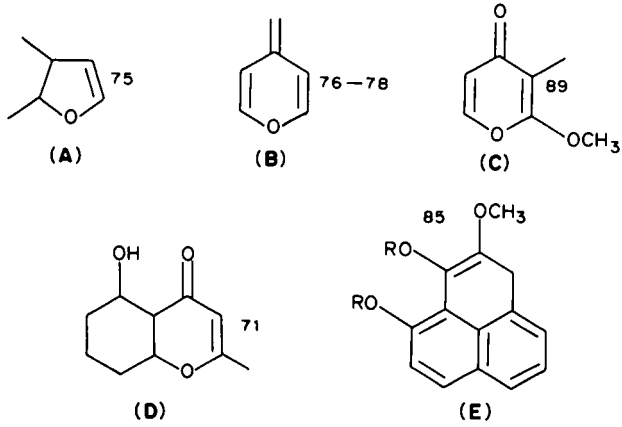
(A) (22) (B)

One-bond coupling constants have also been used to study tautomerism in *o*-hydroxyazo compounds[97] (see Section V.A). ^1J(C-3, C-4) of 1-phenylazo-2-naphthol is only slightly larger than the similar coupling in naphthalene, whereas the value found in 2-phenylazo-1-naphthol is appreciably larger, showing that the keto-hydrazoform isomer is more populated in the latter.[97]

One-bond carbon–carbon couplings also bear promise in the study of β-diketone tautomerism, often encountered in some form in naturally occurring compounds **23**. Typical values for oxygen-containing fragments are given in **24A** to **24E**.

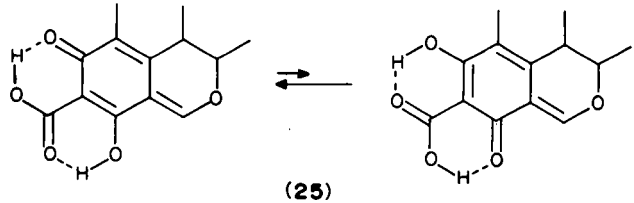


(23)



(24)

As pointed out earlier[77] herquinone clearly falls outside the value given for the similar structure **24E** and likewise asclonitine[98] and citrinine[99] (**25**) fall short of the values shown. The reason could be that the molecules exist in a tautomeric form that is different from that assumed.



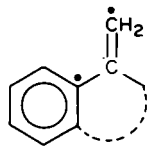
(25)

It was noticed that olefins complexed with metals have low ^1J(C, C) values[73]. Benn and Rufinska[95] observed that ^1J(C, C) of a series of alkyl derivatives of metals such as Li, K, Sn, Zn, Cr, M, W and Pt correlate with C—C bond lengths and do not depend very much on geometrical changes.

2. ^2J(C, C)

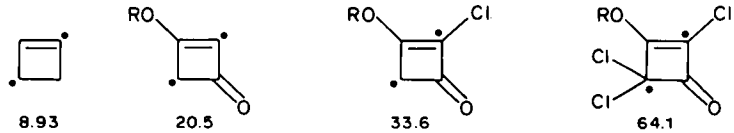
Two-bond carbon–carbon coupling constants across double bonds are generally small[156–158]. The sign is usually positive. This is possible due to the π contribution to the coupling. A large positive two-bond coupling is observed in 2,2-dimethylallene, +8.4 Hz[159]. Electronegative substitutents cause a more positive and hence larger coupling, as judged from aromatic compounds[157,158].

For exocyclic methylenecycloalkanes, ^2J(C=C, C) values increase in going from five- to eight-membered rings (see **2b**).



(26)

Couplings across two bonds can be quite large in cyclobutane derivatives (**27**). This was shown for cyclobutanone[112], but even more so for substituted cyclobutanones as shown for **27C** and **27D**[154].



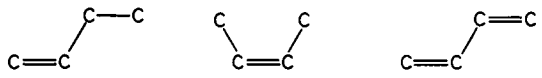
(27)

The two-bond coupling is the sum of two two-bond couplings. As one is across a carbonyl group this is likely to be large[157] (see Section III.B.7).

Electronegative substituents also increase the coupling. The extraordinary magnitude of these two-bond couplings probably not have been predicted exactly, but from a consideration of the structural elements a large coupling is expected[200,209]. Large two-bond couplings do not in the present author's mind give rise to confusion or mix-ups with one-bond coupling constants, as suggested[154,155].

3. $^3J(C, C)$

Three-bond carbon–carbon coupling constants can be classified according to **28I,II** or **28III**. Severson and Maciel[160] calculated the dihedral angle dependence of fragment **I** and found, for the Fermi contact part, a very flat dependence. In case **II** the dipolar part contributes one-third of the total coupling. A distinct dependence on 'W' coupling paths is observed. The results are similar for hexatrienes, butadienes and isopropene. An intermediate case between **I** and **III** is styrene, the stilbenes and tetraphenylethylene.



(28)

Severson and Maciel[160] calculate the values for styrene, which shows a 'W' dipolar coupling pattern. The experimental values $^3J(C_{(2)}, C_\beta)$ of the stilbenes, tetraphenylethylene and 9,10-diphenylphenanthrene show a decrease from 5.0 Hz in *trans* stilbene to 1.44 Hz in tetraphenylethylene, in which the angle is between 43° and 57°. Experimentally, a clearcut decrease with an increase in the dihedral angle is observed. The four experimental values fit the equation.

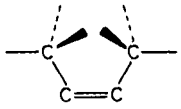
$$^3J = 6.06\cos^2\theta - 1.05 \tag{15}$$

The data can of course also fit other equations. The theoretical considerations by Severson and Maciel[160] suggest that stilbenes will be intermediate between case **I** and case **III** with non-distinct features as the result. However, from calculations zeroing the exchange integrals they conclude that coupling via the π orbitals will follow an expression of the type $^3J = a\cos^2\theta + b$. It is seen, from a comparison with the experimental results, that the coupling via the π-electron system is underestimated in the theoretical calculations.

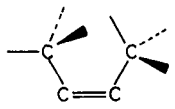
Couplings of type **II** are estimated to be between 3 and 5 Hz[161,162]. This type of coupling has also been investigated theoretically by means of INDO SCFP calculations[163].

The calculations for the **29e** form show much too large couplings, especially for small θ. The s-form, on the other hand, shows the smallest values for small θ values. A calculation

using experimentally determined angles gave a value twice as large as that determined experimentally.



(29e)



(29s)

4. $^1J(C, H)$

a. Correlations. One-bond carbon–hydrogen coupling constants depend on the hybridization as originally suggested by Müller and Pritschard[165]. The relationship is similar to that discussed for carbon–carbon coupling constants, but simpler:

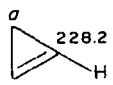
$$^1J(C, H) = 500 S_{CH} \tag{16}$$

where S_{CH} is the fractional S character of the carbon orbital in the C—H bond. For an overview in general see Reference 166. Ring strain will change hybridization[88]. $^1J(C, H)$ depends clearly on ring size. Tokita and colleagues[167] correlate $^1J(C, H)$ with strain energy (E_S) calculated by the force-field method:

$$^1J(C, H) = 0.42 E_S + 124.8, \qquad r = 0.99 \tag{17}$$

Larger values of $^1J(C, H)$ are observed in three- and four-membered rings than in six- and seven-membered rings (see **30–35**).

a Taken from Ref. 168
b Taken from Ref. 169
c Taken from Ref. 161
d Taken from Ref. 170



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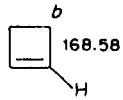

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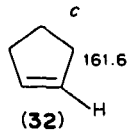

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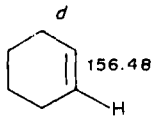

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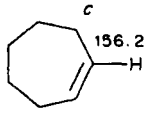

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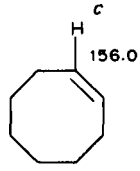
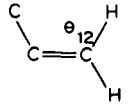


(35)

For methylenecycloalkenes, no large difference in $^1J(C\text{-}\alpha, H\text{-}\alpha)$ is observed in spite of the large difference in bond angles and angle strain[53].

One-bond carbon–hydrogen couplings in crowded olefins may tell about the steric compression and consequently about angle changes. Manatt and coworkers[171] calculated the effect of a change in the C=C—H angle (holding the C=C—C angle constant, see **36**). An increase in θ_{12} decreases ^1J, whereas a decrease in the angle acted in the opposite way if the change in angle is larger than six degrees (see **36**).



(36)

As an example, *t*-butyl substituted ethylenes have been investigated[53,171,173]. The trends so far described are not unambiguous and Garatt and Tidwell[174] call for caution in the use of ^1J(C, H) in determination of in-plane and out-of-plane conformations. More data and a more sophisticated theory are needed.

One-bond carbon–hydrogen couplings for olefins are tabulated in Reference 166. More recently data for substituted allenes and butatrienes have been investigated and compared to vinyl data[70,175]. As discussed previously[1,161] the data of References 175 and 176 do not agree in all cases. It is shown that ^1J(C-1, H-1) of allenes correlate well with ^1J(C-1, H-1) of both ethenes and butatrienes[175].

$$^1J(\text{C-1, H-1})_{\text{ethenes}} = 0.979\,^1J(\text{C-1, H-1})_{\text{allenes}} - 0.2, \qquad r = 0.996 \tag{18}$$

$$^1J(\text{C-1, H-1})_{\text{butatrienes}} = 0.978\,^1J(\text{C-1, H-1})_{\text{allenes}} + 7.8, \qquad r = 0.996 \tag{19}$$

The coupling constants obtained from one compound are thus convertible. The values of ^1J(C-1, H-1) of allenes can also be correlated to ^1J(C, H) of methanes and formaldehydes.

$$^1J(\text{C, H})_{\text{methanes}} = 0.551\,^1J(\text{C-1, H-1})_{\text{allenes}} + 36.3, \qquad r = 0.985 \tag{20}$$

$$^1J(\text{C, H})_{\text{formaldehydes}} = 1.89\,^1J(\text{C-1, H-1})_{\text{allenes}} - 135.6, \qquad r = 0.993 \tag{21}$$

^1J(C-1, H-1), called $^1J_{gem}$, correlates with electronegativity (E_X), but a better fit is obtained when plotting against σ_i[177]:

$$^1J_{gem}(\text{X}) - {}^1J_{gem}(H) = 80.0\sigma_I - 0.6, \qquad r = 0.997 \tag{22}$$

Values for X = CHO, $COCH_3$ and CN fall off the line.

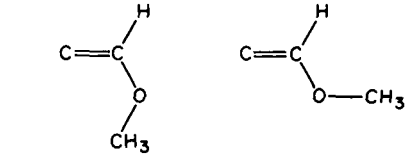
A linear correlation is also obtained for allenes plotting ^1J(C, H) vs. σ_I, again with substituents CN, COOH and Ph falling outside the line. All the mentioned substituents are mesomerically electron-withdrawing[175].

Kalinowski, Berger and Braun[2] have replotted the data of Ewing[177] vs. the field effect parameter F of Swain and Lupton[27] and find likewise a good correlation, but with the same substituents falling off the line as with σ_I. A similar plot for monosubstituted methanes show more scatter, and an even poorer fit is obtained for substituents like NO_2, COX and CN[175].

b. Conformational studies. Prediction of one-bond coupling constants in polysubstituted olefins based on values from mono-substituted ethylenes is, in cases with steric interactions and conformational labile substituents, not straightforward. The fit for *Z*-1,2-dimethoxyethene[175] (**38A**) (predicted value in brackets) in poor compared to the *E*-180.7 (181.3) and the geminal isomer 161.8 (160.6) Hz. The predicted value assumed a s-*cis*, s-*cis* conformation (**38A**). A better prediction is obtained if a mixture of 75% s-*cis*, s-*trans* (**38B**) and 25% s-*trans*,s-*trans* (**38C**) is assumed[175].

The effect of substitution with a OCH_3 group on ^1J(C-1, H-1) is seen to be the same in allenes and ethenes[175]. The effect of an OBu-*t* group is, however, much less. This is explained by assuming an s-*cis* conformation for the OCH_3 derivative as seen in **37** and a s-*trans* conformation for the OBu-*t* one. The ethyl and isopropyl derivatives are mixtures of these two extremes (14% and 32% s-*trans* form, respectively). From the ^1J(C, C) coupling constant values 0 and 42% can be calculated (no temperature given). The former is exclusively s-*cis* (**39A**) at low temperature. Kalabin and coworkers[149] suggest a skew s-*trans* form (**39C**) for the s-*trans* conformer. The study of ^3J(C-α, H-1) does not support such a suggestion, neither do the ^1J(C, C) couplings.

Augé and David[178] assumed in their study of the orientational dependence of ^1J(C, H) in carbohydrates that the equatorial C—H bonds have greater *S* character. The interaction of the oxygen 2*p*-type lone-pair with the antibonding orbital σ^*_{CH} of the axial C—H bond causes the anomeric effect. The calculations show that the anomeric effect is



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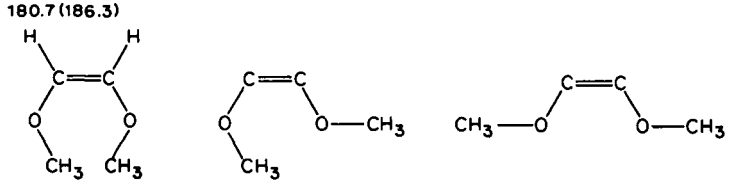

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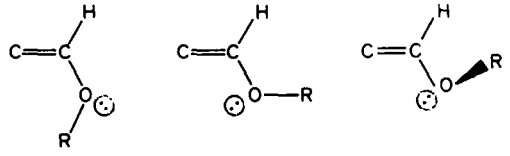
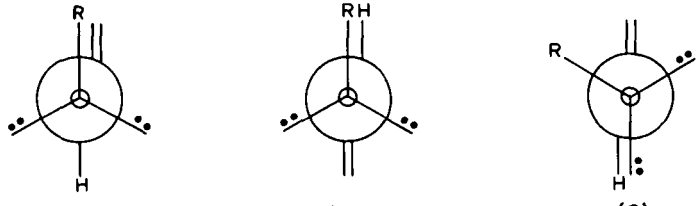


(39)

proportional to the energy difference between the *p*- and *s*-type oxygen lone-pairs. The hybridization at oxygen is not known in the present case. From a theoretical point of view this is of less importance[179]. What is important is the direction of the lone-pairs, as the direction will be different for the s-*cis* and s-*trans* conformations.



(40)

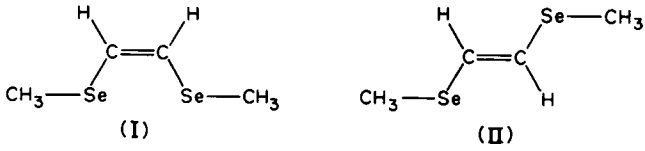
In **39A** and **39B** the oxygen is assumed to be sp^2 hybridized with one lone-pair in a *p*-like orbital (not shown, but perpendicular to the plane of the paper) and the other in a sp^2 orbital. This is the case for the OCH_3 derivative. In **40** sp^3 hybridization is assumed. In the case of both sp^2 and sp^3 hybridization the effect on $^1J(C, H)$ and $^1J(C, C)$ is in opposite directions and of similar magnitude. However, if we assume that the s-*trans* conformation

is of the s-*skew* form, then the lone-pairs will perturb the C—H and the C=C bonds differently.

Studies of ^{17}O chemical shifts of alkyl vinyl ethers revealed that ^{17}O chemical shifts of these compounds behave very much like those of dialkyl ethers. No exceptional features are observed for the *t*-butyl vinyl ether. This can possibly be taken as evidence for a nearly planar structure of this compound, as loss of conjugation in other ^{17}O studies is shown to have a large effect on ^{17}O chemical shifts (see Section III.D.2).

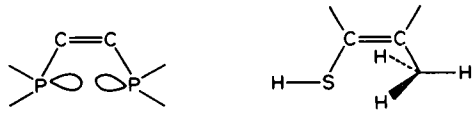
The thio analogues all have similar $^1J(C, H)$ coupling constants and are assumed to have the s-*cis* conformation. As a reason it has been suggested that the C—S—C angle is larger and the C—S bond in longer[175]. ^{13}C chemical shifts of similar compounds were also studied and a different conclusions reached[46].

In continuation of this Contreras and coworkers[181] discuss the transmission of ^{77}Se–^{77}Se coupling in **41I** and **41II**. Theoretical calculations show that **I** and **II** are the most stable conformes, irrespective of whether an sp^2 or an sp^3 hybridization is assumed. In case **II** the depicted form is only five kJ more stable than the s-*cis*, s-*cis* form. The large experimental coupling 96.5 Hz[182], observed in **41I** is easily reproduced, whereas the smaller coupling, 12.0 Hz, of **41II** is not calculated correctly. It is noteworthy that the conformation chosen for **II** is different from that predicted for a sulphur analogue[175].



(41)

cis-Diphosphinoethenes also show large phosphorous phosphorous couplings[183]. This is ascribed to overlap of non-bonding electron pairs of both P atoms[184] (see **42**).



(42) **(43)**

$^4J(F, F)$ can be observed in 1-fluoro-3,3-difluoropropene[186]. The large three-bond coupling $^3J(C\text{-}2, C\text{-}3, S, H)$, in (**43**) is related to the *transoid* coupling path[186]. This geometry is thought to be the result of an interaction between the sulphur lone-pair and the CH_2 part of the CH_3 group pointing toward the sulphur. A much smaller, but still important coupling is observed between the SH proton and the CH_3 protons, 0.6 Hz.

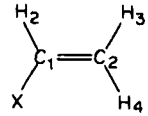
Contreras and colleagues[187] have investigated the case theoretically and suggest that the conformation with a C—H bond pointing towards the *S* lone-pair is probably important in the transmission of the coupling.

c. Electric field effects. The lone-pair effect on neighbouring C—H bonds is not fully understood. One possible contribution could be an electric field effect. The electric fields polarize C—H bonds as discussed for chemical shifts. They can also influence $^1J(C, H)$ couplings, as demonstrated for $^1J(C\text{-}\beta, H\text{-}8)$ and $^1J(C\text{-}\beta, H\text{-}9)$ of 4-substituted styrenes, α-methylstyrenes and α-*t*-butylstyrenes[188] (for an influence on $^1J(C, C)$ see Section II.B.1.a). The dependence is direction-dependent, so an investigation of this kind may also lead to conformational information.

d. Isotope effects. Primary isotope effects on ^1J(C, H) were measured in cyclobutene[169]. A comparison of ^1J(C, H) and ^1J(C, D)*6.51 shows that the latter term is usually the smaller, in agreement with a general trend[166,189] and with theoretical predictions[190].

5. ^2J(C, H)

Two-bond carbon–hydrogen coupling constants across double bonds (as in **44**) may be



(44)

compared with ^2J(C, C), and for ^2J(C-2, H-2) also with ^2J(H, H). ^2J(C, H) can be expressed in MO terms as[171,191].

$$^2J(\mathrm{C,H}) = K\beta^{-3}[-5_1\beta_1^2 + (\beta_2 + \beta_3 + \beta_{CC}trans + \beta_{CC}cis)^2] \qquad (23)$$

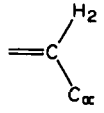
where β_{CC} corresponds to the interaction of the carbon orbitals between not directly bonded carbons. This expression predicts a positive increment for ^1J(C-1, H-3).

Experimentally, a positive increment is established for this type of coupling and likewise a negative increment for ^2J(C-1, H-4). Recent values are given in Reference 175. Similar trends are also observed in aromatic compounds. These are well investigated[2,158,166] and may provide useful reference material for *cis*-substituted olefins. ^2J(C-2, H-1) of ethenes can also be correlated with the similar coupling of allenes[175]:

$$^2J(\text{C-2, H-1})_{\text{ethenes}} = 0.91\ ^2J(\text{C-2, H-1})_{\text{allenes}} + 1.13 \qquad (24)$$

^2J(C-2, H-1) can furthermore be plotted against the electronegativity E_x of the substituent. The variation in ^2J is quite large, from -7 Hz for $SiMe_3$ to $\sim$ 10 Hz for OR substitutents. The trend is thus similar to that observed for ^2J(H, H)[192] of substituted methanes and ^2J(C, H) observed in aliphatic compounds[193].

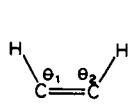
Two-bond hydrogen–hydrogen coupling constants depend strongly on the HCH angle[192]. Likewise, C—H couplings depend on the corresponding CCH angle (**45**). For olefins and allenes (see **45**) ^2J(C-α, H-2) is positive for ethylenes, whereas for allenes it is much smaller and probably negative. A similar trend is observed for the ^2J(H-1, H-2) of ethene (-2.5 Hz)[81] and 1,1-dimethylallene [^2J(H, H) $= -9.0$ Hz][194].



(45)

6. ^3J(C, H)

^3J(C-α, C-H) behaves like ^3J(H, H) and, furthermore, $^3J_{trans} > {}^3J_{cis}$[195,196]. Examples are given in References 158 and 166. This finding is of great use in structural assignments. ^3J(H, H) depends on the two angles θ_1 and θ_2 in **46** Marshall and Seiwell[197] suggest that ^3J(C, H) should decrease 0.2 Hz per degree increase in θ_1 and θ_2. This has however been questioned[198]. Wasylishen and Schaefer[199] studied the behaviour of ^{3}(C-1, H-α) in propene (**47**) by means of theoretical calculations. They find that ^3J(C-1, H-α) displays a minimum for $\theta = 0°$ and a maximum near $\theta = 90°$.



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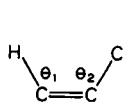
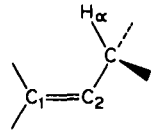
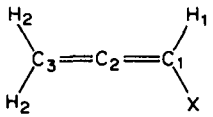




(47)

^3J(C, H) was investigated in allenes (**48**) and butatrienes (**49**)[175]. The couplings in the two types of compounds are similar. A general trend towards larger values for ^3J(C-1, H-2) and smaller values for ^3J(C-3, H-1) with increasing substituent electronegativity[70] seems to be present, but the trend is modified for ^3J(C-1, H-2) in the haloallenes and ^3J(C-1, H-2) decreases from SCH_3 to OCH_3. The latter finding is possibly related to the different conformations of the two types of compounds. ^3J(C-1, H-2) of allenes correlate to some extent with ^3J(C, H) of neopentanes, benzenes, pyridines and pyrimidines[175].



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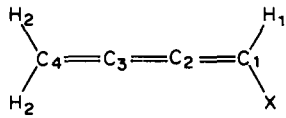


(49)

7. ^nJ(C, H) and ^nJ(H, H)

Long-range carbon–hydrogen coupling constants as well as hydrogen–hydrogen couplings are quite large in cumulenes. ^4J(C-1, H-2) and ^4J(C-4, H-1) of butatrienes range from -3.4 to -5.9 Hz. ^4J(C-4, H-1) values decrease with increasing electronegativity of X, whereas ^4J(C-1, H-2) remains fairly constant. A comparison of ^4J(C, H) of α-substituted allenes and ^4J(H, H) of allenes shows a ratio of 0.55, and the same is true for ^5J(C, H) and ^5J(H, H) of butatrienes (the H, H coupling is always the larger)[175].

C. Isotope Effects on Nuclear Shielding

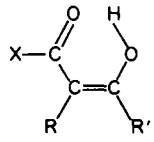
1. $^2\Delta$(C, OD) and $^2\Delta$(C, ND)

Two-bond isotope effects of the following type have been investigated in olefins[51,200–217], and also extensively in aromatic systems (R, R′ equal to C=C—C≡C)[207–209]. In the *Z* isomer, intramolecular hydrogen-bonding usually takes place, but this is not the case in the *E* isomer. Three different systems must be considered: (i) localized, (ii) tautomeric and (iii) conformational. Examples are given in **50–54**. The differences between these systems lie in the different shape of the potential[207]. The magnitudes of $^2\Delta$(C, OD) (see Table 1) have been suggested as a way of estimating the strength of the hydrogen bond[200,207–210]. In a very rough form this yields the equation[208]:

$$\ln(^2\Delta(\mathrm{C, OD})) = 2.783 + 0.354E \tag{25}$$

where E is the hydrogen-bond energy in kcal mol^{-1}, $^2\Delta$ in ppb.

Chemical shifts of OH protons have also been related to hydrogen-bond strength[218]. Plots of δOH vs. $^2\Delta$(C, OD), and likewise for δNH vs. $^2\Delta$(C, ND) and δSH vs. $^2\Delta$(C, SD), show that the spread in the data for OH vs. $^2\Delta$(C, OD) is quite considerable. Data for both static and tautomeric cases are included, as well as data for aromatic systems for comparison. The slopes for olefinic and aromatic systems are equal, but the intersection at the abscissa is different reflecting the difference in chemical shifts the enolic and phenolic



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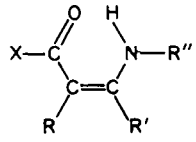

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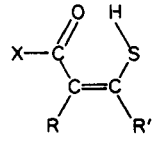

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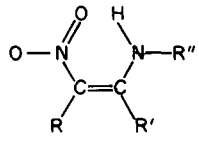

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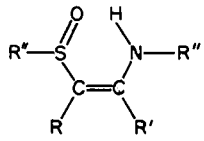


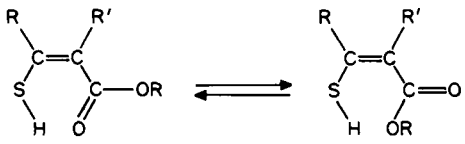
(54)

protons. The spread in the case of NH protons is less, and a characterization according to the acceptor group (XC=O, NO_2 or S=O) can be made. Hydrogen bonding seems to be very weak in the latter case and the conformation could possibly be *E*. It is also seen that the slopes are different and less than for the OH case[211]. The data for the *β*-thioxoesters show a slope similar to that for the OH case, although a different mechanism is proposed[51] (see Section III.C.4). It is interesting to notice that for *β*-ketoesters a limiting value for $^2\Delta$(C, OD) of 0.4 ppm is obtained[211]. It is also of interest that the slope of lines belonging to aromatic and olefinic compounds are similar. This could indicate that one of the factors determining hydrogen-bond strength is the double-bond character for compounds with similar XH groups and similar receptor groups (—Z=Y). This can also be formulated differently: the larger the double-bond character in the parent compound, the more polarize is the system and the stronger the hydrogen bond.

Isotope effects are related to vibrations. Deuteriation leads to a change in the X—D···Y distance compared to the X—H···Y distance[219,220]. Reuben[208] claims that 'the isotope shifts must involve the in-plane C—OH binding vibrations and the associated C—C—OH bond angle distortions. Such a distortion may be regarded as a perturbation on the hybridization, which in aromatic and conjugated systems is likely to spread over the whole molecule'.

However, the results quoted for enaminones[211] seem to indicate that it is primarily the nuclei closely connected to the six-membered ring formed by hydrogen bonding that experience a change in the strength of the hydrogen bond. The carbonyl carbon (see Section III.C.4) and the olefinic carbons as well as the nitrogen show isotope effects that vary between the *Z* isomer in which hydrogen bonding exists and the *E* isomer in which no hydrogen bond takes place, whereas the *α*-alkyl carbons show almost invariant isotope effects.

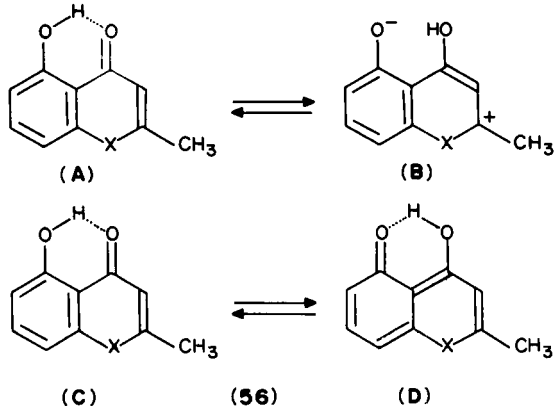
The third case is the conformational equilibrium, which is encountered in *β*-thioxoesters[51] (**55**). The main difference between the *β*-oxyesters and the corresponding thioesters is the weaker hydrogen bond in the latter type. By varying the size and nature of R and R′, the amounts of rotamer **B** can varied. This clearly shows up in $^2\Delta$(C, SD).



(A) (55) (B)

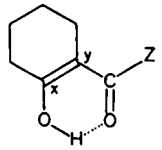
$^2\Delta$(C, SD) values are used to estimate the ratio between **A** and **B**[51]. The $^2\Delta$(C, SD) is nicely related to δSH as seen in **55**, but also to $^4\Delta$(CO, D), which supports the equilibrium idea as this is usually not the case (see Section III.C.4).

Large and especially negative long-range isotope effects are taken as evidence for the presence of tautomeric equilibria[200,207,209,214]. It is also noticeable that the tautomeric systems show very temperature-dependent effects[207,212]. The very large isotope effects observed for most β-thioxoketones can clearly be ascribed to equilibrium isotope effects. The much smaller effects observed in cyclic cyanoenamino ketones[216,217] are less clearcut. If a fast equilibrium exists, then equilibrium isotope effects will play a role[214]. On the other hand, the data are very similar to those found in enaminones[211,212]. Reuben[208] has formulated long-range effects differently, as exemplified in structures **56A–D**. He claims that the polar structure of **B** is important and that this is essential for the transmission of the isotope effect over six bonds and of a magnitude of the order of 0.03 to 0.05 ppm. No explanation is given as to how the transmission takes place.



However, **B** is not as indicated, another mesomeric structure, but rather another tautomeric structure. The choice is hence between the two tautomeric equilibria **56A** $\leftrightarrows$ **56B** and **56C** $\rightleftarrows$ **56D**. Whether one or another equilibrium takes place is difficult to judge, but the essential point seems to be that an equilibrium isotope effect is at play.

Shapet'ko and colleagues[206,212,213] have investigated compounds of the type **57**. A



(57)

study of $^2\Delta$(C, OD) and temperature effects both on the isotope effects and on ^{13}C chemical shifts of carbons X and Y show that the ratios $\Delta^T C_x/\Delta^T C_y$ and $^2\Delta(C_x, OD)/{}^n\Delta(C_y, OD)$ vary both in magnitude and sign, and the authors hence conclude that no tautomeric reaction takes place. They ascribe the variations to the presence of a double-well potential with a low-energy barrier ($\sim 30\,kJ\,mol^{-1}$) in which the enol proton can migrate by a tunneling mechanism. It seems rash to jump to such a conclusion, as the temperature effect

for X differs widely in two different solvents, CD_2Cl_2 and toluene. It appears rather that the temperature effects are not fully understood. The deuterium isotope effects can be pictured as a mean value ~0.8 ppm corrected for equilibrium isotope effects. This was previously suggested for benzoylacetone[207].

2. $^1\Delta(C, D)$ and $^2\Delta(C, D)$

Deuterium isotope effects caused by direct deuterium substitution at the double bond give rise to large one-bond isotope effects of the order of 0.3 ppm. These effects are quite similar to values obtained in aromatic compounds[200,209]. Values for geometrical isotopomers of styrene are 0.283, 0.257 and 0.323 ppm. The largest value is obtained for the geminal isotopomer[221,222]. The large values are associated with the C—H bonds that have the highest stretching frequencies and hence the largest force constants.

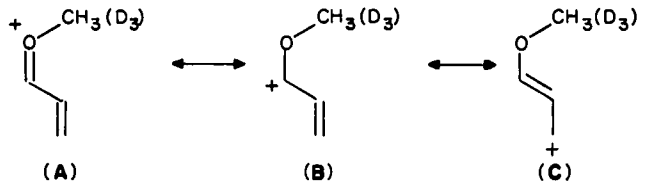
By investigating a series of substituted ethanes, ethylenes and acetylenes and taking substituents into account, Wesener and coworkers[221,222] demonstrated a linear relationship betwen $^1\Delta C(D)$ and the fractional *S* character of the corresponding C—D bond hybrid[222]. The *S* character is derived by means of the Müller–Pritschard relationship (see Section III.A.2). A relationship between $^1\Delta(C, D)$ and $^1J(C, H)$ is also to be expected. One- and two-bond isotope effects are observed in 1-D-cyclobutene. The effect over two bonds is unusually large (0.21 ppm)[169]. The $^1\Delta(C, D)$ values in a series of deuterated enaminones vary from 0.25 to 0.31 ppm and $^2\Delta(C, D)$ values vary from 0.06 to 0.08 ppm[211].

Isotope substitution causes a change in vibrational patterns, that on the average leads to a shorter C—D bond. One way of mimicking the isotope effects is to calculate the ^{13}C chemical shifts by assuming a shorter C—H bond length. A theoretical study predicts quite clearly that the 'deuterated' carbon goes to high field, whereas the effect over two bonds is predicted differently for ethane and ethylene[223].

Fluorine chemical shifts are very sensitive and hence useful in the study of deuterium isotope effects[200]. Osten and colleagues[224] formed the sequence $^2\Delta(F, D)_{gem} > {}^3\Delta(F, D)_{trans} > {}^3\Delta(F, D)_{cis}$ within one compound. $^3\Delta$ depends strongly on substituents at the transmission path. $^2\Delta(F, D)_{gem}$ can be correlated with $^1J(H, F)$.

Deuterium isotope effects on ^1H chemical shifts are much smaller: $^2\Delta(H, D)_{gem} = 0.01$ ppm, $^3\Delta(H, D)_{trans} = 0.007$ ppm and $^3\Delta(H, D)_{cis} \sim -0.002$ ppm. The order is hence the same as found for $^n\Delta F(D)$. The same trends are observed for kinetic isotope effects[225] Relating NMR isotope effects and kinetic isotope effects is a promising possibility.

α,β-unsaturated methoxycarbenium ions may exist in two different planar conformations. The E form is shown in **58**. A ~6 ppm chemical shift difference is observed between the chemical shifts of $C_{(3)}$ in the E- and the Z-isomers. A close relationship to α,β-unsaturated ketones is evident (see Section II.A.5). Forsyth and colleagues[226] relate the difference to non-bonded interactions between the methyl group and the double bond. They support this view by the experimental finding that a CD_3 group only shows isotope effects on the chemical shifts of $C_{(3)}$ in the *Z* isomer, but not in the *E* isomer. The positive isotope effect is explained by a hyperconjugative isotope effect, which should reduce the positive charge at $C_{(3)}$ in the resonance form C.



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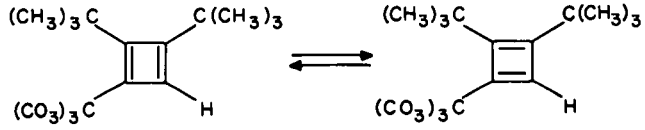
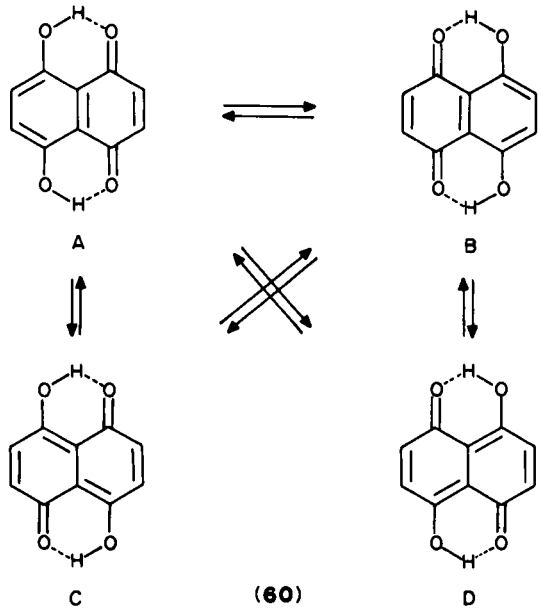
Maier, Kalinowski and Euler[227] show by means of long-range deuterium isotope effects that valence isomerization takes place in cyclobutadienes (**59**).



(**59**)

The chemical shift of $C_{(1)}$ is shifted substantially upfield relative to $C_{(3)}$ when $C_{(1)}$ is substituted with a deuteriated *t*-butyl group. This is explained (based on model studies) by assuming that the *t*-butyl group at position 2 gives a larger high-field shift the larger the double-bond order. Other examples of isotopic perturbation of equilibrium are discussed by Siehl[228].



(**60**)

Naphthazarine (**60**) is another degenerate case. Degeneracy can in principle be lifted due to isotopic perturbation of equilibrium. The isotope effects over four bonds are unusually large in naphthazarine. This has been ascribed to an equilibrium effect[207]. Recent X-ray[229,231] studies and neutron diffraction studies[231] indicate fast intermolecular exchange between forms A and B at room temperature, but not at 60 K. Solid state NMR spectra supports this, as the carbons $C_{(1)}$, $C_{(4)}$, $C_{(5)}$, and $C_{(8)}$ turn into two different signals at low temperature[229,230]. Theoretical calculations show that forms A and B are 25 kcal mol^{-1} more stable than forms C and D. The latter will hence not be populated if this holds true and will hence not contribute to the deuterium isotope effects. The structure of naphthazarine has been investigated in many studies. A recent overview is given by Elöve and Schauble[233].

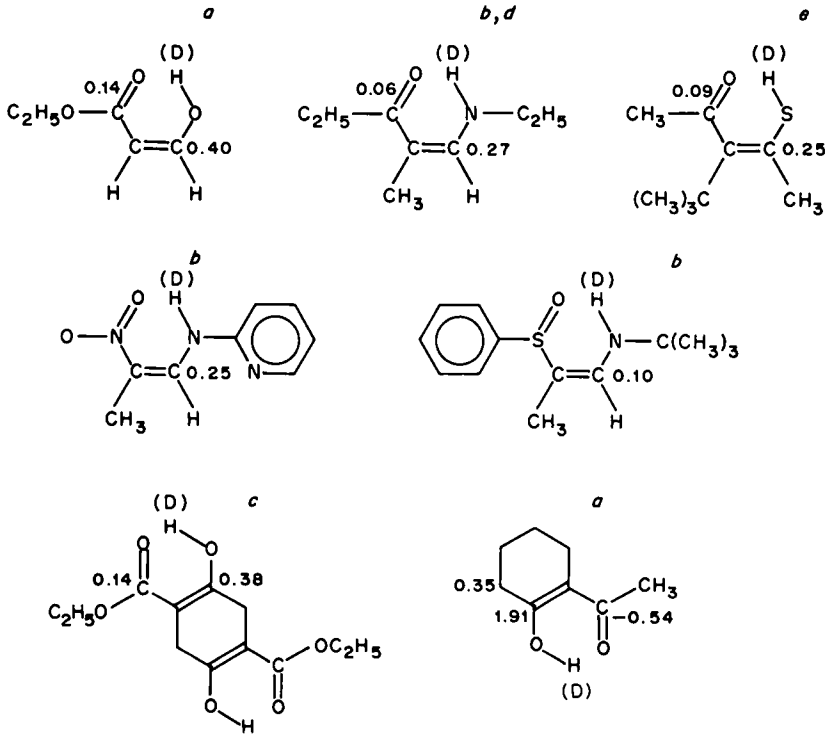


FIGURE 1. Deuterium isotope effects over two bonds, $^2\Delta(C, XD)$
[a]Taken from Reference 207. [b]Taken from Reference 211. [c]Taken from Reference 208. [d]The *E* isomer shows an isotope effect of 0.10 ppm at $C_{(1)}$. [e]Taken from Reference 51.

III. CARBONYL GROUPS

The character of the C=O bond depends very much on the nature of the X substituent and on the degree of conjugation in general. The C=O bond is part of many functional groups, which have different chemical properties and also different NMR characteristics. NMR can thus be of help in characterizing these different compounds. The C=O group is naturally investigated by means of ^{13}C NMR, but more recently also by ^{17}O NMR. The position of the C=O ^{13}C resonance is almost unique. Factors influencing the position are conjugation, electronegativity of X, hydrogen bonding, etc. NMR is hence a useful tool in physical organic investigations of carbonyl groups.

The carbonyl group influences the chemical shifts of neighbouring nuclei, a feature that leads to information about the carbonyl group.

A. ^{13}C Chemical Shifts

The chemical shift range is 160–220 ppm as illustrated in Figure 2. Chemical shifts of carbonyl compounds are tabulated extensively in References 1–3 and 72.

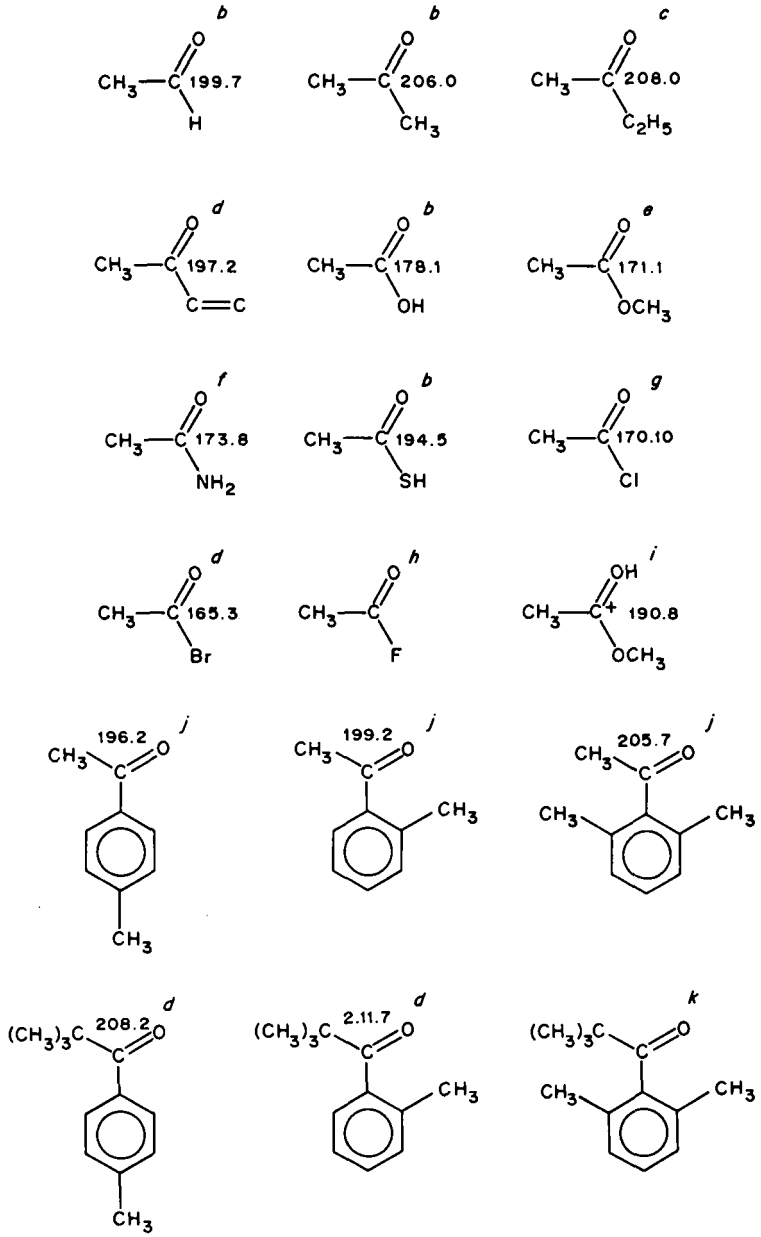
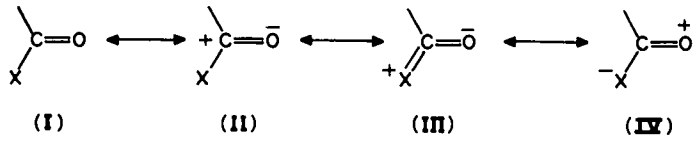


FIGURE 2. Characteristic ^{13}C chemical shifts of carbonyl compounds[a]
[a]Solvent $CDCl_3$ unless otherwise stated. [b]Taken from Reference 234. [c]Taken from Reference 241. [d]Taken from Reference 238. [e]Taken from Reference 235. [f]Taken from Reference 236. Solvent DMSO-D_6. [g]Taken from Reference 237. [h]Taken from Reference 239. Solvent SO_2. [i]Taken from Reference 240. Solvent FSO_3H/SbF_5. [j]Taken from Reference 362. [k]Taken from Reference 271.

The key feature of the carbonyl group in organic chemistry is the partial positive charge at the carbonyl carbon (**61**). The chemical shift of aldehydes and ketones (~ 200 pmm) illustrates this fact as seen in Figure 2. If the positive charge is delocalized via unsaturated parts of the molecule, the chemical shift moves upfield. This is also demonstrated in Figure 2. The carbonyl chemical shift depends also very clearly on conjugation with aromatic rings. This aspect leading to twist angles will be treated fully in Section III.A.2.



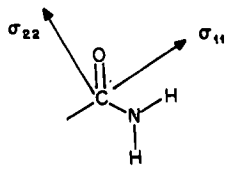
(I) (II) (III) (IV)

(61)

Wehrli and Wirthlin[1] extend this argument to cover the X substituent, which places a positive charge at the carbonyl carbon (**61II**). Judging from acids, esters and amides this could be correct. However, an extension to acyl fluorides shows that the resonance structure (**61IV**) must also be included. The participation of this resonance structure is supported by the high stretching frequency ν_{CO} for acetyl fluoride[242].

1. Carbonyl chemical shift tensors

The double-bond structure of the carbonyl group is reflected in the chemical shift anisotropy of the C=O group. Chemical shift of the carbonyl carbon is a tensorial property as shown in **62**. σ_{22} is approximately along the C=O bond, whereas σ_{33} is perpendicular to the C=O, N plane. Shielding tensors are given in Table 4 together with the averaged chemical shifts σ defined as $(\sigma_{33}+\sigma_{22}+\sigma_{11})/3$ and the anisotropy, δ, $\sigma_{33}-(\sigma_{11}+\sigma_{22})/2$. Other references are given in References 15 and 243.



(62)

These values reveal that the π-electron structure plays an important role in the nuclear shielding. The anisotropy determines the width of the powder spectrum, but also relaxation in those cases in which chemical shift anisotropy becomes an important factor[243].

An inspection of Table 4 shows that σ_{33} is clearly smallest in aldehydes and ketones, acrylamide being an exception. Acids show on the average the largest σ_{33} values, whereas amides seem to fall in between. The trend is hence similar to that found for many other chemical and spectroscopic properties. σ_{22} is roughly constant for the acid derivatives, acids and amides. σ_{22} values for ketones and aldehydes are much larger. Both methyl acetate and acetic anhydride show quite significantly lower values. Individual variations are also seen for the aromatic ketones. Dimedone falls in between (*vide infra*).

Kempf and colleagues[244] conclude, based on molecular orbital calculations, that the variation in σ_{22} is due primarily to variation in the excitation energy of the n–π^* electronic transition. Lattice effects may be responsible for some of the variation in σ_{22}[245]. One such

TABLE 4. ^{13}C shielding tensor elements of carbonyl carbons[a]

	σ_{11}	σ_{22}	σ_{33}	σ^b	$\Delta\sigma^c$	Ref.
Acetaldehyde	274.8	232.8	85.8	197.8	−168	252
	285	231	84	200	−174	253
Acetone	277.8	263.8	77.8	206.5	−193.0	252
Dimedone	284.1	254.9	79.0	206.0	−190.5	246
Acetophenone	278.5	231.5	83.5	197.8	−193.0	252
Benzophenone	271.8	228.8	98.8	199.8	−151.5	244
						257
Methyl acetate	265.8	1588	118.8	181.1	−93.5	255
Acetic anhydride	279.8	140.8	114.8	178.5	−95.5	255
Acetic acid[d]	263.8	179.8	103.8	182.5	−118	256
Benzoic acid-d_6[e]	231	188	103	174	−107	244
Benzoic acid[f]	238	180	103	174	−106	250
Pyromellitic acid[g]	262.3	167.8	104.3	178.1	−110.8	258
[h]	246.3	161.7	105.9	171.3	−98.1	
Malonic acid[i]	243.3	178.3	107.3	176.3	−103.5	258
	247.3	173.8	110.3	177.1	−100.3	
Ammonium malonate	240.6	173.6	102.2	172.1	−104.9	259
Glycine	243.8	179.8	105.9	176.5	−105.9	260
l-Alanine	242.8	182.8	106.8	177.5	−160.8	261
l-Serine	238.2	180.2	106.2	174.9	−103	262
l-Threonine	240.2	164.7	105.0	170.	−97.45	263
l-Asparagine[j]	239.5	179.0	108.6	175.7	−100.65	264
[k]	245.5	195.9	87.8	176.4	−132.9	
Glycylglycine(GlyGly*[l])[m]	243.4	176.4	87.2	169.0	−122.7	265
AlaAla	243.1	176.5	88.4	169.3	−121.4	247
l-[^{13}C]AlaAla[n]	243.3	170.1	94.3	169.2	−112.4	266
Ac-[^{13}C]GlyAlaNH_2	241.4	184.2	89.3	171.6	−124	266
Ac-[^{13}C]GlyTyrNH_2	241.8	164.8	94.6	167.0	−109	266
Ac-[^{13}C]GlyGlyNH_2	242.3	183.5	94.1	173.3	−122	266
$(Gly^*)_n$I[o] (β)	243	174	88	168.3	−121	267
$(Gly^*)_n$ II (3_1)	243[p]	179	94	172.0	−117	267
$(Gly^*)_5$[q]	242	179	93	171.3	−118	267
(Ala, $Gly^*)_n$ (α)	244	178	94	171.3	−118	267
(Leu, $Gly^*)_n$ (α)	242	179	94	171.7	−117	267
(Glu(OBzl), $Gly^*)_n$ (α)	243	178	95[r]	172	−116	267
(Asp(OBzl), $Gly^*)_n$ (α)	243	178	95[r]	172	−116	267
(Asp(OBzl),$Gly^*)_n$ (ω)	243	178	95[r]	172	−117	267
(Val, $Gly^*)_n$ (β)	242	171	93	168.7	−114	267
Acrylamide	257.8	173.8	78.8	173.5	−142	20

[a]Original chemical shift data are often given relative to liquid benzene. These have been converted to TMS by subtracting 127.8 ppm. Values are rounded off. More shielding tensors are given in Reference 243.
[b]Defined as $(\sigma_{11}+\sigma_{22}+\sigma_{33})/3$.
[c]Defined as $\sigma_{33}-(\sigma_{11}+\sigma_{22})/2$,
[d]Temperature 93 K.
[e]Room temperature.
[f]Temperature 55 K.
[g]Twist angle between the aromatic ring and the carboxyl group is 74°.
[h]Angle 18°.
[i]The two carboxylic acid groups are different in the crystal.
[j]COO^- carbon.
[k]$CONH_2$ carbon.
[l]* indicates C=O carbon.
[m]Standard abbreviations are used.
[n][^{13}C] indicates that the peptide is enriched.
[o]Letters in parentheses show conformation.
[p]Given in paper as 343, but this is clearly a misprint.
[q]Random.
[r]Tentative.

TABLE 5. Comparison of shielding tensors[a]

	σ_{xx}	σ_{yy}	σ_{zz}	Ref.
Benzophenone	271.8	228.8	98.8	244
Acetophenone	278.5	231.5	83.5	252
Dimedone	254.9	284.1	79.0	246

[a]As $\sigma_{33} > \sigma_{22} > \sigma_{11}$ by definition, σ_{xx} etc. is used in order to show the interchange in magnitude.

lattice effect is hydrogen bonding[246]. Pines and coworkers[249] suggest that σ_{22} gradually rotates away from the carbonyl bond as the molecule changes from a ketone to an ester, to an asymmetrical acid and finally to a symmetrical acid. A study of benzoic acid at various temperatures shows that two different molecules exist in the unit cell[250]. An extrapolation to zero temperature shows that one of the molecules has a shielding tensor along the C=O bond. At room temperature, an average of the two structures yields an apparent angle of about 24°. The results at room temperature are similar to those reported by Kempf and colleagues[244]. The rotation at room temperature of σ_{22} is in that case clearly an effect of external conditions. Theoretical calculations using localized orbital/local origin methods show great promise, although the actually calculated values for the carbonyl group of acetaldehyde (− 171, − 28, 135 ppm relative to benzene) are somewhat different from the experimental ones[20].

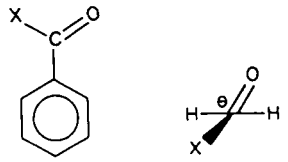
a. Hydrogen bonding. Takegoshi and colleagues[246] found for the dimedone shift tensor values quite different from those of benzophenone and acetophenone (Table 5). The authors ascribe the large change in σ_{yy} to hydrogen bonding in the crystal[246,251]. Hydrogen bonding in crystals is also observed in crystals of amino acids[263]. The individual variations in σ_{22} observed in the dipeptides are linked to hydrogen bonding in the crystal[247]. On the basis of these findings Oas and coworkers[247] question the use of chemical shift tensors of model compounds in orientational studies as proposed by Harbison and colleagues[248]. Glycine-containing polymers show a clearcut difference between β-sheets and α-helical structures. σ_{22} and σ_{33} values vary whereas σ_{11} is fairly constant. The variations in σ_{22} and σ_{33} are however not parallel. The observation of σ_{iso} is thus less descriptive.

b. Conjugation. The chemical shifts of pyromelitic acid show a low-field shift for the most twisted carboxylic acid group, in good agreement with findings in solution (see Section III.A.2.a). The anisotropy increases when the conjugation is removed and approaches the value for acetic acid. The growing empirical knowledge of individual shielding tensor elements combined with a deeper theoretical understanding of the factors influencing these will also make studies of isotropic carbonyl chemical shifts more useful.

2. Isotropic carbonyl chemical shifts

Carbonyl chemical shifts depend (as discussed) on the nature of the X substituent, on mesomeric effects, steric effects, electric field effects and hydrogen bonding. All these factors will be discussed in the following.

a. Conjugation. Aromatic carbonyl compounds have been investigated in great detail. The isotropic chemical shifts of aromatic carbonyl compounds are related to the twist angle θ[269] (see **63**). If the carbonyl group is twisted out of the plane of the aromatic ring, the



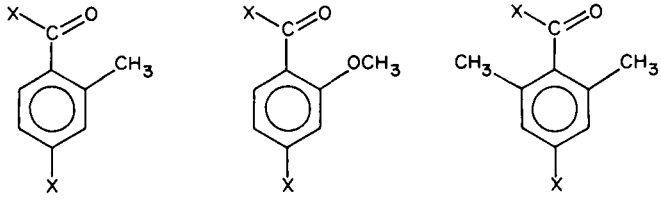
(63)

chemical shift moves to low field (high frequency)[9,269–271]. This was clearly demonstrated for the shift tensors of pyromelitic acid (Table 3). An equation has been proposed[269]:

$$\cos^2\theta = \delta_c^{\theta} - \delta_c^{90}/(\delta_c^0 - \delta_c^{90}) \quad (1)$$

where δ_c^{90} is the chemical shift of a model compound in which the carbonyl group is twisted 90° δ_c^0 is the chemical shift of the planar reference compound. The difficulty of this method lies in the difficulty of obtaining reference values, both δ_c^{90}, and also δ_c^0 in the case of a non-planar compound, e.g. PhCOBu-*t*.

Studies on compounds of the type **64** show that the effect at the carbonyl chemical shift is enhanced in **A** and **B** compared to 4-substituted acetophenones. No such effect is observed in **C** in which the twist angle is larger. A tentative explanation is given by assuming hydrogen bonding between the carbonyl group and the methyl group[271]. From a steric point of view, this can be realized for **A**, but not for **B**.



(A) (B) (C)

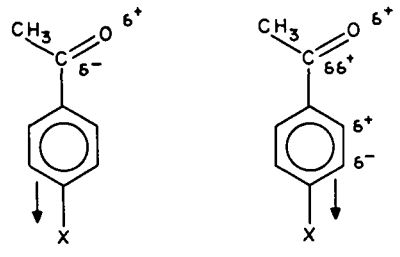
(64)

These results should be seen in connection with determination of rotation barriers for carbonyl groups. Drakenberg and colleagues[273,274,276,277] have investigated both benzaldehydes and acetophenones.

b. Rotational barriers. Temperature studies combined with total band-shape analysis lead to barriers to internal rotation. For *p*-substituted acetophenones they vary from 34.2 kJ mol^{-1} for NMe_2[275] to 19.7 kJ mol^{-1} for CF_3 groups. For 1-naphthaldehyde, an increase from 26.8 to 33.5 kJ mol^{-1} is observed when a 4-methoxy substituent is introduced. Substitution in the 3-position causes a dramatic decrease on the barriers of 2-naphthaldehyde, whereas a 6-methoxy substituent on the other hand increases the barrier[277]. Usually barriers are higher for formyl groups[276]. The difference may be illustrated in ferrocene, in which the difference is 1.7 kJ mol^{-1}[278] and 3.3 kJ mol^{-1} *N*-*t*-butylpyrroles[279]. Drakenberg and colleagues[276] assume that no steric interaction takes place between the acetyl group and the five-membered ring. The barrier to rotation reflects the difference in conjugation of the two rotamers. Barriers to rotation are also reported for benzenedialdehydes[280] and for 2,4,6-trimethylpivalophenones[281]. For early references on derivatives of thiophenes, furanes or pyrroles, see Reference 279.

c. Substituent effects. 4-Substituted acetophenones were studied in great de-

tail[31-34,282-284] in order to understand the mechanism involved in ^{13}C chemical shifts of carbonyl carbons. These studies are parallel to those mentioned in Section II.A.4 dealing with substituted styrenes. Bromilow and colleagues[34] found that the carbonyl chemical shift goes upfield for most substituents, also for those, NO_2 and CN, which are mesomerically electron withdrawing. This is termed a reverse effect and is explained by considering that polarization of the aromatic system plays a vital role. Two different types of polarization are considered, local and extended polarization. The net polarization is a 'sum' of these two effects. The effect of localized polarization is illustrated in **65A** and that of extended polarization in **65B**.



(65)

The dipoles of the substituents induce a transfer of π-electron density in the carbonyl group from the oxygen to the carbonyl carbon, when the increased electron density leads to a high-field shift.

Reverse effects have also been observed for $C_{(1)}$ of *p*-substituted benzophenones, whereas the chemical shifts of the carbonyl carbon show little correlation at all[285]. The reverse effect is also observed at the chemical shifts of the carbonyl carbon of protonated acetophenones[286].

The ^{13}C chemical shifts of carboxyl carbons of substituted benzoic acids show a linear relationship with pK_a values for *m*-substituted and electron-withdrawing *p*-substituents[287]:

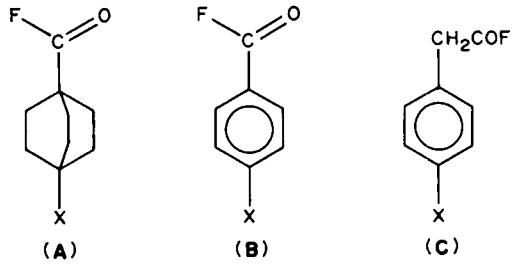
$$\delta_{CO} = 0.81 pK_a - 8.87 \tag{2}$$

Carbonyl chemical shifts in aliphatic ketones can be predicted by the equation proposed by Tanaka and colleagues[288]:

$$\delta_{CO} = 203.9 + (\alpha + \alpha') + \sum \beta_i + \sum \gamma_i \tag{3}$$

This equation is quite similar in structure to those discussed in Section II.B.1. The parameters have also been treated for α-monosubstituted acetones[289] and α-monosubstituted *N,N*-diethylacetamides[290]. Substituent effects are also determined in the systematic study of Beierbeck, Saunders and ApSimon[50]. In α-monosubstituted *N,N*-diethylacetamides it is noticed that δ_{CO} correlates with σ_L (a localized electrical parameter[291]). Orbital interactions between the carbonyl group and the α-substituent have been discussed in detail[292-294].

Both the carbonyl and the C—F bonds of acid fluorides are polarized by a direct electric field effect originating from the X substituent of 4-substituted bicyclo[2.2.2]octane-1-carbonyl fluorides(**66A**). This result supports findings in **66C**. Whereas in *p*-substituted benzoyl fluorides (**66B**) the effects are larger due to extended π-polarization[296,297].



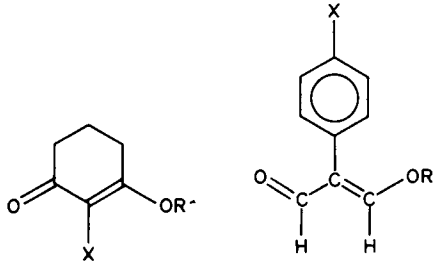
(A) (B) (C)

(66)

3. Hydrogen bonding and protonation

a. Hydrogen bonding. Hydrogen bonding leads to a low-field shift of the carbonyl carbon chemical shifts. A solid-state study reveals that the downfield shift varies inversely with the O···O distance[299].

Intermolecular hydrogen bonding in crystals was also discussed for dimedone and an average 10 ppm downfield shift for the carbonyl carbon in the solid compared to solution was observed[301]. Dibenzoyl methane forms an intramolecular hydrogen bond with a short O···O distance (2.46 Å)[300], thus forming a strong hydrogen bond both in the solid and in solution. The average chemical shifts in the solid and in solution are similar. The effects of hydrogen bonding in the solid state further investigated in the enolic forms of β-diketones of the types **67A** and **67B**(R=H): **67A** forms infinite helices, whereas **67B** form infinite planar zig-zag chains. By also investigating the corresponding ethers the effects of hydrogen bonding can be accurately evaluated[301]. The shielding tensors of similar structures have been discussed for dimedone (see Section III.A.1.a). The effects of intermolecular hydrogen bonding in a β-diketone structural unit were observed in setomimycin[302].



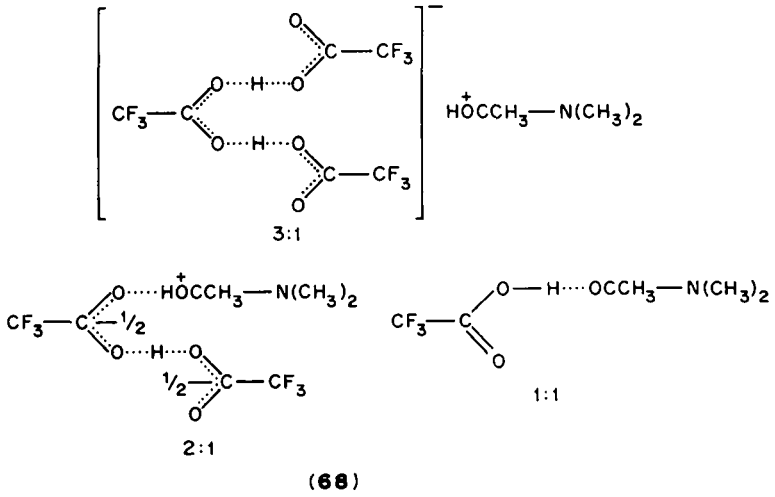
(A) (B)

(67)

Hydrogen bonding also leads to low-field shifts in solution. This holds both for inter- and intramolecular hydrogen bonding. In amides, the effects may be difficult to follow as the low-field shift caused by hydrogen bonding to the carbonyl group is counteracted by hydrogen bonding to the N—H bond[303].

b. Solvent effects. Chemical shift changes upon addition of trifluoroacetic acid were investigated for acetophenone. A low-field shift is observed. No protonation is assumed to take place[304]. This original study was recently greatly expanded to cover a large set of

benzenes and naphthalenes[305]. Equilibrium constants were also evaluated[305,306]. The difficulty in this analysis lies in determining whether a 1:1 or a 1:2 complex is formed and to determine to what extent the solvent forms polymers. Kozerski investigated not only the effect of CF_3COOH but also that of CF_3COOD. Very large isotope shifts on the carbon resonances are observed[307]. Addition of trifluoroacetic acid to a solution of an ester leads also to a low-field shift of the carboxyl carbons. Begtrup concludes that hydrogen bonding rather than protonation takes place[308]. Branched alkyl acetates show slightly increased effects in primary, secondary and tertiary series at the carboxyl and the α carbon. However, the ratio $\Delta\delta_{C=O}/\Delta\delta_{C=O}$ varies. This is tentatively explained by assuming a change in hydrogen bonding at the C=O carbon vs. the C—O carbon. These studies may also be used to estimate basicity parameters[308,309]. Samoilenko and coworkers[310] investigated the system trifluoroacetic acid–*N*,*N*′-dimethylacetamide and found a 1:1 complex and also that protonation takes place as shown in **68**. Fast exchange is present in all stages and the amount of each complex depends on the mol% of trifluoroacetic acid.



(68)

c. Protonation. Chemical shifts of protonated aromatic ketones, aldehydes and acids were recorded in super acids[311,312]. The range of chemical shifts (168–254 ppm) indicates a substantial positive charge delocalization at the carbenium carbon (C_α). Protonation was also studied in chalcones and thiophene-chalcones[313,314]. The protonation shifts are usually larger than the shifts caused by hydrogen bonding.

Some interesting structures of phthalic acid[315] and of phthalic esters[316] were suggested based on ^1H chemical shifts.

4. Other effects

In continuation of the tensor studies Saitô and colleagues[317] investigated chemical shifts in a large number of proteins. Factors influencing the chemical shifts of the amide backbone carbonyl carbon chemical shifts are hydrogen bonding, and the structure of the protein (α_R and α_L helices, β-plated sheets). Hydrogen bonding is strongly connected to the structure. Saito[317] found that the carbonyl carbon resonance of α-helix is displaced downfield compared to β-plated sheets. A similar conclusion is reached by Kainosho and coworkers[318,319]. The change in the chemical shift is considered a consequence of the

changes in the mean excitation energy, ΔE. Tonelli and colleagues[320,321] consider the changes as caused by steric effects and hence of γ-type. γ-effects were originally suggested to arise because of polarization of C—H bonds. It is found that COOH groups in amino acids cause an effect at the γ carbons, although the effects are difficult to quantify[322]. An interesting possibility would be if polarization in C=O bonds could also be achieved. Combined studies of ^{13}C and ^{17}O chemical shifts would also be interesting (Section III.D.1).

5. *Titration shifts*

The chemical shifts of carbonyl carbons are influenced by charges either due to charges at the group itself or due to charges at neighbouring groups. The charges reside typically at COO^-, O^- or NH_3^+ groups. Titration of carboxylic acid groups leads to a significant shift of the carboxylic acid carbon as observed in carboxylic acids and in amino acids, but there are also changes in the chemical shifts of carbonyl carbons quite far away. Examples are aspartic acid and glutamic acid. Titration of the α-carboxylic acid leads to changes in the chemical shift of the side-chain carboxylic acid carbon. This is also true if the group is an amide, as in asparagine and glutamine[323].

Observation of carbonyl titration shifts are used to determine individual pK_a values for all titrating moieties of a molecule even if the pK_a values are very similar. This is demonstrated very nicely in proteins. Titrations in non-aqueous media have also been reported[324].

The theory for titration shifts is outlined by Batchelor[325]. The changes in the chemical shifts due to uniform electric field are, as formulated by Buckingham[326]:

$$\delta_{el} = E_i A_{ij} r_j + E_i E_j B_{ijk} r_k + \cdots \tag{4}$$

where E_i are components of the field vector, r_j is a unit vector of a coordinate system fixed in the molecular framework, A_{ij} and B_{ijk} are second and third order tensor elements.

The second-order term of equation 4 has not been evaluated. As the field from a point charge decreases with distance, the linear term has to be written:

$$\delta_{linear} = E_i A_{ij} r_j + a_{ij} \partial E_i / \partial r_j \tag{5}$$

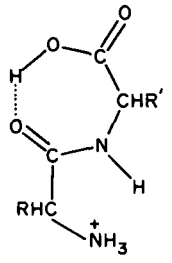
The first term is referred to as the uniform term and the second as the gradient term. The uniform term decreases with the square of the distance from the field source, whereas the gradient term falls off with the third power of the distance[327]. The uniform term will hence dominate for carbonyl groups far away from the field source. The uniform field linear electric field effect (UFLEFS) term also depends in general on the cosine of the angle between the field and the polarized bond:

$$\partial_{UFLEFS} = A_z(C) E \cos\theta \tag{6}$$

A_z for the carboxylate anion is estimated to be about 3×10^{-11} esu, which is of the same order of magnitude as for C=C bonds[327].

Titration shifts for amino acids and proteins[327-342] have been studied intensively. It has been noted that the first C(=O)NH carbonyl carbon after the C terminal shifts to high field when the terminal carbon is deprotonated. This has been explained by Christl and Roberts[329] by assuming an intramolecular hydrogen bond as shown in **69**. This suggestion is unlikely. The titration shifts of most peptides in which the C-terminal carboxylic acid group titrates are usually confined to the first peptide bond. One exception is clearly the pentapeptide Aib-Ala-Aib-Ala-Aib, which is supposed to be 'helical'[330]. For a larger peptide, bovine pancreatic trypsin inhibitor (BPTI), titration shifts due to the titration of the terminal carboxylic acid as well as to the two aspartic and glutamic acid carboxylic acid groups of the side-chain can be observed[339-341]. In addition, effects on both the OH

group of tyrosine and on the NH_3^+ titration were observed[340]. pK_a values were determined[340,341]. Also, the titration shifts can be related to the distance and angle between the field direction and the C=O bond[341].

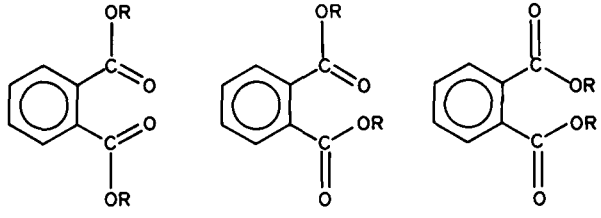


(69)

6. Conformation of carbonyl compounds

The orientation of the carbonyl group plays an essential role in determining the chemical properties, as already discussed for α,β-unsaturated carbonyl compounds (see Section II.A.5).

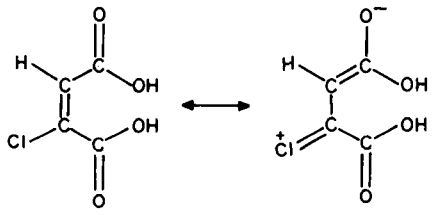
The discussion of this subject can be divided into two parts: (i) the determination of the twist angle and (ii) the determination of the preferred orientation. The first question has been addressed by means of chemical shifts of the carbonyl groups (Section III.A.2). The second has been indirectly touched upon in the discussion of rotational barriers (Section III.A.2.b). The complexity of the problem of determining both the twist angle and the orientation can be illustrated in the case of phthalic esters (**70A–C**).



(70)

This problem has been treated both by means of ^{13}C and ^1H chemical shifts[343] as well as by $^nJ(CO, C)$ coupling constants[344]. Three planar conformations **A**, **B** and **C** together with non-planar ones can be suggested. Bruck and Rabinovitz[343] advocate **A** on the grounds that the system thus constitutes a non-cyclic aromatic system with 10π electrons. Carbon–carbon coupling constants in the dimethyl ester and in phthalic anhydride are fairly similar[344], but all coupling constants are slightly smaller in the ester. This has been connected to a slight twist of the ester groups[344]. The orientations of α,β-unsaturated dicarboxylic acids (**71**, **72**) are discussed by Williamson and coworkers[345]. They find a decreased substituent influence in dicarboxylic acids compared to the anhydride, which indicates a twist of the carboxylic acid groups.

The preferred conformation in this case corresponds to **70C**. An argument in favour of this structure is the better conjugation between the carbonyl group and the double bond.



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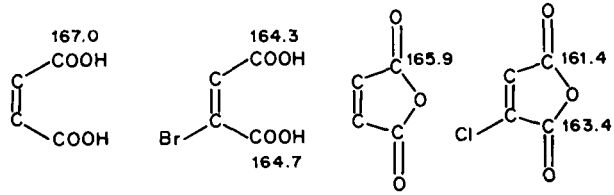
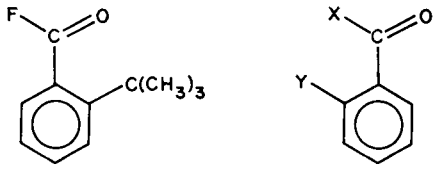


(72)

Substituents at the double bond cause a high-field shift of the carbonyl carbon chemical shift.[345].

Bruck and Rabinovitch conclude that monoesters are planar[343]. Acids and esters were also investigated extensively by Stothers and coworkers[346]. A recent study of 2-ethyl and 2-*t*-butylbenzoic acid shows that these can also be considered planar. The same holds true for benzoyl fluoride derivatives[347] (73). It is hence concluded that it is the interaction of the X substituent with the Y substituent (in most cases H) that causes the twist of the substituents in acids and esters (74). If both *o*-positions are substituted, the carboxylic acid



(73) (74)

group is clearly twisted out of the ring plane[348,349]. In crowded compounds the angle of twist can be considerable. Salman and Kamounah[350] calculated the twist angle, θ, from δ_{CO}:

$$\cos^2\theta = (216.0 - \delta^x_{CO})/20^{351} \tag{7}$$

The conformations of *o*-substituted benzophenones were estimated by means of δ_{CO}[352].

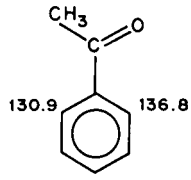
Lanthanide induced shifts (LIS) are also used to estimate the direction of carbonyl groups in α,β-substituted aldehydes, ketones, esters[354,355] and amides[353], 2- and 3-(*p*-methoxybenzoyl)-benzo[*b*]furan- and benzo[*b*]thiophene[355] as well as in 1- and 2-(*p*-methoxybenzoyl)naphthalene[355]. Ceder and Beier[354] warn that the conformation of the organic molecule may change as a consequence of complexation.

7. *Effects on aromatic carbons*

The directional dependence of the chemical shifts of carbons in the vicinity of a COX group may be determined either (i) from solid state spectra, or (ii) from ^{13}C spectra of a

cooled solution in which the rotamers are frozen out, or (iii) from chemical shift comparisons or (iv) from isotopic perturbation of equilibrium studies.

The solid state spectra are either determined on single crystals(from such studies shielding tensors can be obtained, see Section II.A.3) or by means of MAS (magic angle spinning)[298] spectra of powders. The latter technique is becoming very widespread. A number of compounds such as hydroxybenzaldehydes[299] and β-diketones[301] have been investigated by this method. The cooling down technique has been applied to a series of benzaldehydes and acetophenones (see Section III.A.2.b). The difference between *cis* and *trans* conformations are clearly smaller for the ketones than for the aldehydes due to the γ-effect caused by the methyl group of acetophenone. The effect is illustrated in **75**[176]. The effects of carboxylic acid groups are observed in pyromellitic acid[258] exemplifying the effects of a conjugated and a non-conjugated group. It is clearly seen that the *o*-carbons become different, whereas the carbons further away are not influenced to any degree.



(75)[276]

Comparisons of chemical shifts may lead to an estimation of chemical shift differences. An example is the comparison of 2,4-dihydroxy- with 2,6-dihydroxyacetophenone[357]. The result illustrates that the effect of the acetyl group is very different in the hydrogen-bonded case. A study of deuterium equilibrium isotope effects on methyl 2,6-dihydroxy-4-methylbenzoate gives likewise an estimate of the difference in chemical shifts between $C_{(2)}$ and $C_{(6)}$, about 10 ppm[356,357].

Twisting the carbonyl group also leads to a high-field shift of the *o*-carbons as discussed for 2,6-dimethylbenzoic acid derivatives[271,272].

B. Coupling Constants

Coupling constants involving carbonyl carbons can be of several kinds. $^1J(^{13}C, ^{17}O)$ is obvious, but not so well investigated. $^nJ(C{=}O, C)$ are likewise very informative. $^nJ(C{=}O, H)$ have also been investigated in detail. In addition to couplings starting at the carbonyl carbon, the coupling constant across a C=O double bond is also important.

1. $^1J(C{=}O, C)$

One-bond carbon–carbon coupling constants have been tabulated in recent reviews[76–78,156,158,358–360]. An early investigation of $CH_3C(=O)X$ derivatives found no definitive trends between $^1J(C{=}O, C)$ and simple hybridization nor effective nuclear charge densities[360].

The trends observed for aromatic compounds are also found for aliphatic compounds. Twist of the carbonyl or carboxyl group out of the ring plane has a relatively minor effect, as seen in Figure 3, although the trend to smaller values is noticed[271,362].

$^1J(C{=}O, C)$ is well established in aromatic ketones, aldehydes and acid derivatives[362,363]. $^1J(C{=}O, C)$ is different in the different types of derivatives, as seen in Figure 4. The difference in magnitude is related to the difference in inductive effects of the X substituent. Olah and coworkers[361] extend this argument to cover the benzoyl cation in

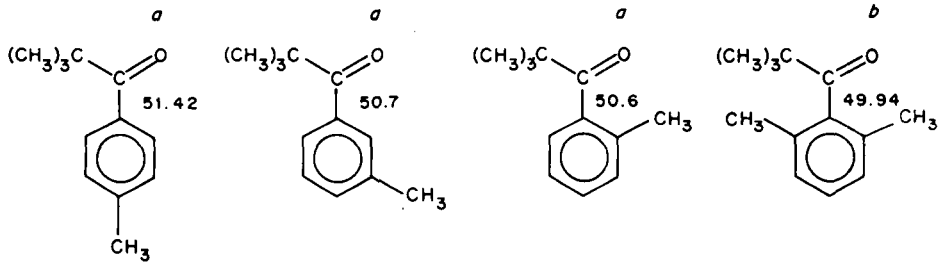


FIGURE 3. One-bond carbon–carbon coupling constants of aromatic carbonyl compounds including sterically hindered ones
[a]Taken from Reference 362. [b]Taken from Reference 271

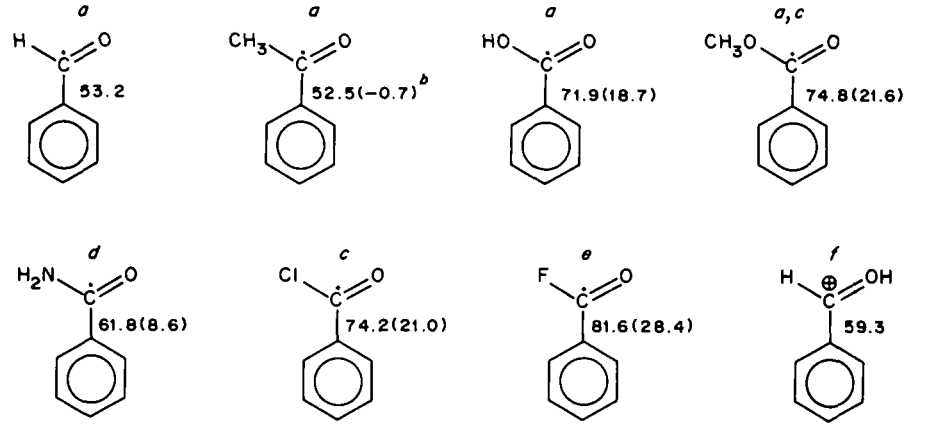


FIGURE 4. One-bond carbon–carbon coupling constants of aromatic carbonyl compounds
[a]Taken from Reference 362. Slightly different values for aldehyde and ketone are given in Reference 364. [b]$\Delta J = {}^1J_{\text{aldehyde}}$. [c]Taken from Reference 361. [d]Taken from Reference 271. [e]Taken from Reference 347. [f]Taken from Reference 364.

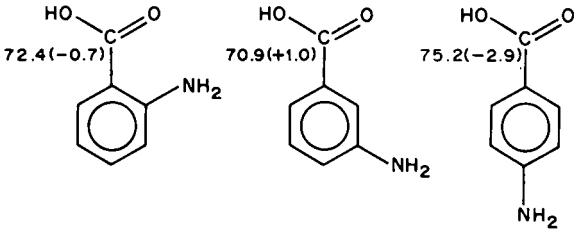
which ΔJ is -31.5 Hz (ΔJ is the difference between the coupling in the compound in question and that of benzoic acid). They consider X as being the empty π orbital in the cation. Substitution in the 4-position in aromatic carbonyl compounds leads to a change in $^1J(C{=}O, C)$. This is explained as a change in the π-bond order of the $C_{(1)}$ C=O bond[364,365]. Electron-attracting substituents lead to a slightly smaller value than in acetophenone or benzaldehyde, respectively. Unfortunately NO_2, the substituent that leads to strong reverse effects at the C=O chemical shift, was not investigated (see Section III.A.2).

Substituent effects are amplified in protonated acetophenones[364], benzaldehydes[365] and benzoyl cations[361].

Theoretical calculations of $^1J(C{=}O, C)$ show that the σ component is dominant but that π components are also significant[366].

$^1J(C{=}O, C)$ coupling constants were reported in cycloalkane carboxylic acids. $^1J(C{=}O, C)$ decreases with increasing ring size[367–369].

^1J(C=O,C) coupling constants are influenced by electric field effects. This was suggested in the study of ^1J(CO,C-γ) of aspartic acid[323]. A study of *o*-, *m*- and *p*-aminobenzoic acids, together with the corresponding cations and anions revealed that chemical shifts and ^1J(C=O,C) coupling constants could not in any way be correlated with charge on the carboxylic carbons as calculated from INDO wave functions. Qualitatively, the shift from the neutral to the cationic case is shown in **76** in parentheses.



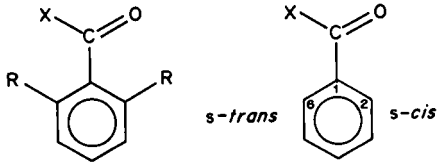
(76)

The value for 4-aminobenzoic acid is much larger than for benzoic acid. The NH_2 group acts similarly to OH and OCH_3. To what extent electric field effects play a role is difficult to judge in these compounds[370].

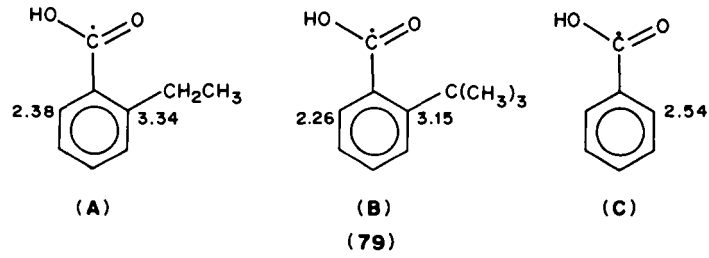
Temperature and solvent can also influence ^1J(C=O,C). The one-bond coupling constants in methyl acetate changes + 0.0018 Hz per degree whereas for sodium acetate the variation is − 0.0003 Hz per degree. ^1J(C=O,C) of *p*-bromophenyl acetate varies from 60.08 to 59.78 Hz with a change in solvent from benzene to chloroform[371].

2. ^2J(C=O, C, C)

Two-bond coupling constants, ^2J(C=O,C,C), have been investigated in aromatic compounds[75,76,157,158,271,344,347,362,363,372-374] usually enriched at the carbonyl carbon(indicated by a dot in the formula) (see **77** and **78**). ^2J(C=O, C_{arom}) depends on the nature of X[347]. It has been established firmly that if R = CH_3, then the C=O group will point towards the methyl group. The two-bond coupling to $C_{(2)}$ is termed $^2J(C{=}O,C)_{s\text{-}cis}$ and the one to $C_{(6)}$, $^2J(C{=}O,C)_{s\text{-}trans}$. From studies of compounds with R and R′ different from H it is clear that $^2J(C{=}O,C)_{s\text{-}cis} > {}^2J(C{=}O,C)_{s\text{-}trans}$ for ketones and aldehydes, whereas the opposite is true for acid derivatives[271,347,362]. It is seen that for acid fluorides $^2J(C{=}O,C)_{s\text{-}cis} \gg {}^2J(C{=}O,C)_{s\text{-}trans}$[347]. The signs of the coupling constants are important. The signs of ^2J(C=O,C) are positive in methyl benzoate[375], *N*,*N*-dimethyl-1-naphthamide[362], phthalates[343] and anthraquinone[362]. In methyl benzoate average values of coupling constants are obtained. A comparison of coupling constants in compounds **A** and **C**, **B** and **C** [see **79**) show that the coupling constants are positive[347]. The signs are rather important, as theoretical calculations predict that negative coupling constants may occur[347]. ^2J(C=O,C) depends, as mentioned, both on the orientation and also on the degree of twist. This is seen in **80**.

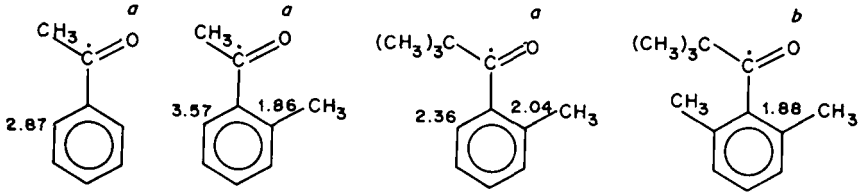


(77) **(78)**



(A) (B) (C)

(79)



(80)

a. From Ref. 362

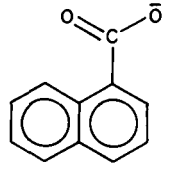
b. From Ref. 271

^2J(C=O, C) depends also on the bond order of the aromatic bond. The larger the bond order, the larger the coupling constant. Theoretical calculations show that the rotamer distribution of, e.g., the methyl group plays a minor role[347]. ^2J(C=O, C) in cyclic compounds depends also on bond angles[362]. The change-over in two-bond couplings can be seen as a substitutent effect. ^2J (C=O, C)$_{s\text{-}cis}$ increases from X = H and X = CH_3 to X = F[347]. It is not quite clear whether the effect is caused by electric field effects or by rear lobe overlap[347].

^2J(C=O, C) has been used to predict the conformation for the degree of twist of a series of similar compounds, nicotinamide[362], 8-nitro-1-naphthoic acid[271], 2-acetylcyclophane[373] and 2-biphenylcarboxylic acid[138]. The case of diethyl phthalates has been discussed in Section III.A.6.

Two-bond couplings also reveal a number of other features.

The carboxyl anion in 1-naphthoate takes up a preferred orientation as shown in **81**. ^2J(C=O, C) values are also observed in olefinic compounds[271,377], but are less significant. ^2J(C=O, C) across aliphatic bonds are expected to behave similarly to ^2J in aromatic compounds[271]. They are generally of the order of 0 to -1.9 Hz[157]. A standard value is evaluated, -1 Hz[161a]. For a series of compounds, a magnitude of 1.6 to 2.0 Hz is arrived at and a negative sign in assumed[378].

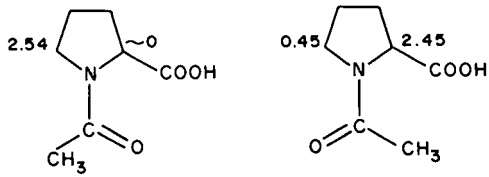


(81)

3. ^2J(C=O, X, C) and ^2J(C=O, X, H)

Two-bond coupling constants across a hetero atom are observed in esters, lactones or amides.

a. $^2J(C{=}O,N,C)$ *and* $^2J(C{=}O,N,H)$. $^2J(C{=}O,N,C)_{s\text{-}trans}$ is shown to be positive and larger than $^2J(C{=}O,N,C)_{s\text{-}cis}$[156,379]. Formamide shows a much larger *trans* coupling than other amides[156,380]. A study of a series of compounds confirms that $^2J(C{=}O,N)_{s\text{-}cis} > {}^2J(C{=}O,N)_{s\text{-}trans}$[378]. The former fall in the range 2–3 Hz, whereas the latter are smaller, 0.5–0.9 Hz. It is hence correct to assume that all $^2J(C{=}O,N,C)_{s\text{-}trans}$ couplings are positive. This has been used to explain the larger couplings observed in five-membered nitrogen heterocycles[156,381]. Studies of $^2J(C{=}O,N,C)$ may be used to determine the *cis/trans* ratio. The method can in principle be used in peptides and proteins[379] (see **82**), but has also been applied to amides in general[378].



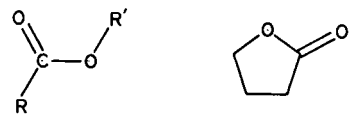
trans *cis*

(82)[379]

$^2J(C{=}O,N,H)$ are investigated by Dorman and Bovey[382]. A detailed investigation paired with sign determination shows features similar to those described for $^2J(C{=}O,N,C)$[383].

b. $^2J(C{=}O,O,C)$. A standard value for this coupling is -1.5 Hz (for four-membered rings -4 Hz must be added[161b]). The sign is negative in esters[75,76].

The geometry in esters is probably as depicted in **83A**[384]. The s-*cis* geometry is in line with a negative coupling constant. A positive coupling constant is to be expected in cyclic compounds in analogy with the result for amides. The large $^{2,3}J(C{=}O,O,C{=}O)$ coupling observed in phthalic anhydride is taken as evidence for a positive coupling[381]. $^2J(C{=}O,O,C)$ clearly has to be explored in detail, as valuable structural information about esters can be deduced from these coupling constants.



(A) **(B)**

(83)

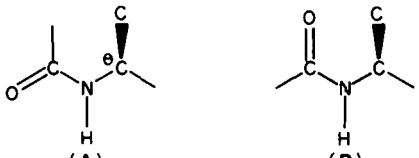
4. $^3J(C{=}O,N,C,C)$ *and* $^3J(C{=}O,N,C,H)$

$^3J(C{=}O,N,C,C)$ depends on the dihedral angle[378]:

$$^3J(C{=}O,N,C,C) = 1.84\cos^2\theta - 0.23\cos\theta + 0.51 \qquad (8)$$

For $\theta = 180°$, $^3J = 2.6$ Hz, which is a rather small value for a three-bond coupling (see **84**).

As the experimental data are obtained from cyclic compounds, only the *cis* orientation is represented. Theoretical calculations show similar magnitudes for the *cis* and *trans* arrangements[378] of the carbonyl group as shown in **84A** and **84B**.



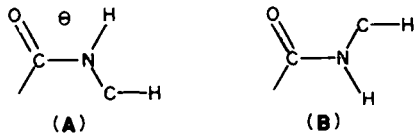
(A) (B)

(84)

^3J(C=O, N, C, H) is determined in cyclic compounds[378]:

$$^3J(\text{C=O, N, C, H}) = 3.96\cos^2\theta - 1.83\cos\theta + 0.81 \quad (9)$$

where θ *is the dihedral angle as shown in* **85A**.



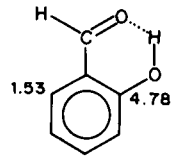
(A) (B)

(85)

As ^3J(C=O, N, C, H) is derived from cyclic compounds, primarily fragments shown in **85A** are represented. Data for the **85B** fragment seem to fall outside the equation[378]. Various data are given in Reference 382.

5. $^3J(H, C_{arom})$

Three-bond couplings from aldehydic protons to ring carbons are used to determine the direction of the aldehyde group. The value obtained in benzaldehyde is an average[385]. However, in salicylaldehyde, the C=O group is rigid. ^3J(H, C-2) > ^3J(H, C-6)[386]. Similar findings are made in gossypol[387]. 2-Methoxy-3, 5-dimethylbenzaldehyde has a similar conformation[388] (see **86**).



(86)

Couplings of the order of 2 Hz are observed in benzenedialdehydes[380]. Theoretical calculations on benzaldehyde show a curve that increases significantly from 0 to 180° [385,386]. This type of coupling is also studied in furan-2- and 3-carboxaldehyde and the thiophene aldehydes. The conformational dependence on solvent polarity was investigated[389]. Couplings to olefinic protons show similar trends[166,390]. Previously $^4J(H_{arom}, H)$ has been used extensively[391–400].

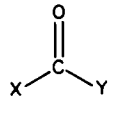
6. $^1J(C{=}O, F)$

In aromatic acid fluorides, ^1J(C=O, F) is predicted to depend on the degree of twist of the C=OF group leading to numerically larger values of the coupling in the case of

conjugation[347]. This is observed experimentally, since the coupling of acetyl fluoride[400,401] is larger than that of benzoyl fluoride[400].

7. $^2J(X, C{=}O, Y)$

The two-bond coupling across a carbonyl group $^2J(X, C{=}O, Y)$ (see **87**) has been noticed because of its large positive magnitude. A positive coupling was also observed for the similar $^2J(H, C{=}O, H)$. This is caused by overlap between the P_y orbital (the orbital in the HCO plane) and the two C—H bonds[402]. Both $^2J(C, C{=}O, H)$ and $^2J(C, C{=}O, C)$ are positive and the ratios have been compared[105,156,158]. $^2J(C, C{=}O, C)$ is close to 12 Hz[156]. Smaller values are observed in scylatone[403] (**88**) and in tenelin[404] about 8–9 Hz (**89**). The smaller coupling constants observed in the latter may be caused by hydrogen bonding[156]. A similar reduction is observed in $^2J(C, C{=}O, H)$ couplings[405].



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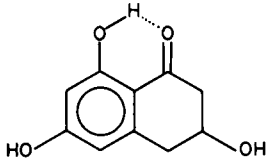
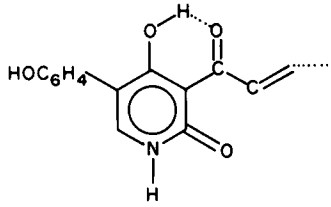
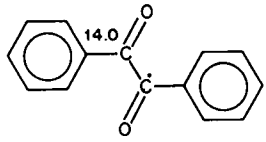


(88)



(89)

Larger couplings are observed in aflatoxin B_1[406] as well as in other biosynthetic compounds[77]. The large coupling in aflatoxin B_1 is the combination of a ^2J and a ^3J coupling path, hence the large value. $^2J(C, C{=}O, C)$ depends also on the hybridization and on substituents on the carbon atoms. Slightly larger coupling constants are observed when the carbons are sp^2 hybridized. Benzil (**90**) is an example[376].

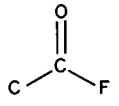


(90)

If the C=O bond is transformed into a $C{=}N{-}NH_2$ bond, the coupling is reduced to 4.9 Hz. A similar reduction is observed when transforming a ketone into an oxime[271] (see also Section IV.B.4).

Even larger couplings of the type $^2J(C, C{=}O, F)$ are observed in acid fluorides (**91**). $^2J(C, C{=}O, F)$ are of the order of 61 Hz[401]. Theoretical calculations predict these poorly[347].

Yet another coupling is $^2J(C, C{=}O, {}^{15}N)$. These are observed in amides (**92**). They are probably negative, because of the negative gyromagnetic ratio of ^{15}N. The coupling constants are large, about 9–10 Hz[407,408].



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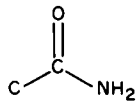

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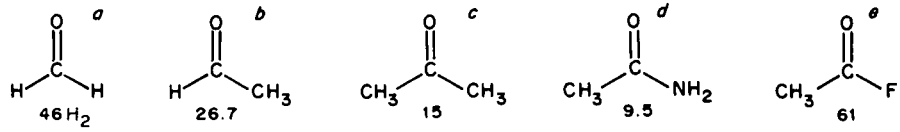


FIGURE 5. Comparison of two-bond couplings, ^2J(X, C=O, Y)
[a]Taken from Reference 411. [b]Taken from Reference 409. [c]Taken from Reference 412. [d]Taken from Reference 407. [e]Taken from Reference 400

A logical extension would be to measure ^2J(C. C=O, ^{17}O). This has so far not been reported.

^2J(X, C=O, Y) as observed in ^2J(H, C=O, H), ^2J(C, C=O, H) and ^2J(C, C=O, C) may be compared. For ^2J(H, C=OH) only one is possible. Äyräs[409] compared ^2J(H, C=O, H) with ^2J(C, C=O, H) and found a relationship:

$$^2J(C, H) = 0.578\,^2J(H, H) + 2.863 \quad (10)$$

Marshall[158] compared ^2J(C, C=O, H) with ^2J(C, C=O, C) (see Figure 5). A ratio close to the gyromagnetic ratio is expected from simple molecular orbital arguments[410].

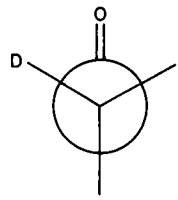
It is seen that the simple predictions are not correct. However, the sign of K (the absolute coupling constant) is positive in all cases[105, 407].

Cho and colleagues[161b] have calculated the variation of ^2J(C, C=O, C) of acetone with the C, C, C angle. The calculations predict a more negative coupling constant for a small angle.

C. Isotope Effects

1. $^2\Delta$(C=O, D)

Since the discovery of a negative deuterium isotope effect on the carbonyl carbon of deuteriated acetone[411] this phenomenon has attracted quite a lot of attention[200,412-414]. The resemblance to hyperconjugation as observed in alkyl substituted benzenes[415] and in carbenium ions[416] has also been pointed out. Morris and Murray[417] found both positive and negative effects in camphor and Simpson and Stenzel[418] found that the *trans* effect is different from the *gauche* effect (**93**).



(**93**)

An orientational dependence related to the π orbital of the C=O bond is likely to be present[419], and the magnitude of the isotope effect depends on the electronegativity of the X substituent. This point has been further investigated[420]. A linear relationship is established between $^2\Delta$(C=O, D) and the chemical shift of the carbonyl carbon. Compounds having C=N or C=C moieties also obey this relationship[420], whereas the

carbonium ions fit in poorly. A study of tritiated acetone[421] shows that:

$$^2\Delta(C{=}O, D)/^2\Delta(C{=}O, T) = {}^1\Delta(C, D)/{}^1\Delta(C, T) = 1.41 \quad (11)$$

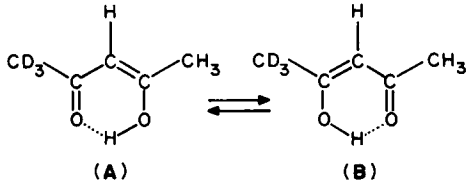
The authors remark that this is interesting, as the one-bond and two-bond effects are believed to be of different origin[421]. The negative two-bond isotope effect is claimed to be the result of isotopic perturbation[415,422]. However, the origin is clearly vibrational[423] and the isotope effects merely resemble hyperconjugation.

Servis and Domenick[424] modelled $^2\Delta(C{=}O, D)$ of acetone by means of *ab initio* calculations. By shortening the C—H bond so as to mimic a C—D bond they obtained a change in atomic charge, which is converted into a change in chemical shift by using the relationship 160 ppm/e. The negative sign for $^2\Delta(C{=}O, D)$ of acetone is nicely reproduced, but unfortunately a negative sign for $^2\Delta(C, D)$ of propene is also predicted, a fact that calls for caution. A different manner of estimating isotope effects would be to calculate the isotope effects by calculating σ' and σ'' using the relationship given by Jameson and Osten[426]. This has been done for formaldehyde, but not for acetone[427].

A number of cyclic compounds have been mentioned. The camphors are rigid, whereas the compounds studied by Simpson and Stenzel[418] are flexible. It was early realized that isotopic substitution could lead to a change in the conformation of the ring[428]. The equilibrium nature of this type of isotope effect is treated both from a theoretical and a practical point of view[200,422].

2. *Isotopic perturbation of equilibrium*

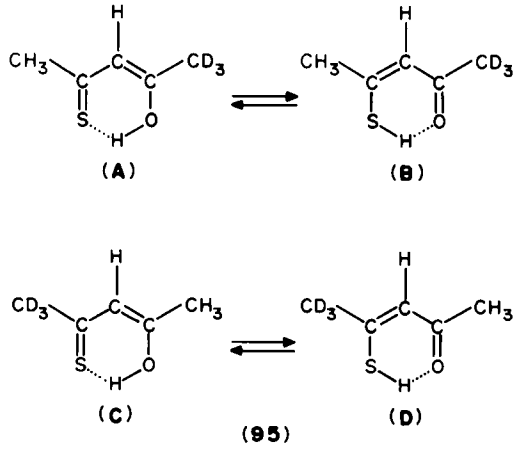
The ^{13}C NMR spectrum of 1, 1, 1-trideutero-2, 4-pentanedione (**94**) shows two carbonyl resonances. At room temperature an isotope effect of 0.17 ppm/D is obtained. Isotopic perturbation of the equilibrium is the likely cause[435,436]. Isotope effects over two bonds of the type described are usually small[207]. A zinc complex shows no signs of isotopic perturbation of the equilibrium indicating a symmetrical structure in that case. **94B** is lower in energy than **94A**. A temperature study reveals a difference of 14.5 cal/D[437]. A CD_3 group effect is also observed in deuterated β-thioxoketone[438].



(94)

95A and **D** are stabilized relative to the other isotopomers. This is fully in line with the observation in acetylacetone[437]. Studies of long-range effects also include perdeuteriated benzene rings. A C_5D_5 ring gives an effect in the same direction as a CD_3 group[438].

The finding that a CD_3 group prefers a C—OH rather than a C=O bond is explained by Saunders[437] by assuming that 'deuterium prefers to be on the stiff bond'. A carbonyl double bond lowers the strength of the C—H bond and thereby the force constant, making the bond less stiff. This principle has been observed in a series of carbenium ions[200,228,422] and is also confirmed from the study of deuteriated acetyl fluoride in which the $—CH_2D$ and $—CHD_2$ isotopomers take up orientations so that the C—D bond is in an *anti-periplanar* position relative to the fluorine. In this case the C—D bond has the highest C—D stretching frequency[419].

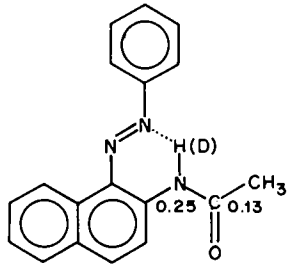


(95)

3. $^2\Delta(C{=}O, ND)$ and $^3\Delta(C{=}O, ND)$

Two-bond deuterium isotope effects on nuclear shielding of amides were proposed as a means of identifying carbonyl carbons of amides dissolved in mixtures of H_2O:D_2O[439]. The magnitude in simple amides is 0.06 ppm. In small peptides a value of 0.08 ppm is obtained[440]. Addition of CH_3OD to, e.g., DMSO solutions is another simple manner of exchanging amide protons[323,440]. $^2\Delta(C{=}O, ND)$ values are studied in peptides and show a small spread in magnitude, 0.05–0.10 ppm[215,318,341,440–443]. In bovine pancreatic trypsin inhibitor, the occurrence of isotope splittings has to be coupled to the disappearance of N—H signals in order to assign the ^{13}C carbonyl spectrum[341].

Slightly larger two-bond isotope effects are observed, when the N—H group is strongly hydrogen bonded[440,444] as demonstrated in **96**. The magnitude of $^2\Delta(C{=}O, ND)$ can possibly be related to hydrogen-bond strength[440].



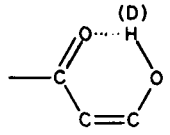
(96)

Deuterium isotope effects over three bonds, $^3\Delta(C{=}O, ND)$, have only been reported in a few cases[215,440]. Effects are seen in viomycin. They are of the order of 0.02 ppm, but the signs are unknown. Effects are observed in Gramicidin S[440] and quite a few are seen in basic pancreatic trypsin inhibitors (BPTI)[440] and in subtilisin inhibitor[441,442]. The latter are positive[440–442]. Small effects are also seen in *o*-acetamido aromatic azo compounds[444]. In aromatic secondary amides values of 0.08 to 0.10 ppm are reported[445].

Combined two- and three-bond effects are observed in amino acids dissolved in CF_3COOD vs. CF_3COOH[446].

4. $^4\Delta(C{=}O, C)$

Long-range deuterium isotope effects on carbonyl carbons are observed in a series of intramolecularly hydrogen-bonded *o*-hydroxy carbonyl carbons of the type **97**.



(97)

The long-range effects are of varying magnitude, as seen in Figure 6. In compounds termed localized, they vary from 0 to 0.14 ppm. This variation is not yet fully understood[207]. No correlation with $^2\Delta(C, OD)$ or $^2\Delta(C, ND)$ is observed. Aromatic esters are found at the higher end[448]. For compounds in which tautomerism may take place, two different patterns are recognized. The more or less symmetrical β-diketones show values of about 0.7 ppm, whereas unsymmetrical β-diketones may show negative isotope effects at the carbonyl carbon. Shapet'ko and coworkers[206] argue that the negative sign is caused by a tunnel effect. The fact that the carbon of the CH_3 group also shows a distinct negative isotope effect clearly supports the tautomerism theory. The decrease in the isotope effect at the carbonyl carbon with decreasing temperature is also in agreement with a decrease in the effect of deuterium substitution as temperature is lowered and the molecules sit lower in the potential well[207,210].

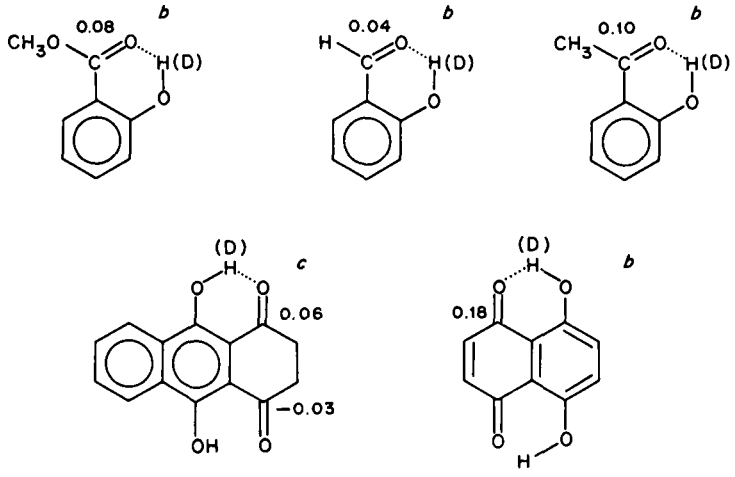


FIGURE 6. $^n\Delta(C{=}O, D)$ of intramolecularly hydrogen-bonded compounds[a]

[a]For values of similar compounds see Fig. 1. [b]Taken from Reference 207. [c]Taken from Reference 208

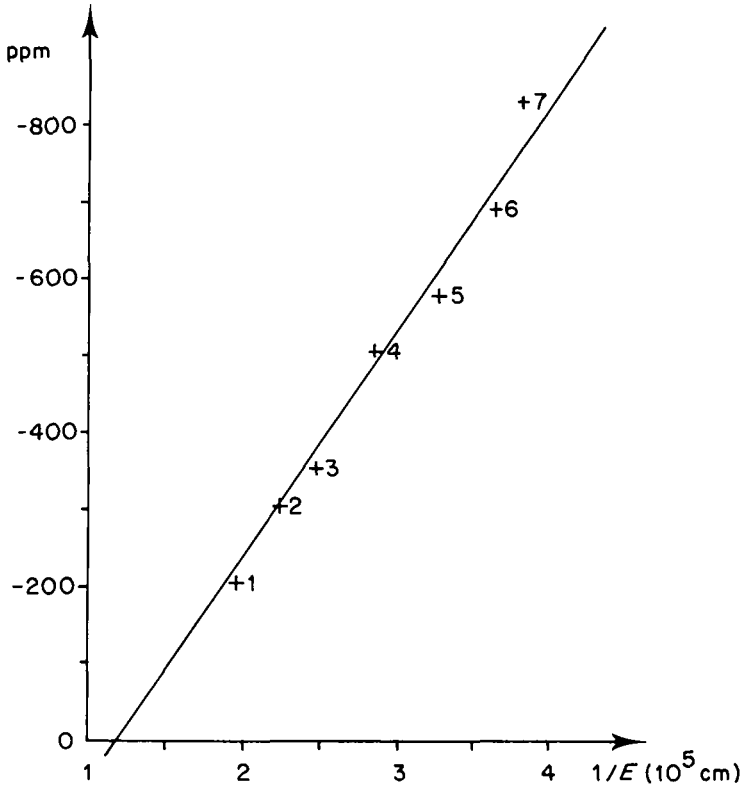


FIGURE 7. ^{17}O chemical shifts vs. $1/E^{a,b}$
^{a}E is the energy of the lowest-energy transition. Taken from Reference 450. $^{b}1$ is $(NH_2)_2CO$, 2 is $HCONH_2$, 3 is $CH_3COOC_2H_5$, 4 is CH_3COCl, 5 is CH_3CHO, 6 is $(C_2H_5)_2$ NNO and 7 is C_4H_9ONO

D. ^{17}O Chemical Shifts

^{17}O chemical shifts of carbonyl compounds were investigated very early[459-452]. ^{17}O chemical shifts are normally referred to $H_2{}^{17}O$[449]. ^{17}O is a quadrupolar nucleus; $I = 5/2$ and the natural isotopic abundance is 0.037%. ^{17}O chemical shifts are hence best studied in labelled compounds. The chemical shift range for ^{17}O is 1000 ppm in general[453]. Wasylishen and coworkers[454] found that $\delta^{17}O/\delta r_e = -1150 \pm 130$ ppm/A.

^{17}O NMR spectroscopy is rapidly emerging as a valuable method for determining structural features of carbonyl compounds[451,452,455,456]. The oxygen of the carbonyl group is a terminal atom, a feature that has aided the analysis of ^{17}O chemical shifts.

^{17}O chemical shifts are very sensitive to the structure of the carbonyl compound, as seen in Figure 7.

1. Correlations

A linear relationship between ^{17}O chemical shifts and the lowest energy transition ($n-\pi^*$) as obtained from UV or visible spectra was realized as early as 1961[457]. de Jeu[458] later

extended this treatment. For second-row elements the paramagnetic term is dominating. The paramagnetic contribution can be written as:

$$\sigma_p^A = \frac{-2e^2h^2 < r^{-3} >_{2p} \sum Q_{AB}}{3m^2c^2\Delta E} \tag{12}$$

where Q_{AB} consists of charge density and bond-order matrix elements for the unperturbed wave functions. The most important feature for this discussion is the average energy, ΔE. The largest contribution to this is the n–π^* transition. Figgis and coworkers[450] observed in accordance with equation 12 that the ^{17}O resonance shifts to higher field with decreasing $\lambda_{max}^{n-\pi^*}$. The relation holds for a range of 400 ppm (600 to 200 ppm). It is likewise tempting to correlate ^{13}C of carbonyl compounds with $\lambda^{n-\pi^*}$. This was first attempted by Savitsky and coworkers[459] for ^{13}C chemical shifts. They observed for cyclic and acyclic ketones that the ^{13}C resonance shifts to lower field with increasing $\lambda_{max}^{n-\pi^*}$. de Jeu[458] showed that a relationship between δ_{CO} and $\delta^{17}O$ could be established for ketones and aldehydes, but not for a broader group of carbonyl containing compounds. The results are discussed in terms of inductive and polarization effects of the C=O bond and the resulting changes in the energy level diagram. St. Amour and colleagues[460] found a good correlation between ^{17}O chemical shift of *p*-substituted acetophenones and $\lambda_{max}^{n-\pi^*}$, again supporting that $\Delta E^{n-\pi^*}$ makes a dominant contribution to ^{17}O chemical shifts. This has been questioned by Brownlee, Sadek and Craik[461]. They also investigated the same group of compounds. A DSP analysis revealed that polar and resonance mechanisms contribute equally and that the shifts correlate well with calculated π-electron densities (1500 ppm per electron). It is concluded that the effect is electronic and that the variation in ΔE is minor, whereas the local π-electron density is the controlling factor. Whether this will be generally true for a larger group of C=O compounds is to be seen.

2. *Conjugation and steric effects*

Conjugation influences ^{17}O chemical shifts as shown by studies in *o*-substituted acetophenones[460]. Increasing deviation from coplanarity between the aromatic ring and the carbonyl group leads to a downfield shift for both the ^{17}O and ^{13}C chemical shifts (see also Section III.A.2). St. Amour and colleagues[460] found furthermore a correlation between $\delta^{17}O$ and θ (the angle between the ring and the carbonyl group as obtained from the corresponding carboxylic acids). This is rather remarkable, as ketones and acids do not necessarily have the same twist angle (see Section III.A.6). In a recent study, $\delta^{17}O$ of acetyl groups of aromatic compounds was correlated with the torsional angle[467] obtained from molecular mechanics calculations of MMR type[468]. Correlation with σ^+ has been found for 4- and 4'-chalcones and for *p*-substituted β-nitrostyrenes[462]. ^{17}O chemical shifts of *p*-substituted benzoic acids correlate with Hammett σ constants and with σ^+.

^{17}O chemical shifts of α,β-unsaturated ketones and acyl derivatives show a correlation with the π-electron density at the β-carbon. From this correlation an estimated value of 530 ppm is arrived at for the $CH_3C{=}O^+$ ion.

^{17}O chemical shifts also correlate with the nuclear quadrupole coupling constant. One exception is acyl chlorides[464]. α,β-unsaturated esters are discussed by Orsini and Severini Ricca[465]. Unusual ^{17}O chemical shifts are explained by assuming twist of the ester groups.

A study of aryl alkyl ketones with alkyl groups of different size shows that $\delta^{17}O$ varies both with respect to direct substituent effects but also due to a twist of the carbonyl group, when the substituents become larger. The first effect is compensated for by a comparison with values obtained from CH_3COR derivatives[470].

Chemical shifts of 1, 2-diketones depend both on the electron density at the oxygen atom and on ΔE. A reasonable correlation is obtained between $\delta^{17}O$ and $\Delta E^{n-\pi^*} q_0^\pi$. The angle θ between the carbonyl group and the aromatic ring is determined indirectly[471]. ^{17}O

chemical shifts depend also on in-plane bond angle distortions as demonstrated in derivatives of phthalic acid[472–474]. *Ortho* substituents lead to a downfield shift with increasing size of the alkyl group[474]. γ-Effects are also observed in amino acids[475,476] and in ketones and aldehydes[477,478]. In aldehydes and ketones β, γ and δ effects are -24, -11 and 5 ppm, respectively[477,478]. For carboxylic acids the effects are approximately half the size[476] of those observed for aldehydes and ketones. The γ-effect is hence in the correct direction if a polarization of the C=O group is considered (see Section III.A.6).

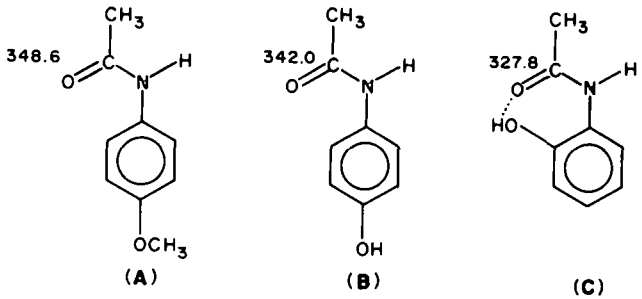
3. *Hydrogen bonding*

Solvent effects and especially hydrogen bonding are realized as being important. Hydrogen bonding affects $\lambda_{max}^{n-\pi^*}$ for acetone. A plot of $\delta^{17}O$ vs. This parameter for acetone in water is linear, whereas the similar plot for the ^{13}C chemical shift is curved. Intramolecular hydrogen bonding perturbs ^{17}O chemical shifts. St. Amour and colleagues studied a number of acetophenones and aldehydes[460] and found that intramolecular hydrogen bonding results in high-field shifts. Hydrogen bonding is also observed in citrinin[479] (**25**) and in 1,4-dihydroxyanthraquinone. Other hydroxyketones such as naphthazarin (**60**) show tautomerism[480], which will be treated later. Dissolving carbonyl compounds in alcohols leads to high-field shifts. ^{17}O chemical shifts are used to follow the protonation of acetone in water[481]. Hydrogen bonding is also assumed to be important in amino acids and proteins[482,483].

Amino acids, proteins and peptides[475,476,482,483,485–488] have been investigated in detail. Titration experiments show that ^{17}O chemical shifts of the carboxylic acid oxygen is shifted to low field (high frequency) by about 13–18 ppm[475,476] upon deprotonation. The side-chain carboxyl group shows a low-field shift of ~ 24 ppm[475]. Deprotonation of the primary α-amino group leads to a low-field shift of the α-carboxylic oxygen of -2.3 to -3.9 ppm (serine and threonine ~ 1.5 ppm). The titration shifts are explained by an inductive shift to low field, counterbalanced by an electric field effect shift to high field[476].

Chemical shifts are also discussed in coumarins[489], in α-substituted acetones[289] and in uracils[490].

One class of compounds that attracted much interest comprises the β-diketones[491,492]. The ^{17}O spectrum shows one signal from the diketo form and one in the symmetrical and two in the unsymmetrical β-diketones from the oxygen atoms of the enol groups[492]. The separation of the oxygens in the latter is about 60 ppm. This difference shows no change upon cooling[492]. A similar although slightly more complicated situation is encountered in citrinin[479]. The high-field shifts observed in **98B** and **98C** are ascribed to inter- and intramolecular hydrogen bonding, respectively[484]. ^{17}O chemical shifts of OH oxygens of similar compounds are also given[493].



(98)

E. ^1J(C, ^{17}O)

Experimental values of $^1J(C,^{17}O)$ in carbonyl compounds have only been reported in a few cases. Acetone gives a value of 22 ± 4 Hz[494], carbon dioxide 16.1–0.1 Hz and carbon monoxide 16.4 ± 0.1 Hz[454]. From general periodic trends Wasylishen and coworkers[454] predict a positive sign for the one-bond coupling constants. This is confirmed by semi-empirical MO calculations[455,495], whereas *ab initio* calculations predict both positive and negative Fermi-contact contributions to $^1J(C, O)$ of carbon monoxide[496,497]. In the equation-of-motion (EOM) many-body treatment of Galasso and Fronzoni[495] all contributions to the isotropic coupling constant are calculated for $^1J(C, O)$ of ketene and carbon monoxide. The total value is ~ 30 Hz. The anisotropy of the coupling tensor is also given.

F. Isotope Effects Involving ^{17}O and ^{18}O

1. $^3\Delta(^{17}O, D)$

Three-bond deuterium isotope effects on ^{17}O chemical shifts have been determined in deuterated acetic acid[498] and in acetyl fluoride[499]. The magnitude can be explained by assuming a directional dependence as found for the fluorine atom of the deuterated acetyl fluorides[499].

2. $^1\Delta(^{13}C, ^{18}O)$

^{18}O isotope effects on ^{13}C chemical shifts were studied intensely in carbonyl compounds. ^{18}O isotope effects are in most cases only observed over one bond. ^{17}O isotope effects have not been reported because of line broadening of the neighbouring carbon resonances. $^1\Delta(C, O)$ isotope effects are reviewed[200,210,500,501]. These effects are normally only observable in enriched compounds. The use of super-high resolution made possible observations in acetone[502]. $^1\Delta(C, O)$ of the simplest carbonyl compound, CO_2, was determined by Wasylishen and coworkers[454]. From this measurement $(\partial\sigma^{13}C/\partial r)_e = -214 \mp 17$ ppm A^{-1} could be derived using the equation suggested by Jameson[503–506].

$$\Delta = (\partial\sigma/\partial\Delta r)_e[<\Delta r> - <\Delta r>'] + (\partial^2\sigma/\partial\Delta r^2)_e[<\Delta r>^2 - <\Delta r^2>'] \qquad (13)$$

The equation gives the relationship between isotope effects and the change in chemical shifts upon bond extension. $\partial\sigma/\partial\Delta r$ has also been determined from the temperature dependence of ^{13}C shielding in the zero pressure limit[504]. Based on equation 13 isotope effects may be related to other physico-chemical constants[507]. Jameson and Osten[508] summarize the factors that influence isotope effects as follows: $(\partial\sigma^A/\partial\Delta_{AX})_e$ depends on the bond properties, and is the greater the stronger the bond. It is hence expected to correlate with bond order and the spin–spin coupling, J_{AX}. It also depends on the absolute shielding of the nucleus[509] and largely on the paramagnetic term. The smaller shielding gives the largest derivatives. This has been demonstrated for a number of compounds[510] leading to equation 14:

$$^1\Delta(^{13}C, O) = 4.16 \times 10^{-2} - 4.38 \times 10^{-4}\delta^{13}C \qquad (14)$$

The shielding is, as discussed in Sections II.A.3 and III.A.1, a tensor property. Stretching of the bond is expected to have the largest effect on the tensor elements perpendicular to the bond[508].

Figure 8 shows that some of the data deviate from the line defined by the equation given by Everett[510]: 1 is averufin[511], 2 is sterigmatocystin[512], 3 is kinamycin[515]. Common for all these compounds three is the fact that the carbonyl group in them is hydrogen-bonded.

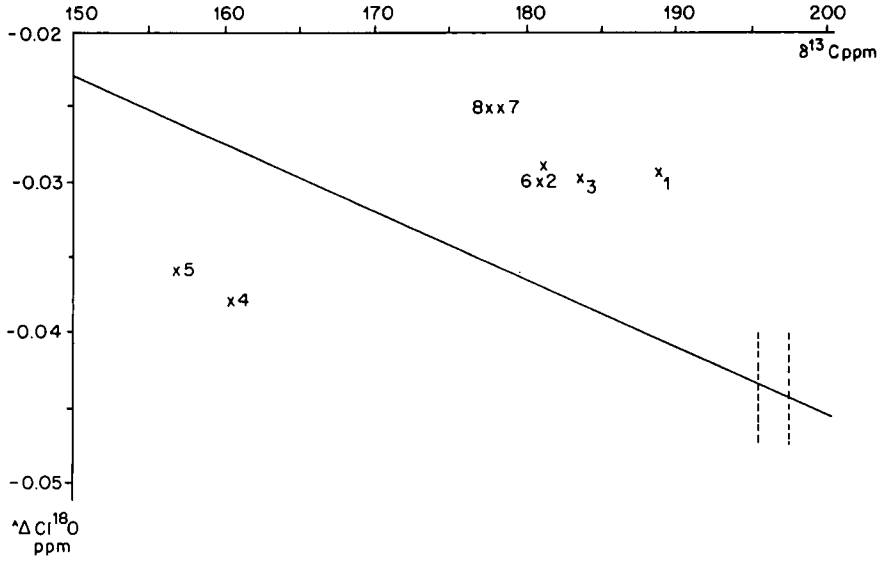


FIGURE 8. $^{1}\Delta(C, ^{18}O)$ vs. ^{13}C chemical shifts[a]
[a]The graph is drawn according to the original equation given in Reference 510. For explanation of deviating points, see text

The second carbonyl group of 1 falls nicely on the line. 4 and 5 are acetyl and benzoyl fluoride[499]. The strong electronegativity reduces the isotope effect in agreement with other findings[517]. The acids are not expected to fall on the line, as the values given for them are average values between those of a C=O double bond and a C—O single bond. The latter gives rise to an isotope effect of ~ 0.015 ppm in esters[517]. The spread for the acids is quite large judging from the values given for monensin A(6), and the carboxylic acids of *syn*- and *anti*-7-carboxynorbornene[514] (7 and 8 in Figure 8).

Risley and coworkers[516] investigated a series of *meta*- and *para*-substituted acetophenones and found no correlation between $^{1}\Delta(C, O)$ and $\delta^{13}C{=}O$. The chemical shift range is narrow, 195.5–197.5 ppm. The range is marked in Figure 8 by two broken lines. A reanalysis of the data given by Risley and coworkers[516] is shown in Figure 9. The data do not fit a single correlation, but is can be proposed that substituents having a positive σ_p^+ fall on one line and those with a negative σ_p^+ fall on the other line. The slope is giving the largest $^{1}\Delta(C, O)$ for the small ^{13}C chemical shifts. The situation is thus similar to that described for ^{13}C chemical shifts as discussed by de Jeu[458] (see also Section III.D.1). Inductive effects either increase or decrease the electron density of both the carbon and the oxygen atoms, whereas mesomeric effects cause a polarization of the bond. The latter is clearly the case for the *p*-substituted acetophenones, whereas the overall fit reflects the normally large influence of inductive effect from the X group. Extensive use of a correlation between $^{1}\Delta(C, O)$ and $\delta^{13}C{=}O$ seems thus not warranted, although a correlation between related compounds can be of use.

Another correlation is one between $^{1}\Delta(C, O)$ and $\delta C_{(1)}$ of *p*-substituted acetophenones[516]. This is expected, since a correlation between σ and $\delta^{13}C_{(1)}$ exists.

$^{1}\Delta(C, O)$ tends to decrease in the series ketones > aldehydes > esters > amides[517]. Carboxylic acid carbons show isotope effects that have values intermediate between C=

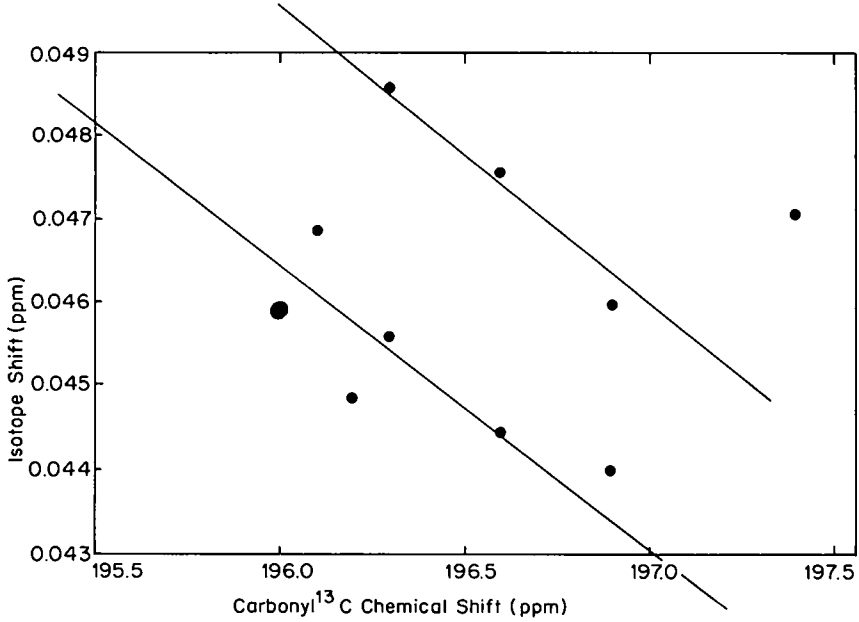
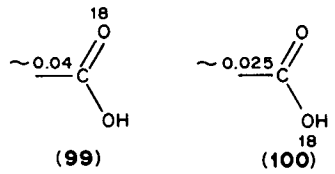


FIGURE 9. $^{1}\Delta(C, ^{18}O)$ vs. ^{13}C chemical shifts of *p*-substituted acetophenones[a]
[a]The original drawing was included in Reference 515. The point for the OCH_3 group, indicated by a slightly larger dot, had been misplaced in the original Figure

O and C—O[518] (**99** and **100**) Isotope effects can be used to follow oxygen exchange in acids[519] or hydrolysis[520]. Another interesting area is biosynthetic incorporation[493,511–513,515,521–526].

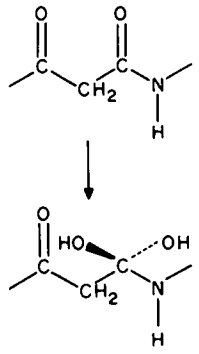


3. *Solvent isotope effects*

A very interesting case is the fate of the ketone, isovaleryl-L-valyl-[3-^{13}C]-(3-oxo-4*S*)-amino-6-methylheptanoyl-1-alanyl-isoamylamide (partial structure in **101**), which is a strong inhibitor of aspartyl serine proteases. When the ketone is added to porcin pepsin, the carbonyl signal moves from 208 to 99.07 ppm. However, if the experiment is performed in D_2O it moves to 98.71 ppm. A deuterium isotope effect is thus observed showing that water adds to the carbonyl groups[527].

IV. C=N BONDS

The carbon–nitrogen double bond is found typically in oximes, Schiff's bases, but also in



(101)

imines, hydrazones, etc. Since they are usually derived from carbonyl compounds certain similarities with the latter are expected.

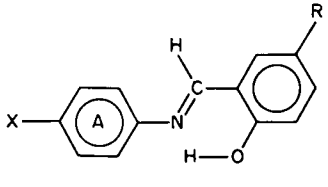
C=N double bonds are naturally investigated by means of ^{13}C and ^{15}N NMR. The amount of published data is much smaller than for C=O. Suggestions must in some cases be based on very meager data.

A. Chemical Shifts

1. Schiff's bases

N-Benzylideneanilines are a typical example of this group of compounds. π-Electron densities at $C_{(7)}$, also called C-α, correlate with ^{13}C chemical shifts[528]. The electron densities were obtained from extended Hückel calculations without taking into account the twist of the rings. Data are also given by Catusse and coworkers[529].

Salicylideneanilines are likewise interesting. In *N*-5′-methylsalicylideneaniline, δC-α or $C_{(4)}$ correlates with *F*, *R* parameters and also fairly well with σ_I and σ_R^0[530]. This is not the case for *N*-salicylideneanilines[531] (**102**) or for *N*-benzylideneanilines[532] (**103**). Kishore and colleagues[530] suggest that this is due to twisting of the aniline (A) ring (θ_N).



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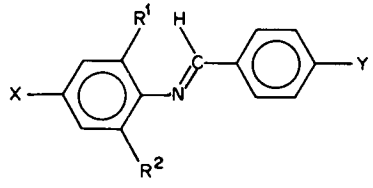


(103)

The conformations of *N*-benzylideneanilines are subject to some debate[533]. Anomalous upfield shifts have been reported for the methine proton[534–537]. It has been argued that the effect is caused by a through-space field effect[536], but more recently twist of the rings has been suggested[538–540].

A detailed analysis of ^1H and ^{13}C chemical shifts as well as $^1J(C_\alpha, H_\alpha)$ made Tokumaru and coworkers[533–535] suggest that for $X = NO_2$ the aniline ring is twisted. If R^1 or R^2 are methyl groups then a similar twist is obtained. If, however, $X = NO_2$ and $Y = NMe_2$ then a push–pull effect occurs and the molecule is planar[541,542]. Likewise the molecule with $X = Y = NMe_2$ is also twisted. No indication of the degree of twist is given.

Fluorination of the A ring increases nitrogen shielding[543]. A fluorine in position 2 causes a 13.8 ppm downfield shift, whereas fluorine substitution in position 4 causes a 3.9 ppm downfield shift. The effects are additive. Perfluorination of the B ring leads also to a downfield shift, 24.1 ppm. Effects of fluorination in the two rings are also additive. The authors hence suggest that the effects are caused mainly by changes in the electron density at nitrogen and not by conformational changes.

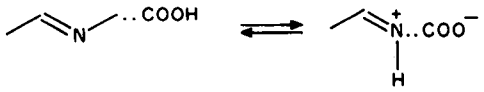
^{15}N chemical shifts of *p*-substituted *N*-phenylbenzylideneimines[544] correlate with σ_p:

$$\delta^{15}N = 19.36\sigma_p - 56.01, \qquad r = 0.993 \tag{1}$$

A change in θ_c occurs upon substitution at the methine carbon[545].

2. Retinals

^{13}C spectra of the retinal-protein complex of ^{13}C-labelled retinal reveals that retinal is attached to the ε-NH_2 group of lysine via an aldimine or a protonated aldimine bond[546]. Results relating to the olefinic carbons were mentioned in Section II.A.3. The condensation product shows an equilibrium (**104**), which is proven by ^{13}C NMR[547]. Protonation shifts were also studied in Schiff's bases obtained from butylamine with butyraldehyde, crotonaldehyde, sorbaldehyde and all-*trans* retinal. The protonation shifts are an order of magnitude larger for ^{15}N than for ^{13}C chemical shifts. Solvent effects are larger for the imine nitrogen than for the iminium one[548].

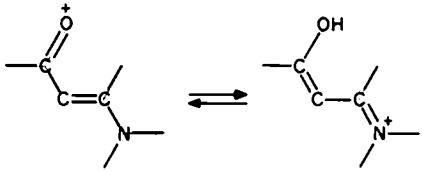


(104)

Iminium ions are also encountered by protonation of enaminones in CF_3COOH as protonation takes place at the nitrogen. The ^{15}N chemical shifts of iminium ions fall between -200 and -230 ppm relative to external CH_3NO_2[59] (**105**). ^1H and ^{13}C data for sulphinylimines are also reported[63,549].

3. Oximes

Determination of *cis–trans* (*syn–anti*) properties of oximes (**106**) is achieved by observation of the H_α chemical shift of oximes[550–555]. The ^{13}C chemical shift of the α carbon can also be related to the *syn–anti* properties[553]. 5-substituted furfuraloximes show good correlation between δH_α or δC_α and F, R parameters. Likewise δN can be correlated to σ_p[554].



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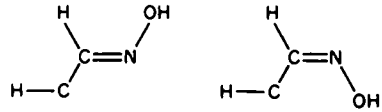


(106)

Gurudata[555] discusses solvent effects on ^{13}C chemical shifts of acetoximes. $\delta C{=}N$ of both *E* and *Z* isomers of oximes correlates with Hammett σ_I values[556]. The same is true for the methyl ethers. The resonance effect of *p*-substituents in benzaldehyde oxime anions is

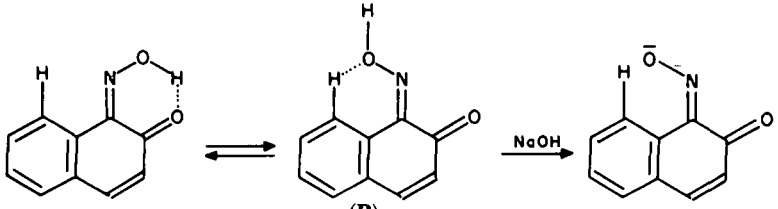
much smaller than in the corresponding oximes:

$$\delta C{=}N = 149.8 - 2.5\sigma_I + 0.3\sigma_R^+ \quad (2)$$

This observation is similar to observations made in *para*-substituted benzoic acid derivatives. Rutkovski and colleagues[557] ascribe this to a strong interaction with solvent.

1-Nitroso-2-naphthol and its disodium 3,6-disulphonate, as well as 2-nitroso-1-naphthol and its sodium 4-sulphonate exist in the oxime form (**107**). ^{13}C spectra give C=N chemical shifts characteristic of oximes. $H_{(8)}$ of 1-nitroso-2-naphthol is deshielded. This is due to the presence of form B[558]. Upon deprotonation, $H_{(8)}$ is further deshielded.

Protonation of 2-nitroenamines leads to oximes, that were investigated in CF_3COOH solution[559].



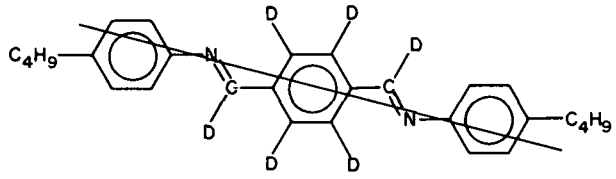
(A) (B) (C)

(**107**)

^{15}N and ^{17}O chemical shifts of C,N-diarylnitrones show a deshielding upon fluorination[543].

4. Liquid crystal systems

The bis(butylaniline) derivative of terephthalicdialdehyde (**108**, TBBA) forms both liquid crystal and smectic phases. By studying quadrupolar coupling constants in d_6-TBBA and using a simplified equation, Luz and colleagues could determine the angle between the direction of molecular alignment and the *para* axis of the central benzene ring as 8°, both in the nematic phase and in the smectic phase A. It is also concluded that the outer benzene rings are rotated out of the plane of the central ring[560,561]. Proton decoupled ^{13}C spectra of *p*-methoxybenzylidene *p'*-butylamine deuterated at $C_{(7)}$ show dipolar C–D splittings from which an order parameter and a rotation axis can be derived[562,563]. Similarly ^{15}N substitution may also be useful.



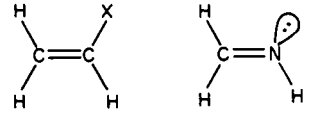
(**108**)

B. Coupling Constants

1. $^1J(C,H)$

The presence of a nitrogen lone pair is the determining factor. A carbon–nitrogen double bond presents a case analogous to that found in substituted olefins (**109A**). The

non-bonded electron pair can be considered to act like an electropositive substituent[191], because the non-bonding orbital will be more *s*-like than the bonding orbitals. Ewing[564] predicts that ^1J(C, H) *cis* to the lone pair will be larger than that with the C—H bond *trans* to the lone pair (**109**). The argumentation is hence similar to that presented by Augé and David[178] (see Section II.B.4.b).



A **B**

(109)

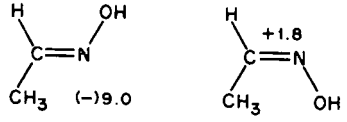
2. ^1J(N, C)

One-bond nitrogen–carbon couplings of oximes are quite small, often less than 5 Hz[565]. The absolute value of ^1J(N, C) is larger in the *E* than in the *Z* isomer[566]. Theoretical calculations show that the Fermi contact term contribution to the coupling constant is small[567]. This is generally true if the nitrogen lone pair is in an orbital with considerable *s* character. A coupling close to zero is observed in nitroguanidine[568].

One-bond C–N couplings are observed in the hydrazo form of *o*-hydroxy azo compounds[569–571]. For a structure, see (**117B**). The magnitude varies with the percentage of hydrazo compound. Standard values can be obtained from 2-phenyl hydrazonopropanedinitriles and methyl 2-phenyl hydrazonocyanoacetates[572]. ^1J(C, N) ~ 6–8.6 Hz. Values obtained in phenylazoacetoacetamides are only half of the size[577] of the just mentioned compounds.

3. ^2J(N, C)

This type of coupling is greatly enhanced when the nitrogen lone pair lies *cis* to the terminal carbon (**110A**)[565,574]. The sign is assumed, but not determined. For similar compounds without an OH group, couplings of the same order of magnitude are obtained[575]. The effect can hence again be related to the lone pair.



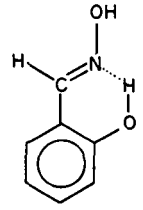
A **B**

(110)

4. Various coupling constants

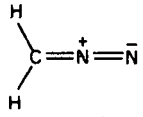
^3J(C, N, O, H) is observed in a hydrogen-bonded oxime[576] (**111**). ^1J(C=N, C_α) depends on the orientation of the OH group. The coupling constant is 8–9 Hz smaller in the *syn* than in the *anti* isomer. This difference is ascribed to the orientation of the lone pair. The situation is thus similar to that discussed for vinyl ethers (see Section II.B.4.b) although the lone pair in the oxime case must be in an sp^2 orbital.

^2J(H, C=N, H) of diazomethane (**112**) is 4.56 Hz. Theoretical calculations (INDO–SOS type including Configuration Interaction) show a good correlation with experi-



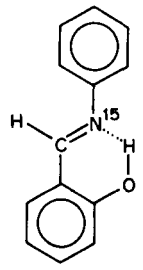
(111)

mental values for a series of compounds[577]. The sign of ^2J(H, C=N, H) is likely positive[577]. The magnitude is, however, fairly small, 4.56 Hz. ^2J(C, C=N, C) of benzilhydrazone is smaller than the corresponding coupling across a C=O bond[344]. Wasylishen and Schaefer[199] compared theoretical calculations regarding $^3J(C_{(3)}, H)$ of propionaldehyde and its oxime and the trend shown above is confirmed, although too large coupling constants are calculated.



(112)

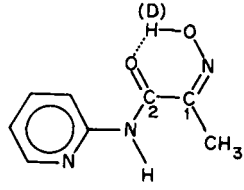
A coupling between the OH proton and the ^{15}N is observed in **113**. Temperature studies reveal that no tautomerism takes place[583].



(113)

C. Isotope Effects

Deuterium isotope effects at $C_{(1)}$ are observed in **144**[549]. Gurudata[555] found a positive deuterium isotope effect, 0.08 ppm at the C=N carbon of acetone-d_6 oxime. The sign is different from that observed in acetone (see Section III.C.1).



(114)

Isotope effects on ^{15}N are observed for the iminium ions of protonated enaminones using CF_3COOH and CF_3COOD as protonation reagents. The isotope effects are between -0.06 and 0.10 ppm[59].

A ^{15}N isotope effect is found at the OH proton in salicylideneaniline (**113**) when the aniline nitrogen is enriched. The effect is of the order of 5 ppb to low field[578]. Similar effects could be expected in hydrogen-bonded *o*-hydroxy ketones and aldehydes enriched with either ^{17}O or ^{18}O at the carbonyl oxygen, but no such effects have as yet been reported.

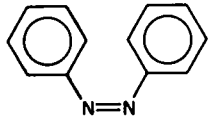
V. N=N DOUBLE BONDS

N=N double bonds are found in azo, but also azoxy and azodioxy compounds. Azo compounds containing an OH or an NH_2 group may take part in tautomerism. N=N groups are investigated by means of ^{15}N NMR spectroscopy.

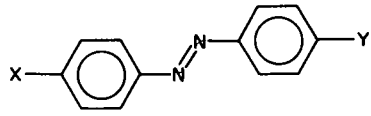
A. Chemical Shifts

Good reviews covering this field have been published[579–584]. Aromatic azo compounds (**115**) are probably the best investigated group of azo compounds. ^{15}N chemical shifts are characteristic for the azo bond and, again, a difference is observed for *cis* and *trans* compounds[584]. The chemical shifts are largely independent of solvent.

Substitution at the *p*-position causes changes in the chemical shifts of both the α and β nitrogens[585,586]. Substitutent effects are additive[587]. *Para*-substituted azobenzenes (**116**) show rather poor correlation with Hammett σ_p for N-α, but a resonable correlation for N-β[588]. No correlation is observed with σ_p in 4-fluoro derivatives[587].



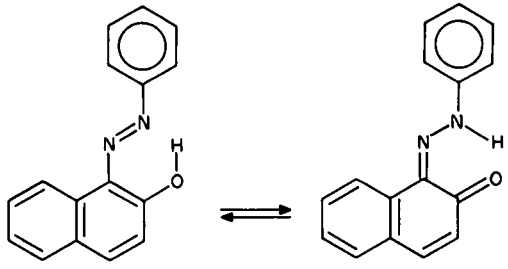
(**115**)



(**116**)

Witanowski and colleagues[583] suggest a DSP analysis. In the light of what was discussed in Section II.A.4, an analysis taking into account polarization effects would probably be appropriate.

Hydroxy substitution at the *o*-position leads often to tautomeric equilibria. ^{15}N chemical shifts are a very suitable way of determining the azo–hydrazo ratio[586,569,570] as the chemical shifts are very different for the two forms (**117**). The difference in ^{15}N chemical shifts of the azo form and of the hydrazo form is about 280 ppm. The azo–hydrazo equilibrium can also be determined from ^{13}C chemical shifts, especially in phenyl



(**117**)

substituted azobenzenes[569,570,586,589]. Other ^{13}C studies cover a large range of azo compounds[589–596]. ^{13}C NMR studies also include solid state studies[597,598]. Protonation of azo compounds leads to high-field shift of the ^{15}N chemical shift[599].

^{15}N chemical shifts of azoxybenzenes show only a minor difference between the N-oxide nitrogen and the other one, whereas both are shifted considerably to high field[579,600] compared to azobenzene. Fluorination of the benzene rings leads to a high-field shift[543].

^{17}O chemical shifts of azoxybenzenes are shifted downfield upon fluoro substitution at the benzene rings. CH_3 or CF_3 groups in the *p*-position have the same effects[543].

B. Coupling Constants

1. $^1J(N, N)$

One-bond nitrogen–nitrogen couplings in azo compounds have not been investigated intensively. A few examples are given below (see Figure 10).

From theoretical calculations, $^1J(N, N)$ is expected to depend on the presence of lone pairs and their mutual orientation[605,606]. A negative value is expected in the *trans* isomer, whereas a positive value is calculated for the *cis* isomer. However, a positive sign is found experimentally[607,608]. The discrepancy is explained by a large contribution from the orbital-dipole term, which was not taken into account in the original calculations. The fact that the Fermi contribution is small and that the orbital-dipole term plays an important role is similar to the picture seen for $^1J(N, C)$. It can be seen from the data of Figure 10 that $^1J(N, N)_{trans} > {}^1J(N, N)_{cis}$ (*cis* and *trans* refer in this context to the orientation of the

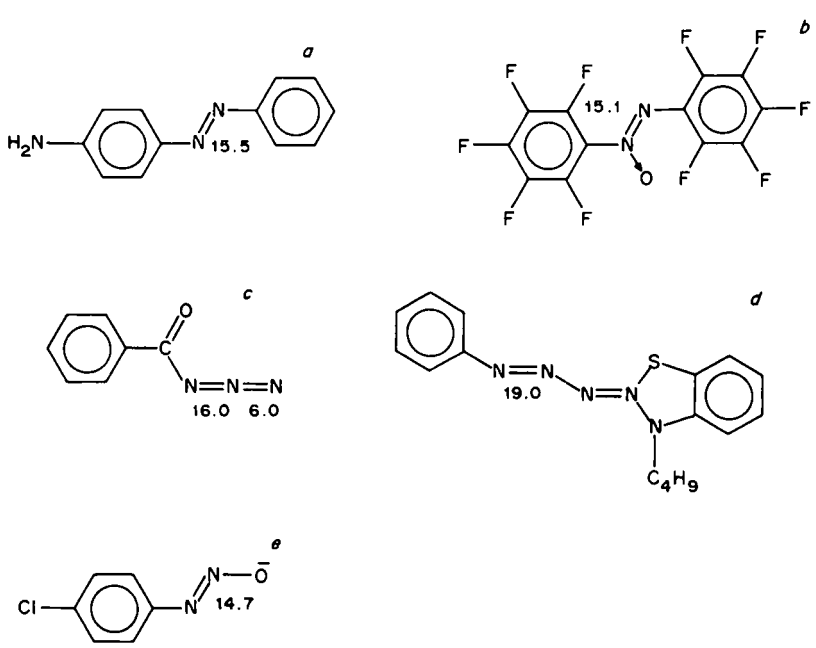


FIGURE 10. One-bond nitrogen–nitrogen coupling constants
[a]Taken from Reference 599. [b]Taken from Reference 601. [c]Taken from Reference 602. [d]Taken from Reference 603. The coupling constant is 13.2 Hz in the isomer in which the phenyl group is *cis*. [e]Taken from Reference 604

substituents). A larger *trans* than *cis* coupling is also observed in *p*-bromophenyldiazocyanide[609]. Further examples are given by Schultheiss and Fluck[610].

^1J(N, N) is used to determine the percentage of azo tautomer in azo–hydrazo tautomers[571,586,611].

2. ^3J(C, N=N, C)

The large three-bond carbon–carbon coupling constants observed across N=N double bonds[612], and larger than across C=C double bonds, have also been treated theoretically in order to elucidate the coupling mechanism. The calculations (INDO–SOS) reflect quite well the experimental trends, e.g. that ^3J is larger for azo than for azoxy compounds[613]. It is not quite clear from the experimental results if ^3J(C, N=N, C)$_{trans}$ is larger than ^3J(C, N=N, C)$_{cis}$. They seem to be of the same magnitude. The theoretical calculations show (Table 6) that ^3J(C, N=N, C)$_{cis}$ depends quite strongly on the rotamer distribution of the two methyl groups. Compound **2C**, which can be considered a pseudo-6π-electron system, gives the smallest coupling constant. This is contrary to calculations in the corresponding ethylene (II.B.3.) Protonation, which has not been studied experimentally, gives rise to a large decrease in the coupling constant, which is again dependent on the rotamer distribution since the 'through-space' coupling path is independent of the charge on nitrogen. In view of the decrease in ^3J(C, N=N, C) both for azoxy compounds and in the protonated azo compounds, it is concluded that the lone pair on nitrogen is essential for the transmission of the coupling. The double bond is likewise vital, as hydrazides show small ^3J(C, N, N, C) couplings according to calculations.

A large ^3J(C, N=N, C) is not observed in 1-phenylazo-2-naphthol nor in 2-phenylazo-1-naphthol, since both these exist mainly in the hydrazo form[589].

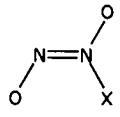
C. Isotope Effects

1. Intrinsic effects

$^1\Delta$(C, N) is observed in *cis*- and *trans*-azobenzene. In *trans*-azobenzene the effects are positive as expected[608], whereas they are reported to be negative in *cis*-azobenzene[614]. $A^1\Delta$(N, ^{15}N) is also observed in azo compounds and is positive[586].

Long-range deuterium isotope effects on ^{15}N chemical shifts are not observed in azobenzene[615].

^{15}N isotope effects on ^{14}N chemical shifts were determined for a series of compounds of the type shown in **118**. They are mostly positive in D_2O, but turn negative in CH_2Cl_2 at low temperature[610].



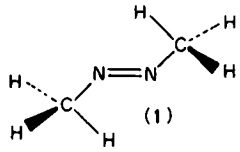
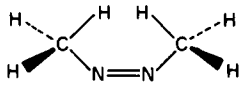
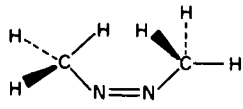
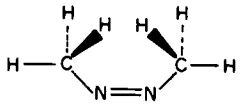
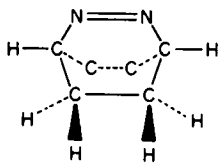
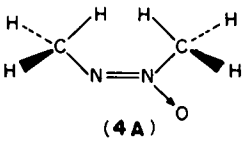
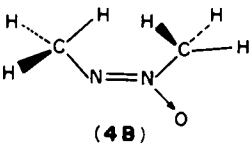
(118)

2. Equilibrium isotope effects

Equilibrium isotope effects are observed upon protonation of ^{15}N azobenzene. Protonation occurs ~ 5% more readily at the ^{15}N than at the ^{14}N atom. This fits the fact that the pK_a of ^{15}N is by 0.02 pK_a values larger than that of ^{14}N[608].

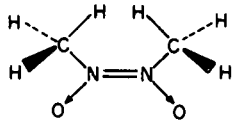
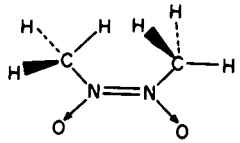
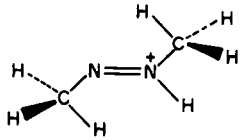
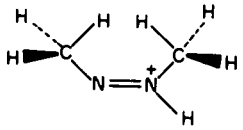
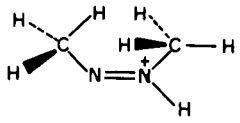
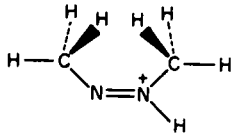
Another long-range effect is shown in **119**. Substitution of the β nitrogen with ^{15}N as

TABLE 6. ^3J(C, N, N, C) coupling constants of azo, azoxy and hydrazonium compounds

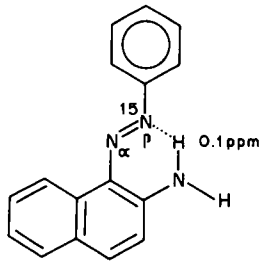
Compound	^3J(C, N, N, C)
 (1)	4.95
 (2A)	5.92
 (2B)	3.93
 (2C)	3.57
 (3)	8.35
 (4A)	1.89
 (4B)	0.92

(continued)

TABLE 6. (*continued*)

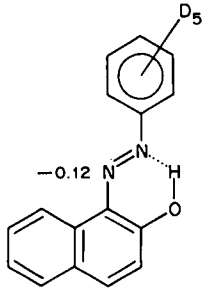
Compound	^3J(C, N, N, C)
 (5A)	2.04
 (5B)	1.40
 (6A)	1.35
 (7A)	3.05
 (7B)	1.66
 (7C)	1.48

shown in **119** leads to a 0.1 ppm low-field shift of the N—H proton. This effect is linked to the presence of a quadrupolar moment at the ^{14}N nucleus[616]. In view of what is observed for azobenzene, it seems that the ^{15}N atom forms a stronger hydrogen bond, which could lead to a low-field shift of the N—H proton.



(119)

Deuteriation of the hydroxy proton of *o*-hydroxyazo dyes may cause equilibrium isotope effects on ^{15}N chemical shifts (and ^{13}C chemical shifts). Very large effects are observed in 1-phenylazo-2-naphthol[617]. The isotope effects observed in these systems consist of two contributions, the intrinsic and the equilibrium part. The intrinsic part can be estimated. The very large isotope effect means that ^{15}N is a very sensitive probe in the determination of even very small changes of tautomeric equilibria caused, e.g., by remote isotopic substitution, as illustrated in **120**[615].



(120)

VI. ACKNOWLEDGEMENT

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The Chemistry of Double-bonded Functional Groups
Edited by S. Patai

CHAPTER **4**

The photoelectron spectroscopy of double-bonded CC, CN, NN and CO groups

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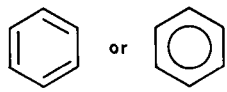
I. INTRODUCTION

It is always necessary to define one's topic precisely. Indeed, one should strive to provide the requisite amount of definition in the essay title and, given the above title, it would seem that such has been achieved. Certainly, with respect to the words 'photoelectron spectroscopy', no further elaboration is needed[1]. However, the term 'double-bonded' must give one some pause. Should one, for example, discuss all compounds in whose structural formula one is 'forced' to write a double bond? Or would it be better to concentrate on only those cases where photoelectron spectroscopy (PES) unequivocally indicates the presence of a double bond? These are not idle questions.

In PES, the presence of a double bond will always be indicated by a π-ionization, $I(\pi)$, event and, in the cases of CN, CO and NN groups, by a concurrent lone-pair ionization, $I(n)$, event. However, the recognition of $I(\pi)$ and $I(n)$ PES bands need not be obvious and, in fact, may be made quite difficult by the mutual interactions of doubly-bonded groups. In any case, chemical experience suggests that few examples of exactly double-bonded groups exist. That is, one must be wary. We will illustrate the need for caution (and for further specificity) using benzene as an example.

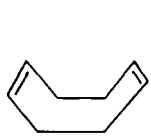
Benzene is usually formulated diagramatically in one of two ways,



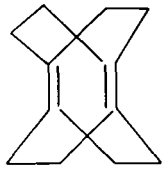
One formulation suggests the presence of three double and three single bonds; the second, the presence of six 'one and one half' bonds. The fact that even this latter interpretation of the rightmost representation has been questioned[2] highlights the conceptual problem of a 'double bond': the three observed $I(\pi)$ bands of benzene [better two, since two of the $I(\pi)$ events are degenerate] are equally well interpretable on the basis of the interaction of the π-group orbitals of three C=C groups or the six C2p_z 'atomic' orbitals of six carbon atoms. Since we deem it best to avoid this sort of dialectic (and, in the process, circumscribe the breadth of this essay) we will disavow any discussion of conjugated molecules and religiously restrict our attention to compounds either with only one double bond or with multiple so-called 'isolated' double bonds. We do recognize that any discussion of the latter type of molecule will inevitably demand a discussion of the concepts of 'through space', or homoconjugative (TS), and 'through bond', or hyperconjugative (TB), interactions[3], as well as various other special types of conjugations[4] (e.g. homoconjug-

ation[5], spiroconjugation[6], circumannular conjugation, etc.) that are deemed necessary in order to provide a proper account for the experimental fact that double bonds 'feel' their surroundings (i.e. their atomic environment in the molecule in question) and, in particular, the presence of other double bonds in the same molecule.

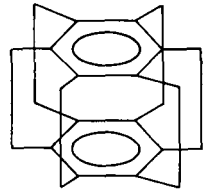
The discussion of such interactions is facilitated by simple orbital pictures. Indeed, the necessary conditions for the significance of these interactions in a particular molecule (i.e. proper symmetry, similar energy and proximity of interacting units) are easily elaborated and understood. Beautiful examples of the strong interplay of TS and TB interactions have been presented by Heilbronner and coworkers[7] for the $I(\pi)$ bands of 1, 5-cyclooctadiene (COD) and tricyclo[4.2.2^{2,5}.2^{1,6}] dodecadiene-1(2), 5(6) (TDD) which, surprisingly, have been found to have very similar $I(\pi)$ PES signatures. Thus, even though TS interactions in TDD split the π_+ and π_- orbital combinations by more than 3 eV, since the TB coupling of a_g states (to which the upper π_+ combination belongs) via the $-CH_2CH_2-$ bridge is symmetry forbidden, only the energy of the lower π_- combination is affected and, as a result, π_- is raised energetically and becomes almost degenerate with the π_+ MO. It is not surprising that this same phenomenon of forbidden hyperconjugation is also observed in the cyclophanes[9], since TDD is the ethylene analogue of superphane to which the cyclophanes are related.



COD



TDD



Superphane

In sum, the understanding and the experimental validation of such simple models is of great importance to the development of theoretical models of chemical compounds and their properties. PES has played a seminal role in proving the validity of many such approaches to electronic structure concepts that are useful in the interpretation of diverse chemical properties. Consequently, we will pay some attention to them in this essay.

II. PHOTOELECTRON SPECTROSCOPY (PES)

Photoelectron spectroscopy discriminates the energy and counts the number of electrons released from a system as a result of the interaction of light with that system. This technique, under heavy development for the last thirty years, is now applicable, using obligatory high vacuum conditions that prevent re-absorption and scattering of the photoelectrons, to solid, liquid and gaseous systems. The incident photons of ultraviolet or X-ray radiation produce photoionization events and a consequent photoemission current associated with the ionization of valence and core electrons, respectively. If the photon energy exceeds the ionization energy, the surplus excitation energy is transferred as kinetic energy to the ejected electron. Methods which measure this excess energy are known as UV and X-ray photoelectron spectroscopy (UPS and XPS), respectively. A plot of the excess kinetic energy, E_k, against the number of photoelectrons is a photoelectron spectrum. When the photon energy is obtained by tunable laser or monochromatized synchrotron radiation and is exactly equal to the ionization energy, the photoelectrons escape with zero kinetic energy. A count of these electrons as a function of the photon

energy around the threshold point characterizes threshold photoelectron spectroscopy (TPS).

The roster of ionization energies, E_i (or I, or the ionization potentials, I_p, or the electron binding energies, BE) is a set of characteristic physical parameters of the illuminated sample. The values of I_p are related to the discrete quantum levels that describe the motions and interactions of the system electrons prior to their photoejection. In order to determine the value of I_p by PES, the kinetic energy E_k of the ejected photoelectrons must be measured. For gas-phase samples, the pertinent equation is

$$I_k = h\nu - E_k; \quad k = 1,2\cdots,w; \quad I_w < h\nu$$

where I_k is the k-th ionization potential, $h\nu$ is a *fixed* incident photon energy and E_k is the excess kinetic energy of the photoelectron. In the MO picture, these photoelectrons are supposed to be ejected from specific electronic orbitals of the molecular (or atomic) ground-state configuration, each such non-degenerate orbital being occupied by two electrons of opposite spin (Figure 1a). If the photoelectron generation process is a single-event, the UPS and XPS processes in this single configuration picture are represented by the MO diagrams of Figure 1b and c, respectively. Provided that some inherent approximations are satisfied[10], namely that

(i) discussion is restricted to vertical ionization events,

(ii) the correlation and relaxation energies happen to be zero or to compensate each other.

(iii) the non-relativistic approximation is appropriate, and

(iv) discussion is restricted to closed-shell systems,

such processes follow the dictates of Koopmans' theorem. This very desirable state of affairs implies that there is a mapping of the MO energies onto the ionization potentials and that this mapping is isomorphic. We will use this implication widely but cautiously in dicussing the gas-phase UPS spectra of molecules with double-bonded groups.

Photoemission, however, need not consist solely of such simple single-event processes. For example, electron excitation can accompany electron ejection (shake up); two electrons can be ejected simultaneously (shake off); a second electron can subsequently be ejected from the ion produced in XPS (Auger process); a Rydberg electron can

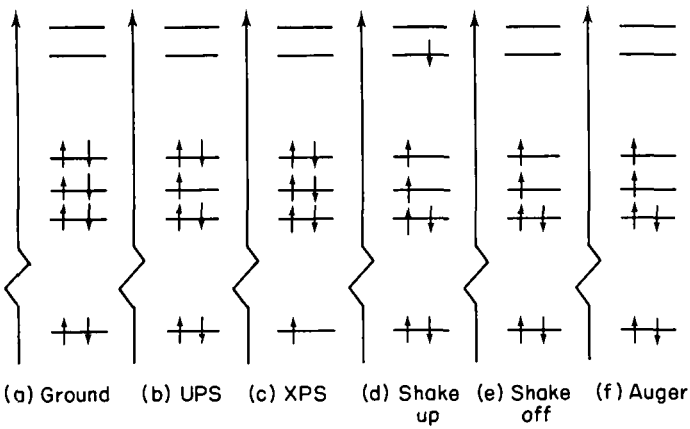


FIGURE 1. Ionization processes (a)–(f) in the single configuration approximation. Simple MO electron configuration pictures of molecular or atomic ionization processes. The ground state of the system is schematized in (a)

simultaneously enter a lower energy level (shake down); etc. Generally, the probability of such processes increases with the incident photon energy and is greater in dense solid and liquid samples.

In the case of solid samples, the specimen and the spectrometer must be electrically interconnected in order to equilibrate the Fermi level of the entire system of specimen and spectrometer. Under these conditions, the measured value of E_k is related to the energy E'_k at the surface of the specimen by

$$E_k = E'_k + \phi_s - \phi_{sp}$$

where ϕ_s and ϕ_{sp} are the specimen work function and the spectrometer work function, respectively. The pertinent equation is then

$$I^F = h\nu - E_k - \phi_{sp}$$

where I^F is the binding energy relative to the Fermi level. Consequently, when ϕ_s can be determined, we have

$$I = I^F + \phi_s$$

where I is the standard ionization potential referenced to vacuum. Because of experimental restrictions relating to the inherent bandwidth of X-ray sources, the resolution and, hence, the accuracy of these measurements may be an order of magnitude lower than those for the gas phase and/or ones which use UV photons.

In the case of liquid samples, the biggest problem is the maintenance of the pressures in the spectrometer at sufficiently low levels ($< 10^{-4}$ torr). Techniques developed by Siegbahn and coworkers[22,38] which continuously replenish the liquid source in the form of a free jet or a thin flux carried on a translating wire, and in which efficient differential pumping between the sample chamber and analyzer permit adequate sample usage, suffice for the measurement of relatively non-volatile liquids (e.g. formamide) and solutions in them.

Unlike UPS, the ionization processes measured by the XPS (or ESCA, Electron Spectroscopy for Chemical Analysis[1a,b]) method must be referenced to a final state in which the electron reorganization produced by the creation of a deep, positive, core hole may be extensive. To be specific, the surrounding electrons may start to fill the core hole during the process of the photoelectron escape and, since the hole fillers are also negatively charged, they make photoelectron escape that much easier. Consequently, somewhat lower ionization energies are observed. XPS has proven to be very useful in elucidating the gross electronic properties of molecules. The shifts of the inner-core electron energies (ESCA chemical shifts) are closely related to the formal atomic charges in the molecule[11] and, thereby, to other properties observed by NMR or Mössbauer spectroscopy, to proton affinity, etc. The full *ab initio* theoretical treatment of an ESCA chemical shift requires a ground state calculation for the compound and a hole-state calculation of the molecular ion that is produced by the photoionization act. In a model in which the electrons of the molecule are described by orbital wave functions (i.e. the independent particle model), the basic theory of XPS processes is well understood[12]. The ionization of a core orbital produces a main line which, because of the inadequacy of the independent particle model, is sometimes accompanied by satellite lines. However, if creation of the core hole leads to such strong charge transfer that shake-up energies may become small or even negative, even a quasi-particle picture may break down. In such cases (e.g. *p*-nitroaniline), it is not possible to identify any line as the main line and the concept of chemical shift becomes devoid of meaning[13]. However, the great majority of XPS results is not subject to such limitations. On the contrary, and perhaps because of the low resolution of XPS, even very simple computational approaches work surprisingly well and provide good correlation with experiment[14,15].

III. BONDING CHARACTERISTICS AND NOMENCLATURE OF DOUBLE-BONDED GROUPS

Much of the richness and variety of organic chemistry is attributable to the ability of carbon and nitrogen to form multiple bonds with themselves, with each other and with a variety of other atoms. The existence of such compounds was a major conundrum to chemists of the 19th century, and certainly slowed down the development of a modern chemical notation. Indeed, it was only in 1861 that the first graphic notation of a multiple bond, as represented by a corresponding number of lines connecting atomic symbols, was introduced by A. Crum Brown[16]. Thanks to Brown, we now can define the object of our essay to be a discussion of the double-bonded combinations C=C, N=N, C=N and C=O. These four double-bonded groups differ in many regards, the reason being the very different electron configurations pertinent to the four atoms. Nonetheless, a very simplified picture is adequate to the task of providing a vocabulary that can deal with a variety of PES results.

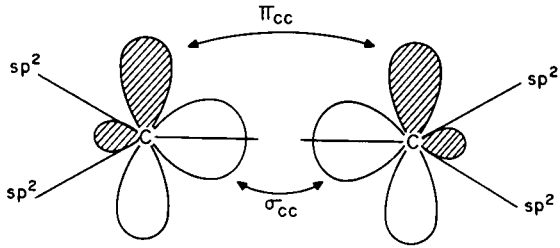
Each of the atoms of carbon, nitrogen and oxygen has two core 1s electrons ($1s^2$-core configuration), but four, five and six valence electrons, respectively. Thus in forming double bonds, while we expect practically no core changes, we must come to grips with the following quite different valence electron configurations:

Carbon: three hybrid orbitals of a rough sp^2 composition, Csp^2, and one $C2p_z$ orbital; each orbital occupied by one electron.

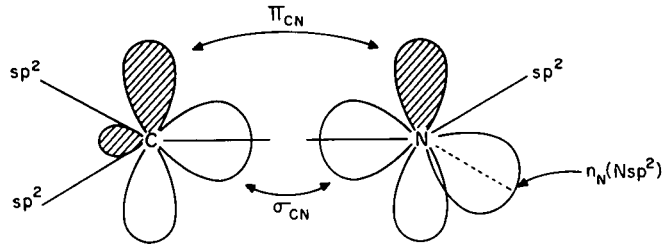
Nitrogen: two Nsp^2 hybrid orbitals and one $N2p_z$ orbital, each occupied by one electron; and one Nsp^2 hybrid orbital occupied by two electrons, also referred to as the nitrogen lone pair, n_N.

Oxygen: $O2p_x$ and $O2p_z$ orbitals, each occupied by one electron; and the two remaining O2s and $O2p_y$ orbitals, each occupied by two electrons, also referred to as the oxygen lone pairs $2s_O$ and n_O. The reason we do not expect hybridization in oxygen is attributable to the large s/p splitting in this atom.

The C=C double bond, therefore, may be visualized as a composite of (i) a single CC bond, σ_{CC}, formed between the two Csp^2 hybrids, and (ii) a π_{CC} bond formed by the overlap of the two spatially aligned $2p_Z$ orbitals. The two remaining Csp^2 orbitals, one on each of the two carbon atoms, are available for bonding with four other atoms or groups.

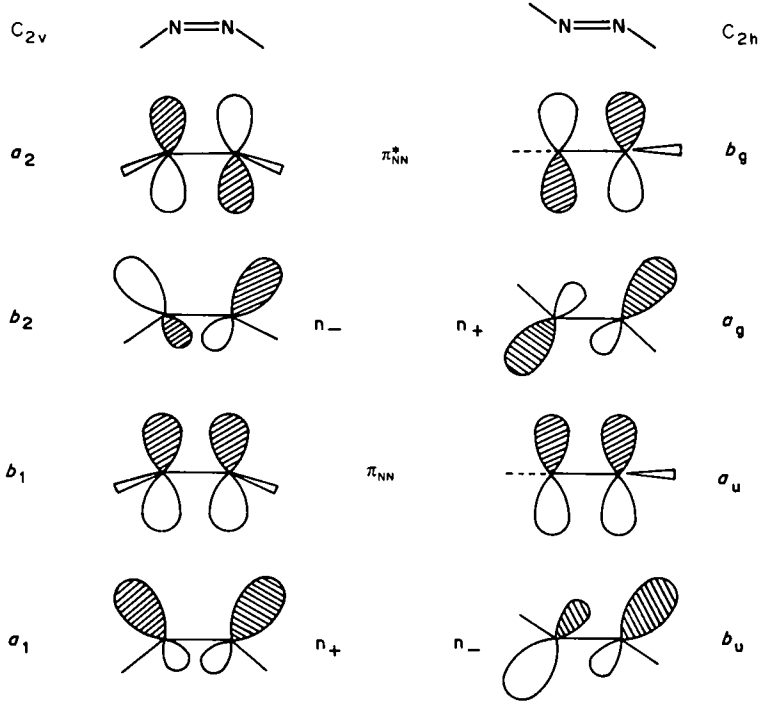


The C=N double bond consists of (i) the single σ_{CN} bond between the sp^2 orbitals on carbon and nitrogen, and (ii) the π_{CN} bond formed by the overlap of the spatially aligned



$2p_z$ orbitals. Three sp^2 hybrid orbitals, two on carbon and one on nitrogen, remain available for bonding with other atoms or groups. One sp^2 orbital on nitrogen is occupied by two electrons that remain non-bonding and which are known as the nitrogen lone pair, n_N.

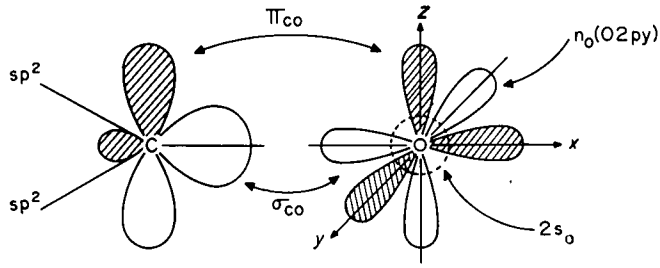
The N=N double bond consists of one bond between the two Nsp^2 hybrid orbitals and another between the two $N2p_z$ orbitals which form the σ_{NN} and π_{NN} bonds, respectively. However, since there are now two lone-pair orbitals, one on each N atom, these may interact to produce n_+ and n_- non-bonding combinations. The situation is also complicated by the two possible mutual conformations of N=N derivatives, which arise from restricted rotation around the double bond. The resultant *cis* and *trans* isomers possess symmetry C_{2v} and C_{2h}, respectively. According to group theoretical convention, the lowest-energy antisymmetric combination of the n_N orbitals in C_{2v} symmetry (i.e. the *cis* isomer) is termed n_- whereas in C_{2h} symmetry (i.e. the *trans* isomer) it is known—a convention that begets some little confusion—as n_+. Thus Scheme 1 arises. The property of prohibited rotation around double bonds is very important to the chemistry of C=C, C=N and N=N derivatives. On the one hand, it defines the existence of *cis* and *trans* isomers and, on the other, it bears on the energetics, stereochemistry and mechanism of isomer formation and, since 'prohibited' does not mean 'impossible', also on their interconversion. PES has played an important role in providing insight into these latter problems.



SCHEME 1

The C=O double bond, in this simplified picture, is a composite of (i) a $Csp^2/O2p_x$ bond that yields σ_{CO} and (ii) a $C2p_z/O2p_z$ bond that yields π_{CO}. In addition, the two non-bonding electron pairs, the high-energy $2s_O$ ($I_p \sim 30$ eV) and the low-energy n_O ($I_p \sim 10$ eV) generally remain such (i.e. non-bonding) in the various monocarbonyl derivatives that are

formed when the remaining two Csp^2 orbitals are used to bond additional atoms or groups.

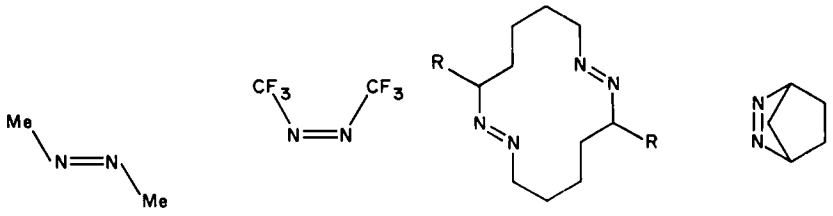


Despite the fact that these descriptions of double bonding account adequately for structures and chemical properties, a review of the PES data for these groups and their derivatives suggests that only the π and lone-pair ionizations, $I(\pi)$ and $I(n)$, fulfill the requirement of group specificity. In other words, their presence in PES indicates the indisputable presence of the corresponding double-bonded group. The core 1s, as well as the normal σ-ionizations, have properties that relate better to their atomic parentage or to the molecular topology, respectively, than they do to their bonding characteristics. This happenstance does not mean, however, that proper refinement and manipulation of these PES data cannot provide sensitive probes into the details of the double bond in question.

Disregarding C_2, a molecule important in interstellar space but of disputable bond order[17], the simplest representative of compounds with a C=C group is ethene (ethylene), which is also the simplest alkene or olefin. Since the location of the C=C group is of some importance for UPS (and chemical) properties, we subdivide the non-cyclic alkenes into those containing terminal (—CH=CH_2), peripheral (> C=CH_2) and central (all others) double bonds; and the cyclic into those with endo-, exo-, intra- and inter-cyclic double bonds. All other classes of compounds containing a C=C group can be considered to be substituted ethylenes. They can be non-cyclic or cyclic and they may be considered to be either unsaturated hydrocarbon derivatives (alcohols, amines, etc.) or heterocyclic compounds. Heteroatoms, when either attached to or properly oriented with respect to the C=C group, can interact with that group because of their differential electronegativity (inductive effects) and their lone-pair electrons (conjugative effects, π-back donation), and these interactions will be reflected in PES. The resemblance of some such interactions to those between two C=C groups has led, in some cases (e.g. the aromatic heterocycles), to a postulate of spectral equivalency for an S atom and a CH=CH group.

The simplest C=N double-bonded compound is methanimine, CH_2=NH. According to IUPAC nomenclature[18], only compounds with NH grouping are imines. These imines may be either non-cyclic or exo-cyclic. Substitution at the nitrogen centre leads to the class of azomethines. However, since (X, Y)C=NZ can readily be obtained from carbonyls (X, Y)C=O and amines H_2NZ, various other classes of pertinent compounds (e.g. hydroxylamines, hydrazones, phenylhydrazones, etc.) can exist and these may be non-cyclic. exo-cyclic or endo-cyclic.

The simplest N=N double-bonded compound is diazene (or diimine), HN=NH. The class of XN=NY compounds, most of them symmetrically substituted (i.e. X = Y), have been known[19] since 1856. They may appear as *trans* or the usually less stable *cis* forms and be non-cyclic or cyclic. The *cis* bond lengths in the azo group are practically equal in the aromatic and aliphatic azo compounds: N=N is 1.23 Å in both azobenzene and azomethane; and C—N is 1.46 Å in azobenzene and 1.47 Å in azomethane, which is also the length of a resonance-free C—N bond[20].



trans *cis* *trans* *cis*

Formaldehyde, $H_2C{=}O$, is the simplest compound with a carbonyl group. This group is an essential part of several classes of very important molecules such as aldehydes, ketones, carboxylic acids and their derivatives (e.g. esters, halogenides, amides etc.) Compounds of composition (X, Y)C=O may be viewed as derivatives of carbonic acid, a compound not yet investigated by PES.

IV. XPS OF DOUBLE-BONDED GROUPS

The available XPS results can be divided into those concerned with core electrons, valence shell electrons and simultaneous core and valence observations. Gaseous, liquid and solid samples have been studied. A great deal of work is available for small molecules adsorbed on well-defined metal surfaces, the driving force being the importance of the catalyzed transformations of double bonds for many old and some new chemical, industrial processes. An attempt to unravel the complexities of the methanation process was made by Worley and coworkers[21] in an XPS study of formaldehyde, CO, CO_2 and O adsorbed on the W (100) face of a tungsten single crystal. However, they detected no surfacial or gaseous intermediate that could be uniquely tied to the CH_4 product.

ESCA diffraction patterns[22] can be generated from the angular distributions of the photoelectrons released from core levels. One may either record the angular distributions at various small surfacial angles ($\theta < 20°$) at a fixed X-ray energy or one may work at a fixed angle and vary the radiation wavelength (i.e. use synchrotron radiation), and obtain the same information. It is likely that such ESCA diffraction patterns for adsorbed molecular surface layers will be a topic of extensive study[23,24].

The use of monochromatized synchrotron radiation for XPS is a burgeoning business. Such measurements provide better and more reliable cross-sectional dependencies for photoionization efficiency as a function of excitation energy than do those using multiple discrete line sources. Such dependency is shown in Figure 2 for various orbitals of a carbon centre. The complementary method of photoionization mass spectrometry using synchrotron radiation[24] is also developing rapidly.

The main goal of ESCA is the determination of chemical shifts from measurements of

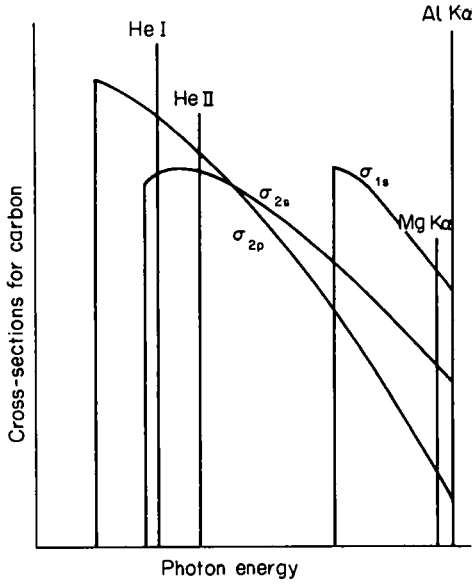


FIGURE 2. Theoretical variation of cross-section for photoionization as a function of energy for sub-shells of carbon.

the binding energies of core electrons, the use of these shifts to identify the chemical environment of particular atoms and, thence, to deduce the molecular and electronic structure of the system in question. The main cause of the chemical shift is the change of the atomic charge on the centre from which the photoelectron issues, a change that is dictated by the electronegativity of atoms attached to that centre. Attached hydrogen atoms, for example, are essentially ineffective in producing chemical shifts, whereas attached fluorines are very effective. Thus, the C(1s) shift between CH_4 and CF_4 is approximately 11 eV (see Figures 3a and 3b). However, by virtue of the H-atom insensitivity, in many instances in which sensitivity would be of gross advantage, it does not exist. For example, the chemical shifts for ethane (− 0.2 eV), ethylene (− 0.1 eV) and acetylene (+ 0.4 eV)[25] are shown in Figure 4. These compounds are prototypes for single, double and triple carbon–carbon bonds and it is clear that the ESCA data are hardly discriminatory. On the other hand, the N(1s) spectra of Figure 3b are highly discriminatory. While the binding energy does tend to increase as one proceeds from sp^3 to sp hybridization states, the effect is so small as to be detectable only at very high resolution. The best resolution now available in XPS is illustrated in Figures 5a and 5b. The highest resolution is generally available in gas-phase spectra. Consequently, it is not surprising that ESCA cannot discriminate ethylene and acetylene when they are adsorbed on a metal surface[26]. There is, however, a small dividend: the area of the ESCA peaks is found to be proportional to the number of adsorbed molecules. Thus, as shown in Figure 6, acetylene is adsorbed more on cobalt (by 40%) than is ethylene.

Carbon, nitrogen and oxygen 1s shifts have been determined for numerous compounds[1a,b,j-m,27]. The characteristic values for C, N and O are C(1s) ~ 300 eV, N(1s) ~ 400 eV and O(1s) ~ 530 eV. It is clear from the above references that it is not the type of compound but rather the intimate atomic surroundings (neighbours) that determine the

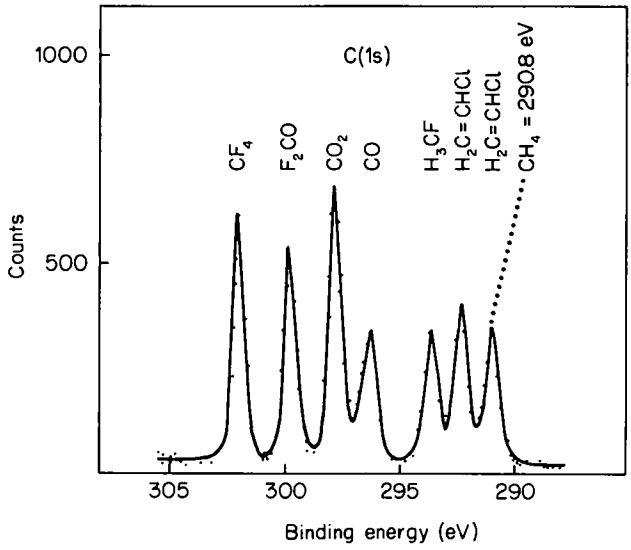


FIGURE 3a. C(1s) ESCA bands in a gas mixture of CF_4, F_2CO, CO_2, H_3CF and $H_2C{=}CHCl$. The location of the C(1s) band of pure, gaseous CH_4 is also shown

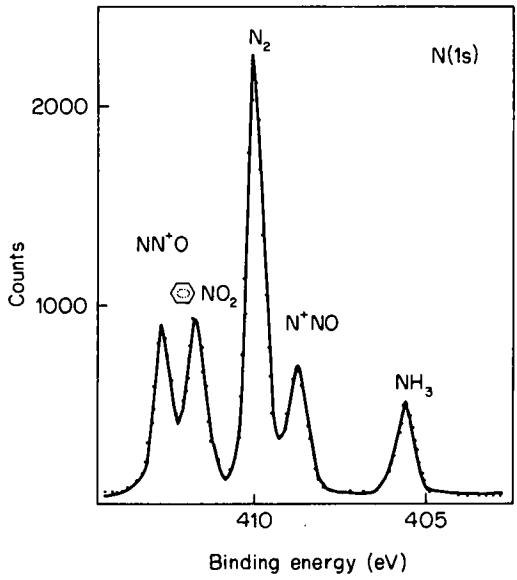


FIGURE 3b. N(1s) ESCA bands in a gas mixture of N_2O, nitrobenzene, N_2 and NH_3

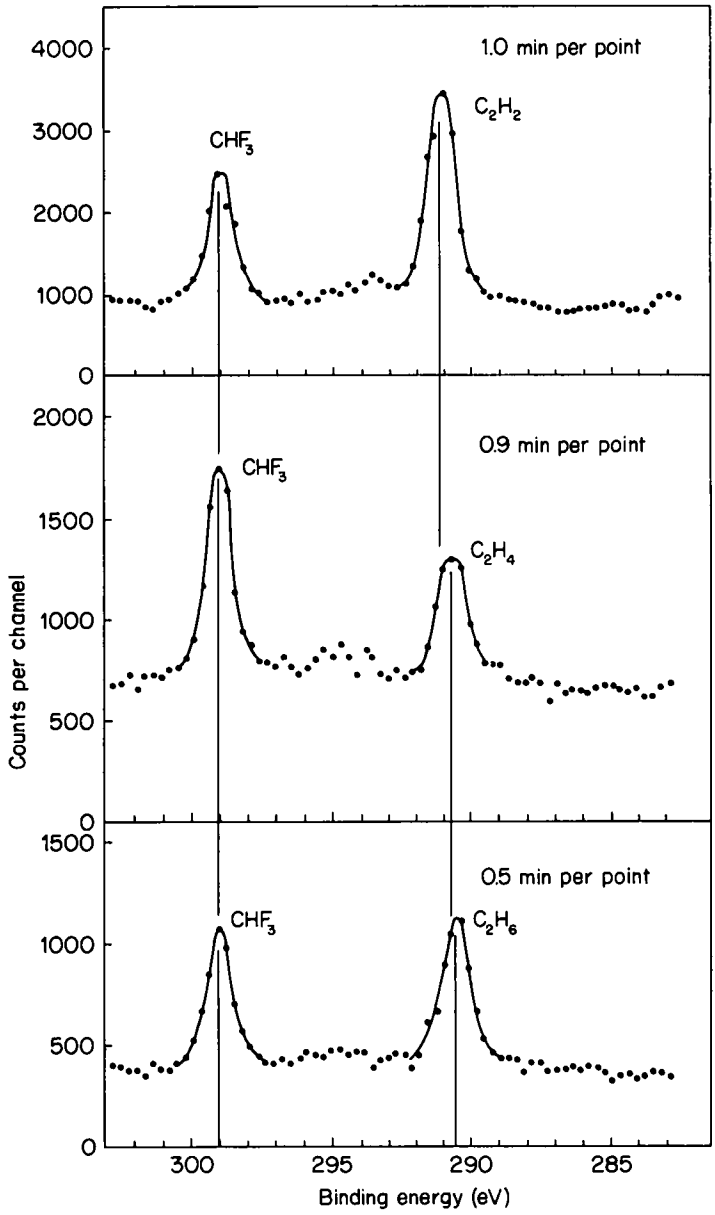


FIGURE 4. Spectra of the carbon 1s electrons of acetylene, ethylene and ethane relative to fluoroform. Radiation is magnesium $K\alpha$ X-rays. From Reference 25

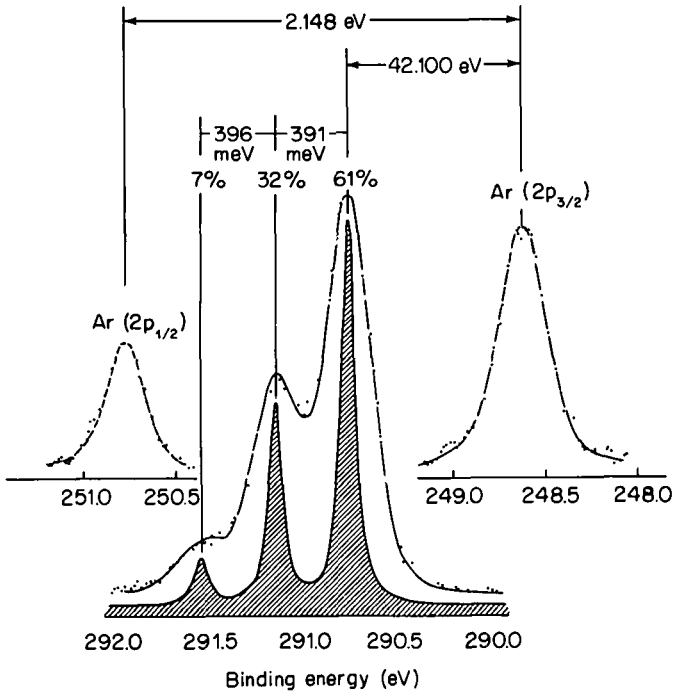


FIGURE 5a. Core vibrational components of C(1s) of gaseous methane at high resolution. Argon calibrations are also shown

chemical shift. This short-range dependency of the chemical shifts makes the discrimination of elaborate linkage isomers possible in polymers[28]. In Figure 7, the O(1s) and C(1s) core level spectra of poly-n-hexylmethacrylate and polyphenylmethacrylate are shown. The characteristic doublet of O(1s), essentially the same band profile for both compounds, and the C(1s)/O(1s) areal ratios permit one to determine the stoichiometries of the repeat units (i.e. two types of oxygen and C_6 side-chain). However, a distinction between these two C_6 derivatives is possible only because of the appearance of a shake-up satellite band (*vide infra*) that characterizes the unsaturated side-chain.

While an increase in resolution does produce some relief for the lack of discrimination inherent in the insensitivity of core level excitations to bonding properties, particularly to double bonds, this relief is inadequate. Some surcease is provided by some other physical parameters associated with the photoionization process. The satellite structure on C(1s) ESCA spectra is one such discriminant. Satellite structure occurs because of the presence of shake-up processes. It has been noted[29] that the solid-state XPS spectra of unsaturated compounds exhibit a sharp satellite peak that appears close (5–10 eV) to the main C(1s) excitation peak. This satellite peak has been assigned to a $\pi\pi^*$ shake up and it has been correlated for different series of molecules as a function of substituents. Later gas-phase measurement by Banna and Shirley[30] and Carlson and coworkers[31] established the assignment and also revealed additional parts of a satellite band corresponding to the excitation of σ orbitals. The ESCA spectra of ethylene, propene, 1-butene and propane are shown in Figure 8. The $\pi\pi^*$ shake-up intensity decreases as the chain length gets smaller.

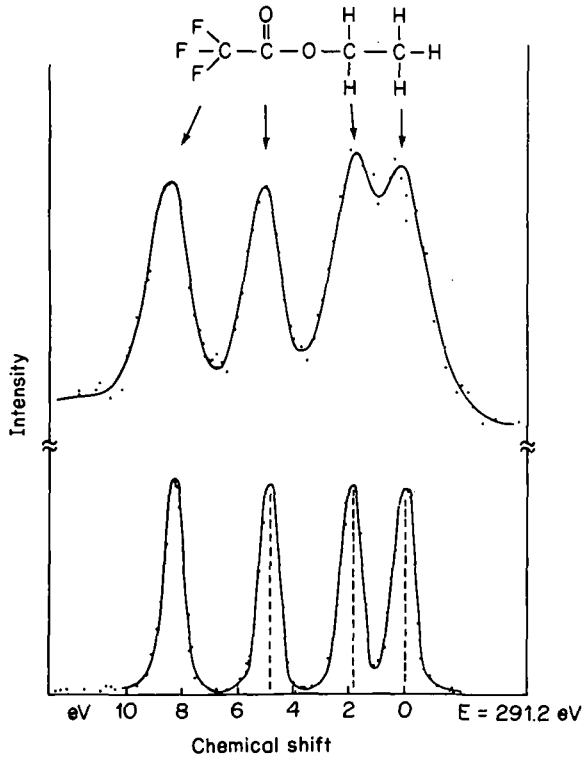


FIGURE 5b. C(1s) ESCA shifts for four different carbons

In butadiene, which contains two double bonds, two $\pi\pi^*$ satellite peaks appear. Indeed, in principle, the method may possess the ability to count the number of double bonds.

Cederbaum and coworkers[32] have suggested another approach, namely the measurement of the spectra associated with creation of double core vacancies instead of the single core vacancies sensed by conventional XPS. Such two electron/one photon processes were detected quite recently in inert gases, cross-sections being very low. If such measurements are feasible for molecules, since the two core holes need not be localized on the same atoms, Cederbaum and coworkers predict that considerable splitting of the C(1s) spectra of carbon atoms involved in different kinds of bonding should occur, the primary source of discrimination residing in differences in the relaxation energies. The Cederbaum ideas are schematized in Figure 9.

Unlike core electron spectroscopy, valence electron spectroscopy can generate information about molecular orbital constitutions because the 2s and 2p orbitals exhibit a large cross-sectional dependence on incident radiation energy (Figure 2). In CH_4, for example, Hamrin and coworkers[33] have shown that the removal of electrons from the $2a$ orbital (mostly C2s) is 3–4 times more efficient than removal from the $1t_2$ orbital (mostly C2p) even though there are three times as many electrons in the latter. Banna and Shirley[30] studied gaseous ethylene using HeI (21.2eV), HeII (40.8eV); Y Mξ (132.3eV) and Mg $K\alpha$ (1253.6eV) photons. The outer four orbitals exhibit very low intensity at 1253.6eV

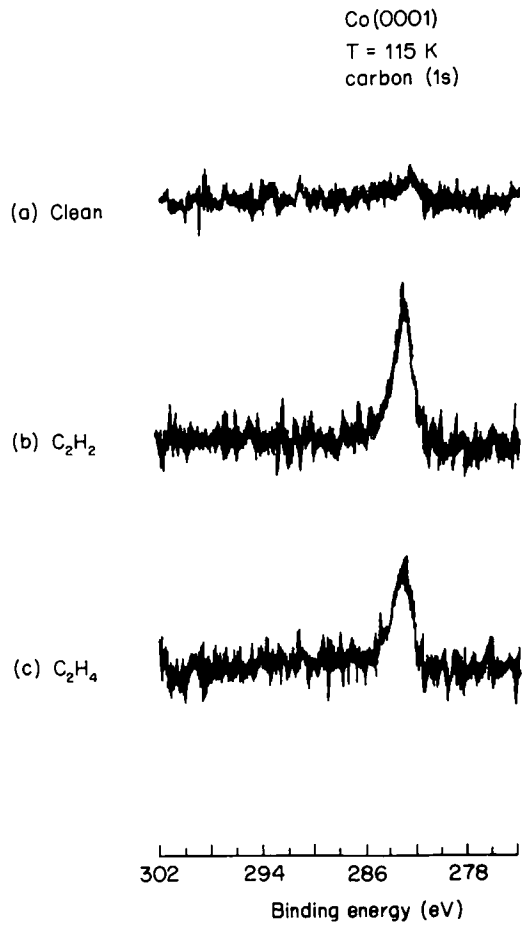


FIGURE 6. C(1s) ESCA spectra for acetylene and ethylene absorbed on a cobalt surface, Co(0001), at 115 K

excitation because they are predominantly 2p in character, nor do they change much in going from a HeI to a HeII excitation. A compilation of results for ethylene is tabulated in Table 1. The use of synchrotron radiation is of great advantage relative to standard line sources. In such a recent study, Brennan and coworkers[35] determined the relative partial photoionization cross-section and photoelectron branching ratios of the valence bands of ethylene up to photon energies of 100 eV and have been able to deduce, by comparison of experiment and *ab initio* calculations, the percentage atomic orbital parentage of the valence MOs (Table 2).

Many fundamental chemical properties (e.g. acidity, basicity, ionization energy, hydrogen bonding ability, the rates of acid–base catalyzed reactions, etc.) depend on the ability of a molecule to accept charge at certain sites. Discussions of this topic have usually been couched in the language of field and resonance effects and correlations have usually invoked Hammett σ parameters. Latterly, however, the emphasis has shifted to the roles played by the initial state charge distribution and the final state charge rearrangement. For

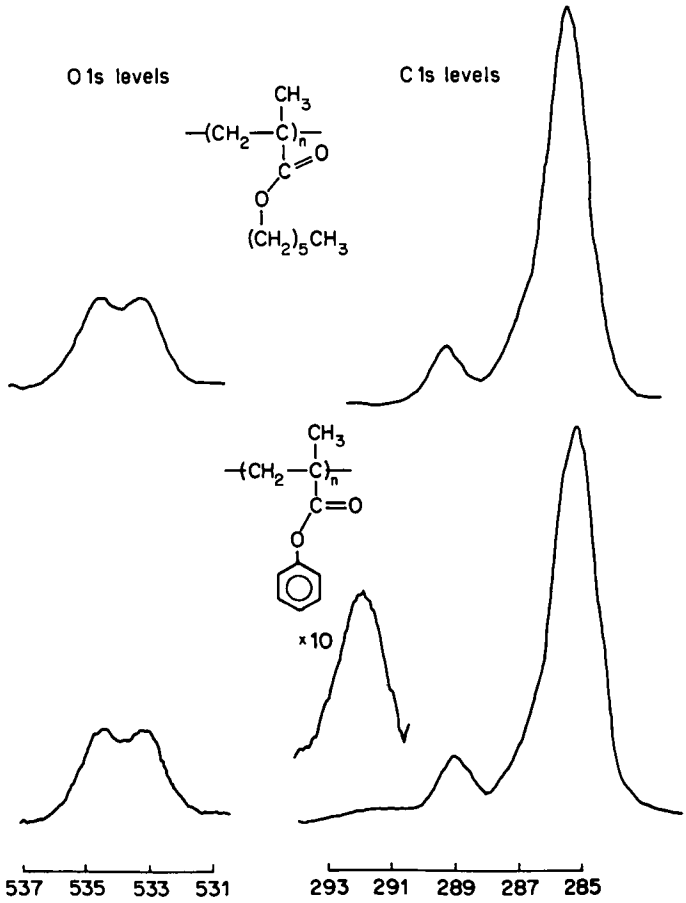


FIGURE 7. Core level spectra for poly-n-hexyl- and phenylmethacrylates showing low-energy shake-up structure for the latter

TABLE 1. Results for ethylene

Orbital	I (eV)	Differential photoionization cross-section ratios			
		21.2 eV[a]	40.8 eV[a]	132.3 eV	1253.6 eV
$1b_{1u}$	10.51	0.9	0.9	0.9	0.05
$1b_{1g}$	12.85	1.31	1.12	0.6	
$3a_g$	14.66	1.41	1.33	2.4	0.35
$1b_{2u}$	15.87	0.89	1.02		
$2b_{3u}$	19.23	0.20	0.21	1.2	0.93
$2a_g$	23.65		0.24	1.0	1.0
MO shake up	27.39			0.2	0.39
$1a_g 1b_{3u}$	290.7				70
Core shake up	299.10				10

[a]From Rabalais and coworkers[34]; these authors also give theoretical cross-section ratios

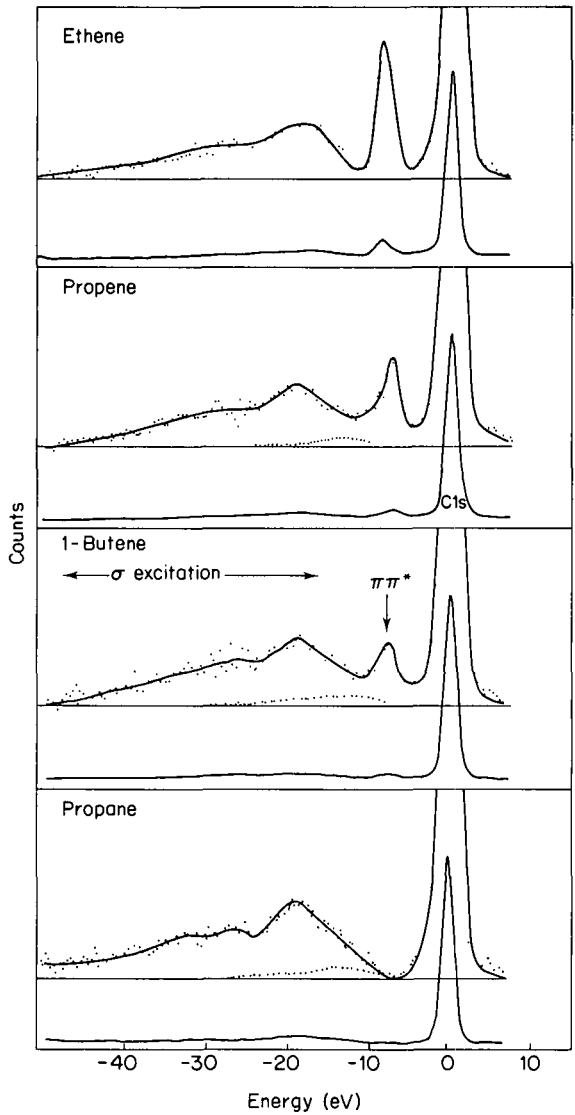


FIGURE 8. Photoelectron spectroscopy of some alkenes and propane, showing the satellite structures plotted as a function of kinetic energy relative to the main peak, Mg $K\alpha$ X-rays (1254 eV) were used as a photon source. The spectra are plotted with the height of the main peaks approximately equal. To help view the satellite structure, the plots are also blown up by a factor of 10. Dotted curves give the contribution of characteristic energy losses

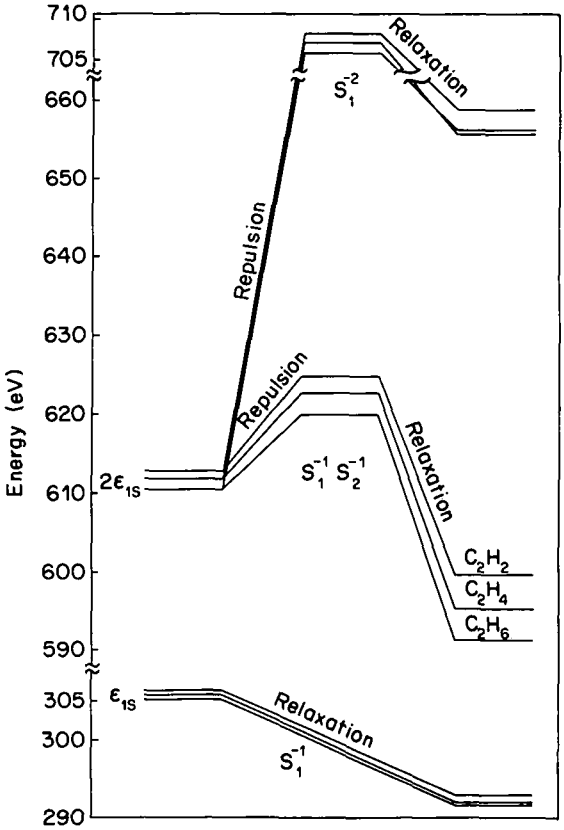


FIGURE 9. The various contributions to the energy needed to create a single core vacancy S_1^{-1} and double-core vacancies S_1^{-2} and $S_1^{-1}S_2^{-1}$, where two core holes are at the same and at different atomic sites, respectively. The carbon core orbital energies ϵ_{1s} and the repulsion and relaxation energies for C_2H_2, C_2H_4 and C_2H_6 are shown. From Reference 32

TABLE 2. Percentage atomic orbital parentage of valence MOs

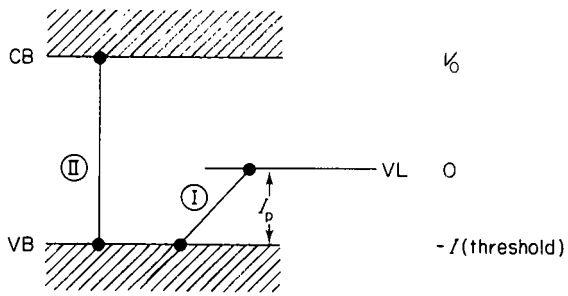
	Percentage population		
Orbital	C2s	C2p	H
$1b_{1u}$	0	100	0
$1b_{1g}$	0	48	52
$3a_g$	0	73	27
$1b_{2u}$	0	60	40
$3b_{3u}$	49	15	36
$2a_g$	81	8	11

example, comparisons of core ionization energies with Auger kinetic energies (or gas-phase acidities) have led Siggel and coworkers[36] to conclude that the charge-acceptance difference between X-substituted ethanes and ethylenes (X = F, Cl, Br, I) is almost entirely due to differences of the initial state charge distributions and is negligibly dependent on differences in the valence electron rearrangements. The somewhat surprising result of their studies, namely that molecules with double bonds are not more polarizable than their saturated counterparts, is explained as follows: the contribution from the π-electron polarization in aromatics is matched by that from the extra hydrogens of the aliphatics (i.e. the π polarization in ethylene is matched in ethane by a comparable contribution from the two extra hydrogens).

The existence of a perfluoro effect (p. 24) has recently been observed for core level spectra by Robin and coworkers[183].

V. UPS OF SOLID STATE SAMPLES

UPS is a powerful tool for the study of the electronic structure and electron transport properties of solids. The organic solids in which most interest has been shown are the aromatics, long-chain alkanes, polymers and some very small molecules. The basic quantity obtained from UPS is the threshold ionization potential, which is the energy of the top of the occupied valence band (VB). If the energy V_0 of the bottom of the conduction band (CB) is also available, such important characteristics as the electronic structure and photoemission mechanism of the solid can be determined. If $V_0 > 0$, the bottom of CB lies above the vacuum level (VL) and no bulk electronic states intervene between CB and VL. Theoretically, the electrons can be emitted to VL directly from VB (path I) or indirectly through excitation into CB (path II).



Comparison with the gas-phase ionization energy yields a measure of the interaction energy (i.e. the polarization energy) of the ionized molecule with its neighbours in the solid.

Seki and Inokuchi[37] have recently investigated several saturated medium-sized hydrocarbons and solid 1-hexene using NeI, HeI and HeII excitation. Spectra of 1-hexene are shown in Figure 10. The good correspondence with the gas-phase spectrum (apart from a shift of the energy scale by approximately 1.0 eV) indicates that the solid photoemission can be regarded as photoionization of the molecule in the solid state. Photoemission from CB should give rise to PES bands which always correspond to the same E_k (i.e. E_k should be independent of $h\nu$). Such bands, however, were observed only for $E_k \sim 0$ (i.e. scattered, secondary electrons). Similar behaviour was also exhibited by all compounds in the Seki–Inokuchi study, in direct contrast to the results for long-chain alkanes where the CB features dominate. In addition, these authors determined that direct ionization (path I) from VB was the preferred photoemission mechanism.

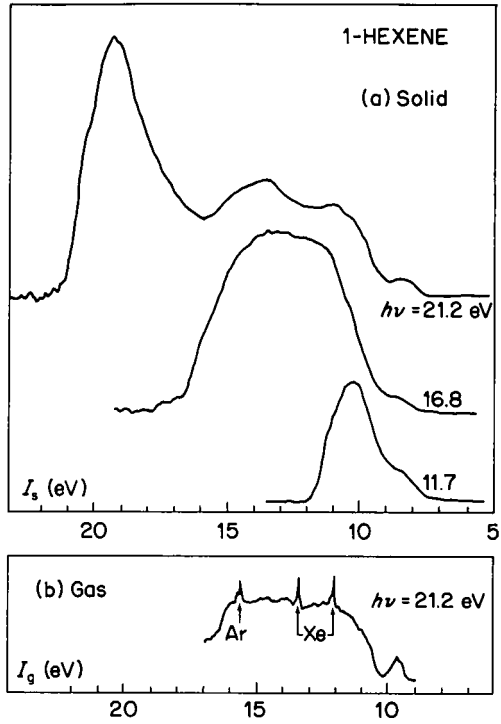


FIGURE 10. PES of 1-hexene in solid (a) and gaseous (b) phases obtained using HeI (21.22 eV), NeI (16.67 and 18.85 eV) and ArI (11.62 and 11.83 eV) light sources. Energy scales are displaced relatively by 1 eV in order to display correspondences between the two phases. From Reference 37

VI. PES OF LIQUID SAMPLES

PES of liquids is a relatively new field. One usually probes the sample at the liquid–vacuum interface, with the consequence that one obtains simultaneous liquid and gas phase signals. Since the procedure also permits measurements on solutions (i.e. the determination of *in situ* results for dissolved species), it is not surprising that the following interests have come to the fore: (i) ions in solution (their electronic structure and dynamics, solvation and reaction energies, complex formation abilities and colloids); (ii) intermolecular forces (valence and core-level effects); (iii) liquid–vacuum interface (surface activity); and (iv) molten substances.

Since formamide is a very advantageous solvent, it has been thoroughly investigated by Siegbahn and coworkers[38] by both XPS and UPS. The O(1s), N(1s) and C(1s) bands of liquid and vapour formamide are shown in Figure 11 whence it becomes obvious that a very small trace of a water contaminant provides a signal that is fully comparable to that of the O(1s) of the formamide. The liquid spectrum exhibits a lower binding energy, the same for all bands. An isotropic behaviour of the liquid is suggested. Either the gas or the liquid

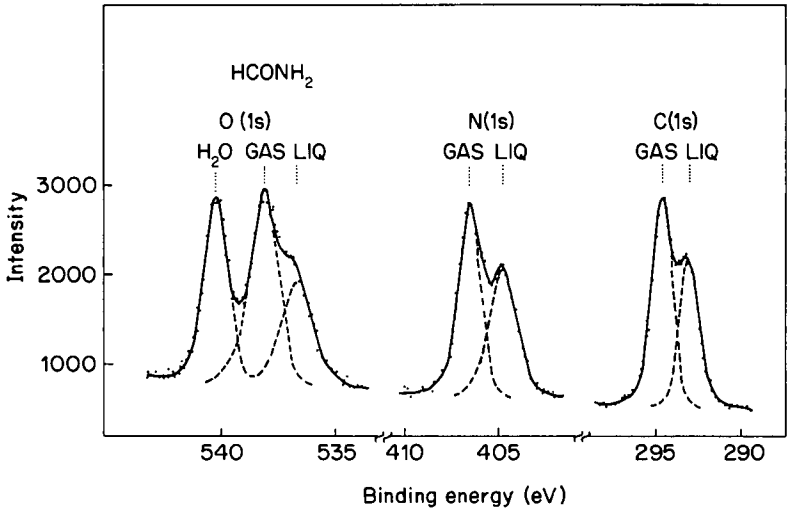


FIGURE 11. The C(1s) electron lines from the liquid and the vapour of $HCONH_2$ for oxygen, nitrogen and carbon. A very small trace of water in the liquid yields an O(1s) line from the vapour phase which is comparable in intensity to the C(1s) signal from the formamide

signal can be suppressed by adjusting the direction of the liquid beam or jet. An example of this is shown in Figure 12.

VII. GAS-PHASE UPS RESULTS

Classical PES works dating from the early 1960s already exhibited interest in and contained data for numerous compounds with double-bonded groups. Indeed, the UPS method, which made feasible the ability to quantify much chemical intuition concerning organic chemistry, deserves considerable credit for the spread of quantum chemistry among organic chemists. In fact, one could say, UPS gave much of its modern meaning to the term *molecular electronic structure*: that is, the interplay of quantum chemistry and UPS results to generate images of the spatial and energetic distribution of valence electrons in a molecule, and the use of these images as predictors of observable, molecular physical properties.

Several reviews are available, the most comprehensive being that of Rao, Basu and Hedge[39], which covers much of the UPS data for organic molecules (more than 500 references) available up until 1977. About 100 references on organic compounds are given in the more recent 1983 Annual Report by Urch[40] and more than 400 in a review article on non-bonding and transannular interactions by Martin and Mayer[4]. In the remainder of this section we will attempt an overview of those results which, in our opinion, are particularly significant for any understanding of the PES properties of double bonded groups. We will begin with examples of the most typical representatives of the various types of double bonds (i.e. ethylene, methanimine, diazene and formaldehyde) and will endeavour to show how the properties of these representors are preserved in assorted, other classes of compounds. Finally, we will attempt to correlate the results for the different types of double bonds of interest here.

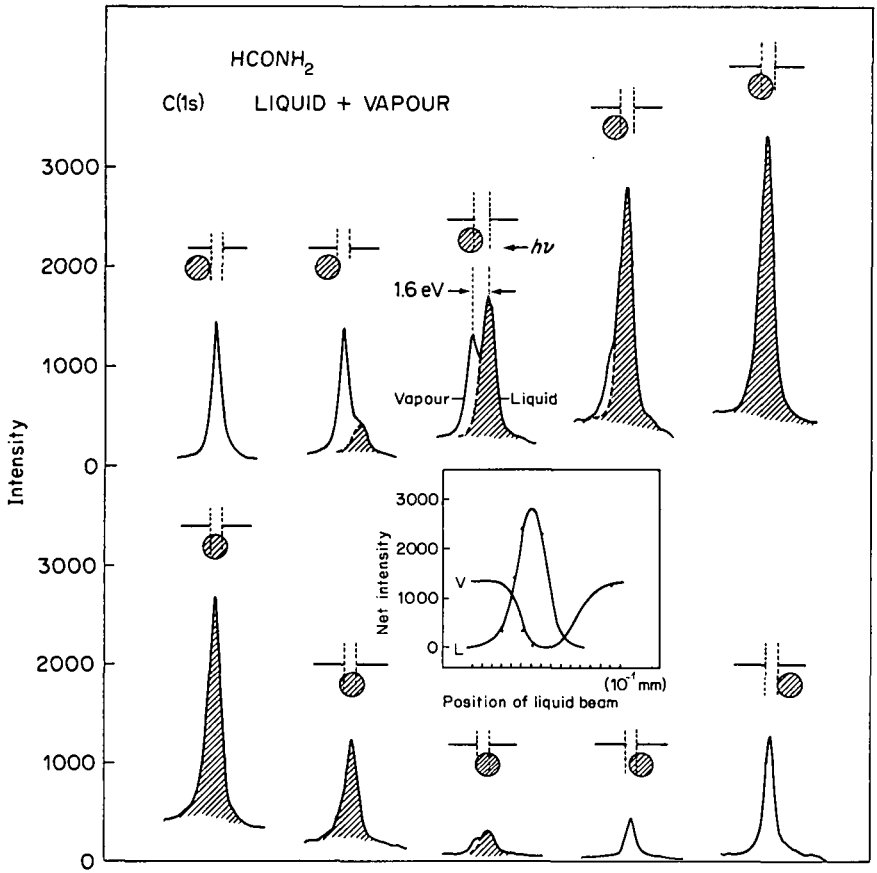


FIGURE 12. C(1s) ESCA lines for formamide as a function of liquid beam position. A splitting of the 1.6 eV line occurs because of a difference of C1s binding energy in the liquid relative to the vapour. At certain positions in the liquid beam, the vapour signal may be completely suppressed

Before turning to specific double-bonded groups, we will briefly describe those techniques which are useful for the assignment of the characteristic of π and n ionizations of double-bonded groups. The list of techniques breaks down into two categories. The first, the *spectral feature method*, studies the details of the information contained in the spectrum of a given compound whereas the second, the *correlational method*, compares UPS results for different, but somehow related compounds or compares UPS results with those obtained by complementary experimental techniques or by theoretical models and calculations.

The *spectral features* of interest are:

Vibrational Fine Structures: If present and resolvable, they are very important to band assignments. Bands of similar origin usually contain characteristic vibrational frequencies associated with the excitation of certain totally-symmetric modes of the ion. (Because of symmetry selection rules, only totally-symmetric modes are normally observed in UPS.) These modes are easily recognized and identified.

Band Shape Analysis: Even if vibrational structure is not discernible, the band contour

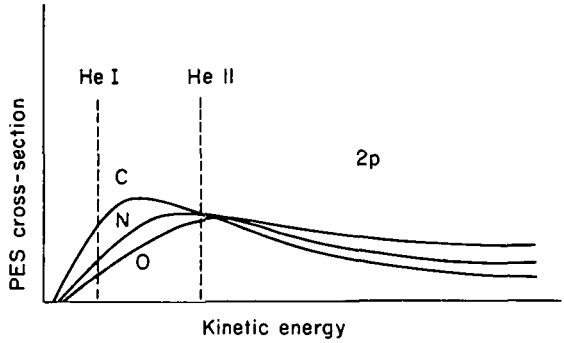


FIGURE 13. The dependence of ionization cross-section as a function of the kinetic energy of the ejected photoelectron for the p orbitals of C, N and O. The cross-sections are seen to be quite different for HeI and HeII excitations

can differentiate between ionization events that remove electrons of a weak-bonding or non-bonding nature, usually the π and n ionizations, and those that remove electrons of a strong-bonding (or anti-bonding) nature. Actually, bands of similar shape in related molecules usually provide the first clue to an assignment. Band contours, therefore, are also important from a correlational viewpoint.

Band Intensity Analysis: Changes of the photoionization cross-section as a function of the photon energy can indicate the type of orbital from which the photoelectrons orignate. The dependence of the ionization cross-section for p orbitals of carbon, nitrogen and oxygen[41] is plotted against photoelectron kinetic energy in Figure 13, and is seen to vary considerably. Since HeI and HeII lines differ by nearly 20 eV, the HeI/HeII band intensity ratio can sometimes be a very useful assignment tool.

Angular Distribution of Photoelectrons: By angular distribution we mean the dependence of the photoelectrons count, $I(\theta)$, on the angle, θ, of the count direction relative to that of the incident light beam. The angular distribution is given by

$$I(\theta) \approx 1 + \tfrac{\beta}{2}(\tfrac{3}{2}\sin^2\theta - 1)$$

where β, the asymmetry parameter, contains information on the orbital nature. Spherically symmetric s-type orbitals are isotropic and yield $\beta = 0$, whereas orbitals with angular momentum generate a range $-1 \leqslant \beta \leqslant 2$. The angular dependence of the UPS of butadiene[42] is shown in Figure 14, whence it seems clear that the events at 9 and 11 eV correspond to $I(\pi_{CC})$ values.

Correlation Function Analysis: Such an analysis has been shown[43] to yield the time evolution of the excited-state wave function. The correlation function can be obtained from the Fourier transformation of the photoelectron partial cross-section, $\sigma(E)$. Since it is $I(E)$ and not $\sigma(E)$ that is measured by UPS, $I(E)$ must be deconvoluted into the instrument response function and $\sigma(E)$. Such a deconvolution requires a knowledge of the instrument response function and this is usually determined by measuring the UPS of a rare gas[44k].

Correlational techniques are concerned with the interdependence of the spectra of related compounds, additional proof for the proposed assignment being taken from other complementary experimental methods and/or quantum chemical computations. It is hard to define what a 'related compound' is. Related compounds may differ by as little as a deuterium/hydrogen interchange or by so much that they only possess the same

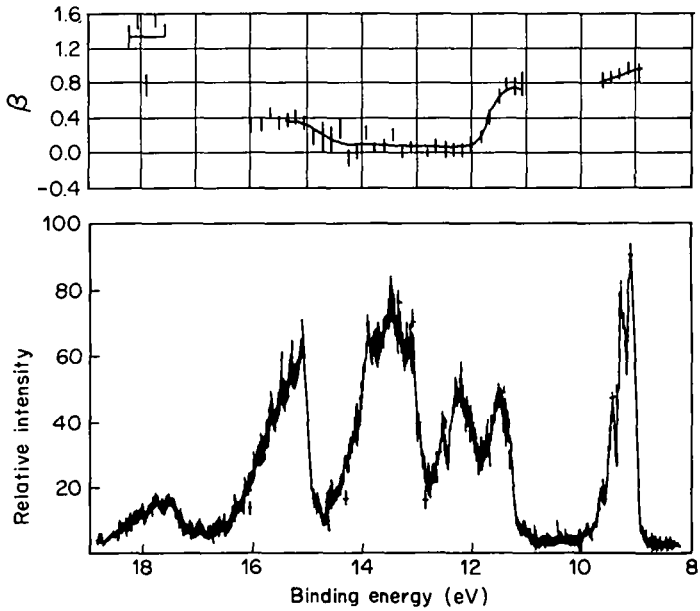


FIGURE 14. HeI PES of butadiene and the angular parameter β

topological connectivity; they may be of the same geometrical sctucture or they may contain some common building unit. Usually, however, 'relatedness' can be expressed in terms of pertinent substitutions. The resulting substituent effects can be traced and studied in different ways (e.g. by introducing the same substituents(s) into different but related molecules or by introducing different substituents(s) into the same molecule, etc.).

Substitution Tactics: The most commonly used substitution tactics are:

(i) The Perfluoro Effect, which leaves π and n orbitals relatively unchanged in energy but strongly increases I_p values of σ ionizations;
(ii) Extensive Alkylation, which reduces I_p values of π ionizations by similar increments (see also additivity effects);
(iii) Electronegativity Trends; and
(iv) Additivity Effects.

Let us also just mention the complementary methods, models and calculations used in correlative studies.

Experimental Methods: Other experimental techniques that are in some form complementary to UPS and which may be used correlationally are:

(i) Gas Phase Absorption and Emission of Ions;
(ii) Rydberg Spectra;
(iii) Photoion Spectroscopy (PIS);
(iv) Multiphoton Spectroscopy (MPI);
(v) Mass Spectra (especially charge-exchange MS);
(vi) Molecular Beam Experiments;
(vii) Electron Transmission Spectroscopy (ETS);
(viii) Electron Energy Loss Spectrometry (EELS); and
(ix) Cyclic Voltammetry (CV).

Models: Theoretical approaches, not involving significant computational effort, that may be used correlationally are:

(i) Orbital Interaction Schemes;
(ii) Symmetry Considerations;
(iii) Composite Molecule Methods (Atom in Molecule and Molecule in Molecule);
(iv) Linear Free Energy Relationship (LFER) dependence; and
(v) Thermodynamic Considerations.

Quantum Chemistry: A variety of methods, all heavily computational, are available: (i) Semiempirical [HMO, EHT, LCBO, SCF-MO, CNDO, CNDO/S, INDO, SPINDO, MNDO, X_α, HAM/3, even some with configuration interaction (CI) or geometry optimization included]; (ii) *Ab Initio* [SCF-CI with various complexity of basis functions (GTO, STO) and optimization procedures]; and (iii) Green's Function (propagator, GF) methods.

A. The C=C Double Bond

1. Ethylene

On the UPS of ethylene one could write a book!

The behaviour of the ethylene molecular ion in various of its electronic states, as well as the photoionization process and the multiple channels available to it in ethylene, have been the subject of numerous theoretical and experimental studies. Papers dealing with the HeI spectrum of ethylene and its deuterated analogues have been combined into References 44a–q. The complete HeI spectrum has been reported several times because the steadily increasing information content produced by better resolution and recording conditions required such. The HeI spectrum[44k], as shown in Figure 15 (top), consists of four band systems X, A, B and C, each of considerable complexity in its own right. The insert shows relative abundances of $C_2H_4^+$, $C_2H_3^+$ and $C_2H_2^+$ from PE-PI coincidence measurement[44l].

The $\tilde{X}$ band is associated with the removal of a π electron from the double bond. It is the lowest energy PES event. The ion state transforms as $\tilde{X}^2B_3$ (D_2 symmetry assumed). Its energy, 0–0 transition, relative to the X^1A_g ethylenic ground state, is 10.51 eV. The band consists of partially resolved peaks, splittings of 10–100 meV, which have been assigned to excitation of the vibrational modes ν_2 (C—C stretch, 1500 cm^{-1}), ν_3 (H—C—H bend, 1260 cm^{-1}) and ν_4 (torsion) (Figure 15, middle). The ν_4 mode, which is not totally symmetric, should only be observed in a progression of even numbers of quanta but, in fact, bands associated with excitation of odd numbers of quanta are observed. The ν_4 torsional mode produces characteristic doublets whose spacing and intensity are very sensitive to isotopic (deuterium) substitution. The rather irregular behaviour can be explained by a vibrational mixing of the ν_2 and ν_3 modes which would otherwise be expected to be degenerate (or nearly so) in $C_2H_4^+$ (and *cis*-$C_2H_2D_2^+$)[44h,m,p]. The first progression in the torsional mode ν_4 shows a strong anharmonicity and is very similar to the vibrational structure of the $\tilde{X}^1A_g \rightarrow 3s$ Rydberg (R3s) transition. The most likely explanation of this is that the upper electronic state is non-planar. Merer and Schoonveld[45] showed that R3s is twisted by 25° and has an inversion barrier of 390 cm^{-1}. Recent studies by Köppel and coworkers[46] and Sannen and coworkers[47] indicate the same for the $\tilde{X}^2B_3$ state of $C_2H_4^+$ (25° and 30 cm^{-1}, respectively). The spectrum, from which all ν_2 and ν_3 activity has been substracted, is shown in Figure 15, bottom; the three ν_4 and four ν_4 harmonics are clearly evident. The potential well and the vibrational energy levels for $C_2H_4^+$ and $C_2D_4^+$ are shown[44k] in Figure 16; they agree well with other calculations[44o] and with the experimental data[44k,q] for $C_2D_4^+$. The electronic transitions of mono-olefins have been discussed by Watson and coworkers[44r,s].

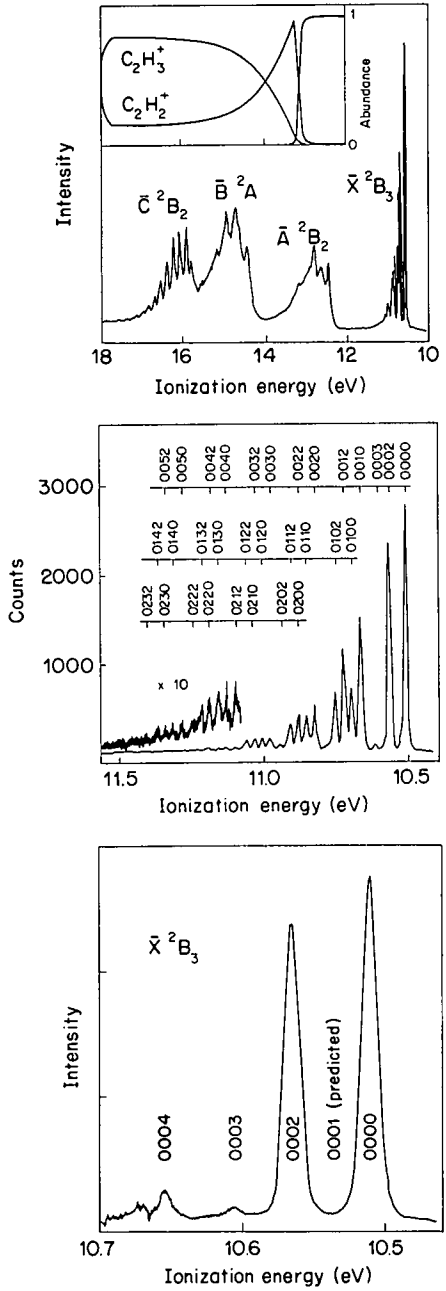


FIGURE 15. HeI PES spectra of ethylene

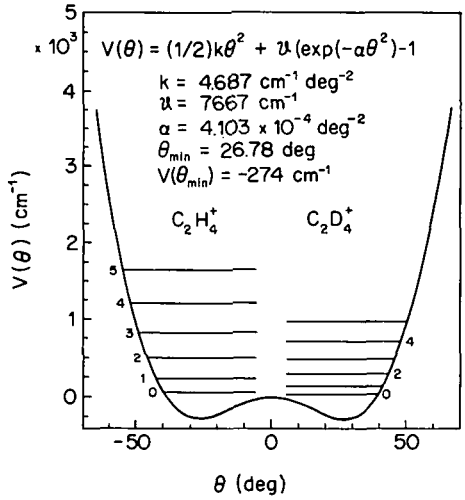


FIGURE 16. The torsional potential energy curve of the $\tilde{X}^2B_3$ state with the calculated energy levels for $C_2H_4^+$ and $C_2D_4^+$. The potential parameters were determined by matching the experimental peak positions for $C_2H_4^+$. From Reference 44k

2. Alkenes

The non-cyclic alkenes have attracted considerable interest. Whether viewed as an analogue of the C_n alkane isomers or as the various combinations of four independent alkyl substituents at a double bond, it is clear that a very large number of such alkenes exists. It is therefore necessary to attempt a generalization such that the PES of any member of the class can be predicted with some accuracy.

It was recognized early that alkyl substituents decrease $I(\pi_{CC})$ of ethene and that the resultant ΔI is characteristic of both substituent type and substituent number. Indeed, in 1970, Cocksey and coworkers[48] interpreted the vertical ionization energies of aliphatic aldehydes, ketones, alcohols, iodides and ethers in terms of two parameters, an alkyl group substituent parameter and a homologous series parameter, and showed that (i) a similar approach was also valid for the ionization energies of other homologous series, and (ii) the substituent parameters correlated well with the Taft σ^* values.

A similar procedure was adopted for the alkylethenes by Heilbronner and Maier[49], who also gave a theoretical justification for the correlation with the Taft σ values and reformulated the values of the alkyl parameters, P_R. These values are presented in Table 3. The parameters for the substituents in an alkylethene determine its ionization energy I_p as

$$I_p(\text{eV}) = 10.565 - 0.883\sum P_{Ri} + 0.076(\sum P_{Ri})^2$$

to an accuracy of 0.1 eV. The non-linear behaviour implies a deviation from simple additivity effects.

Another approach[50], that yields I_p to the same accuracy but depends on just a single parameter, namely the sum of significant bond walks in the alkylethene, W_B, is based on molecular topology[51] (connectivity). It yields

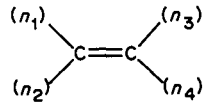
$$I_p\ (\text{eV}) = 10.452 - 0.665 \ln W_B$$

TABLE 3. Values of alkyl parameters, P_R

Substituent	P_R	Substituent	P_R
H	0	*n*-Bu	−1.20
Me	−0.89	*i*-Bu	−1.26
Et	−1.08	*t*-Bu	−1.36
n-Pr	−1.18	$>n$-C_5	−1.22[a]
i-Pr	−1.24	$>i$-C_5	−1.27[a]

[a]Extrapolated value

In order to determine W_B, the number of C—C bonds in the longest carbon chain of each substituent (i.e. n_1, n_2, n_3 and n_4) must be known.



It follows that the values of n for Et, *i*-Pr and *t*-Bu are the same and equal to 2. Thus, the value of W_B may be formulated as

(a) 1 (for the C=C bond) *plus*

(b) the sum of (the longest) substituent chain lengths (note that the C=C group is considered to be terminal for each substituent) *plus*

(c) the sum of the longest combined *gem*-substituent chain length(s) (note that the C=C group is considered to be peripheral) *plus*

(d) the sum of all non-equivalent longest chain lengths (i.e. paths that traverse the two alkyl substituents and the C=C bond).

Sums (c) and (d) apply only if both substitutents yielding the increment exist in the molecule.

The value of W_B is then

$$W_B = 1 + n_1 + n_2 + n_3 + n_4$$

$$+(n_1 + n_2) \quad \text{if both } n_1 \textit{ and } n_2 \neq 0$$
$$+(n_3 + n_4) \quad \text{if both } n_3 \textit{ and } n_4 \neq 0$$
$$+(n_1 + n_3 + 1) \quad \text{if both } n_1 \textit{ and } n_3 \neq 0$$
$$+(n_1 + n_4 + 1) \quad \text{if both } n_1 \textit{ and } n_4 \neq 0$$
$$+(n_2 + n_3 + 1) \quad \text{if both } n_2 \textit{ and } n_3 \neq 0$$
$$+(n_2 + n_3 + 1) \quad \text{if both } n_2 \textit{ and } n_4 \neq 0$$

This approach accounts for the observed differences of ionization energies for *gem*- vs. *cis* or *trans* derivatives but lacks a quantum chemical basis.

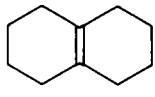
Not counting the *cis* and *trans* isomers which, according to both of the above models, should exhibit the same ionization energies, a very large number of isomers exists even for quite small molecules (e.g. 66 isomers for octene). Since $Me_3CCHMeCH{=}CH_2$ should have the largest ionization energy of 9.5 eV (not as yet measured) and since the lowest ionization energy should be exhibited by one of the three isomeric Et_2Me_2–ethylenes (measured as 8.16–8.17 eV[52g]; calculated[49,50] as 8.266 and 8.216 eV, respectively), the range of ionization energies covered by the octenes extends for $\sim$1.3 eV. The lowest ionization energy measured thus far for a non-cyclic alkene is 8.04 eV[52g] for

n-$PrEt_3$–ethylene which is smaller than that of $(i\text{-Pr})_4$–ethylene, $I = 8.13$ eV, for which Mollere and coworkers[52e] could not demonstrate the presence of any steric effects.

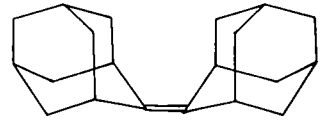
Relevant works on the UPS of non-cyclic alkenes are collected in Reference 52. Among those, we emphasize the works of Clark[52d], Masclet and coworkers[52g], Carlier and coworkers[53], Wielesek and Koenig[52h], Kimura and coworkers[52j], Van Hoorn[54] and Krause and coworkers[52m]. Linear correlations between the ionization energies of molecules and the changes in them caused by alkyl groups have been given by Houk and coworkers[55]. A compilation of ionization energies for ethylenes with Me, Et and *t*-Bu substituent groups is given in Table 4.

Cyclic alkenes have been investigated extensively[52a,b,e,i,l,56a–m,57a,b]. Heilbronner and coworkers have determined the interactions of double bonds in different types of cycloalkenes and in more highly unsaturated cycloalkenes. In both the exo- and endo-cyclic alkenes, $I(\pi_{CC})$ reaches saturation rather rapidly at ~ 9 eV, but achieves it somewhat faster in the exo-cyclic series. A typical ionization energy progression in the endo series is 9.43, 9.18, 9.12, 9.04, 8.98 and 8.98 eV for cyclobutene through cyclodecene (with cyclononene missing) respectively[56b,c,j], and in the exo series is 9.5, 9.19, 9.15 and 9.13 eV for methylenecyclopropane through methylenecyclohexane, respectively[1c,57a,b]. These values suggest that $W_B = 1 + (\text{number of bonds in the cycle})$.

Examples of an intra- and inter-cyclic alkene are given below.



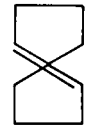
Octahydronaphthalene[56b]
$I(\pi_{CC}) = 8.3$ eV
$W_B = 1 + 2 \times 6 + 11 = 24$
$I(\text{calc}) = 8.34$ eV



Adamantylideneadamantane[52k]
$I(\pi_{CC}) = 7.84$ eV
$W_B = 1 + 2 \times 8 + 2 \times 17 = 51$
$I(\text{calc}) = 7.84$ eV

The sensitivity of $I(\pi)$ to distortion of (rotation around) a double bond has received much attention. Cyclic compounds, because of their well-defined geometry, have been important to this study. Suffice it here to say that sensitivity is quite small. Large changes of I, when observed, are always the result of TS and/or TB interactions with other π or σ bonds. Thus, in the only example where a clear difference of $I(\pi)$ was evident[49,56i],

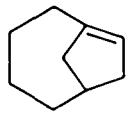
cis-Cyclooctene
$I(\pi_{CC}) = 8.98$ eV



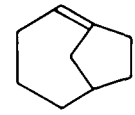
trans-Cyclooctene
$I(\pi_{CC}) = 8.69$ eV

$W_B = 1 + 8 = 9$
$I(\text{calc}) = 8.98$ eV

this difference could well be caused by TS interactions since, for example, in the structures at the top of the next page the ionization energies are the same, within experimental error, as those that would be expected for the corresponding substituted but fully planar π bond. Consequently, Heilbronner concluded that 'the C=C double bond is quite insensitive to changes in local geometry as far as its ionization energy is concerned'[7a].



bicyclo[4.2.1]non-1(8)ene
$I(\pi_{cc}) = 8.37$ eV
$W_B = 1 + 7 + 5 + 8 = 21$
I(calc) = 8.43 eV



bicyclo[4.2.1]non-1(2)ene
$I(\pi_{CC}) = 8.45$ eV
$W_B = 1 + 5 + 8 + 7 = 21$
I(calc) = 8.43 eV

Electron transmission spectroscopy (ETS), which yields electron affinity EA (i.e. the energy of LUMO), indicates that EA is less variable than I in the alkenes but more variable than I in the endo-cyclic alkenes[58]. These dependencies are shown in Figure 17a and 17b.

3. *Haloethenes*

Haloethenes were covered extensively by Wittel and Bock in this Series[59]. Consequently, we will merely update their data insofar as double-bond properties[60] are concerned.

TABLE 4. Values (in eV) of vertical $I(\pi_{CC})$ for substituted ethenes

Substituent	Me	Et	*t*-Bu	F	Cl	Br	*I*	CN
X	10.03	9.72	9.7	10.58	10.15	9.87	9.35	10.84
gem-X_2	9.45	9.06	8.98	10.72	10.00	9.78	—	11.35
cis-X_2	9.35	8.95	8.69	10.43	9.80	9.63	9.86(8.96[a])	11.15
trans-X_2	9.37	8.97	8.74	10.38	9.80	9.55	9.60(8.92[a])	11.15
X_3	8.92	8.46	8.17	10.54	9.65	—	—	—
X_4	8.41	—	—	10.54	9.34	9.26	8.82(8.65[a])	11.79

[a]The lowest ionization energy is assigned to $I(n_l)$[60a].

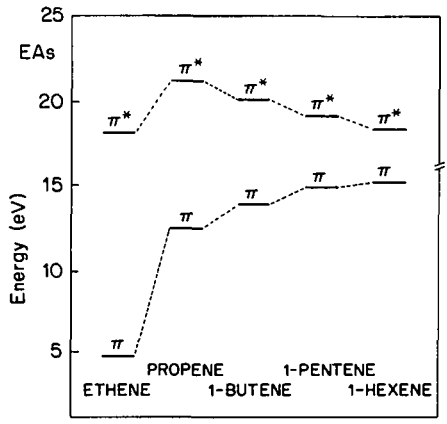


FIGURE 17a. Correlation diagram showing experimental values of vertical electron affinities and ionization potentials for the alkenes

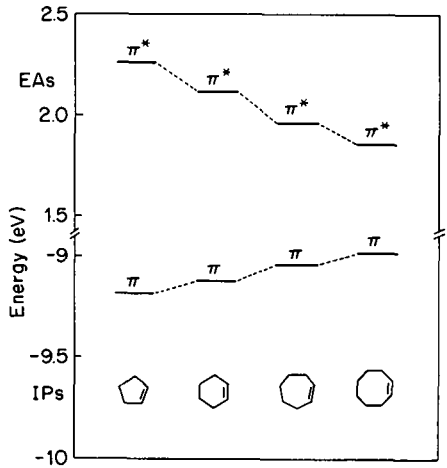


FIGURE 17b. Correlation diagram of experimental vertical EAs and Ips for *cis*-cycloalkenes

Although the number of haloethenes studied represents, so far, only about 20% of the 174 possible combinations, it can be anticipated that the electronic structure of the outer valence region and, particularly, the nature of the π_{CC} orbital is well understood. However, we must note that the past contained several surprises and one ought not to be too smug about the future. Thus, tetrafluoroethene was among the compounds for which a perfluoro effect[44e] was first observed. In *cis*-difluoroethene, the *cis* effect[61] (i.e. the phenomenon of a TS attraction between fluorine atoms stabilizing a *cis* conformation) was discovered. Haloethenes have been used as models for interaction schemes, as test-beds for quantum chemical calculations and as exemplifiers of spin–orbit coupling effects. It is a good experimental knowledge of these compounds that led to the halogen parameters used in semi-empirical MO calculations, that suggested the additive behaviour exhibited by the UPS of these compounds and, last but not least, provided insight into the interactions of lone-pair electrons.

Apart from fluoro substitution[60n], which increases $I(\pi)$ for the double bond a little and $I(\sigma)$ dramatically, the effect of the higher halogens on $I(\pi_{CC})$ is definitely destabilizing (see Tables 4 and 5). In the case of multiple substitution by the higher halogens, spin–orbit and other interactions produce two PES bands for each halogen. These bands are usually resolved and are easily recognizable by their shape and their HeI/HeII intensity dependence. Except when there are two or more iodines present in the molecule, the lowest ionization event is $I(\pi_{CC})$[60g]. Thus, in C_2I_4 the lone-pair $\pi(3b_{3g})$ ionization energy, dominantly associated with the iodines, is about 0.2 eV lower than that of the $\pi(2b_{3u})$ ionization event associated with the C=C bond[60r]. (The UPS of this compound, first reported[60o] as that of CI_4, has since been corrected[60p,r].)

4. *Allyl derivatives*

Allyl derivatives, an interesting group of compounds closely related to the monosubstituted ethenes, contain a substituent that is separated from the double bond by an

TABLE 5. Vertical ionization energies $I(\pi_{CC})$ in eV of some vinyl and allyl derivatives[39]

X	H	Me	Et	*n*-Pr	*n*-Bu	*t*-Bu	
Vinyl	10.51	10.03	9.72	9.52	9.48	9.7	
Allyl	10.03	9.72	9.52	9.48	9.44	9.6	
X	F	Cl	Br	I	SMe	SiH_3	$SiMe_3$
Vinyl	10.58	10.15	9.87	9.33	11.00[b]	10.37	9.8
Allyl	10.60	10.20	10.01	10.30[a]	9.95[b]	9.49	9.0
X		NH_2[182]		NO_2[63]		PH_2[182]	
Vinyl[d]	8.6($\pi_{CC}-\pi_N$); 12.17($\pi_{CC}+\pi_N$)			11.14(π_O^A); 11.45(π_{CC})		9.6(n_p); 10.85(π_{CC})	
X	OH	NH_2	NMe_2	P(*n*-Bu)$_2$	SH	$GeMe_3$	$SnMe_3$
Allyl[c]	10.22	10.04 (9.44)	9.37 (8.47)	9.77 (8.25)	10.05 (9.25)	10.4 (8.85, 10.2)	10.7 (8.5, 9.7)

[a] Events at 9.30 and 9.75 eV assigned as $I(n_t)$.
[b] Events at 8.51 (vinyl) and 9.65 (allyl) eV assigned as $I(n_s)$.
[c] Events lower than $I(\pi_{CC})$ are given in parentheses.
[d] Assignments are given in parentheses

insulating CH_2 group. Thus, direct conjugation of substituent and double bond is intercepted. Such interactions as do exist can be divided into TS and TB parts, the TS component being deducible by comparison with the vinyl analogue. For this reason, a great variety of substituents have been tested. Some PES results are given in Table 5.

The vinyl/allyl UPS differentiation of $I(\pi_{CC})$ in the alkyl damps rapidly with the number of carbon atoms and is less than 0.1 eV at n-Pr. The PES behaviour of the halo compounds indicates that they do not conjugate at all strongly. However, in those compounds in which X is one of the heavier heteroatoms, the X lone-pair ionizations, $I(n_X)$, may well be the lowest-energy ionization events.

5. *Other substituted ethylenes and ethylene heterocycles*

We will discuss here some specifically-substituted ethylenes and some heterocyclic compounds containing an endo- or exo-cyclic carbon–carbon double bond.

Endo Exo

Y, Z = heteroatom

Substituents other than alkyl, substituted alkyls, halogens and the cyano group contain lone-pair electrons on atoms that may be directly attached to the double bond, may interact with it and make its description as a C=C bond almost meaningless. Results pertinent to this point have been obtained by Bock and coworkers[62] from the PES of mono-, di- and tetra-substituted ethylenes, the substituents being SMe, OMe, OEt, NMe_2 and CN. The lowest ionization event in the cyanoethylenes[62b,c] is $I(\pi_{CC})$ whereas, in the other four types of compound, the (hyper)conjugative π/n_X interaction plays a determinative role.

The UPS of nitroethene, measured only recently[63], exhibits $I(\pi_{CC})$ at ~ 11.5 eV, right between the $I(\pi_O)$ and $I(n_O)$ bands at 11.14 and 11.55 eV, respectively. These two latter events are shifted by 0.2 eV and happen to be essentially of the same shape as their counterparts in nitromethane at 11.32 and 11.73 eV, respectively. Consequently, one concludes that conjugation between C=C and the NO_2 group is negligible, the main effect being the inductive shift of $I(\pi_{CC})$ by ~ 1 eV. Similar behaviour is evident in carbonyl substituents: the acid[52i], aldehyde[52i] and alkylketone[64] derivatives all have nearly identical $I(\pi_{CC})$, all close in value to $I(\pi_{CC})$ of ethylene (see Table 6).

The 'heterocyclic ethylenes', which are unsaturated heterocycles containing either one *endo* or one *exo* double bond, have a well-defined molecular structure, which makes them valuable as indicators of heteroatom/double bond interactions. We cite, as an example, the work of Schmidt and Schweig[65] who reassigned[66] the spectrum of 2.5-dihydrofuran as a result of a correlative study involving tetrahydrofuran and *cis*-butene. The results of this study are depicted in Figure 18. The actual interacting orbitals are those of *cis*-butene, π_1

TABLE 6. Vertical ionization energies, $I(n_O)$ and $I(\pi_{CC})$, for vinyl derivatives[52i,64]

X	COOH	COH	COMe	COEt	COPr-*i*
$I(n_O)$	10.6	10.11	9.61	9.50	9.39
$I(\pi_{CC})$	10.8	10.93	10.62	10.56	10.52

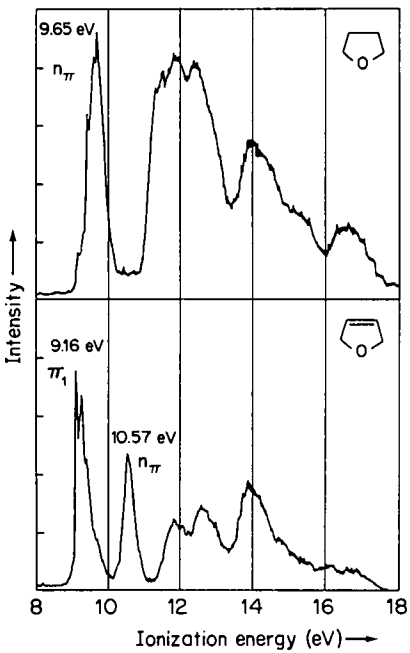


FIGURE 18a. The PES of tetrahydrofuran and 2,5-dihydrofuran

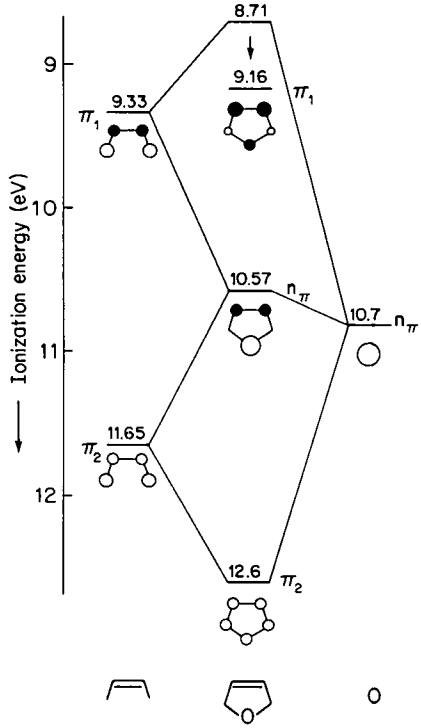


FIGURE 18b. A correlation diagram for the HOMOs of *cis*-butene, 2,5-dihydrofuran and the 'oxygen atom'. The inductive effect of oxygen on the HOMO of 2,5-dihydrofuran is indicated by an arrow

and π_2, and the 'hyperconjugation-free' lone pair of oxygen, n_π. The value of $I(n_\pi)$ for this latter lone pair was estimated by extrapolating $I(n_\pi)$ for the dialkyl ethers (9.52, 9.63 and 10.04 eV for Pr, Et and Me, respectively) to $n \rightarrow 0$, whence $I(n_\pi) = 10.7 \pm 0.2$ eV. The energy decrease of 0.45 eV in the π-MO, as indicated by an arrow in Figure 18, is the inductive stabilization induced by the oxygen atom which more than counteracts the hyperconjugative destabilization of the π_1-MO.

We now list a number of other studies that are of interest:

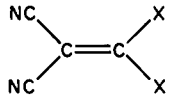
The UPS of 2,5-dihydrothiophene has been assigned[67]. The discussion of hyperconjugative and transannular n/π interactions in this compound bear on that given above for tetrahydrofuran.

The UPS of cyclic six-membered unsaturated ethers and thioethers has been reported by Planckaert and coworkers[68]. Assignments were based on a correlation with the spectra of the corresponding saturated heterocycles, the methyl vinyl ethers and the thioethers. No evidence was found that would implicate S3d AO participation in the low-lying excited states of the unsaturated thioethers.

The UPS of the 'electron-rich olefins' $C_2(NMe_2)_4$ (**1**) and $\{C[N(Me_2CH_2]_2\}_2$ (**2**), in which all four ethylene positions are substituted by alkylated amino groups, were reported by Cetinkaya and coworkers[69]. These compounds, which in terms of electronegativity can

be considered as opposites of tetracyanoethylene (TCNE), are characterized by exceptionally low ionization energies of 6 eV (5.95 and 6.06 for **1** and **2**, respectively) vs. 11.79 eV for TCNE[62c]. The low ionization energies are attributable to conjugative π effects rather than to σ effects. The Me_2N group is known to exercise the largest of all + M conjugative effects even when only one alkylated amino group is present, and the effect of this group is off-set by a substituent such as COOEt, as demonstrated by the very low first ionization event, 7.63 eV, in the 'push–pull ethylene', β-diethylaminoethyl acrylate[70].

The UPS spectra of a series of 'push–pull' compounds of general structure



X=H, Me, SMe, SeMe, NMe_2 and
XX=$S(CH_2)_nS$ or $Se(CH_2)_nSe$
with n=1, 2 or 3

have been examined by Betteridge and coworkers[71a], who attempted to identify the 'push' effect of the X group and the 'pull' effect of CN and to correlate these with chemical behaviour. It was found that the first ionization energy was indeed a measure of the 'push–pull' effect, which increased $\sim$ 1.5 eV when H was replaced by CN but decreased by 1.1, 2.1, 2.4 and 3.1 eV when H was replaced by X = Me, SMe, SeMe and NMe_2, respectively. Similar compounds have also been investigated by Colonna and coworkers[71d].

The UPS of 1,2-dithiete[71b], 1,2-diselenete[71c] and 1,2-thiaselenete[71c], compounds which, through the S/CH=CH correspondence, may be related to benzene, have been reported by Schweig and coworkers.

6. *Double-bond interaction models*

The structural formula is one of the backbones of chemistry. We should anticipate that such a formula, if 'correctly' written, would contain some high percentage, perhaps 90% but certainly more than 50%, of the correct information about the relations between the atoms in that molecule. Unfortunately, a molecule is an ensemble of atoms all of which, and not just the bonded pairs, are mutually interactive. Consequently, the structural formula, which restricts interactions to bonded pairs, cannot ever be completely faithful. Thus, while the structural model, whether stick, bar or line, can be a great comfort, we must also have available some means of including all those other interactions, bonding or antibonding, which are omitted in the structural formula. It is not surprising, then, that a recent comprehensive review of non-bonding transannular interactions, ones traceable by PE spectroscopy, by Martin and Mayer[4] contains nearly 30 types of such interactions, all listed by name, classified in groups and categorized by the distance (i.e. the number of bonds) over which these interactions are effective.

We have already implied (cf. Introduction) that TS and TB interactions should suffice to describe the interactions between non-neighbour orbitals and, for that reason, we redefine these interactions here:

Through space (TS) represents interactions mediated by the direct overlap of orbitals; these interactions *are not* represented by line(s) in a structural formula.

Through bond (TB) represents the interactions of two orbitals mediated by their mutual interaction with some third orbital; this third orbital is represented by a line in the structural formula.

However, since Martin and Mayer[4] have collected and defined the numerous subconcepts, ones not always used in a consistent manner, associated with the interactions of double-bonded groups, we believe it informative to list these here:

Homoconjugation: Describes the TS interaction of π bonds that are separated from each other by insulating atoms or groups such as $(CH_2)_x$. In general, homoconjugation is

characterized by an experimentally observable effect related to the sum of all interactions of non-conjugated π systems (see e.g. Reference 5).

Transannular Conjugation: This term has been used to describe homoconjugation restricted to π overlaps; thus, it is a component of homoconjugative interactions.

Homoaromaticity: Homoaromatics are cyclic $(4n+2)$ π systems interrupted in one or more places by saturated centres, but whose geometry is such that overlap of the p orbitals is maintained across the formally-isolating gap[72]. Classical examples of homo-, bishomo- and trishomoaromatics exist in the chemistry of carbocations. Homoconjugative interactions in neutral closed-shell systems seem, with some few exceptions[73], to produce destabilization.

Hyperconjugation: This expression, as coined by Mulliken[74], describes the overlap of suitably oriented σ: bonds (CH_3, CH_2, C—C) with π systems. Hyperconjugation is important in stabilizing certain ion conformations[75,76], hence, it is very important in PE spectroscopy.

Homohyperconjugation: Whereas hyperconjugation can be comprehended as a β- or a 1,2-vicinal effect, homohyperconjugation describes the corresponding γ- or 1,3-through-space (TS) effect[77,78].

Through-Space (TS) and Through-Bond (TB) Interaction: These involve homoconjugative and multiple hyperconjugative interactions, respectively[3].

Spiro-, Lati- and Longicyclic Conjugation: These terms characterize topologies formed by the union of two or three polyene ribbons[79]. The interaction between the π units in these polycycles consists of homo- and hyperconjugation.

σ,π Conjugation and Vertical Stabilization: Polarizable σ bonds stabilize neighbouring cationic centres without leading to a change of either bond lengths or bond angles[80]. This, too, is a case of hyperconjugation for which the more fitting description of 'vertical stabilization' is preferable. Since these interactions are important in Franck–Condon processes, they are clearly significant for PES.

p-Conjugation: The classical $p_\pi p_\pi$ conjugation in the allyl cation, for example, is the result of an allylic overlap of a vacant cationic p orbital with a double bond[81].

Perpendicular Conjugation: This is a type of homoconjugation in which the participating p or π orbitals form a more or less perpendicular structure. This kind of conjugation is realized in some polycycles or propellanes[82].

Supra-annular Effect: Axial electron-withdrawing substituents in the 4-position in cyclohexenes purportedly interact electronically with the π bond. It is questionable whether such effects exist[83].

cis-Effect: This term relates to the higher stability exhibited by many *cis*-disubstituted ethylenes compared to their *trans* isomers[61].

Circumannular Conjugation: This term describes the interaction between oppositely situated π centres across an interposed CH_2 group. It is especially evident in four-membered rings. It is a hyperconjugative effect which is distinct from direct transannular homoconjugation[84].

Non-equivalent Orbital Extension: π Orbitals can rehybridize and distort unsymmetrically under the influence of neighbouring σ orbitals. The geometry of the molecule may be altered by the 'tilting' of the π orbitals[85].

π-Electron Steric Effect: This effect describes the axial–equatorial equilibrium in 1-methoxy-3-(methylene) cyclohexane which is affected by dipole–dipole and orbital interactions[86].

A classical example[87,88] of the transannular interaction of π bonds (homoconjugation) is provided by norbornadiene (ND). Evidence for this interaction exists in both the chemical and photochemical behaviour of ND. Since ND has been proposed as a reservoir for solar energy storage, extensive studies by many spectroscopic methods [i.e. UV spectroscopy, circular dichroism (CD)[89], electron energy loss spectroscopy (EELS)[90],

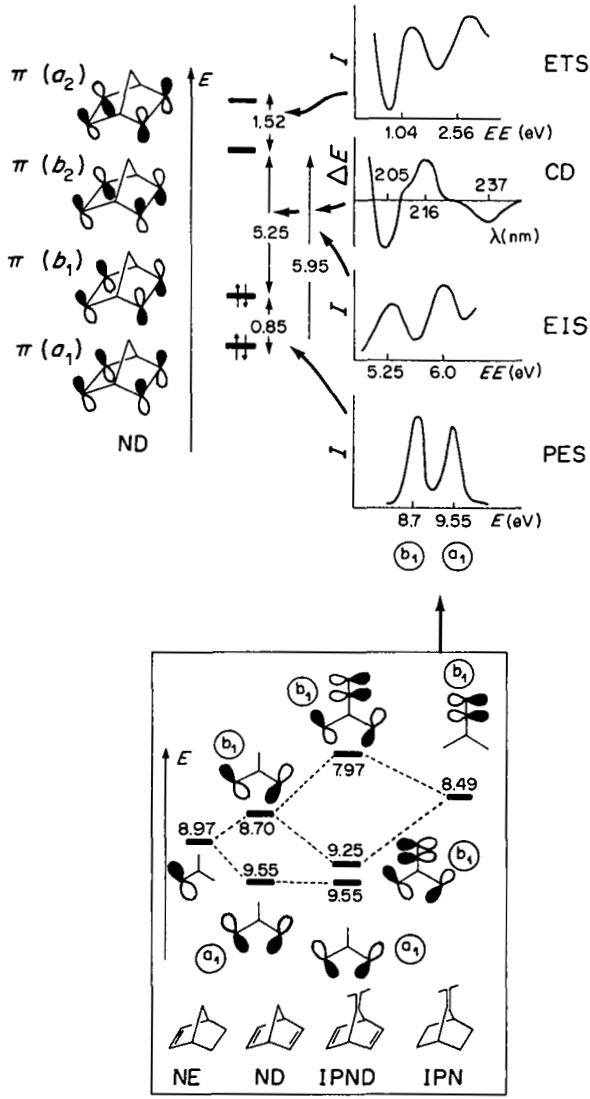
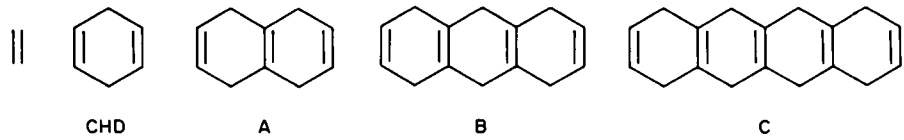


FIGURE 19. Orbital energy differences for norbornadiene (ND), ΔE(eV), obtained by electron transmission spectroscopy (ETS)[91], circular dichroism (CD)[89], electron impact spectroscopy (EIS)[90] and photoelectron spectroscopy (PES)[88] are shown in the upper diagram. A correlation diagram of the PES data for NE, ND, IPND and IPN is shown in the lower diagram

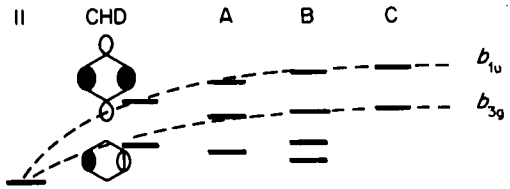
electron transmission spectroscopy (ETS)[91] and UPS[88]] have provided a reliable term scheme. The UPS results for the related compounds norbornene (NE), 7-isopropylidenenorbornane (IPN) and 7-isopropylidene norbornadiene (IPND) have been instrumental in establishing this term scheme (i.e orbital sequence) in ND. This orbital sequence is given in Figure 19. It has also been confirmed by *ab initio* calculations[92].

Some chemical consequences of homoconjugation in ND and hyperconjugation in NE are (i) photocyclization of ND to quadricyclane after $\pi(b_1) \rightarrow \pi^*(b_2)$ excitation[93], (ii) a homo-Diels–Alder reaction under the polarizing influence of dienophyles[94] and (III) exo-stereoselectivity[95].

It is of some interest to compare the 'related' cyclohexadiene (CHD) to ND since this example shows that considerable care must be taken in defining 'relatedness'. CHD is definitely part of the series[96]

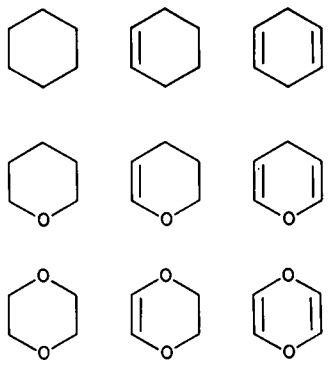


for which the following correlation of ionization energies holds:



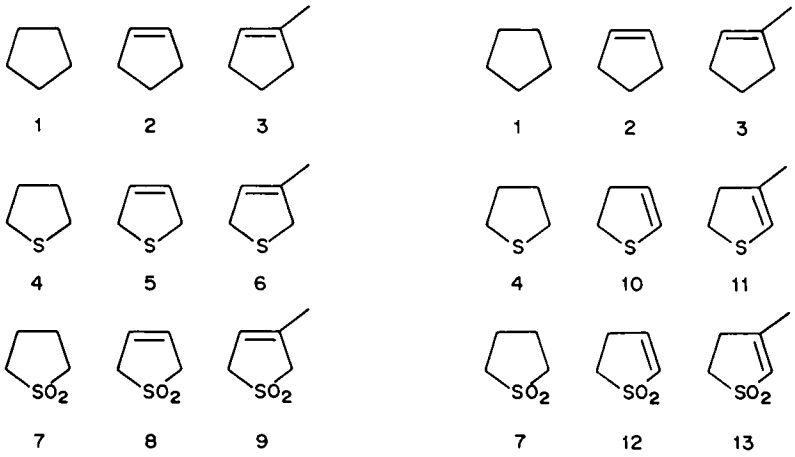
Thus, in going from ND, with dihedral angle $\Theta = 111°$, to CHD, with $\Theta = 189°$, a crossing of the $\pi(b_1)$ and $\pi(a_1)$ orbitals must occur. This crossing is independently supported by angular dependence measurements[97] which yield $\beta(\pi(b_1)) = 0.8$ and $\beta(\pi(a_1)) = 0.55$ for NBD, and $\beta(\pi(b_1)) = 0.47$ and $\beta(\pi(b_{3g})) = 0.73$ for CHD. Since β should be larger for antisymmetric than for symmetric orbitals, the inversion of the orbital sequence between ND and CHD is clearly demonstrated.

A beautiful correlation scheme involving the matrix of the following nine compounds:



was suggested by Heilbronner and coworkers[98] as a means of unambiguously assigning their PES. Unfortunately, it did not work. Kuhn and coworkers[99] have recently shown,

however, that the approach was correct and that the difficulty lay in the undefined, variable dihedral angles exhibited by the above set of nine compounds (i.e. in their non-planarity). Kuhn chose thirteen compounds, which are grouped into two matrices:



By superimposing these two matrices and adding a third one containing compounds 1–3 in vertical rows, a three-dimensional array can be obtained. This array yields a total of 3^3 correlations of which only 17 are feasible for this particular set of 13 compounds. In this case, the correlation approach worked, yielding parameters suited to the assignment of other compounds not in the set of thirteen shown above.

B. The C=N Double Bond

1. Methanimine, $H_2C{=}NH$

The title compound, also called formaldimine or methyleneimine, is the simplest of the alkanimines. The alkanimines are unstable and reactive compounds with a tendency to polymerize and hydrolyze[100]. Methanimine is an important interstellar molecule and is present in large quantities in hydrogen-rich nebulae[101]. It was first prepared (actually, merely detected in a matrix experiment) in 1961 and was later detected in the gas phase by mw spectroscopy. The first UPS was obtained by Peel and Willett[102] by investigating the pyrolysis products of methylamine

$$CH_3NH_2 \xrightarrow{\Delta} CH_2{=}NH + H_2 \xrightarrow{\Delta} HCN + 2H_2$$

using a numerical spectrum-stripping technique on time-averaged digitized spectra[102].

The compound is also produced in a weak mw discharge in CH_3NH_2 and in the thermal decomposition of azetidine (trimethylene amine), and UPS derived from these sources has been reported[103,104]. The primary preparative path to methanimine is the thermal decomposition of methyl azide[105]. It has recently been isolated as a pure substance[106,107].

The HeI PE spectrum exhibits four bands, as shown in Figure 20, with maxima at 10.56, 12.44, 15.0 and 17.0 eV. The two lowest energy bands correspond to the n_N and π_{CN} ionization events, respectively. The $I(n_N)$ in these compounds always appears broad and without any pronounced structure. Quantum chemical calculations using the MNDO procedure for the equilibrium geometries of the molecular ground state and the ionic $^2A_1$

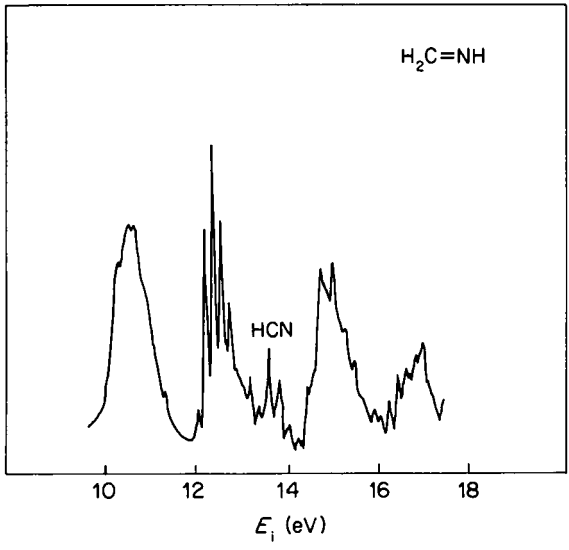


FIGURE 20. The PES of methylenimine as deduced from decomposition spectra of azetidine (trimethyleneamine) at ~800 °C and ~0.05 mbar

state, as well as CNDO/S, LNDO/S and MNDO in conjunction with both the simple Koopmans' (KT) and Schweig's perturbation CI (PERTCI) approaches (which latter incorporates electron reorganization and relaxation) for the ionization energies have been performed by Schulz and Schweig[104]. They obtained the results shown in Table 7. The most pronounced geometry effect, namely a widening of the CNH angle from 114° in the molecule to ~160° in the ion, and a simultaneous out-of-plane movement of N—H by 12° are in agreement with the expectation that the single n_N electron of the ion requires less space than does the two-electron lone pair of the neutral molecule. The calculated ground-state geometry is also in good agreement with experiment[108].

Another preparative route for these important unstable compounds was discovered by Frost and coworkers[109], who obtained $CH_2{=}NCH_3$ and $CH_3CH{=}NH$ by pyrolysis of hexahydro-*s*-triazines. The C-methyl compound should exhibit *cis*–trans isomerism attributable to inversion of the NH group. The *trans* compound was shown by *ab initio* calculation[110] to be 7 kJ mol^{-1} more stable than the *cis* compound. However, since the

TABLE 7. Calculated and measured vertical ionization energies of methanimine and assignment of photoelectron bands

CNDO/S		LNDO/S		MNDO		Experimental assignment	
KT	PERTCI	KT	PERTCI	KT	PERTCI		
12.31	11.50	11.50	11.05	11.26	10.68	10.56	n_N
11.86	12.04	12.47	12.19	12.16	12.15	12.44	π_{CN}
16.27	16.00	15.56	15.33	15.07	14.54	15.0	σ
20.01	19.22	18.22	17.61	17.71	17.12	17.0	σ

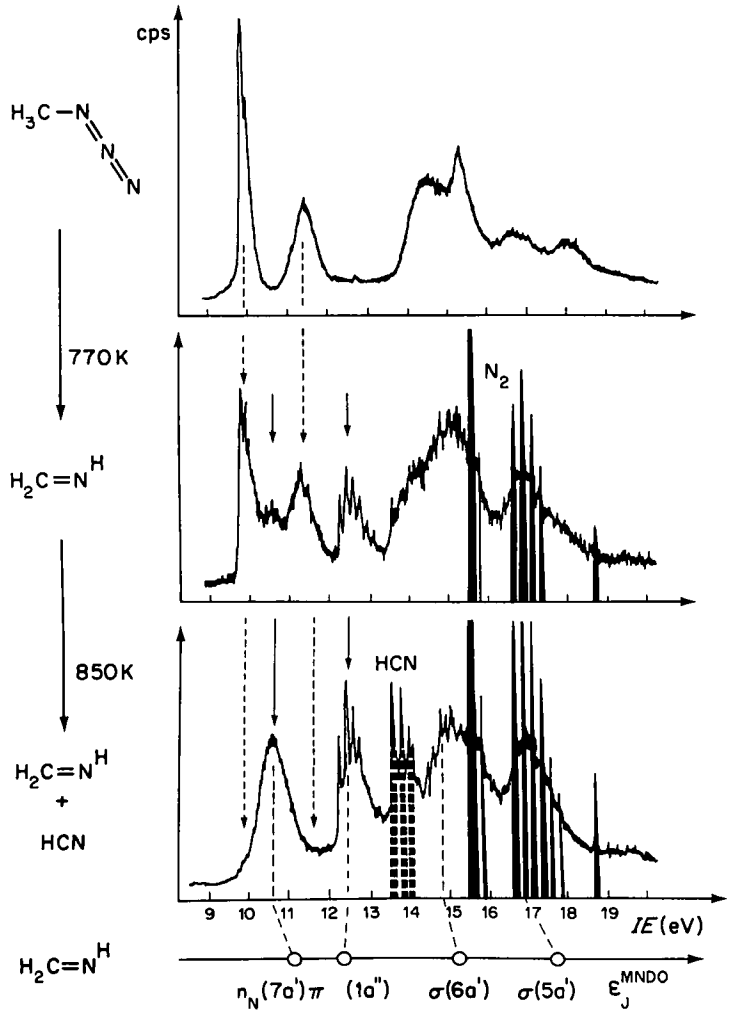


FIGURE 21. He(I) PES of methyl azide and its decomposition products at 770 and 850 K. The start of the pyrolysis is recognized by the appearance of the unmistakable N_2 ionization needles (black) between 15.5 and 18.7 eV, and complete decomposition by the disappearance of the characteristic azide bands (---→). At 770 K, the characteristic bands of $H_2C{=}NH$ (⟶), here assigned by Koopmans' correlation with MNDO calculations, are first observed. The second thermal reaction pathway to $H{-}C{\equiv}N$ (PES bands between 13.6 and 14.21 eV) and H_2 is populated at temperatures above 820 K (because of its low ionization cross-section, H_2 becomes visible only after PES subtraction or after freezing out the remaining products in a 77 K cold trap. From References 107

first three ionization energies for both compounds are computed to be virtually identical, the presence of both isomers in the reported UPS spectrum could not be excluded or verified.

2. *Imines and azomethines*

Various pyrolytic routes that yield simple alkylidene imine and azomethine products have been explored by Bock and Dammel[107]. The non-cyclic imines, cyclic imines and the azomethines have been detected by UPS as intermediates in the gas-phase pyrolyses of alkyl azides or other organic compounds with unsaturated NNN units (e.g. 1,2,3-triazoles, tetrazenes, tetrazoles, etc.). They have also been isolated at low temperatures and characterized. The small imines are shortlived; however since they exhibit characteristic $I(n_N)$ and $I(\pi_{CN})$ bands of relatively low energy, UPS is an effective analytical gas-phase tool, and it has helped to optimize their syntheses. The PES real-time analysis[107,111] of such a reaction is shown in Figure 21.

The $I(n_N)$ and $I(\pi_{CN})$ ionization events of the compounds $X_2C{=}NX$ are greatly influenced by H, F, CH_3, CF_3, Et, *i*-Pr and $(CH_2)_n$ substituents. As shown in Figure 22, changes in $I(n_N)$ as large as 4 eV and in $I(\pi_{CN})$ as large as 3.4 eV may be observed. $I(n_N)$ is normally lower in energy than $I(\pi_{CN})$. Perfluorination, however, affects $I(\pi_{CN})$ negligibly and $I(n_N)$ considerably, and reverses the normal orbital sequence. A CH_3 group attached to nitrogen lowers $I(n_N)$ more than $I(\pi_{CN})$ and causes these bands to overlap; two CF_3 groups attached to the carbon lower both $I(n_N)$ and $I(\pi_{CN})$ by 1.3 eV relative to the unsubstituted compound. Methyl substituents, being hyperconjugative and inductive interactors, act as donors and lower both ionization energies. The change in $I(\pi_{CN})$ is about the same for both C and N substitution whereas the shift of $I(n_N)$ is more pronounced upon N substitution. In the case of higher alkyl substitution[111] (e.g. Et, *i*-Pr, etc.) the ionization energies continue to decrease but saturate rapidly. The value of $I(n_N)$ of the (endo)cyclic cyclopropanimine is comparable[112] to that of $(CH_3)_2C{=}NH$. In the cyclic azomethines such as 2*H*-azirine, $I(n_N)$ and $I(\pi_{CN})$ are each about 1 eV higher energetically than in the

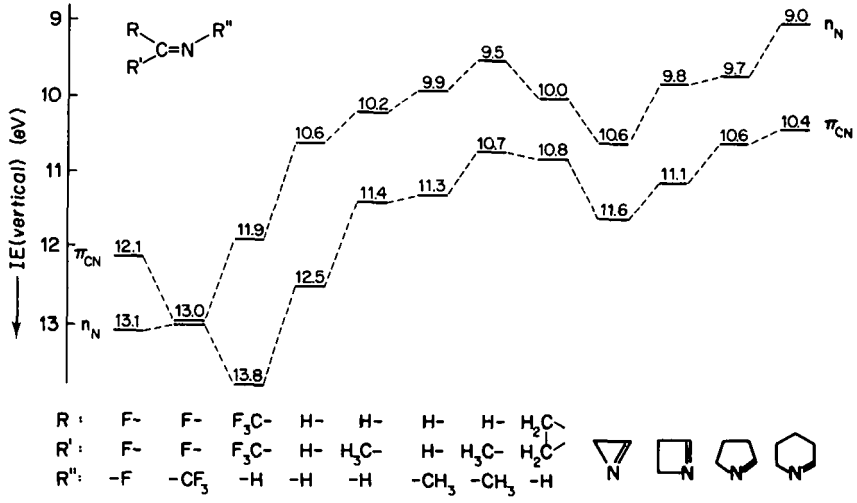
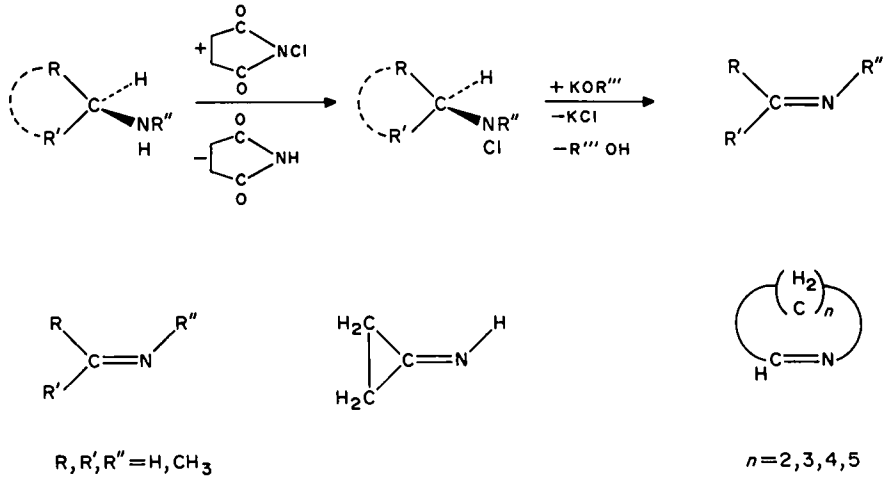


FIGURE 22. Vertical $I(n_N)$ and $I(\pi_{CN})$ ionization energies of some imines and azomethines

analogous non-cyclic dimethyl compound, MeCH=NMe[113,114]. However, in the larger ring compounds, both $I(n_N)$ and $I(\pi_{CN})$ decrease rapidly in energy as ring size increases, suggesting that the initial 1 eV gap relative to the non-cyclic compound may be the result of a forced unfavourable conformation. In accord with this supposition, the vibrational fine structure analysis of the $I(n_N)$ band indicates that 2,3-dihydroazete ('1-azetine') experiences considerable distortion during the ionization process[115].

Bock has shown that PES analysis can detect reactive imines and azomethines as intermediates in the pyrolysis of azides and can be used to optimize new procedures for their preparation. For example, 2*H*-azirine is best prepared by elimination of HCl and N_2 from *β*-chloroethyl azide whereas other imines and azomethines are best generated by successive chlorination of gaseous alkylamines on solid *N*-chlorosuccinimide and, thereafter, dehydrochlorination of the *N*-chloroamines with potassium *t*-butanolate or adamantolate[116].



In the gas phase, the syntheses are best carried out in a double-oven apparatus such as that shown in Figure 23. This apparatus consists of modules which permit PES optimization of the various reaction parameters.

The larger, stable higher compounds containing a C=N bond are obtained by reactions of aldehydes and ketones with amines, hydroxylamine, hydrazine(s) as the Schiff's base(s), oximes, hydrazones and azines. The first UPS data for the oximes $R^1R^2C{=}NOH$ were reported by Dargelos and Sandorfy[117] where R^1R^2 is H_2(**1**); Me, H(**2**); Me_2(**3**); or n-Bu, H(**4**). Unlike the alkyl imines and azomethines, in which $I(n_N) < I(\pi_{CN})$, the opposite, namely $I(\pi_{CN}) > I(n_N)$, is the case for the oximes because of the large shift of $I(n_N)$ to higher energies: 11.13, 10.79, 10.46 and 10.45 eV for **1–4**, respectively, and the relatively insensitive position of $I(\pi_{CN})$: 10.62, 10.20, 9.67 and 9.93 eV for **1–4**, respectively. The PES of the hydrazones $R^1R^2N^aN^b{=}CR^3R^4$ where R^{1-4} is Me_2, H, H; Me, H, H, Me; Me_2, HMe; MeH Me_2; and Me_4 (**1–5**, respectively) were measured by Zverev and coworkers[118], who found the lowest ionization event to be a *π*-type lone-pair ionization from N^a (8.35, 8.22, 8.08, 8.22 and 7.97 eV for **1** through **5**, respectively); the next to be an $I(n_N)$ event (10.04, 10.11, 9.77, 9.97 and 10.03 eV, respectively); and the third to be an $I(\pi_{CN})$ event (11.92, 11.61, 11.47, 11.61 and 10.94, respectively). In the aliphatic azines $R^1R^2C{=}N{-}N{=}CR^3R^4$, which are condensed hydrazines on both sides, the spectra are

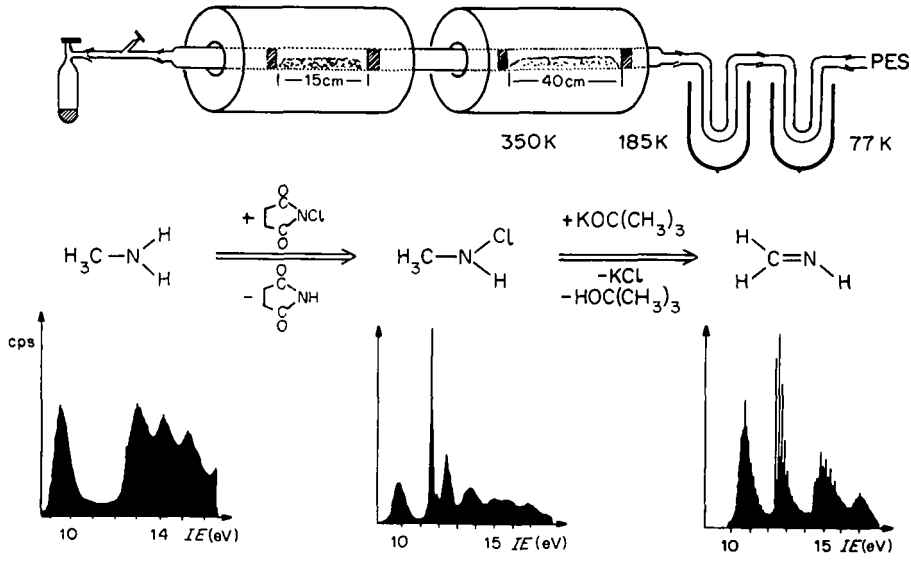


FIGURE 23. Preparation of methanimine by successive chlorination of gaseous methylamine using solid *N*-chlorosuccinimide and dehydrochlorination of the *N*-chloromethylamine formed with potassium *tert*-butanolate. The PES ionization patterns of the pure compounds used in the optimization of the reaction conditions are also shown. From Reference 116

complicated by the interaction of the two adjacent nitrogen lone pairs and the two nearby π_{CN} pairs, as well as by the unknown rotational angle between the two C=N subunits. In the azines of acetaldehyde, acetone and cyclohexanone angles of $\sim 60°$ have been suggested[119].

C. The N=N Double Bond

1. *Diazene, HN=NH*

The HeI spectra of diazene, its deutero analogue and its methyl derivative, MeN=NH, were reported by Frost and coworkers[120,121] in 1975. All are short-lived, transient species with lifetimes of the order of minutes in the gas phase. N_2H_2 was generated either by a microwave discharge in N_2H_4 or by pyrolysis of sodium tosylhydrazide. Four distinguishable PES bands, all with pronounced vibrational structure, are evident, as shown in Figure 24. The PES of N_2D_2 and MeN=NH, as well as the PES of previously reported[44e,113,114] N_2F_2 and MeN=NMe molecules, when analyzed with the help of *ab initio* calculations[122], led to a conclusive PES assignment in N_2H_2: the vertical events at 10.02, 14.39 and 15.03 eV were identified as $I(n_+)$, $I(\pi_{NN})$ and $I(n_-)$, respectively. The following points of interest may be noted:

(i) The large n_+/n_- splitting, 5.1 eV, indicates that the compound exists in the *trans* form.

(ii) The perfluoro effect shifts $I(n_+)$ by 3.4 eV but induces a negative shift of 0.3 eV in $I(\pi_{NN})$.

(iii) The energetic order of the n_+, π and n_- MOs remains the same in diazene through $CH_3N=NH$ to azomethane.

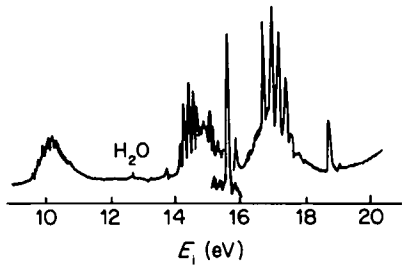


FIGURE 24. PES of diazene, N_2H_2

Frost and coworkers[121] have analyzed such diverse aspects of the PES of N_2H_2 as the vibrational fine structure, band shapes, Franck–Condon factors, correlation with the VUV spectrum and comparison with the isoelectronic molecules B_2H_6, C_2H_4, CH_2NH and CH_2O. The observation that the π_{NN} ionization event in the HeI spectrum of N_2H_2 is of greater intensity than the n_+ or n_- ionization events was attributed to the fact that the π_{NN} MO bonds two almost pure N2p orbitals whereas the n_N MO contains much admixture of N2s AOs.

The large value of $I(\pi_{NN}) = 14.35$ eV in C_2N_2 is surprising relative to its values in other N=N systems where the π-MOs occur between 10.5 and 13.2 eV[56d,113,123–125], the only exceptions being N_2F_2[44e] (14.1 eV) and difluorodiazirine[56d] (15.1 eV). This happenstance may be explained by the fact that the π bond in N_2H_2 is of pure N2p character and, therefore, very similar to the same bond in N_2.

The similarity of N_2H_2 to N_2 suggests that partial formation of a triple bond occurs in N_2H_2, as indicated by the high force constant of the N—N vibration[126] and by its ready transformation to N_2. The same argument has been used to explain the ease of elimination of N_2 from azo compounds containing cyclopropane rings[127].

2. *Diazene derivatives*

Azomethane was the first N=N derivative studied by PES, and its assignment by Heilbronner and coworkers[113,114] is crucial to all subsequent research. In particular, it permitted the development, testing and comparison of several qualitative and quantitative approaches that have become very useful in understanding PES and relating it to molecular electronic structure. Because of the presence of (i) two interacting lone pairs of the same nominal energy, (ii) at least two well-defined molecular conformations and (iii) a double bond with two substituents, these compounds are ideally suited to a study of the effects of constitutional factors on the electronic structure. The most important PES features of these compounds then is the location and splitting of the two lone-pair bands, $I(n_+)$ and $I(n_-)$, and their position relative to the $I(\pi_{NN})$ band. The n_-/n_+ split is a sensitive function of the NNX bond angle and several quantum chemical methods[128] have been tested on it: Gimarc has analyzed YXXY molecules in general and has discussed diazene orbital energies in particular using the EHT method; Baird and coworkers discussed the n_N MO energy in azoalkanes as a function of angle and performed *ab initio* calculations for *cis*-azomethane at various CNN angles; and Brogli and coworkers[129] have performed HMO and MINDO/2 calculations for diazene. These last calculations are shown in Figure 25.

The calculated orbital energies are very dependent on the computational method, varying by as much as 0.3–12 eV for Δn. However, all methods predict Δn to be considerably larger, the average of n_+ and n_- to be bigger, and the vertical ionization

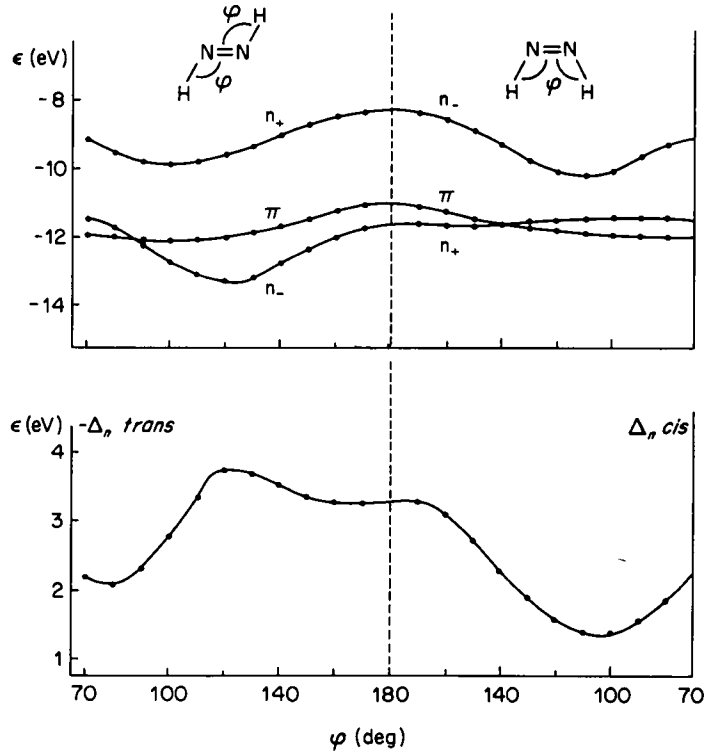


FIGURE 25. n_+,n_- and π MO energies as a function of the angle φ are shown on top. The quantity $\Delta n \equiv \varepsilon_{n+} - \varepsilon_{n-}$ is shown below as a function of the same angle φ. All computations are based on the MINDO/2 method. From Reference 129

events to be lower for the *trans*—than for the corresponding *cis*—isomers. Some researchers (e.g. Houk and coworkers[130]) have chosen to avoid group theoretical conventions, and refer to the anti-bonding combinations in both types of compounds as n_-, a tactic with the advantage that, in the study of the angle dependence of isomerization, no sign change appears at 180°. The *trans* configuration is usually more stable but there are exceptions. For example, gas-phase hexafluoroazomethane is more stable in the planar *cis* configuration[131]. As a result, PES comparisons of the perfluoro effect for these two compounds are not strictly valid[44e]: the first ionization event is shifted by 2.37 eV relative to azomethane, a shift that is smaller than the one that occurs in proceeding from diazene to F_2N_2 (+ 3.56 eV) and that parallels the behaviour of the ketones, where the fluorination of acetone results in an equal shift of 2.37 eV. However, the second PES band of azomethane, $I(\pi_{NN}) = 11.8$ eV, shifts to > 15.35 eV in the hexafluoromethyl derivative. Thus, the different geometry of the two materials produces a smaller $I(n_N)$ splitting in the *cis* compound and, contrary to direct fluoro substitution of a double bond which has little or no effect on the ionization event, perfluorination of a methyl group that is attached to a double bond causes the σ/π distinction to disappear and shifts the ionization events associable with the double bond quite strongly. Brundle and coworkers[44e] found that the

azo series parallels the keto and olefin series and that, consequently, perfluoro effects on compounds containing CF_3 groups are of little or no value.

A series of cyclic azo compounds has been investigated by Brogli and coworkers[129]. They started the assignment process with azomethane and diazirine, which had been analyzed by Robin[56h] and Haselbach[123]. The correlation assignment was also supported by quantum chemical (MINDO/2 and EHT) calculations. The compounds used in the correlation diagram (see Figure 26) indicate considerable TB interaction between the πMOs and that the splitting Δn(4-ring) = 1.55–1.60 eV is small relative to that for the other size rings: Δn(3-ring) = 3.44 eV and Δn(5-ring) = 3.10 eV. The ring size effect has been investigated by Domelsmith and coworkers[132] for 3,3-dimethyldiazirine, 3,3,4,4-tetramethyldiazetine and 3,3,5,5-tetramethylpyrazoline. Their spectra indicate that the 'normal' order, $I(n_-) < I(\pi_{NN}) < I(n_+)$, for azo compounds is altered to $I(n_-) < I(n_+) < I(\pi_{NN})$ in the four-membered ring compound. This behaviour accords with *ab initio* STO-3G calculations for these compounds and their demethylated analogues. The computations confirm the observed strong decrease of $I(n_+)$ that occurs in going from the 3- to 4-analogue and the increase that again takes place in the five membered ring compound (13.33, 10.36 and 11.26 eV, respectively). Houk and coworkers[130] have reported PES data for a large series of non-cyclic and cyclic azo compounds (Figure 27) from which they were able to deduce empirical linear correlations of $I(n_-)$ and $I(n_+)$ with substituent parameters σ_I and even estimate the effects of angle deformation on the PES of cyclic *cis*- azoalkanes.

An interesting set of azo compounds has been investigated by Bock and coworkers[133], namely $R_3XN{=}NYR_3$ (X, Y = C, Si) and $PhN{=}NXR_3$ (X = C, Si, Ge). Unfortunately, only the lowest ionization events, 7.1, 7.6 and 8.2 eV (for Si, Si, Si, C; and C, C; respectively) and 8.35, 7.85 and 7.65 eV (for C, Si; and Ge, Si:, respectively) were clearly identified as $I(n_N)$.

D. The C=O Double Bond

The general, theoretical aspects of the carbonyl group were covered in this Series by Berthier and Serre[134] in 1966. They reported the determination of ionization potentials for several carbonyls.

1. *Formaldehyde, $H_2C{=}O$*

The PES of formaldehyde and its deuterium analogues, HDCO and D_2CO, were reported by Turner and coworkers[135]. Formaldehyde exhibits four HeI bands at 10.88, 14.5, 16.0 and 16.6 eV (vertical). The PES is shown in Figure 28. It contains fine structure associated with excitation of the three totally symmetric vibrational modes: ν_1(C—H stretching), ν_2(C=O stretching) and ν_3(H—C—H bending). All three modes are excited in the $\tilde{X}^2B_2$ ionic ground state, their frequency being but little changed relative to the ground state of the neutral molecule. This fact, together with the high intensity of the 0, 0, 0 component, leads one to conclude that a non-bonding electron is involved and that the lowest ionization event is $I(n_O)$. The second band consists of a long series of doublets. Both the length of the series and the reduction of the C=O stretching frequency indicate removal of a strongly bonding electron. Consequently, the second PES band is securely assignable to an $I(\pi_{CO})$ event. The third band of H_2CO is assigned to an $I(\sigma_{CO})$ event. This PES band merges into the fourth band, in which the fine structure is somewhat less detailed, which is assigned to a pseudo $I(\pi_{CH_2})$ event.

The first two bands, $I(n_O)$ and $I(\pi_{CO})$, particularly their dependence on substituents, are the most important PES markers for the electronic structure of carbonyls. Since all such compounds are obtained by replacing the two hydrogen atoms, some simple rules for

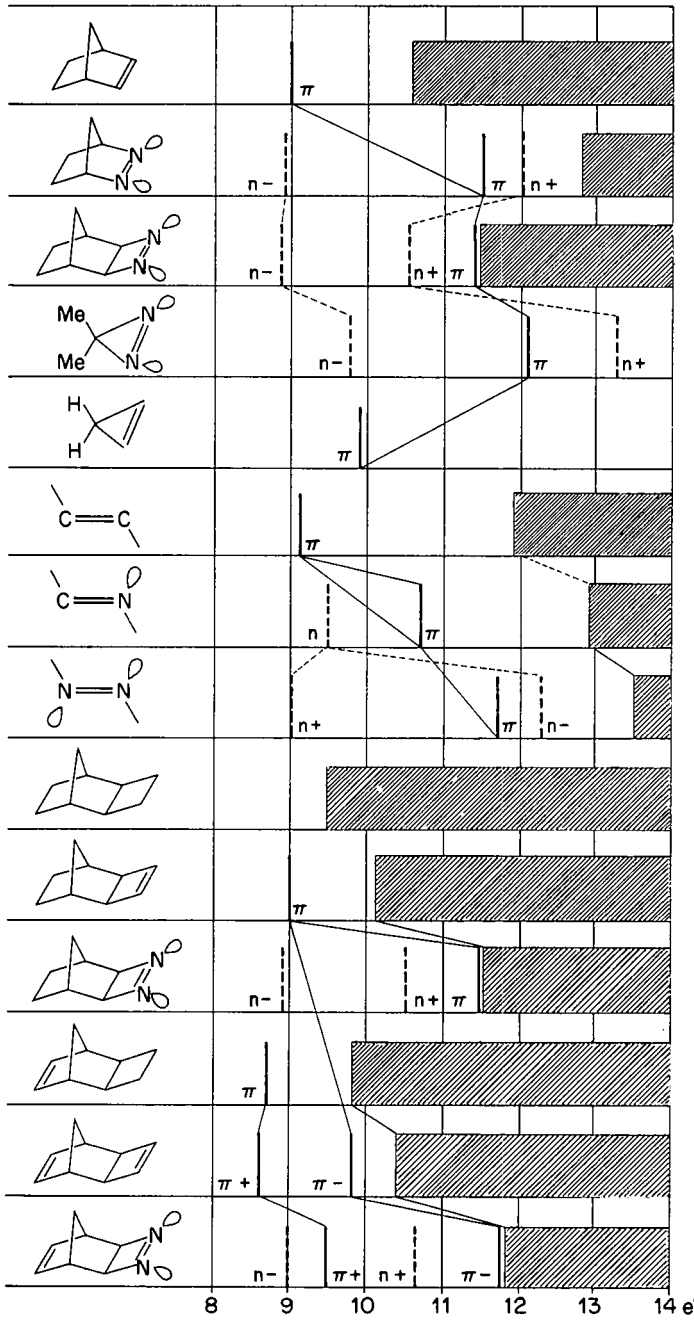


FIGURE 26. A correlation diagram for the $I(\pi)$ and $I(n)$ events in a variety of azoalkanes. From Reference 129

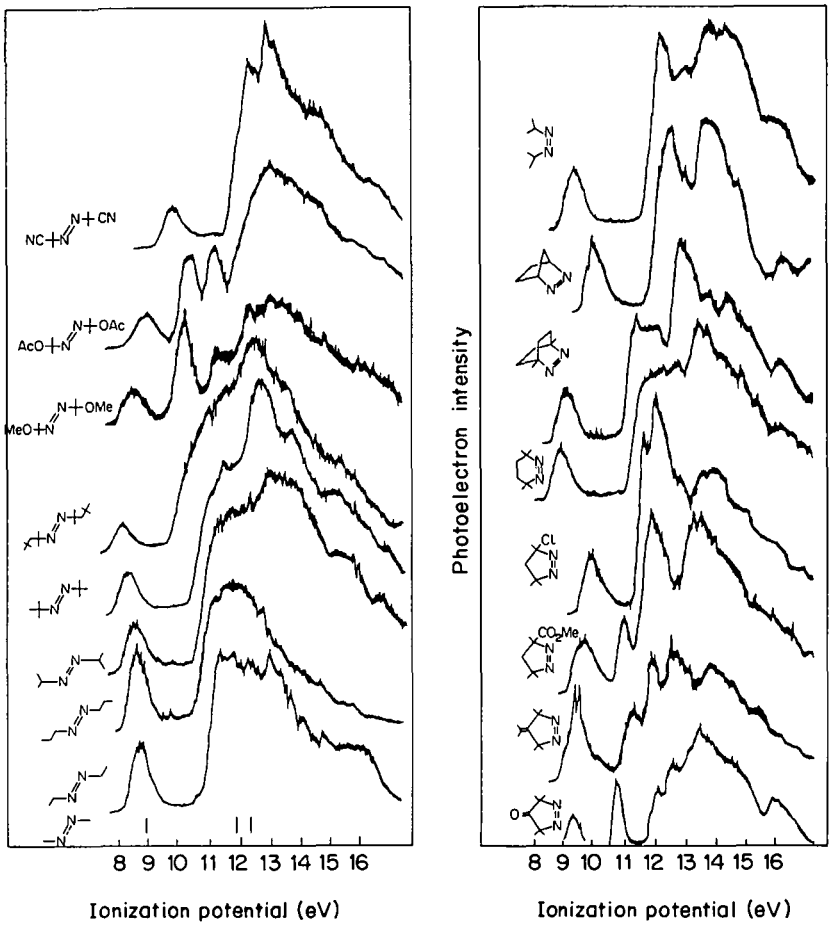


FIGURE 27. PES data for non-cyclic and cyclic azo compounds. From Reference 130

expected changes of $I(n_O)$ and $I(\pi_{CO})$ should exist. In order to elicit these rules, we will study perfluorination, methylation and deuteration.

Perfluorination yields carbonyl fluoride, in which a strong shift of $I(n_O)$, 2.7 eV, and a negligible shift of $I(\pi_{CO})$, 0.1 eV, occur. However, whereas the PES profile of $I(\pi_{CO})$ remains also essentially unchanged in F_2CO, that of $I(n_O, 5b_1)$ becomes very non-vertical, displays a long progression in the C=O stretch mode ($1550\,cm^{-1}$) and exhibits some activity at $530\,cm^{-1}$ which, tentatively, is either an F—C—F bending or a C—F stretching mode. As in acetaldehyde, the n_O lone-pair orbital in H_2CO is somewhat delocalized over the carbon and hydrogen atoms; in F_2CO, however, calculations indicate that the amplitudes on both the carbon and fluorine centres is diminished. The extensive delocalization explains the observation of all three totally-symmetric vibrational modes in H_2CO (and at least six of them in CH_3CHO). Nor is it surprising that such a long progression in the C=O stretch mode is excited in the perfluoro analogue. Brundle and coworkers[44e] suggest that this long progression is caused by the electronic reorganization and its effects on the molecular geometry of the ion and/or by the fact that the CO bonding population in the $5b_1$ orbital of F_2CO is much more effective than the CO anti-bonding population in the

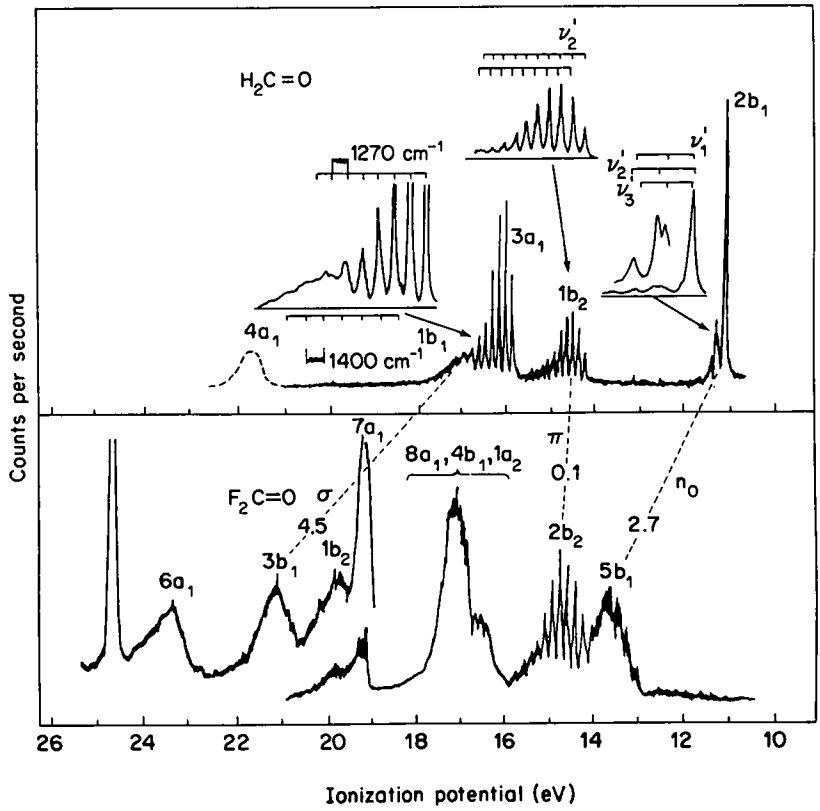


FIGURE 28. Photoelectron spectra of formaldehyde and carbonyl fluoride. Spectra at energies greater than 21 eV in formaldehyde and greater than 19 eV in carbonyl fluoride were obtained using HeII excitation. From Reference 44e

$2b_1$ orbital of H_2CO in dictating such reorganization. However, it is common for vertical transitions in the hydrogen derivatives to become highly non-vertical and to exhibit long progressions in the PES of the perfluorinated analogues (e.g. aromatic hydrocarbons).

A comparison of spectra and computations for H_2CO, HFCO and F_2CO led Wittel[136] to note the constancy of $I(\pi_{CO})$ and the large variation of $I(n_O)$ in going to the F and F_2 compounds (1.6 and 2.6 eV, respectively), and the fact that these observations discord with the 25 vs 400% increase in Koopmans' defects along the H_2CO/F_2CO series for $I(n_O)$ and $I(\pi_{CO})$, respectively. Wittel concluded that correlation and reorganization effects are major contributory factors to the perfluoro effect.

The PES of acetaldehyde (see Figure 29)[137] suggests that the n_O MO plays a determining role for the bond angles of the ion (and presumably also the molecule). Indeed, the fine structure of the $I(n_O)$ event at 10.21 eV contains at least six totally symmetric modes, among them the CCO (bend), CC (stretch), CH_3 (deform) and CH_3 (rock) motions which involve motions at a distance from the supposedly 'localized' n_O electrons. On the other hand, the fine structure of $I(\pi_{CO})$ at 13.24 eV is unaffected by deuteration because the dominant excitations, ν_4(CO stretch) and ν_{10}(CCO bend), do not depend, at least in a first approximation, on the hydrogen atoms. In fact, however, the π_{CO} MO is heavily localized

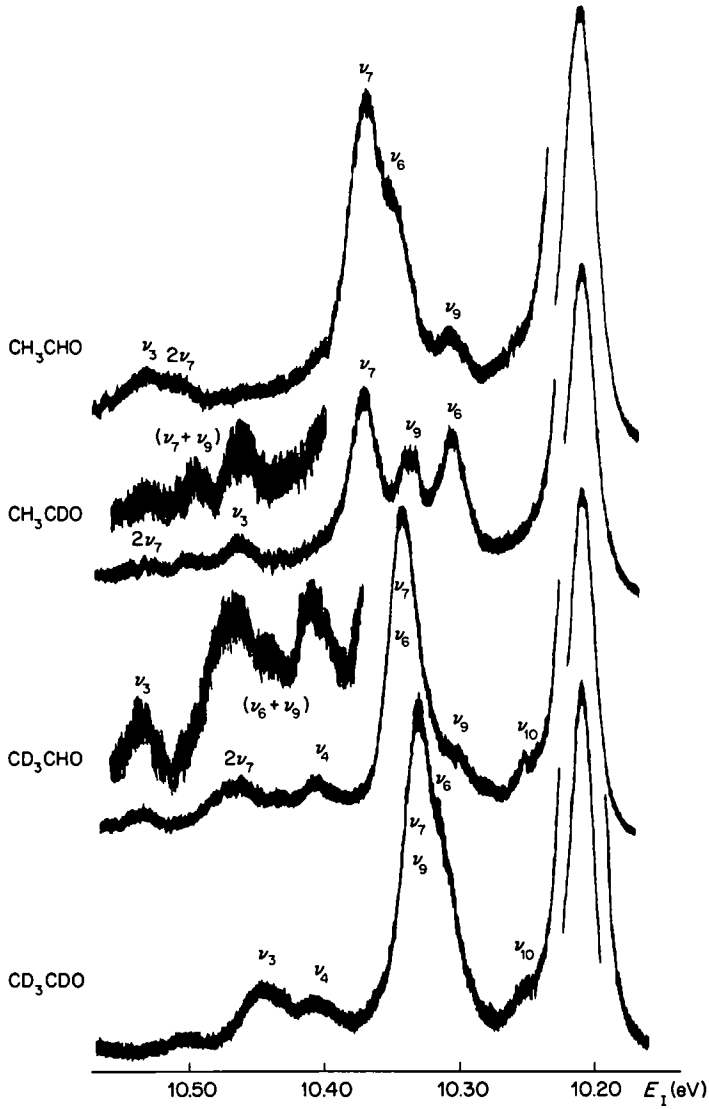


FIGURE 29a. High-resolution PES of the first electronic system ($\tilde{X}$) of acetaldehyde-d_0, -d_1, -d_3, and -d_4

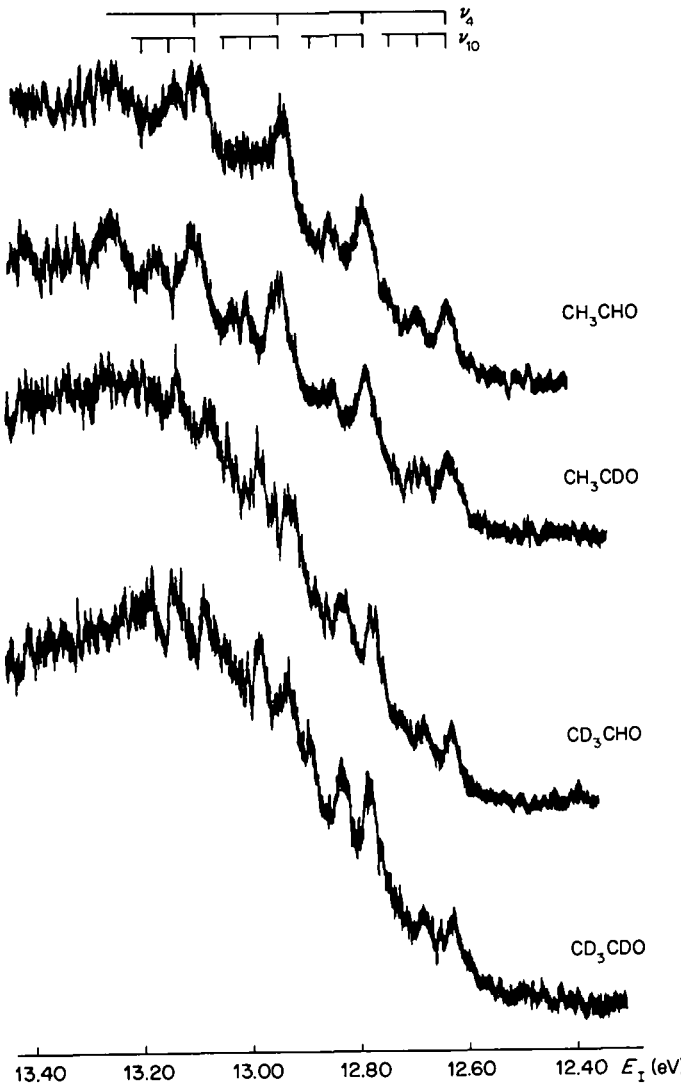


FIGURE 29b. High-resolution PES of the second electronic system ($\tilde{A}$) of acetaldehyde-d_0, -d_1, -d_3, and -d_4

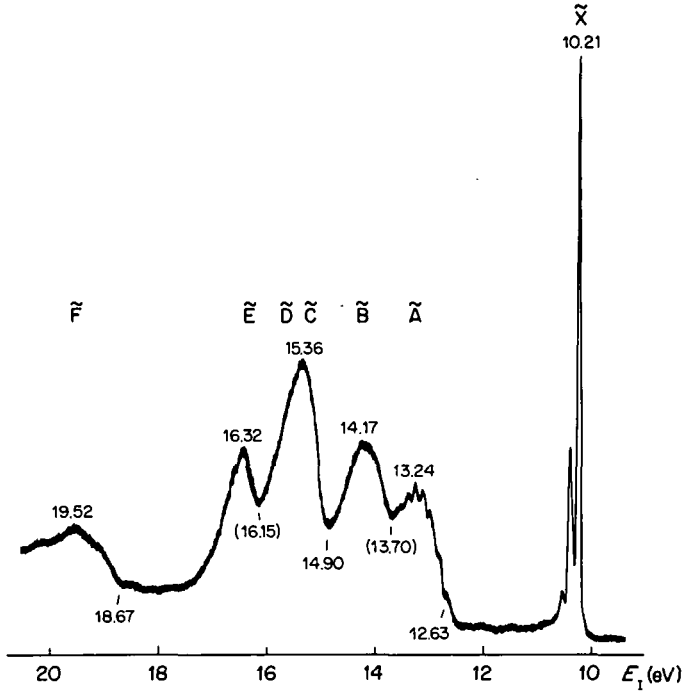


FIGURE 29c. HeI PES of acetaldehyde

on the oxygen atom and, for that reason, it experiences the changes in CO bonding: ν_4 decreases about 20% and ν_{10} remains much the same as in the molecular ground state. It is also of note that usually $I(n_O) < I(\pi_{CO})$ for aliphatic monocarbonyl compounds, and that, if no conjugated double bonds exist, no heteroatoms with low-energy lone pairs occur and no easy keto/enol tautomerization is feasible, $I(n_O)$ will be the lowest energy event in the PES of carbonyl compounds.

2. *Aldehydes, ketones, carboxylic acids and carboxylic acid derivatives*

These classes of compounds have been extensively investigated. The high degree of interest is not surprising since many of these compounds are biologically and industrially important. Thus, a vast PES literature for saturated and unsaturated, cyclic and non-cyclic carbonyl compounds, has been amassed and the spectra are well understood. The carbonyl and conjugated hydrocarbon moieties behave almost additively and interact little if at all. As a result, $I(n_O) < I(\pi_{CC})$ is generally valid for aliphatics but, if an aromatic ring is attached to the carbonyl group, $I(\pi) < I(n_O)$ is the rule. The shifts of $I(n_O)$ and $I(\pi_{CO})$ induced by particular substituents (*vide infra*) can be used to assign and interpret the spectra. The same approach can even be extended to substituted α-dicarbonyls[166]. Following the early measurements of simple carbonyls[52a,b,138,139], systematic PES studies of aldehydes[48,52j,64b], ketones[48,52j,64c,140–148], carboxylic acids[52j,140,149–153] and their derivatives[150,154–174] have been reported. An extensive list of references for mono- and α-dicarbonyls is given in Reference 10, citation 77.

Considerable information is also available for biological molecules[175], which

have proven to be surprisingly stable species. Indeed, PES provides insight into their electronic structure/activity relationship. Thus, the amino acids, certain peptides, DNA bases and a number of steroids have been measured. In the keto steroids, the $I(n_O)$ event is usually of lowest energy I_p. Typical spectra are shown in Figure 30. Steroids possess a fixed geometry and do not form intramolecular (head-to-tail) adducts in which both TB and TS interactions can propagate. Consequently, only TB interactions are expected. The PES of compounds in which separate keto groups are positioned at different distances from each other makes it possible to assess the distances over which TB can take place. Such investigations reveal the presence of long-range interactions and suggest that electron transfer[176] can take place over as much as ten carbon–carbon bonds.

3. *Additivity effects in the PES of carbonyl compounds*

Among the various experimental criteria used to relate PES to the ionization of electrons from specific molecular orbitals, correlations based on simple additive behaviour occupy an important niche. Specifically, the ionization potential $I(i, NX)$, where i is an MO index, X is a substituent index and N is the number of substituents, is found to be

$$I(i, NX) = I(i) + N\Delta I(i, X) \tag{1}$$

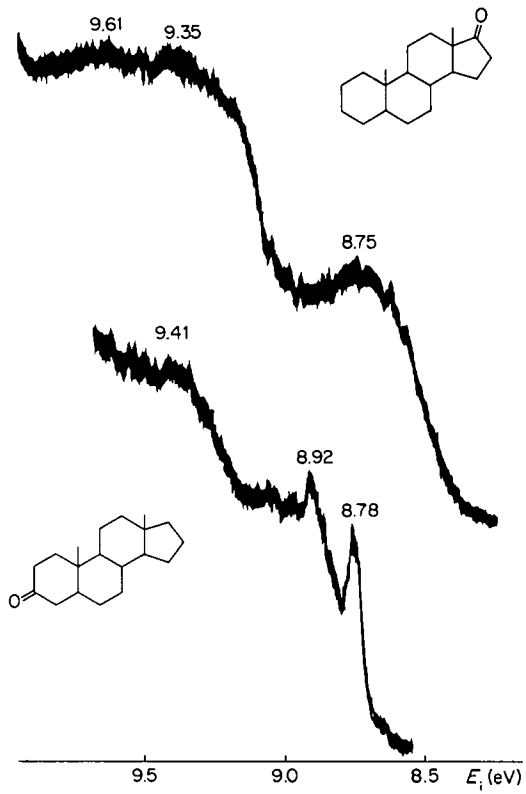


FIGURE 30. PES of some steroids

where $I(i)$ is the type-i ionization potential of some specified, unsubstituted, parent molecule and $\Delta I(i, X)$ is a constant for a given substituent X within a class of closely related parent molecules. The catch in our phraseology resides in the phrase 'closely related parent molecules'. The limits associated with this phrase are yet to be defined. Indeed, for carbonyl and α-dicarbonyl compounds, equation 1 exhibits an unusually broad range of validity.

As an example, consider the assignment by Brundle and coworkers[44e] of the 13.4 eV band of acetone to $I(\pi_{CO})$, where π_{CO} is the π MO localized on the C=O group. This assignment may be validated by considerations of the series: formaldehyde (H_2CO), acetaldehyde (CH_3CHO) and acetone (CH_3COCH_3). The $I(\pi_{CO})$ band of formaldehyde has a value of 14.5 eV (vertical) or 14.09 eV (adiabatic). The $I(\pi_{CO})$ band of formaldehyde may be correlated with either the second or third PES band of acetaldehyde which occur at I(second) = 13.2 eV (vertical) or 12.61 eV (adiabatic) and I(third) at 14.19 eV (vertical) or 13.54 eV (adiabatic)[137]. The $I(\pi_{CO})$ band of formaldehyde may also be correlated with the second or third band of acetone which occur at I(second) = 12.6 eV (vertical) or 11.99 eV (adiabatic) and I(third) = 13.4 eV vertical or 12.79 eV (adiabatic). If the three sets of data are evaluated simultaneously, the adiabatic ionization potential differences for correlation of $I(\pi_{CO})$ of H_2CO with I(second) of CH_3CHO and $(CH_3)_2CO$ are

$$H_2CO \xrightarrow{-1.48} CH_3CHO \xrightarrow{-0.62} (CH_3)_2CO \tag{2}$$

whereas an assumed correlation of $I(\pi_{CO})$ of H_2CO with I(third) yields

$$H_2CO \xrightarrow{-0.59} CH_3CHO \xrightarrow{-0.71} (CH_3)_2CO \tag{3}$$

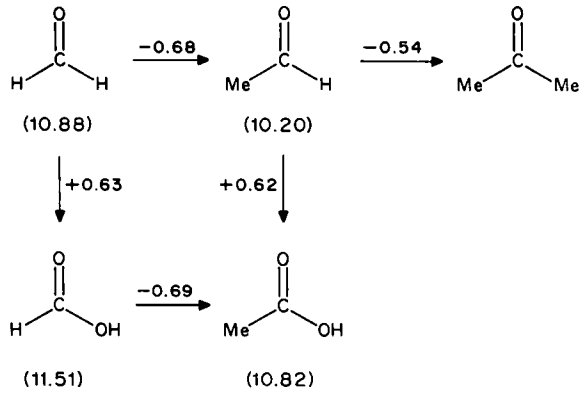
The latter scheme exemplifies the view expressed in equation 1 and, to the extent that equation 1 is meaningful, it supports the acetone assignment $I(\pi_{CO}) = 13.4$ eV. Other evidence supportive of this same assignment are:

(i) The $I(\pi)$ values for methylated ethylenes[52a] are: $CH_2{=}CH_2$ (10.50 eV); $CH_2{=}CHCH_3$ (9.73 eV); $CH_2{=}C(CH_3)_2$ (9.23 eV); $CH_3CH{=}C(CH_3)_2$ (8.67 eV); $(CH_3)_2C{=}C(CH_3)_2$ (8.30 eV). The $CH_2{=}C$ and $C{=}C(CH_3)_2$ groups are 'isoelectronic' with the C=O group and the average values of $\Delta I(\pi_{CO}, CH_3)$ for the ethylenic groups, −0.64 and −0.47 eV respectively, are comparable to the values of −0.59 and −0.71 eV found for the carbonyl group in equation 3.

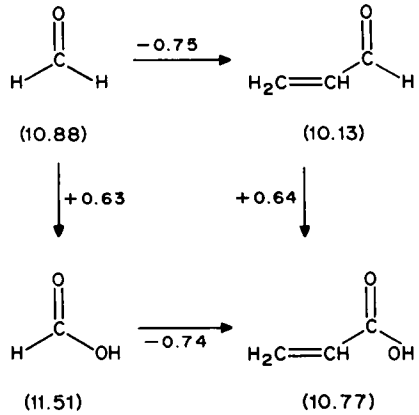
(ii) The adiabatic ionization potentials of equation 2, 12.61 (13.2, vertical) and 11.99 eV (12.6, vertical) for CH_3CHO and $(CH_3)_2CO$ respectively, correspond to the first PES band of CH_4 at 12.5 (13.5, vertical) and undoubtedly represent ionization of an electron which has significant amplitude on the $-CH_3$ group.

As a result, both the correctness of the Brundle assignment[44e] and the usefulness of equation 1 have been demonstrated. However, in dealing generally with substitution effects, the n_O MOs, the π_{CO} MOs, as well as those conjugated to the latter through π interactions, π_{XCO} (i.e. lone-pair electrons on heteroatoms X interacting with π_{CO}), must also be investigated. Let us start with the n_O ionization.

a. n_O ionization. The effects of $-CH_3$ and $-OH$ substitution on $I(n_O)$ of formaldehyde are shown in Scheme 2, where $\Delta I(n_O, CH_3)$, in eV, is indicated on the horizontal arrows, $\Delta I(n_O, OH)$ on the vertical arrows, and $I(n_O)$ is in parentheses below the molecular representation. Methylation of either formaldehyde or formic acid yields similar $\Delta I(n_O, CH_3)$ values. Substitution of an —OH group in either formaldehyde or acetaldehyde yields identical $\Delta I(n_O, OH)$ values. It also appears that multiple substitution is only slightly saturative, as witness the small change from —0.68 to —0.54 eV caused by



SCHEME 2



SCHEME 3

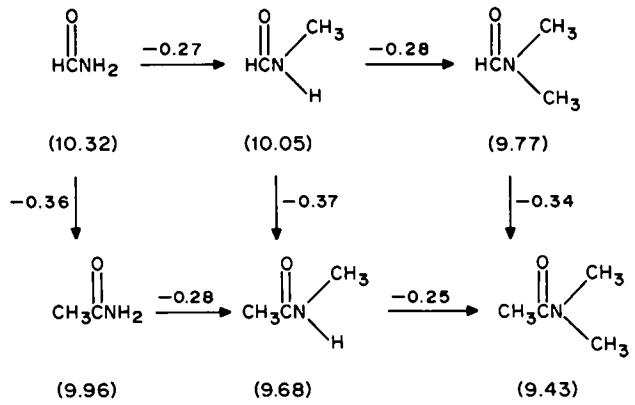
methylation in the series which yields acetone. These additivity effects are also found in an acrolein/acrylic acid cycle[52i] and are shown in Scheme 3.

Finally, the effects of $-CH_3$ and $-NR_2$ (R = H, CH_3) substitution on $I(n_O)$ of formamide are illustrated for the formamide/*N*, *N*-dimethylacetamide series[139,150] in the cycle shown in Scheme 4. It appears that N-methylation decreases $I(n_O)$ by 0.27 eV whereas C-methylation produces a decrease of 0.36 eV.

The effects of methylation on the simplest homologs are

$$H_2CO \longrightarrow CH_3CHO \qquad \Delta I(n_O) = -0.68$$
$$HCOOH \longrightarrow CH_3COOH \qquad \Delta I(n_O) = -0.69$$
$$HCONH_2 \longrightarrow CH_3CONH_2 \qquad \Delta I(n_O) = -0.36$$

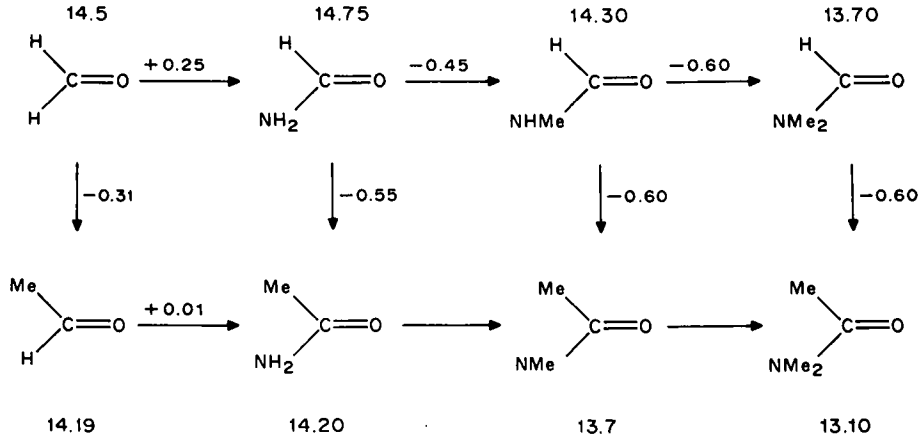
The small magnitude of the last value relative to the first two entries demands explanation. In formaldehyde/acetaldehyde, the adiabatic and vertical ionization energies are coincident. The vertical ionization energies of formic/acetic acids are coincident with the second vibrational peaks of the coupled vibrational progression in the >C=O stretching mode.



SCHEME 4

Hence, the $\Delta I(n_O)$ values are identical for those two couples whether we use vertical or adiabatic ionization values. In formamide/acetamide, the vertical energies occur at the second and third vibrational peaks, respectively, of the coupled vibrational progression in the >C=O stretching mode. Hence, the adiabatic $\Delta I(n_O)$ for this couple differs from the vertical $\Delta I(n_O)$ by one quantum of a >C=O stretching vibration. In this fashion, we find for formamide/acetamide that $\Delta I(n_O)$ is −0.55 eV (adiabatic) and −0.36 eV (vertical). Hence, the apparent discrepancy in the above tabulation is resolved to within the error of experiment. At the same time, this example points up a limitation intrinsic to the use of vertical $\Delta I(n_O)$ quantities.

b. π_{CO} ionization. Similar cycles may be formulated for $I(\pi_{CO})$. Several such cycles, all pertinent to the formaldehyde/*N*,*N*-dimethylacetamide series[52b,139,150], are shown in Scheme 5. Some comment on the left-most cycle, where obvious discrepancies occur, is required. These discrepancies are associated with the fact that the vertical ionization

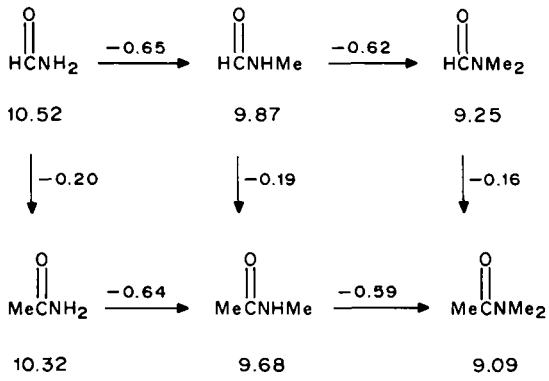


SCHEME 5

potentials differ from the adiabatic ionization energies by varying numbers of vibrational quanta. To be specific, in the formaldehyde/acetaldehyde couple, the vertical ionization energy of formaldehyde occurs on the third vibration peak, whereas in acetaldehyde it must, in order to bring the value −0.31 into accord with the other values for C-methylation, fall on the fifth vibrational peak. If 1210 cm^{-1} is used for the coupled vibrational quantum, this correction yields $\Delta I(\pi_{CO}) = -0.61$ eV for the formaldehyde/acetaldehyde couple. In addition, the same assertion yields $\Delta I(\pi_{CO}) =$ 0.31 eV for the acetaldehyde/acetamide couple and removes the discrepancy which existed with respect to the formaldehyde/formamide couple. Finally, this supposition leads to an adiabatic ionization energy of 14.59 eV for $I(\pi_{CO})$ of acetaldehyde, a value that is in excellent agreement with the value 14.5 eV found by Gaussian analysis of the photoelectron spectrum.

In terms of the cited cycle and the analysis just given, we find that $\Delta I(\pi_{CO}, CH_3)$ for C-methylation is remarkably constant at −0.55 eV, $\Delta I(\pi_{CO}, NH_2)$ at +0.25 eV, $\Delta I(\pi_{CO}, NHCH_3)$ at −0.25 eV, $\Delta I(\pi_{CO}, N(CH_3)_2)$ at −0.85 eV and $\Delta I(\pi_{CO}, CH_3)$ for N-methylation at approximately −0.55 eV.

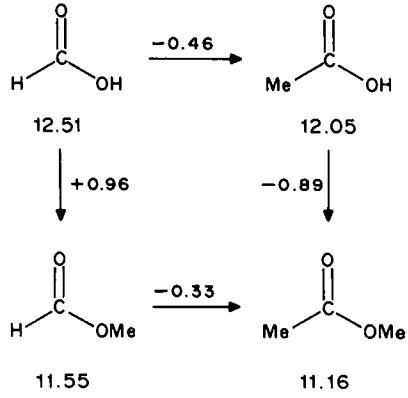
c. π_{XCO} ionization. The effects of methylation on $I(\pi_{XCO})$ in the formamide/*N*, *N*-dimethylacetamide cycle[139,150] are shown in Scheme 6. The decrements for



SCHEME 6

N-methylation are surprisingly constant at ~0.6 eV and for C-methylation at ~0.2 eV. A comparable cycle for C-methylation and O-methylation in the formic acid/methyl acetate series[139,150] is shown in Scheme 7.

d. Substituent effects. The totality of ΔI values, referred to formaldehyde as a parent molecule, are listed for $\Delta I(n_O)$ and $\Delta I(\pi_{CO})$ in Table 8. No $\Delta I(\pi_{XCO})$ values are listed since these may not be referred to a formaldehyde 'parent'. The $I(\pi_{XCO})$ ionizations are, in fact, introduced by the substituent groups themselves, in the sense that these ionizations involve removal of an electron which is heavily group localized. Thus, in an effort to refer the $I(\pi_{XCO})$ ionizations to the appropriate substituent group, Table 8 includes a listing $\delta I(\pi_{XCO})$. The quantity $\delta I(\pi_{XCO})$ is defined as $I(\pi_{XCO})$ for an HCOX molecule *minus* the lowest ionization energy of an HX molecule, both energies being vertical. Thus, the number listed under —$NHCH_3$ for $\delta I(\pi_{XCO})$ is $I(\pi_{XCO})$ for $HCONHCH_3$ minus the vertical energy of the first PES bond of NH_2CH_3. In view of the small values of $\delta I(\pi_{XCO})$ found in



SCHEME 7

TABLE 8. Effects of substitution on ionization potentials (in eV) of formaldehyde

Substituent, X	$\Delta I(n_O)$	$\Delta I(\pi_{CO})$	$\delta I(\pi_{XCO})$
—H	—	—	
—OH	+0.63		−0.10
—OCH_3	+0.14		−0.28
—NH_2	−0.36[a]	+0.25	−0.33
—CH_3	−0.68	−0.55[b]	−0.30
—CH=CH_2	−0.75		
—$NHCH_3$	−0.85	−0.20	+0.17
—$N(CH_3)_2$	−1.12	−0.80	+0.35

[a]See text.
[b]Vertical ionization energy of acetaldehyde has been adjusted by two quanta to obtain this value (see text).

this way, the π_{XCO} identifications given appear to be relatively secure. That is, all π_{XCO} PES bands assigned in HCOX molecules are energetically very similar to the lowest-energy bands of related HX molecules. All PES band identifications for HCOX molecules are summarized in Figure 31.

Meeks and coworkers[166] have shown that this additivity scheme can also be extended to α-dicarbonyls. The compounds studied were of general structure XCOCOY where X, Y = {H, R, OH, OR, NH_2, NHR, NR_2, Cl} and R = {Me, Et}. They specify two basic classes: symmetric when X = Y and non-symmetric when X ≠ Y and, for purposes of MO designation, introduce a secondary classification based on the degree of substitution. Thus, if we define substitution as the introduction of a group, X or Y, which yields an easily ionizable MO of type π_{XCO}, we can subdivide the α-dicarbonyl compounds into 'unsubstituted', 'monosubstituted' and 'disubstituted' types.

As in the azo compounds where the two nitrogen lone pairs give rise to symmetric and anti-symmetric n_+ and n_- linear combinations, such combinations also exist for the two oxygen lone-pair orbitals n_O, which we term $_\oplus$ and $n_\ominus$, and also for the two π_{CO} orbitals, which we term $\pi_\oplus$ and $\pi_\ominus$. A similar situation occurs for the π_{XCO} of 'disubstituted' dicarbonyls, and we term these $\pi_{X\oplus}$ and $\pi_{X\ominus}$.

The utility of the above subdivision is embodied in Table 9 where the various types of

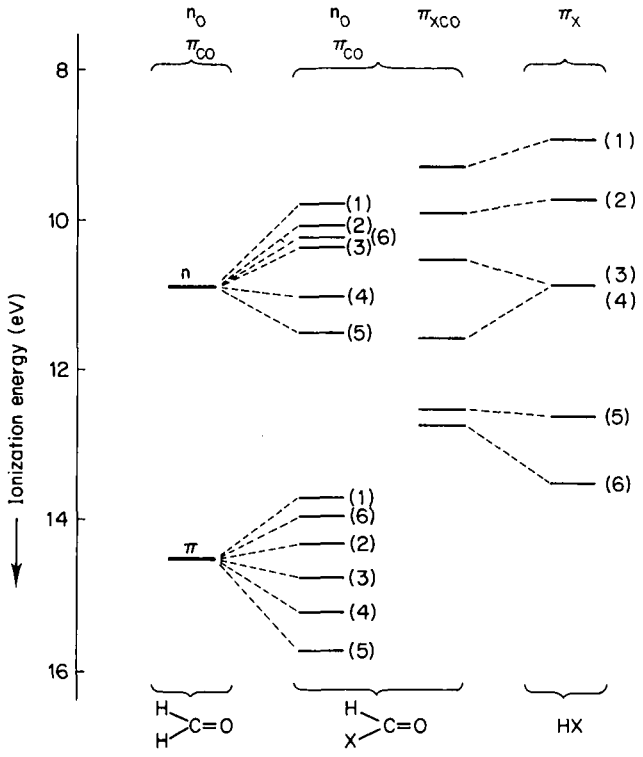


FIGURE 31. A correlation diagram detailing PES assignments in HCOX

MOs are related to each other and to those of the monocarbonyls. Some comments on this table are in order:

(i) The $\pm$ subscripting in the case of the πMOs (i.e. $\pi_{\oplus}$, $\pi_{\ominus}$, $\pi_{X\oplus}$ and $\pi_{X\ominus}$) refers to the phasing in the —C—C— bond region of the α-dicarbonyl; that is, each member of a pair is bonding (i.e. plus subscript) or anti-bonding (i.e. minus subscript) in the carbon–carbon bond region.

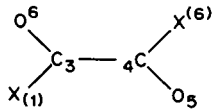
(ii) The n_O MO of a monocarbonyl has been described. The nomenclature used for the n_O MOs of a dicarbonyl should convey physical meaning and should be general enough to cover a wide variety of dicarbonyls (i.e. $\alpha, \beta, \gamma, \ldots$, saturated or unsaturated, X group or H).

(iii) The group orbitals formed from the two n_OAOs may be distinguished with respect to the phasing of the individual n_O components or with respect to their transformation properties under some pertinent symmetry element of the molecular point group of the dicarbonyl. The term 'phasing' is defined with respect to a line joining the two atomic centres of interest (i.e. the carbon centres in the case of the π orbitals discussed previously; the oxygen centres in the case of n orbitals). The resulting molecular orbitals of type n are defined as being negatively phased, designated $n_{\ominus}$, if atomic orbitals on these centres are effectively orthogonal with respect to this 'bond line', and positively phased, designated $n_{\oplus}$, if they are non-orthogonal (i.e. exhibit bonding character) with respect to this same 'bond line'. The term 'transformation properties' which refers to symmetry or antisymmetry[177], designated n^S and n^A, respectively, varies with the symmetry of the dicarbonyl. The

TABLE 9. n and π MOs of monocarbonyl and α-dicarbonyl compounds[a]

Monocarbonyls		α-Dicarbonyls		
Unsubstituted	Substituted	Unsubstituted	Monosubstituted	Symmetric disubstituted
MO (1) 2 3	MO 2 3	MO (1) 2 3 4 5 (6)	(1) 2 3 4 5 (6)	MO (1) 2 3 4 5 (6)
$n_O(\cdot) + \cdot$	$n_O(\cdot) + \cdot$	$n_\oplus(\cdot) + \cdots + (\cdot)$	$n_\oplus(\cdot) + \cdot\cdot + (\cdot)$	$n_\oplus(\cdot) + \cdot\cdot + (\cdot)$
		$n_\ominus(\cdot) + \cdot\cdot - (\cdot)$	$n_\ominus(\cdot) + \cdot\cdot - (\cdot)$	$n_\ominus(\cdot) + \cdot\cdot - (\cdot)$
			$(\cdot) - - + + (-)$	$\pi_{x\ominus}(+) - - + + (-)$
	$\pi_{xCO}(-) + +$	π_O	or	
			$(\cdot) + + + + (-)$	
				$\pi_\oplus(-) + + + + (-)$
$\pi_{CO}(\cdot) + +$	$\pi_{CO} + + +$	$\pi_\ominus(\cdot) + + - - (\cdot)$	$\pi_\ominus(\cdot) - - + + (+)$	$\pi_\ominus(-) - - + + (+)$
		$\pi_\oplus(\cdot) + + + + (\cdot)$	$\pi_\oplus(\cdot) + + + + (+)$	$\pi_\oplus(+) + + + + (+)$

[a]This table, modified to some degree, is taken from Meeks and coworkers[166]. The + and − signs refer to the phasing of the wave functions on the various atomic centres. The dot indicates zero or near-zero wave-function amplitude. The numbering system for the atomic centres is



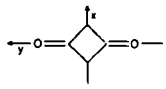
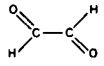
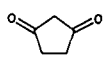
The n and π nomenclature used is strictly valid for wholly planar α-dicarbonyls but retains qualitative significance even when X = CH_3, C_2H_5 or when the α-dicarbonyl is non-planar.

physical content of both of these notations need not be identical. Hence, we must evolve a physically more consistent notation.

(iv) The zero-order degeneracy of the two n_O group orbitals is removed by interactions with the carbon skeleton. If we restrict our initial considerations to a centro-symmetric point group, we find that inversion symmetry permits definite statements to be made about these interactions. One must first, however, discard the possibility of large interactions of the n_O group orbitals with virtual orbitals of a skeletal nature, a supposition which, based on energy denominator criteria, seems quite safe. Thus, one of $n^{S/A}$ may interact with either σ-bonding or other σ-non-bonding but symmetric orbitals. Since the former constitute the majority of ground-state orbitals, interactions of n^S with these are the most likely and calculation supports this conclusion. The other one of $n^{S/A}$ may intract only with non-bonding, anti-symmetric, skeletal orbitals and, again, calculation supports this conclusion. Thus, the two MOs resulting from n^A and n^S interactions with the molecular skeleton may now be relabeled n^σ and n^O, respectively. The physicochemical connotations of this nomenclature are obvious. Unfortunately, this notation does not correlate with that based on phasing of the n_O orbitals, nor does it correlate with the one based on symmetry in non-centro-symmetric point groups.

The highest symmetry of dicarbonyl compounds is D_{2h} (i.e. cyclobutanedione or quinone); virtually all other dicarbonyl compounds with symmetry greater than C_1 belong to one of the three point groups C_{2h}, C_{2v} or C_s, all of which are subgroups of D_{2h}. The point group C_{2v}, however, is not a subgroup of C_{2h} but, with careful definition of molecular symmetry axes, a symmetry correlation which maintains the uniqueness of the n^σ and n^O notations (and renders them distinguishable with respect to at least one symmetry element) can be obtained. Such a correlation is detailed in Table 10. Thus, the statements

TABLE 10. Notations

Group[a]	D_{2h}	$C_{2h}(C_{2y})$	$C_{2v}(C_{2x})$	$C_s(\sigma_{xz})$
Example				

Correlation criteria	Γ	i	P	Γ	i	P	Γ	C_{2x}	P	Γ	σ_{xz}	P
n^{σ}	b_{2g}	n^{S}	n^{-}	a_g	n^{S}	n^{-}	b_2	n^{A}	n^{-}	a′	n^{S}	n^{+}
n^{O}	b_{3u}	n^{A}	n^{+}	b_u	n^{A}	n^{+}	a_1	n^{S}	n^{+}	a″	n^{A}	n^{-}

[a]The symmetry element listed in brackets after the group symbol is the element of D_{2h} which is taken to be the principal element of the group in question. Axes for all groups are defined in the specific case of D_{2h}. The notations which are correlated are Γ: the group representation for which $n^{\sigma/O}$ forms a basis; i, C_{2x} or σ_{xy}: the manner in which $n^{\sigma/O}$ transforms under the symmetry operation in question; and p: the phasing of $n^{\sigma/O}$ as defined in the text.

made for the centro-symmetric point group are valid for all these groups, and the nomenclature retains its physical significance.

In sum, the simple symmetry designations, $n^{S/A}$, are not generally satisfactory; for example, n^{σ} is symmetric in C_s and C_{2h} but anti-symmetric in C_{2v} and D_{2h}. Thus, the notation $n^{\sigma/O}$ provides the only unique designation, unique in the sense that the physical meaning remains invariant. This meaning is straightforward: n^{σ}, having interacted with bonding skeletal orbitals, has considerable amplitude on the —C—C— part of the molecule whereas n^{O} has none or very little.

On the basis of a simple one-electron approximation, one expects the energy of the resultant orbitals to be $n^{\sigma} > n^{O}$ (i.e. n^{σ} to be the highest-energy ground-state MO in all cases) and, in fact, experimental evidence supports this conclusion. Ionization of the n^{σ} orbital should be accompanied by a distinct change in molecular geometry in the cationic state (because of the coupling with a skeletal bonding orbital). As a result, one may expect the photoelectron spectrum to exhibit a band in which the adiabatic and vertical ionizations are not coincident and in which both the carbonyl and the skeletal vibrations are approximately equally excited. On the other hand, ionization of the n^{O} orbital should not cause a significant change in geometry; as a result, one may expect the photoelectron spectrum to exhibit a band in which the adiabatic and vertical ionizations are coincident (or, at most, separated by one quantum of vibration) and in which the vibrational activity is predominantly carbonyl. The above conclusions are borne out by all the available PES data for α- and β-dicarbonyls with one exception: in tetramethylcyclobutanedione, for reasons we do not understand, the n^{O} orbital is more readily ionized than n^{σ}.

For the sake of consistency with previous authors, we now define $n^{\sigma} \equiv n_{\oplus}$ and $n^{O} \equiv n_{\ominus}$ and we will use this latter nomenclature throughout this paper.

The ionization events of interest in this work are those which involve n_O, π_{XCO} and π_{XO} electrons in the monocarbonyls and $n_{\oplus}$, $n_{\ominus}$, $\pi_{\oplus}$ and $\pi_{\ominus}$ electrons in the α-dicarbonyls. The ionizations which involve $\pi_{X\oplus}$ and $\pi_{X\ominus}$ electrons in the α-dicarbonyls will not be discussed here in any detail but, because of their great susceptibility to methyl perturbations (i.e. N-alkylation, O-alkylations, etc.), they do remain of interest[164].

4. α-Dicarbonyl compounds

The ionization potentials $I(n_{\oplus})$, $I(n_{\ominus})$, $I(\pi_{\oplus})$ and $I(\pi_{\ominus})$ of the symmetric α-dicarbonyls are listed in Table 11. The substituent effects were evaluated using

$$\Delta I(i, X) = \tfrac{1}{2}[I(i, HCO)_2 - I(i, XCO)_2] \quad (4)$$

Thus, $\Delta I(n_{\oplus}, OH) = \frac{1}{2}(10.52 - 11.20) = +0.34$ eV. The list of substituent effects is given in Table 12. Ionization potentials of non-symmetric α-dicarbonyls may be computed from Table 12 using

$$I(i, XCOCOY) = I(i, HCO)_2 + \Delta I(i, X) + \Delta I(i, Y) \quad (5)$$

or, equivalently, from Table 11 using

$$I(i, XCOCOY) = -\tfrac{1}{2}[I(i, XOC)_2 + I(i, YCO)_2] \quad (6)$$

Equation 4 makes possible the extraction of the $\Delta I(i, X)$ values of Table 12 and serves no other purpose.

Ionization potentials for the non-symmetric α-dicarbonyls, as obtained from Table 12 are listed in Table 13 where they are compared with the experimental values. The agreement of calculated and experimental quantities in Table 13 is well within experimental error in all instances except one. The sole exception is $I(n_{\oplus})$ of $C_2H_5OCOCON(CH_3)$; this exception is noteworthy because this is the only compound in Table 12 for which the dicarbonyl dihedral angle is $0° \ll \theta \ll 180°$ and for which our additive approach is clearly invalid anyway. Table 13 confirms both the additive $\Delta I(i)$

TABLE 11. Vertical ionization potentials (in eV) of 'symmetrical' α-dicarbonyls

Molecule	$I(n_+)$	$I(n_-)$	$I(\pi_-)$	$I(\pi_+)$
HCOCOH[a]	10.52	12.19	13.85	15.88
$CH_3COCOCH_3$	9.55	11.46	13.20	14.73
$H_2NCOCONH_2$	9.80	11.72	13.39	16.15
HOCOCOOH	11.20	13.25	14.40	16.62
$CH_3OCOCOOCH_3$	10.36	11.74	13.48	16.38
$C_2H_5OCOCOOC_2H_5$	10.19	11.41	13.19	16.30
$CH_3NHCOCONHCH_3$	9.33	11.20	12.42	—
$(CH_3)_2NCOCON(CH_3)_2$	9.02	10.49	12.32	—
ClCOCOCl	11.26	—	—	—

[a]The assignments quoted for glyoxal are from Turner and coworkers[1c]. All other assignments in this table are discussed elsewhere[164].

TABLE 12. Effects of substitution on ionization potentials (in eV) of glyoxal

Substituent	$\Delta I(n_+)$	$\Delta I(n_-)$	$\Delta I(\pi_-)$	$\Delta I(\pi_+)$
H	—	—	—	—
Cl	+0.37	—	—	—
OH	+0.34	+0.53	+0.28	+0.37
OCH_3	−0.08	−0.22	−0.34	+0.25
OC_2H_5	−0.16	−0.39	−0.61	+0.21
NH_2	−0.36	−0.24	−0.23	+0.14
CH_3	−0.48	−0.36	−0.32	−0.58
$NHCH_3$	−0.60	−0.50	−0.71	—
$N(CH_3)_2$	−1.50	−0.85	−0.76	—

TABLE 13. Experimental and calculated ionization potentials (in eV) of non-symmetric α-di carbonyls

Molecule	Origin	$I(n_+)$	$I(n_-)$	$I(\pi_-)$	$I(\pi_+)$
$CH_3COCOOH$	Calc.	10.38	12.36	13.81	15.67
	Expt.	10.42	12.31	13.79	15.64
$CH_3COCOOCH_3$	Calc.	9.96	11.61	13.19	15.55
	Expt.	9.88	11.56	13.04	15.42
$CH_3COCONH_2$	Calc.	9.68	11.59	13.30	15.44
	Expt.	9.71	11.48	13.01	15.54
$HOCOCONH_2$	Calc.	10.50	12.48	13.90	16.39
	Expt.	10.51	12.40	14.21	16.40
$C_2H_3OCOCONH_2$	Calc.	10.00	11.56	13.00	16.22
	Expt.	9.85	11.73	13.15	—
$C_2H_3OCOCOCl$	Calc.	10.73	—	—	—
	Expt.	10.77	—	—	—
$C_2H_3OCOCON(CH_3)_2$	Calc.[a]	8.86	10.95	—	—
	Expt.	9.31	11.09	—	—

[a]This molecule is twisted (i.e. $\theta \simeq 90°$) as is the symmetric $(CH_3)_2NCOCON(CH_3)_2$ entity of Table 11 from which the $—N(CH_3)_2$ substituent effect of Table 12 is obtained. Since these are the only two molecules of Tables 11 and 13 which are severely twisted, it is not improbable that the discrepancy between $I(n_+)$, calculated and experimental, for $C_2H_5OCOCON(CH_3)_2$ in Table 13 is a result of these non-planarities. In turn, this discrepancy may imply that conjugative effects on $I(n_+)$, while small, are not negligible.

approach and the correlation of levels listed under a given $I(i)$. It must be emphasized, however, that the i assignments which have been made require specific identifications (i.e. $i = n_\oplus, n_\ominus, \pi_\oplus$ or $\pi_\ominus$) for one compound, preferably the parent molecule glyoxal. Such identifications, fortunately, are available[1c].

Table 11 points up the largely inductive nature of the effects being studied: the better donors produce large negative ΔI values, the better acceptors produce small positive ΔI values and the overall order of ΔI agrees with ordinary chemical notions of a donor–acceptor character. The order of substituent effects is identical in all cases, implying that identifications in the monocarbonyls may, in many cases, be used to classify n/π types in the α-dicarbonyls. The ΔI values also tend to be larger for n MOs than for π MOs. Thus, the enumerated ΔI effects appear to be largely inductive. As a result, and in view of the fact that the ratio $\Delta I(i, X)$ is, in most instances, not larger than 5% of $I(i)$, the approximate validity of a perturbation theory approach is assured. This, we believe, provides the rationale for the additivity regularities which have been observed.

To suppose that conjugative interactions are entirely negligible would be wrong. Indeed, conjugative effects must be held responsible for the opposite values of $\Delta I(\pi_\pm)$ found in many instances. Such effects are undoubtedly related to overlap densities in the —X—C regions, densities which are assuredly determined by the nodal differences of the $\pm$ MOs of π type.

5. *Computational results*

The results of CNDO/S computations for various amides are given in Figure 32.

a. Computed ΔI values. As seen in Figure 32, the n_O and π_{XCO} energies behave quite differently with respect to the two, N and C, types of methylation. In fact, for the

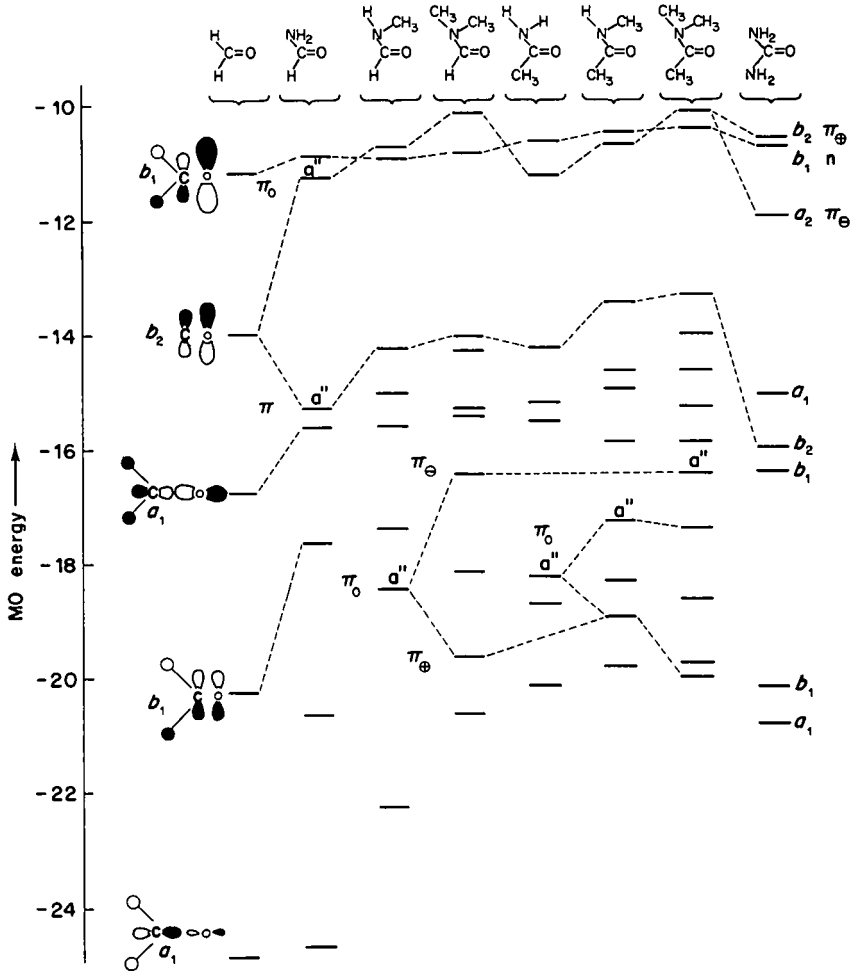


FIGURE 32. A correlation diagram of CNDO/S computational results for various amides

monocarbonyls, the values of $\Delta I(i, \mathrm{X})$ where

$$\Delta I(i, \mathrm{X}) \equiv [\Delta I(i, \mathrm{X}) + \Delta I(i, N\mathrm{X})]/(N+1) \tag{7}$$

are given in the following table.

$\Delta I(i, \mathrm{X})$	CNDO/S	Experiment
$\Delta I(n_O$, Me on N)	−0.12	−0.27
$\Delta I(n_O$, Me on C)	−0.29	−0.35
$\Delta I(\pi_{XCO}$, Me on N)	−0.52	−0.63
$\Delta I(\pi_{XCO}$, Me on C)	−0.03	−0.18

The agreement with the experimental values, not only with regard to order but even with respect to magnitudes, is excellent. The results support the additivity attitudes.

b. Molecular orbital energies. Figure 32 indicates that the n_O and π_{XCO} MOs of formamide reverse order in *N*-methylformamide and that this latter order is retained in *N*,*N*-dimethylformamide, in *N*,*N*-dimethylacetamide and in urea. A second reversal to the original formamide order is shown to occur in acetamide and in *N*-methylacetamide. Whether or not we believe the results of Figure 32, it is clear that the n_O/π_{XCO} order in *N*-methylformamide (which, incidentally, is also the order found by Brundle and coworkers[139]) cannot be used to infer a similar order in *N*-methylacetamide. Such an inference has been made[150].

The predicted n_O/π_{XCO} orderings of Figure 32 agree with all previously available assignments except for the one instance of *N*-methylacetamide which will be discussed later.

c. Methylation effects on $I(\pi_{XCO})$ and $I(n_O)$. A plot of $I(\pi_{XCO}) - I(n_O)$ for various formyl and acetyl derivatives is given in Figure 33. The two correlation lines are roughly parallel and exhibit a vertical separation of 0.18 eV. Since this vertical separation also equals

$$[I(\pi_{XCO}, \text{Me}) - I(\pi_{XCO}, \text{H})] - [I(n_O, \text{Me}) - I(n_O, \text{H})]$$

where substitution is on the formyl carbon, this vertical separation can be computed from the $\Delta I(\pi_{CO}, \text{Me})$ and $\Delta I(n_O, \text{Me})$ values of Table 12. The result is 0.18 eV!

Figure 33 is essentially identical with Figure 7 of Sweigart–Turner[150] except in two regards: the HCONHMe point is taken from Brundle and coworkers[139] and corresponds to their $\tilde{B}$ and $\tilde{A}$ band energy separation; and the MeCONHMe point is obtained by assuming that the 9.68 eV PES maximum represents the vertical process for both the n_O and π_{XCO} ionizations. In any event, simple parallelism of the two curves of Figure 33 supports the assumption of near-coincidence of the vertical values of $I(\pi_{XCO})$ and $I(n_O)$ in *N*-methylacetamide.

d. N-Methylacetamide. The additivity attitudes used here are a remarkable vindication of the Sweigart–Turner assignments. In only one instance, *N*-methylacetamide, do we find any disagreement. The assignments made here for *N*-methylacetamide, $I(n_O) = I(\pi_{XCO}) = 9.68$ eV, differ from those of Sweigart–Turner, $I(n_O) = 9.85$ and $I(\pi_{XCO}) = 9.68$ eV, by only 0.17 eV and that only for $I(n_O)$. Nonetheless, it is important to decide which set of assignments is the more reasonable. Such a determination should provide a critical test of additivity attitudes.

The Sweigart–Turner assignment was made for two reasons.

(1) It seemed logical on the basis of inductive considerations. Since the considerations indulged here are inductive also, the differences lie not in the attitudes but in the manner of their use. Hence, further discussions along inductive lines will not resolve the dilemma.

(2) It was thought[150] that the $I(n_O)/I(\pi_{XCO})$ order in *N*-methylacetamide should be the same as in *N*-methylformamide, where quite secure identifications did exist and where $I(\pi_{XCO}) > I(n_O)$. This sort of argument, as shown above, is not in agreement with computational CNDO/s results.

We now return to the experimental basis for the Sweigart–Turner assignment. The lowest-energy PES band of *N*-methylacetamide has a maximum at 9.68 eV and in inflection at 9.85 eV. It is clear, on the basis of both intensity and correlative arguments, that this PES band encompasses two ionization events. However, it is not obvious that these events correspond, respectively, to the 9.68 (max) and 9.85 (infl) eV features. In fact, since the separation of the two features is 1452 cm^{-1}, it is equally logical to suppose that the inflection is of a vibrational nature (i.e. a C=O stretching quantum). Indeed, since the

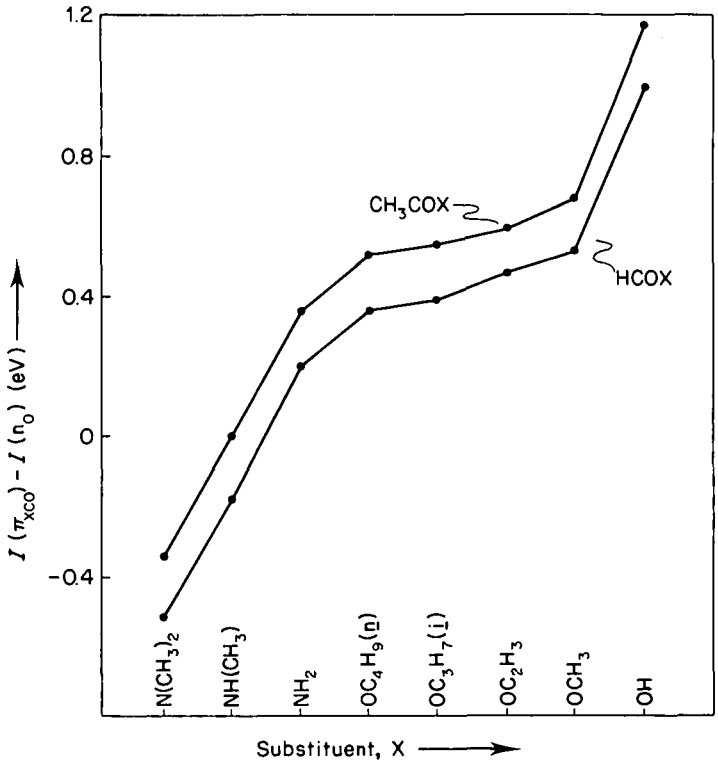


FIGURE 33. Correlation lines for formyl and acetyl derivatives

halfwidth of this band, ~0.7 eV, is fully as small as that for molecules in which the I(n) band is totally resolved (~0.6 eV in CH_3COOH, ~0.5 eV in HCOOH), it is equally sensible to assume that the n_O and π_{xCO} vertical ionizations both lie at the maximum (i.e. at 9.68 eV).

6. *Conclusions*

Substituent additivity arguments somewhat similar to ours have been generated by other authors: Sustmann and Schubert[178], Hashmall and Heilbronner[179] and Johnstone and Mellon[180]. However, the molecules of interest to these authors[178-180] were quite different from ours and, additionally, the additivity algorithm was not used for assignment purposes. Since we have validated many of our assignments by independent means in other places[164], we conclude that the additivity approach introduced here is a valid and viable correlative tool for PES assignments. However, as with all correlative algorithms, it must be used carefully.

This latter caution should be obvious from the textual discussion. In order to be specific, however, it is clear that the additivity algorithm is restricted to the use of adiabatic ionization energies. The vertical ionization energies differ from the adiabatic values by varying numbers of vibrational quanta and, unless these are known, the $\Delta I(i)$ results may be wholly misleading. Unfortunately, the adiabatic values are rarely known experiment-

ally and must be obtained by Gaussian resolution or other inferential techniques. Thus, since the direct experimental results are usually of a vertical nature, one is forced to make use of these quantities. It is thought that this work demonstrates the proper use of these quantities and, on their basis, makes useful correlative arguments relating to cationic state identifications.

Vertical ionization potentials are commonly used in photoelectron spectroscopy for two reasons: (i) they are the only type readily measurable (in other words, it is difficult to extract an adiabatic potential from a vibronically unstructured PES band but rather easy to read off the band maximum.); (ii) if the Franck–Condon principle is valid, the vertical ionization event refers to the production of a cationic state which is geometrically identical with the ground state; as such, by invoking Koopmans' theorem, we can equate the vertical ionization energy to a ground-state canonical SCF MO energy–a result which is both fortunate and convenient.

Consequently, the effects of substituents on individual vertical ionization energies correspond, in a theoretical sense, to a study of substituent effects on individual MO energies. It is in this specific context that the interpretation of PES spectra becomes 'easy'. The effects of substituents on individual adiabatic ionization energies correspond, in a theoretical sense, to a study of substituent effects on the energy difference between 'vibrationless' cationic and ground states, each in its minimum-energy geometric configuration. In this latter context, the interpretation of PES spectra could become exceedingly difficult. As long as the difference I(vertical $-$ I(adiabatic) is not altered by substitution (or, more specifically, if $\Delta I_{v-a} = h\sum_i v_i' \nu_i'$, where v_i' is the number of quanta of the normal mode i of frequency ν_i' excited in the cationic state, is invariant to substitution), the interpretation of adiabatic ionization energy differences reverts to that pertinent to the vertical differences and also becomes 'easy'. When, however, ΔI_{v-a} is altered by substitution, as is the case in some instances reported here, the meaning of adiabatic energy differences grows complex.

Thus, the finding that the substituent additivity algorithm applies to adiabatic processes but not to vertical processes is a bit unfortunate: Additivity applies in a realm which is interpretively difficult (i.e. adiabatic events) and not in one which is interpretively 'easy' (i.e. vertical events). In any event, the results obtained do not necessarily contravene Koopmans' theorem; they merely note that MOs do not, in general, exhibit additivity effects. Whether or not the observation that the adiabatic ionization energies do exhibit additivity effects implies that the molecular orbitals of the cation are not simply or smoothly related to those of the neutral molecules (and, hence, that Koopmans' theorem does not apply) is a matter for conjecture.

VIII. FINAL REMARKS

Having treated the four double-bonded groups separately, some generalization of the common characteristics would appear to be in order. In agreement with their unsaturated, double-bond character, ethylene, methanimine, diazene and formaldehyde are reactive molecules, those two containing nitrogens being particularly so. However, even from the PES point of view, all of these compounds and their derivatives are quite different. Consequently, we have made an attempt to correlate their 'double-bond' PES bands, the result being Figure 34. Inspection of this simple diagram for C_2H_4, CH_2NH, N_2H_2 and H_2CO, the PES bands being labelled by suitable π, n and σ quantities, makes the root of the differences clear: the increasing electronegativity that occurs in proceeding from carbon to nitrogen to oxygen (or two nitrogens) causes the $I(\pi)$ values to shift to higher energies by 2 eV/N atom and by another 2 eV as the NH group is replaced by an oxygen atom.

One could say, in a very rough way, that all these compounds have an ionization event

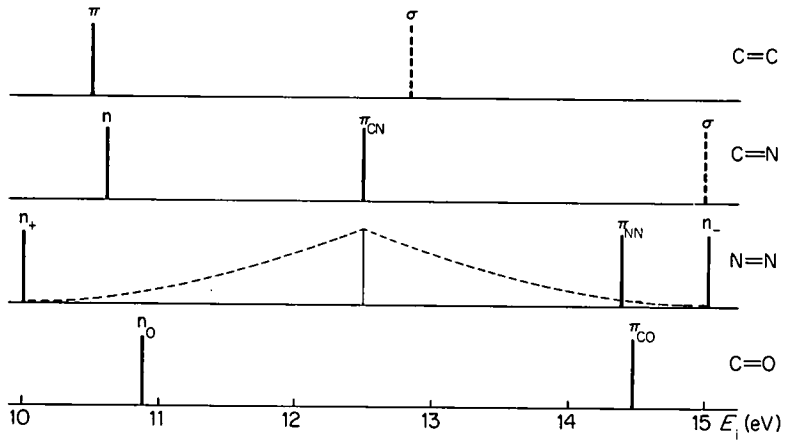


FIGURE 34. A correlation of the 'double-bond' PES bands for C_2H_4, CH_4NH, N_2H_2 and H_2CO

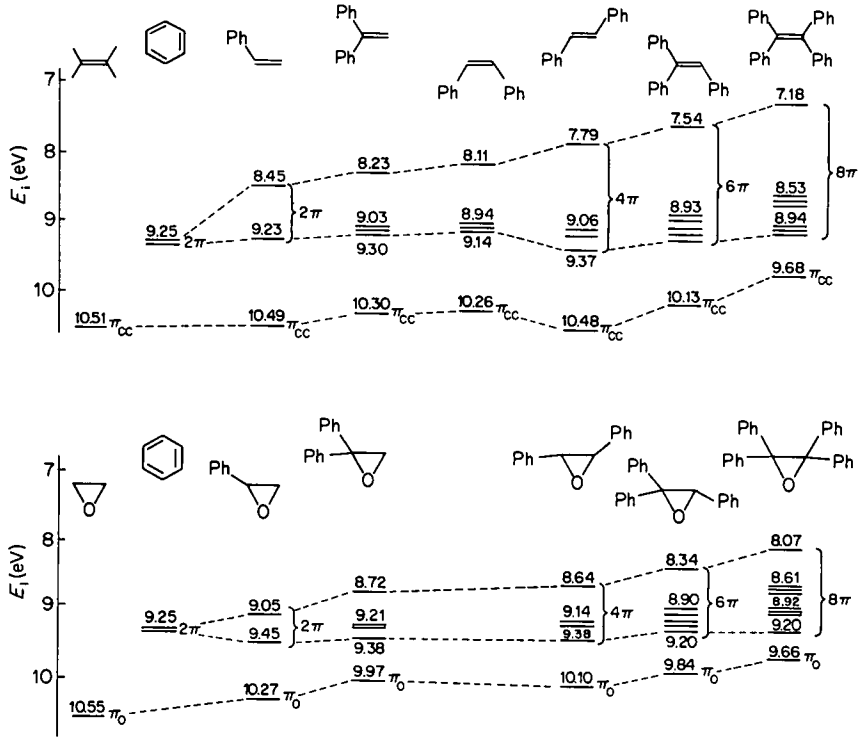


FIGURE 35. PES correlation diagrams for phenylethylenes and ethylene oxides. From Reference 181

in the 10–11 eV region. However, the twenty years of PES investigations that are subsumed in Figure 34 indicate that these ionization events are very different in nature and that conclusions vested solely in the energy are often misleading. Indeed, in view of Figure 34, it is not surprising that the sensitivity of these bands to substitution and conformational changes is, as we have seen, dramatically different (e.g. perfluoro effects, n_+/n_- splitting in *cis–trans* azo compounds, etc.).

On the other hand, some substituents, for example the methyl group, which interacts with both n and π electrons, possess the remarkable property that their PES spectra look like those of the parent molecules and one might think in these instances that the possibility of error would be absent. Not so, however. The formal approach can induce wrong conclusions: methyl substitution lifts (disturbs) the σ/π differentation, as indicated by a non-specific perfluoro effect, and, consequently, it will affect the double-bond properties. We have to a large degree evaded any tight discussion of the integrity of the double-bond concept. Nonetheless, some of our examples have emphasized the fact that there are conceptual problems associated with the PES assignment for double-bonded compounds. It is for that reason that we have omitted compounds in which the phenyl group appears as a substituent, even though the double-bond property in some such compounds may be better defined than in a polyalkyl derivative. As an example illustrative of our reluctance to consider phenyl substituents, we present two correlation diagrams[181], one for phenylethylenes and the other for the corresponding ethyleneoxides in Figure 35. Although the 10 eV PES bands are assigned differently as $I(\pi_{CC})$ in the first set and as $I(\pi_O)$ in the second set, there is no doubt that the electronic structures of both sets are closely related. Thus, a large question is posed concerning the extent to which the carbon–carbon bond at the bridge can be considered to be a double bond.

IX. ACKNOWLEDGEMENT

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The Chemistry of Double-bonded Functional Groups
Edited by S. Patai

CHAPTER **5**

Directing and activating effects of doubly bonded groups*

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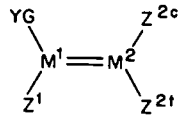
I. DOUBLY BONDED GROUPS

A. Types of Doubly Bonded Groups

The purpose of this work is to describe by means of structure property quantitative relationships the effects of doubly bonded groups on chemical reactivities, chemical and physical properties and biological activities. We must first define doubly bonded groups. Such groups are of the type **1** in which M^1 and M^2 are joined by a σ and a π bond; Z^1, Z^{2c} and Z^{2t} may be any atom or group of atoms, or a lone pair; M^1 is attached by a σ bond to a



(1)

skeletal group G, to which the active site γ is also bonded. It is at Y that the measured phenomenon which is to be modelled occurs. Alternatively, X may be bonded directly to Y, as in directly substituted carbocations, carbanions and radicals. π bonds may be classified as p, p or p, d depending on the types of atomic orbitals from which they are constructed. p, p π bonds may be further classified according to the periods of the periodic chart in which the elements M^1 and M^2 are located. Examples of double-bond types are given in Table 1 with their π-bond energies, bond lengths and stretching force constants when available. Where π-bond energies E_{pi} are unavailable, they have been estimated from the equation

$$E_{pi} = a_l l_{M^1-M^2} + a_{chi}\Delta_{chi} + a_0 \tag{1}$$

where $l_{M^1-M^2}$ is the bond length in picometers and Δ_{chi} is the difference in electronegativity between the sp^2 hybridized atoms M^1 and M^2.

The equation obtained by correlation of the bond lengths and Δ_{chi} values with equation

TABLE 1. Properties of p, p π bonds of the main group elements[a]

Bond	E_π[b]	Ref.	l[c]	Ref.	k[d]	Ref.
C=C	64.3(69.6)	1–4	133.91, 134.2	5	9.6	6
C=N	70(80.8)	2	127.3, 130	5	13.4–14.3	7
C=O	93(93.4)	2,8	120.9, 120.7, 121.0	5	12.1	6
C=Si	34(36.1)	1,3, 9	176.4, 170.2	10, 11	5.60–5.77	7
C=P	51(49.4)	*e*	167.1	5	5.62–6.68	7
C=S	58(55.7)	*e*	161.1	5	6.357	7
C=Ge	31	4				
C=Sn	19	4				
N=N	63.5	12,2 13,8	125.4, 125	5,14		
N=O	103	8	119.7, 122	5		
N=P	47	12, 13				
P=P	36	12,13, 15	203.4	18		
Si=Si	22(24.2)	3	214.0, 214.3	16		
Ge=Ge	20.1	15	234.7	17		
As=As	28.0	15				
Sb=Sb	20.8	15				
Si=O	42(55.8)	8				

[a]The references cited in this table are given below.
[b]π-Bond energies in kcal mol^{-1}. Values in parentheses are from Ref. 19.
[c]Bond lengths in pm.
[d]Force constants in $10^2\,N\,m^{-1}$.
[e]Calculated from equation 2.

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1 is

$$E_{pi} = -0.467(\pm 0.102)l_{M^1-M^2} + 10.6(\pm 4.49)\Delta_{chi} + 125(\pm 18.5) \quad (2)$$

Values of the bond length for doubly bonded groups can be estimated from the equation

$$l_{M^1-M^2} = b_1 N_{\pi 1} + b_2 N_{\pi 2} + b_3 s + b_4 \Delta_\chi + b_0 \quad (3)$$

where $N_{\pi 1}$ and $N_{\pi 2}$ represent the state of occupancy of the first and second π orbitals respectively and take the values 1 for a full, 0.5 for a half full and 0 for an empty orbital; s is the sum of the covalent radii of M^1 and M^2; and Δ_χ again is the electronegativity difference (Allred–Rochow) between M^1 and M^2. Correlation of bond lengths with equation 3 gave the relationship

$$l_{M^1-M^2} = -20.2N_{\pi 1} - 13.5N_{\pi 2} + 1.02s - 6.63\Delta_\chi - 2.60 \quad (4)$$

which has a standard error of 2.0 pm. It may be used to give reasonably good estimates of the bond length of p, p π-bonded groups of second and third period elements.

In this work only the C=C, C=N, C=O, C=S, N=N and N=O p, p π bonds will be considered. This is due not to a lack of interest in other p, p double bonds, but rather to a lack of information. Though compounds containing Si=Si, Ge=Ge, C=Si and C=P double bonds have now been synthesized, no data are available which would permit a description of the substituent effects of groups containing these bonds. Hopefully, experimentalists will undertake chemical reactivity and spectral studies which will make possible the parametrization of the substituent effects of groups containing these bonds.

B. Related Unsaturated Groups

1. Allenyl and cumulenyl groups

Allenyl and cumulenyl substituents have two or more adjacent p, p double bonds. Although these groups have been studied as skeletal groups[1] they have received little or no attention as possible substituents. In allenyl systems, the π orbitals do not interact directly but are independent of each other. In the butatrienyl group and similar systems the terminal double bonds are conjugated, while in the higher cumulenyl groups two separate conjugated systems perpendicular to each other are present. A further complication arises from the fact that the terminal carbon atoms in the allenyl and cumulenyl groups are hybridized sp^2 while the central atoms are hybridized sp.

2. Cyclopropyl and heterocyclopropyl groups

Though cyclopropyl groups are not doubly bonded, many authors have pointed out similarities in the chemical reactivity, and the chemical and physical properties, between cyclopropanes and the corresponding carbon–carbon doubly bonded systems. These similarities result from the nature of the bonding which is found in the three-membered ring.

II. SUBSTITUENT EFFECTS

A. Introduction

In the earliest stage of modern chemistry compounds were characterized by their percent composition. When it became possible to determine the structural formulae of compounds, the existence of structural isomerism was observed. Compounds with the same empirical formula could have very different chemical and physical properties and

chemical properties. Inherent in this observation is the concept that these properties and reactivities vary with molecular structure. It is of both theoretical and practical importance to describe quantitatively that structural variation. This quantitative description may be achieved in three different ways:

1. Quantum chemical calculations.
2. Molecular mechanics.
3. Correlation analysis (also known as linear free energy relationships)[2-5].

Quantum chemical calculations have the strongest theoretical basis of the three fundamental methods, but in practice all of them are empirical. Of the three methods correlation analysis is the easiest and the least expensive to use. In this work we consider only that method.

B. Structure–Property Quantitative Relationships (SPQR)

1. The nature of SPQR

It will be useful to classify the properties we wish to describe. Properties which do not involve a permanent change in chemical bonds or intermolecular forces are physical properties. Examples are spectra (IR, NMR, UV, visible), molecular geometry (bond length, bond angle) and dipole moment. Properties which involve a difference between inter- or intramolecular forces in initial and final states are chemical properties. Examples are equilibrium constants for partition, hydrogen bonding and charge transfer complex formation, chromatographic quantities such as R_M, and capacity factors, melting and boiling points, and conformational equilibria. Properties which involve the forming and/or breaking of chemical bonds are chemical reactivities. Those which involve biological materials, ranging from pure enzymes to live multicellular organisms, are bioactivities. There are therefore four types of structure–property quantitative relationships (SPQR):

1. Quantitative structure–reactivity relationships (QSRR) which model chemical reactivities.
2. Quantitative structure–chemical property relationships (QSCR) which describe chemical properties.
3. Quantitative structure–physical property relationships (QSPR).
4. Quantitative structure–biological activity relationships (QSAR).

2. The function of SPQR

We may want an SPQR in order to be able to predict values of a property for some structural variations of interest. Thus, QSAR have been used for many years in the design of medicinal drugs and pesticides, and for the prediction of toxicity and other properties of environmental interest. SPQR may also be used to store in a convenient, compact format the experimental results obtained in studies of the variation of properties with structural change. They are of use in the determination of reaction mechanism. Most importantly, they can aid in the understanding of how and why structural variations result in property changes.

We now consider how a substituent can influence molecular properties. A substituent exerts three types of effects: electrical, steric and intermolecular-force effects. Electrical effects, and in some cases steric effects as well, are sufficient to account for structural effects on most chemical reactivities in solution and on many chemical and physical properties. Gas-phase reactivities and physical and chemical properties generally require in addition a term in polarizability. All of the parameters are frequently required to account for structural effects on bioactivity.

TABLE 2. Values of σ_I, σ_d and σ_e[a]

Substituent	σ_I	σ_d	σ_e
Substituted ethynyl			
C≡CH	0.29	−0.02	−0.10
C≡CMe	0.30	−0.29	−0.089
C≡CEt	0.30 E	−0.29 E	−0.089 E
C≡CCF$_3$	0.35 E	0.17 E	−0.01 E
C≡C—C≡CH	0.39	0.04	−0.10
C≡CPh	0.33	−0.25	−0.14
Substituted vinyl			
E—CH=CHNO$_2$	0.36 E	0.05 E	−0.15 E
CH=CH$_2$	0.11	−0.08	−0.12
E-CF=CFCF$_3$	0.35 E	0.14 E	−0.030 E
CH=CHCN	0.28 E	0.00 E	−0.11 E
Z-CH=CHCF$_3$	0.15 E	0.12 E	−0.10 E
E-CH=CHCF$_3$	0.23 E	0.01 E	−0.037 E
E-CH=CHMe	0.07	−0.18	−0.089
CMe=CH$_2$	0.10	−0.10	−0.078
CH=C(CN)$_2$	0.43 E	0.29 E	−0.020 E
E-CH=CHEt	0.07 E	−0.18 E	−0.089 E
C(CN)=C(CN)$_2$	0.67 E	0.27 E	−0.030 E
CH=CH—CH=CH$_2$	0.12 E	−0.37 E	−0.12 E
E, *E*-(CH=CH)$_2$CH=CH$_2$	0.12 E	−0.51 E	−0.12 E
E-CH=CHPh	0.13 E	−0.33	−0.12
E, *E*-(CH=CH)$_2$Ph	0.13 E	−0.48 E	−0.12 E
Substituted phenyl			
C$_6$Cl$_5$	0.26 E	−0.01 E	−0.010 E
C$_6$F$_5$	0.31	0.08	−0.068
4-BrC$_6$H$_4$	0.15	−0.01 E	−0.064 E
3-ClC$_6$H$_4$	0.16	−0.05 E	−0.035 E
4-ClC$_6$H$_4$	0.15	−0.01 E	−0.070 E
3-O$_2$NC$_6$H$_4$	0.20	0.03 E	−0.088 E
4-O$_2$NC$_6$H$_4$	0.23	−0.01	−0.045
Ph	0.12	−0.12	−0.12
4-CF$_3$C$_6$H$_4$	0.19 E	0.00 E	−0.035 E
4-MeC$_6$H$_4$	0.10	−0.12 E	−0.041 E
4-MeOC$_6$H$_4$	0.11	−0.15	−0.062
4-EtC$_6$H$_4$	0.01 E	−0.12 E	−0.041 E
4-PhC$_6$H$_4$	0.13	−0.17 E	−0.12 E
Carbonyl			
ClCO	0.44	0.31 E	−0.060 E
FCO	0.46 E	0.31 E	−0.070 E
HCO	0.30 E	0.27	−0.10
CO$_2$H	0.30	0.17	−0.051
COCF$_3$	0.52 E	0.33 E	−0.050 E
Ac	0.30	0.25	−0.095
CONH$_2$	0.28	0.12	−0.055
CO$_2$Me	0.32	0.16	−0.070
COEt	0.30 E	0.25 E	−0.095 E
CO$_2$Et	0.30	0.18	−0.064
COPr	0.30 E	0.25 E	−0.095 E
COPr-*i*	0.30 E	0.25 E	−0.095 E
CO$_2$Pr	0.31 E	0.17 E	−0.067 E
CO$_2$Bu	0.31 E	0.17 E	−0.067 E

TABLE 2 (*continued*)

Substituent	σ_I	p_d	σ_e
Bz	0.30	0.22	−0.11
N-substituted azenyl, cyano			
CH=NH	0.18 E	0.09 E	−0.060 E
E-CH=NOH	0.20 U	0.12 E	−0.020 E
CH=NPh	0.31 E	0.17 E	−0.060 E
CN	0.57	0.12	−0.055
Nitroso, nitro			
NO	0.44 E	0.54 E	−0.070
NO_2	0.67	0.18	−0.077
C-substituted azenyl			
$N{=}CH_2$	0.20 E	−0.02 E	−0.060 E
N=CHPh	0.13 E	−0.07 E	−0.063 E
Diazenyl			
N=NH	0.31 E	0.27 E	−0.080
$N{=}NCF_3$	0.44 E	0.24 E	0.06
N=NBu-*t*	0.21	0.07	−0.075
N=NPh	0.27	0.12	−0.059
Allenyl, heteroallenyl			
$CH{=}C{=}CH_2$	0.12 E	−0.02 E	−0.11 E
N=C=O	0.34 E	−0.17 E	0.070 E
N=C=S	0.54 E	−0.11 E	−0.090 E
N_3	0.43	−0.27 E	−0.12 E
Other			
H	0	0	0
F	0.54	−0.48	0.041
Cl	0.47	−0.28	−0.011
Br	0.47	−0.27	−0.018
I	0.40	−0.20	−0.057
Me	−0.01	−0.14	−0.030
Et	−0.01	−0.12	−0.036
c-Pr	0.01	−0.17	−0.069
CF_3	0.40	0.13	−0.026
$SiMe_3$	−0.11	0.13	−0.046
NHAc	0.28	−0.35	−0.088
NHEt	0.17 E	−0.66 E	−0.15 E
NMe_2	0.17	−0.66	−0.24
PMe_2	0.10 E	−0.50 E	−0.27 E
$POMe_2$	0.30	0.14	−0.036
$PO(OMe)_2$	0.36	0.24 E	−0.033 E
OMe	0.30	−0.55	−0.064
OSO_2Me	0.55	−0.23 E	−0.065 E
OAc	0.38	−0.24 E	−0.005 E
SMe	0.30	−0.38	−0.13
SAc	0.39	−0.08 E	−0.057 E
SOMe	0.54 E	−0.09	−0.10
SO_2Me	0.59	0.13	−0.052
SeMe	0.28 E	−0.40 E	−0.14 E

[a] Values labelled E are estimates, regarded as generally less reliable than unlabelled ones.

III. ELECTRICAL EFFECTS

A. Introduction

The complete range of substituent effects at carbon is well described by the triparametric equation[6]

$$Q_X = L\sigma_{IX} + D\sigma_{dX} + R\sigma_{eX} + h \tag{5}$$

where σ_{IX} is the descriptor of the localized (field and/or inductive) electrical effect and is identical to the σ_I constant[7]; σ_{dX} represents the intrinsic delocalized electrical effect and is the descriptor of the delocalized effect when the electronic demand in the system studied is zero; σ_{eX} represents the sensitivity of the delocalized electrical effect of the X group to electronic demand; L, D and R are the coefficients of the electrical effect parameters σ_I, σ_d and σ_e while h is the intercept of the line; Q_x is the experimental value of the quantity measured for the data set member bearing the X substituent.

Table 2 reports values of σ_I, σ_d and σ_e for doubly bonded groups. Values of these parameters are also given for triply bonded and aromatic groups for purposes of comparison.

The electronic demand η is given by the ratio

$$\eta = R/D \tag{6}$$

When η is held constant the LDR equation reverts to the familiar LD equation[7,8]

$$Q_X = L\sigma_{IX} + D\sigma_{DX} + h \tag{7}$$

The σ_D parameters are composite. They are given by the relationship[8]

$$\sigma_{DX} = \eta\sigma_{eX} + \sigma_{dX} \tag{8}$$

Values of η for the common σ_D parameters are given in Table 3. If there is *a priori* knowledge of the approximate value of the electronic demand, then the data can be correlated with the LD equation.

An alternative diparametric relationship which can be written is the CR equation

$$Q_X = C\sigma_{IdX} + R\sigma_{eX} + h \tag{9}$$

where σ_{Id} is a composite parameter defined by the relationship

$$\sigma_{IdX} = I\sigma_{IX} + d\sigma_{dX} \tag{10}$$

Its percent composition P_D is defined as

$$P_D = (d \cdot 100)/(I + d) \tag{11}$$

For correlations with the LDR and LD equations, P_D is given by

$$P_D = (|D| \cdot 100)/(|L| + |D|) \tag{11a}$$

As $C = D$, equation 11a can also be used to calculate P_D in correlations with the CR equation.

TABLE 3. Values of η for σ_D parameters

σ_D	σ_R	σ_R^0	σ_R^+	σ_R^-	σ_R^-	σ_R^+
η	0.380	−0.376	2.04	−1.40	3.31	−2.98

TABLE 4. Values of σ_D and σ_{Id}[a]

X	Parameter Type $\sigma_R^{\ominus}$	σ_R^-	σ_R^0	σ_R	σ_R^+	$\sigma_R^{\oplus}$
Substituted ethynyl						
C≡CH	0.28	0.13	−0.04	−0.04	−0.12	−0.45
C≡CMe	−0.03 E	−0.20	−0.27	−0.27	−0.27	−0.78
C≡CEt	−0.03 E	−0.18	−0.24 E	−0.30 E	−0.42 E	−0.70 E
C≡CCF$_3$	0.20 E	0.21 E	0.17	0.16	0.23 E	0.13 E
C≡C—C≡CH	0.34 E	0.19	0.02 E	0.01 E	−0.17	−0.36 E
C≡CPh	0.16 E	−0.14	−0.21	−0.21	−0.21	−1.03
Substituted vinyl						
E-CH=CHNO$_2$	0.50 E	0.30 E	0.14	−0.10	−0.20 E	−0.54 E
CH=CH$_2$	0.45	−0.08	−0.15	−0.15	−0.15	−0.56
E-CF=CFCF$_3$	0.23 E	0.21 E	0.14	0.11	0.16 E	0.02 E
CH=CHCN	0.33 E	0.18 E	0.11	−0.11	−0.16 E	−0.45 E
Z-CH=CHCF$_3$	0.42 E	0.30 E	0.12	0.02	−0.01 E	−0.27 E
E-CH=CHCF$_3$	0.12 E	0.08	−0.02 E	−0.03 E	0.00 E	−0.16 E
E-CH=CHMe	0.08 E	−0.09	−0.16	−0.16	−0.16	−0.67
CMe=CH$_2$	0.13 E	−0.07	−0.05	−0.05	−0.05	−0.60
CH=C(CN)$_2$	0.35 E	0.36 E	0.29	0.27	0.33 E	0.23 E
E-CH=CHEt	0.08 E	−0.06 E	−0.15 E	−0.20 E	−0.31 E	−0.57 E
C(CN)=C(CN)$_2$	0.36 E	0.36 E	0.27	0.24	0.29 E	0.17 E
CH=CH—CH=CH$_2$	−0.02 E	−0.23 E	−0.29 E	−0.38 E	−0.57 E	−0.91 E
E, E-(CH=CH)$_2$CH=CH$_2$	−0.16 E	−0.38 E	−0.40 E	−0.51 E	−0.72 E	−0.07 E
E-CH=CHPh	0.02 E	−0.23	−0.30	−0.30	−0.30	−1.01
E, E-(CH=CH)$_2$Ph	−0.13 E	−0.35 E	−0.37 E	−0.49 E	−0.53 E	−1.04 E
Substituted phenyl						
C$_6$Cl$_5$	0.02 E	0.01 E	−0.01	−0.02	0.04 E	−0.08 E
C$_6$F$_5$	0.28 E	0.20 E	−0.02	0.02	0.01 E	−0.19 E
4-BrC$_6$H$_4$	0.18 E	0.09 E	−0.03 E	−0.03	−0.14	−0.28 E
3-ClC$_6$H$_4$	0.05 E	0.00 E	−0.07 E	−0.06	−0.12	−0.22 E
4-ClC$_6$H$_4$	0.20 E	0.10 E	−0.03 E	−0.03	−0.15	−0.30 E
3-NO$_2$C$_6$H$_4$	0.29 E	0.18 E	0.01 E	0.00	−0.15	−0.33 E
4-NO$_2$C$_6$H$_4$	0.12 E	0.06 E	−0.03 E	0.03	−0.18	−0.21 E
Ph	0.28	−0.04	−0.11	−0.11	−0.17	−0.69
4-CF$_3$C$_6$H$_4$	0.10 E	0.06 E	−0.01	−0.01	−0.08	−0.16 E
4-MeC$_6$H$_4$	0.00 E	−0.07 E	−0.12 E	−0.13	−0.20	−0.32 E

(*continued*)

TABLE 4 (*continued*)

X	Parameter Type $\sigma_R^{\ominus}$	σ_R	σ_R^0	σ_R	σ_R^+	$\sigma_R^{\oplus}$
4-$MeOC_6H_4$	0.03 E	−0.01	−0.19	−0.19	−0.27	−0.43 E
4-EtC_6H_4	0.00 E	−0.07 E	−0.12 E	−0.13 E	−0.14 E	−0.32 E
4-PhC_6H_4	0.18 E	0.00 E	−0.14 E	−0.20 E	−0.36 E	−0.68 E
Carbonyl						
ClCO	0.49 E	0.45 E	0.31	0.25	0.27 E	0.10 E
FCO	0.52 E	0.46 E	0.31	0.24	0.25 E	0.06 E
HCO	0.57 E	0.53	0.15	0.15	0.15	−0.04
CO_2H	0.32 E	0.31	0.11	0.11	0.11	−0.03 E
$COCF_3$	0.48 E	0.45 E	0.33	0.28	0.31 E	0.16 E
Ac	0.56	0.41	0.20	0.20	0.06	−0.05
$CONH_2$	0.28 E	0.23	0.08	0.08	0.08	−0.10
CO_2Me	0.37 E	0.30	0.11	0.11	0.11	−0.12
COEt	0.53 E	0.44 E	0.18 E	0.20 E	0.13 E	−0.10 E
CO_2Et	0.37 E	0.31	0.11	0.11	0.11	−0.06 E
COPr	0.41	0.44 E	0.18 E	0.20 E	0.13 E	−0.10 E
COPr-*i*	0.53 E	0.44 E	0.18 E	0.20 E	0.13 E	−0.10 E
CO_2Pr	0.37 E	0.30 E	0.11 E	0.14 E	0.11 E	−0.09 E
CO_2Bu	0.37 E	0.30 E	0.11 E	0.14 E	0.11 E	−0.09 E
Bz	0.61	0.41	0.11	0.11	0.11	−0.13
N-substituted azenyl, cyano						
CH=NH	0.27 E	0.20 E	0.05 E	0.06 E	0.04 E	−0.15 E
E-CH=NOH	0.18 E	0.17 E	0.06 E	−0.10 E	−0.12	0.04
CH=NPh	0.35 E	0.29	0.11 E	0.11	0.12	−0.06 E
CN	0.26	0.26	0.08	0.08	0.08	−0.10
Nitroso, nitro						
NO	0.75 E	0.72 E	0.40 E	0.47	0.49 E	0.33 E
NO_2	0.41	0.37	0.10	0.10	0.10	−0.08
C-substituted azenyl						
$N=CH_2$	0.16 E	0.07 E	−0.04 E	−0.04 E	−0.08 E	−0.28 E
N=CHPh	0.11 E	0.06	−0.08 E	−0.13	−0.14 E	−0.35 E

Diazenyl						
N=NH	0.51 E	0.43 E	0.19 E	0.23 E	0.19 E	−0.02 E
$N{=}NCF_3$	0.06 E	0.18 E	0.24	0.30	0.45 E	0.48 E
N=NBu-*t*	0.29 E	0.20 E	0.09	0.07	−0.06	−0.23 E
N=NPh	0.29 E	0.23 E	0.13	0.10	−0.07	−0.11 E
Allenyl, heteroallenyl						
$CH{=}C{=}CH_2$	0.31 E	0.15 E	−0.02 E	−0.05 E	−0.18 E	−0.47 E
N=C=O	−0.39 E	−0.30 E	−0.17	−0.10	0.04 E	0.05 E
N=C=S	0.15 E	0.02 E	−0.07	−0.16	−0.24 E	−0.50 E
N_3	0.08 E	−0.11 E	−0.21 E	−0.31	−0.47 E	−0.67
Other						
H	0	0	0	0	0	0
F	−0.61 E	−0.58	−0.44	−0.48	−0.37	−0.25 E
Cl	−0.25 E	−0.30	−0.25	−0.25	−0.21	−0.41
Br	−0.21	−0.28	−0.25	−0.25	−0.19	−0.44
I	−0.06 E	−0.18	−0.16	−0.16	−0.16	−0.57
Me	−0.03	−0.09	−0.16	−0.16	−0.16	−0.25
Et	−0.01	−0.07	−0.14	−0.14	−0.14	−0.28
c-Pr	0.01	−0.08 E	−0.15 E	−0.19	−0.27	−0.43
CF_3	0.20 E	0.18	0.11	0.11	0.15	0.00
$SiMe_3$	0.26 E	0.19	0.12	0.12	0.12	−0.10
NHAc	−0.09 E	−0.28	−0.25	−0.35	−0.47	−0.75
NHEt	−0.22 E	−0.51 E	−0.50 E	−0.66 E	−0.94 E	−1.36
NMe_2	0.05 E	−0.30	−0.44	−0.88	−1.22	−1.38
PMe_2	0.30 E	−0.14 E	−0.35 E	−0.55 E	−1.03 E	−1.63 E
$POMe_2$	0.24 E	0.22 E	0.08 E	0.12 E	0.14 E	0.00 E
$PO(OMe)_2$	0.34 E	0.33 E	0.15 E	0.21 E	0.25 E	0.12 E
OMe	−0.36	−0.51	−0.44	−0.58	−0.66	−0.83
OSO_2Me	−0.43 E	−0.36 E	−0.26	−0.24	−0.39	−0.04 E
OAc	−0.23 E	−0.16	−0.22 E	−0.23	−0.26	−0.32 E
SMe	0.01	−0.24	−0.31	−0.38	−0.55	−0.97
SAc	0.09 E	0.00 E	−0.08	−0.09 E	−0.13 E	−0.34 E
SOMe	0.13	0.05	0.00	0.00	−0.10	−0.70
SO_2Me	0.18	0.35	0.11	0.11	0.11	−0.12
SeMe	0.01 E	−0.23 E	−0.31 E	−0.42 E	−0.65 E	−1.02 E

[a]Values labelled E are estimates, regarded as generally less reliable than unlabelled ones.

(*continued*)

TABLE 4 (*continued*)

Values of $\sigma_{Id,k}$

Group	k = 10	20	30	40	50	60	70	80
Substituted ethynyl								
C≡CH	0.29	0.29	0.28	0.28	0.27	0.26	0.24	0.21
C≡CMe	0.27	0.23	0.18	0.11	0.01	−0.14	−0.38	−0.86
C≡CEt	0.27	0.23	0.18	0.11	0.01	−0.14	−0.38	−0.86
$C{\equiv}CCF_3$	0.37	0.39	0.42	0.46	0.52	0.61	0.75	1.03
C≡C—C≡CH	0.39	0.40	0.41	0.42	0.43	0.45	0.48	0.55
C≡CPh	0.30	0.27	0.22	0.16	0.08	−0.05	−0.25	−0.67
Substituted vinyl								
E-$CH{=}CHNO_2$	0.37	0.37	0.38	0.39	0.41	0.44	0.48	0.56
$CH{=}CH_2$	0.10	0.09	0.08	0.06	0.03	−0.01	−0.08	−0.21
E-$CF{=}CFCF_3$	0.37	0.39	0.41	0.44	0.49	0.56	0.68	0.91
CH=CHCN	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28
Z-$CH{=}CHCF_3$	0.16	0.18	0.20	0.23	0.27	0.33	0.43	0.63
E-$CH{=}CHCF_3$	0.23	0.23	0.23	0.24	0.24	0.25	0.25	0.27
E-CH=CHMe	0.05	0.03	−0.01	−0.05	−0.11	−0.20	−0.35	−0.65
$CMe{=}CH_2$	0.09	0.08	0.06	0.03	0.00	−0.05	−0.13	−0.30
$CH{=}C(CN)_2$	0.46	0.50	0.55	0.62	0.72	0.87	1.11	1.59
E-CH=CHEt	0.05	0.03	−0.01	−0.05	−0.11	−0.20	−0.35	−0.65
$C(CN){=}C(CN)_2$	0.70	0.74	0.79	0.85	0.94	1.08	1.30	1.75
$CH{=}CH{-}CH{=}CH_2$	0.08	0.03	−0.04	−0.13	−0.25	−0.44	−0.74	−1.36
E,E-$(CH{=}CH)_2CH{=}CH_2$	0.06	−0.01	−0.10	−0.22	−0.39	−0.65	−1.07	−1.92
E-CH=CHPh	0.09	0.05	−0.01	−0.09	−0.20	−0.37	−0.64	−1.19
E,E-$(CH{=}CH)_2Ph$	0.08	0.01	−0.08	−0.19	−0.35	−0.59	−0.99	−1.79
Substituted phenyl								
C_6Cl_5	0.26	0.26	0.26	0.25	0.25	0.25	0.24	0.22
C_6F_5	0.32	0.33	0.34	0.36	0.39	0.43	0.50	0.63
4-BrC_6H_4	0.15	0.15	0.15	0.15	0.14	0.14	0.13	0.11
3-ClC_6H_4	0.15	0.15	0.14	0.13	0.11	0.09	0.04	−0.04
4-ClC_6H_4	0.15	0.15	0.15	0.14	0.14	0.14	0.13	0.11
3-$NO_2C_6H_4$	0.20	0.21	0.21	0.22	0.23	0.25	0.27	0.32
4-$NO_2C_6H_4$	0.23	0.23	0.23	0.22	0.22	0.22	0.21	0.19
Ph	0.11	0.09	0.07	0.04	0.00	−0.06	−0.16	−0.36
4-$CF_3C_6H_4$	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19

4-MeC_6H_4	0.09	0.07	0.05	0.02	−0.02	−0.08	−0.18	−0.38
4-$MeOC_6H_4$	0.09	0.07	0.05	0.01	−0.04	−0.12	−0.24	−0.49
4-EtC_6H_4	0.09	0.07	0.05	0.02	−0.02	−0.08	−0.18	−0.38
4-PhC_6H_4	0.11	0.09	0.06	0.02	−0.04	−0.13	−0.27	−0.55
Carbonyl								
ClCO	0.47	0.52	0.57	0.65	0.75	0.91	1.16	1.68
FCO	0.49	0.54	0.59	0.67	0.77	0.93	1.18	1.70
HCO	0.33	0.37	0.42	0.48	0.57	0.71	0.93	1.38
CO_2H	0.32	0.34	0.37	0.41	0.47	0.56	0.70	0.98
$COCF_3$	0.56	0.60	0.66	0.74	0.85	1.02	1.29	1.84
Ac	0.33	0.39	0.41	0.47	0.55	0.68	0.88	1.30
$CONH_2$	0.29	0.31	0.33	0.36	0.40	0.46	0.56	0.76
CO_2Me	0.34	0.36	0.39	0.43	0.48	0.56	0.69	0.96
COEt	0.33	0.36	0.41	0.47	0.55	0.68	0.88	1.30
CO_2Et	0.32	0.35	0.38	0.42	0.48	0.57	0.72	1.02
COPr	0.33	0.36	0.41	0.47	0.55	0.68	0.88	1.30
COPr-*i*	0.33	0.36	0.41	0.47	0.55	0.68	0.88	1.30
CO_2Pr	0.33	0.35	0.38	0.42	0.48	0.57	0.71	0.99
CO_2Bu	0.33	0.35	0.38	0.42	0.48	0.57	0.71	0.99
Bz	0.32	0.36	0.39	0.45	0.52	0.63	0.81	0.18
N-substituted azenyl, cyano								
CH=NH	0.19	0.20	0.22	0.24	0.27	0.32	0.39	0.54
E-CH=NOH	0.21	0.23	0.25	0.28	0.32	0.38	0.48	0.68
CH=NPh	0.33	0.35	0.38	0.42	0.48	0.57	0.71	0.99
CN	0.58	0.60	0.62	0.65	0.69	0.75	0.85	1.05
Nitroso, nitro								
NO	0.50	0.58	0.67	0.80	0.98	1.25	1.70	2.60
NO_2	0.69	0.72	0.75	0.79	0.85	0.94	1.09	1.39
C-substituted azenyl								
$N=CH_2$	0.20	0.20	0.19	0.19	0.18	0.17	0.15	0.12
N=CHPh	0.12	0.11	0.10	0.08	0.06	0.03	−0.03	−0.15
Diazenyl								
N=NH	0.34	0.38	0.43	0.49	0.58	0.72	0.94	1.39
$N=NCF_3$	0.47	0.50	0.54	0.60	0.68	0.80	1.00	1.40

(*continued*)

TABLE 4 (*continued*)

Group	*k* 10	20	30	40	50	60	70	80
N=NBu-*t*	0.22	0.23	0.24	0.26	0.28	0.32	0.37	0.49
N=NPh	0.28	0.30	0.32	0.35	0.39	0.45	0.55	0.75
Allenyl, heteroallenyl								
$CH{=}C{=}CH_2$	0.12	0.12	0.11	0.11	0.10	0.09	0.07	0.04
N=C=O	0.32	0.30	0.27	0.23	0.17	0.09	−0.06	−0.34
N=C=S	0.53	0.51	0.49	0.47	0.43	0.38	0.28	0.10
N_3	0.40	0.36	0.31	0.25	0.16	0.03	−0.20	−0.65
Other								
H	0	0	0	0	0	0	0	0
F	0.49	0.42	0.33	0.22	0.06	−0.18	−0.58	−1.38
Cl	0.44	0.40	0.35	0.28	0.19	0.05	−0.18	−0.65
Br	0.44	0.40	0.35	0.29	0.20	0.06	−0.16	−0.61
I	0.38	0.35	0.31	0.27	0.20	0.10	−0.07	−0.40
Me	−0.03	−0.05	−0.07	−0.10	−0.15	−0.22	−0.34	−0.57
Et	−0.02	−0.04	−0.06	−0.09	−0.13	−0.19	−0.29	−0.49
d-Pr	−0.01	−0.03	−0.06	−0.10	−0.16	−0.25	−0.39	−0.67
CF_3	0.41	0.43	0.46	0.49	0.53	0.60	0.70	0.92
$SiMe_3$	−0.10	−0.08	−0.05	−0.02	0.02	0.09	0.19	0.41
NHAc	0.24	0.19	0.13	0.05	−0.07	−0.25	−0.54	−1.12
NHEt	0.10	0.01	−0.11	−0.27	−0.49	−0.82	−1.37	−2.47
NMe_2	0.10	0.01	−0.11	−0.27	−0.49	−0.82	−1.37	−2.47
PMe_2	0.04	−0.03	−0.11	−0.23	−0.40	−0.65	−1.07	−1.90
$POMe_2$	0.32	0.34	0.36	0.39	0.44	0.51	0.63	0.86
$PO(OMe)_2$	0.39	0.42	0.46	0.52	0.60	0.72	0.92	1.32
OMe	0.24	0.16	0.06	−0.07	−0.25	−0.53	−0.98	−1.90
OSO_2Me	0.52	0.49	0.45	0.40	0.32	0.21	0.01	−0.37
OAc	0.35	0.32	0.28	0.22	0.14	0.02	−0.18	−0.58
SMe	0.26	0.21	0.14	0.05	−0.08	−0.27	−0.59	−1.22
SAc	0.38	0.37	0.36	0.34	0.31	0.27	0.20	0.07
SOMe	0.53	0.52	0.50	0.48	0.45	0.41	0.33	0.18
SO_2Me	0.60	0.62	0.65	0.68	0.72	0.79	0.89	1.11
SeMe	0.24	0.18	0.11	0.01	−0.12	−0.32	−0.65	−1.32

For any given value of P_D the σ_{IdX} parameter is given by the equation

$$\sigma_{IdX,k'} = \sigma_{IX} + [P_D/(100 - P_D)]\sigma_{dX} \tag{12}$$

The CR equation is useful for the determination of η in small data sets. Values of the σ_D and σ_{Id} parameters are reported in Table 4.

Holding the electronic demand constant ($\eta = k$) converts the LDR equation into the diparametric LD equation while holding the composition P_D constant ($P_D = k'$) converts it into the diparametric CR equation. If both η and P_D are held constant, the monoparametric Hammett equation

$$Q_X = \rho\sigma_X + h \tag{13}$$

results. The composite parameter σ_X is given by the relationship

$$\sigma_X = l\sigma_{IX} + d\sigma_{dX} + r\sigma_{eX} \tag{14}$$

where

$$r = d\eta \tag{15}$$

For any monoparametric electrical-effect substituent constant, both the composition and the electronic demand are fixed. The constant is therefore characterized by its values of P_D and η. It may therefore be written as $\sigma_{k'/k,X}$ where k' is the value of P_D and k the value of η. Similarly σ_D values, for which η is fixed, may be written in the form $\sigma_{Rk,X}$ while σ_{Id} values for which P_D is fixed may be written in the form $\sigma_{Idk',X}$.

The $\sigma_{k'/k,X}$ values are useful in describing the overall electrical effect of a group and in providing a convenient and clear picture of its variation as a function of electrical-effect composition and electronic demand. A table of values of $\sigma_{k'/k,X}$ calculated from the relationship

$$\sigma_{k'/k,X} = \sigma_{IX} + [P_D/(100 - P_D)](\sigma_{dX} + \eta\sigma_{eX}) \tag{16}$$

is useful for this purpose. In the table for each group the horizontal rows show the variation of the group electrical effect with change in substituent effect composition (P_D) at a fixed value of the electronic demand (η). The vertical columns show the variation of the group electrical effect with change in the electronic demand at a fixed value of the substitution effect composition. If the P_D and η values are plotted on the x and y Cartesian axes and the $\sigma_{k'/k}$ values on the z axis, a surface is generated which characterizes the electrical effect of the substituent. Consider, for example, the $\sigma_{k'/k,X}$ constants for the vinyl group given in Table 5. They show clearly that this group is an overall electron donor

TABLE 5. Values of $\sigma_{k'/k}$ for some doubly bonded groups[a]

η	P_D 10	20	30	40	50	60	70	80
$CH{=}CH_2$								
−6	**0.18**	**0.27**	**0.38**	**0.54**	**0.75**	**1.07**	**1.60**	**2.67**
−5	**0.17**	**0.24**	**0.33**	**0.46**	**0.63**	**0.89**	**1.33**	**2.19**
−4	**0.15**	**0.21**	**0.28**	**0.38**	**0.51**	**0.71**	**1.04**	**1.71**
−3	**0.14**	**0.18**	**0.23**	**0.30**	**0.39**	**0.53**	**0.76**	**1.23**
−2	**0.13**	**0.15**	**0.18**	**0.22**	**0.27**	**0.35**	**0.48**	**0.75**
−1	**0.11**	**0.12**	**0.13**	**0.14**	**0.15**	**0.17**	**0.20**	**0.27**
0	**0.10**	**0.09**	**0.08**	**0.06**	0.03	−0.01	*−0.08*	*−0.21*
1	**0.09**	**0.06**	0.02	−0.02	*−0.09*	*−0.19*	*−0.36*	*−0.69*

(continued)

TABLE 5 (*continued*)

g	P_D 10	20	30	40	50	60	70	80
2	**0.07**	0.03	−0.03	*−0.10*	*−0.21*	*−0.37*	*−0.64*	*−1.17*
3	**0.06**	0.00	*−0.08*	*−0.18*	*−0.33*	*−0.55*	*−0.92*	*−1.65*
4	0.05	−0.03	*−0.13*	*−0.26*	*−0.45*	*−0.73*	*−1.20*	*−2.13*
5	0.03	*−0.06*	*−0.18*	*−0.34*	*−0.57*	*−0.91*	*−1.48*	*−2.61*
6	0.02	*−0.09*	*−0.23*	*−0.42*	*−0.69*	*−1.09*	*−1.76*	*−3.09*
E-CH=CHMe								
−6	**0.11**	**0.16**	**0.22**	**0.31**	**0.42**	**0.60**	**0.90**	**1.49**
−5	**0.10**	**0.14**	**0.18**	**0.25**	**0.34**	**0.47**	**0.69**	**1.13**
−4	**0.09**	**0.11**	**0.14**	**0.19**	**0.25**	**0.33**	**0.48**	**0.77**
−3	**0.08**	**0.09**	**0.11**	**0.13**	**0.16**	**0.20**	**0.27**	**0.42**
−2	**0.07**	**0.07**	**0.07**	**0.07**	**0.07**	**0.07**	**0.07**	**0.06**
−1	**0.06**	0.05	0.03	0.01	−0.02	*−0.07*	*−0.14*	*−0.29*
0	0.05	0.03	−0.01	−0.05	*−0.11*	*−0.20*	*−0.35*	*−0.65*
1	0.04	0.00	−0.05	*−0.11*	*−0.20*	*−0.33*	*−0.56*	*−1.01*
2	0.03	−0.02	*−0.08*	*−0.17*	*−0.29*	*−0.47*	*−0.77*	*−1.36*
3	0.02	−0.04	*−0.12*	*−0.23*	*−0.38*	*−0.60*	*−0.97*	*−1.72*
4	0.01	*−0.06*	*−0.16*	*−0.29*	*−0.47*	*−0.73*	*−1.18*	*−2.07*
5	0.00	*−0.09*	*−0.20*	*−0.35*	*−0.56*	*−0.87*	*−1.39*	*−2.43*
6	−0.01	*−0.11*	*−0.24*	*−0.41*	*−0.64*	*−1.00*	*−1.60*	*−2.79*
CHO								
−6	**0.40**	**0.52**	**0.67**	**0.88**	**1.17**	**1.61**	**2.33**	**3.78**
−5	**0.39**	**0.49**	**0.63**	**0.81**	**1.07**	**1.46**	**2.10**	**3.38**
−4	**0.37**	**0.47**	**0.59**	**0.75**	**0.97**	**1.31**	**1.86**	**2.98**
−3	**0.36**	**0.44**	**0.54**	**0.68**	**0.87**	**1.16**	**1.63**	**2.58**
−2	**0.35**	**0.42**	**0.50**	**0.61**	**0.77**	**1.01**	**1.40**	**2.18**
−1	**0.34**	**0.39**	**0.46**	**0.55**	**0.67**	**0.86**	**1.16**	**1.78**
0	**0.33**	**0.37**	**0.42**	**0.48**	**0.57**	**0.71**	**0.93**	**1.38**
1	**0.32**	**0.34**	**0.37**	**0.41**	**0.47**	**0.56**	**0.70**	**0.98**
2	**0.31**	**0.32**	**0.33**	**0.35**	**0.37**	**0.41**	**0.46**	**0.58**
3	**0.30**	**0.29**	**0.29**	**0.28**	**0.27**	**0.26**	**0.23**	**0.18**
4	**0.29**	**0.27**	**0.24**	**0.21**	**0.17**	**0.11**	0.00	*−0.22*
5	**0.27**	**0.24**	**0.20**	**0.15**	**0.07**	−0.05	*−0.24*	*−0.62*
6	**0.26**	**0.22**	**0.16**	**0.08**	−0.03	*−0.20*	*−0.47*	*−1.02*
$CONH_2$								
−6	**0.33**	**0.39**	**0.47**	**0.58**	**0.73**	**0.96**	**1.33**	**2.08**
−5	**0.32**	**0.38**	**0.45**	**0.54**	**0.68**	**0.87**	**1.20**	**1.86**
−4	**0.32**	**0.37**	**0.43**	**0.51**	**0.62**	**0.79**	**1.07**	**1.64**
−3	**0.31**	**0.35**	**0.40**	**0.47**	**0.57**	**0.71**	**0.94**	**1.42**
−2	**0.31**	**0.34**	**0.38**	**0.43**	**0.51**	**0.63**	**0.82**	**1.20**
−1	**0.30**	**0.32**	**0.36**	**0.40**	**0.46**	**0.54**	**0.69**	**0.98**
0	**0.29**	**0.31**	**0.33**	**0.36**	**0.40**	**0.46**	**0.56**	**0.76**
1	**0.29**	**0.30**	**0.31**	**0.32**	**0.35**	**0.38**	**0.43**	**0.54**
2	**0.28**	**0.28**	**0.28**	**0.29**	**0.29**	**0.30**	**0.30**	**0.32**
3	**0.28**	**0.27**	**0.26**	**0.25**	**0.24**	**0.21**	**0.17**	**0.10**
4	**0.27**	**0.26**	**0.24**	**0.21**	**0.18**	**0.13**	0.05	*−0.12*
5	**0.26**	**0.24**	**0.21**	**0.18**	**0.13**	0.05	*−0.08*	*−0.34*
6	**0.26**	**0.23**	**0.19**	**0.14**	**0.07**	−0.04	*−0.21*	*−0.56*

[a]The type style represents the nature of the overall electrical effect. Boldface indicates electron-acceptor behavior; italics indicates electron-donor behavior; and ordinary type signifies that there is no meaningful electrical effect.

TABLE 6. Values of σ_m, σ_p, σ_p^0, σ_p^+ and σ_p^- [a]

Group	Parameter				
	σ_m	σ_p	σ_p^0	σ_p^+	σ_p^-
Substituted ethynyl					
C≡CH	0.24	0.21	0.26	0.05	0.50
C≡CMe	0.15	−0.04	0.06	−0.34	0.14
C≡CEt	0.15	−0.04	0.06	−0.34	0.14
C≡CCF$_3$	0.43	0.53	0.50	0.67	0.73
C≡C—C≡CH	0.36	0.37	0.41	0.26	0.72
C≡CPh	0.16	−0.01	0.11	−0.39	**0.39**
Substituted vinyl					
E-CH=CHNO$_2$	0.30	**0.26**	0.38	0.10	0.76
CH=CH$_2$	0.02	−0.05	0.02	−0.30	0.21
E-CF=CFCF$_3$	0.41	0.48	0.47	0.57	0.71
CH=CHCN	0.23	0.21	0.26	0.04	0.53
Z-CH=CHCF$_3$	0.15	0.20	0.22	0.12	0.51
E-CH=CHCF$_3$	0.23	0.23	0.24	0.21	0.38
E-CH=CHMe	−0.04	−0.17	−0.10	−0.42	−0.02
CMe=CH$_2$	**−0.05**	−0.05	0.00	−0.23	0.11
CH=C(CN)$_2$	0.55	0.72	0.68	0.92	1.01
E-CH=CHEt	−0.04	−0.17	−0.10	−0.42	−0.02
C(CN)=C(CN)$_2$	0.78	0.94	0.91	1.13	1.31
CH=CH—CH=CH$_2$	−0.08	−0.33	−0.20	−0.76	−0.17
E,E-(CH=CH)$_3$H	−0.14	−0.47	−0.32	−0.98	−0.36
E-CH=CHPh	−0.06	−0.28	−0.16	−0.68	**0.13**
E,E-(CH=CH)$_2$Ph	−0.12	−0.43	−0.28	−0.42	−0.31
Substituted phenyl					
C$_6$Cl$_5$	0.27	0.26	0.26	0.28	0.36
C$_6$F$_5$	0.32	0.35	0.37	0.32	0.63
4-BrC$_6$H$_4$	0.12	0.10	0.13	0.01	0.29
3-ClC$_6$H$_4$	0.14	0.10	0.12	0.04	0.21
4-ClC$_6$H$_4$	0.12	0.10	0.13	0.00	0.29
3-NO$_2$C$_6$H$_4$	0.17	0.17	0.21	0.06	0.44
4-NO$_2$C$_6$H$_4$	0.22	0.20	0.22	0.15	0.37
Ph	0.01	−0.08	0.00	**−0.51**	**0.08**
4-CF$_3$C$_6$H$_4$	0.19	0.18	0.19	0.15	0.32
4-MeC$_6$H$_4$	0.04	−0.04	0.00	−0.16	0.04
4-MeOC$_6$H$_4$	0.03	−0.07	−0.02	−0.25	0.04
4-EtC$_6$H$_4$	0.04	−0.04	0.00	−0.16	0.04
4-PhC$_6$H$_4$	0.00	−0.12	−0.03	−0.42	0.11
Carbonyl					
ClCO	0.54	0.72	0.69	0.86	1.10
FCO	0.56	0.73	0.71	0.85	1.14
HCO	0.36	**0.45**	0.50	0.53	0.91
CO$_2$H	0.35	0.44	**0.41**	0.50	**0.78**
COCF$_3$	0.64	0.83	0.80	1.00	1.22
Ac	**0.38**	**0.50**	**0.46**	0.51	**0.82**
CONH$_2$	0.31	0.37	0.37	0.39	**0.62**
CO$_2$Me	0.36	0.44	**0.46**	**0.49**	**0.74**
COEt	0.35	**0.48**	0.49	0.51	0.88
CO$_2$Et	0.35	0.44	**0.46**	**0.49**	**0.74**

(*continued*)

TABLE 6 (*continued*)

Group	Procedure σ_m	σ_p	σ_p^0	$\sigma_p^{+}{}_{p}^{-}$	
COPr	0.35	**0.48**	0.49	0.51	0.88
COPr-*i*	0.35	**0.48**	0.49	0.51	0.88
CO_2Pr	0.35	0.44	0.44	0.47	0.75
CO_2Bu	0.35	0.44	0.44	0.47	0.75
Bz	0.33	0.44	0.46	0.42	0.86
N-substituted azenyl, cyano					
CH=NH	0.19	0.24	0.24	0.22	0.46
E-CH=NOH	0.25	0.32	0.30	0.40	0.47
CH=NPh	0.36	0.45	0.44	0.49	0.74
CN	**0.61**	**0.65**	**0.69**	**0.66**	**1.02**
Nitroso, nitro					
NO	0.63	0.94	0.87	1.20	1.43
NO_2	**0.74**	**0.77**	**0.82**	**0.79**	**1.29**
C-substituted azenyl					
$N{=}CH_2$	0.17	0.15	0.18	0.06	0.33
N=CHPh	0.08	0.02	0.06	−0.10	0.18
Diazenyl					
N=NH	3.38	0.53	0.52	0.59	0.90
$N{=}NCF_3$	0.60	0.75	0.67	1.08	0.85
N=NBu-*t*	0.21	0.23	0.25	0.18	0.49
N=NPh	0.30	0.36	0.36	0.37	**0.61**
Allenyl, heteroallenyl					
$CH{=}C{=}CH_2$	0.06	0.02	0.08	−0.16	0.29
N=C=O	0.34	0.25	0.24	0.33	0.15
N=C=S	0.46	0.38	0.46	0.21	0.70
N_3	0.27	0.08	0.20	−0.25	0.38
Other					
H	0	0	0	0	0
F	**0.34**	**0.06**	**0.17**	**−0.07**	0.03
Cl	**0.37**	**0.22**	**0.27**	**0.11**	0.28
Br	**0.34**	**0.22**	**0.26**	**0.15**	0.30
I	**0.35**	**0.24**	**0.27**	**0.13**	0.35
Me	**−0.06**	**−0.17**	**−0.15**	**−0.31**	−0.15
Et	−0.06	**−0.15**	−0.12	**−0.28**	−0.11
c-Pr	**−0.08**	**−0.22**	−0.15	**−0.46**	**−0.09**
CF_3	0.46	0.53	0.52	0.61	**0.74**
$SiMe_3$	**0.11**	**0.01**	−0.03	**0.02**	0.11
NHAc	0.11	−0.12	0.00	−0.46	0.03
NHEt	−0.16	−0.59	−0.39	−1.25	−0.46
NMe_2	−0.22	−0.67	**−0.44**	−1.50	−0.35
PMe_2	−0.25	−0.61	−0.37	−1.40	−0.18
$POMe_2$	0.35	0.43	0.42	0.50	0.65
$PO(OMe)_2$	**0.46**	**0.59**	0.56	0.73	0.87
OMe	**0.11**	**−0.28**	**−0.12**	**−0.78**	−0.25
OSO_2Me	0.53	0.40	0.42	0.45	0.35

(*continued*)

TABLE 6 (*continued*)

Group	Parameter				
	σ_m	σ_p	σ_p^0	σ_p^{++}	σ_p^-
OAc	0.31	0.16	0.21	0.06	0.20
SMe	0.09	−0.17	−0.02	**−0.60**	**0.04**
SAc	0.34	0.28	0.33	0.18	0.50
SOMe	0.47	**0.54**	0.47	0.21	0.74
SO_2Me	0.63	0.70	0.71	0.75	**1.13**
SeMe	0.05	−0.21	−0.06	−0.68	0.03

[a] Values in boldface are from Reference 7 or from O. Exner, in *Correlation Analysis in Chemistry: Recent Advances* (Eds. N. B. Chapman and J. Shorter), Plenum Press, New York, 1978, pp. 439–540. The remaining values were estimated from the equations

$$\sigma_{mX} = 1.02\sigma_{iX} + 0.385\sigma_{dX} + 0.661\sigma_{eX} + 0.0152$$

$$\sigma_{pX} = 1.02\sigma_{iX} + 0.989\sigma_{dX} + 0.837\sigma_{eX} + 0.0132$$

$$\sigma_{pX}^0 = 1.06\sigma_{iX} + 0.796\sigma_{dX} + 0.278\sigma_{eX} - 0.00289$$

$$\sigma_{pX}^+ = 1.10\sigma_{iX} + 1.61\sigma_{dX} + 2.76\sigma_{eX} + 0.0394$$

$$\sigma_{pX}^- = 1.33\sigma_{iX} + 1.36\sigma_{dX} - 1.28\sigma_{eX} + 0.0176$$

when P_D and η are large and that it is an overall electron acceptor when η is negative and/or P_D is small. By contrast, the table for the formyl group shows that it is an acceptor except for the very small region of η less than or equal to -4 and P_D greater than or equal to 70.

The σ_m constants used for substituents in the *meta* position on a benzene ring have P_D values of about 28 while for the σ_p constants used for substituents in the *para* position, P_D is usually about 50. Values of σ_m and σ_p, σ_p^0, σ_p^+ and σ_p^- are given in Table 6.

B. Variation of Electrical Effect with Electronic Demand

Traditionally, groups have been conveniently classified as electron donors or electron acceptors depending on their ability to stabilize an electron-poor or an electron-rich active site. Over the past decade, however, evidence has accumulated which shows that some groups normally considered to be strong acceptors when directly bonded to cationic carbon can stabilize the positive charge[8]. Similarly, some groups normally considered to be electron donors can stabilize anionic carbon. Examples of the former are cyano, acetyl, carbomethoxy and phenyldiazenyl (phenylazo). Examples of the latter are phenyl, vinyl, ethynyl and acetylamino. In order to demonstrate this point values of $\sigma_{Rk,X}$ and $\sigma_{50/k}$ for a number of groups are reported in Table 7. Values of η used range from +6 to −6. Groups are considered overall electron donors if $\sigma_{X,50/k} < -0.05$, electron acceptors if $\sigma_{X,50/k} > 0.05$ and neither if $-0.05 \leqq \sigma_{X,50/k} \leqq 0.05$.

C. Variation of Electronic Demand Sensitivity with Substituent Type

If all substituents had delocalized effects with the same sensitivity to electronic demand, only two parameters would suffice for the characterization of substituent electrical effects. This is clearly not the case. Substituents are conveniently classified into groups depending on the type of molecular orbitals involved in the delocalized effect. The categories are:

X_n groups in which the first atom of the substituent has a full nonbonding orbital. Examples are F, OMe, NH_2, SMe.

TABLE 7. Values of $\sigma_{R,k}$.[a]

Group	η =	−6	−5	−4	−3	−2	−1	0	1	2	3	4	5	6
Substituted ethynyl														
C≡CH		**0.58**	**048**	**0.38**	**0.28**	**0.18**	**0.08**	−0.02	*−0.12*	*−0.22*	*−0.32*	*−0.42*	*−0.52*	*−0.62*
C≡CMe		**0.24**	**0.16**	**0.07**	−0.02	*−0.11*	*−0.20*	*−0.29*	*−0.38*	*−0.47*	*−0.56*	*−0.65*	*−0.74*	*−0.82*
C≡CEt		**0.24**	**0.16**	**0.07**	−0.02	*−0.11*	*−0.20*	*−0.29*	*−0.38*	*−0.47*	*−0.56*	*−0.65*	*−0.74*	*−0.82*
C≡CCF$_3$		**0.23**	**0.22**	**0.21**	**0.20**	**0.19**	**0.18**	**0.17**	**0.16**	**0.15**	**0.14**	**0.13**	**0.12**	**0.11**
C≡C—C≡CH		**0.64**	**0.54**	**0.44**	**0.34**	**0.24**	**0.14**	**0.04**	*−0.06*	*−0.16*	*−0.26*	*−0.36*	*−0.46*	*−0.56*
C≡CPh		**0.59**	**0.45**	**0.31**	**0.17**	**0.03**	*−0.11*	*−0.25*	*−0.39*	*−0.53*	*−0.67*	*−0.81*	*−0.95*	*−1.09*
Substituted vinyl														
E-CH=CHNO$_2$		**0.95**	**0.80**	**0.65**	**0.50**	**0.35**	**0.20**	**0.05**	*−0.10*	*−0.25*	*−0.40*	*−0.55*	*−0.70*	*−0.85*
CH=CH$_2$		**0.64**	**0.52**	**0.40**	**0.28**	**0.16**	**0.04**	*−0.08*	*−0.20*	*−0.32*	*−0.44*	*−0.56*	*−0.68*	*−0.80*
E-CF=CFCF$_3$		**0.32**	**0.29**	**0.26**	**0.23**	**0.20**	**0.17**	**0.14**	**0.11**	**0.08**	0.05	0.02	−0.01	−0.04
CH=CHCN		**0.66**	**0.55**	**0.44**	**0.33**	**0.22**	**0.11**	0.00	*−0.11*	*−0.22*	*−0.33*	*−0.44*	*−0.55*	*−0.66*
Z-CH=CHCF$_3$		**0.72**	**0.62**	**0.52**	**0.42**	**0.32**	**0.22**	**0.12**	0.02	*−0.08*	*−0.18*	*−0.28*	*−0.38*	*−0.48*
E-CH=CHCF$_3$		**0.23**	**0.20**	**0.16**	**0.12**	**0.08**	0.05	0.01	−0.03	*−0.06*	*−0.10*	*−0.14*	*−0.17*	*−0.21*
E-CH=CHMe		**0.35**	**0.27**	**0.18**	**0.09**	**0.00**	*−0.09*	*−0.18*	*−0.27*	*−0.36*	*−0.45*	*−0.54*	*−0.63*	*−0.71*
CMe=CH$_2$		**0.37**	**0.29**	**0.21**	**0.13**	**0.06**	−0.02	*−0.10*	*−0.18*	*−0.26*	*−0.33*	*−0.41*	*−0.49*	*−0.57*
CH=C(CN)$_2$		**0.41**	**0.39**	**0.37**	**0.35**	**0.33**	**0.31**	**0.29**	**0.27**	**0.25**	**0.23**	**0.21**	**0.19**	**0.17**
E-CH=CHEt		**0.35**	**0.27**	**0.18**	**0.09**	0.00	−0.09	*−0.18*	*−0.27*	*−0.36*	*−0.45*	*−0.54*	*−0.63*	*−0.71*
C(CN)=C(CN)$_2$		**0.45**	**0.42**	**0.39**	**0.36**	**0.33**	**0.30**	**0.27**	**0.24**	**0.21**	**0.18**	**0.15**	**0.12**	**0.09**
CH=CH—CH=CH$_2$		**0.35**	**0.23**	**0.11**	−0.01	*−0.13*	*−0.25*	*−0.37*	*−0.49*	*−0.61*	*−0.73*	*−0.85*	*−0.97*	*−1.09*
E,E-(CH=CH)$_2$CH=CH$_2$		**0.21**	**0.09**	−0.03	*−0.15*	*−0.27*	*−0.39*	*−0.51*	*−0.63*	*−0.75*	*−0.87*	*−0.99*	*−1.11*	*−1.23*
E-CH=CHPh		**0.39**	**0.27**	**0.15**	0.03	*−0.09*	*−0.21*	*−0.33*	*−0.45*	*−0.57*	*−0.69*	*−0.81*	*−0.93*	*−1.05*
E,E-(CH=CH)$_2$Ph		**0.24**	**0.12**	**0.00**	*−0.12*	*−0.24*	*−0.36*	*−0.48*	*−0.60*	*−0.72*	*−0.84*	*−0.96*	*−1.08*	*−1.20*
Substituted phenyl														
C$_6$Cl$_5$		0.05	0.04	0.03	0.02	0.01	0.00	−0.01	−0.02	−0.03	−0.04	−0.05	*−0.06*	*−0.07*
C$_6$F$_5$		**0.49**	**0.42**	**0.35**	**0.28**	**0.21**	**0.15**	**0.08**	0.01	*−0.06*	*−0.12*	*−0.19*	*−0.26*	*−0.33*
4-BrC$_6$H$_4$		**0.37**	**0.31**	**0.25**	**0.18**	**0.12**	0.05	−0.01	*−0.07*	*−0.14*	*−0.20*	*−0.27*	*−0.33*	*−0.39*
3-ClC$_6$H$_4$		**0.16**	**0.13**	**0.09**	**0.06**	0.02	−0.01	−0.05	*−0.07*	*−0.11*	*−0.14*	*−0.18*	*−0.22*	*−0.26*
4-ClC$_6$H$_4$		**0.41**	**0.34**	**0.27**	**0.20**	**0.13**	**0.06**	−0.01	*−0.08*	*−0.15*	*−0.22*	*−0.29*	*−0.36*	*−0.43*
3-NO$_2$C$_6$H$_4$		**0.56**	**0.47**	**0.38**	**0.29**	**0.12**	0.03	*−0.06*	*−0.06*	*−0.15*	*−0.23*	*−0.32*	*−0.41*	*−0.50*
4-NO$_2$C$_6$H$_4$		**0.26**	**0.22**	**0.18**	**0.13**	**0.08**	0.04	−0.01	−0.05	*−0.10*	*−0.14*	*−0.19*	*−0.24*	*−0.28*
Ph		**0.60**	**0.48**	**0.36**	**0.24**	**0.12**	0.00	*−0.12*	*−0.24*	*−0.36*	*−0.48*	*−0.60*	*−0.72*	*−0.84*
4-CF$_3$C$_6$H$_4$		**0.21**	**0.18**	**0.14**	**0.11**	**0.07**	0.04	0.00	−0.03	*−0.07*	*−0.10*	*−0.14*	*−0.17*	*−0.21*

4-MeC_6H_4	**0.13**	**0.09**	0.04	0.00	−0.04	*−0.08*	*−0.12*	*−0.16*	*−0.20*	*−0.24*	*−0.28*	*−0.33*	*−0.37*
4-$MeOC_6H_4$	**0.21**	**0.16**	**0.10**	0.04	−0.03	*−0.09*	*−0.15*	*−0.21*	*−0.27*	*−0.34*	*−0.40*	*−0.46*	*−0.52*
4-EtC_6H_4	**0.13**	**0.09**	0.04	0.00	−0.04	*−0.08*	*−0.12*	*−0.16*	*−0.20*	*−0.24*	*−0.28*	*−0.33*	*−0.37*
4-PhC_6H_4	**0.55**	**0.43**	**0.31**	**0.19**	**0.07**	−0.05	*−0.17*	*−0.29*	*−0.41*	*−0.53*	*−0.65*	*−0.77*	*−0.89*
Carbonyl													
ClCO	**0.67**	**0.61**	**0.55**	**0.49**	**0.43**	**0.37**	**0.31**	**0.25**	**0.19**	**0.13**	**0.07**	**0.01**	−0.05
FCO	**0.73**	**0.66**	**0.59**	**0.52**	**0.45**	**0.38**	**0.31**	**0.24**	**0.17**	**0.10**	0.03	−0.04	*−0.11*
HCO	**0.87**	**0.77**	**0.67**	**0.57**	**0.47**	**0.37**	**0.27**	**0.17**	**0.07**	−0.03	*−0.13*	*−0.23*	*−0.33*
CO_2H	**0.48**	**0.43**	**0.37**	**0.32**	**0.27**	**0.22**	**0.17**	**0.12**	**0.07**	0.02	−0.03	*−0.08*	*−0.14*
$COCF_3$	**0.63**	**0.58**	**0.53**	**0.48**	**0.43**	**0.38**	**0.33**	**0.28**	**0.23**	**0.18**	**0.13**	**0.08**	0.03
Ac	**0.82**	**0.73**	**0.63**	**0.54**	**0.44**	**0.35**	**0.25**	**0.16**	**0.06**	−0.03	*−0.13*	*−0.22*	*−0.32*
$CONH_2$	**0.45**	**0.40**	**0.34**	**0.29**	**0.23**	**0.18**	**0.12**	0.07	0.01	−0.04	*−0.10*	*−0.15*	*−0.21*
CO_2Me	**0.58**	**0.51**	**0.44**	**0.37**	**0.30**	**0.23**	**0.16**	**0.09**	0.02	−0.05	*−0.12*	*−0.19*	*−0.26*
COEt	**0.82**	**0.73**	**0.63**	**0.54**	**0.44**	**0.35**	**0.25**	**0.16**	**0.06**	−0.03	*−0.13*	*−0.22*	*−0.32*
CO_2Et	**0.56**	**0.50**	**0.44**	**0.37**	**0.31**	**0.24**	**0.18**	**0.12**	0.05	−0.01	*−0.08*	*−0.14*	*−0.20*
COPr	**0.82**	**0.73**	**0.63**	**0.54**	**0.44**	**0.35**	**0.25**	**0.16**	**0.06**	−0.03	*−0.13*	*−0.22*	*−0.32*
COPr-*i*	**0.82**	**0.73**	**0.63**	**0.54**	**0.44**	**0.35**	**0.25**	**0.16**	**0.06**	−0.03	*−0.13*	*−0.22*	*−0.32*
CO_2Pr	**0.57**	**0.51**	**0.44**	**0.37**	**0.30**	**0.24**	**0.17**	**0.10**	0.04	−0.03	*−0.10*	*−0.16*	*−0.23*
CO_2Bu	**0.57**	**0.51**	**0.44**	**0.37**	**0.30**	**0.24**	**0.17**	**0.10**	0.04	−0.03	*−0.10*	*−0.16*	*−0.23*
Bz	**0.88**	**0.77**	**0.66**	**0.55**	**0.44**	**0.33**	**0.22**	**0.11**	0.00	*−0.11*	*−0.22*	*−0.33*	*−0.44*
N-substituted azenyl, cyano													
CH=NH	**0.45**	**0.39**	**0.33**	**0.27**	**0.21**	**0.15**	**0.09**	0.03	−0.03	*−0.09*	*−0.15*	*−0.21*	*−0.27*
E-CH=NOH	**0.24**	**0.22**	**0.20**	**0.18**	**0.16**	**0.14**	**0.12**	**0.10**	**0.08**	**0.06**	0.04	0.02	0.00
CH=NPh	**0.54**	**0.47**	**0.41**	**0.35**	**0.29**	**0.23**	**0.17**	**0.11**	0.05	−0.01	*−0.07*	*−0.13*	*−0.19*
CN	**0.45**	**0.40**	**0.34**	**0.29**	**0.23**	**0.18**	**0.12**	**0.07**	0.01	−0.04	*−0.10*	*−0.15*	*−0.21*
Nitroso, nitro													
NO	**0.96**	**0.89**	**0.82**	**0.75**	**0.68**	**0.61**	**0.54**	**0.47**	**0.40**	**0.33**	**0.26**	**0.19**	**0.12**
NO_2	**0.64**	**0.57**	**0.49**	**0.41**	**0.33**	**0.26**	**0.18**	**0.10**	0.03	−0.05	*−0.13*	*−0.20*	*−0.28*
C-substituted azenyl													
$N=CH_2$	**0.34**	**0.28**	**0.22**	**0.16**	**0.10**	0.04	−0.02	*−0.08*	*−0.14*	*−0.20*	*−0.26*	*−0.32*	*−0.38*
N=CHPh	**0.31**	**0.25**	**0.18**	**0.12**	**0.06**	−0.01	*−0.07*	*−0.13*	*−0.20*	*−0.26*	*−0.32*	*−0.39*	*−0.45*
Diazenyl													
N=NH	**0.75**	**0.67**	**0.59**	**0.43**	**0.35**	**0.27**	**0.19**	**0.19**	**0.11**	0.03	−0.05	*−0.13*	*−0.21*
$N=NCF_3$	*−0.12*	*−0.06*	0.00	**0.06**	**0.12**	**0.18**	**0.24**	**0.30**	**0.36**	**0.42**	**0.48**	**0.54**	**0.60**

(*continued*)

TABLE 7 (*continued*)

Group	$\eta =$	−6	−5	−4	−3	−2	−1	0	1	2	3	4	5	6
N=NBu-*t*		**0.52**	**0.45**	**0.37**	**0.30**	**0.22**	**0.15**	**0.07**	0.00	*−0.08*	*−0.15*	*−0.23*	*−0.31*	*−0.38*
N=NPh		**0.47**	**0.42**	**0.36**	**0.30**	**0.24**	**0.18**	**0.12**	**0.06**	**0.00**	*−0.06*	*−0.12*	*−0.17*	*−0.23*
Allenyl, heteroallenyl														
$CH=C=CH_2$		**0.64**	**0.53**	**0.42**	**0.31**	**0.20**	**0.09**	−0.02	*−0.13*	*−0.24*	*−0.35*	*−0.46*	*−0.57*	*−0.68*
N=C=O		*−0.59*	*−0.52*	*−0.45*	*−0.38*	*−0.31*	*−0.24*	*−0.17*	*−0.10*	−0.03	0.04	**0.11**	**0.18**	**0.25**
N=C=S		**0.43**	**0.34**	**0.25**	**0.16**	**0.07**	−0.02	*−0.11*	*−0.20*	*−0.29*	*−0.38*	*−0.47*	*−0.56*	*−0.65*
N_3		**0.45**	**0.33**	**0.21**	**0.09**	−0.03	*−0.15*	*−0.27*	*−0.39*	*−0.51*	*−0.63*	*−0.75*	*−0.87*	*−0.99*
Other														
H		0	0	0	0	0	0	0	0	0	0	0	0	0
F		*−0.73*	*−0.69*	*−0.64*	*−0.60*	*−0.56*	*−0.52*	*−0.48*	*−0.44*	*−0.40*	*−0.36*	*−0.32*	*−0.27*	*−0.23*
Cl		*−0.21*	*−0.22*	*−0.24*	*−0.25*	*−0.26*	*−0.27*	*−0.28*	*−0.29*	*−0.30*	*−0.31*	*−0.32*	*−0.33*	*−0.35*
Br		*−0.16*	*−0.18*	*−0.20*	*−0.22*	*−0.23*	*−0.25*	*−0.27*	*−0.29*	*−0.31*	*−0.32*	*−0.34*	*−0.36*	*−0.38*
I		**0.14**	**0.09**	0.03	−0.03	*−0.09*	*−0.14*	*−0.20*	*−0.26*	*−0.31*	*−0.37*	*−0.43*	*−0.49*	*−0.54*
Me		0.04	0.01	−0.02	−0.05	*−0.08*	*−0.11*	*−0.14*	*−0.17*	*−0.20*	*−0.23*	*−0.26*	*−0.29*	*−0.32*
Et		**0.10**	**0.06**	0.02	−0.01	−0.05	*−0.08*	*−0.12*	*−0.16*	*−0.19*	*−0.23*	*−0.26*	*−0.30*	*−0.34*
c-Pr		**0.24**	**0.18**	**0.11**	0.04	−0.03	*−0.10*	*−0.17*	*−0.24*	*−0.31*	*−0.38*	*−0.45*	*−0.52*	*−0.58*
CF_3		**0.29**	**0.26**	**0.23**	**0.21**	**0.18**	**0.16**	**0.13**	**0.10**	**0.08**	0.05	0.03	0.00	−0.03
$SiMe_3$		**0.41**	**0.36**	**0.31**	**0.27**	**0.22**	**0.18**	**0.13**	**0.08**	0.04	−0.01	−0.05	*−0.10*	*−0.15*
NHAc		**0.18**	**0.09**	0.00	*−0.09*	*−0.17*	*−0.26*	*−0.35*	*−0.44*	*−0.53*	*−0.61*	*−0.70*	*−0.79*	*−0.88*
NHEt		**0.24**	**0.09**	*−0.06*	*−0.21*	*−0.36*	*−0.51*	*−0.66*	*−0.81*	*−0.96*	*−1.11*	*−1.26*	*−1.41*	*−1.56*
NMe_2		**0.78**	**0.54**	**0.30**	**0.06**	*−0.18*	*−0.42*	*−0.66*	*−0.90*	*−1.14*	*−1.38*	*−1.62*	*−1.86*	*−2.10*
PMe_2		**1.12**	**0.85**	**0.58**	**0.31**	0.04	*−0.23*	*−0.50*	*−0.77*	*−1.04*	*−1.31*	*−1.58*	*−1.85*	*−2.12*
$POMe_2$		**0.36**	**0.32**	**0.28**	**0.25**	**0.21**	**0.18**	**0.14**	**0.10**	**0.07**	0.03	0.00	−0.04	*−0.08*
$PO(OMe)_2$		**0.44**	**0.41**	**0.37**	**0.34**	**0.31**	**0.27**	**0.24**	**0.21**	**0.17**	**0.14**	**0.11**	**0.08**	0.04
OMe		*−0.17*	*−0.23*	*−0.29*	*−0.36*	*−0.42*	*−0.49*	*−0.55*	*−0.61*	*−0.68*	*−0.74*	*−0.81*	*−0.87*	*−0.93*
OSO_2Me		*−0.62*	*−0.55*	*−0.49*	*−0.42*	*−0.36*	*−0.29*	*−0.23*	*−0.16*	*−0.10*	−0.03	0.03	**0.10**	**0.16**
OAc		*−0.21*	*−0.21*	*−0.22*	*−0.22*	*−0.23*	*−0.23*	*−0.24*	*−0.24*	*−0.25*	*−0.25*	*−0.26*	*−0.26*	*−0.27*
SMe		**0.40**	**0.27**	**0.14**	0.01	*−0.12*	*−0.25*	*−0.38*	*−0.51*	*−0.64*	*−0.77*	*−0.90*	*−1.03*	*−1.16*
SAc		**0.26**	**0.21**	**0.15**	**0.09**	0.03	−0.02	*−0.08*	*−0.14*	*−0.19*	*−0.24*	*−0.31*	*−0.36*	*−0.42*
SOMe		**0.51**	**0.41**	**0.31**	**0.21**	**0.11**	0.01	*−0.09*	*−0.19*	*−0.29*	*−0.39*	*−0.49*	*−0.59*	*−0.69*
SO_2Me		**0.44**	**0.39**	**0.34**	**0.29**	**0.23**	**0.18**	**0.13**	**0.08**	0.03	−0.03	*−0.08*	*−0.13*	*−0.18*
SeMe		**0.44**	**0.30**	**0.16**	**0.02**	*−0.12*	*−0.26*	*−0.40*	*−0.54*	*−0.68*	*−0.82*	*−0.96*	*−1.10*	*−1.24*

Substituted ethynyl													
C≡CH	**0.87**	**0.77**	**0.67**	**0.57**	**0.47**	**0.37**	**0.27**	**0.17**	**0.07**	−0.03	*−0.13*	*−0.23*	*−0.23*
C≡CMe	**0.54**	**0.46**	**0.37**	**0.28**	**0.19**	**0.10**	**0.01**	*−0.08*	*−0.17*	*−0.26*	*−0.35*	*−0.44*	*−0.52*
C≡CEt	**0.54**	**0.46**	**0.37**	**0.28**	**0.19**	**0.10**	**0.01**	*−0.08*	*−0.17*	*−0.26*	*−0.35*	*−0.44*	*−0.52*
C≡CCF$_3$	**0.58**	**0.57**	**0.56**	**0.55**	**0.54**	**0.53**	**0.52**	**0.51**	**0.50**	**0.49**	**0.48**	**0.47**	**0.46**
C≡C—C≡CH	**1.03**	**0.93**	**0.83**	**0.73**	**0.63**	**0.53**	**0.43**	**0.33**	**0.23**	**0.13**	0.03	*−0.07*	*−0.17*
C≡CPh	**0.92**	**0.78**	**0.64**	**0.50**	**0.36**	**0.22**	**0.08**	*−0.06*	*−0.20*	*−0.34*	*−0.48*	*−0.62*	*−0.76*
Substituted vinyl													
E-CH=CHNO$_2$	**1.31**	**1.16**	**1.01**	**0.86**	**0.71**	**0.56**	**0.41**	**0.26**	**0.11**	−0.04	*−0.19*	*−0.34*	*−0.49*
CH=CH$_2$	**0.75**	**0.63**	**0.51**	**0.39**	**0.27**	**0.15**	0.03	*−0.09*	*−0.21*	*−0.33*	*−0.45*	*−0.57*	*−0.69*
E-CF=CFCF$_3$	**0.67**	**0.64**	**0.61**	**0.58**	**0.55**	**0.52**	**0.49**	**0.46**	**0.43**	**0.40**	**0.37**	**0.34**	**0.31**
CH=CHCN	**0.94**	**0.83**	**0.72**	**0.61**	**0.50**	**0.39**	**0.28**	**0.17**	**0.06**	−0.05	*−0.16*	*−0.27*	*−0.38*
Z-CH=CHCF$_3$	**0.87**	**0.77**	**0.67**	**0.57**	**0.47**	**0.37**	**0.27**	**0.17**	**0.07**	−0.03	*−0.13*	*−0.23*	*−0.33*
E-CH=CHCF$_3$	**0.46**	**0.43**	**0.39**	**0.35**	**0.31**	**0.28**	**0.24**	**0.20**	**0.17**	**0.13**	**0.09**	**0.06**	**0.02**
E-CH=CHMe	**0.42**	**0.34**	**0.25**	**0.16**	**0.07**	−0.02	*−0.11*	*−0.20*	*−0.29*	*−0.38*	*−0.47*	*−0.56*	*−0.64*
CMe=CH$_2$	**0.47**	**0.39**	**0.31**	**0.23**	**0.16**	**0.08**	0.00	*−0.08*	*−0.16*	*−0.23*	*−0.31*	*−0.39*	*−0.47*
CH=C(CN)$_2$	**0.84**	**0.82**	**0.80**	**0.78**	**0.76**	**0.74**	**0.72**	**0.70**	**0.68**	**0.66**	**0.64**	**0.62**	**0.60**
E-CH=CHEt	**0.42**	**0.34**	**0.25**	**0.16**	**0.07**	−0.02	*−0.11*	*−0.20*	*−0.29*	*−0.38*	*−0.47*	*−0.56*	*−0.64*
C(CN)=C(CN)$_2$	**1.12**	**1.09**	**1.06**	**1.03**	**1.00**	**0.97**	**0.94**	**0.91**	**0.88**	**0.85**	**0.82**	**0.79**	**0.76**
CH=CH—CH=CH$_2$	**0.47**	**0.35**	**0.23**	**0.11**	−0.01	*−0.13*	*−0.25*	*0.37*	*−0.49*	*−0.61*	*−0.73*	*−0.85*	*−0.97*
E,E-(CH=CH)$_2$CH=CH$_2$	**0.33**	**0.21**	**0.09**	−0.03	*−0.15*	*−0.27*	*−0.39*	*−0.51*	*−0.63*	*−0.75*	*−0.87*	*−0.99*	*−1.11*
E-CH=CHPh	**0.52**	**0.40**	**0.28**	**0.16**	**0.04**	*−0.08*	*−0.20*	*−0.32*	*−0.44*	*−0.56*	*−0.68*	*−0.80*	*−0.92*
E,E-(CH=CH)$_2$Ph	**0.37**	**0.25**	**0.13**	0.01	*−0.11*	*−0.23*	*−0.35*	*−0.47*	*−0.59*	*−0.71*	*0.83*	*−0.95*	*−1.07*
Substituted phenyl													
C$_6$Cl$_5$	**0.31**	**0.30**	**0.29**	**0.28**	**0.27**	**0.26**	**0.25**	**0.24**	**0.23**	**0.22**	**0.21**	**0.20**	**0.19**
C$_6$F$_5$	**0.80**	**0.73**	**0.66**	**0.59**	**0.53**	**0.46**	**0.39**	**0.32**	**0.25**	**0.19**	**0.12**	0.05	−0.02
4-BrC$_6$H$_4$	**0.52**	**0.46**	**0.40**	**0.33**	**0.27**	**0.20**	**0.14**	**0.08**	0.01	−0.05	*−0.12*	*−0.18*	*−0.24*
3-ClC$_6$H$_4$	**0.32**	**0.29**	**0.25**	**0.22**	**0.18**	**0.15**	**0.11**	**0.08**	0.04	0.01	−0.03	*−0.07*	*−0.10*
4-ClC$_6$H$_4$	**0.56**	**0.49**	**0.42**	**0.35**	**0.28**	**0.21**	**0.14**	**0.07**	0.00	*−0.07*	*−0.14*	*−0.21*	*−0.28*
3-NO$_2$C$_6$H$_4$	**0.76**	**0.67**	**0.58**	**0.49**	**0.41**	**0.32**	**0.23**	**0.14**	0.05	−0.03	*−0.12*	*−0.21*	*−0.30*
4-NO$_2$C$_6$H$_4$	**0.49**	**0.45**	**0.40**	**0.36**	**0.31**	**0.27**	**0.22**	**0.18**	**0.13**	**0.09**	0.04	−0.01	−0.05

(*continued*)

TABLE 7 (*continued*)

Group	$\eta =$	−6	−5	−4	−3	−2	−1	0	1	2	3	4	5	6
Ph		0.72	0.60	0.48	0.36	0.24	0.12	0.00	−0.12	−0.24	−0.36	−0.48	−0.60	−0.72
4-$CF_3C_6H_4$		0.40	0.37	0.33	0.30	0.26	0.23	0.19	0.16	0.12	0.09	0.05	0.02	−0.02
4-MeC_6H_4		0.23	0.19	0.14	0.10	0.06	0.02	−0.02	−0.06	−0.10	−0.14	−0.18	−0.23	−0.27
4-$MeOC_6H_4$		0.33	0.27	0.21	0.15	0.08	0.02	−0.04	−0.10	−0.16	−0.23	−0.29	−0.35	−0.41
4-EtC_6H_4		0.23	0.19	0.14	0.10	0.06	0.02	−0.02	−0.06	−0.10	−0.14	−0.18	−0.23	−0.27
4-PhC_6H_4		0.68	0.56	0.44	0.32	0.20	0.08	−0.04	−0.16	−0.28	−0.40	−0.52	−0.64	−0.76
Carbonyl														
ClCO		1.11	1.05	0.99	0.93	0.87	0.81	0.75	0.69	0.63	0.57	0.51	0.45	0.39
FCO		1.19	1.12	1.05	0.98	0.91	0.84	0.77	0.70	0.63	0.56	0.49	0.42	0.35
HCO		1.17	1.07	0.97	0.87	0.77	0.67	0.57	0.47	0.37	0.27	0.17	0.07	−0.03
CO_2H		0.78	0.73	0.67	0.62	0.57	0.52	0.47	0.42	0.37	0.32	0.27	0.22	0.16
$COCF_3$		1.15	1.10	1.05	1.00	0.95	0.90	0.85	0.80	0.75	0.70	0.65	0.60	0.55
Ac		1.12	1.03	0.93	0.84	0.74	0.65	0.55	0.46	0.36	0.27	0.17	0.08	−0.02
$CONH_2$		0.73	0.68	0.62	0.57	0.51	0.46	0.40	0.35	0.29	0.24	0.18	0.13	0.07
CO_2Me		0.90	0.83	0.76	0.69	0.62	0.55	0.48	0.41	0.34	0.27	0.20	0.13	0.06
COEt		1.12	1.03	0.93	0.84	0.74	0.65	0.55	0.46	0.36	0.27	0.17	0.08	−0.02
CO_2Et		0.86	0.80	0.74	0.67	0.61	0.54	0.48	0.42	0.35	0.29	0.22	0.16	0.10
COPr		1.12	1.03	0.93	0.84	0.74	0.65	0.55	0.46	0.36	0.27	0.17	0.08	−0.02
COPr-*i*		1.12	1.03	0.93	0.84	0.74	0.65	0.55	0.46	0.36	0.27	0.17	0.08	−0.02
CO_2Pr		0.88	0.82	0.75	0.68	0.61	0.55	0.48	0.41	0.35	0.28	0.21	0.15	0.08
CO_2Bu		0.88	0.82	0.75	0.68	0.61	0.55	0.48	0.41	0.35	0.28	0.21	0.15	0.08
Bz		1.18	1.07	0.96	0.85	0.74	0.63	0.52	0.41	0.30	0.19	0.08	−0.03	−0.14
N-substituted azenyl, cyano														
CH=NH		0.63	0.57	0.51	0.45	0.39	0.33	0.27	0.21	0.15	0.09	0.03	−0.03	−0.09
E-CH=NOH		0.44	0.42	0.40	0.38	0.36	0.34	0.32	0.30	0.28	0.26	0.24	0.22	0.20
CH=NPh		0.84	0.78	0.72	0.66	0.60	0.54	0.48	0.42	0.36	0.30	0.24	0.18	0.12
CN		1.02	0.97	0.91	0.86	0.80	0.75	0.69	0.64	0.58	0.53	0.47	0.42	0.36
Nitroso, nitro														
NO		1.40	1.33	1.26	1.19	1.12	1.05	0.98	0.91	0.84	0.77	0.70	0.63	0.56
NO_2		1.31	1.24	1.16	1.08	1.00	0.93	0.85	0.77	0.70	0.62	0.54	0.47	0.39
C-substituted azenyl														
$N=CH_2$		0.54	0.48	0.42	0.36	0.30	0.24	0.18	0.12	0.06	0.00	−0.06	−0.12	−0.18
N=CHPh		0.44	0.38	0.31	0.25	0.19	0.12	0.06	0.00	−0.07	−0.13	−0.19	−0.26	−0.32

Diazenyl													
N=NH	**1.06**	**0.98**	**0.90**	**0.82**	**0.74**	**0.66**	**0.58**	**0.50**	**0.42**	**0.34**	**0.26**	**0.18**	**0.10**
$N{=}NCF_3$	**0.32**	**0.38**	**0.44**	**0.50**	**0.56**	**0.62**	**0.68**	**0.74**	**0.80**	**0.86**	**0.92**	**0.98**	**1.04**
N=NBu-*t*	**0.73**	**0.66**	**0.58**	**0.51**	**0.43**	**0.36**	**0.28**	**0.21**	**0.13**	**0.06**	−0.02	*−0.10*	*−0.17*
N=NPh	**0.74**	**0.69**	**0.63**	**0.57**	**0.51**	**0.45**	**0.39**	**0.33**	**0.27**	**0.21**	**0.15**	**0.10**	0.04
Allenyl, heteroallenyl													
$CH{=}C{=}CH_2$	**0.76**	**0.65**	**0.54**	**0.43**	**0.32**	**0.21**	**0.10**	−0.01	*−0.12*	*−0.23*	*−0.34*	*−0.45*	*−0.56*
N=C=O	*−0.25*	*−0.18*	*−0.11*	−0.04	0.03	**0.10**	**0.17**	**0.24**	**0.31**	**0.38**	**0.45**	**0.52**	**0.59**
N=C=S	**0.97**	**0.88**	**0.79**	**0.70**	**0.61**	**0.52**	**0.43**	**0.34**	**0.25**	**0.16**	**0.07**	−0.02	*−0.11*
N_3	**0.88**	**0.76**	**0.64**	**0.52**	**0.40**	**0.28**	**0.16**	0.04	*−0.08*	*−0.20*	*−0.32*	*−0.44*	*−0.56*
Other													
H	0	0	0	0	0	0	0	0	0	0	0	0	0
F	*−0.19*	*−0.15*	*−0.10*	*−0.06*	−0.02	0.02	**0.06**	**0.10**	**0.14**	**0.18**	**0.22**	**0.27**	**0.31**
Cl	**0.26**	**0.25**	**0.23**	**0.22**	**0.21**	**0.20**	**0.19**	**0.18**	**0.17**	**0.16**	**0.15**	**0.14**	**0.12**
Br	**0.31**	**0.29**	**0.27**	**0.25**	**0.24**	**0.22**	**0.20**	**0.18**	**0.16**	**0.15**	**0.13**	**0.11**	**0.09**
I	**0.54**	**0.49**	**0.43**	**0.37**	**0.31**	**0.26**	**0.20**	**0.14**	**0.09**	**0.03**	−0.03	*−0.09*	*−0.14*
Me	0.03	0.00	−0.03	*−0.06*	*−0.09*	*−0.12*	*−0.15*	*−0.18*	*−0.21*	*−0.24*	*−0.27*	*−0.30*	*−0.33*
Et	**0.09**	0.05	0.01	−0.02	*−0.06*	*−0.09*	*−0.13*	*−0.17*	*−0.20*	*−0.24*	*−0.27*	*−0.31*	*−0.35*
d-Pr	**−0.25**	**0.19**	**0.12**	0.05	−0.02	*−0.09*	*−0.16*	*−0.23*	*−0.30*	*−0.37*	*−0.44*	*−0.51*	*−0.57*
CF_3	**0.69**	**0.66**	**0.63**	**0.61**	**0.58**	**0.56**	**0.53**	**0.50**	**0.48**	**0.45**	**0.43**	**0.40**	**0.37**
$SiMe_3$	**0.30**	**0.25**	**0.20**	**0.16**	**0.11**	**0.07**	0.02	−0.03	*−0.07*	*−0.12*	*−0.16*	*−0.21*	*−0.26*
NHAc	**0.46**	**0.37**	**0.28**	**0.19**	**0.11**	0.02	*−0.07*	*−0.16*	*−0.25*	*−0.33*	*−0.42*	*−0.51*	*−0.60*
NHEt	**0.41**	**0.26**	**0.11**	−0.04	*−0.19*	*−0.34*	*−0.49*	*−0.64*	*−0.79*	*−0.94*	*−1.09*	*−1.24*	*−1.39*
NMe_2	**0.95**	**0.71**	**0.47**	**0.23**	−0.01	*−0.25*	*−0.49*	*−0.73*	*−0.97*	*−1.21*	*−1.45*	*−1.69*	*−1.93*
PMe_2	**1.22**	**0.95**	**0.68**	**0.41**	**0.14**	*−0.13*	*−0.40*	*−0.67*	*−0.94*	*−1.21*	*−1.48*	*−1.75*	*−2.02*
$POMe_2$	**0.66**	**0.62**	**0.58**	**0.55**	**0.51**	**0.48**	**0.44**	**0.40**	**0.37**	**0.33**	**0.30**	**0.26**	**0.22**
$PO(OMe)_2$	**0.80**	**0.77**	**0.73**	**0.70**	**0.67**	**0.63**	**0.57**	**0.57**	**0.53**	**0.50**	**0.47**	**0.44**	**0.40**
OMe	**0.13**	**0.07**	0.01	*−0.06*	*−0.12*	*−0.19*	*−0.25*	*−0.31*	*−0.38*	*−0.44*	*−0.51*	*−0.57*	*−0.63*
OSO_2Me	*−0.07*	0.00	**0.06**	**0.13**	**0.19**	**0.26**	**0.32**	**0.39**	**0.45**	**0.52**	**0.58**	**0.65**	**0.71**
OAc	**0.17**	**0.17**	**0.16**	**0.16**	**0.15**	**0.15**	**0.14**	**0.14**	**0.13**	**0.13**	**0.12**	**0.12**	**0.11**
SMe	**0.70**	**0.57**	**0.44**	**0.31**	**0.18**	0.05	*−0.08*	*−0.21*	*−0.34*	*−0.47*	*−0.60*	*−0.73*	*−0.86*
SAc	**0.65**	**0.60**	**0.54**	**0.48**	**0.42**	**0.37**	**0.31**	**0.25**	**0.20**	**0.14**	**0.08**	0.03	−0.03
SOMe	**1.05**	**0.95**	**0.85**	**0.75**	**0.65**	**0.55**	**0.45**	**0.35**	**0.25**	**0.15**	0.05	−0.05	*−0.15*
SO_2Me	**1.03**	**0.98**	**0.93**	**0.88**	**0.82**	**0.77**	**0.72**	**0.67**	**0.62**	**0.56**	**0.51**	**0.46**	**0.41**
SeMe	**0.72**	**0.58**	**0.44**	**0.30**	**0.16**	0.02	*−0.12*	*−0.26*	*−0.40*	*−0.54*	*−0.68*	*−0.82*	*−0.96*

[a]The type style represents the nature of the overall electrical effect. Boldface indicates electron-acceptor behavior; italics indicates electron-donor behavior; and ordinary type signifies that there is no meaningful electrical effect.

X_π groups in which the first atom of the substituent is involved in a π orbital. Examples are —CH=CH_2, Ac, —C≡CH, —C≡N, Ph.

X_h groups, in which the delocalized electron are in σ orbitals on the first atom of the substituent. Examples are Me, CF_3, CH_2Cl, $CHBr_2$.

X_e groups, in which an empty orbital on the first atom is involved in delocalization. The best known example is $SiMe_3$.

$X_{\pi(pd)}$ groups in which the first atom of the group is involved in a pd π bond. Examples are SO_2Me, SO_2CF_3, $PO(OEt)_2$.

$X_{n,\pi}$ groups in which the first atom of the substituent involves both a full nonbonding orbital and a π orbital. Such groups include N=CPh, N=NPh and N=O.

The range of σ_e observed for each of these types of substituent for which it is available is shown in Table 4. X_n groups show a very wide range of sensitivity to electronic demand. It has been shown that this is a function of the electronegativity of the first atom in the group[9], and of the number and type of fragments attached to it. Thus, for a group of the type MZ_n where n may have integer values of 0, 1, 2 or 3,

$$\sigma_e = a_1\chi_M + a_2 n + a_0 \tag{17}$$

where χ_M is the Allred–Rochow electronegativity value of the atom M[10].

The X_π groups have only about half the range of substituent electronic demand observed for the X_n groups. The X_h groups exhibit an even smaller range. Thus, the order seems to be $X_n > X_\pi > X_h \sim X_{\pi(pd)}$. The number of groups of the X_e and $X_{n,\pi}$ types for which values of σ_e are available is too small to permit any comparison.

D. Electrical-effect Substituent Constants for Doubly Bonded Groups

The localized and intrinsic delocalized electrical effects of second period element multiply bonded groups are a linear function of the electronegativities of the multiply bonded atoms, the bond order of the multiple bond, and the nature and number of other groups bonded to the atoms forming the multiple bond. Thus the σ_I values of the groups —M^1=M^2 and —M^1R^1=$M^2R^{2c}R^{2t}$ are given by the relationship

$$\sigma_{IX} = 0.0907(\pm 0.0277)\chi_1 + 0.0779(\pm 0.0163)\chi_2 + 0.198(\pm 0.0401)b_0 - 0.785(\pm 0.128) \tag{18}$$

$100R^2 = 87.71$, $F = 23.80$, $s_{est} = 0.0650$, $s^0 = 0.415$, $n = 14$
when R is H, alkyl or Ph. The σ_d values are given by

$$\sigma_{dX} = 0.130(\pm 0.0479)\chi_1 + 0.115(\pm 0.0161)\chi_2 - 0.146(\pm 0.0380)b_0 - 0.165(\pm 0.0449)n_{AK} - 0.446(\pm 0.137) \tag{19}$$

$100R^2 = 96.68$, $F = 21.10$, $s_{est} = 0.0495$, $s^0 = 0.273$, $n = 9$
when R^2 is H or alkyl. Also

$$\sigma_{dX} = 0.193(\pm 0.321)\chi_1 + 0.119(\pm 0.108)\chi_2 - 0.128(\pm 0.0255)b_0 - 0.224(\pm 0.0301) - 0.686(\pm 0.0916) \tag{20}$$

$100R^2 = 98.75$, $F = 79.14$, $s_{est} = 0.0332$, $s^0 = 0.168$, $n = 9$
when R^2 is H or Ph. In these equations χ_1 and χ_2 are the electronegativities of the sp^2 hybridized M^1 and M^2 atoms[11], b_0 is the bond order of the multiple bond, and n_{Ak} and n_{Ph} are the number of alkyl or phenyl groups respectively which are bonded to M^2. The electronegativity is a linear function of the fraction of p character, F_p, of the hybrid orbitals. Thus

$$\chi_{M,sp^n} = b_1 F_p + b_0 \tag{21}$$

Values of χ_{sp^2} and χ_{sp} for a number of elements have been calculated from this relationship.

Equations 18, 19 and 20 permit estimation of the σ_I and σ_d parameters for a number of multiply bonded groups of interest including —CH=NH, —N=CH_2 and —N=NH. Unfortunately, no relationship of this type exists for σ_e parameters.

1. Groups containing the C=C bond

The vinyl group, CH=CH_2, shows the behaviour characteristic of all unsubstituted π-bonded groups whose framework is built up of sp^2 hybridized C atoms. It has a small positive σ_I value, a small negative σ_d value and a comparatively large negative σ_e value. These values account for the fact that, like the phenyl group which has essentially the same values for these parameters, the vinyl group can act as either an electron donor or an electron acceptor depending on the nature of the electronic demand. Thus, when $P_D = 50$ and $\eta = 6$ the vinyl group is a strong electron donor whereas when $P_D = 50$ and $\eta = -6$ it is a strong electron acceptor. The effect of substitution on the electrical effects of the vinyl group is well known only for the *trans*-2-substituted vinylene derivatives. The only *cis*-2-substituted derivative for which parameters are available is Z—CH=$CHCF_3$; the only 1-substituted derivative for which parameters are available is MeC=CH_2. For E—XCH=CH groups the σ_I values are described by the relationship

$$\sigma_{I,CH=CHX} = 0.291(\pm 0.0304)\sigma_{IX} + 0.174(\pm 0.0464)\sigma_{dX} - 0.279(\pm 0.146)\sigma_{eX} + 0.0903(\pm 0.0136) \quad (22)$$

$100R^2 = 96.98$, $F = 64.22$, $s_{est} = 0.0202$, $s^0 = 0.224$, $n = 10$.

A similar relationship is obtained for 4-substituted phenyl groups,

$$\sigma_{I,4\text{-PnX}} = 0.136(\pm 0.00658)\sigma_{IX} + 0.103(\pm 0.00741)\sigma_{dX} - 0.0845(\pm 0.0435)\sigma_{eX} + 0.116(\pm 0.00311) \quad (23)$$

$100R^2 = 99.30$, $F = 235.0$, $s_{est} = 0.00465$, $s^0 = 0.113$, $n = 9$.

The similarity of the two equations is clearly shown by a comparison of the composition of the electrical effect and of the electronic demand. The P_D values of the substituted vinyl and substituted phenyl groups are 37.4(± 10.9) and 43.0(± 3.59) respectively; clearly there is no significant difference between these values. The value of η for the substituted vinyl groups is −1.60(± 0.725), not significantly different from the value of 0.824(± 0.420) obtained for the substituted phenyl groups. Equations of this type are also obtained for the $\sigma_{d,CH=CHX}$ and $\sigma_{d,4\text{-PnX}}$ constants, thus

$$\sigma_{d,CH=CHX} = 0.239(\pm 0.0905)\sigma_{IX} + 0.500(\pm 0.158)\sigma_{dX} + 2.19(\pm 0.366)\sigma_{eX} - 0.0640(\pm 0.0226) \quad (24)$$

$100R^2 = 98.04$, $F = 83.27$, $s_{est} = 0.0331$, $s^0 = 0.188$, $n = 10$;
and

$$\sigma_{d,4\text{-PnX}} = 0.220(\pm 0.0320)\sigma_{IX} + 0.0879(\pm 0.0361)\sigma_{dX} + 0.893(\pm 0.212)\sigma_{eX} - 0.0884(\pm 0.0152) \quad (25)$$

$100R^2 = 93.40$, $F = 23.58$, $s_{est} = 0.0227$, $s^0 = 0.345$, $n = 9$.

Only qualitative comparisons can be made between these two relationships as the errors in the P_D values are very large and they cannot be determined for the η values. In both equations, however, the electronic demand is large and positive.

We find that the effect of the variable substituent on σ_e values for substituted vinyl and phenyl groups are not described by the LDR equation. Some generalizations can be made, however. Thus, alkyl substitution has little effect on the σ_e values of substituted vinyl, ethynyl and carbonyl groups. X_n substituents such as F, Cl and OMe raise (make less negative) the σ_e values of substituted vinyl, ethynyl and phenyl groups. The CF_3 group

causes a large increase in σ_e when W_π is *trans* vinylene, ethynylene, 4-phenylene or carbonyl.

We cannot apply the LDR equation to the description of the effect of X on the electrical substituent effect parameters for substituted ethynyl groups, because both the range of substituent type and the number of groups for which data are available are too small.

Finally, σ_d values for some π-bonded carbon atom substituents have been calculated from the relationship

$$\sigma_{dX} = 3.23(\pm 0.744)q - 1.80(\pm 0.373) \tag{26}$$

$100R^2 = 86.27$, $F = 18.85$, $s_{est} = 0.0731$, $s^0 = 0.478$ and $n = 5$, where q is the charge on the exocyclic carbon atom of the 4-substituted benzylcarbenium ion, $4\text{-}XC_6H_4CH_2^+$. X, the 4-substituent, is restricted to groups composed of π-bonded carbon atoms such as vinyl, phenyl and 1,3-butadienyl. q is calculated by the method of Dewar and Longuet-Higgins for the entire $XC_6H_4CH_2^+$ system[12,13].

2. *Groups containing the C=O bond*

These groups are characterized by medium to large positive values of σ_I; the range is 0.2 to 0.6. The σ_d values are also positive; they lie in the range 0.1 to 0.4. It follows then that these groups under most conditions are electron acceptors. Only in the region of large positive electronic demand ($\eta > 6$) do they begin to change over into overall electron donors. At values of η greater than 3 they begin to be delocalized effect electron donors, however. It is this which accounts for their ability to stabilize a cationic carbon atom to which they are directly bonded. The effect of substitution on the σ_I and σ_d values for these groups is described by the equations

$$\sigma_{I,XC=O} = 0.420(\pm 0.0529)\sigma_{IX} + 0.204(\pm 0.0357)\sigma_{dX} + 0.307(\pm 0.0178) \tag{27}$$

$100R^2 = 91.55$, $F = 37.92$, $s_{est} = 0.0287$, $s^0 = 0.347$ and $n = 10$; and

$$\sigma_{d,XC=O} = 0.140(\pm 0.0503)\sigma_{IX} + 0.184(\pm 0.0327)\sigma_{dX} + 0.568(\pm 0.180)\sigma_{eX} + 0.281(\pm 0.0176) \tag{28}$$

$100R^2 = 93.23$, $F = 27.55$, $s_{est} = 0.0233$, $s^0 = 0.336$, $n = 10$.

Again, no such description of the σ_e constants is possible.

3. *Groups containing the C=N bond*

Our data for these groups are sparse. We have available values for three N-substituted azenyl groups, —CH=NX, and two C-substituted azenyl groups, —N=CX^1X^2. Also available are σ_I values for two more C-substituted azenyl groups. The values of σ_I and σ_d for—CH=NH and—N=CH_2 were estimated from equations 18 and 19, the σ_e values were assumed to be equal to the values of the corresponding groups in which X or X^1 is Ph. The N-substituted azenyl groups are localized electrical effect electron acceptors and delocalized effect donors as well. In the region of high electronic demand they are capable of acting as delocalized effect electron donors, however. It is interesting to compare these groups with the carbonyl group. There seems to be a trend toward somewhat smaller values of σ_I, σ_d and σ_e for the N-substituted azenyl groups than is normally observed for carbonyl-containing groups. It is also of interest to compare the parameters of the cyano group with those for the N-substituted azenyl groups. The σ_I value for cyano is much larger but the σ_d and σ_e values are of comparable magnitude.

The σ_I values for C-substituted azenyl groups are positive and lie in the range from 0.1 to 0.4, again showing an electron-acceptor effect. Of greater interest are the small but

negative values of σ_d indicating an electron-donor delocalized effect. In this respect the C-substituted azenyl groups are more like vinyl groups than like carbonyl groups.

It is of interest to compare the behavior of the isocyano group with that of the C-substituted azenyl groups. The isocyano group has a much larger σ_I value. The value of σ_d calculated from equation 19 is also much larger, being positive rather than negative. Unfortunately, no value of σ_e for isocyano is available. It is probably not much different from the value for cyano of -0.055.

4. *Groups containing the N=N bond*

Parameter values are available for four diazenyl groups, —N=NX, with X equal to H, *t*-Bu, Ph and CF_3. The values of σ_I are in the range 0.2 to 0.5, again showing that these groups are localized effect electron acceptors. The σ_d values run from 0.1 to 0.3 indicating an electron-acceptor intrinsic delocalized effect. The σ_e values for X = *t*-Bu or Ph are $-0.067(\pm 0.008)$. The value obtained for —N=NCF_3 seems to be too large. These groups should exhibit electron-acceptor effects over most of the range of electronic demand. In the region of high positive electronic demand, with η greater than six, they can function as overall electron donors, stabilizing cationic carbon atoms and electrophilic radicals to which they are directly bonded. Their behavior is reminiscent of that of carbonyl groups.

5. *Groups containing the N=O bond*

NO and NO_2 are the only groups in this category. The NO group is a moderately strong localized electrical effect acceptor. Introducing the second oxygen atom to form NO_2 has the expected effect of increasing the value of σ_I. What is surprising is that the introduction of the second oxygen atom decreases the magnitude of the intrinsic delocalized electrical effect, thus NO is a stronger delocalized effect acceptor than is NO_2. The σ_e values of the two groups are comparable. The nitroso group is unique in one respect; even at the very high η value of 6 it is still an overall delocalized effect acceptor. By contrast, the nitro group becomes a delocalized effect donor at values of η greater than 3.

6. *Groups containing the C=S bond*

Although the C=S is the best and longest known of the p, p π bonds between second and third period elements, very little in the way of quantitative chemical or physical data is available for groups containing them. Although we may estimate values of σ_I and σ_d for CH=S and CMe=S from equations 18 and 19, it is uncertain whether or not they are applicable to any multiple bonds other than those between two second period elements, as it is from multiple bonds between second period elements that these equations were obtained. The only thiocarbonyl group for which substituent constants have been reported is the N-methyl thiocarbamido group, —C(NHMe)=S, for which values of σ_m and σ_p have been determined[14]. From these values we may estimate σ_I by means of the relationship

$$\sigma_{IX} = 1.64\sigma_{mX} - 0.635\sigma_{pX} - 0.00213 \tag{29}$$

The value obtained is 0.27. We then calculate from the equation

$$\sigma_{pX} = \sigma_{IX} + \sigma_{RX} \tag{30}$$

a σ_R of 0.07. The only guide we have to the electronic demand of sulfur π-bonded to carbon are the σ_e values for the 2- and 3-thienyl groups. For both of these groups σ_e is -0.11. Assuming this to be the value of σ_e for the HC=S and MeC=S groups, and if the

methylamino group has the same effect on σ_e for the thiocarbonyl group as it has on the carbonyl group, then the value of σ_e is about -0.055. We may now estimate the value of σ_d from the equation[6]

$$\sigma_{RX} = 0.934\sigma_{dX} + 0.308\sigma_{eX} - 0.00129 \tag{31}$$

The value obtained is 0.09. As the values of σ_I and σ_d estimated for both the HC=S and MeC=S groups are 0.13 and -0.02 respectively, it seems likely that equations 18, 19 and 20 are not applicable to multiple bonds between second and third period elements. Clearly, the electrical effects of substituted thiocarbonyl groups represent an important gap in our present knowledge.

7. Groups containing adjacent double bonds

The three multiply bonded atoms of groups with two adjacent double bonds are collinear. In allenes each of the two π orbitals extends over only two atoms. In ketenes and ketimines one of the π orbitals extends over two atoms, the other over three. In a third type of substituent the three-atom multiply bonded fragment is isoelectronic with carbon dioxide; each π orbital extends over all three multiply bonded atoms.

No data exist for substituent effects of the allenyl group. Assuming equations 18 and 19 are applicable we may calculate values of 0.12 and -0.02 for σ_I and σ_d respectively. For σ_e we may assume that the value is close to those for the vinyl and ethynyl groups, -0.12 and -0.10 respectively, and therefore assign a value of -0.11. We have one piece of experimental data available to use as a check on these estimates. The pK_a of 2,3-butadienoic acid, $H_2C{=}C{=}CHCO_2H$, in 0.1 M NaCl at 25 °C is 3.685[15]. A correlation of the pK_a values of XCO_2H with the LDR equation gave the relationship

$$pK_{a,X} = -9.63(\pm 0.696)\sigma_{IX} - 1.61(\pm 0.799)\sigma_{dX} - 6.09(\pm 1.78)\sigma_{eX} + 4.237(\pm 0.129) \tag{32}$$

$100R^2 = 96.37$, $F = 159.1$, $s_{est} = 0.280$, $s^0 = 0.211$, $n = 22$.

Using the σ_I, σ_d and σ_e values estimated above for the allenyl group, we calculate a pK_a value of 3.784 for allenic acid, in very good agreement with the observed value. While this does not prove the validity of the estimated parameters it does support it. A pK_a value of 3.695 is also available[15] for 4-phenylbutadienoic acid, suggesting that the substituent constants for the phenylallenyl group, PhCH=C=CH—, are similar to those of the allenyl group.

Values of σ_I, σ_d and σ_e are available for three groups of the third type: azido, isocyanato and isothiocyanato. The value of σ_e for the isocyanato group is probably too large. Very few groups exhibit positive values of σ_e. The largest known is that for *F*, 0.041. That the value for the isocyanato group should be almost twice this seems very unlikely. The values of σ_I and σ_d for the isocyanato group seem reasonable, however. It is interesting to note that all three of these groups have negative σ_d values showing that they have an electron-donor intrinsic delocalized effect, as did the C-substituted azenyl groups. A reasonable supposition therefore is that the fragment —N=C will probably have an electron-donor intrinsic delocalized effect.

No data are available at the present time which would permit the parametrization of cumulene or heterocumulene substituents. It seems reasonable that the σ_I value for the butatrienyl group is not less than, and probably approximately equal to that of the allenyl group, and that its σ_d and σ_e values are not greater than, and may be approximately those of the 1,3-butadienyl group, but unfortunately there are no quantitative data with which to test these values. It should be noted that the 1,3-butadienyl group, —C≡C—C≡CH, has a σ_d value of 0.04 while that of the 1,3-butadienyl group, —CH=CH—CH=CH_2, is

-0.37. Presumably, the σ_d value for the 1,2,3-butatrienyl group, $-CH=C=C=CH_2$, lies somewhere between these values and probably closer to that of the butadienyl group.

8. Groups containing three-membered rings

Analogies between the chemical reactivities of cyclopropanes and alkenes are well known[16,17]. It is therefore of interest to compare the electrical-effect parameters of the cyclopropyl group with those of the vinyl group, and of other X_π groups which involve carbon–carbon π bonds such as phenyl, ethynyl and allenyl on the one hand and alkyl groups on the other. Since alkyl groups have constant electrical effects[18,19] comparisons will be made with the mean values of the alkyl group parameters. The σ_I value for the cyclopropyl group, 0.01, is not significantly different from the mean value obtained for alkyl groups of $-0.01(\pm 0.01)$. It is significantly smaller than the values of 0.11 and 0.12 for vinyl and phenyl and the estimated value of 0.12 obtained for allenyl. As expected from the much higher electronegativity of sp hybridized carbon, the σ_I value of 0.29 for ethynyl is much larger. The σ_d value for cyclopropyl of -0.17 is slightly larger than the mean value for alkyl groups of $-0.14\ (\pm 0.013)$; the difference is not significant. The values of σ_d for vinyl and phenyl of -0.08 and -0.12 are slightly less than the mean value for alkyl groups. The value for phenyl is not significantly different from the alkyl value. The values of σ_d for the ethynyl and allenyl groups are the smallest, -0.02. It is the value of σ_e however which most clearly distinguishes the cyclopropyl group from both alkyl groups and from the vinyl, phenyl, allenyl and ethynyl groups. The mean value of σ_e for alkyl groups is $-0.036(\pm 0.003)$. The value for the cyclopropyl group of -0.069 has about twice the magnitude. The values for vinyl, phenyl, ethynyl, and the estimated value for allenyl are -0.12, -0.12, -0.10 and -0.11 respectively, thus they are nearly twice the magnitude of the cyclopropyl value. To sum up:

$$\sigma_{I,cPr} \simeq \bar{\sigma}_{I,Ak} < \sigma_{I,Vi} \simeq \sigma_{I,Ph} = \sigma_{I,CH=C=CH_2} < \sigma_{I,C=CH}$$

$$\sigma_{d,C=CH} = \sigma_{d,CH=C=CH_2} < \sigma_{d,Vi} < \sigma_{d,Ph} \simeq \bar{\sigma}_{d,Ak} \simeq \sigma_{d,cPr}$$

$$\bar{\sigma}_{e,Ak} < \sigma_{e,cPr} < \sigma_{e,Vi} = \sigma_{e,Ph} \simeq \sigma_{e,CH=C=CH_2} \simeq \sigma_{e,C=CH}$$

In conclusion, though the σ_I and σ_d values for the cyclopropyl group are not significantly different from the mean values for alkyl groups, the sensitivity of the cyclopropyl group to the electronic demand of a phenomenon is intermediate between that of alkyl group and that of X_π groups. As a result of this property the cyclopropyl group can act as an electron acceptor in the region of negative electronic demand with η less than -3. It will also be a much more effective electron donor than an alkyl group in the region of positive electronic demand with η greater than 4.

The 2-oxiranyl, 2-thiiranyl, and the 1- and 2-aziranyl groups might possibly show some relationship to the C=O, C=S, —N=C and —C=N groups respectively. Values of σ_I and σ_R^0 have been determined for these groups from F^{19} NMR studies[20–22]. Allowing for small differences in scaling between these values and those we have been using, it seems clear that σ_I and σ_d values for these groups are similar to those for the corresponding substituted methyl groups in the case of the 2-oxiranyl, 2-thiiranyl and 2-aziridinyl groups. The 1-aziridinyl group is analogous in its properties to the NR_2 groups where R is H or Me. Unfortunately, the available data do not permit any estimate of the σ_e values for these groups. By analogy with the cyclopropyl group this is where a significant difference in behavior is most likely to be found.

E. The Use of Correlation Analysis for the Description of Electrical Effects

Tables 2,4,6 and 7 provide substituent constants for use with all of the possible types of

electrical effect equation including the monoparametric Hammett equation, the diparametric LD and CR equations, and the triparametric LDR equation. Which of these relationships is used depends on the nature of the problem being studied. There are four cases which must be considered:

(1) The nature of the electrical effect is known. Thus approximate values of both P_D and η are available. Consider the rate constants for the alkaline hydrolysis of a set of 1-bicyclo[2.2.2]octyl 4'-substituted benzoates in 88% aqueous ethanol at 30 °C. A considerable body of data is available for similar alkaline hydrolyses of alkyl 4-substituted benzoates. The rate constants are generally well correlated by the Hammett equation using the σ_p constants for which P_D is 50 and $\eta = 0.4$. Thus the simple Hammett equation should give an adequate model for this data set if the correlation is carried out using the σ_p constants.

(2) The value of η is known, the value of P_D is not. Consider the pK_a's of the 2-(4'-substituted phenyl)-1-ethanephosphonic acids in 50% aqueous ethanol at 25 °C. Generally, a system in which a substituted benzene ring is separated from an active site by one or more methylene groups is best modelled by the LD equation using the σ_R^0 constants, for which $\eta = -0.4$, while P_D can vary from 40 to 50. Thus the data should be correlated with the LD equation using σ_R^0 as the σ_D parameter. The value of P_D can then be calculated from the values of L and D obtained using equation 11a.

(3) The value of P_D is known while that of η is unknown. Consider the rate constants for the reaction of 8-substituted-5-chloro-6-nitroquinolines with methoxide ion in methanol at 25 °C. Similar reactions have a P_D value of about 50. The η value should be in the range -1 to -2.5. In this case the data set can be correlated with the CR equation using the $\sigma_{Id,50}$ and σ_c constants. The value of η can then be calculated from the regression equation using equation 6 and the fact that $C = D$.

(4) Neither η or P_D is known. Consider for example the rate constants for the reaction of Z-5-substituted pentatrienoic acids with diazodiphenylmethane in 2-methoxyethanol at 25 °C. The distance from the substituent to the carboxyl group should be more than 500 pm which precludes the existence of steric effects. If the number of data points available is sufficient (at least ten are required for reliable results), the LDR equation is the correlation equation of choice. If fewer data points are available, the set may be correlated first with the LD equation using in turn the $\sigma_{R,-2}$, $\sigma_{R,-1}$, σ_d, $\sigma_{R,1}$ and $\sigma_{R,2}$ constants as σ_D. An approximate value of η is determined by the σ_D constant that gives the best fit. The value of P_D can be calculated from equation 11a using the L and D values obtained from the best regression equation. Alternatively, a series of correlations with the CR equation can be carried out using $\sigma_{Id,k'}$ values with $k' = 30, 40, 50$ and 60 in turn. The best regression equation obtained will give an approximate value of P_D (it is equal to k') and a value of η can be calculated from equation 6.

These examples are intended to show how the LDR, LD, CR and Hammett equations can be applied to the quantitative description of electrical effects and what determines the choice of an equation in a particular problem.

Finally, the tabulated $\sigma_{k'/k}$ values (Table 5) are useful in choosing the members of a data set when the η and P^D values for the phenomenon of interest are known.

IV. STERIC EFFECTS

A. Introduction

It has long been known that when a substituent and an active site are in proximity to each other (usually situated on adjacent atoms of a skeletal group) steric effects are often observed. Steric effects results from repulsions between occupied valence shell orbitals on atoms which are not bonded to each other. They may be intermolecular or intramolecular.

Steric effects always result in an increase in the energy of the species involved. Their effect on a measured property however may be either incremental or decremental. Thus, for example, in the case of chemical reactivity the incremental or decremental nature of the steric effect depends on whether it is greater in the reactant or in the product or transition state. Steric effects can be manifested in various ways. Intramolecular steric effects include:

1. Relief of steric strain. Repulsions are greater in the reactant than in the product or transition state. This produces an incremental effect in an equilibrium or rate constant relative to a reference substrate free of steric effects.

2. Steric inhibition of resonance. When a planar π-bonded substituent or active site attached to a π-bonded skeletal group undergoes a rotation out of the plane of the skeletal group due to the steric effect exerted by an adjacent substituent or active site, the delocalized electrical effect of the first substituent or active site is reduced.

3. Steric effect on conformational preference. Steric effects may determine the position of the conformational equilibria extant in a substrate. If only one conformation is involved in the phenomenon being studied, this will result in a steric effect.

4. Steric hindrance to intramolecular active site solvation. This process can change the energy of the reactant relative to that of the product or transition state. It involves 'solution' of the active site by another part of the same molecule.

Intermolecular steric effects include.

1. Steric shielding of the active site. As the size of an adjacent substituent increases, the region of space available to an attacking reagent is decreased.

2. Steric inhibition of solvation. The substituent can decrease the access of solvent molecules to the active site.

B. Intermolecular Force Proximity Effects

When a substituent and an active site are adjacent to each other, intramolecular forces can operate. These are not true steric effects. They do not result from repulsions between occupied orbitals on nonbonded atoms. They have nevertheless traditionally been described in the literature as steric effects. They are more properly referred to as intramolecular force proximity effects or, more simply, imf proximity effects. The most clearcut examples involve the formation of 'strong' intramolecular hydrogen bonds.

C. Steric Effect Properties

Steric effects are characterized by a number of properties which must be understood if they are to be successfully parameterized. They include:

1. The observed steric effect may be composite. Components of several different types contribute to the observed effect.

2. Steric effects are vector rather than scalar properties. They depend on both magnitude and direction.

3. Steric effects obey the principle of minimal steric interaction (MSI). This principle states that a nonsymmetric substituent will prefer that conformation which minimizes steric repulsions.

4. The major part of the steric effect of a polyatomic substituent may be exerted at any point in the main chain of the substituent. Where it occurs depends on the steric requirements of the phenomenon being studied.

D. Steric Effect Parametrization

For many years there has been general agreement that the best measure of atomic size is the van der Waals radius. The distance between the nuclei of two nonbonded atoms in

contact is equal to the sum of their van der Waals radii. The van der Waals radii of monatomic groups can be used directly as a measure of the steric effect[23]. It is more convenient however to define a steric parameter based on van der Waals radii[24–26] for which the value for hydrogen is zero. Thus, the steric parameter υ is defined as

$$\upsilon_X = r_{VX} - r_{VH} = r_{VX} - 1.20 \tag{33}$$

for the monatomic substituents H, F, Cl, Br, I. For groups of the type $X = M(lp)_nH_{3-n}$ it seems valid to assume that $r_{VX} = r_{VM}$. Thus values for OH, SH, SeH, NH_2, PH_2, AsH_2 are readily obtained. Values of υ for tetrahedral groups of the type MZ_3 can be calculated easily from the length of the MZ bond and r_{VZ}. For this type of group there are three radii of interest: the minimum and maximum radii perpendicular to the group axis and the radius parallel to the group axis. The most often used is the minimum perpendicular radius. In this way υ values for CH_3, CF_3, CCl_3, CMe_3, $SiMe_3$, and similar groups may be calculated. For cylindrically symmetric groups, —C≡C—Z and —C≡N, the minimal perpendicular radius and the parallel radius can be calculated. The former is equivalent to the radius of the cylinder. In this manner υ parameters have been developed for a number of groups. For the remaining nonsymmetric groups $MZ^1_2Z^2$ and $MZ^1Z^2Z^3$ υ values can be calculated from the regression equation resulting from the correlation of sterically dependent data sets in which all of the substituents in the set have conformationally independent steric effects. The correlation equation used is

$$Q_X = S\upsilon_X + h \tag{34}$$

where Q is the quantity correlated, S is the coefficient of υ and h is the intercept.

One large class of substituents remains to be discussed, the planar π-bonded groups. Doubly bonded groups fall into this class. The steric effect of a planar π-bonded group varies from a minimum value which is equal to the half thickness of the group to maximum value in the plane of the group perpendicular to the group axis. The minimum value is given by υ_{ef}, the maximum value by υ_{mn}. It should be noted that although υ_{mn} is a measure of the maximum steric effect exerted by the planar π-bonded group, it is at the same time the maximum radius in the plane of the group. For a nonsymmetric group this is υ_{mn}, the larger of the two radii in the plane of the group being designated υ_{mx}. Values of υ_{ef} and υ_{mn} for planar π-bonded groups are reported in Table 8.

The steric effect of a planar π-bonded group is further complicated by the fact that when such a group is bonded to a planar π-bonded skeletal group G or active site Y, the dihedral angle θ formed by X_π with G or Y will vary with the size of G or Y. Both σ_d and the electronic demand will be a function of θ. It follows then that both the delocalized effect of X_π and its steric effect will be a function of the dihedral angle θ[27]. Consider a typical X_π group of the type MZ^1Z^2 (Figure 1). Z^1 may or may not be identical to Z^2. Examples of these groups are the acetyl groups in which Z^1 is O and Z^2 is Me, and the nitro group in which $Z^1 = Z^2 = O$. When Z^1 and Z^2 are different, the MSI principle shows that the smaller of the two Z groups will determine the steric effect of MZ^1Z^2; this is the group we designate as Z^1. The steric effect of the MZ^1Z^2 group must lie between its υ_{mx} and υ_{mn} values. The geometry of a typical system in which MZ^1Z^2 is bonded to a planar π-bonded skeletal group G_π, which in turn is bonded to an active site that is in close proximity to MZ^1Z^2, is shown in Figure 2. In general, the dependence of a property Q on the dihedral angle θ is best represented by the relationship

$$Q_\theta = Q_0 \cdot \cos^2\theta \tag{35}$$

where Q_θ is the value of the property when the dihedral angle is equal to θ and Q_0 when it is equal to zero. Then, from the geometry in Figures 1 and 2 and equation 35 we have

$$\sigma_{dX\theta} = \cos^2\theta \cdot \sigma_{dX\theta} \tag{36}$$

TABLE 8. Values of υ_{mx}, υ_{mn}, υ_{ef}, n_1, n_2, n_3 and n_b[a]

Group	Parameter						
	υ_{mx}	υ_{mn}	υ_{ef}	n_1	n_2	n_3	n_b
Substituted ethynyl							
C≡CH	0.58	0.58	0.58	1	0	0	1
C≡CMe	0.58	0.58	0.58	1	1	0	2
C≡CEt	0.58	0.58	0.58	1	1	1	3
$C{\equiv}CCF_3$	0.58	0.58	0.58	1	2.45	0	1.82
C≡C—C≡CH	0.58	0.58	0.58	1	1	1	3
C≡CPh	0.58	0.58	0.58	1	1	1	5
Substituted vinyl							
E-CH=CHNO₂	0.95		0.57	1	.87	0	1.87
CH=CH₂	0.95	2.11	0.57	1	0	0	1
E-CF=CFCF₃			0.57	1	2.45	0	1.82
CH=CHCN	0.95		0.57	1	1	1	3
Z-CH=CHCF₃	0.95		0.57	1	2.45	0	1.82
E-CH=CHCF₃	0.95		0.57	1	2.45	0	1.82
E-CH=CHMe	0.95		0.57	1	1	0	2
CMe=CH₂		0.57	1	0	0	1	
CH=C(CN)₂	0.95		0.57	1	1	1	3
E-CH=CHEt	0.95		0.57	1	1	1	3
C(CN)=C(CN)₂			0.57	1	1	1	3
CH=CH—CH=CH₂	0.95		0.57	1	1	1	3
E,E-(CH=CH)₃H	0.95		0.57	1	1	1	5
E-CH=CHPh	0.95		0.57	1	1	1	5
E,E-(CH=CH)₂Ph	0.95		0.57	1	1	1	7
Substituted phenyl							
C_6Cl_5			0.57	1	1	1	4.13
C_6F_5			0.57	1	1	1	3.82
$4\text{-}BrC_6H_4$	2.15	2.15	0.57	1	1	1	4.25
$3\text{-}ClC_6H_4$	2.15		0.57	1	1	1	3
$4\text{-}ClC_6H_4$	2.15	2.15	0.57	1	1	1	4.13
$3\text{-}NO_2C_6H_4$	2.15		0.57	1	1	1	3
$4\text{-}NO_2C_6H_4$	2.15	2.15	0.57	1	1	1	4.87
Ph	2.15	2.15	0.57	1	1	1	3
$4\text{-}CF_3C_6H_4$	2.15	2.15	0.57	1	1	1	4.82
$4\text{-}MeC_6H_4$	2.15	2.15	0.57	1	1	1	4
$4\text{-}MeOC_6H_4$	2.15	2.15	0.57	1	1	1	5
$4\text{-}EtC_6H_4$	2.15	2.15	0.57	1	1	1	5
$4\text{-}PhC_6H_4$	2.15	2.15	0.57	1	1	1	7
Carbonyl							
ClCO	1.39		0.50	1.13	0	0	1.13
FCO		1.39	0.50	0.87	0	0	0.87
HCO	0.95	1.39	0.50	0.87	0	0	0.87
CO₂H	1.39	1.39	0.50	0.87	0	0	0.87
COCF₃	1.39		0.90	2.45	0	0	1.82
Ac	1.39		0.50	1	0	0	1
CONH₂	1.39		0.50	0.91	0	0	0.91
CO₂Me	1.39		0.50	0.87	1	0	1.87
COEt	1.39		0.50	1	1	0	2
CO₂Et	1.39	1.39	0.50	0.87	1	1	2.87

(*continued*)

TABLE 8 (*continued*)

Group	Parameter						
	υ_{mx}	υ_{mn}	υ_{ef}	n_1	n_2	n_3	n_b
COPr	1.39		0.50	1	1	1	3
COPr-i	1.39		0.50	1	2	0	2
CO_2Pr	1.39	1.39	0.50	0.87	1	1	3.87
CO_2Bu	1.39	1.39	0.50	0.87	1	1	4.87
Bz	1.39		0.57	1	1	1	4
N-substituted azenyl, cyano							
CH=NH	0.95		0.40	0.91	0	0	0.91
E-CH=NOH	0.95		0.40	0.91	0.87	0	1.78
CH=NPh	0.95		0.40	0.91	1	1	3.91
CN	0.40	0.40	0.40	0.91	0	0	0.91
Nitroso, nitro							
NO	0.35		0.35	0.87	0	0	0.87
NO_2	1.39	1.39	0.35	0.87	0	0	0.87
C-substituted azenyl							
$N{=}CH_2$	0.35		0.35	1	0	0	1
N=CHPh	0.35		0.35	1	1	1	4
Diazenyl							
N=NH	0.35		0.35	0.91	0	0	0.91
$N{=}NCF_3$	0.35		0.35	0.91	1	2.45	2.73
N=NtBu	0.35		0.35	0.91	1	3	2.91
N=NPh	0.35		0.35	0.91	1	1	4.91
Allenyl, heteroallenyl							
$CH{=}C{=}CH_2$	0.95		0.57	1	1	0	2
N=C=O	0.35		0.50	1	0.87	0	1.87
N=C=S	0.35		0.57	1	1.18	0	2.18
N_3	0.35		0.35	0.91	0.91	0	1.82
Other							
H	0	0	0	−2.17	0	0	−2.17
F	0.27	0.27	0.27	−1.04	0	0	−1.04
Cl	0.55	0.55	0.55	0.12	0	0	0.12
Br	0.65	0.65	0.65	0.54	0	0	0.54
I	0.78	0.78	0.78	1.08	0	0	1.08
Me	0.52	1.03	0.52	0	0	0	0
Et	0.52		0.56	1	0	0	1
c-Pr			0.64	1	0	0	1
CF_3	0.90	1.53	0.90	2.45	0	0	0.82
$SiMe_3$	1.40	2.28	1.40	3.21	0	0	1.08
NHAc	0.93		0.50	1	1	0	2
NHEt	0.35		0.59	1	1	0	2
NMe_2	0.52		0.52	2	0	0	1
PMe_2	0.60	2.26	0.84	2.16	0	0	1.08
$POMe_2$	1.22	2.26	0.84	3.10	0	0	1.08
$PO(OMe)_2$	1.04	1.77	1.04	2.83	2	0	1.94
OMe	0.32		0.36	1	0	0	1
OSO_2Me	0.32			1	2.99	0	2.07

(*continued*)

TABLE 8 (*continued*)

Group	Parameter						
	υ_{mx}	υ_{mn}	ef	n_1	n_2	n_3	n_b
OAc	0.32		0.50	1	1	0	2
SMe	0.60		0.64	1.07	0	0	1.07
SAc	0.60		1.09	1.07	1	0	2.07
SOMe	0.60		0.66	1.87	0	0	1.07
SO_2Me	1.03		1.13	2.94	0	0	1.07
SeMe	0.70		0.74	1.30	0	0	1.30

[a]Groups in italics are planar π-bonded. For these groups υ_{ef} represents the half thickness; υ_{mx} and υ_{mn} lie in the plane of these groups.

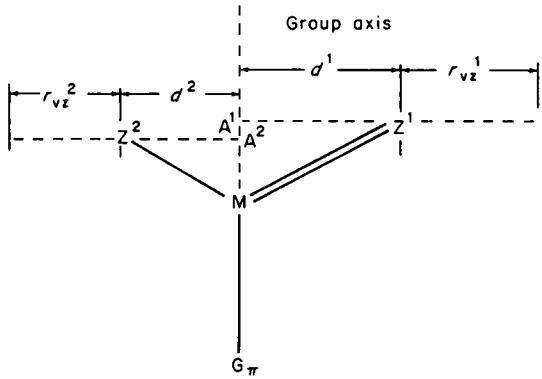


FIGURE 1. Top view of a planar π-bonded group bonded to a planar π-bonded skeletal group. $\upsilon_{mn} = d^2 + r_{VZ^2}$.

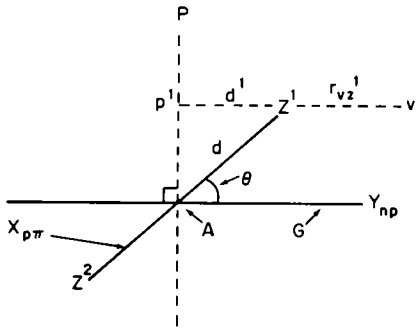


FIGURE 2. End view of a planar π-bonded group bonded to a planar π-bonded skeletal group to which a nonplanar active site Y_{np} is also bonded.

$$\sigma_{eX\theta} = \cos^2\theta \cdot \sigma_{eX\theta} \tag{37}$$

$$\upsilon_X = d \cdot \cos\theta + r_{VZ'} - 1.20 \tag{38}$$

From these equations we may write for $\sigma_{d\theta}$

$$|\sigma_{d\theta}|^{1/2} = b_1 \upsilon_{X\pi} + b_0 \tag{39}$$

where

$$b_1 = |\sigma_{d0}|^{1/2}/d \tag{40}$$

and

$$b_0 = |\sigma_{d0}|^{1/2} \cdot (1.20 - r_{VZ'})/d \tag{41}$$

For $\sigma_{e\theta}$ we may write the analogous relationship

$$|\sigma_{e\theta}|^{1/2} = b_{11} \upsilon_{X\pi} + b_{00} \tag{42}$$

where

$$b_{11} = |\sigma_{e0}|^{1/2}/d \tag{43}$$

and

$$b_{00} = |\sigma_{e0}|^{1/2} \cdot (1.20 - r_{VZ'})/d \tag{44}$$

Values of $\sigma_{d\theta}$ and $\sigma_{e\theta}$ may now be calculated for any given value of υ.

At the present time we do not yet have sufficient knowledge of the variation of θ with medium and electron demand to be able to assign values of θ *a priori*. The inclusion of X_π values in a data set in which steric effects occur is possible only by an iteration method[28]. In the first step the correlation is carried out with all X_π groups excluded from the data set. Typically, the LDRS equation

$$Q_X = L\sigma_{IX} + D\sigma_{dX} + R\sigma_{eX} + S\upsilon_X + h \tag{45}$$

is used as the correlation equation. The iteration is carried out by correlation of the data set including the value of an X_π group and varying θ by increments, usually of 5° and 10°. For each value of θ the corresponding values of υ, σ_d and σ_e are used. The proper value of θ is assumed to be that which gives the best fit of the data to the correlation equation. For the best fit $100R^2$ and F are maximal, s_{est} and s^0 are minimal. It is also necessary that the coefficients of the best equation show no significant difference from those obtained excluding the X_π group.

Values of $\sigma_{d\theta}$ and $\sigma_{e\theta}$ as a function of υ for a number of common doubly bonded groups are reported in Table 9.

E. Branching Parameters

A major disadvantage of monoparametric treatments of the steric effect is that nonsymmetric substituents will exhibit a variable steric effect which is a function of the steric demand of the system studied. If the steric requirements of the system studied resemble those of the reference system used to determine the steric parameters for the nonsymmetric groups, then there is little or no problem. Unfortunately, however, this is often not the case. There are two alternative approaches for dealing with this problem. One of these consists in the definition of a number of different sets of steric parameters for nonsymmetric groups. The set chosen for a particular problem is that in which the steric demand in the reference system most closely matches that in the data set to be modelled. Regrettably, it is frequently difficult to determine *a priori* which set of steric parameters to choose. This approach also results in a plethora of sets of steric parameters which tends to overwhelm the inexperienced user. The other approach is the use of a multiparametric model. A suitable model of this type is obtained from a topological method which results in

TABLE 9. Values of $\sigma_{d\theta}$, $\sigma_{d\theta}$ and υ as a function of θ

Group	υ	$\sigma_{d\theta}$	$\sigma_{e\theta}$	θ
$CH{=}CH_2$	0.57	0	0	—
	0.62	−0.04	−0.059	45.7
	0.67	−0.04	−0.067	41.5
	0.72	−0.05	−0.076	37.1
	0.77	−0.06	−0.086	32.3
	0.82	−0.06	−0.096	26.7
	0.87	−0.07	−0.11	20.1
	0.92	−0.08	−0.12	10.8
	0.95	−0.08	−0.12	0
Ph	0.57	0	0	—
	0.62	−0.01	−0.015	69.6
	0.67	−0.02	−0.016	68.2
	0.72	−0.02	−0.019	66.8
	0.77	−0.02	−0.021	65.4
	0.82	−0.02	−0.023	64.0
	0.87	−0.03	−0.026	62.5
	0.92	−0.03	−0.028	61.1
	0.97	−0.03	−0.031	59.6
	1.02	−0.03	−0.034	58.1
	1.07	−0.04	−0.036	56.6
	1.12	−0.04	−0.039	55.0
	1.17	−0.04	−0.043	53.4
	1.22	−0.05	−0.046	51.8
	1.27	−0.05	−0.049	50.2
	1.32	−0.05	−0.053	48.5
	1.37	−0.06	−0.056	46.8
	1.42	−0.06	−0.060	45.1
	1.47	−0.06	−0.064	43.3
	1.52	−0.07	−0.067	41.4
	1.57	−0.07	−0.071	39.5
	1.62	−0.08	−0.076	37.5
	1.67	−0.08	−0.080	35.4
	1.72	−0.08	−0.084	33.3
	1.77	−0.09	−0.088	31.0
	1.82	−0.09	−0.093	28.6
	1.87	−0.10	−0.097	26.0
	1.92	−0.10	−0.10	23.1
	1.97	−0.11	−0.11	20.0
	2.02	−0.11	−0.11	16.4
	2.07	−0.11	−0.11	12.1
	2.12	−0.12	−0.12	6.0
	2.15	−0.12	−0.12	0
$CONH_2$	0.50	0	0	—
	0.55	0.01	−0.004	74.0
	0.60	0.01	−0.006	71.2
	0.65	0.02	−0.007	68.4
	0.70	0.02	−0.009	65.6
	0.75	0.03	−0.012	62.7
	0.80	0.03	−0.014	59.7
	0.85	0.04	−0.017	56.7

(*continued*)

TABLE 9 (*continued*)

Group	υ	$\sigma_{d\theta}$	$p_{e\theta}$	h
	0.90	0.04	−0.019	53.6
	0.95	0.05	−0.022	50.3
	1.00	0.06	−0.026	46.9
	1.05	0.06	−0.029	43.4
	1.10	0.07	−0.033	39.6
	1.15	0.08	−0.036	35.5
	1.20	0.09	−0.040	31.1
	1.25	0.10	−0.044	26.0
	1.30	0.11	−0.049	20.1
	1.35	0.11	−0.053	12.1
	1.39	0.12	−0.055	0
Ac	0.50	0	0	—
	0.55	0.02	−0.007	74.0
	0.60	0.03	−0.010	71.2
	0.65	0.03	−0.013	68.4
	0.70	0.04	−0.016	65.6
	0.75	0.05	−0.020	62.7
	0.80	0.06	−0.024	59.7
	0.85	0.08	−0.029	56.7
	0.90	0.09	−0.033	53.6
	0.95	0.10	−0.039	50.3
	1.00	0.12	−0.044	46.9
	1.05	0.13	−0.050	43.4
	1.10	0.15	−0.063	39.6
	1.15	0.17	−0.063	35.5
	1.20	0.18	−0.070	31.0
	1.25	0.20	−0.077	26.0
	1.30	0.22	−0.084	20.1
	1.35	0.24	−0.091	12.1
	1.39	0.25	−0.095	0
CO_2Me	0.50	0	0	—
	0.55	0.01	−0.005	74.0
	0.60	0.02	−0.007	71.2
	0.65	0.02	−0.009	68.4
	0.70	0.03	−0.012	65.6
	0.75	0.03	−0.015	62.7
	0.80	0.04	−0.018	59.7
	0.85	0.05	−0.021	56.7
	0.90	0.06	−0.025	53.6
	0.95	0.07	−0.029	50.3
	1.00	0.07	−0.033	46.9
	1.05	0.08	−0.037	43.4
	1.10	0.09	−0.042	39.6
	1.15	0.11	−0.046	35.5
	1.20	0.12	−0.051	31.1
	1.25	0.13	−0.057	26.0
	1.30	0.14	−0.062	20.1
	1.35	0.15	−0.067	12.1
	1.39	0.16	−0.070	0

(*continued*)

TABLE 9 (*continued*)

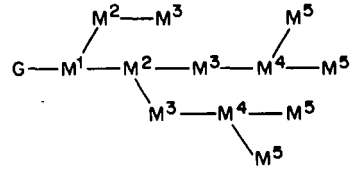
Group	υ	$\sigma_{d\theta}$	$\sigma_{e\theta}$	θ
Bz	0.50	0	0	—
	0.55	0.02	−0.008	74.0
	0.60	0.02	−0.011	71.2
	0.65	0.03	−0.015	68.4
	0.70	0.04	−0.019	65.6
	0.75	0.05	−0.023	62.7
	0.80	0.06	−0.028	59.7
	0.85	0.07	−0.033	56.7
	0.90	0.08	−0.039	53.6
	0.95	0.09	−0.045	50.3
	1.00	0.10	−0.051	46.9
	1.05	0.12	−0.058	43.4
	1.10	0.13	−0.065	39.6
	1.15	0.15	−0.073	35.5
	1.20	0.16	−0.081	31.1
	1.25	0.18	−0.089	26.0
	1.30	0.19	−0.097	20.1
	1.35	0.21	−0.11	12.1
	1.39	0.22	−0.11	0
NO_2	0.35	0	0	—
	0.40	0.00	−0.001	82.1
	0.45	0.01	−0.003	79.4
	0.50	0.01	−0.004	76.7
	0.55	0.01	−0.006	74.0
	0.60	0.02	−0.008	71.2
	0.65	0.02	−0.010	68.4
	0.70	0.03	−0.013	65.3
	0.75	0.04	−0.016	62.7
	0.80	0.05	−0.020	59.7
	0.85	0.05	−0.023	56.7
	0.90	0.06	−0.027	53.6
	0.95	0.07	−0.031	50.3
	1.00	0.08	−0.036	46.9
	1.05	0.10	−0.041	43.4
	1.10	0.11	−0.046	39.6
	1.15	0.12	−0.051	35.5
	1.20	0.13	−0.056	31.1
	1.25	0.15	−0.062	26.0
	1.30	0.16	−0.068	20.1
	1.35	0.17	−0.074	12.1
	1.39	0.18	−0.077	0

the simple branching (SB) equation

$$Q_X = S \sum_{i=1}^{m} a_i' n_i + a_0 = \sum_{i=1}^{m} a_i n_i + a_0 \tag{46}$$

where n_i is the total number of branches on the i-th atoms of the substituent X, a_i is its coefficient and a_0 is the intercept. Consider, for example, the substituent 2 which is shown bonded to a skeletal group G. As hydrogen atoms are not considered as branches, **2** is

shown as a hydrogen suppressed structure. n_i is equal to the number of M atoms labelled $i + 1$. Then, for 2, the n_i values are: $n_1 = 2$, $n_2 = 3$, $n_3 = 2$, $n_4 = 4$.



(2)

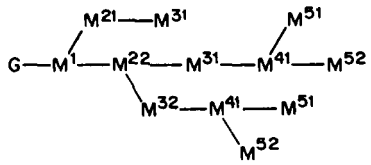
In this very simple model a major assumption is made: the effect of branching is the same for all branches. This assumption is at best a crude approximation. Frequently, the first branch on an atom has little in the way of a steric effect while the effect of the third branch is large. Thus for the series CH_3, CH_2Me, $CHMe_2$ and CMe_3 the υ values are 0.52, 0.56, 0.76 and 1.24. Thus the first, second and third branches increase the size of the methyl group by factors of 1.08, 1.46 and 2.38 respectively. This is the result of the MSI principle (Section III.C.). The effect of the first branch can be minimized by a suitable conformation of the substituent in which the branch is rotated away from the active site. Such a rotation becomes much more difficult to achieve on introduction of a second branch and impossible on introduction of a third.

When all of the atoms M are not identical, a second approximation often made is that the effect of all second or third period elements as either skeletal or branch atoms is about the same. This approximation is also crude. Nevertheless, the simple branching equation can often give a reasonable description of steric effects[29-31].

The expanded branching (XB) equation, which takes into account the effect of the order of branching, gives a much improved description of steric effects. It takes the form

$$Q_X = \sum_{i=1}^{m} \sum_{j=1}^{3} a_{ij} n_{ij} + a_{00} \tag{47}$$

where n_{ij} is the total number of j-th branching atoms bonded to the i-th atoms in the substituent and a_{ij} is its coefficient. We may consider the same example as before. This time, however, it will be numbered so as to indicate the order of branching. n_{ij} is equal to the number of atoms bearing the lable $(i + 1)j$. Then for 3: $n_{11} = n_{12} = 1$, $n_{21} = 2$, $n_{22} = 1$, $n_{31} = n_{41} = n_{42} = 2$, all other $n_{ij} = 0$.



(3)

Though the XB equation is a far better model of steric effects than is the SB equation, it requires many more idependent variables. It is therefore useful only when the data set to be studied is very large, a most desirable but rarely encountered situation. It is also possible to take into account the variation in atomic size when applying the branching method. Values of n_i or n_{ij} can be multiplied by an appropriate factor for this purpose. In Table 8, n_i values of this type are reported.

When the SB equation is applied to doubly bonded groups, all of which are members of the steric class planar π-bonded groups, it is normally assumed on the basis of the MSI principle that the half-thickness of the group determines its steric effect. An evaluation of the branching parameters for the phenyl group gave $n_1 = n_2 = n_3 = 1$. It was assumed that the values for C=C, C=N, C=O and N=N are comparable.

Finally, it is useful at times to have a parameter which can serve as a measure of group length. A crude but useful length parameter is n_b, which is defined as the number of bonds in the group skeleton. The group skeleton is the longest chain of atoms in the group; n_b is therefore given by

$$n_b = i_{max} - 1 \tag{48}$$

where i_{max} is the highest value of i for any atom in the group. Thus, the value of n_b for **2** or **3** is 4.

V. INTERMOLECULAR FORCES

A. Introduction

Many chemical properties such as melting and boiling points; solubility; chromatographic quantities such as R_M values, retention times and capacity factors; and equilibrium constants for hydrogen bonding or charge transfer complex formation are a function of the difference in intermolecular forces (imf) between an intial state, 1, and a final state, 2. Thus

$$Q_X = f[(\text{imf}_X)_2 - (\text{imf}_X)_1] = f[\Delta\text{imf}_X] \tag{49}$$

Many types of biological activities are also well represented by equation 49. In order to model these quantities we must determine what imf are involved and parametrize them. Intermolecular forces and their parametrization are summarized in Table 10. The parameters not described previously are: the polarizability parameter α, the hydrogen bonding parameters n_H and n_n, the ionic parameter i, and the charge transfer parameters n_D and n_A.

B. Intermolecular Force Parameters

The polarizability parameter is defined by the relationships

$$\alpha_X = (MR_X - MR_H)/100 \tag{50}$$

and

$$\alpha = MR_X/100 - 0.0103 \tag{51}$$

where MR_X and MR_H are the molar refractivities of X and H, respectively[32,33]. There are many other polarizability parameters all of which are linear functions of α. There is no reason for preferring any one of them over any other. The only requirements for the polarizability parameter are that values are either readily available or easily estimated for all common substituents, and that they are scaled such that when they are used in a correlation equation, the coefficient obtained from the regression analysis will be of a magnitude comparable to that of the coefficients of the other parameters. The fact that we are already equipped with a surplus of polarizability parameters has not deterred some authors from a search for new examples, presumably in an overwhelming desire to assuage the publication itch.

The n_H parameter is defined as equal to the number of NH and/or OH bonds in the group X. Quantity n_n is defined as the number of lone pairs on O and/or N atoms in the X group. If one of the two states referred to in equation 49 is an aqueous phase, or

TABLE 10. Values of the intermolecular force parameters[a]

Group	Parameter					
	α	n_H	n_n	i	n_D	n_A
Substituted ethynyl						
C≡CH	0.085	0	0	0	1	0
C≡CMe	0.131	0	0	0	1	0
C≡CEt	0.178	0	0	0	1	0
C≡CCF_3	0.115	0	0	0	0	1
C≡C—C≡CH	0.170	0	0	0	1	0
C≡CPh	0.322	0	0	0	1	0
Substituted vinyl						
E-CH=$CHNO_2$	0.152	0	4	0	0	1
CH=CH_2	0.100	0	0	0	1	0
E-CF=$CFCF_3$	0.128	0	0	0	0	1
CH=CHCN	0.142	0	0	0	0	1
Z-CH=$CHCF_3$	0.130	0	0	0	0	1
E-CH=$CHCF_3$	0.130	0	0	0	0	1
E-CH=CHMe	0.135	0	0	0	1	0
CMe=CH_2	0.135	0	0	0	1	0
CH=$C(CN)_2$	0.186	0	0	0	0	1
E-CH=CHEt	0.182	0	0	0	1	0
C(CN)=$C(CN)_2$	0.220	0	0	0	0	1
CH=CH—CH=CH_2	0.190	0	0	0	1	0
E, E-$(CH=CH)_3H$	0.270	0	0	0	1	0
E-CH=CHPh	0.331	0	0	0	1	0
E, E-$(CH=CH)_2Ph$	0.423	0	0	0	1	0
Substituted phenyl						
C_6Cl_5	0.485	0	0	0	1	0
C_6F_5	0.230	0	0	0	1	0
4-BrC_6H_4	0.321	0	0	0	1	0
3-ClC_6H_4	0.292	0	0	0	1	0
4-ClC_6H_4	0.292	0	0	0	1	0
3-$NO_2C_6H_4$	0.305	0	4	0	0	1
4-$NO_2C_6H_4$	0.305	0	4	0	0	1
Ph	0.243	0	0	0	1	0
4-$CF_3C_6H_4$	0.273	0	0	0	0	1
4-MeC_6H_4	0.290	0	0	0	1	0
4-$MeOC_6H_4$	0.310	0	2	0	1	0
4-EtC_6H_4	0.337	0	0	0	1	0
4-PhC_6H_4	0.476	0	0	0	1	0
Carbonyl						
ClCO	0.116	0	2	0	0	1
FCO	0.055	0	2	0	0	1
HCO	0.059	0	2	0	0	1
CO_2H	0.059	1	4	1	0	1
$COCF_3$	0.096	0	2	0	0	1
Ac	0.102	0.	2	0	0	1
$CONH_2$	0.088	2	3	0	0	1
CO_2Me	0.118	0	4	0	0	1
COEt	0.149	0	2	0	0	1
CO_2Et	0.164	0	4	0	0	1
COPr	0.195	0	2	0	0	1
COPr-*i*	0.196	0	2	0	0	1
CO_2Pr	0.211	0	4	0	0	1
CO_2Bu	0.258	0	4	0	0	1

(*continued*)

TABLE 10 (*continued*)

Group	Parameter					
	α	n_H	n_n	i		
Bz	0.293	0	2	0	0	1
N-substituted azenyl, cyano						
CH=NH	0.080	1	1	0	0	1
E-CH=NOH	0.093	1	3	0	0	1
CH=NPh	0.313	0	1	0	1	0
CN	0.053	0	0	0	0	1
Nitroso, nitro						
NO	0.042	0	3	0	0	1
NO_2	0.063	0	4	0	0	1
C-substituted azenyl						
$N=CH_2$	0.080	0	1	0	0	1
N=CHPh	0.313	0	1	0	1	0
Diazenyl						
N=NH	0.070	1	2	0	0	1
$N=NCF_3$	0.100	0	2	0	0	1
N=NBu-*t*	0.246	0	2	0	0	1
N=NPh	0.303	0	2	0	1	0
Allenyl, heteroallenyl						
$CH=C=CH_2$	0.138	0	0	0	1	0
N=C=O	0.078	0	3	0	0	1
N=C=S	0.162	0	1	0	0	1
N_3	0.092	0	1	0	0	0
Other						
H	0	0	0	0	0	0
F	−0.001	0	0	0	0	0
Cl	0.050	0	0	0	0	0
Br	0.079	0	0	0	0	0
I	0.129	0	0	0	0	0
Me	0.046	0	0	0	0	0
Et	0.093	0	0	0	0	0
c-Pr	0.125	0	0	0	0	0
CF_3	0.040	0	0	0	0	0
$SiMe_3$	0.239	0	0	0	0	1
NHAc	0.139	1	3	0	0	1
NHEt	0.140	1	1	1/0	1	0
NMe_2	0.145	0	1	1/0	1	0
PMe_2	0.202	0	0	0	1	0
$POMe_2$	0.189	0	2	0	0	1
$PO(OMe)_2$	0.208	0	6	0	0	1
OMe	0.068	0	2	0	1	0
OSO_2Me	0.145	0	6	0	0	1
OAc	0.114	0	4	0	0	1
SMe	0.128	0	0	0	1	0
SAc	0.174	0	2	0	0	1
SOMe	0.127	0	2	0	0	1
SO_2Me	0.125	0	4	0	0	1
SeMe	0.160	0	0	0	1	0

[a]When the given value of i is in the form 1/0, i is equal to 1 if the substituent is bonded to sp^3 hybridized carbon, otherwise it is equal to 0.

alternatively a phase involving some other low-molecular-weight protonic solvent, then the use of these parameters is justified as they are based on the assumption that in 55 molar water any hydrogen bond that can form will do so[34-36].

The ionic parameter i takes the value 1 for ionic substituents and the value 0 for nonionic substituents.

The charge transfer parameter n_D takes the value 1 when the substituent can act as a charge transfer donor or the value 0 when it cannot. The n_A parameter takes the value 1 when the substituent can act as a charge transfer or the value 0 when it cannot. Values of the intermolecular force parameters for doubly bonded groups are given in Table 10, as are values for triply bonded and aryl groups for comparison.

Chemical properties and many biological activities are well modelled by the intermolecular force (IMF) equation

$$Q_X = L\sigma_{IX} + D\sigma_{dX} + R\sigma_{eX} + A\alpha_X + H_1 n_{HX} + H_2 n_{nX} + Ii_X + C_1 n_{DX} + C_2 n_{AX} + S\upsilon_X + B^0 \quad (52)$$

where L, D, R, A, H_1, H_2, I, C_1, C_2 and S are the coefficients of σ_I, σ_d, σ_e, α, n_H, n_n, i, n_D, n_A and υ, respectively, while B^0 is the intercept[34-36].

In an alternative form of the IMF equation the steric effect term $S\upsilon_X$ is replaced by the simple branching (SB) equation.

VI. DIRECTING AND ACTIVATING EFFECTS OF DOUBLY BONDED GROUPS

A. Introduction

The terms 'directing' and 'activating', though often used by organic chemists to describe properties of functional groups, are ill defined. For the purpose of this work we define directing effects as those which determine orientation or regioselectivity in chemical reactivity, a preference for a particular tautomer, a configurational preference or a conformational preference. Thus, when a substituent causes a preference for one product, tautomer, configuration or conformation over another, we consider this to be a directing effect. Activation has often been used to mean that a group makes possible a reaction which might otherwise not occur. We prefer to define an activating effect as a substituent effect which increases the magnitude of a rate or equilibrium constant.

B. Activating Effects

We have restricted our discussion of substituent effects on chemical reactivity to systems in which the substituent X is directly bonded to the active site Y (XY systems). These systems provide the greatest challenge to modelling as they exhibit a wide range of electronic demand, generally from -6 to 6. By contrast, systems in which X and Y are bonded to a phenylene skeletal group (typical XGY systems) have a much narrower range of electronic demand, generally from -3 to 3.

In our discussion of the electrical effects of doubly bonded groups we will make use of a reference set which contains typical examples of each type. Included in this reference set are the vinyl, *trans* propenyl, formyl, carboxamido, N-phenylazenyl, C-phenylazenyl, phenylazo, nitroso, nitro, allenyl, azido and cyclopropyl groups. The overall electrical effect of a group in a particular data set of interest, as was noted above, can be determined easily from a table of its $\sigma_{k'/k}$ constants by using the η and P_D values that have been determined for the data set. The $\sigma_{k'/k}$ value required is that for which the η and P_D values most closely match those of the data set. As the value of ρ in the Hammett equation

$$Q_X = \rho\sigma_{k'/k,X} + h \quad (53)$$

is equal to that of L in the LDR equation, values of Q_X can be estimated from the values of L and h obtained with the *LDR* equation and the value of $\sigma_{k'/k,X}$.

1. Substituent effects at cationic carbon

Data sets of interest include the ionization potentials of substituted methyl radicals (set 72) and of substituted benzenes (set 18), and the rates of hydration of $XCH{=}CH_2$ and $XCMe{=}CH_2$ (sets 109 and 110 respectively). Gas-phase elimination reactions of 1-substituted-1-chloroethanes (set 11.1) and 2-substituted-2-acetoxypropanes (set 14) were also examined[37,38]. The $\sigma_{k'/k,X}$ values for the members of the doubly bonded group reference set are given in Table 11, as are also the η, P_D, L and h values of the data sets. Donor groups such as vinyl, allenyl and cyclopropyl decrease the ionization potential and increase the rate of hydration; acceptor groups such as formyl, nitroso and phenylazo do the reverse. Thus, for hydration of the double bond, donors are activating and acceptors are deactivating. This is also the case for gas-phase elimination of the acetates. In the case of the gas-phase elimination of the chlorides, the combination of a large positive electronic demand coupled with a large P_D value results in electrical effects for the formyl, carboxamido and phenylazo groups which are not significantly different from zero and a very much reduced electron-acceptor effect for the nitro group. This combination also probably accounts for the now well-established stabilization of carbocatonic transition states by groups such as nitro, carbomethoxy, cyano and other π-bonded groups which, under more normal conditions, are electron acceptors[6,8,31,39,40].

2. Substituent effects at radical carbon

As radical reactions may involve the attack of either nucleophilic or electrophilic radicals, their η values may be either negative or positive. Relative rates of addition of methyl radicals and rates of addition of polystyryl radicals to $XCH{=}CH_2$ (sets 84 and S174), relative rates of thermal decomposition of 2,5-disubstituted-2,5-dimethyl-3,4-

TABLE 11. $\sigma_{k'/k}$ values for doubly bonded groups linked to cationic carbon[a]

Set	72	18	109	110	11.1	14
η	2.98	2.64	1.62	0.961	3.69	3.20
P_D	63.1	53.7	57.4	62.2	71.9	46.4
L	1.13	1.19	−21.1	−13.7	−3.10	−2.52
h	8.76	9.31	−4.985	−1.161	−2.10	0.542
X						
$CH{=}CH_2$	−0.55	−0.33	−0.37	−0.19	−1.20	−0.33
E-CH=CHMe	−0.60	−0.38	−0.47	−0.33	−1.18	−0.38
CHO	0.41	0.37	0.56	0.71	0.00	0.37
$CONH_2$	0.21	0.24	0.30	0.38	0.05	0.24
CH=NPh	0.29	0.26	0.32	0.35	0.29	0.26
N=CHPh	0.26	0.13	−0.16	−0.07	−0.62	−0.13
N=NPh	0.18	0.21	0.27	0.36	0.00	0.21
NO	0.94	0.77	1.04	1.15	1.05	0.77
NO_2	0.59	0.62	0.71	0.82	0.37	0.62
$CH{=}C{=}CH_2$	−0.41	−0.23	−0.24	−0.08	−0.95	−0.23
N_3	−0.52	−0.20	−0.34	−0.16	−1.32	−0.20
c-Pr	−0.56	−0.22	−0.45	−0.35	−1.03	−0.22

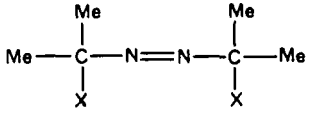
[a]Set numbers refer to Table 6 of Reference 6 unless otherwise noted. Sets 11 and 14 are from Reference 37.

TABLE 12. $\sigma_{k'/k}$ values for doubly bonded groups linked to radical carbon[a]

Set	84	S174	266	S89	179
η	−4.32	−6.92	−6.77	2.62	0.872
P_D	69.1	46.8	57.3	51.9	59.5
L	1.18	2.70	5.22	−3.14	5.23
h	1.492	−0.192	2.24	0.306	0.407
X					
$CH{=}CH_2$	1.04	0.75	1.07	−0.33	−0.19
E-CH=CHMe	0.48	0.42	0.60	−0.38	−0.60
CHO	1.86	1.17	1.61	0.27	0.56
$CONH_2$	1.07	0.73	0.96	0.24	0.38
CH=NPh	0.67	0.44	0.56	0.26	0.35
N=CHPh	0.55	0.44	0.59	−0.13	−0.07
N=NPh	1.10	0.74	0.98	0.21	0.36
NO	2.35	1.40	1.88	0.77	1.15
NO_2	1.81	1.31	1.63	0.62	0.82
$CH{=}C{=}CH_2$	1.10	0.76	1.08	−0.23	−0.08
N_3	0.92	0.88	1.11	−0.20	−0.16
c-Pr	0.26	0.23	0.38	−0.37	−0.35

[a]Set numbers refer to Table 6 of Reference 6. $\sigma_{k'/k}$ values for sets S174 and 266 are for $k = -6$.

diaza-3-hexenes **4** (set 266), relative rates for the reaction of **5** with Br˙ (set S89), and rates of the thermal cleavage of the 1,4 bond in 4-substituted-1-chloro[2.2.0]bicyclohexanes, **6** (set 179), are included in the sets studied. The appropriate $\sigma_{k'/k,X}$ values for the members of the reference set together with the η, P_D, L and h values for the data sets are given in Table 12. Rates of addition of methyl and polystyryl radicals to $CH_2{=}CHX$ increased by overall electron acceptors and decreased by electron donors, likewise also rates of thermal decomposition of **4**. All of the members of the reference set act as acceptors in these reactions and are therefore activating. Rates of substitution at the methylene group of **5** are increased by donors and decreased by acceptors. Thus, in this reaction, the vinyl, *N*-phenylazenyl and allenyl groups are activating while groups such as the formyl, phenylazo and nitro are deactivating. In the thermal cleavage of the 1,4 bond in **6** the situation is reversed, with acceptors activating and donors deactivating.



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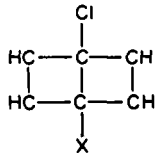


(6)

3. *Substituent effects at anionic carbon*

Data sets of interest include the pK_as in Me_2SO of XCH_2Z with Z = NO_2, SO_2Me and Bz, and of 9-substituted fluorenes **7** (sets P97, S170, P172 and S173, respectively), the gas-phase proton affinities of MeX (SET s23) and the rates of elimination of 1-substituted-2-phenoxyethanes with ethoxide in ethanol (set 216). Values of $\sigma_{k'/k,X}$ for the reference set together with the η, P_D, L and h values for the data sets are reported in Table 13. In all of

TABLE 13. $\sigma_{k'/k}$ values for doubly bonded groups linked to anionic carbon[a]

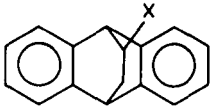
Set	P97	S170	P172	S173	S23	216
η	−3.10	−2.70	−2.70	−1.81	−5.45	−2.62
P_D	45.2	50.9	39.1	45.9	49.4	67.2
L	−11.7	−20.6	−18.3	−18.7	−45.4	8.20
h	16.55	29.5	24.4	21.4	415	−9.67
X						
$CH{=}CH_2$	0.39	0.39	0.30	0.27	0.63	0.76
E-CH=CHMe	0.16	0.16	0.13	0.07	0.34	0.27
CHO	0.87	0.87	0.68	0.77	1.07	1.63
$CONH_2$	0.57	0.57	0.47	0.51	0.68	0.94
CH=NPh	0.38	0.38	0.32	0.36	0.42	0.62
N=CHPh	0.25	0.25	0.21	0.19	0.38	0.41
N=NPh	0.57	0.57	0.47	0.51	0.69	0.96
NO	1.19	1.19	0.94	1.12	1.33	2.19
NO_2	1.08	1.08	0.94	1.00	1.24	1.63
$CH{=}C{=}CH_2$	0.43	0.43	0.33	0.32	0.65	0.84
N_3	0.52	0.52	0.49	0.40	0.76	0.64
c-Pr	0.05	0.05	0.03	−0.02	0.19	0.10

[a]Set numbers refer to Table 6 of Reference 6.

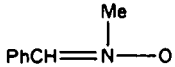
the pK_a and proton affinity data sets electron-acceptor groups are activating; this is also the case for the rates of elimination. Examination of the $\sigma_{k'/k}$ values in Table 13 shows that, except for the cyclopropyl group in set S173, all of the groups in the reference set are acting as electron acceptors.

4. Other XY systems

Values of η, P_D, L and h are given in Table 14 for rate constants for the thermal dissociation of 2-substituted dibenzocyclo[2.2.2]octanes[41], **7** (set P 319), and for the addition of diazomethane[42], *C*-phenyl-*N*-methylnitrone[43], **8** and diphenylnitrilimine[44], **9**, to substituted ethylenes (sets 201, 349 and 350, respectively). Rate constants for the thermal



(**7**)



(**8**)

(**9**)

decomposition of iron tetracarbonyl substituted ethylene complexes[45] $(OC)_4Fe(CH_2{=}CHX)$ (**10**) to give iron tetracarbonyl and substituted ethylenes were correlated with the LDRT equation

$$Q_X = L\sigma_{IX} + D\sigma_{dX} + R\sigma_{eX} + T_\tau + h \tag{54}$$

The temperature parameter τ is defined as

$$\tau = 1000/(t + 273.15) \tag{55}$$

where t is the temperature in degrees Celsius. This form of the LDR equation is convenient for the correlation of rate data obtained at various temperatures in a single data set. Values of η, P_d, L and h are given for this set (set T3) in Table 14.

TABLE 14. $\sigma_{k'/k}$ values for doubly bonded groups linked to other XY systems

Set	P319	201	349	350	T3
η	−11.8	−0.272	−0.864	−1.08	1.20
P_D	74.7	60.7	79.5[a]	36.5	67.5
L	0.573	6.23	1.21[a]	4.89	−1.45
h	−0.102	1.36	1.078	−0.479	12.16
X					
$CH{=}CH_2$	1.60	−0.01	0.27	0.14	−0.36
E-CH=CHMe	0.90	−0.20	−0.29	0.01	−0.56
CHO	2.33	0.71	1.78	0.55	0.70
$CONH_2$	1.33	0.46	0.98	0.40	0.43
CH=NPh	0.76	0.38	0.76	0.29	0.43
C=CHPh	0.85	0.03	0.10	0.13	−0.18
N=NPh	1.38	0.45	0.99	0.39	0.41
NO	2.68	1.25	2.88	0.85	1.54
NO_2	2.17	0.94	1.70	0.84	0.91
$CH{=}C{=}CH_2$	1.61	0.09	0.48	0.18	−0.18
N_3	1.48	0.03	−0.17	0.33	−0.48
c-Pr	0.58	−0.15	−0.39	−0.06	−0.55

[a]Values of $\sigma_{k'/k}$ for set 349 are for $\eta = -6$. As σ_I and σ_d are highly collinear in this set, the values of P_D and L are uncertain.

In the thermal decomposition of **7**, all of the substituents in the reference set will act as acceptors. The substituted carbonyl groups, nitro, nitroso, phenylazo and *N*-phenylazenyl groups act as electron acceptors in all of the other reactions, while the cyclopropyl group is an electron donor, and the *trans*-propenyl group is either an electron donor or has no significant electrical effect. The allenyl, azido, vinyl and C-substituted azenyl groups vary in their behaviour.

C. Directing Effects of Doubly Bonded Groups

Directing effects are conveniently classified into those involving a choice between structural isomers, those involving a choice between configurations and those involving a choice between conformational isomers.

1. *Structural isomerism*

Substituents are known to determine regioselectivity in a very wide range of reactions, including electrophilic, homolytic and nucleophilic aromatic substitutions; eliminations, addition to carbon–carbon double bonds, homolytic hydrogen abstraction and cycloadditions of various types. We will restrict our discussion to a few examples.

In a kinetically controlled reaction the partial rate constant for the formation of the *i*-th product is given by the relationship

$$k_i = f_i k / n_i \tag{56}$$

where k_i is the partial rate constant, f_i is the fraction of the total product which is *i*, k is the overall rate constant and n_i is the number of equivalent reaction sites at which attack of the reagent leads to the formation of the *i*-th product. Applying the LDR equation gives

$$\log k_{iX} = L_i\sigma_{IX} + D_i\sigma_{dX} + R_i\sigma_{eX} + h_i \tag{57}$$

Frequently orientation (regioselectivity) is expressed as the ratio of the fraction of the *i*-th product,

$$\phi_{ij} = f_i/f_j \tag{58}$$

Then, as

$$f_i = k_i n_i/k \tag{59}$$

and

$$f_j = k_j n_j/k \tag{60}$$

we have

$$\phi_{ij} = k_i n_i/k_j n_j \tag{61}$$

and

$$\log \phi_{ij} = \log k_i - \log k_j + \log (n_i/n_j)$$

$$= L_i\sigma_{1X} + D_i\sigma_{dX} + R_i\sigma_{eX} + h_i \tag{62}$$

$$-(L_j\sigma_{1X} + D_j\sigma_{dX} + R_j\sigma_{eX} + h_j) + \log (n_i/n_j) \tag{63}$$

$$= L_{ij}\sigma_{1X} + D_{ij}\sigma_{dX} + R_{ij}\sigma_{eX} + h_{ij} + \log (n_i/n_j) \tag{64}$$

where $L_{ij} = L_i - L_j$, $D_{ij} = D_i - D_j$, $R_{ij} = R_i - R_j$ and $h_{ij} = h_i - h_j$.

As $100 \cdot f_i$ equals P_i, where P_i is the percent of the *i*-th component in the product.

$$\phi = P_i/P_j \tag{65}$$

Orientation is therefore a function of the difference in substituent effects between the reaction which leads to the *i*-th product and that which leads to the *j*-th product. In the general case the composition of the electrical effect differs in the two reactions. As a result, although the ratio ϕ can be quantitatively described by the LDR equation or some relationship derived from it, no mechanistic conclusion can be drawn from the resulting regression equation. Thus correlation of rate constants by the LDR equation will give L and D values of the same sign if there is a single rate-determining step. Differet signs of L and D are diagnostic for a rate determined by more than one process. This may involve two competing rate-determining steps or a combination of a rate-determining step with an equilibrium. It is not at all unusual for a correlation of ϕ_{ij} values which are also a combination of two rate constants to have L and D values of different signs.

From the vast number of examples of directing effects which involve a preference among structural isomers, we have chosen three cases:

a. Partial rate factors for the reaction of substituted benzenes with cyano radicals[46] in equimolar PhH—PhX at 15–20 °C were correlated with the LDRS equation in the case of f_o and with the LDR equation for the f_m and f_p values[47] to give

$$\log f_{oX} = -0.466\sigma_{1X} - 0.463\sigma_{dX} - 3.31\sigma_{eX} - 0.116\upsilon_X + 0.0264 \tag{66}$$

$$\log f_{mX} = -0.340\sigma_{1X} - 0.0194\sigma_{dX} - 0.00959\sigma_{eX} + 0.0342 \tag{67}$$

$$\log f_{pX} = -0.366\sigma_{1X} - 0.675\sigma_{dX} - 3.08\sigma_{eX} - 0.0193 \tag{68}$$

Then

$$\log (f_o/f_{pX}) = -0.100\sigma_{1X} + 0.212\sigma_{dX} - 0.116\upsilon_X + 0.0457 \tag{69}$$

and

$$\log (f_m/f_{pX}) = 0.656\sigma_{dX} - 3.07\sigma_{eX} + 0.0535 \tag{70}$$

Thus, the choice between *ortho* and *para* substitution is dependent on σ_1, σ_d and υ, while the choice between *meta* and *para* is a function of σ_d and σ_e.

b. Selectivities for hydrogen abstraction from 1-substituted butanes by Cl·[48]. The selectivity at position n relative to that at position 4 is given by S_4^n where

$$S_4^n = f_n/f_4 \tag{71}$$

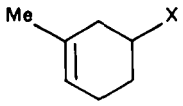
Applying the LDR equation gives[49]

$$\log S_4^1 = -1.57\sigma_{1X} - 1.91\sigma_{dX} - 4.98\sigma_{eX} - 0.0671 \tag{72}$$

and

$$\log S_4^2 = -0.456\sigma_{1X} + 0.677\sigma_{dX} + 4.20\sigma_{eX} + 0.684 \tag{73}$$

c. Cycloaddition reactions. The reaction of isoprene with substituted ethylene dienophiles gives rise to two products, 5- and 4-substituted-1-methylcyclohexenes, **11** and **12**



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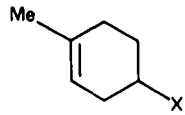


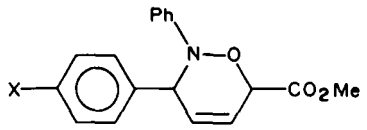
(12)

respectively[50]. The ratio $\phi = P_{11}/P_{12}$ when correlated with the LDR equation gives

$$\log \phi_X = 0.557\sigma_{1X} - 0.656\sigma_{dX} - 3.39\sigma_{eX} - 0.00906 \tag{74}$$

As ϕ equals 1 when X is H, this data point was included in the data set.

Partial rate constants for the reaction of nitrosobenzene with methyl 5-(4′-substituted phenyl)-2,4-pentadienoates[51] were correlated with the LDRT equation. The products of the reaction are 2-phenyl-3-(4′-substituted phenyl)-6-methoxycarbonyl-3,6-dihydro-1,2-oxazines, **13**, and 2-phenyl-6-(4′-substituted phenyl)-3-methoxycarbonyl-3,6-dihydro-



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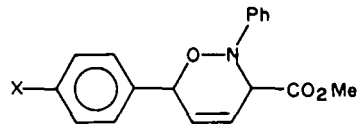


(14)

1,2-oxazines, **14**. The regression equations obtained are

$$\log k_{13} = -0.368\sigma_{1X} - 0.219\sigma_{dX} - 0.0119\sigma_{eX} - 3.71\tau + 12.837 \tag{75}$$

Correlation of the k_{14} values with the LDRT equation gave suspicious results. Exclusion of the data points for the cyano group gave a very different and improved model,

$$\log k_{14} = -0.172\sigma_{1X} - 0.169\sigma_{dX} - 1.240\sigma_{eX} - 3.66\tau + 12.048 \tag{76}$$

Then orientation is determined by the equation

$$\log (k_{13}/k_{14})_X = -0.196\sigma_{1X} - 0.050\sigma_{dX} - 1.23\sigma_{eX} + 0.789 \tag{77}$$

Tautomeric equilibria represent a type of phenomena in which there is a preference for one structural isomer over another. We consider here two examples of prototropic tautomerism. Values of K for the enamine–imine equilibrium shown in Scheme 1 have been determined[52] with

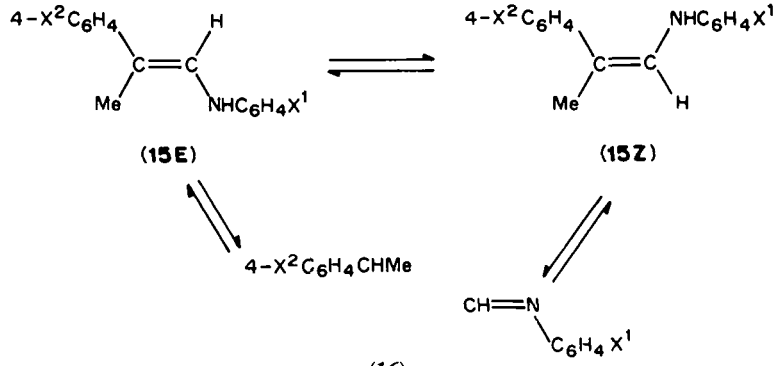
$$K_{Ze/i} = P_{15Z}/P_{16} \tag{78}$$

$$k_{Ee/i} = P^{15E}/P_{16} \tag{79}$$

Results for X^2 equals H and X^1 in the 3 position are

$$\log K_{Ee/i,X} = 0.521\sigma_{1X} + 0.157\sigma_{dX} + 0.104\sigma_{eX} + 0.270 \tag{80}$$

$$\log K_{Ee/i,X} = 0.419\sigma_{1X} + 0.138\sigma_{dX} - 0.378\sigma_{eX} + 0.975 \tag{81}$$



(16)

SCHEME 1

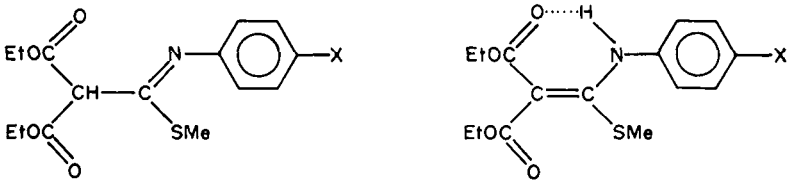
while for X^1 in the 4 position we obtain

$$\log K_{Ze/i,X} = 1.19\sigma_{IX} + 2.05\sigma_{dX} - 0.844\sigma_{eX} + 0.266 \quad (82)$$

$$\log K_{Ee/i,X} = 0.893\sigma_{IX} + 1.71\sigma_{dX} - 0.617\sigma_{eX} + 1.011 \quad (83)$$

The concentration of both *cis* and *trans* enamines will be decreased by the formyl, carboxamido, phenylazo, nitro, nitroso and *N*-phenylazenyl groups.

Another example of enamine–imine tautomerism[53] is that of the diethyl [(4′-substituted phenylimino)(methylthio)methyl]malonates shown by structures **17** and **18** with



(17) **(18)**

$$K_{i/e} = P_{18}/P_{17} \quad (84)$$

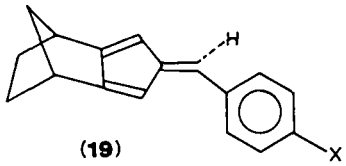
Correlation with the LDR equation gives

$$\log K_{i/e,X} = -0.681\sigma_{IX} - 0.564\sigma_{dX} - 0.240\sigma_{eX} + 0.577 \quad (85)$$

Again, substituted carbonyl groups, nitro, nitroso, phenylazo and *N*-phenylazenyl groups decrease the concentration of the enamine.

2. *Configurational isomerism*

A recent report[54] has shown that the reaction of the isodicyclopentafulvenes **19** with *Z*-1,2-bis(phenylsulfonyl)ethylene gives rise to the products **20** and **21**. The ratio $\phi = P_{21}/P_{20}$ is a function of the X group. In the reaction which leads to the formation of **20**, there is a significant possibility of a charge transfer interaction between the substituted phenyl group acting as an electron donor when X is H, Me, OMe, NMe_2, F and Cl, and the phenyl group bonded to the nearer sulfonyl group acting as an electron acceptor. The NO_2, CN and CF_3 groups should not allow the substituted phenyl group to act as an electron donor



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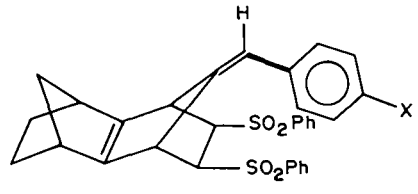

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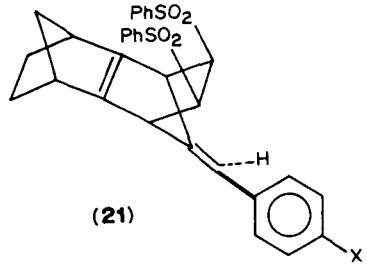


(21)

and should therefore be excluded from the data set. Correlation of the data points for the remaining groups with the LDR equation gives

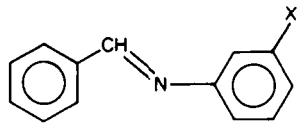
$$\log \phi_{21/20.X} = 0.216_{IX} + 0.379\sigma_{dX} + 0.397\sigma_{eX} + 0.563 \tag{86}$$

While **21** is preferred to **20** in all cases, the amount of **20** increases with the expected extent of charge transfer interaction. There is a remote possibility that the substituted phenyl groups bearing the nitro, cyano and trifluoromethyl substituents are acting as electron acceptors in a charge transfer interaction in which an oxygen atom of the nearer sulfonyl group acts as the electron donor. We predict that the substituted carbonyl, nitroso, phenylazo and *N*-phenylazenyl groups should behave like the nitro, cyano and trifluoromethyl groups, whereas the vinyl, *trans*-propenyl, allenyl, azido, *C*-phenylazenyl and cyclopropyl groups should permit the substituted phenyl group to act as an electron donor.

Rate constants for the thermal relaxation of photoisomerized 3′-substituted-*N*-benzylidene anilines[55] **22** were correlated with the LDR equation giving

$$\log k_{t,X} = 1.596\sigma_{IX} + 0.5422\sigma_{dX} + 2.54\sigma_{eX} + 0.217 \tag{87}$$

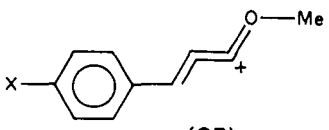
The cyclopropyl, vinyl, *trans*-propenyl, allenyl, azido and *C*-phenylazenyl groups will decrease the rate of isomerization; the remaining members of the reference set will increase it.



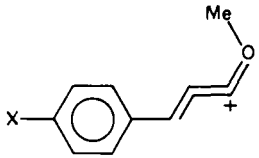
(22)

3. Conformational isomerism

Rate constants have been reported[56] for the conversion of **23** to **24**. Correlation with the



(23)



(24)

LDR equation gives

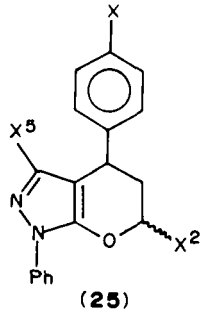
$$\log k_X = -2.70\sigma_{IX} - 3.90\sigma_{dX} - 11.7\sigma_{eX} + 2.376 \quad (88)$$

The rate constants will be decreased by the formyl, carboxamido, nitro, nitroso, phenylazo and *N*-phenylazenyl groups; they will be increased by the vinyl, *trans*-propenyl, allenyl, azido, cyclopropyl and *C*-phenylazenyl groups.

$\Delta G°$ values for the equilibrium[57]

pseudo e⇌pseudo a

(where pseudo e and pseudo a refer to the pseudo-equatorial and pseudo-axial conformations respectively) in 4-(4-substituted phenyl)-2-isopropoxy-5-substituted-7-



(25)

(25a) $X^2 = Z—OPr\text{-}i$, $X^5 = H$
(25b) $X^2Z—OPr\text{-}i$, $X^5 = Ph$
(25c) $X^2 = E—OPr\text{-}i$, $X^5 = Ph$

phenyl-2,3-dihydropyran[2,3-*c*]pyrazoles, **25**, were correlated with the LDR equation giving

$$\Delta G°_{25a,X} = -0.710\sigma_{IX} - 0.578\sigma_{dX} - 0.359\sigma_{eX} + 0.63 \quad (89)$$

$$\Delta G°_{25b,X} = -0.434\sigma_{IX} - 0.214\sigma_{dX} + 0.342\sigma_{eX} - 0.07 \quad (90)$$

$$\Delta G°_{25c,X} = 0.777\sigma_{IX} + 0.594_{dX} + 0.304\sigma_{eX} - 0.07 \quad (91)$$

The configuration of the isopropoxy group in position 2 seems to determine the nature of the electrical effect on the conformational equilibria. $\Delta G°$ for **25a** and **25b** will be decreased by the formyl, carboxamido, nitro, nitroso, phenylazo and *N*-phenylazenyl groups, and increased by the vinyl, *trans*-propenyl, allenyl, azido, *C*-phenylazenyl and cyclopropyl groups. For **25c** the situation is reversed.

VII. CONCLUSIONS

Directing and activating effects of substituents are determined by their electrical, steric and intermolecular force effects. Parametrization of these effects makes possible the

quantitative description of substituent effects on chemical reactivity, physical properties and biological activities by means of the LDR and IMF equations or relationships derived from them. Values of electrical, steric and intermolecular force parameters for 47 p, p-type doubly bonded groups are reported here.

VIII. APPENDIX I. GLOSSARY

General

X	A variable substituent.
Y	An active site. The atom or group of atoms at which a measurable phenomenon occurs.
G	A skeletal group to which X and Y may be attached.
Parameter	An independent variable.
Pure parameter	A parameter which represents a single effect.
Composite parameter	A parameter which represents two or more effects.
Monoparametric equation	A relationship in which the structural effect on a property or reactivity is represented by a single, generally composite parameter.
Diparameteric equation	A relationship in which the structural effect on reactivity or properties is represented by two parameters. In the case of electrical effects, either both parameters are composite or one is and the other is not. Examples are the LD and CR equations. Other examples are the Taft, Ehrenson and Brownlee DSP (Dual Substituent Parameter), Yukawa–Tsuno YT, and the Swain, Unger, Rosenquist and Swain SURS equations. The DSP equation is a special case of the LD equation with the intercept set equal to zero. It is inconvenient to use and has no advantage. The F and R parameters of the SURS equation, though intended to be pure localized and delocalized electrical effect parameters, are in fact composite, making interpretation of the results more difficult. Our results concerning the nature of the σ_R° parameters throw some doubt on the interpretation of the results obtained from correlation with the YT equation. We prefer the use of the LDR, LD, CR and Hammett equations for which the interpretation of the results is clear and unambiguous.
Triparametric	The structural effect is represented by three parameters. They may all be composite parameters, they may all be pure parameters or they may be a combination of pure and composite parameters.
LDR equation	A triparametric equation which models electrical effects of substituents.

Electrical Effect Parametrization

σ_l	The localized electrical effect parameter. It is identical to σ_I. Though other localized effect parameters such as σ_I^q and σ_F have been proposed, there is generally no advantage in their use. The σ^* parameter is also sometimes used as a localized electrical effect parameter. This is acceptable only if the values used are for CH_2X. In general it is best to avoid using this parameter.
σ_d	The intrinsic delocalized (resonance) electrical effect parameter. It represents the delocalized effect in a system with zero electronic demand.
σ_e	The electronic demand sensitivity parameter. It adjusts the de-

localized effect of a group to meet the electronic demand of the system.

σ_D — A composite delocalized effect parameter which is a function of σ_d and σ_e. Examples of σ_D constants are σ_R^+ and σ_R^- constants. The $\sigma_{R,k}$ constants, where k designates the value of the electronic demand η, are also examples of σ_D constants.

σ_{Id} — A composite parameter which is a function of σ_I and σ_d. Its composition is designated by k', the value of P_D.

σ — A composite parameter which is a function of σ_I, σ_d and σ_e. Examples are σ_p°, σ_p^* and σ_m. Alternatively, these constants may be written in the form $\sigma_{k'/k}$ where k designates the value of η and k' that of P_D.

η — The electronic demand of a system. It is equal to the ratio R/D, where R and D are the coefficients of σ_e and σ_d, respectively. They are obtained from the correlation of a data set with the LDR equation. It is a descriptor of the nature of the electrical effect in a given system.

P_D — The percent delocalized effect. It too is a descriptor of the electrical effect exerted by a substituent in a given system.

Steric Effect Parametrization

r_V — The van der Waals radius. The distance between the nuclei of two nonbonded atoms in contact is equal to the sum of their van der Waals radii.

υ — A steric parameter. For groups whose steric effect is at most minimally dependent on conformation, it represents the steric effect due to the first atom of the longest chain in the group and the branches attached to that atom. The only alternative monoparametric method for describing steric effects is that of Taft which uses the E_S parameter. This was originally developed only for alkyl and substituted alkyl groups and for hydrogen. Hansch and Kutter have estimated E_S values for other groups from the υ values using a method which in many cases disregards the MSI principle. It is best to avoid their use.

Simple branching (SB) equation — A topological method for describing steric effects by using as parameters n_i the number of atoms other than H that are bonded to the i-th atoms of the substituent.

Expanded branching (EB) equation — A topological method for describing steric effects which takes into account the order of branching by using as parameters n_{ij}, the number of j-th branching atoms bonded to the i-th atoms of the substituent.

n_b — The number of bonds in the longest chain of a substituent. It is a steric parameter which serves as a measure of the length of a group along the group axis.

MSI principle — The principle of minimal steric interaction which states that the preferred conformation of a group is that which results in the smallest possible steric effect.

Intermolecular Force Parametrization

α — A polarizability parameter defined as the difference between the group molar refractivities for the group X and for H divided by 100. Many other polarizability parameters, such as the van der Waals volume, the group molar volume and the parachor, can be used in its

	place. All of these polarizability parameters are very highly linear in each other.
n_H	A hydrogen-bonding parameter which represents the lone-pair acceptor (proton donor) capability of a group. It is defined as the number of OH and/or NH bonds in the group.
n_n	A hydrogen-bonding parameter which represents the lone-pair donor (proton acceptor) capability of the group. It is defined as the number of lone pairs on O and/or N atoms in the group.
i	A parameter which represents ion–dipole and ion-induced dipole interactions. It is defined as 1 for ionic groups and 0 for nonionic groups.
n_D	A charge-transfer donor parameter which takes the values 1 when the substituent can act as a charge-transfer donor and 0 when it cannot.
n_A	A charge-transfer acceptor parameter which takes the values 1 when the substituent can act as a charge-transfer acceptor and 0 when it cannot.
IMF equation	A multiparametric equation which models phenomena that are a function of the difference in intermolecular forces between an initial and a final state.
Statistics	
Correlation equation	An equation with which a data set is correlated by simple (one parameter) or multiple (two or more parameters) linear regression analysis.
Regression equation	The equation obtained by the correlation of a data set with a correlation equation.
n	The number of data points in a data set.
Degrees of freedom (DF)	Defined as n minus the number of parameters N_p plus 1 [$DF = n - (N_p + 1)$].
F statistic	A statistic which is used as a measure of the goodness of fit of a data set to a correlation equation. The larger the value of F, the better the fit. Confidence levels can be assigned by comparing the F value calculated with the values in an F table for the N_p and DF values of the data set.
$100R^2$	A statistic which represents the percent of the variance of the data accounted for by the regression equation. It is a measure of the goodness of fit.
s_{est}	The standard error of the estimate. It is a measure of the error to be expected in predicting a value of the dependent variable from the appropriate parameter values.
s°	Defined as the ratio of s_{est} to the root mean square of the data. It is a measure of the goodness of fit. The smaller the value of s°, the better the fit.
r_{ij}	Zeroth order partial correlation coefficient. A measure of the collinearity of the ith and jth independent variables.

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The Chemistry of Double-bonded Functional Groups
Edited by S. Patai

CHAPTER **6**

Double bonds from a biochemical perspective

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I. INTRODUCTION

In a review in this series more than twenty years ago, Eisenberg[1] pointed out that carbonyl groups are found in most metabolic pathways. A complete description of the roles of these and other types of double bonds in known biochemical systems would require an enormous summary of the overwhelming literature of biochemistry. Therefore, instead of an attempt to deal with the entire field of biochemistry, this article is restricted to several topics that illustrate various functions of double bonds in enzymatic catalysis and in specific recognition of molecules.

The first topic considered is the group of reactions that alter amino acids in many different ways after the amino group has interacted with a double bond in a cofactor or in the enzyme responsible for the catalysis. These reactions are of current interest because of the detailed insights gained from intensive study of a few enzymes and the many questions raised by the specific properties of the large number of enzymes about which little is yet known.

The second general area described concerns the derivatives of polyunsaturated fatty acids. These compounds have been known for decades as essential in the diet of animals but only recently have their roles as the precursors of a large series of physiological regulators been revealed. Now it is of interest to gain a better understanding of the basis of specificity in the metabolism of these compounds, including the contributions of the double bonds to both recognition and reactivity.

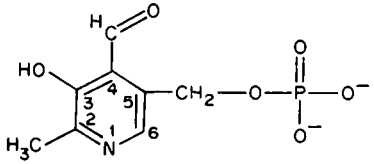
In contrast to the elaborate pattern of structural modifications of the unsaturated fatty acids, the metabolism of vitamin A is not known to involve extensive modification of the

structure in order to fulfill its essential functions. Recent studies have described many biological effects that depend upon the unsaturated structure of the vitamin or its oxidation products, the corresponding aldehyde and acid, but at this time there is only conjecture about the basic mechanism(s) involved.

II. DOUBLE BONDS THAT REACT WITH THE AMINO GROUPS OF AMINO ACIDS

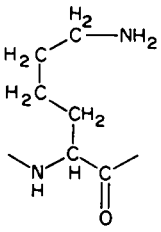
A. Pyridoxal Phosphate Enzymes

One of the most versatile biochemical reagents is pyridoxal phosphate, which is the cofactor for most metabolic reactions of amino acids but also participates in reactions

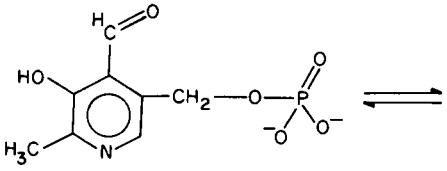


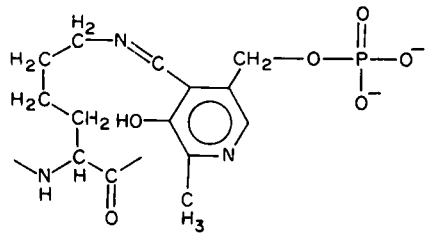
Pyridoxal phosphate

involving substrates without amino groups. As discussed later in more detail, the initial reaction of the coenzyme with the protein to form a holoenzyme results in the formation of a Schiff base of the aldehyde of pyridoxal and an ε-amino group of a lysine residue in the protein[2]. In dilute solutions ($< 10^{-3}$ M) of small molecules, the equilibrium of Schiff base



Lysyl residue





Schiff base

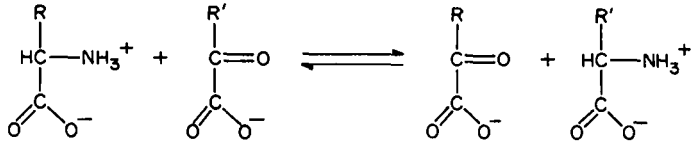
formation and dissociation results in very little condensation product[3]. The interaction of enzymes with other groups of the coenzyme increases the binding energy to the extent that

dissociation constants are usually in the micromolar to nanomolar range. The tight binding of the coenzyme does not, however, restrict the reactivity of the Schiff base; the carbonyl carbon is facilely transferred to the amino group of the appropriate substrate in the first step of the catalytic mechanism. In this reaction the binding of the substrate to the enzyme in the formation of the Michaelis complex effectively increases the concentration of the amino group so that the Schiff base is relatively stable. The catalytic mechanisms responsible for the specific enzyme activity, transamination, decarboxylation, racemization, β-elimination, β-replacement, γ-elimination or γ-replacement, then convert the substrate to a structure that ultimately does dissociate from the enzyme. In cases in which the product retains its amino group, the enzyme reverts to its initial Schiff base form. In the case of transamination, however, the overall reaction proceeds in steps; in the first step the amino acid substrate is released as a keto acid while the coenzyme is converted to the corresponding pyridoxamine and the keto-substrate reacts with the enzyme-pyridoxamine to produce a new amino acid and the Schiff base of enzyme with pyridoxal phosphate. Thus, the formation of the Schiff base of pyridoxal phosphate initiates a process in which the double bond is shifted to facilitate the flow of electrons to permit bond breakage at any of several positions in specific substrates and the double bond may be located on either side of the nitrogen atom when the Schiff base dissociates.

The energetics of Schiff base formation with pyridoxal phosphate are similar to those of other aromatic aldehydes. The nitrogen of the pyridine ring plays a critical role in stabilizing shifts of electrons[4]. The substituents other than the 4-formyl group will be seen to perform functions that vary in importance for various enzymes. Thus, the hydroxymethyl group is essential for all coenzyme functions, in which a phosphate ester is required[5]. Model reactions proceed without such an ester but all enzymes require an anchor, although in some cases other acid groups can replace the phosphate[5]. Elimination or replacement of the methyl group and addition of substituents at position 6 alter the strength of binding and the rates of reaction to variable extents with various enzymes[6].

1. *Transaminases*

In the 1930s several investigators presented evidence that glutamic acid was degraded by various tissue preparations without the release of ammonia[7]. At the end of the decade Braunstein and his associates demonstrated the reversible transfer of an amino group with a proton and two electrons from an amino acid to a keto acid[8]. The reaction was named transamination and the enzymes are popularly called transaminases, although the IUB designation is aminotransferases. The suggestion by Snell in 1945 that pyridoxal is a cofactor[9] was confirmed and extended in 1947 with identification of pyridoxal phosphate as the coenzyme[10]. Subsequently many specific transaminases were isolated from all types of organisms. Some of these are among the most thoroughly analyzed enzymes.



General transaminase reaction

a. Glutamic-oxaloacetic transaminase (aspartate aminotransferase, L-aspartate: 2-oxoglutarate aminotransferase) (EC 2.6.1.1). This activity has been found ubiquitously in nature. Whereas prokaryots contain a single enzyme species, eukaryotic cells contain distinct enzymes in their cytosols and mitochondria[11]. X-Ray crystallographic analysis of enzymes from both pig and chicken heart muscle have shown that the basic structures are

very similar[12] and comprehensive studies with a large variety of physical and chemical methods indicate that all members of this group of enzymes use the same catalytic mechanism. These enzymes are dimers of subunits with molecular weights near 45,000[13]. Each subunit contains an active site that includes a molecule of pyridoxal phosphate and appears to act catalytically independently of the other subunit.

From elaborate studies in many laboratories it has been possible to construct a detailed model of the reaction mechanism. Some aspects of general interest of this model are summarized here. In the absence of substrate the carbonyl group of pyridoxal phosphate forms a Schiff base with an ε-amino group. The double bond is at an angle of 30° with the plane of the pyridine ring and the nitrogen of the aldimine inclines toward the phenolic hydroxyl group, which is ionized and is hydrogen bonded to a tyrosine hydroxyl group[14]. The protonated pyridine nitrogen is also hydrogen bonded, in this case to the carboxyl groups of an aspartate residue. The phosphate group is doubly ionized and elaborately associated with a backbone nitrogen, the hydroxyl groups of two threonines, a serine and a tyrosine and the guanidininium group of an arginine residue. These interactions together with van der Waals interactions with the ring result in the coenzyme occupying a deep pocket.

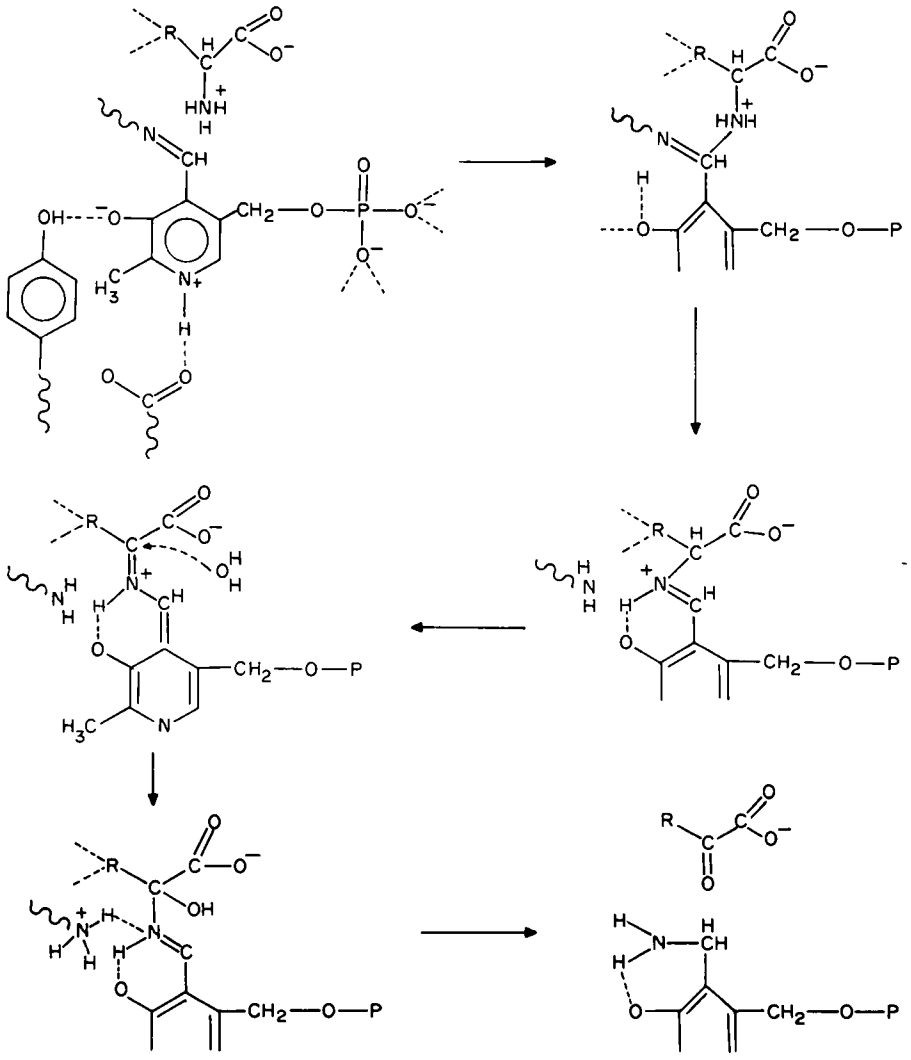
The addition of an amino acid to the free enzyme brings a second nitrogen atom near the aldimine carbon atom because of the positioning of the amino acid of the substrate through another set of hydrogen bonds and other interactions with groups in the active site and the transfer of a proton from the ammonium group of the amino acid to the imine (ε-amino group). The substrate amino group is thus able to add to the aldimine carbon atom to form a geminal diamine; this reaction is accompanied by a tilt of the pyridine ring[15]. The transfer of another proton from the substrate nitrogen to that of the lysine results in elimination of the latter and completes the first step of catalysis, transimination.

The new Schiff base can undergo tautomerization with removal of the α-hydrogen and the formation of a quinonoid structure of the coenzyme. These reactions are presumably facilitated by the participation of the nearby lysine amino group. Subsequent protonation of the aldimine carbon produces a ketimine, which is hydrated to the carbinolamine and dissociates to a keto acid and the pyridoxamine-form of the enzyme[16]. This series of reactions is reversed by the addition of a keto acid to the enzyme.

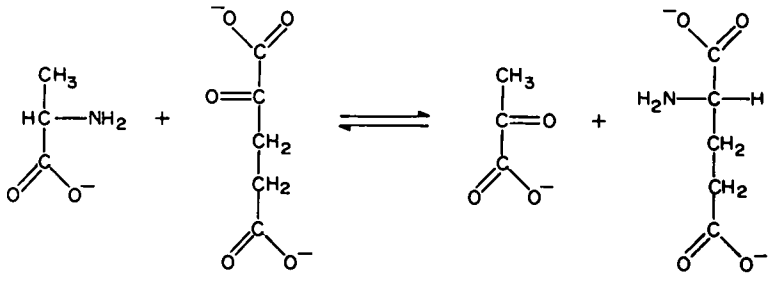
b. Alanine aminotransferase (EC 2.6.1.2). The reactivity of pyruvate in crude transaminating systems was noted in the earliest descriptions of this type of reaction[17]. Eventually pure enzymes were isolated frøm various mammalian tissues and shown to be specific for the reversible reaction of L-alanine with α-ketoglutarate; only the nonphysiological amino acid, α-aminobutyrate, reacts at about 1% the rate of alanine[18]. The cytosolic enzymes appear to resemble greatly the aspartate enzyme in consisting of two submits of molecular weight about 50,000. A mitochondrial enzyme, however, is reported to be a monomeric protein[19].

The kinetic properties of the alanine enzyme are consistent with the reaction mechanism described for the aspartate enzyme. An interesting reaction of double bonds is seen in the action of a suicide inactivator, β-chloroalanine. This compound acts as a substrate, but once in 500 turnovers the chlorine is eliminated to give the α,β-unsaturated aldimine with enzyme-bound pyridoxal phosphate. This intermediate alkylates some group in the enzyme and prevents reaction with another molecule of substrate even though the catalytic process continues to form pyridoxamine and a β-bound pyruvate residue.

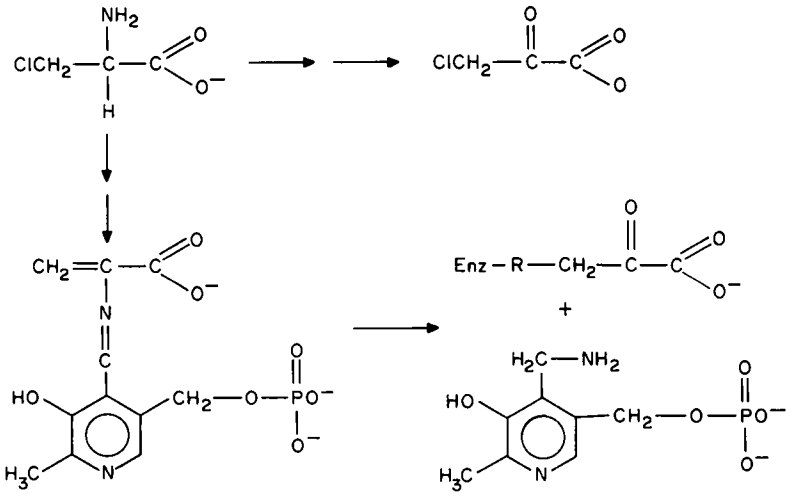
c. Tyrosine aminotransferase (EC 2.6.1.5). The aspartate and alanine transaminases participate in major metabolic processes, interconverting amino acids with intermediates of the tricarboxylic cycle (oxaloacetate) and glycolysis (pyruvate). Several transaminases, in contrast, serve limited functions in specific tissues under specific circumstances. The



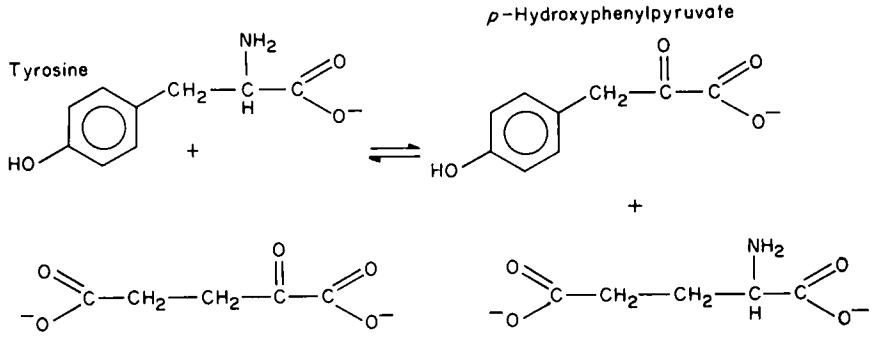
Model of transamidination and transamination



Reaction of alanine-α-ketoglutarate transaminase



Reaction of β-chloroalanine as a suicide inactivator

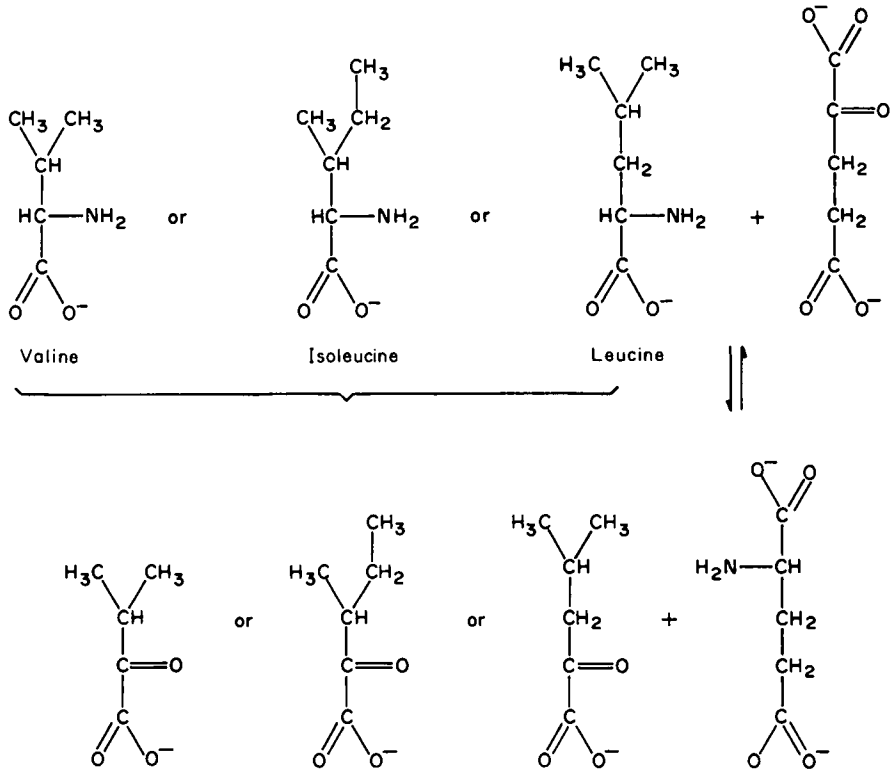


Reaction of tyrosine transaminase

tyrosine enzyme is an example of an enzyme found primarily in liver, where it is rapidly induced when excess tyrosine requires catabolic degradation[20]. The induction requires the presence of glucocorticoid hormones in addition to the amino acid[21]. The major pathway of tyrosine degradation is absolutely dependent upon transamination with α-ketoglutarate. The reverse reaction has little significance in animal metabolism. In contrast, a less specific enzyme in bacteria is required for the biosynthesis of tyrosine from its precursor, *p*-hydroxyphenylpyruvate[22].

d. Branched chain amino acid transaminase (EC 2.6.1.42). The catabolism of the three naturally occurring branched chain amino acids, leucine, isoleucine and valine, is similar to tyrosine catabolism in that the first step is a transamination. A single enzyme shows high specificity for these three amino acids and for α-ketoglutarate as the amino acceptor[23].

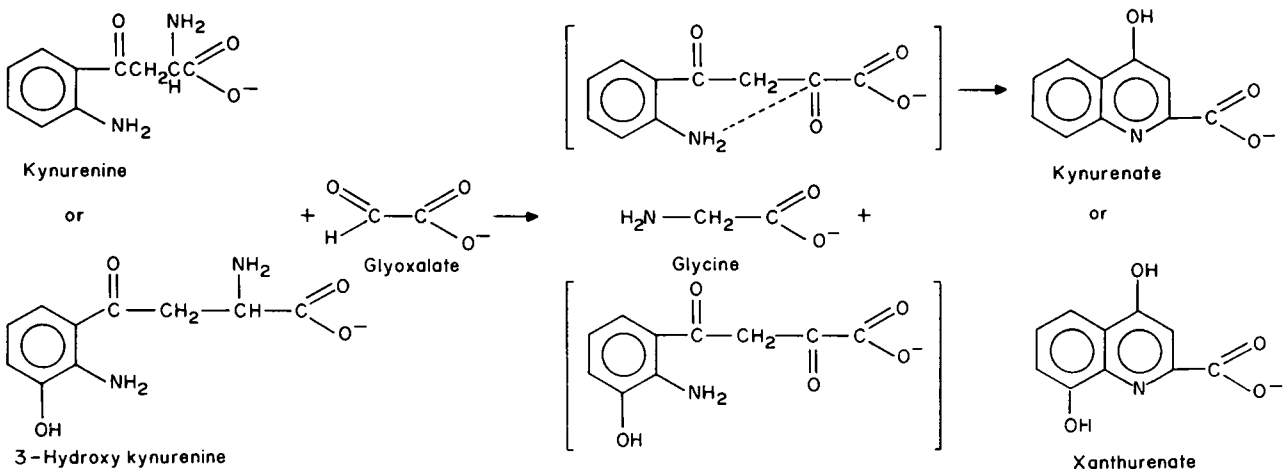
e. Kynurenine transaminase (EC 2.6.1.7). In the major pathway of tryptophan catabolism, intermediates on the way to nicotinic acid or complete oxidation to CO_2 and H_2O



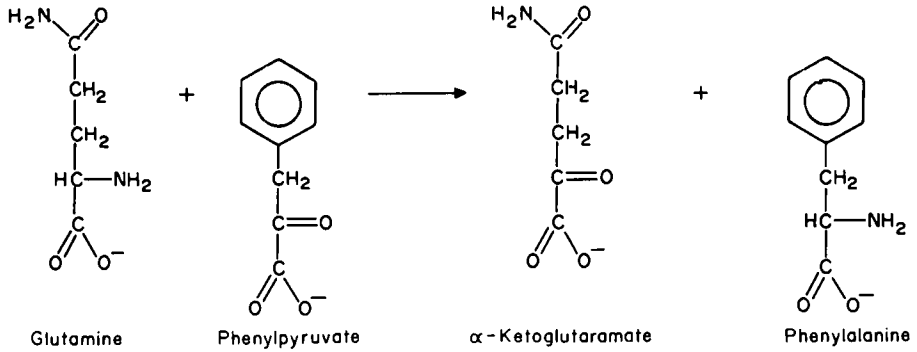
Reactions of branched chain amino acid transaminase

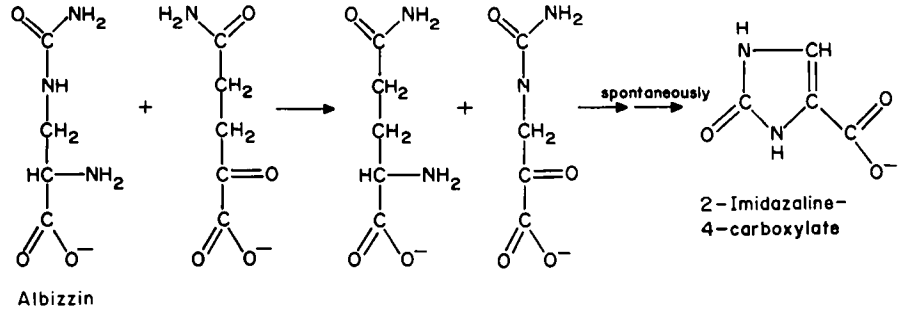
include kynurenine and 3-hydroxy kynurenine. These compounds are both substrates for two kinds of pyridoxal phosphate-requiring enzymes. One of these, kynureninase, will be discussed in Section II.A.5; the other is a transaminase. Separation of enzyme activities has revealed that at least four enzymes can transfer the amino group from kynurenine to appropriate acceptors, which may be glyoxalate or pyruvate as well as α-ketoglutarate[24]. The novel feature of this reaction, regardless of keto acid, is that the keto acid corresponding to kynurenine or 3-hydroxykynurenine is not detected. Instead, the Schiff base formed by an intramolecular condensation of the α-carbon with the aromatic amino group becomes part of the very stable quinoline ring of the actual products, kynurenic acid and xanthurenic acid, respectively.

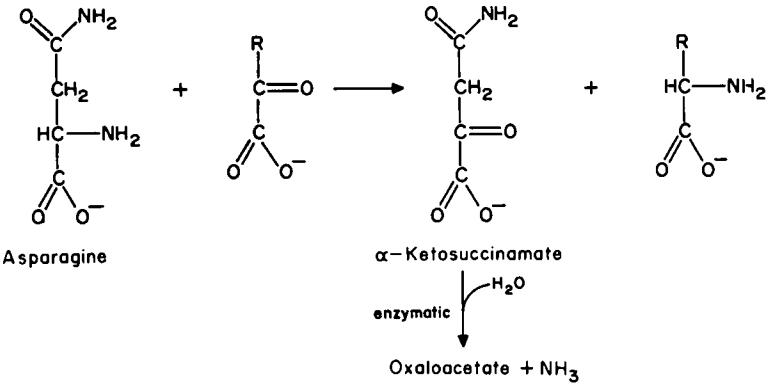
f. Glutamine as amino group donor. At least two types of transaminase occur in animal tissues that do not use glutamate as the donor of amino groups but specifically require glutamine (EC 2.6.1.15). These are distinguished by the relatively greater activity of the kidney type with phenylpyruvate and the relatively greater activity of the liver type with albizzin[25]. These enzymes are found as both cytosolic and mitochondrial isozymes. Their biological functions are not obvious because of the varied ketoacids they can use as acceptors, including the α-keto analogue of methionine (an intermediate in a salvage pathway), phenylpyruvate and glyoxalate. The existence of a hydrolytic enzyme that converts α-ketoglutaramic acid to α-ketoglutarate and ammonia[26] suggests that the



Reactions of kynurenine transaminase



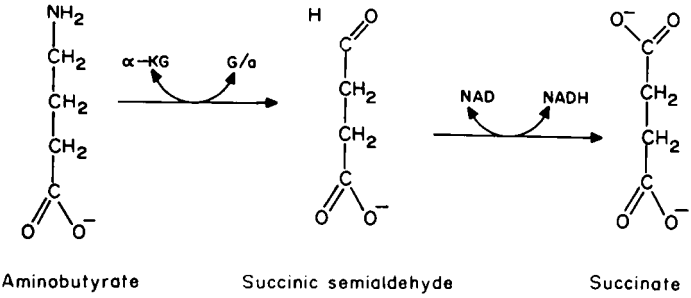




Reactions of glutamine and asparagine transaminases

reactions that are reversible *in vitro* act only to transfer amino groups from glutamine to various keto acids *in vivo*. A related enzyme with similar broad specificity using asparagine as the amino donor has been found widely distributed among vertebrates, invertebrates and plants[27].

g. ω-Transaminase. Amino groups in positions other than α to a carboxyl group are also substrates for pyridoxal phosphate dependent transaminases. In the metabolism of brain, glutamic acid (itself a neurotransmitter) is decarboxylated to yield another important neurotransmitter, γ-aminobutyrate. The necessary elimination of this physiological agent is accomplished by a transaminase (EC 2.6.1.21) with molecular and catalytic properties similar to those of the aspartate transaminase[28]. The partner in this reaction is α-ketoglutarate and the product, succinic semialdehyde, is oxidized by a simple pyridine-nucleotide dehydrogenase to the tricarboxylic acid cycle intermediate, succinate.



Metabolism of γ-aminobutyrate via ω-transamination

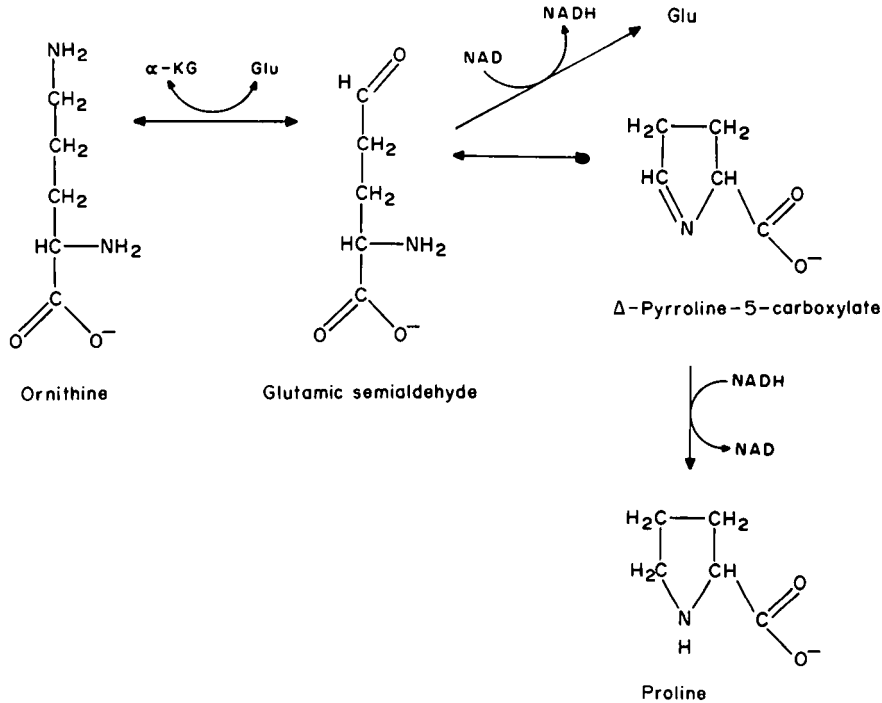
Another ω-transaminase of importance in animal metabolism attacks the δ-amino group of ornithine, not the α-amino group (EC 2.6.1.13). This enzyme as purified from rat liver is a tetramer, molecular weight 177,000, containing four equivalents of pyridoxal phosphate[29]. In the reaction with α-ketoglutarate the ornithine is converted to glutamic semialdehyde, which is subsequently oxidized to glutamate for the most part, but which is also metabolized as the cyclic Schiff base, Δ^1-pyrroline-5-carboxylate, which can be reduced to proline.

The proceeding paragraphs illustrate some of the chemical and biological properties of the pyridoxal phosphate requiring transaminases. In addition to the enzymes described, there are many variants known that differ from these in relative specificities, in subunit structure and other properties. There have also been many more transminases described in various organisms; by 1978, sixty transaminases were recognized by the Commission on Nomenclature of the International Union of Biochemistry.

2. *Amino acid decarboxylases*

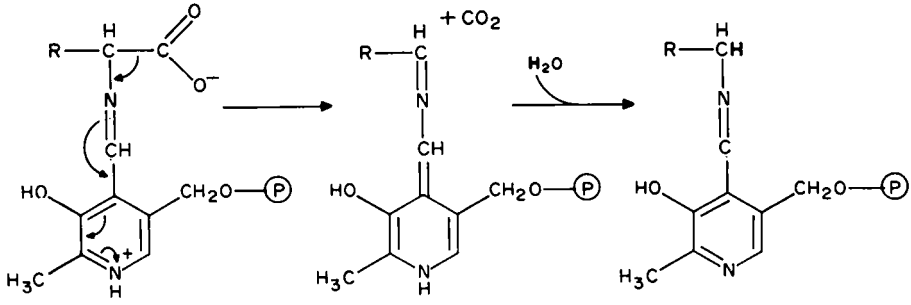
Studies on a new cofactor required for the decarboxylation of tyrosine by a bacterial enzyme led to the synthesis of pyridoxal phosphate and its establishment as the cofactor of both amino acid decarboxylases and transaminases. As least a dozen amino acid decarboxylases in bacteria and animal tissues are now known that are dependent upon this coenzyme. However, as discussed later, there are exceptional amino acid decarboxylases that do not use a dissociable cofactor.

The mechanism of amino acid decarboxylation was shown not to involve labilization of

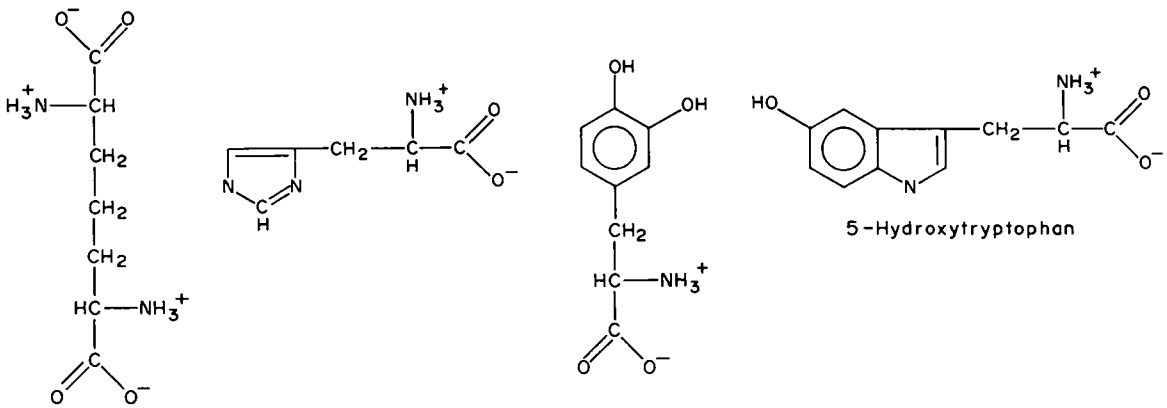


Metabolism of ornithine via ω-transamination

the α-hydrogen[30]. A single hydrogen from the medium is incorporated in the amine that is produced. Decarboxylation in the presence of $H_2{}^{18}O$ does not introduce ^{18}O into the CO_2 produced. These results support a mechanism in which a Schiff base is formed between the aldehyde of pyridoxal phosphate and the amino group and in which electron flow from the negatively charged oxygen of the carboxyl group through the conjugated series of double bonds to the pyridinium nitrogen causes loss of CO_2. Subsequent protonation of the original α-carbon atom restores the original sequence of double bonds and allows the amine to dissociate by reversal of the reactions that formed the Schiff base.



Mechanism of decarboxylation of amino acids

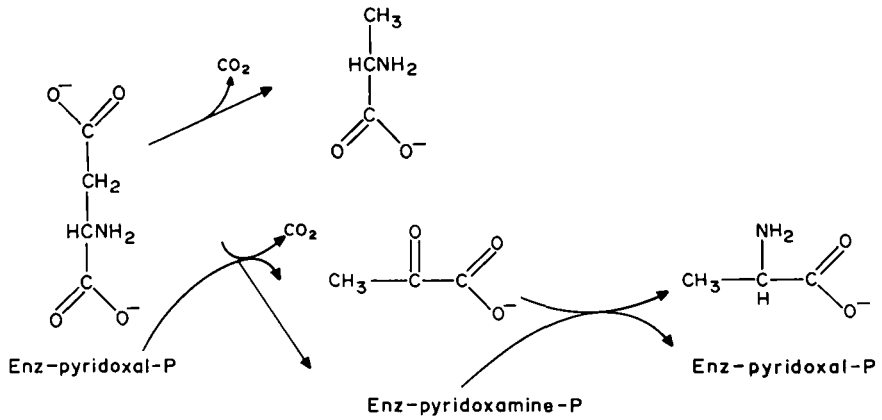


Reactions of representative amino acid decarboxylases

Since all amino acid decarboxylases that have been studied are inactivated by borohydride in a reaction that joins the carbonyl carbon of pyridoxal phosphate to a specific ε-amino group, the coenzyme must participate in a transimination reaction in the formation and cleavage of the Schiff base with the amino acid substrate and amino product, respectively.

Although several amino acid decarboxylases appear to be produced by bacteria for physiological reasons, in order to maintain a favorable environmental pH (e.g. arginine, ornithine, glutamic acid), other enzymes of this group participate in important biosyntheses. Thus, diaminopimelic acid serves as a precursor of lysine in bacteria; histidine is the source of the powerful physiological agent histamine in animals; glutamic acid, dihydroxyphenylalanine and 5-hydroxytryptophan are decarboxylated to the neurotransmitters γ-aminobutyrate, dopamine and serotonin, respectively; and ornithine yields the putrescine upon which polyamines are constructed in the early steps of cell divisions.

Bacteria of several species possess an enzyme that catalyzes the β-decarboxylation of aspartic acid (EC 4.1.1.12). The properties of a purified enzyme illustrate how remarkable the specificities of most pyridoxal phosphate enzymes are. In the β-decarboxylase, reactions that are very minor side-reactions in other cases occur to a significant extent. Thus, the Schiff base that enables the α-hydrogen to dissociate and establishes a structure that easily loses the β-carboxyl group also permits a transamination to occur so that pyruvate is produced in addition to alanine[31]. To the extent that pyruvate is formed, the enzyme is inactivated by conversion of pyridoxal phosphate to pyridoxamine phosphate. However, pyruvate (when it is allowed to accumulate) or other keto acids added to the enzyme can participate in the second phase of transamination and restore decarboxylase activity.

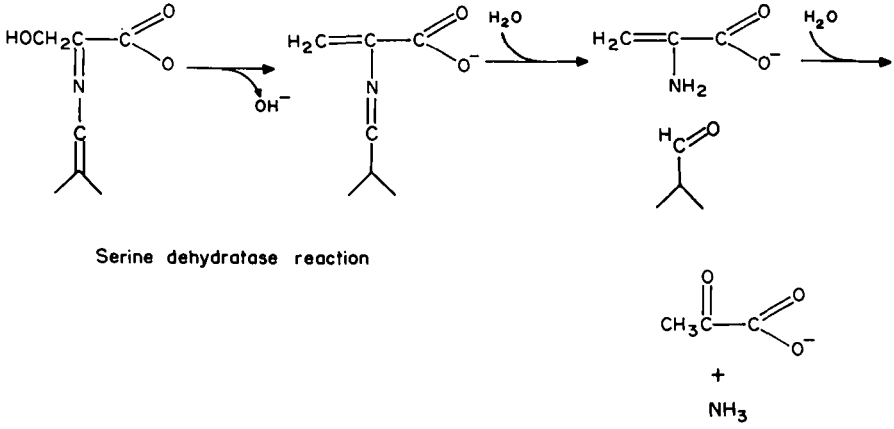


Reactions of aspartic acid β-decarboxylase

3. *β-Elimination reactions*

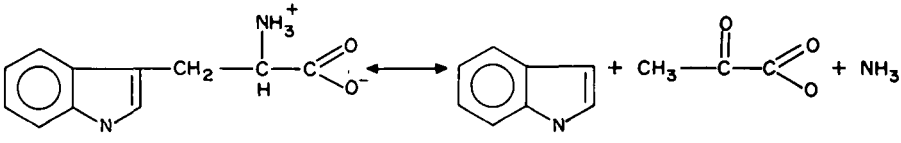
A group of enzymes that catalyze β-elimination reactions emphasizes the power of protein structure in determining the direction of a multipotential reaction system. These enzymes form the same sort of Schiff bases as do other pyridoxal phosphate enzymes, then, after abstracting the α-hydrogen, eliminate a β-substituent[32]. The hypothetical unsaturated intermediate hydrolyzes to form an α-keto acid and ammonia.

Enzymes comprising a prominent subgroup of these enzymes degrade serine (EC 4.2.1.13) and threonine (EC 4.2.1.16) to pyruvate and α-ketobutyrate, respectively, plus ammonia. It would seem reasonable, therefore, to name the catalysts deaminases. However, isotope exchange reactions show that the hydroxyl group of the amino acid equilibrates with oxygen of the medium, presumably while the amino group is part of a Schiff base[33]. Therefore, the reaction mechanism is considered to start with β-elimination and the enzymes are named dehydratases.



Serine dehydratase reaction

The degradation of serine is purely catabolic in allowing excess serine to be used for production of energy, forming the product pyruvate, which is always produced in large quantities from carbohydrate. In bacteria, however, inducible enzymes convert threonine to α-ketobutyrate as needed for synthesis of isoleucine. Although the β-elimination reactions proceed in the direction of α-ketoacid and ammonia production under coventional reaction conditions, in the presence of high concentrations of these products, the reactions can proceed in the direction of synthesis, as has been demonstrated with tryptophanase (EC 4.1.99.1)[34]. This enzyme can use various substituted indoles in addition to the unsubstituted ring to synthesize ring modified tryptophan by condensation with pyruvate and ammonia.

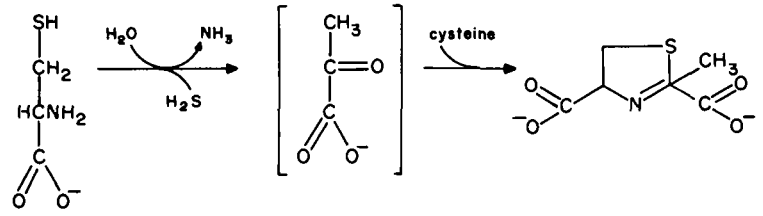


Tryptophan Indole

Tryptophanase reaction

The versatility of some bacterial enzymes suggests that they serve as scavenger agents. An enzyme named tyrosine phenol-lyase (ECY. 1.99.2) catalyzes the β-elimination of phenol from tyrosine and converts the side-chain to pyruvate and ammonia[35]. However, this enzyme not only acts on substituted phenols in both the degradative and reverse (synthetic) directions, it also attacks smaller substrates, including D- and L-serine, D- and L-cysteine, *S*-methylcysteine and β-chloroalanine.

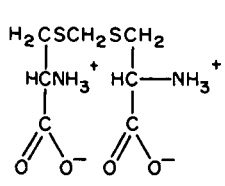
A more specific enzyme is cysteine desulfhydrase (EC 4.4.1.1). This enzyme does, however, use β-chloroalanine in addition to cysteine and several *S*-alkylated cysteines. With cysteine as the substrate, the reactive Schiff base intermediate after elimination of the sulfur condenses with another molecule of cysteine to form 2-methyl-2,4-thiazolidine dicarboxylate[36].



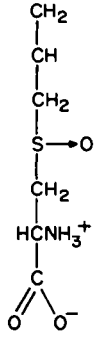
Cysteine

Cysteine desulfhydrase reaction

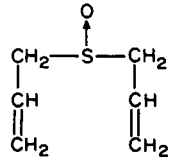
Another related enzyme, *S*-alkylcysteine lyase (EC 4.4.1.6), also catalyzes the β-elimination and hydrolysis of cysteine but acts more rapidly on djenkolic acid and djenkolate sulfoxide and other derivatives of cysteine[37]. An enzyme with more stringent substrate requirements in alliin lyase (EC 4.4.1.4), which attacks only *S*-allylcysteine sulfoxides[38]. This enzyme is garlic eliminates allylsulfenic acid, which spontaneously condenses to the odoriferous allicin.



Djenkolic acid



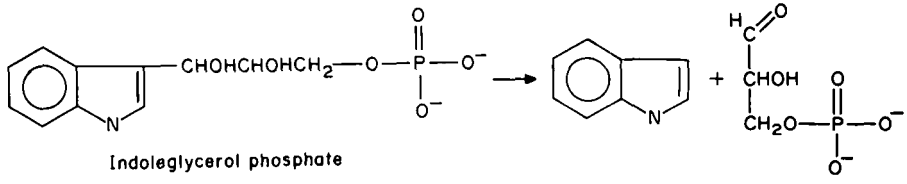
S-Allylcysteine sulfoxide



Allicin

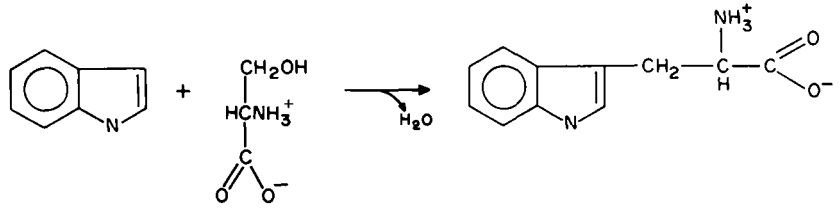
4. β-Replacement reactions

The synthesis of tryptophan has been thoroughly studied in bacteria. Tryptophan synthase (4.2.1.20) has played an extremely prominent role in the history of biochemistry and molecular biology as the enzyme whose primary sequence was first related to the positions of mutations in its structural gene to provide evidence for colinearity of the gene and the gene product[39]. There are many other interesting properties of this thoroughly studied molecule[40]. From the point of view of the role of pyridoxal phosphate in the mechanism of catalysis, it is important to point out that the enzyme is composed of two dissimilar types of subunits, and is a tetramer. The overall reaction catalyzed the formation



Indoleglycerol phosphate

(reaction 1)



(reaction 2)

Tryptophan synthase reaction

of tryptophan and glyceraldehyde 3-phosphate from indoleglycerol phosphate and serine and can be written as the sum of two steps:

(1) indoleglycerol phosphate → indole + glyceraldehyde 3-phosphate

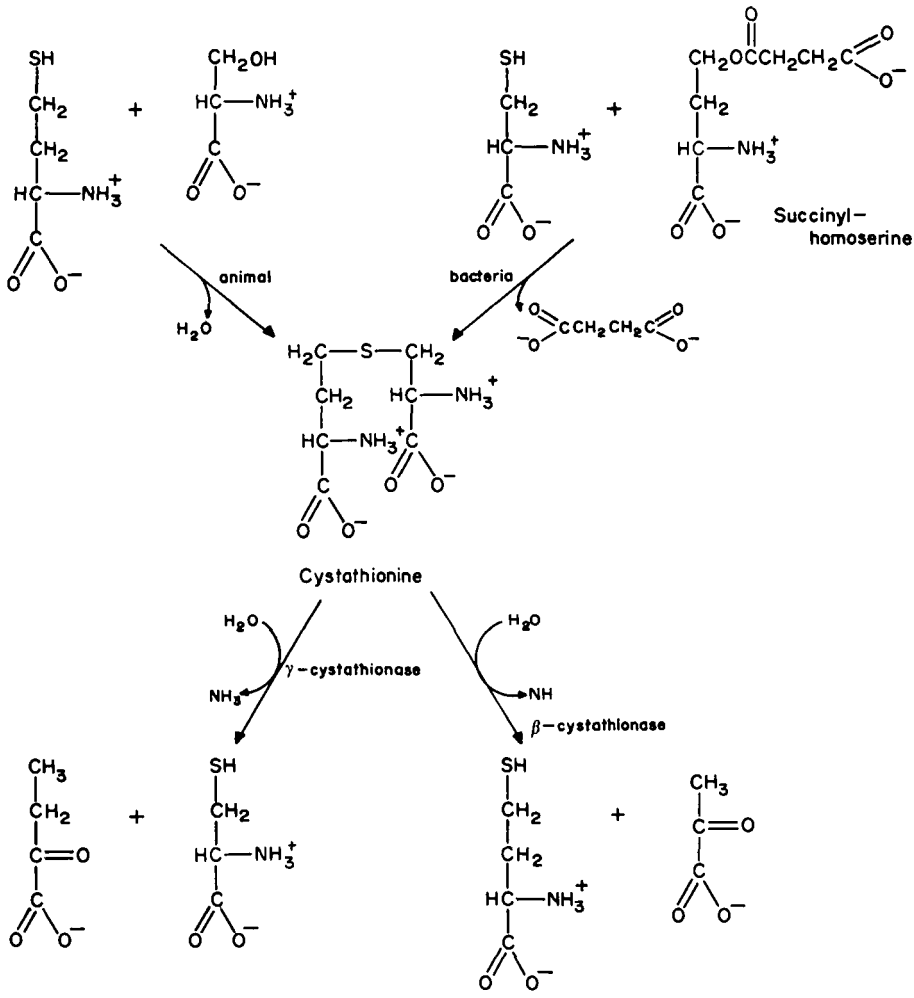
(2) indole + serine → tryptophan + H_2O

Step (1) is catalyzed by the α-subunit alone. This is usually described as an aldol cleavage. The β-subunit appears to be a simple protein, as are some other aldolases. The α-subunit, however, contains an equivalent of pyridoxal phosphate, which is necessary for the activation of the β-carbon of serine and enables it to condense with indole, which replaces the β-hydroxyl group.

Although the two steps can be studied individually, the complete enzyme tetramer not only catalyzes the individual steps more rapidly than the isolated subunits but carries out a net synthesis of tryptophan from indolylglycerol phosphate and serine without detectable formation of free indole. Presumably indole is transferred from the α-subunit to the β as rapidly as it is formed when the holoenzyme is supplied with both substrates.

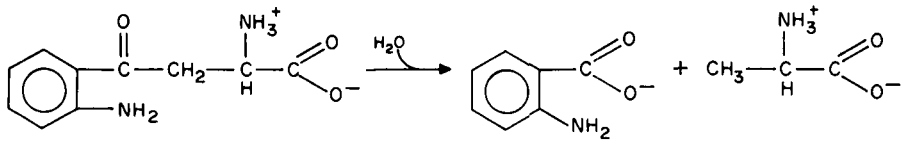
5. γ-Substitution

Cystathionine is a major intermediate in the biosynthesis of sulfur-containing amino acids. In bacteria, where cysteine is synthesized *de novo*, methionine is synthesized by a β-replacement reaction of a pyridoxal phosphate Schiff base. The primary substrate is an ester that presumably provides a better leaving group than the hydroxyl group of homoserine. *O*-Succinyl homoserine condenses with cysteine to form cystathionine and succinate (EC 4.2.99.9)[41]. In the absence of cysteine, succinylhomoserine is degraded to α-ketobutyrate, ammonia and succinate. In both cases, the Schiff base of the substrate loses first an α-hydrogen, then a β-hydrogen and finally the succinate, to form an α,β-unsaturated compound. This intermediate can be attacked by the specific substrate cysteine or isomerize to form the aldimine that hydrolyzes to yield α-ketobutyrate.

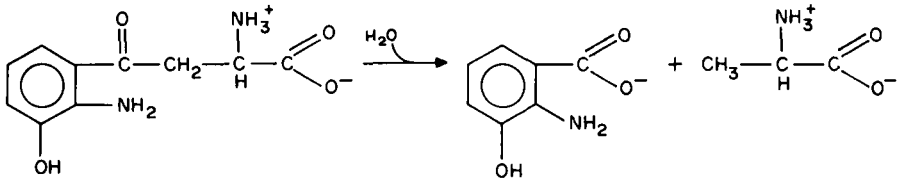


Reactions of cystathionine

The synthesis of cystathionine in animals is carried out by an exchange at the β-position of serine (EC 4.2.1.22). Although *in vitro* studies have shown that other sulfur compounds can add to the activated β-carbon, the principal substrate *in vivo* is homocysteine, derived from *S*-adenosylhomocysteine produced during methyl transfer reactions from *S*-adenosylmethionine[42]. The subsequent breakdown of cystathionine in animals is catalyzed by γ-cystathionase (EC 4.4.1.1)[43]. Thus, the role of proteins in directing reactions is again emphasized. In bacteria the synthesis of cystathionine involves γ-activation and breakdown is a β-elimination (EC 4.4.1.8). In animals the reverse occurs; β-exchange is used for synthesis and γ-elimination produces cysteine, which cannot be synthesized by any other route but which is normally available in the diet. The specificities of the respective enzyme systems make cysteine the principal sulfur amino acid in bacteria whereas methionine is an essential amino acid in mammals and cysteine is not.



Kynurenine Anthranilate



3-Hydroxykynurenine 3-Hydroxyanthranilate

Reactions of kynureninase

In the degradation of kynurenine in the catalobism of tryptophan, a unique pyridoxal phosphate dependent reaction catalyzes an unusual hydrolysis. The result of this reaction is to add the hydroxyl group of water to the γ-carbon atom while the β, γ-bond is cleaved to yield alanine and anthranilic acid[44]. The reaction with kynurenine itself is a very minor event but the major part of tryptophan metabolism depends upon the same enzyme, kynureninase (EC 3.7.1.3), attacking 3-hydroxykynurenine to form 3-hydroxy-anthranilate.

6. *Racemases*

Racemization of amino acids appears to be the simplest reaction catalyzed by pyridoxal phosphate enzymes but an understanding of the mechanism has not yet been achieved. Racemases have been identified only among bacteria, many of which contain D-amino acids as constituents of their cell walls. D-Amino acids are also found in several antibiotics. However, catabolism of L-alanine in some bacteria requires racemization (EC 5.1.1.1).

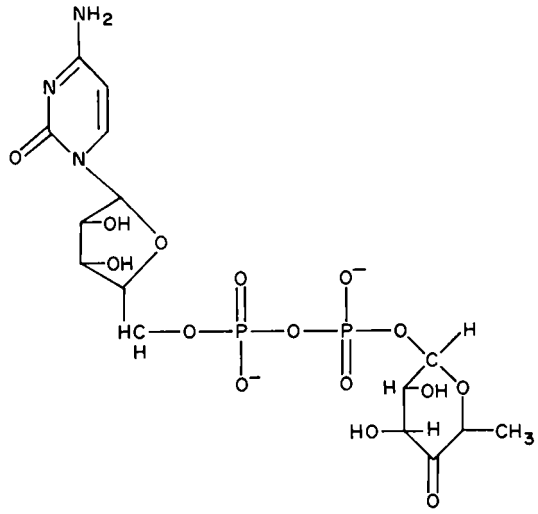
Alanine racemases are relatively specific for the simple side-chain and require pyridoxal phosphate[45]. Much less specific racemases (arginine racemase, EC 5.1.1.9)[46] and a 'low substrate specificity' racemase (EC 5.1.1.10)[47] are also typical pyridoxal phosphate enzymes. Attempts to distinguish between mechanisms involving one or two bases in the enzyme (i.e. groups that can accept and donate protons) have not been conclusive. In some cases a labeled hydrogen in the α-position is partially retained (0.75–10%) but in other cases there is no retention[48]. Very recent analyses of the rates of partial reactions, studied with substrate and solvent isotope effects, have shown differences among the pyridoxal phosphate-requiring alanine racemases but were not able to define a reaction mechanism in the absence of information about the three-dimensional structures[49]. Some amino acid racemases do not use pyridoxal phosphate or any other known cofactor and also use unidentified mechanisms.

7. Glycogen phosphorylase (EC 2.4.1.1)

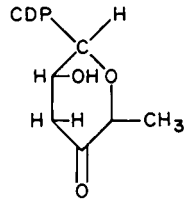
The enzyme phosphorylase has been well studied since 1940 and carries out only the (reversible) phosphorolysis of the nonreducing terminal residues of glycogen. Clearly there is no conventional function for pyridoxal phosphate in the reaction mechanism but in 1957 the enzyme was found to contain pyridoxal phosphate that is required for activity[50]. However, in contrast to all other enzymes that contain this coenzyme, reduction with borohydride, which forms a secondary amine from the Schiff base with an ε-amino group, does not inactivate phosphorylase[51]. The evidence at this time does not allow a mechanistic role for the coenzyme to be fully described but strongly suggests that the phosphate group of pyridoxal phosphate is involved in the catalytic process.

8. Reduction of CDP-4-keto-6-deoxyglucose (EC 1.17.1.1)

At this time, in contrast to the large number of enzymes that require pyridoxal phosphate as the coenzyme in a variety of reactions, only a single enzyme from a bacterium has been found to require pyridoxamine phosphate. This enzyme participates in a pathway that produces a modified sugar. Many modifications of sugar residues occur with the



CDP-4-keto-6-deoxyglucose



CDP-4-keto-3,6-dideoxyglucose

monosaccharide attached to a nucleotide 'handle'. In this case cytidine diphosphate (CDP) is the carrier. An enzyme system from *Pasteurella pseudotuberculosis* carries out the reduction of CDP-4-keto-6-deoxyglucose to CDP-4-keto-3, 6-dideoxyglucose[52]. This reductase transfers electrons from either NADH or NADPH to the Schiff base of the carbonyl group of the sugar. The process requires two proteins. The coenzyme is bound to one of the two proteins noncovalently, with a major contribution from ionic interaction of the phosphate group. The bound coenzyme is not involved in a Schiff base with the enzyme but contains a free amino group. The formation of a Schiff base with the substrate labilizes the 3-hydroxyl group of the sugar and enables the other protein to reduce the carbon 3 to form the dideoxysugar.

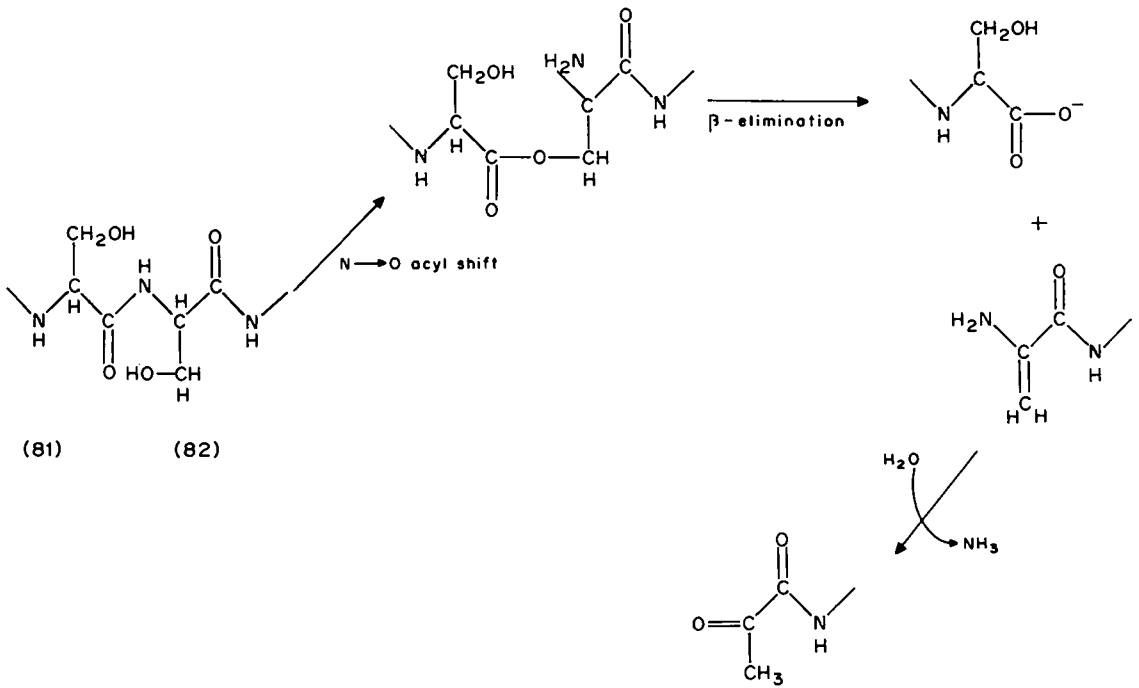
B. Pyruvoyl Enzymes

The apparent universality of pyridoxal phosphate as the cofactor for amino acid decarboxylases caused skepticism about evidence that a bacterial histidine decarboxylase (EC 4.1.1.22) did not use this coenzyme[53]. Eventually analyses were performed on pure crystalline enzyme that demonstrated convincingly that another structure must be responsible for the inactivation by cyanide, phenylhydrazine and borohydride[54]. The effects of these reagents indicated the presence of a carbonyl group. This group was identified by the isolation of radioactive lactic acid after treatment of the enzyme with tritiated borohydride and acid hydrolysis. Evidence that the pyruvoyl residue blocked the N-terminus was the isolation of the phenylhydrazone of pyruvoylphenylalanine from an enzymatic digest of the enzyme that had been treated with phenylhydrazine[54].

The origin of the pyruvoyl residue involves a modification of a polypeptide by a mechanism that is not yet understood. Mutants of lactobacilli were isolated on the basis of defective production of histidine decarboxylase and were found to produce an immunologically cross-reacting material, which gradually was converted to active enzyme[55]. The proenzyme was isolated as a polypeptide of molecular weight about 35,000. During incubation at pH 7 the proenzyme is activated and is split into two chains: α, consisting of 81 residues with serine at both N- and C- termini, and β, consisting of 224 amino acids with an N-terminal pyruvoyl group. The proenzyme contains serine residues at positions 81 and 82. Studies with ^{18}O showed that the cleavage of the proenzyme is not hydrolytic. Cleavage in $H_2{}^{18}O$ does not introduce the oxygen isotope into the carboxyl group of serine 81. However, biosynthesis of the proenzyme by bacteria given serine with ^{18}O in the β-hydroxyl group resulted in incorporation of ^{18}O into the carboxyl groups of the C-terminus of the α-chain[56]. These observations show that the cleavage is an elimination, presumably following an $N \rightarrow O$ acyl shift. Since activation occurs with pure proenzyme but only when it is in a native conformation, and since the rate of activation is first order, the elimination appears to be autocatalytic[57]. The structure of the residue at position 82 is presumably converted first to dehydroalanine, which hydrolyzes spontaneously to a pyruvoyl residue.

Pyruvoyl residues have been found in histidine decarboxylases of several unrelated species of bacteria, all of which are composed of two dissimilar subunits, consistent with formation of active enzyme by elimination from a serine residue. The primary sequences of these enzymes are not necessarily similar; antibodies raised against the enzyme from a lactobacillus do react with the enzyme from a micrococcus but not with the histidine decarboxylase from a clostridium[58]. Mammalian histidine decarboxylases, on the other hand, do not contain pyruvoyl residues but require pyridoxal phosphate[59].

There are a few other amino acid decarboxylases that do not use pyridoxal phosphate and also yield labeled lactic acid from hydrolysates of enzyme treated with tritiated borohydride. These include *S*-adenosylmethionine decarboxylase from bacteria, yeast and mammals (EC 4.1.1.50)[60–62], phosphatidylserine decarboxylase (EC 4.1.1.65)[63], aspartate



Proposed mechanism of formation of pyruvoyl residues in proteins

α-decarboxylase[64], and 4′-phosphopantothenoylcysteine decarboxylase (EC 4.1.1.36)[65], all from *E. coli*. These enzymes are components of biologically essential pathways. Although *S*-adenosylmethionine is best known as the major donor of methyl groups, it is also the precursor of the propylamino groups of the polyamines, spermine and spermidine, which play an unidentified but critical function in cell division. Phosphatidylserine decarboxylase is important as the only agent known to carry out a *de novo* synthesis of ethanolamine, an essential component of membrane lipids. The removal of the α-carboxyl group of aspartate is the mechanism for making the β-alanine that is incorporated into pantothenic acid, a vitamin for mammals that is a component of coenzyme A, and the cysteamine group of this coenzyme is formed by decarboxylation of 4′-phosphopantothenoyl cysteine. The pyruvate is alkali-labile, suggesting an ester linkage[55].

Among the reactions peculiar to anaerobic bacteria, the reduction of proline to δ-aminovalerate is catalyzed by a pyruvoyl enzyme (EC 1.4.1.6). Presumably a Schiff base of D-proline and interaction with the dithiol reducing agent required by the enzyme are involved in a concerted ring opening and reduction[66]. Proline reductase is unusual in another respect also. Very mild treatments cleave the enzyme into two peptides, a small peptide with N-terminal pyruvate and C-terminal serine and a large fragment with N-terminal glutamic acid. Several bits of evidence support the conclusion that native enzyme is an undissociable peptide containing an ester linkage between the γ-carboxyl of the glutamic acid and the C-terminal serine[67].

C. Dehydroalanine in Enzymes

A few enzymes attack specific amino acids to eliminate the α-amino group and a hydrogen atom in *trans* configuration to produce an unsaturated product. Two of the enzymes, histidine ammonia lyase, also known as histidase (EC 4.3.1.3)[68], and phenylalanine ammonia lyase (EC 4.3.1.5)[69], are inhibited by carbonyl reagents and borohydride but do not contain pyridoxal phosphate or pyruvoyl residues. When these enzymes were reduced with tritiated borohydride, the inactive proteins were found to have incorporated only about one mole of tritium per mole and part of this tritium was lost during acid hydrolysis. The only radioactive compound identified in the hydrolyzate was alanine. It was suggested that the alanine was formed from a dehydroalanine residue in the native enzyme. A similar conclusion was reached from studies in which nitromethane was incorporated in histidase[70]. Two equivalents of the reagent were incorporated per mole of protein and were converted to similar amounts of three products by catalytic reduction and acid hydrolysis. These were identified as 2,4-diaminobutyrate, 4-amino-2-hydroxybutyrate and β-alanine. To explain these findings it is necessary to assume that the dehydroalanine residue is located in an unusual environment, which is necessary to activate it for abstracting the amino group from the substrate. It should be noted that the kinetic mechanism of histidase indicates that the organic product, urocanate, dissociates from the enzyme before the ammonia is released[71]. It should also be noted that the enzyme appears to be a tetramer[72] but complete inactivation occurs with only one or two residues modified. Thus, it is not clear whether only some of the subunits contain dehydroalanine or whether the peculiar environment of the reaction center is composed of elements from several subunits so that modification of one or two active sites alters the conformation of the entire tetramer.

D. Overview of Reactions of Amino Acids

The amino acids are logically considered as closely related metabolites because of their mutual dependence in protein synthesis, which proceeds only in the presence of all twenty of the primary components and because of similarities in their metabolic processes.

However, each amino acid serves one or more unique metabolic function(s). The pervasive role of pyridoxal phosphate can be seen from this perspective as a versatile reagent that can facilitate the great variety of reactions of the individual amino acids and emphasizes the fundamental importance of the Schiff base formation in subsequent reactions. The attributes of pyridoxal phosphate in shifting electrons should not be exaggerated, however, in view of the existence of pyruvoyl enzymes that catalyze similar or identical reactions. The precise structure of dehydroalanine enzymes and the way in which the double bond reacts with amino groups remains a tantalizing mystery.

III. METABOLISM OF ARACHIDONIC ACID AND RELATED POLYUNSATURATED ACIDS

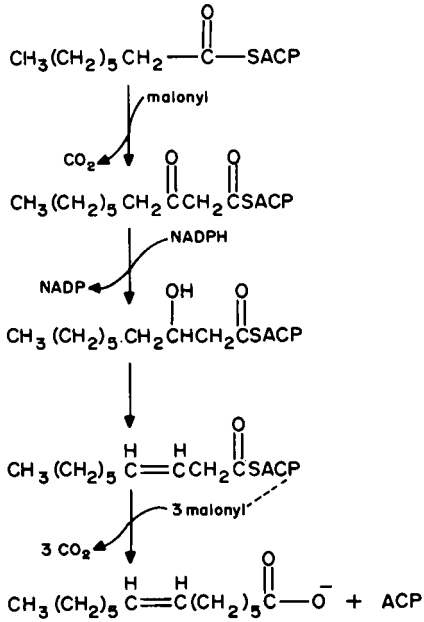
The need for polyunsaturated fatty acids in the diet was established many decades ago, but only in recent years has the role of 'essential' fatty acids been established. The identification of prostaglandins[73] initiated a still expanding field of investigation concerned with the metabolism of arachidonic acid and similar compounds that give rise to many products: prostaglandins, prostacyclins, thromboxanes and leukotrienes, all compounds with important physiological functions. This field is reviewed frequently in articles and monographs and is reported in specialized journals in addition to general journals of biochemistry, physiology pharmacology and others. A few examples have been abstracted from this large literature to describe the roles of double bonds.

From the point of view of double bonds, each step in arachidonic acid metabolism illustrates how compounds are recognized biologically by the specific locations of unsaturations and how specific bonds are selected for modification. Very little is known about how the receptors discriminate among similar metabolites or how they transmit signals to induce physiological responses. Thus, the following paragraphs do not presume to explain chemical mechanisms but are intended to indicate the many types of problems that have been raised by rapid developments in identification of prostanoids and their numerous biological effects.

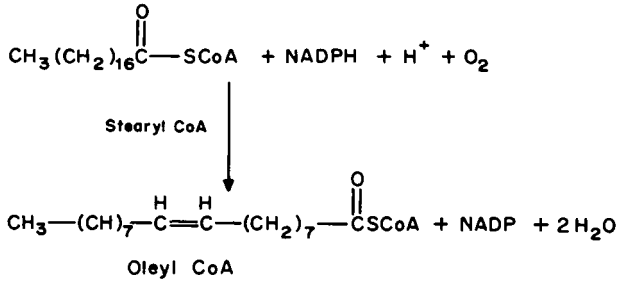
A. Synthesis of Unsaturated Fatty Acids

The introduction of double bonds into fatty acids occurs by a variety of mechanisms in bacteria, plants and animals. One mechanism diverts an intermediate in the synthesis of saturated fatty acids, in which the growing chain is condensed with a 2-carbon fragment of a malonyl residue while both are bound to a small protein, the acyl carrier protein (ACP), as thioesters. An anaerobic mechanism in some bacteria dehydrates some intermediate chain length β-hydroxy fatty acyl–ACP thioesters to the corresponding β,γ-unsaturated compounds instead of the α,β-unsaturated compounds that are the usual intermediates in the biosynthesis of saturated fatty acids[74]. Continued chain elongation results in the location of the double bound in the middle of the chain, for example, in the 9,10-position characteristic of oleic acid and other mono-unsaturated acids that occur prominently in membrane lipids to regulate physical properties such as fluidity.

The major production of unsaturated fatty acids in plants and animals is initiated by a complex enzyme that requires molecular oxygen and NADPH and forms a *cis*-double bond at carbons 9–10 in fatty acyl CoA thioesters[75]. In animals, a similar mechanisms can introduce additional double bonds between the ester carbon and the first double bond and the chain can be elongated by adding two carbon units (from malonyl CoA) to the unsaturated thioester to produce chain lengths up to 24 carbon atoms with one, two or three double bonds[76]. However, the most distal double bond is always at least seven carbon atoms from the terminal methyl group (ω-7). The essential fatty acids are based on

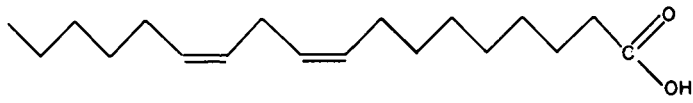


Anaerobic synthesis of an unsaturated fatty acid

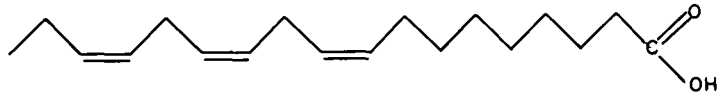


Aerobic introduction of a double bond

linoleic acid, which is synthesized in plants from oleic acid (C18-Δ9) by the introduction of a second double bond, 12, which involves C13, the sixth carbon atom from the methyl carbon (ω-6). Plants also introduce a third double bond 15 to form linolenic acid. This is the parent compound of the ω-3 fatty acids that have recently been credited with beneficial effects in human cardiovascular disease but whose biochemical functions have not yet been elucidated.

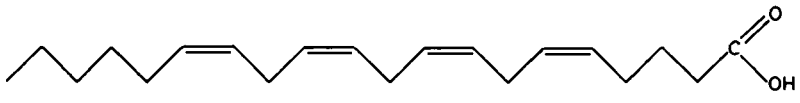


Linoleic acid



α - Linolenic acid

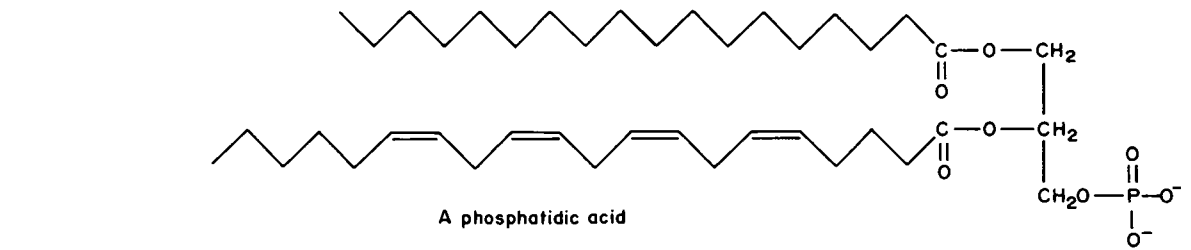
γ - Linolenic acid



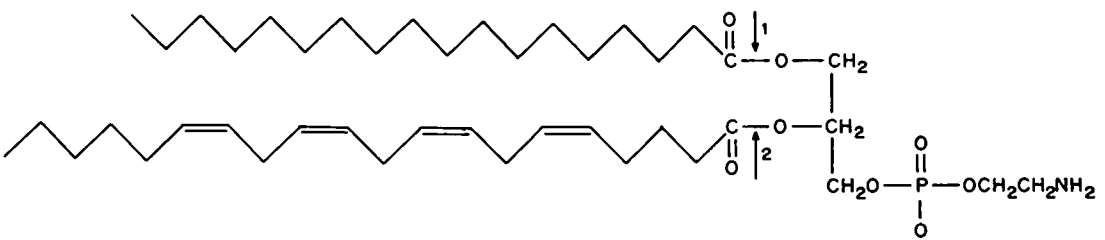
Arachidonic acid

B. Storage of Polyunsaturated Fatty Acids

All known enzymatic modification of the fatty acid chains occur when the acids are esterified to the thiol of CoA or acyl carrier protein (ACP). The CoA thioesters are substrates for the enzymes that transfer the fatty acid to the hydroxyl groups of α-glycerolphosphate in two steps, to form the monoacyl glycerolphosphate by esterifying the free primary alcohol, then adding a second acyl group from a phosphatidic acid. The synthetic enzymes are not highly specific, but they do show preferences for placing saturated fatty acyl residues in the 1 position and unsaturated residues in position 2 of the glycerol. Exchange reactions with similar preference tend to concentrate unsaturated fatty acids in position 2, so that most of the arachidonic acid and other polyunsaturated fatty acids are found in this position of phospholipids[78]. The phosphatidic acid is the precursor of all phospholipids, which are formed by transfer of the hydroxyl group of choline or serine from the ester with cytidine diphosphate. Most of the phosphatidyl serine is converted by decarboxylation or exchange to phosphatidyl ethanolamine[79]. These phospholipids are found in the outer membranes of almost all mammalian cells.



A phosphatidic acid



A phospholipid
(phosphatidyl ethanolamine)

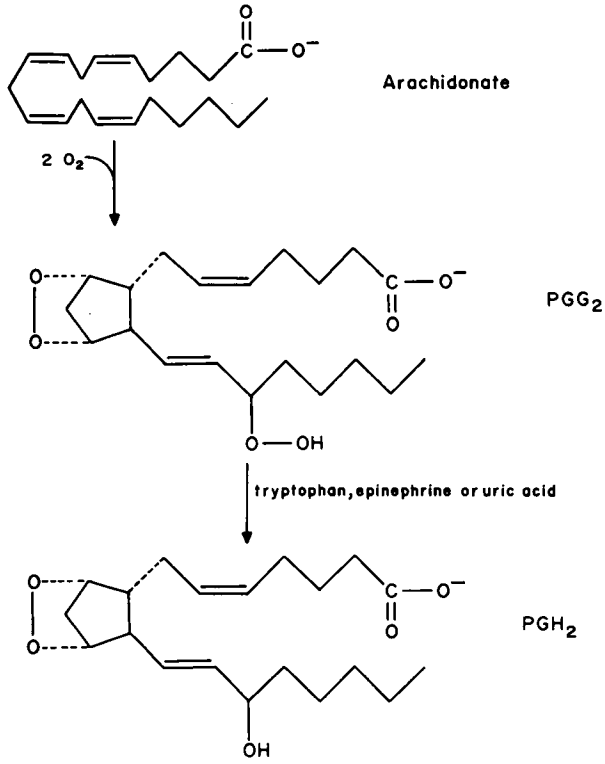
arrow 1 indicates the attack of phospholipase A_1
arrow 2 indicates the attack of phospholipase A_2

C. Release of Polyunsaturated Fatty Acids

Synthesis of prostanoids is initiated by stimulation of the release of the free polyunsaturated fatty acids by any of a large variety of stimuli, which activate hydrolytic enzymes. These enzymes, phospholipases, are also associated with cell membranes so that they have been difficult to characterize. Two types of phospholipase activity have been solubilized and identified as phospholipase A_1, specific for the (mainly) saturated residue, esterified carbon-2 of glycerol, and phospholipase A_2, specific for residues at carbon-2. Phospholipase A_2 is thus responsible for release of arachidonic acid but is not specific for the fatty acid[80]. Another mechanism has been found in platelets that include hydrolysis of phosphatidylinositol to phosphatidic acid, from which a calcium-activated hydrolase release arachidonic acid[81].

D. Oxidation of Polyunsaturated Fatty Acids

Two major pathways produce the two series of biologically active derivatives of arachidonic acid. One series is initiated by the complex reaction of an enzyme, cyclooxygenase. The other series starts with the reaction of fatty acid lipoxygenase. These two kinds of enzymes both add molecular oxygen to arachidonic acid, but the cyclooxygenase adds atoms of oxygen to carbons 9, 11 and 15 while carbons 8 and 12 react to form a cyclopentane ring, whereas lipoxygenases initially produce a hydroperoxide at carbons 5, 12 or 15 by the addition of a single molecule of oxygen.



Reactions of cyclooxygenase

1. Formation of prostaglandins

The discovery of prostaglandins did not follow a systematic pathway and, consequently, the nomenclature is nonevocative. To simplify the description of the chemical changes that occur during the metabolism of these compounds, only derivatives of arachidonic acid will be presented.

The first product of the cycloxygenase reaction contains as five-membered carbon ring with a dioxygen bridge. Compounds with this ring system have been named prostaglandins of the G series, or PGG. Since two of the four double bonds of arachidonic acid were lost during ring formation and oxygenation, only two remain in the side-chains and these are indicated by subscript 2. The corresponding PGG derived from linolenic acid has only one double bond in the side-chains and is designated PGG_1, and product from eicosapentaenoic acid is correspondingly PGG_3.

The cyclooxygenase has been purified and shown to be a dimer of subunits of about 70,000 MW[82]. It is a complex enzyme with complex functions that are not fully understood, as indicated by its classification EC 1.19.99.1 among 'miscellaneous (requires further characterization)'. The reaction with molecular oxygen obviously is a function of the heme, which is required and which dissociates easily. One molecule of oxygen is used to form the bridge[83]. This was shown by the use of a mixture of ^{16}O:^{16}O and ^{18}O:^{18}O containing very little ^{16}O:^{18}O. Mass spectrometric analysis of the products showed that both atoms of oxygen in each molecule were either ^{16}O or ^{18}O. At the same time that the endoperoxide is formed between carbons 8 and 12, a second molecule of oxygen is added to carbon 15 to form a hydroperoxide. In the presence of any of a heterogeneous group of compounds, including tryptophan, epinephrine and uric acid, a second catalytic property of the cyclooxygenase is activated. This peroxidase activity converts the 15 peroxy group to a hydroxyl group, forming PGH_2[82]. The cyclooxygenase is inactivated during each of its catalytic actions, apparently by a side-reaction of radical intermediates.

2. Prostaglandin isomerases

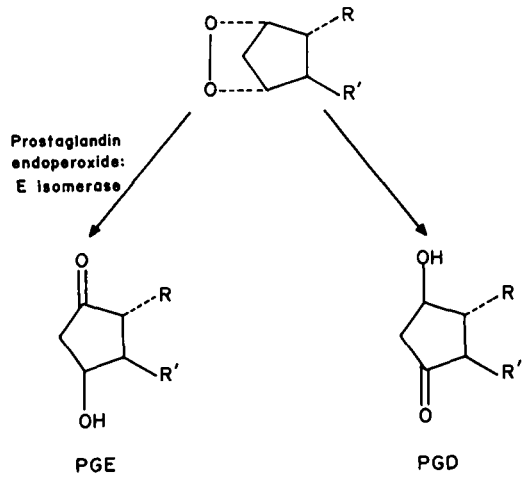
The endoperoxides of PGG and PGH are unstable at physiological pH values. Most of the material is converted to the 9-keto-11-hydroxy derivative, which had been isolated as the naturally occurring prostanoid designated PGE. The distribution of electrons that gives the isomeric 9-hydroxy-11-keto derivative also occurs to form another compound designated PGD. However, the syntheses of these potent physiological agents do not depend upon spontaneous reactions.

An enzyme partially purified from microsomes catalyzes the formation of PGE from PGH in the presence of glutathione[84]. The glutathione cannot be replaced by any other sulfhydryl compound or reducing agent and is not used stoichiometrically during the reaction. The enzyme (EC 5.3.99.3) has been named prostaglandin endoperoxide: E isomerase. Immunochemical evidence indicates that at least three different proteins in sheep spleen have prostagandin E isomerase activity dependent upon glutathione[85].

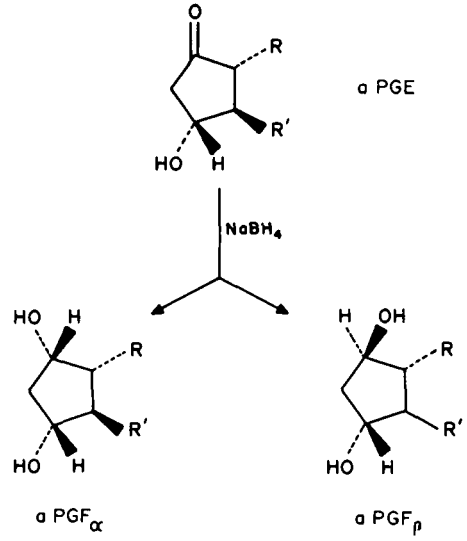
Distinct enzymes isomerize PGH to PGD (EC 5.3.99.2). An enzyme partially characterized from rat spleen also requires glutathione and has the activity of glutathione S-transferase. Another enzyme from rat brain produces PGD in the absence of glutathione and has no transferase activity[86].

3. Reduced prostaglandins

Reduction of the carbonyl group of any PGE with borohydride produces two isomers of the corresponding dihydroxy prostanoid, designated PGF_α and PGF_β, respectively. The α-isomers are identical with naturally occurring prostaglandins, e.g., $PGF_{1\alpha}$. Paper



Prostaglandin isomerization reactions

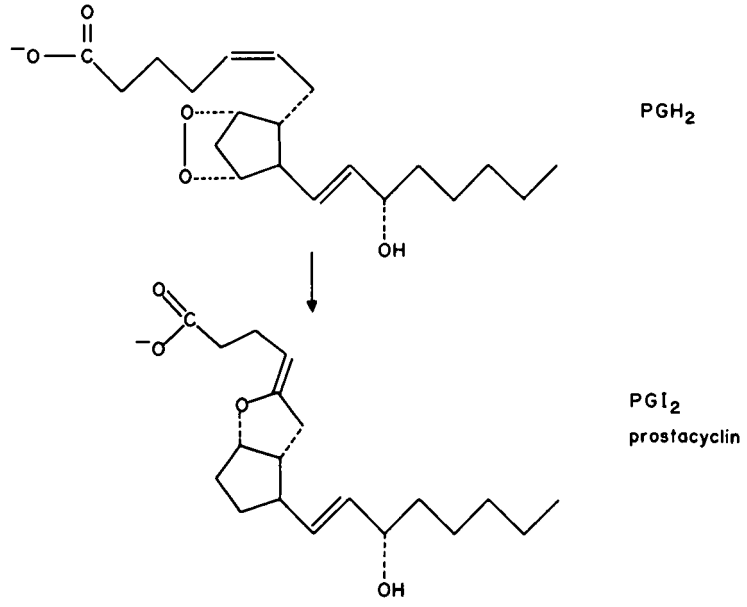


Reduction of PGE

chemistry and experiments with crude systems suggested that an enzyme (with unidentified properties) might reduce PGD to PGF, albeit sterospecifically. However, an enzyme purified from rabbit lung[87] has rather broad specificity for ketones and attacks PGH_2 with NADPH as the preferred reductant to yield PGF_2 without going through PGD_2 as an intermediate. The same enzyme is capable, however, of reducing PGD_2 to PGF_2.

4. Prostacyclin synthesis

A reaction observed with several cell and tissue preparations, especially with cardiovascular material, produces a bicyclic compound from arachidonic acid, PGG_2 or PGH_2[88]. These observations suggest that the initial reactions of prostaglandin synthesis produce PGH_2 and that this is the substrate for a reaction in which the peroxide oxygen at carbon 9 is given a positive charge that enables it to react with carbon 6 of the 5–6 double bond. The bicyclic compound is called prostacyclin or PGI_2.



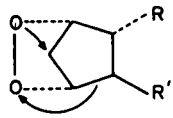
Reaction of prostacyclin synthase

An enzyme purified from bovine aorta converts PGH_2 to PGI_2[89]. The purified enzyme is a 52,000 MW protein that contains a heme group. It has been suggested that this prostacyclin synthase may be a cytochrome P 450[90].

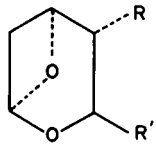
5. Thromboxanes

An outstanding accomplishment of modern bichemistry was the discovery and identification of a factor derived from arachidonic acid that causes aggregation of platelets but has a half-life of only half a minute[91]. The lability of the material, named thromboxane A_2 (TXA_2), has precluded direct measurements of its biological occurrence; instead, the relatively biologically inactive product of spontaneous breakdown, thromboxane B (TXB), is measured. This analysis has shown that thromboxane A_2 is produced in many organs, where it is a powerful constrictor of blood vessels and, in the lung, where it also constricts bronchioles.

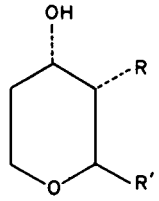
The synthesis of thromboxane is similar to that of prostacylin in that it is made by a rearrangement of PGH. An enzyme purified from human platelets has been shown to have spectral characteristics of a cytochrome P 450[92]. The reaction is unusual in that the groups



PGH

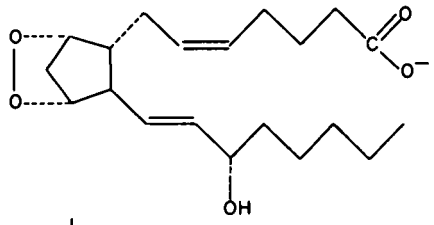


Thromboxane A

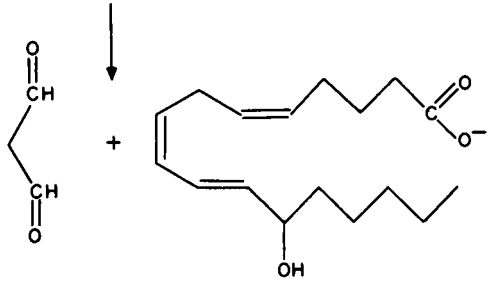


Thromboxane B

Synthesis of thromboxanes



PGH_2



Malonic dialdehyde 12-Hydroxyheptadecatrienoate

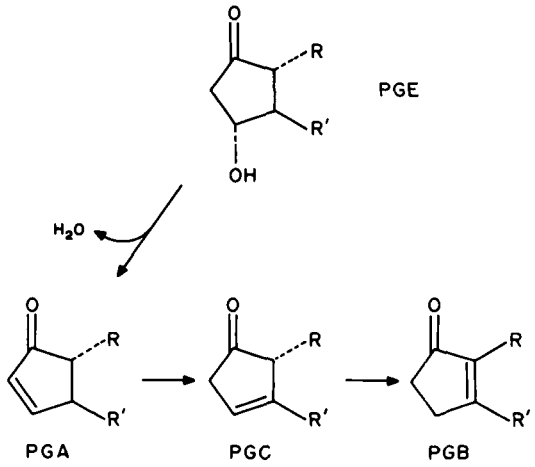
Side-reaction of thromboxane synthase

oxidized and reduced are parts of the same molecule and that the iron in the prosthetic group appears to be always ferric. A reaction mechanism may involve attack by the oxygen atom attached to carbon 11 on carbon 12 to form a tetrahydropyran ring, while the oxygen on carbon 9 forms a four-membered ring by reacting with carbon 11. This strained ring reacts with H_2O to yield a dihydroxytetrahydropyran, TXB_2.

The simultaneous production of products that are not C-20 compounds by thromboxane synthase provides evidence that the enzyme uses a radical mechanism[93]. The enzyme was purified as the catalyst that produces the physiologically important TXA_2, but a similar amount of the substrate PGH_2 is cleaved to form malonic dialdehyde from carbons 9, 10 and 11 by elimination from carbons 8 and 12, leaving the larger part of the molecule as 12-hydroxyheptadecatrienoic acid.

6. *Prostaglandins A, B and C*

Although prostaglandin A was indentified early as one of the prostanoids with biological activity, amazingly little interest has been shown in this compound or its isomers, PGB and PGC. An enzyme has been partially purified from cat blood serum as the catalyst for dehydrating PGE to PGA[94]. Subsequent isomerization shifts the double bond from 10, 11 to 11, 12 (PGC_1), then to 8, 12 (PGB_1). The isomerization of PGC to PGB can be accounted for by nonspecific effects of sulfhydryl groups in major serum proteins, especially serum albumin[95].



Dehydration of PGE and subsequent isomerization

7. *Further metabolism and physiology of prostanoids*

The reactions described in this section dealing with the formation of prostanoids were selected to illustrate the ways in which specific compounds are synthesized by enzymes that recognize patterns of double bonds and in many cases catalyze reactions in which double bonds participate. Each of the prostanoids described produces physiological effects on various organs, and mechanisms exist for rapid inactivation so that the physiological processes can be regulated. The inactivation reactions do not seem to be very specific. Oxidation of the hydroxyl groups (e.g. 15-OH) to the corresponding ketone is a prominent reaction. Another nonspecific reaction is ω-oxidation. To some extent the

mitochondrial enzymes of fatty acid oxidation shorten the side-chains of prostanoids. These and other reactions result in the production of many metabolites that are excreted.

From a chemical point of view it is premature to examine the mechanism of action of prostanoids. At this time specific receptors are being found for most of these compounds on the membranes of various cells. In some cases the binding of the prostanoid causes a change in the intracellular concentration of the 'second messenger' cAMP (the 3', 5'-cyclic phosphodiester of adenosine, *c*yclic *a*denosine *m*ono*p*hosphate) that is produced in response to the binding of several hormones (e.g., epinephrine, glucagon, ACTH); in some cases the prostanoid appears to alter ion flux across the cell membrane. However, until the specific receptors are better characterized, it is not possible to define the chemical basis for specific recognition or the ways in which specific molecules induce physiological responses.

8. *Leukotrienes*

The *bio* in biochemistry is emphasized by the discovery and characterization of the leukotrienes. These compounds play regulatory roles in specialized biological processes, including constriction of bronchioles (responsible for major problems in asthma), contraction of other smooth muscles and aggregation of polymorphonuclear neutrophils and other phenomena in inflammation. Since many other physiological materials also influence each of these processes, complex pharmacological systems were required to separate effects of the unknown leukotrienes from those of histamine and other agents.

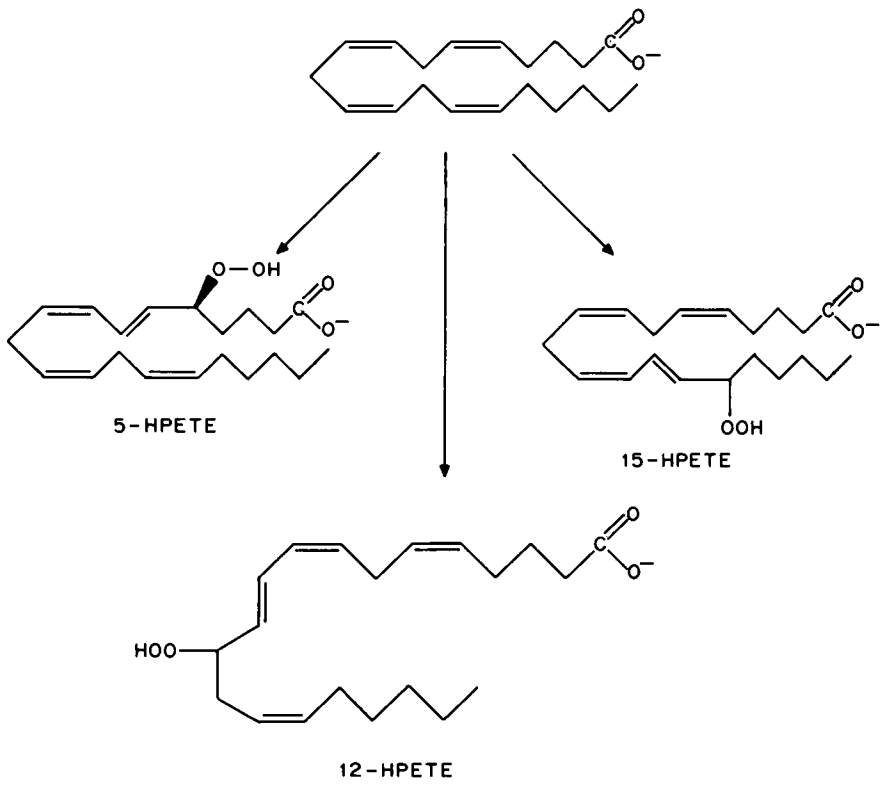
After the identification of a new type of biological effector was established, the elucidation of the structures of members of this group of substances depended greatly upon biochemical techniques, such as labeling suspected precursors and demonstrating incorporation of ^{3}H, ^{35}S and ^{14}C from various known molecules into the biologically active compounds. To obtain sufficient material for structural analysis required the use of isolated cell types and purified enzymes.

The leukotrienes are a family of compounds with related structures derived from polyunsaturated 20-carbon atom fatty acids. These derivatives have specific biological effects that will not be described here. One basis for the differences is that the starting material can be trienoic, tetraenoic (arachidonic acid) or pentaenoic. At this time the action of the initial enzymes, the lipoxygenases, appears to be the same for all members of the group, so the following discussion will deal only with arachidonic acid to illustrate the kinds of transformations that occur during the metabolism of all leukotrienes.

a. Lipoxygenases. It has long been common knowledge that unsaturated fatty acids undergo autooxidation to form peroxides which ultimately form the aldehydes that give the characteristic odors of rancidity. The discovery of enzymes in plants that carry out the formation of peroxides of the polyunsaturated fatty acids was difficult to fit into a rational scheme of biochemistry for many years, even after an enzyme was purified and crystallized from soybeans[96]. Only after the chemistry of leukotrienes was revealed were these enzymes related to a meaningful pathway.

Two types of lipoxygenase have been described in plants, one from soybean that at high pH values produces almost exclusively ω-6 products, such as 15-hydroperoxyeicosatetraenoic acid from arachidonic acid[97], and one from potato that attacks the double bond nearest the carboxyl group[98]. In preparations of mammalian cells, arachidonic acid has been shown to give rise to monooxygenated products at positions 5, 8, 9, 11, 12 and 15[99]. However, only two enzymes have been well purified and partially characterized. These are two homologous proteins that form hydroperoxides at positions 5[100] and 15[101], respectively. The 5-lipoxygenase purified from human leukocytes requires a membrane-associated stimulatory factor in addition to Ca^{2+} and ATP[102]. The gene for this enzyme

has been cloned and sequenced[103]. An arachidonate 12-lipoxygenase has been purified from porcine leukocytes[104].



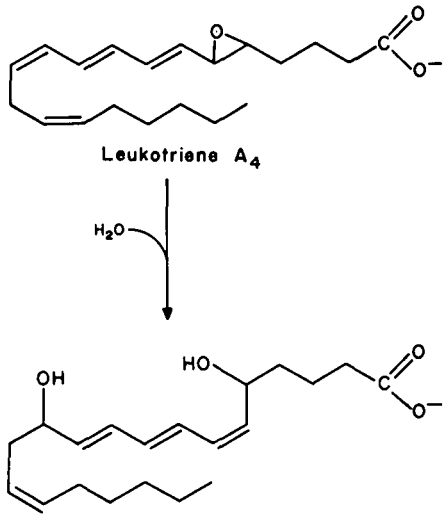
Primary products of lipoxygenases: hydroperoxyeicosatetraenoates

Although the first purified plant lipoxygenase was shown to contain ferric iron[96], other lipoxygenases from both plant and animal sources do not uniformly require iron[105]. The enzyme 5-lipoxygenase activated by Ca^{++} and all enzymes of this group seem to contain essential sulfhydryl groups.

b. Reactions of peroxy-unsaturated fatty acids. Hydroperoxy derivatives of polyunsaturated fatty acids can be reduced to the corresponding hydroxy derivatives by peroxidases. These may be precursors of polyhydroxy derivatives that have biological activity. These will not be described here. The reaction of greatest interest at this time is the conversion of 5-hydroperoxy tetraenoic acid (5-HPETE) to the 5, 6 epoxide. The discovery of this labile compound[106], the deduction of its structure from analyses of products and finally proof by synthesis comprised a monumental work by Samuelsson and his associates. In the formation of the epoxide, the double bonds shifts to form a conjugated series, 7, 8; 9, 10; and 11, 12. This contributed the *triene* part of the generic name for the family of compounds derived from this intermediate. The *leuko* refers to the leukocytes that were

used to catalyze the syntheses. As the parent compound, the epoxide is designated A and the specific compound formed from arachidonic acid is leukotriene A_4 (LTA_4).

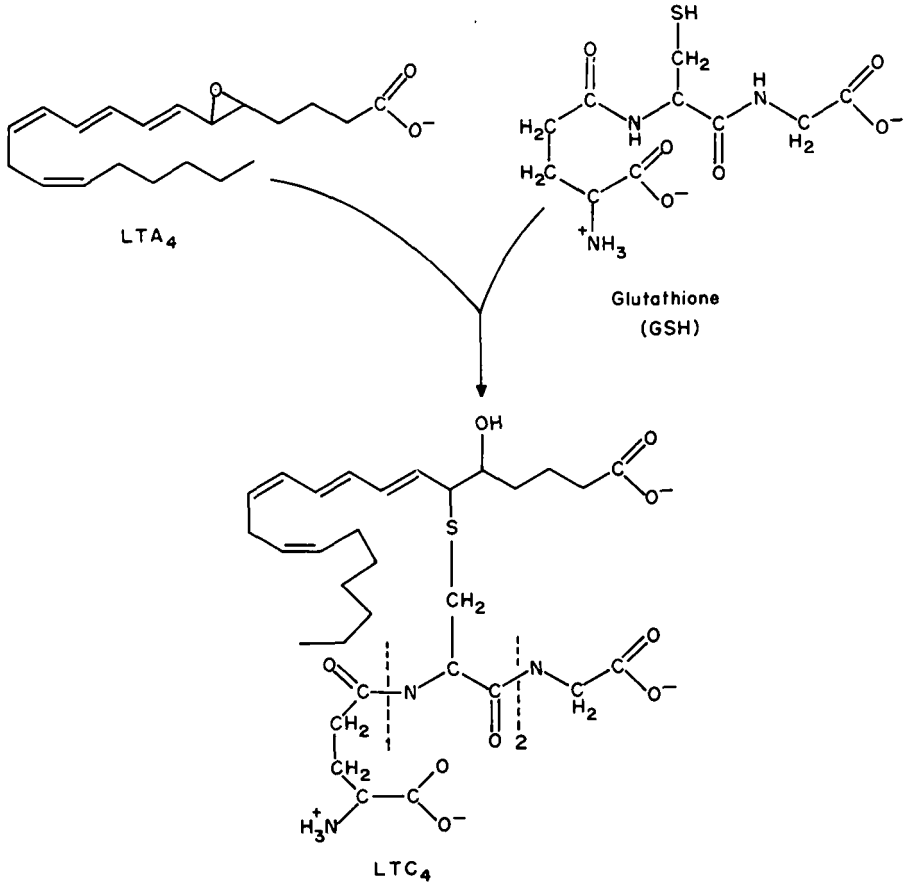
It is not clear whether any biological activity is associated with LTA_4 because in all biological systems it is rapidly changed. The major product of LTA_4 metabolism is the 5,12-dihydroxy derivative, LTB. Enzymes in many tissues carry out this hydrolysis. An enzyme purified from human leukocytes has a molecular weight of about 70,000[107], similar to an enzyme from human lung[108]. A smaller enzyme (MW 54 000) with other differences was purified from erythrocytes[109]. These enzymes add a hydroxyl group from water to carbon 12 while opening the expoxide to the 5-hydroxy compound. All of these enzymes are inactivated by their substrates by an unknown mechanism. Since the product LTB_4 is a potent agent in inflammation, a teleological reason for the inactivation is that it is preferable for the enzyme to commit suicide than for the organism to suffer excessive inflammatory response. Inactivation of LTB (by cytochrome P-450 monooxygenases) also serves to limit inflammatory reactions.



c. Leukotrienes C, D and E: thioethers of cysteine. Early studies on the slow reacting substances of anaphylaxis showed that they differed from other known derivatives of arachidonic acid, in that they contained amino acids in addition to fatty acid derivatives. The identification of the sulfur-containing amino acid, cysteine, and less consistently glutamic acid and glycine as constituents of active material led quickly to the implication of glutathione as a precursor[110].

A group of enzymes has been well characterized as the agents that metabolize a variety of foreign compounds by forming thioethers with glutathione. These are called glutathione S-transferases and are found widely distributed among many animal cells. Leukotriene A_4 is a substrate for addition of glutathione but the reaction has been observed only with cells associated with blood: monocytes, macrophages, polymorphonuclear leukocytes and leukemia cells. The most comprehensively studied cells are rat basophilic leukemia cells.

Cell-free extracts of rat basophilic leukemia cells condense glutathione with leukotriene A_4[111]. In this reaction the 5,6-epoxide opens to form a 5-hydroxy compound as the sulfur of the glutathione adds to carbon 6. The adduct is called leukotriene C_4 (LTC_4).



Hydrolysis at 1 yields LTD_4; subsequent hydrolysis at 2 yields LTE_4

When the extracts were fractionated, the LTC_4 synthetase was found entirely in a membrane fraction whereas other glutathione S-transferases were found in both the membrane and soluble fractions. When the membrane-bound activities were solubilized with detergents and fractionated, the LTC_4 synthetase was completely separated from other transferase activities so that it is concluded that a specific transferase that recognizes LTA is responsible for the addition of amino acids through the formation of a thioether[112].

In addition to LTC_4, two other amino acid-containing lipids are known to have biological activity on smooth muscle. These compounds, LTD_4 and LTE_4, are derived from LTC_4 by cleavage of the peptide bonds of glutathione in two steps. An enzyme of the 'glutathione cycle', a mechanism for transport of amino acids into cells, is γ-glutamyl transferase, which transfers the γ-carboxyl group of the tripeptide to the amino group of another amino acid[113]. This enzyme carries out the same reaction with the glutathione–leukotriene thioether to leave only cysteinylglycine attached to the lipid; this is LTD_4[114]. A nonspecific dipeptidase from kidney is capable of hydrolyzing the remaining peptide bond, releasing glycine and forming LTE_4[115].

Leukotrienes affect the functions of various cell types. The most specific and potent

effects of the aminoacylated leukotrienes (LTC_4, LTD_4 and LTE_4) are on the smooth muscle of bronchioles. Similar effects of constriction are also seen in arterioles. These compounds also cause increases in vascular permeability. Leukotriene B causes none of the physiological effects of the aminoacylated leukotrienes but instead has profound effects on leukocytes: adhesion of neutrophils to endothelial cells, chemotaxis of eosinophils and monocytes as well as of neutrophils, generation of superoxide in neutrophils and perhaps other effects[106]. However, nothing is known about the nature of receptors for these agents, transducing mechanisms or even possible metabolic conversions as part of their reaction mechanisms.

IV. VITAMIN A

A. Introduction

The vitamin activity and chemistry of vitamin A have been known for many decades. Since the discovery of a fat-soluble factor required for growth in 1913[116] much has been learned about the structure of the vitamin and its relationship to carotenes[117]. The carotenes and vitamin A are characterized by a large series of conjugated double bonds, whose function in biological systems cannot be explained at this time at a chemical level except for the light absorbing properties of the visual pigment.

Early studies that related the vitamin to a component of the visual pigment have been reviewed by Wald, who was the major contributor to that area[118]. More recently, the biosynthesis of the carotenes has been elucidated as a pathway very similar to that previously established for sterols and other polymers of isoprene[119]. However, despite the large amount learned about the chemistry of the vitamin and its role in vision, its essential function in animal metabolism remains obscure. Current interest is based on recent studies that have started to describe the physiology of absorption and transport, the metabolism of the carotenoids and vitamin A and some preliminary aspects of the way the vitamin and its metabolites, especially retinoic acid, affect cellular functions.

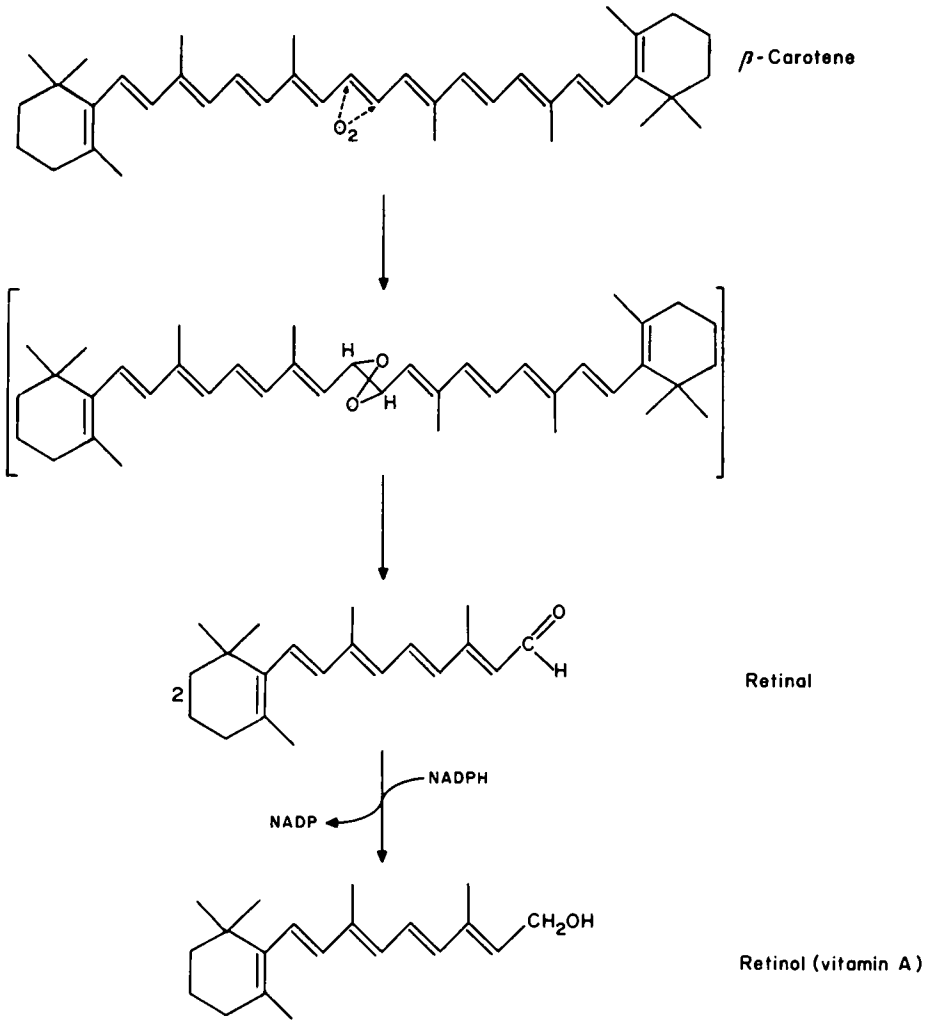
B. Synthesis of Vitamin A from Carotenes

Dietary vitamin A occurs only in foods of animal origin, but carotenes in plants serve as sources of the vitamin. An enzyme found in intestinal mucosa and liver of several animals cleaves β-carotene into two molecules of retinaldehyde with the incorporation of one atom from a molecule of oxygen into each of the products[120]. Although the enzyme has not been highly purified from any source, it so far has been found to react only with compounds containing a β-ionone ring, indicating a specificity for precursors of vitamin A[121].

The reduction of retinaldehyde to the vitamin, retinol, is catalyzed by a nonspecific alcohol dehydrogenase. An enzyme from rat mucosa is most active with aliphatic aldehydes with 4 to 8 carbon atoms and uses either NADH or NADPH as a reducing agent[121].

C. Transport of Vitamin A

There appears to be little specificity in the digestion or absorption of vitamin A and related compounds. In general, these compounds are handled like other lipids in that they are emulsified in the gut and incorporated in chylomicrons by the intestinal mucosa. In this form they are ultimately transferred to the liver, where they are stored mainly as retinyl esters of saturated fatty acids[122]. The liver contains enzymes that synthesize and hydrolyze retinyl esters. The novel element is a large amount of a protein that binds retinol, named cellular retinol-binding protein, CRBP[123]. This is one of a group of proteins that



Biosynthesis of vitamin A from β-carotene

apparently carry out specific functions in the transport and metabolic effects of retinol and its derivatives.

Retinol is released from the liver as needed to maintain a fairly constant concentration in the blood. As is true for all nonpolar materials that are transported in blood, the retinol is bound to a protein. Whereas the transport from the intestine to the liver involved nonspecific incorporation in chylomicrons, the vitamin A released by the liver is associated with a specific retinol-binding protein (RBP)[124].

RBP is a polypeptide chain of 180–185 amino acid residues as isolated from several vertebrate species[125]. No materials other than amino acids have been reported to be

incorporated in these proteins. Thus, the binding site for the one retinol that is tightly bound ($K_D = 1.9 \times 10^{-7}$) must be composed of amino acid residues. The binding is not very specific: retinoic acid shows essentially the same dissociation constant and many analogues of the vitamin are also bound. Especially interesting is that several isomers of retinol[126] and retinaldehyde[127] bind well to RBP, including 9-*cis*, 11-*cis* and 13-*cis* retinaldehyde, which indicates some flexibility of the binding site. On the other hand, the structure of the cyclohexene ring appears to be important in the binding[126].

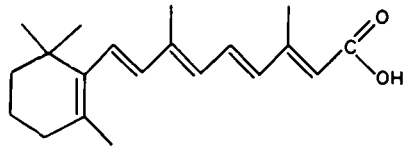
The transfer of retinol from RBP to peripheral cells has been studied primarily with pigment epithelial cells from the retina, which store retinol for use by rod cells as part of the visual pigment rhodopsin. The pigment epithelial cells bear receptors for RBP that enable the retinol or analogue to be transferred to the cell. Isolated membranes from these cells have been shown to convert bound retinol to retinyl esters, which are the forms stored in these cells[128].

The mobilization of retinol from its esters is catalyzed by a specific hydrolase[129] whose activity is controlled by the acceptor of the free retinol. This is the cellular retinol-binding protein (CRBP). CRBP is a small monomeric protein (MW 13,000–15,000 in various species) that differs from the serum RBP in showing great specificity for retinol[130]. *Cis* isomers of retinol are bound, although less tightly than the all-*trans* retinol. Also, α-retinol is bound. Modification of the alcohol, however, by esterification or oxidation to retinal or retinoic acid effectively eliminates binding to CRBP.

D. Biological Functions of Retinoids

1. Multiple functions of retinoids

Vitamin A is an essential component of rhodopsin and consequently is essential for vision. The chemistry of the visual cycle is fairly well established, as described below, although the physiological process by which neural transmission is initiated is less completely understood. However, this process, which requires retinol and cannot substitute retinoic acid, is clearly different from the role of the vitamin in supporting growth, in which retinol can be replaced entirely by retinoic acid.



Retinoic acid

2. The visual cycle

Photoreactive proteins that contain 11-*cis*-retinaldehyde occur in bacteria, invertebrates and vertebrates[118]. The following discussion will consider only the reactions that occur in the vertebrate retina. There the pigment rhodopsin occurs in rod cells. Rhodopsin is a protein of about 350 amino acid residues to which one retinaldehyde is bound to an ε-amino group as a Schiff base[131]. The protein is a transmembrane component of the membrane of the cell; seven peptide segments traverse the lipid membrane[132]. When rhodopsin is illuminated, the molecule undergoes a number of confirmational changes that terminate in the dissociation of all-*trans*-retinaldehyde from the protein[133].

Free all-*trans*-retinaldehyde is reduced to all-*trans*-retinol by a dehydrogenase specific

for NADPH[134]. Retinol is transported to adjacent cells, the retinal pigment epithelium. An enzyme in the membrane of the epithelial cells converts most of the retinol to esters of long-chain fatty acids[135]. The acyl donor has not been identified. A microsomal system that forms retinyl esters in rat intestinal mucosa apparently does not use acyl-CoA[136] and may be related to the system in the pigment epithelial cells. Enzymes in membranes of the epithelial cells are also known that hydrolyze retinyl esters[129]. The relationship between these processes is not clear, however the net result is that a large amount of retinol is stored as ester but some free all-*trans*-retinol is always present. This is the substrate for an isomerase, also found in the membrane of pigment epithelial cells, that forms the 11-*cis*-isomer[137,138]. The transport of 11-*cis*-retinol and oxidation to 11-*cis*-retinal are carried out *in vivo* but the mechanisms have not been elucidated.

The function of the visual cycle is to initiate a nerve impulse by causing changes in the ion channels in the cell membrane. The physiological changes are a catalytic function of the photoactivated rhodopsin acting through a GTP-binding protein, transducin[139]. Since the membrane phenomena have no direct connection with the unsaturated retinoids, they will not be described further.

The isomerization of the double bond at C-11 is clearly established as an integral component of the mechanism of action of rhodopsin and related photoreceptors. At this time there are questions that focus attention on the isomerization, including: What is the mechanism of selective isomerization of one of the four double bonds in the side-chain? How does isomerization relate to the conformational changes that affect protein–protein interaction? How are 11-*cis*- and all-*trans*-retinol distinguished in the synthesis of all-*trans*-retinaldehyde and how is this oxidation accomplished?

3. General effects of vitamin A

a. Stimulation of growth. The diversity of biological functions associated with vitamin A is illustrated by the methods developed for assay of the vitamin. The original assays measured the rate of growth of young animals[116]. In addition to extending this type of assay to various organisms, growth of cells in culture has also been measured (as an increase of nucleic acid content) in response to the addition of vitamin A[140]. A specific role for the vitamin, the metabolism of skin and other epithelial has been implicated since the early 1920s[141] and is assayed by inhibition of keratinization *in vivo*[142] or *in vitro*[143]. The keratinization of epithelial cells is an indication of differentiation. A deficiency of vitamin A causes an increase in keratinization of various organs and this process can be reversed *in vitro* by retinoids, showing that the effect is a direct one on the epithelial cells, not mediated through hormones, and that the effect is not a simple triggering of an irreversible process[144].

b. Inhibition of growth. The effects of retinoids on several transformed cell lines are very different from those on normal epithelial cells. Instead of stimulating growth, retinoids inhibit the proliferation of mouse melanoma cells[145]. In other systems, they induce differentiation in mouse teratoma cells[146] and human leukemia cells[147]. The transformation of normal mouse fibroblasts by methylcholanthrene is suppressed by retinoids[148].

An unanswered question is whether a single action of retinoids is expressed in a variety of ways in different cells or under different physiological circumstances, or whether there are different ways in which retinoids participate in stimulating or inhibiting metabolic processes.

c. Alteration of enzyme activity. The search for primary effects of retinoids has revealed changes in enzyme activities in treated cells that correlate with changes in cell division

or differentiation. Specifically, ornithine decarboxylase, known to increase as the earliest response to induction of cell division, was shown to decrease in cell cultures treated with high concentrations of retinoids[149]. Similarly, an enzyme activity associated with differentiation of keratin-producing cells, transglutaminase, increases after treatment with retinoids[150]. Although most studies of effects of retinoids involved long periods (days) of treatment of intact cells, recently an increase of transglutaminase in rat liver *in vivo* was demonstrated only hours after injection of retinoic acid and at least part of the increase represented synthesis of new protein, as indicated by prevention of the increase by actinomycin D. A rapid induction of transglutaminase has also been observed in mouse peritoneal macrophages, where the effect of retinoic acid is potentiated by cAMP[151].

d. Effects on specific genes and general properties of cells. Retinoic acid has been shown to influence several properties of cells in addition to alterations of specific enzyme activities. Treatment of human promyelocytes with retinoic acid, which induces differentiation to granulocytes, also causes an increase of intracellular pH of 0.3 units more rapidly than visible evidence of differentiation[152]. At the level of gene expression, retinoic acid treatment of mouse teratocarcinoma cells, which induces differentiation, causes a rapid decrease (50% in 3h) of the mRNA transcribed from the cellular oncogene c-*myc* and a slower large increase in the mRNA of another oncogene c-*erb*.[153] Vitamin A deficiency causes an increase in hepatocytes of 2–4-fold in the mRNA of fibronectin, a protein implicated in intercellular structure, and the administration of retinoic acid caused a reversion to control values after more than 12 h[154]. These changes in the mRNA were reflected in fibronectin secretion and the specificity of the retinoic acid effect was shown by the lack of response by control cells.

e. Oligosaccharide transfer. A different concept of vitamin A action is based on the similarity of its structure to that of dolichol, the very long chain polyprene that functions to transfer oligosaccharides in the synthesis of glycoproteins. Histological examination of tissues from vitamin A deficient animals showed a decrease in the fixed carbohydrate[155], which is visualized by periodic acid treatment followed by Schiff staining of the aldehyde groups. This observation was extended by measurement of incorporation of labeled mannose into a lipid component of membranes of rat liver; the rate of incorporation in membranes from vitamin A-deficient animals was increased by the addition of retinol and ATP[156].

Attempts to elucidate the mechanism by which vitamin A influences the formation of glycoproteins (and also glycolipids) have not yet permitted a definite model to be constructed. Early studies showed that retinol could be phosphorylated to form an analogue of dolichol phosphate and that retinol phosphate could be glycosylated[157]. However, studies with membranes from vitamin A-deficient rat liver showed that retinol-phosphatemannose cannot function as a mannose carrier[158]. Another complication is that retinoic acid, which cannot be reduced to retinol, is more efficient than retinol in supporting glycoprotein synthesis[159].

f. Direct action on DNA. The existence of intracellular binding proteins for retinol and retinoic acid has led to another hypothesis to explain their biological functions. It has been seen that these water-insoluble compounds can be metabolized and transferred in association with appropriate binding proteins, but it has been suggested that one or more binding proteins might act like the carriers of steroid hormones and bind to specific regions of chromosomes to regulate gene expression[160]. At this time there is no direct evidence to support or refute the hypothesis. The fact that a given gene is transcribed

in the presence of an inducer does not establish a mechanism, since there are many possibilities for indirect effects.

E. Practical Questions

Why is it important to determine the mechanism of retinoid action? The complex effects on diverse cell types strongly suggest that the major physiological function of the vitamin (excluding its role in vision) is regulatory. For several years analogues have been used with some success in the treatment of cancers[161]. Recently, 13-*cis*-retinoic acid (isotretinoin) has been extensively used as an effective treatment of adolescent acne but public concern has been raised about the serious malformations induced when the drug is given during pregnancy. The genetic disease xeroderma pigmentosum is the result of a defective DNA repair mechanism and is characterized by multiple cutaneous carcinomas. A current report[162] indicates that many of these can be prevented by 13-*cis*-retinoic acid. These practical applications are based on poorly understood empirical relationships that must be more completely analyzed before vitamin A metabolism can be regulated rationally to yield maximum benefit with minimum harm.

V. CONCLUDING THOUGHTS

Unsaturated compounds have been familiar elements of biochemistry for many decades but only a few, such as fumaric acid, have been understood as participants in meaningful reactions in which the double bond plays a role. Within the last several years the description of large numbers of reactions in the prostanoid and retinoid systems has raised many questions about the contribution of double bonds to recognition by enzymes and receptors, about the stereochemical relations of these compounds to protein conformation and about the mechanisms of reactions involving the double bonds. The success in analyzing the structure and reaction mechanisms of a transaminase offers encouragement for the eventual understanding of all biochemical reactions and serves as a model for the research that will eventually explain the functions of the many structures essential for life.

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The Chemistry of Double-bonded Functional Groups
Edited by S. Patai

CHAPTER 7

Intramolecular 1,3-dipolar cycloadditions to double bonds

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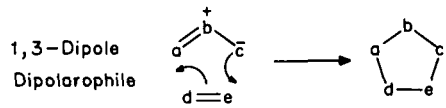
I. INTRODUCTION

Huisgen in the early 1960s fully recognized the general concept and scope of 1,3-dipolar cycloaddition reactions[1-3] and since that time 1,3-dipolar cycloadditions have become a most valuable method for the synthesis of a great variety of five-membered heterocycles. 1,3-Dipolar cycloadditions are generally bimolecular in nature and involve the addition of a 1,3-dipole to a multiple bond system (dipolarophile) (Scheme 1). It is generally accepted that 1,3-dipolar cycloadditions are single-step, four-centered, concerted reactions, in which the two new σ-bonds are formed simultaneously, although not necessarily at an equal rate[2-4]. A two-step reaction involving a spin-paired diradical intermediate has also been proposed[5].

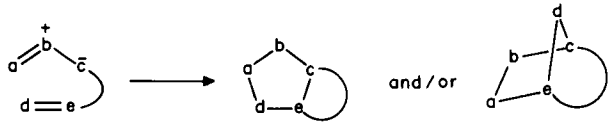


SCHEME 1

1,3-Dipolar cycloadditions are susceptible to electronic and steric influences which affect the nature of the transition state. The question of reactivity and substituent effects in 1,3-dipolar cycloaddition reactions has been rationalized successfully by the application of perturbation theory to determine the relative energies of the interacting frontier orbitals

of the dipole and dipolarophile[6,7]. Reactions have been classified[8] into three types depending on whether the dominant interaction is between the HOMO of the dipole and the LUMO of the dipolarophile, or the dipole LUMO and the dipolarophile HOMO, or whether both these interactions are of equal significance. The energies of both HOMOs are increased by the presence of electron-donating (including alkyl) and conjugating substituents and the energies of both LUMOs are decreased by electron-withdrawing and conjugating substituents[6,7]. This frontier orbital model also deals with the problem of regioselectivity of cycloaddition[8].

Because numerous possibilities for variation are available by changing the structure of both the dipole and dipolarophile, copious literature dealing with bimolecular 1,3-dipolar cycloadditions has appeared and no end is yet in sight[10,11]. Intramolecular versions and their uses in organic syntheses have developed quite rapidly in recent years[12] and represent a general scheme for the synthesis of novel fused and/or bridged heterocycles (Scheme 2). This useful synthetic idea was first investigated by LeBel and Whang in 1959[13].



SCHEME 2

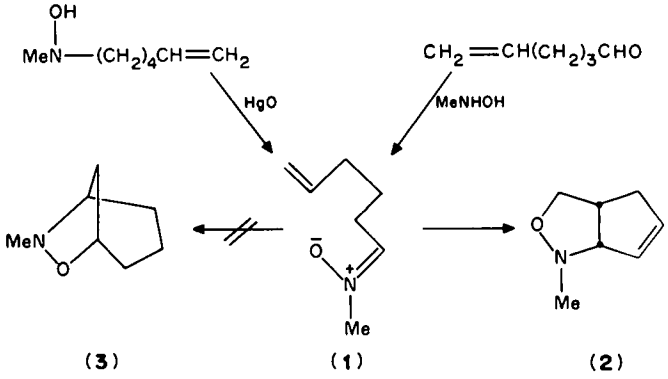
The aim of this chapter is to review the intramolecular 1,3-dipolar cycloaddition reactions covering the literature for the last approximately ten years.

II. NITRONES

A. C-Alkenylnitrones

Bimolecular 1,3-dipolar cycloadditions of nitrones have been reported involving a variety of dipolarophiles such as alkenes, alkynes, allenes, ketenes, isocyanates, isothiocyanates, phosphoranes and compounds having a carbon–sulfur double bond[10,14]. However, intramolecular cycloaddition variants do not seem to extend beyond cycloadditions to carbon–carbon double bonds.

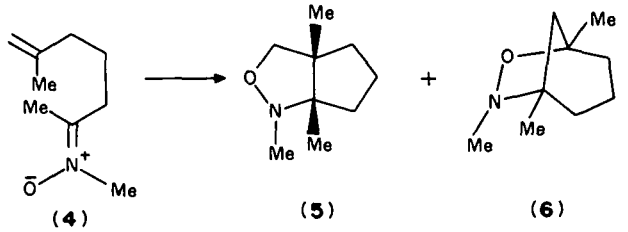
The pioneering investigations of intramolecular nitrone cycloadditions were carried out by LeBel and coworkers[13,15]. It was demonstrated that, under conditions of kinetic



SCHEME 3

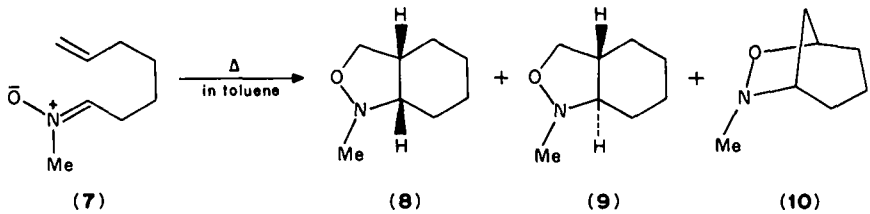
control, C-(pentenyl)nitrone **1** shows a pronounced tendency to form the fused-octyl adduct **2** rather than the bridged-octyl adduct **3** (Scheme 3), as shown also by the formation of fused-octyl systems such as **2** in the intramolecular cycloadditions of other nitrones bearing an alkenyl moiety separated by a propylene chain.

In the cyclization of nitrone **4** bearing methyl groups at both the 2-position of the alkene and the α-position of the nitrone, however, a 55:45 mixture of fused adduct **5** and bridged adduct **6** was obtained[16] (Scheme 4). Apparently, in this case the methyl–methyl interaction in the transition state leading to **5** renders the alternative transition state leading to **6** competitive.



SCHEME 4

Cyclization of the homologous nitrone **7** having an alkenyl moiety separated by a butylene chain, generated *in situ* by oxidation of the related *N*-alkenylhydroxylamine, afforded a 2:1 mixture of *cis*-fused **8** and *trans*-fused adducts **9**, together with a minor amount of the bridged adduct **10**[17] (Scheme 5). Again the inherent preference for the fused adduct is observed.



SCHEME 5

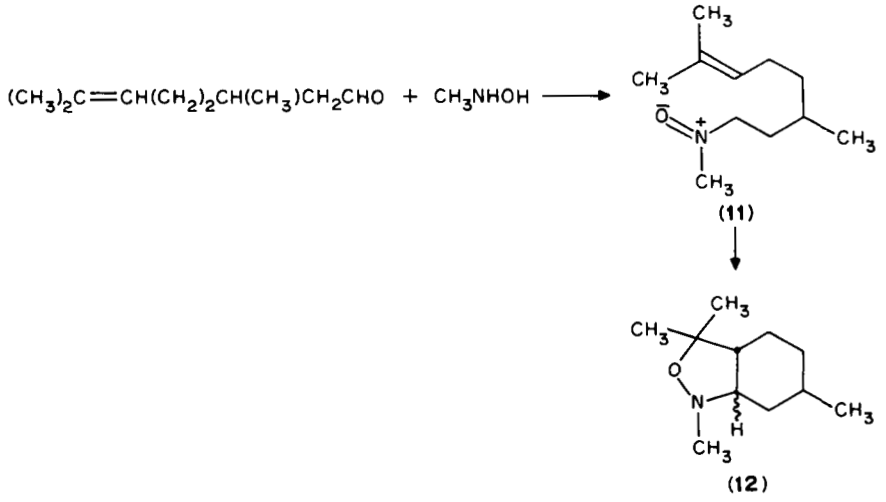
Although the C-(4-pentenyl)nitrones appear to form *cis*-fused adducts exclusively, their C-(5-hexenyl) counterparts generally a mixture of *cis*- and *trans*-fused adducts. It has been shown that the *trans*-fused adducts predominate under conditions of kinetic control, but the *cis*-fused adducts dominate under conditions of thermodynamic control[18]. This equilibrium presumably results from cycloreversion of the initially formed isoxazolidines under more forcing equilibrium conditions. Experimental details for several intramolecular cycloadditions (e.g. **11** → **12**) have appeared[19] (Scheme 6).

1. Nitrone systems bearing an alkenyl moiety separated by an aromatic ring

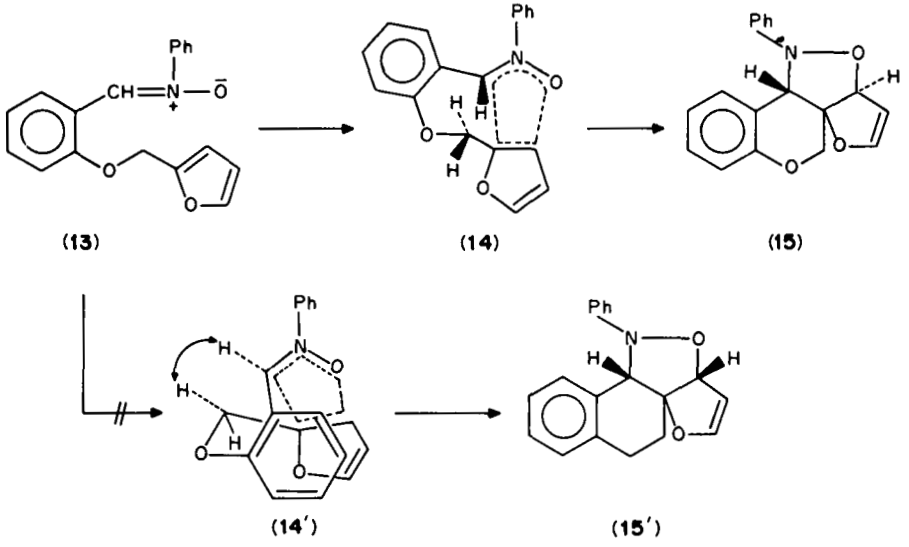
Oppolzer and coworkers[20] have extended the intramolecular cycloaddition of nitrone–alkene systems and generally incorporated a benzene ring and a heteroatom.

Nitrones can add to furan[21], and the intramolecular variant was found to give good yields of cycloadducts. Thus, on heating in toluene under reflux, nitrone **13** gives 76% yield of a spiro-cycloadduct **15** as the sole product[22] (Scheme 7), in which 2*a*-H and 11*b*-H are *trans*. This was rationalized in terms of transition state **14** leading to **15**. The transition

state **14'** leading to a stereoisomer **15'** is rather unfavorable because of a significant interaction between the azomethine hydrogen and the methylene groups.



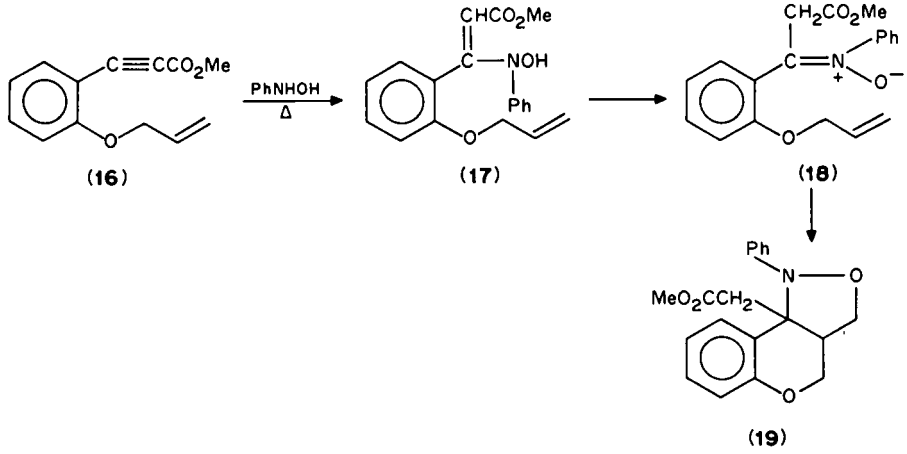
SCHEME 6



SCHEME 7

A route to nitrones which involves the addition of hydroxylamines to activated acetylenes has been recently developed[23]. Treatment of methyl (*o*-allyloxy)phenylpropynoate **16** with *N*-phenylhydroxylamine in refluxing benzene afforded 86% yield of cycloadduct **19** through an internal cycloaddition of nitrone **18** derived

from a hydrogen shift of the initial adduct **17** (Scheme 8). A different pattern of reactivity was encountered in the reaction of *N*-methylhydroxylamine with butynone **20**, which gave a mixture of the stereoisomeric nitrones **21** which did not undergo internal cycloaddition owing to lack of two-plane orientation approach of the dipole and dipolarophile. In the presence of water, however, the same reaction gave a *cis–trans* mixture of *N*-hydroxyenamide **22**, which on heating in benzene afforded cycloadduct **23** via a nitrone like **18**. Heating a mixture of (*o*-allyloxy)phenylacetylene **24** and *N*-methylhydroxylamine in benzene at 110 °C gave an isoxazolidine **25** which was identical with the intramolecular cycloadduct of nitrone **27** derived from the aryl ketone **26** (Scheme 9).

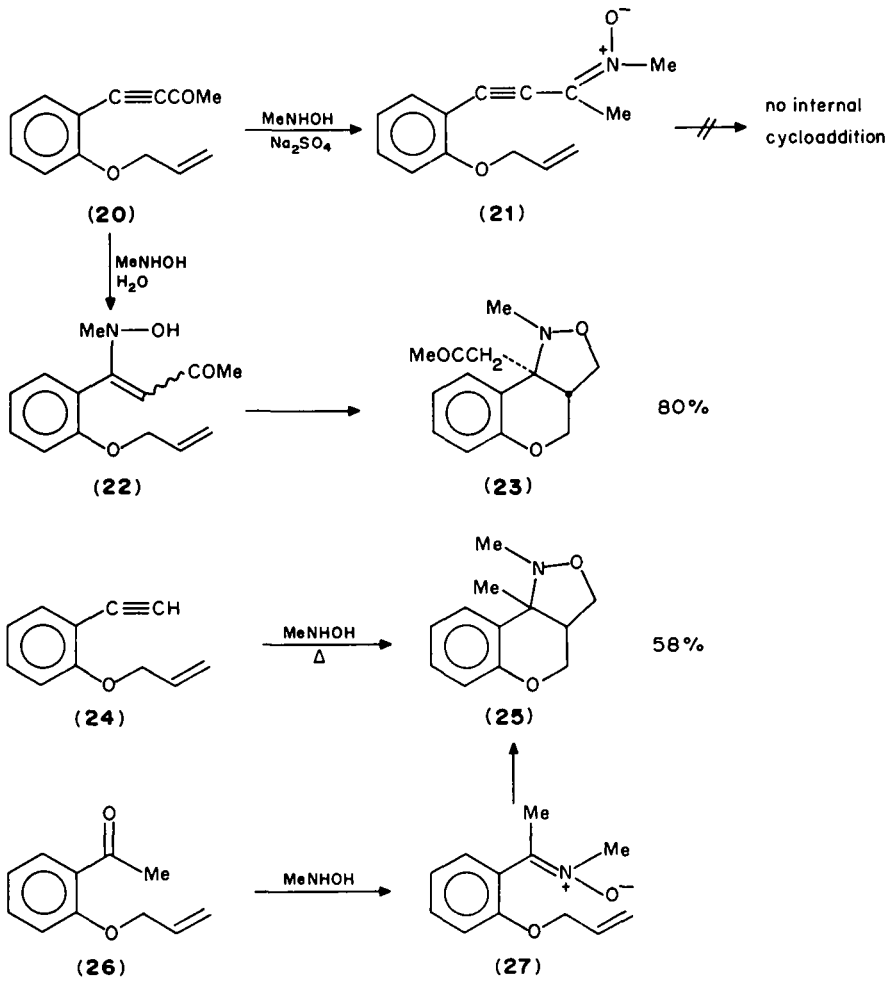


SCHEME 8

It has recently been demonstrated that the iminium salt derived from benzaldehyde oxime and (trimethylsilyl)methyl triflate can serve as a common precursor for both azomethine ylides and nitrone dipoles[24]. The reaction of the triflate salt of **28** with cesium fluoride gives the intramolecular cycloadduct **31** (81%) which is formally derived from *N*-methyl-C-arylnitrone **32** (Scheme 10).

A novel preparation of carbon-bridged dibenzocycloheptanes and dibenzazepine was achieved by key intramolecular nitrone–alkene cycloaddition[25]. The nitrone **36** prepared from 5*H*-dibenzocycloheptene-5-carboxaldehyde **33** and *N*-methylhydroxylamine undergoes an intramolecular nitrone–alkene cycloaddition in refluxing toluene to yield tetracyclic isoxazolidine **39** in quantitative yield. The case of the corresponding cycloaddition of the nitrone **37** derived from the homologous aldehyde **34** was evidenced by spontaneous formation of **40** at room temperature. The azastilbene-derived aldehyde **35** did not undergo cycloaddition directly but produced the nitrone **38**, which was then cyclized in refluxing toluene to the cycloadduct **41** (Scheme 11). Adducts **39–41** were further converted into carbon-bridged dibenzazocines and dibenzodiazocines[26].

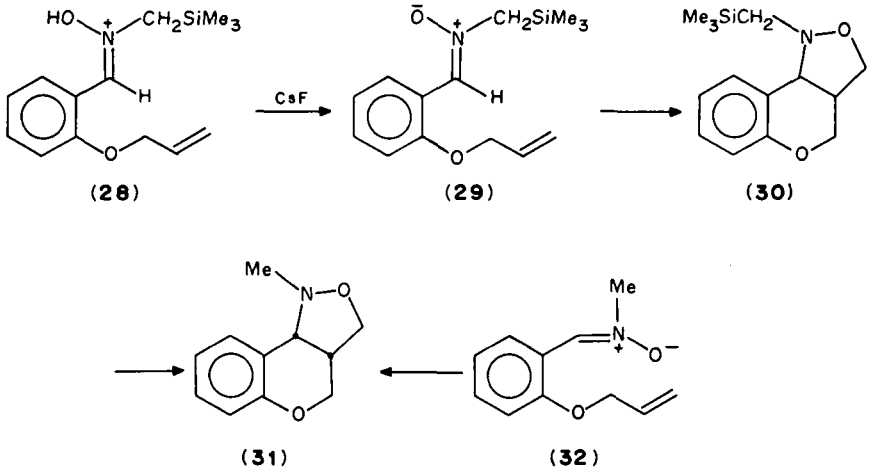
The indole alkaloids, (±)-chanoclavine I **46** and (±)-isochanoclavine I **47**, have been synthesized through the use of intramolecular nitrone cycloaddition methodology[27,28] (Scheme 12). The key step involves a transient nitrone **43** which gives cycloadduct **44** through a regio- and stereoselective intramolecular cycloaddition to a 1,2-disubstituted alkenyl moiety. Reduction of the ester function, followed by hydrogenolysis, *N*-blocking and diol cleavage, produced the aldehyde **45**, which was converted into **46** and **47** through the use of Wittig and Horner–Emmons strategies, respectively.



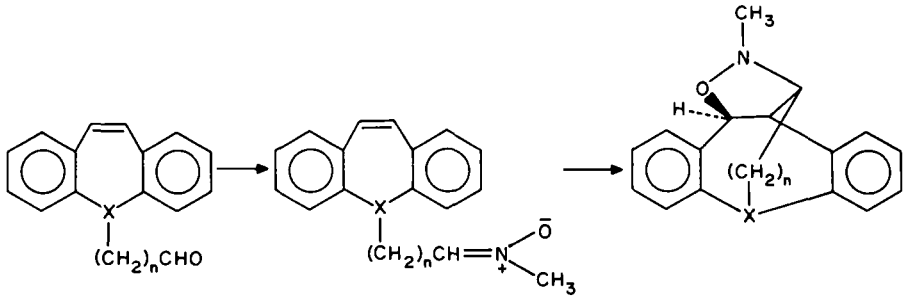
SCHEME 9

2. C-Cycloalkenylnitrones

LeBel and coworkers have also prepared polycyclic isoxazolidines by using the intramolecular cycloadditions of C-cycloalkenylnitrones[29-31]. The synthesis of several adamantyl derivatives by intramolecular cycloadditions of C-bicycloalkenylnitrones has been reported[32]. C-Bicycloalkenylnitrones **48** and **49** underwent a smooth intramolecular cycloaddition, affording 2,4-(epoxyimino)noradamantane **50** and 2,4-(epoxyimino)-protoadamantane **51**, respectively. The intramolecular cycloaddition of **48** proceeds under very mild conditions: this can be ascribable to entropic assistance because such a factor is more effective for the relatively rigid bicycloalkenyl system than for the corresponding acyclic and monocyclic alkenyl systems. On the other hand, the intramolecular cycloaddition of nitrone **52** gave the 2,4-oxaaza-bridged protoadamantane



SCHEME 10



(33) X=CH, n=0
(34) X=CH, n=1
(35) X=N, n=1

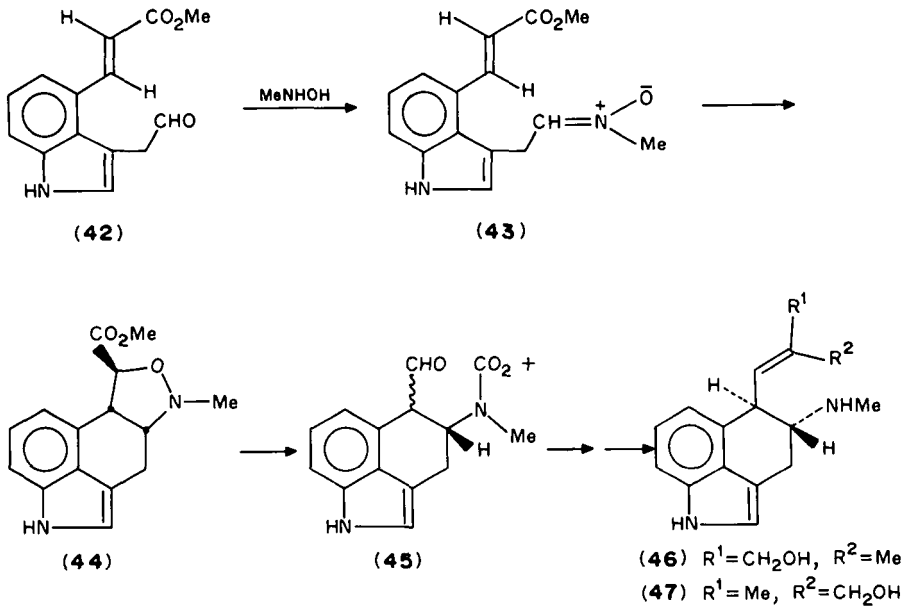
(36) X=CH, n=0
(37) X=CH, n=1
(38) X=N, n=1

(39) X=CH, n=0
(40) X=CH, n=1
(41) X=N, n=1

SCHEME 11

53, adamantane **54** and 2-ax-amino-4-ax-hydroxyadamantane derivatives **55**, whose relative yields depended upon the substituent (R) and reaction conditions, especially the nature of the solvent. The cycloaddition reaction proceeded nonregioselectively to afford both **53** and **54**; the formation of **53** was favored in benzene, but that of **54** in ethanol (Scheme 13). The adducts **50**, **51** and **53** were reductively cleaved to give the corresponding amino alcohol derivatives, which are difficult to obtain otherwise.

Annelation of nitrone **56** at room temperature led quantitatively to the hydrindane **57** whose stereochemistry was tentatively assigned as depicted[33] (Scheme 14). Attempts to lengthen the alkenyl side-chain resulted in the need for more forcing conditions. When the nitrone **58** was heated in refluxing benzene, it gave rise to a 1:1 mixture of regioisomeric adducts **59** and **60**. The nitrone having a 9-decenyl side-chain gave no cyclized product, but

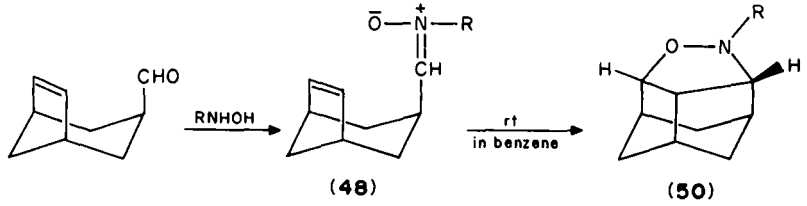


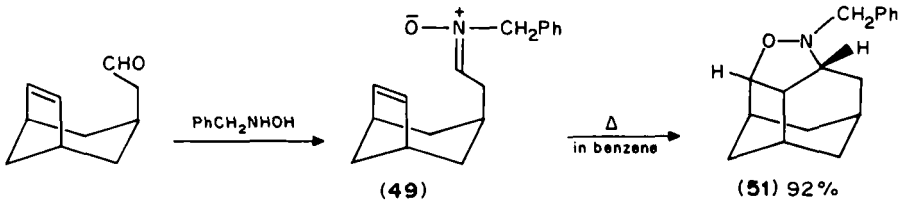
SCHEME 12

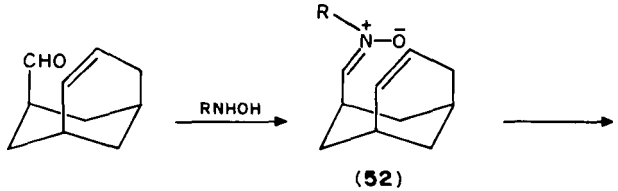
decomposed on heating at 120°C. It is to be stressed that these cycloadditions are especially valuable in the preparation of substituted cyclopentane rings. 2-(3-Butenyl)-*N*-methylcycloheptanimine *N*-oxide **61** underwent an intramolecular cycloaddition to give a perhydroazulene compound **62** in 84% yield. The cycloadduct **62** was subsequently converted into **63**.

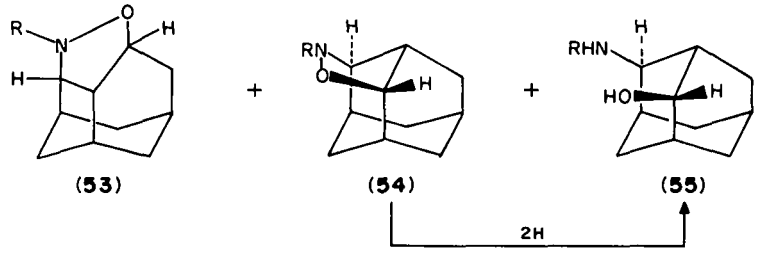
Intramolecular cycloadditions of various exocyclic nitrones bearing a *β*-alkenyl side-chain have also been investigated, and this methodology was applied to the total synthesis of the sesquiterpenes (±)-7,12-secoishwaran-12-ol, (±)-hirsutene and (±)-coriolin[34]. The reaction of cycloalkanones **64** or **67** with a hydroxylamine in refluxing benzene affords a high yield of a single *exo*-adduct through an intramolecular cycloaddition of nitrone **65** or **68**, respectively. The yields are not appreciably affected by the alkyl group (R) or by a *β*-hydroxyl in the cycloalkanone (e.g. **64c**). However, when serious 1,3-diaxial interactions are encountered in the transition state (e.g. **71** and **74**), higher temperatures are required to effect cyclization and yields are severely attenuated (Scheme 15).

The cycloaddition is also successful for nitrones with 3-butenyl side-chains in the *β*-position. For example, the intramolecular cycloaddition of nitrone **77** is stereospecific and produced only the *exo* isomer **78**. The sensitivity of the exocyclic nitrone cycloaddition to steric and torsional parameters is further apparent in this example. The yield is lower and higher temperature is required to effect cycloaddition, presumably reflecting destabilizing interactions encountered from a boat-like conformation of the bridging atoms. However, the conformationally restricted nitrone **80** proceeds efficiently to isoxazolidine **81**. If the *β*-alkenyl side-chain is lengthened by an additional methylene group, the reaction fails completely (e.g. **82** ⇸ **83**). The cycloaddition of nitrone **85** generated from 4-(2-propenyl)-cyclohexanone **84** proceeds to give **86** in satisfactory yield (Scheme 16), although a *γ*-propenyl group is not competitive with a *β*-propenyl group in the cycloaddition of 3,4-di(2-propenyl)cyclohexanone nitrone.





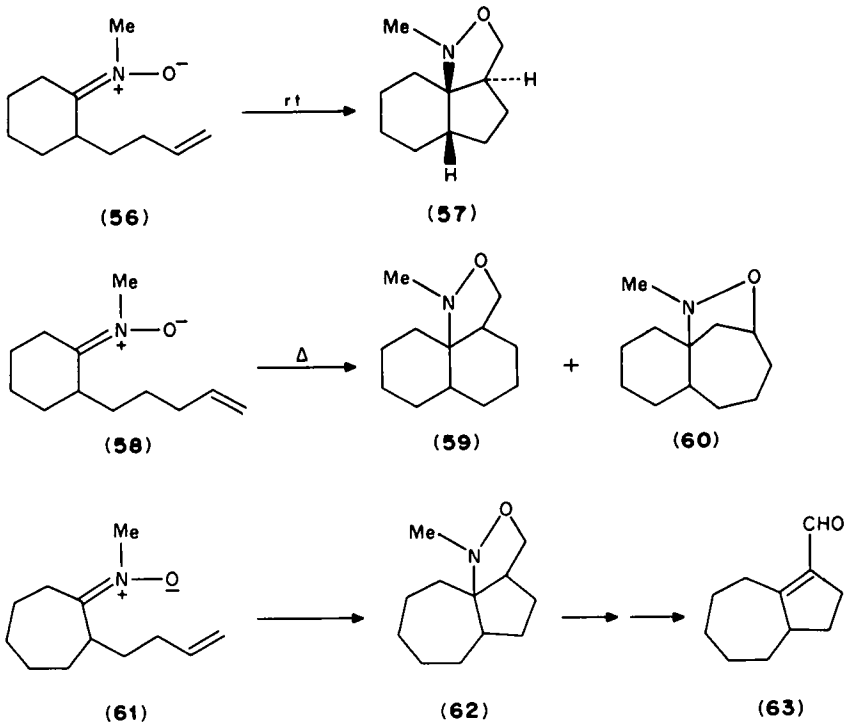




SCHEME 13

This methodology was applied to the total synthesis of some sesquiterpenes. Treatment of the *trans*-decalone **87** with *N*-benzylhydroxylamine in refluxing ethanol afforded 80% yield of the intramolecular nitrone–alkene cycloadduct **88**. The catalytic hydrogenation and subsequent hydrodeamination gave alcohol **89**, which was converted into (±)-7,12-secoishwaran-12-ol **90** via several steps (Scheme 17).

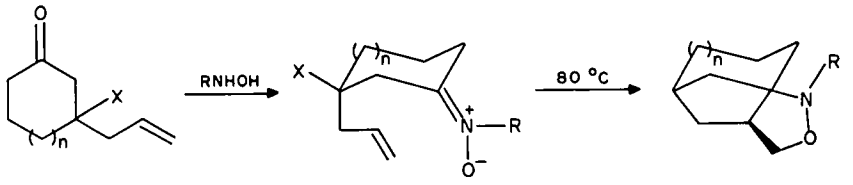
A total synthesis of the linearly fused tricyclopentanoids, (±)-hirsutene and (±)-coriolin, has also been demonstrated. Cyclopentenylmethylcyclopentanone **91** with *N*-



SCHEME 14

methylhydroxylamine afforded 75% yield of the stereospecific cycloadduct **93** via an *anti*-nitrone intermediate **92**. *N*-Methylation of **93**, followed by N–O scission and subsequent Cope elimination gave alcohol **94**, which was converted into the known ketone **95** from which (±)-hirsutene **96** was previously prepared[35]. Furthermore, the alcohol **94** was converted into the enone **97** which has been previously converted into (±)-coriolin **98**[36] (Scheme 18).

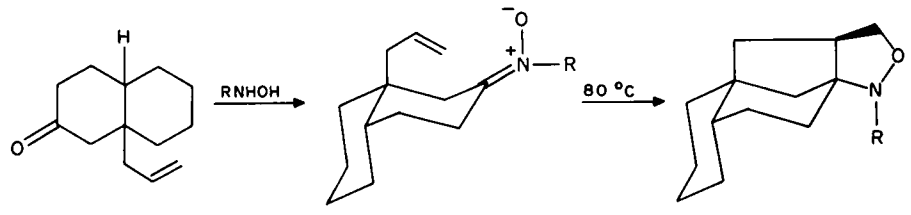
Recently, (±)-α-eudesmol and its three possible diastereomers, 7-epi-, 5-epi- and 5-epi-7-epi-α-eudesmol, as well as (±)-β-eudesmol and 7-epi-β-eudesmol, have been synthesized by intramolecular nitrone–alkene cycloaddition[37] (Scheme 19). (*SR*, *RS*)-Nitrone **99** derived from (*SR*, *RS*)-monocyclofarnesal and *N*-methylhydroxylamine underwent intramolecular cycloaddition at 90 °C to the *trans–anti–trans* tricycle **100** and its *trans–anti–cis* diastereomer **101** in 50 and 12% yields, respectively. The same products were isolated at 140 °C in yields of 44 and 20%, respectively. The analogous cycloaddition of (*SS*, *RR*)-nitrone **102** derived from (*SS*, *RR*)-monocyclofarnesal at 90 °C afforded the *cis–anti–trans* tricycle **103** and *cis–anti–cis* diastereomer **104** in 9 and 74% yields, respectively. The isoxazolidine product distribution changed dramatically in refluxing xylene (140 °C) with **103** and **104** being obtained in yields of 34 and 31%, respectively. By application of a reductive deamination sequence, isoxazolidines **100**, **101**, **103** and **104** were converted into (±)-α- **105** and (±)-β-eudesmol **106**, (±)-7-epi-α- **107** and (±)-7-epi-β-eudesmol **108**, 5-epi-7-epi-α-eudesmol **109** and 5-epi-α-eudesmol **110**, respectively.



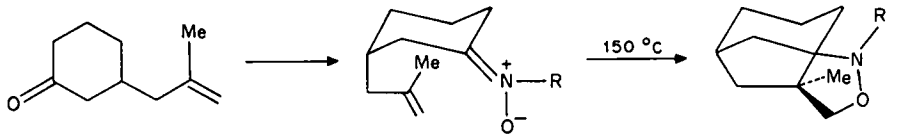
(64)
(a) $n=1$, X=H
(b) $n=2$, X=H
(c) $n=1$, X=OH

(65)
R=Me, CH_2Ph

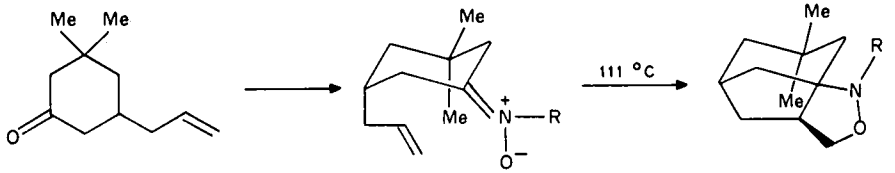
(66)
66—100%



(67) (68) (69)
R=CH_2PH 94%



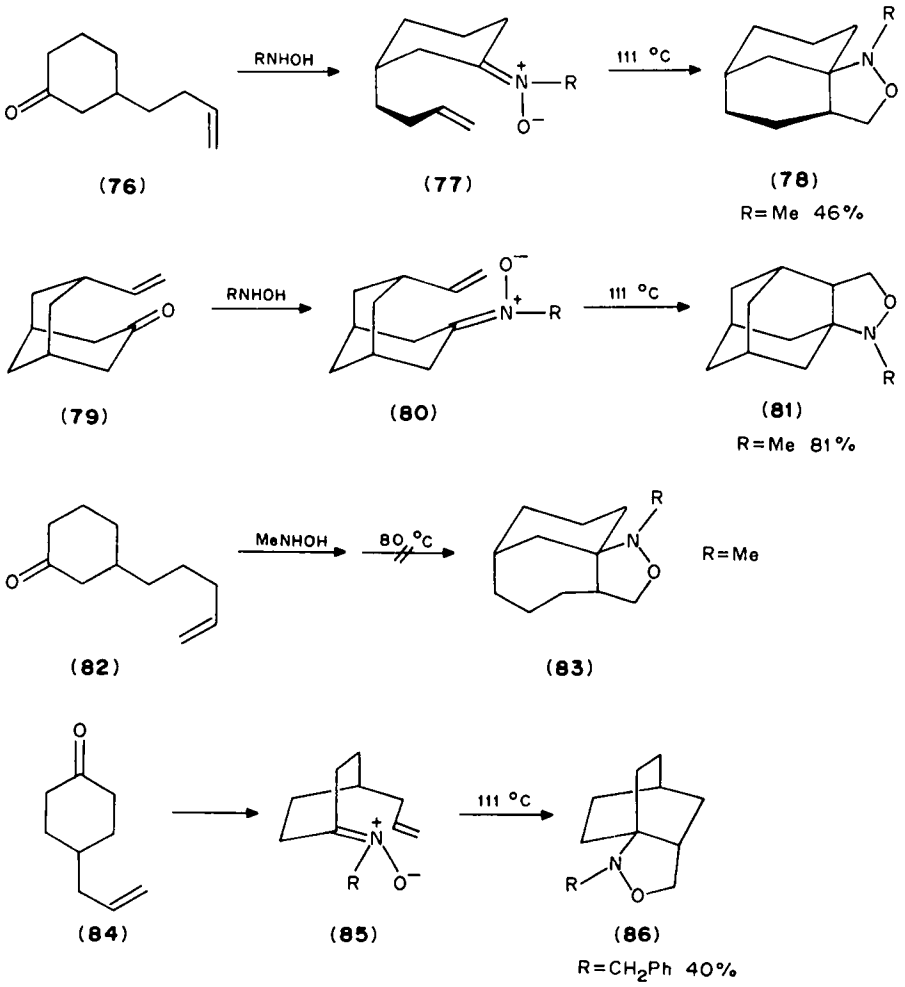
(70) (71) (72)
R=CH_2Ph 8%



(73) (74) (75)
R=Me 34%

SCHEME 15

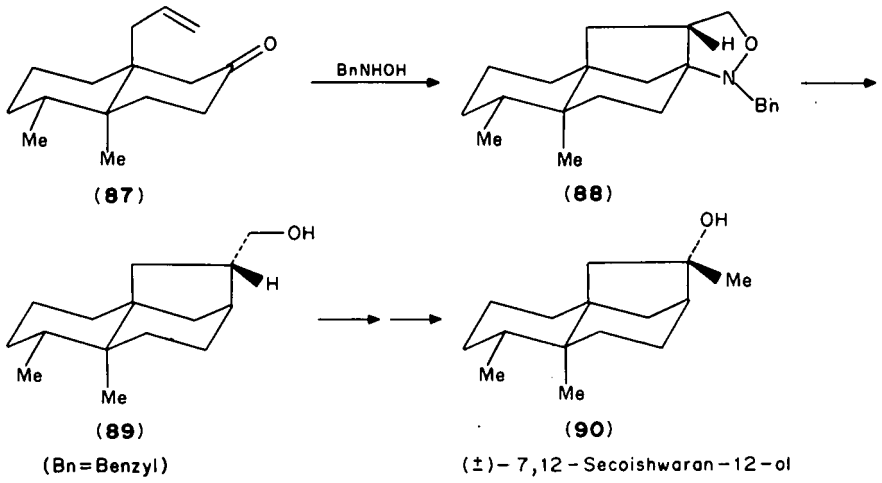
A stereorational total synthesis of (−)-ptilocaulin has been achieved by using an intramolecular nitrone cycloaddition as a key step[38]. The reaction of aldehyde [112]



SCHEME 16

(mixture of epimers) with *N*-benzylhydroxylamine in refluxing benzene containing a molecular sieve afforded 80% yield of a mixture of tricyclic isoxazolidines **113a** and **113b** which were readily separable by column chromatography. The stereochemical outcome of this reaction is consistent with either a *Z*-nitrone undergoing cyclization via the *exo* transition state **A** or an *E*-nitrone proceeding via the *endo* transition state **B**. The alternative *Z- endo* **C** and *E-exo* **D** transition states, leading to the unobserved C-3*a* epimers of **113**, suffer serious torsional strain and nonbonded interactions. The cycloadduct **113** was eventually converted into (−)-ptilocaulin **114** (14 steps from **111**, 7.4% overall yield) (Scheme 20), establishing its absolute stereochemistry as shown in **115**.

Adaline **118** has been synthesized from nitrone **116**[39]. The tricyclic adduct **117** was converted to (±)-adaline **118** by hydrogenolysis and oxidation (Scheme 21).

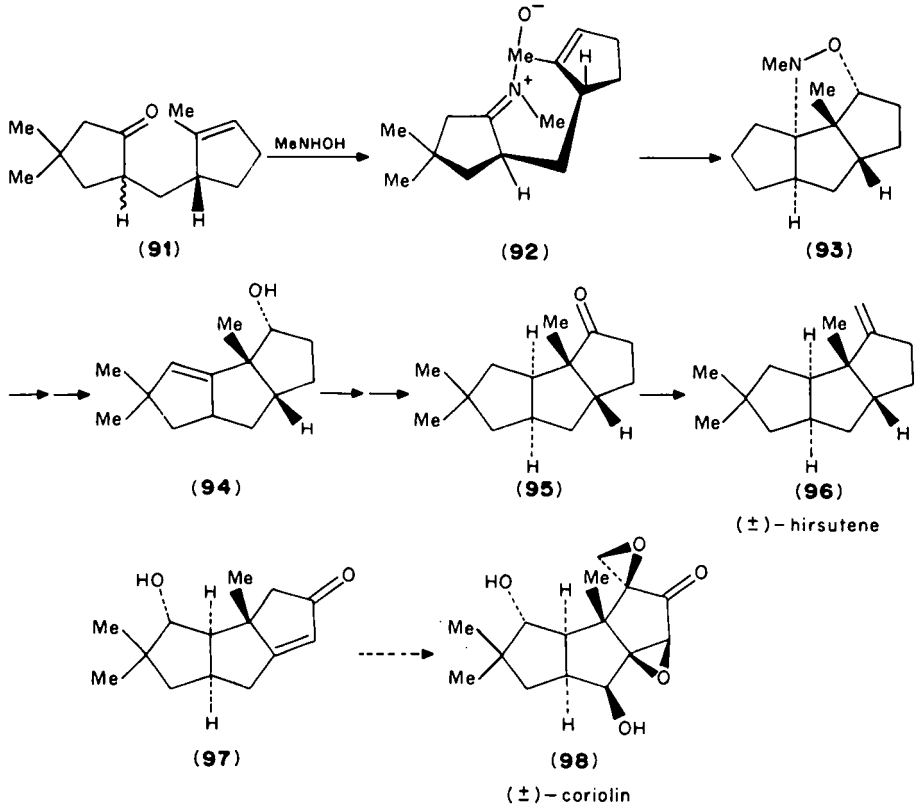


(87) (88) (89) (90)

(Bn=Benzyl)

(±)-7,12-Secoishwaran-12-ol

SCHEME 17



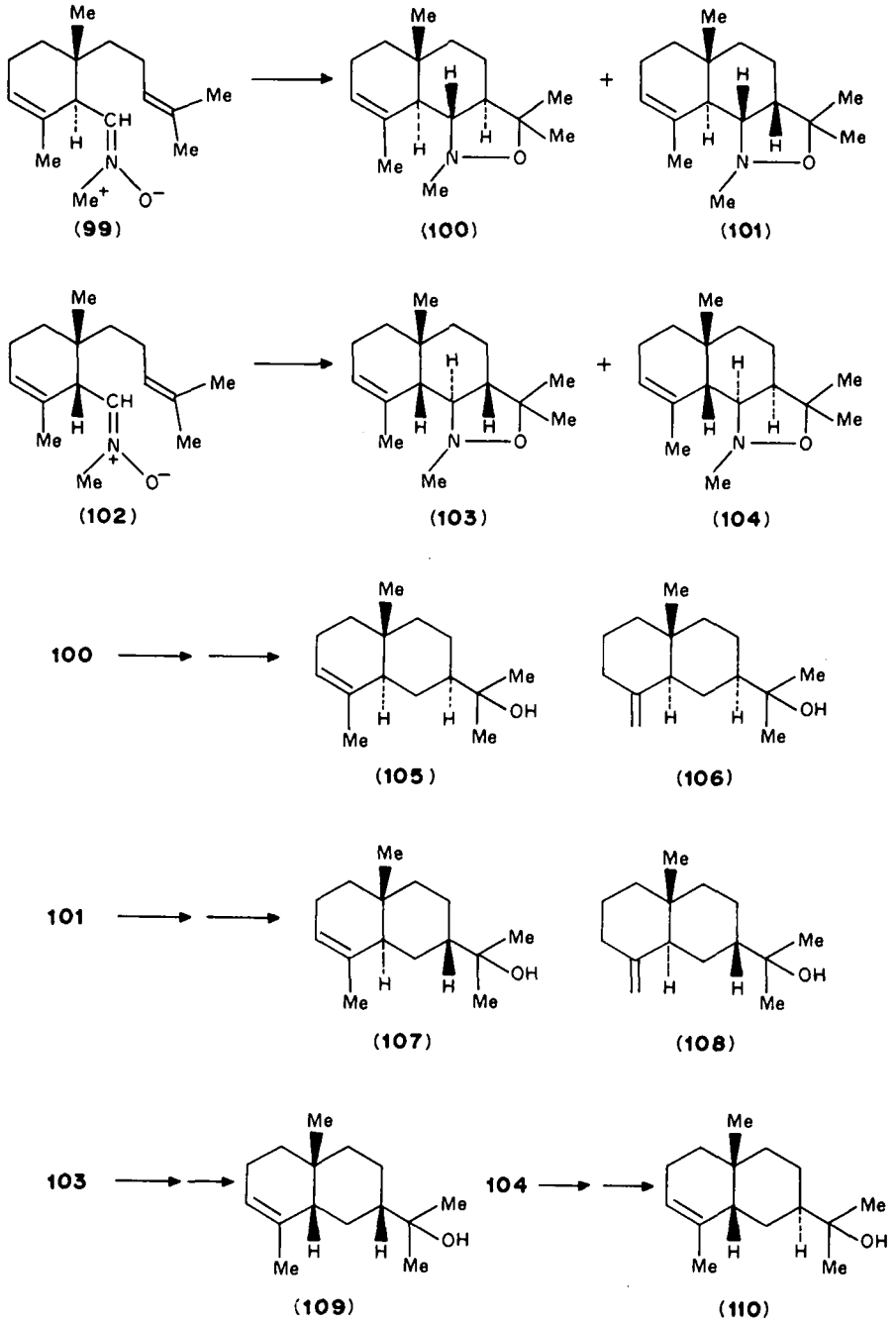
(91) (92) (93) (94) (95) (96)

(±)-hirsutene

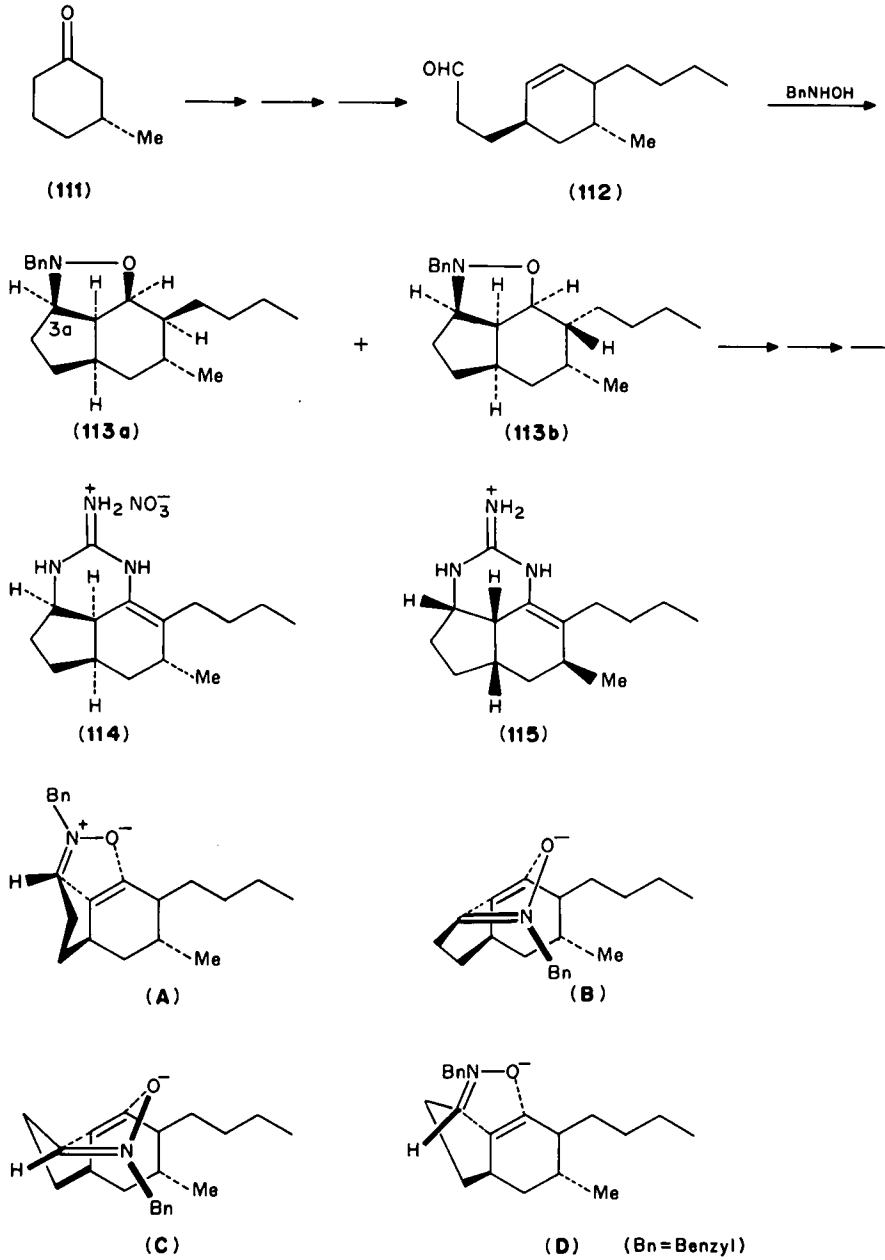
(97) (98)

(±)-coriolin

SCHEME 18



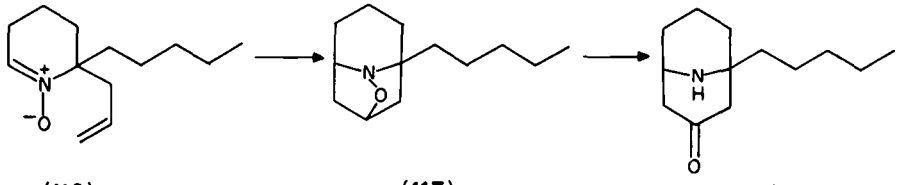
SCHEME 19



SCHEME 20

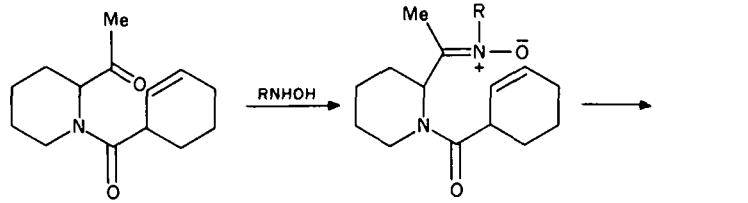
An interesting study of amidonitrone cyclization has been undertaken[40]. It was shown, for example, that amidonitrones **120**, which were generated *in situ* from the related ketone

119 with *N*-methyl- and *N*-benzylhydroxylamines, added intramolecularly to the alkene moiety to give lactams **121** stereo- and regiospecifically (Scheme 22).

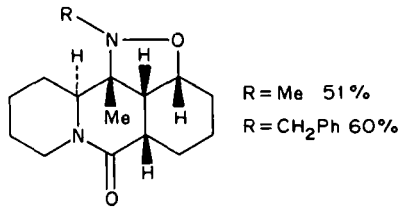


(116) (117) (118)

SCHEME 21



(119) (120)

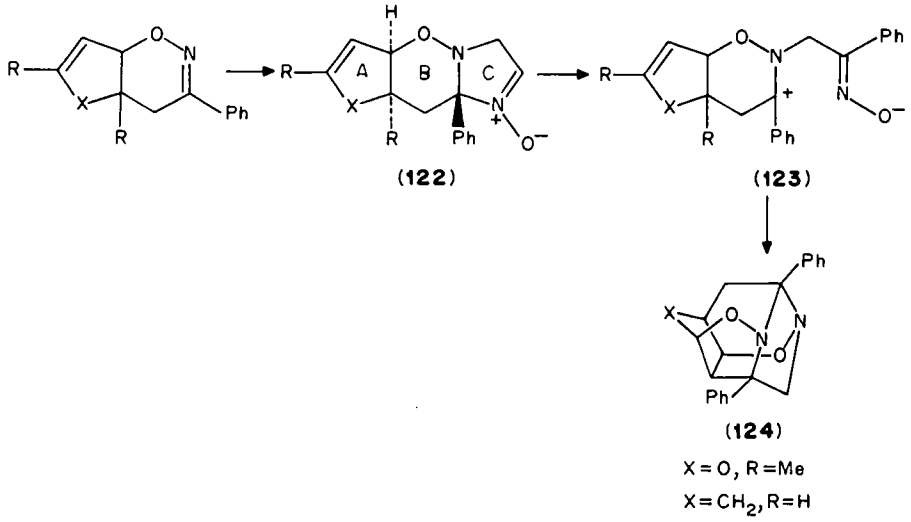


(121)

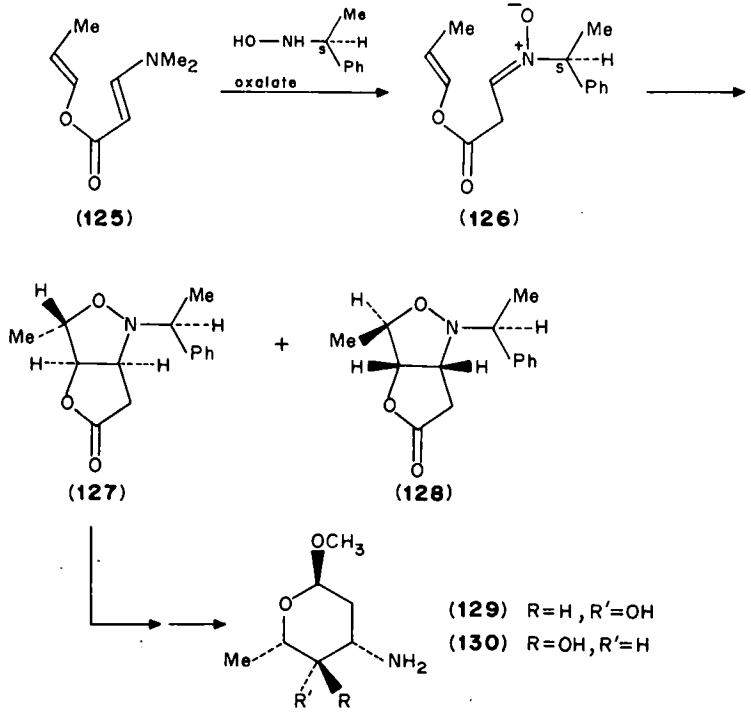
SCHEME 22

Tricyclic nitrones **122**, which are readily available from the cycloaddition of α-nitrostyrene to the imino group of bicyclic oxazines[41], were found to undergo high-yield intramolecular 1,3-dipolar cycloaddition, giving highly hetero-substituted pentacyclic cage compounds **124**[42] (Scheme 23). The isomerization, **122** → **125**, requires in effect an *anti* → *syn* isomerization at the B/C ring junction, followed by 1,3-dipolar cycloaddition of the enol ether double bond of ring A to the nitrone of ring C. The stereochemical change has been suggested to involve the opening of **122** to the stabilized dipole **123**, which epimerizes at nitrogen and recyclizes. This is the first example of an intramolecular reaction of a cyclic ene with a cyclic nitrone.

In a chiral synthesis of L-daumosamine and of L-acosamine, the key intermediate was prepared by an enantioselective cycloaddition of a chiral nitrone[43]. The chiral nitrone **126** was prepared from the reaction of the all-*trans* vinylogous urethane **125** as a masked aldehyde with (*S*)-(−)-*N*-hydroxy-α-methylbenzenemethanamine oxalate in refluxing xylene, and **126** underwent intramolecular cycloaddition to give an 82:18 mixture of diastereomers **127** and **128** (68% yield). Since the intermolecular cycloaddition of a nitrone



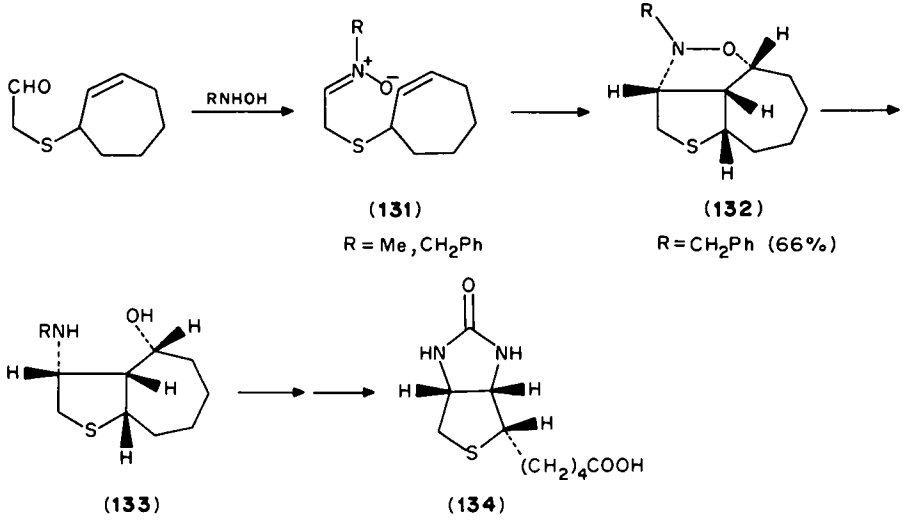
SCHEME 23



SCHEME 24

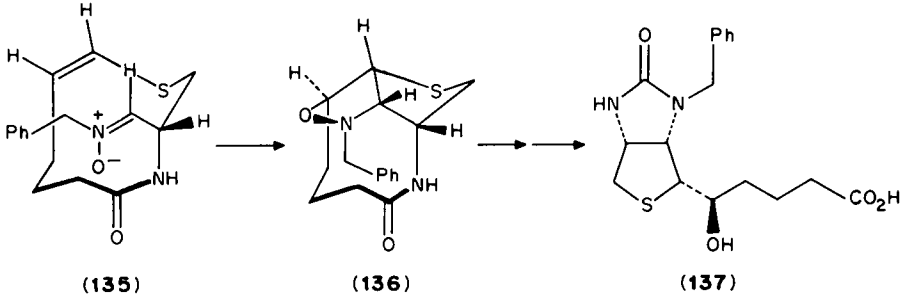
to a heteroatom-substituted alkene generally gives the product in which the nitrone oxygen is attached to the heteroatom end of the alkene, this intramolecular cycloaddition of **126** represents the first example in which the preference of the nitrone oxygen to add to the oxygen-bearing carbon of the enol ether or esters has been reversed. Subsequent elaboration of **127** provided L-α-methyl daunosamide **129** and L-α-methyl acosamide **130** (Scheme 24).

Two synthetic routes to biotin using an intramolecular cycloaddition have been developed[44,45]. One is the intramolecular cycloaddition of nitrone **131** giving isoxazolidine **132**, which is a key intermediate in the synthesis of biotin[44]. The resulting isoxazolidine **132** was stereospecifically produced with the correct stereochemistry for elaboration into the target molecule (Scheme 25). The all-*cis* tetrahydrothiophene intermediate **133** was converted into (±)-biotin **134** through conventional reactions.



SCHEME 25

In an alternate route[45], nitrone **135** (Scheme 26), on heating in toluene, underwent intramolecular cycloaddition with exclusive formation of the tricyclic intermediate **136**. Reductive cleavage of the isoxazolidine ring in **136**, followed by acylation of the free amine

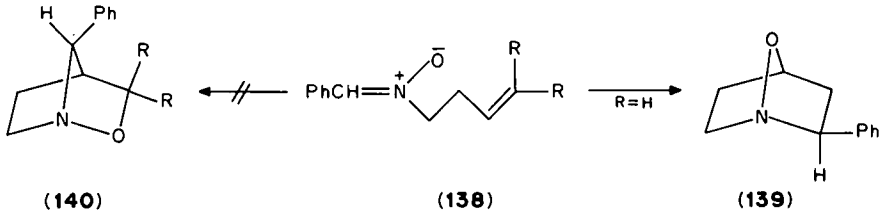


SCHEME 26

and hydrolysis of the lactam moiety, afforded imidazolidinone **137**, which was converted into d-biotin in high yield.

B. *N*-Alkenylnitrones

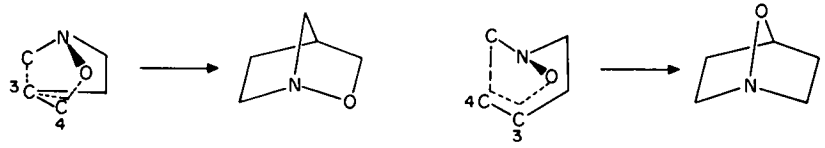
Lumma[46] first investigated the intramolecular cycloaddition of nitrone in which an alkenyl function is attached to the nitrone's nitrogen atom. The intramolecular cyclization of N(3-butenyl)nitrone **138** (R = H) gave the 1-aza-7-oxabicycloheptane **139** (R = H) in 72% yield. The corresponding 1-aza-2-oxabicycloheptane **140** (R = H) was not formed (Scheme 27); this was attributed to poor orbital overlap in the transition state leading to **140** (R = H). Nitrone **138** (R = Me) gave no isoxazolidine under the same conditions, presumably owing to considerable steric hindrance in the transition state.



(140) **(138)** **(139)**

SCHEME 27

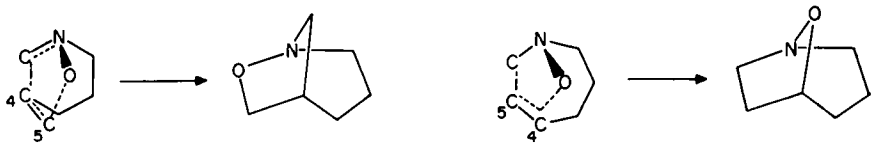
An extensive investigation of the cycloaddition of N-alkenylnitrones has been reported[47]. For N-(3-alkenyl)nitrones, it was suggested that C—C bond formation to the nearer alkenic center (C-3) implies a strained transition state **E** leading to 1-aza-2-oxabicycloheptane system **141**, whereas the exclusively observed formation of 1-aza-7-oxabicycloheptane system **142** involves the unstrained transition state **F** incorporating C—C bond formation to the more remote C-4 of the alkenyl unit. This view is based on the assumption that the new C—C bond formation is more advanced than the C—O bond formation in the corresponding transition state (Scheme 28).



(E) **(141)** **(F)** **(142)**

SCHEME 28

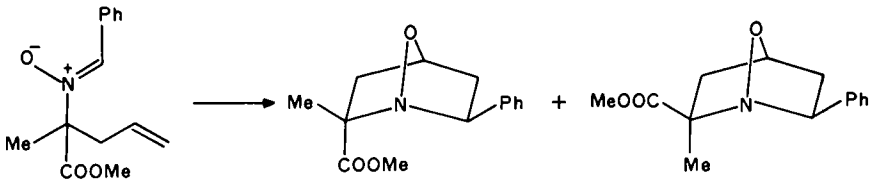
In the N-(4-alkenyl)nitrone cycloadditions, both transition state **G** leading to 1-aza-2-oxavicyclooctane system **143** and transition state **H** leading to 1-aza-8-oxabicyclooctane system **144** do not exhibit strain. In the case of nitrones bearing 4, 5-disubstituted alkenyl units, entropically favored closure to **143** through **G** is observed. When the alkenyl double bond is monosubstituted, a balance is struck between formation of **143** and **144**, with the former predominant. This is consistent with the tendency of the nitrone carbon to become bonded to the less substituted carbon of an alkenyl moiety. This tendency is further enhanced in 4,4-disubstituted nitrones where a path through transition state **H** becomes dominant[47] (Scheme 29).



(G) (143) (H) (144)

SCHEME 29

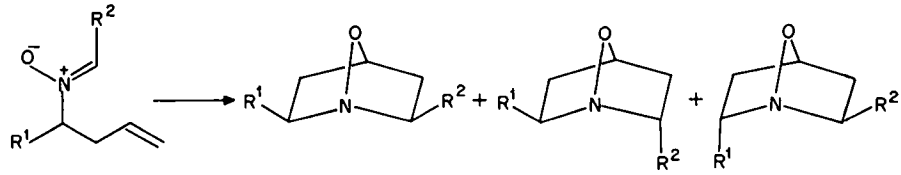
The stereochemistry for the formation of the 1-aza-7-oxabicycloheptane system such as **142** has been examined. In the intramolecular cycloaddition of N-(3-alkenyl)nitrone **145** bearing α, α-disubstituents, two stereoisomeric adducts **146** and **147** were formed in a 1:2 ratio[48] (Scheme 30).



(145) (146) (147)

SCHEME 30

It has been found that the intramolecular cycloaddition of α-substituted N-(3-alkenyl)nitrones **148** led to the three stereoisomeric 1-aza-7-oxabicycloheptanes **149**, **150** and **151**, with a selectivity of about 80% in favor of the *exo*, *exo*-disubstituted adduct **149**[49]. The nitrone **148b** or **148c** (presumably of *Z* geometry) should lead to two cycloadducts **149b** and **151b**, and **149c** and **150c**, respectively, since the geometry of the nitrone double bond should be reflected in the configuration of the adducts. However, noticeable amounts of the isomers **150b** and **151c** were also detected (Scheme 31). The formation of the latter isomers was assumed to be due to *E*/*Z* isomerization of the starting nitrones[50] or to an aza-Cope rearrangement[51] interconverting the nitrones **148b** and **148c**.

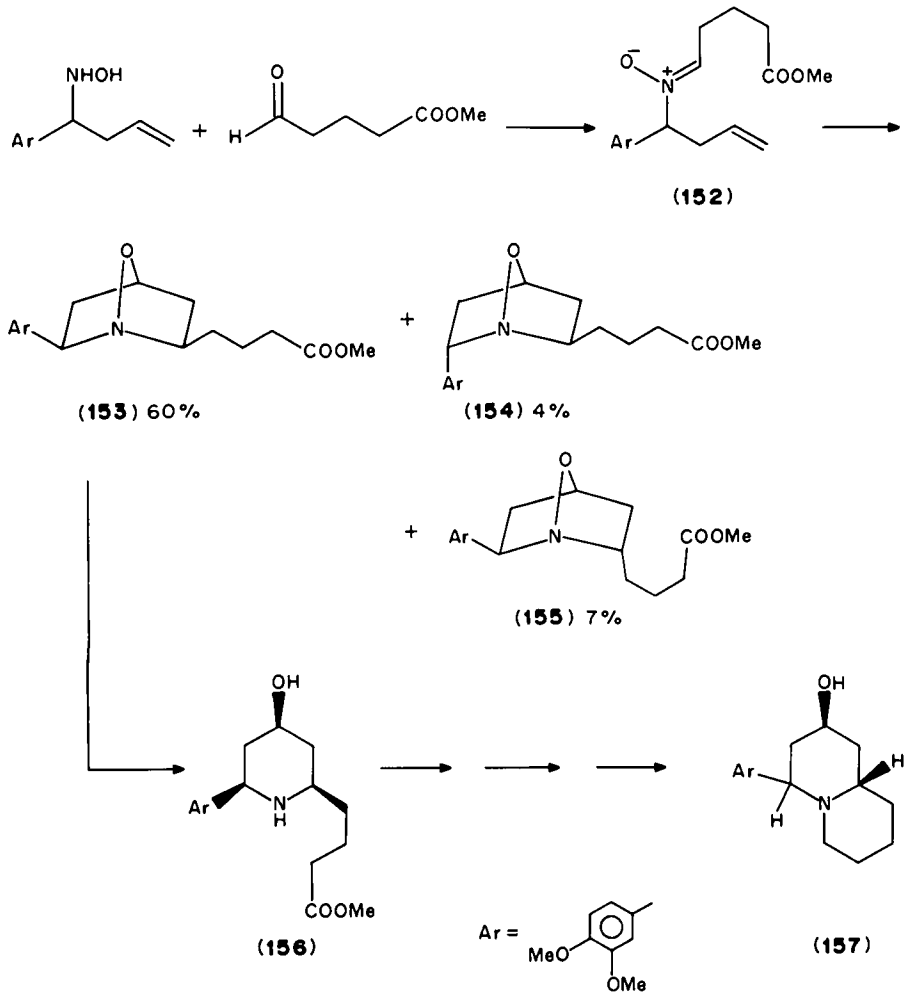


(148)	(149)		(150)		(151)
(a) $R^1 = R^2 = Ph$	7	:	3		
(b) $R^1 = Ph, R^2 = i\text{-}Pr$	80	:	9	:	11
(c) $R^1 = i\text{-}Pr, R^2 = Ph$	83	:	10	:	7

SCHEME 31

The *exo*, *exo*-disubstituted adducts **149** could be reduced to give the all-*cis*-2,6-disubstituted-4-hydroxypiperidines. This method was applied to synthesis of a quinol-

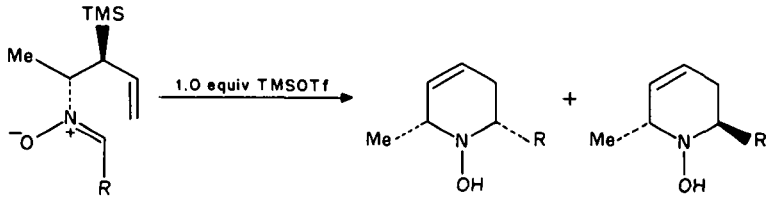
izidine alkaloid, lasubine II[49]. On heating in xylene, the nitrone **152** gave three 1-aza-7-oxabicycloheptane **153**, **154** and **155** with an 83% selectivity for the *exo*, *exo*-disubstituted isomer **153** (Scheme 32). Reduction of **153** gave the all-*cis*-2,6-disubstituted-4-hydroxypiperidine **156** which is the key compound for the synthesis of lasubine II **157**.



SCHEME 32

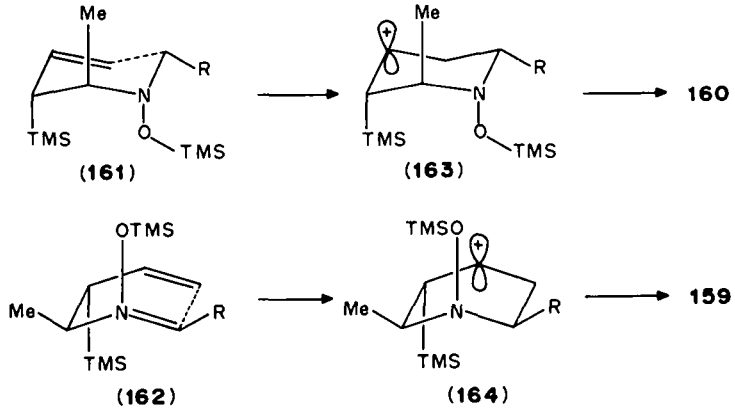
It has been reported that bimolecular cycloaddition of nitrones to allylsilane proceeded in usual fashion to give the expected isoxazolidines[52–54]. More recently the reaction of nitrones with allylsilanes in the presence of trimethylsilyl triflate (TMSOTf) as a catalyst has been found to proceed at room temperature giving homoallylhydroxylamines (major) together with cycloadducts[55]. This reaction is clearly catalyzed by TMSOTf, because without it temperatures over 100 °C are required to achieve the usual 1, 3-cycloaddition. The intramolecular version of the reaction of *anti*-nitrone **158** bearing an allylsilane

moiety was more facile (−40 °C, 8 h) and gave a mixture of *cis*- **159** and *trans*-tetrahydropyridine **160** in high yield (Scheme 33).



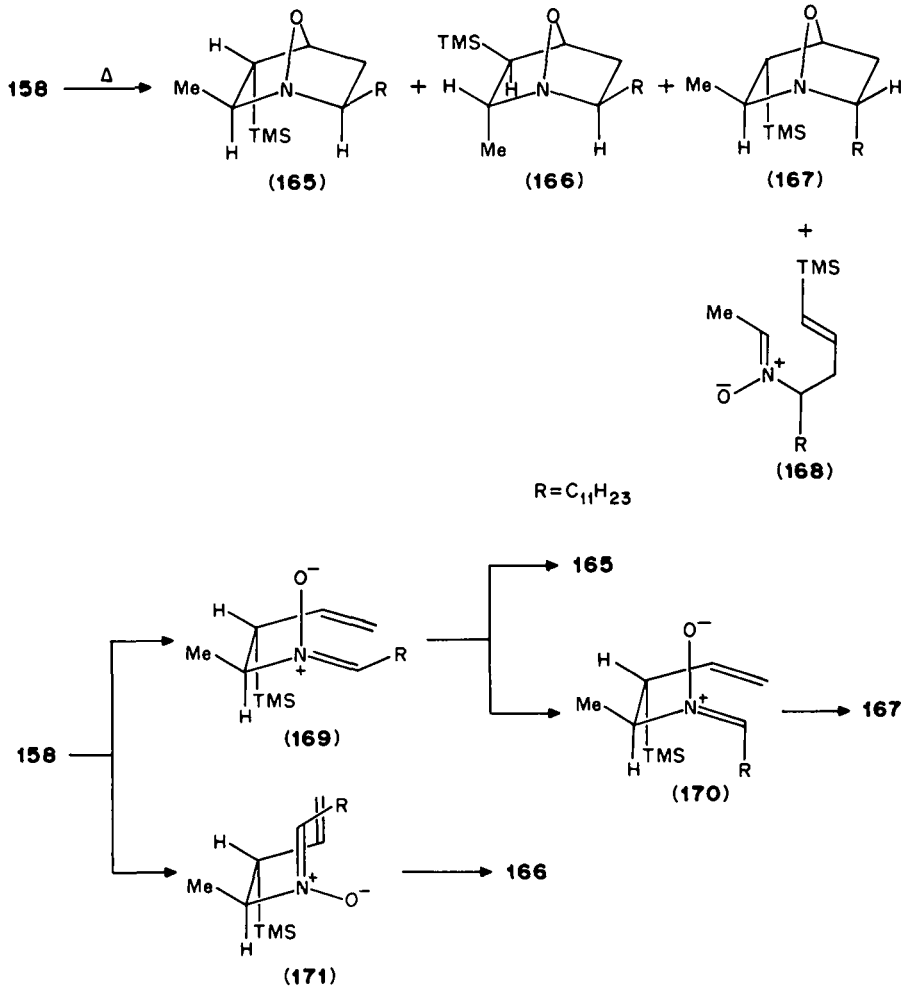
SCHEME 33

The *cis*/*trans* isomers were envisioned to arise from the chair and boat transition states **161** and **162**, respectively, which have the silyl group in an axial position, thus achieving σ–π stabilization of the developing silyl cation in intermediates **163** and **164** (Scheme 34).



SCHEME 34

In contrast to the above TMSOTf-catalyzed intramolecular additions, the thermal reactions proceed in the usual direction to give the 1-aza-7-oxabicycloheptanes[46]. Thus the cycloaddition of nitrone **158** (R = Ph) proceeded smoothly by heating in benzene or toluene, giving three isomeric bicyclic isoxazolidines, **165**, **166** and **167** (each R = Ph), in high yield (82–87%). In the case of nitrone **158** ($R = C_{11}H_{23}$), only two bicyclic adducts **165** and **166** (each $R = C_{11}H_{23}$) were obtained along with nitrone **168** ($R = C_{11}H_{23}$) derived from a Cope rearrangement. The formation of the major product **165** was suggested to be possible, since the steric effect of the *endo* TMS group may be overcome by a favorable electronic stabilization in the transition state **169** leading to **165**. Such stabilization is geometrically not possible for transition state **171** and therefore **165** is favored over **166**. On the other hand, conjugation facilitates nitrone isomerization from **158** (R = Ph) to **170** (R = Ph) which accounts for the formation of isomer **167** (R = Ph)[55] (Scheme 35).

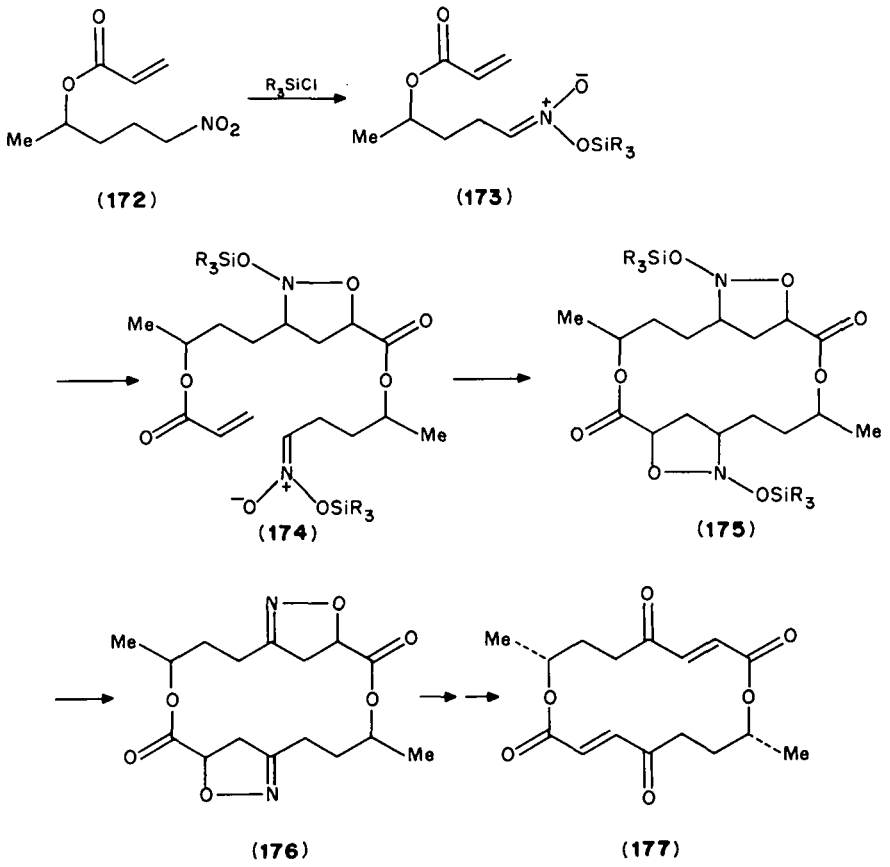


SCHEME 35

The 16-membered ring of (±)-pyrenophorin **177** has been assembled[56] starting from 1-methyl-4-nitrobutyl acrylate **172**, which underwent 1, 3-dipolar cycloaddition via its silyl nitronate **173** to give the isoxazoline derivative **176**. The key step involves a bimolecular cycloaddition to yield **175**, which was subsequently converted into (±)-pyrenophorin **177** via **176** (Scheme 36).

The oxidation of hydroxylamine **178** with silver carbonate on celite has been found to generate both C-alkenylnitrone **179** and N-alkenylnitrone **180**[57]. Under the reaction conditions, both the nitrones **179** and **180** underwent an intramolecular cycloaddition to give the products **183** and **184** through the transition states **181** and **182**, respectively (Scheme 37).

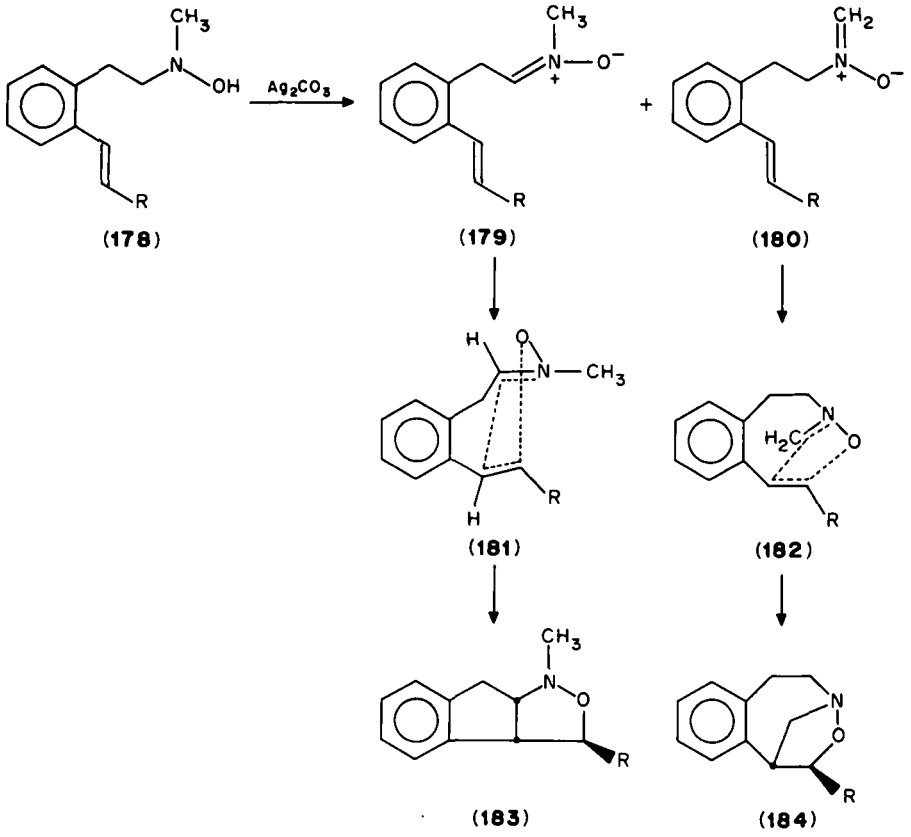
A novel annelation of a cyclic diene to amino- and azabicylic diols has been developed[58]. Bimolecular cycloaddition of N-methylnitrone, generated *in situ* from



SCHEME 36

paraformaldehyde and N-methylhydroxylamine, to 1,5-cyclooctadiene afforded the unsaturated isoxazolidine **185**. The N-selective oxidation of **185** with *m*-chloroperbenzoic acid (MCPBA) produced the N-hydroxyoxazine **186**, which on heating generated both C-alkenylnitrone **187** and N-alkenylnitrone **188**. The former cyclized to the tricyclic adduct **189** but the latter gave two regioisomeric adducts **190** and **191**. Hydrogenolysis of **189**, **190** and **191** gave the amino- and azabicyclic diols **192**, **193** and **194**, respectively (Scheme 38).

Intramolecular cycloadditions to alkenes are controlled kinetically at relatively low temperatures[19,59,60]. Steric interaction within the cyclic transition states determines the regioisomeric structures of the resulting isoxazolidines. The exclusive formation of **189** from nitrone **187** is not surprising, since stereomodels indicate that the transition from the nitrone conformer **195** to the regioisomer **197** is hindered by a severe 1,5-transannular interaction of two hydrogen atoms of the methylene groups of **196**. Similar interactions account for the formation of five- rather than six-membered carbocycles in related intramolecular nitrone–alkene cycloadditions[61,62]. The preferential formation of cycloadduct **190** (32%) over **191** (10%) was due to entropic discrimination between the seven-membered cyclic transition state **198** leading to **190** and eight-membered cyclic transition

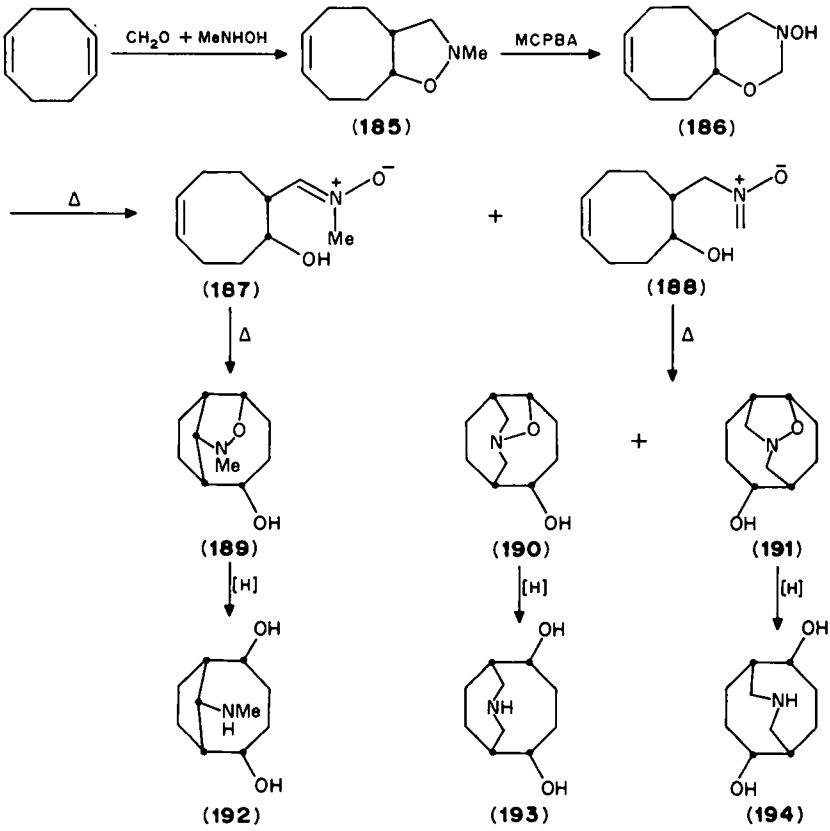


SCHEME 37

state **199** leading to **191** (Scheme 39). Similar entropic discrimination was invoked in intramolecular cycloadditions of other N-(5-alkenyl)nitrones[47].

Intermolecular cycloaddition of N-methylnitrone to 1,4- and 1,3-cyclohexadienes, followed by MCPBA N-oxidation of the resulting unsaturated isoxazolidines, **200** and **204**, and intramolecular cycloaddition of nitrones derived from N-hydroxyoxazines, **201** and **205**, gave tricyclic isoxazolidines, **202** and **206**, which converted into diols **203** and **207**, respectively (Scheme 40). Entropic discrimination between six- and seven-membered cyclic transition states also accounts for the preferential formation of cycloadducts **202** and **206**.

The synthesis of the powerful poison anatoxin-a, was achieved by using consecutive intermolecular and intramolecular nitrone cycloadditions as the key reactions[63]. Intermolecular cycloaddition of 1-pyrroline 1-oxide **208** to dienol **209** proceeded with high stereoselectivity, regioselectivity and site selectivity to give the adduct **210**. After oxidation of **210** with active MnO_2, to the enone **211**, the oxidative cleavage of the isoxazolidine with MCPBA afforded the adduct **213** through an intramolecular cycloaddition of the exclusively formed less substituted nitrone **212**. The conversion of **213** into anatoxin-a (**214**) was both direct and efficient (Scheme 41).

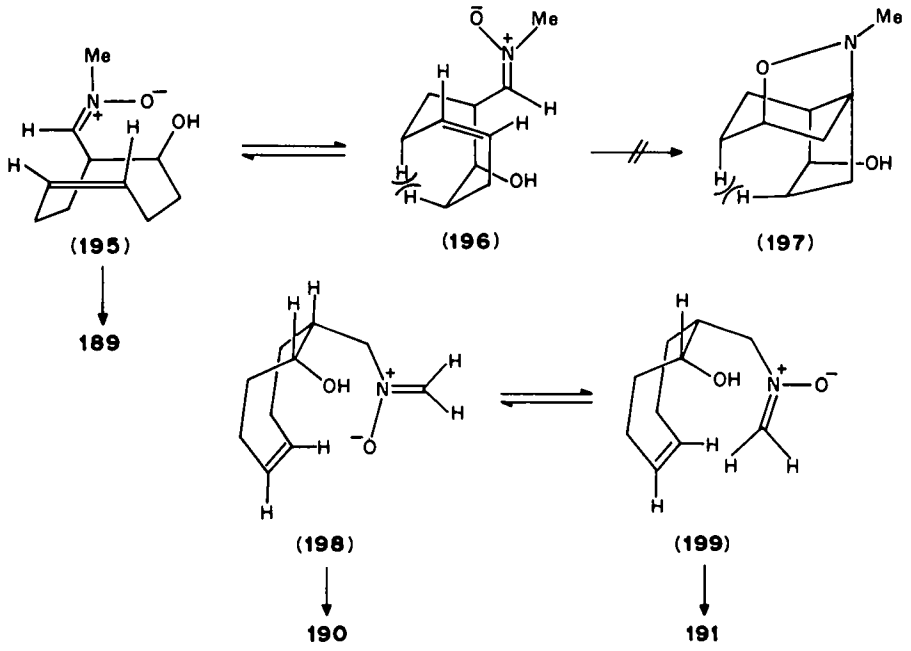


SCHEME 38

Although intermolecular cycloaddition of nitrones to alkylidenephosphoranes has been reported to afford 1,2,5-oxaazaphospholes[64], azophosphoranes **215** did not react intermolecularly with nitrones[65]. Thus, intramolecular reaction of compounds **216** carrying a nitronyl substituent at the *o*-position of the azophosphorane has been examined[65]. The reaction in toluene or DMSO with one exception proceeded from an initial attack of nitrogen atom α to the ylidic carbon on the nitrone carbon to yield a cyclic species **217**, which then converted into stable indazoylmethylenephosphoranes **218** with the elimination of a nitroso compound. The compound **216** (R^1 = Me, R^2 = COOMe) gave the corresponding indazoyl derivative **218** (R^2 = COOMe) in DMSO (at 100 °C), but the imidazoindazole **219** was formed in refluxing toluene (Scheme 42).

III. AZOMETHINE YLIDES

In the late 1970s, the investigations of azomethine ylides were mainly focused on heteroaromatic and highly stabilized N-ylides, because the only practical generation methods were the deprotonation of iminium salts and the thermal ring opening of aziridines[11]. However, the chemistry of azomethine ylides has made remarkable progress and several new methodologies for the generation of the ylides have been developed



SCHEME 39

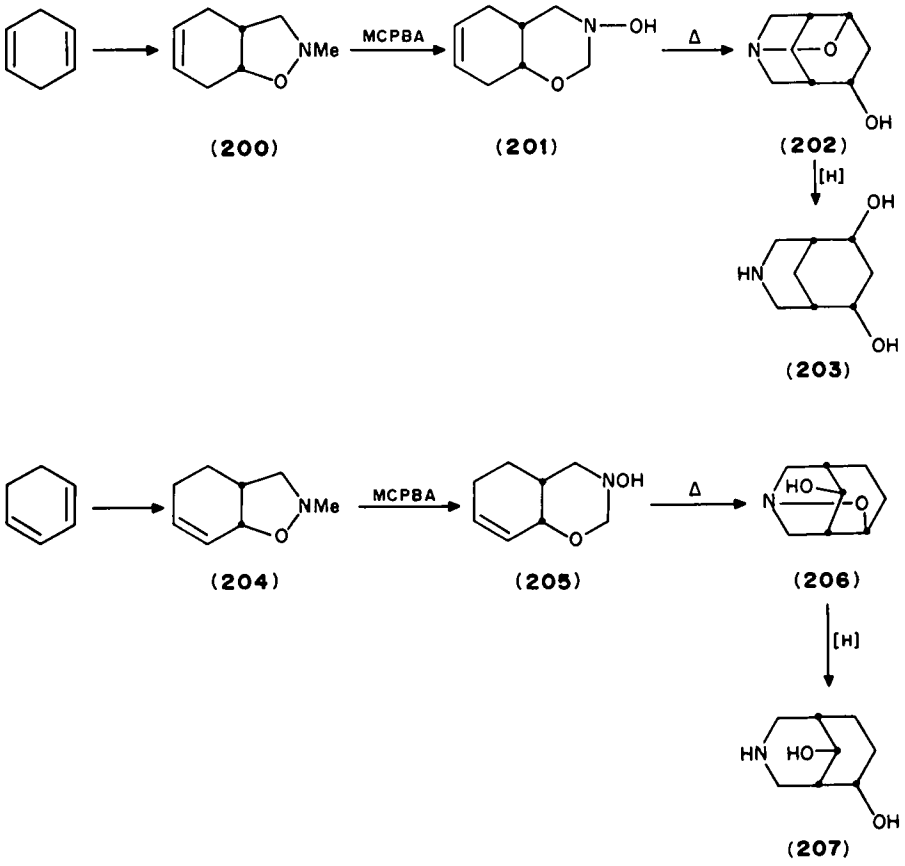
recently. The intramolecular 1, 3-dipolar cycloaddition reactions of azomethine ylides are here classified according to generation methods.

A. Ring Opening of Aziridines

The first example for the carbon–carbon cleavage of an aziridine generating an azomethine ylide was reported in 1965 by Heine and Peavy[66], who obtained a pyrroline by heating 1, 2, 3-triphenylaziridine with diethyl acetylenedicarboxylate. Other groups soon provided further examples of additions of alkenes across the 2, 3-bond of the aziridine ring[67,68]. It was observed that aziridines bearing electron-withdrawing groups were usually more reactive[66–70]. Huisgen and coworkers[71] explained the stereochemical course of azomethine ylide generation by aziridine ring-opening: the thermal and photochemical ring cleavages of aziridines involve stereospecific, conrotatory and disrotatory reactions, respectively. Although the bimolecular cycloadditions of azomethine ylides generated from aziridines have been well investigated[11,72], there are only a few examples dealing with the intramolecular version in the literature.

Padwa and Ku reported the first examples of intramolecular cycloadditions of aziridine-derived azomethine ylides[73]. Thus heating either *cis*- or *trans*-aziridine **200** bearing an ester-activated alkene gave high yields of *cis*-fused [5.5]bicyclic lactone **201** as a sole product. When an aziridine **202** bearing an alkenyl chain on the aziridine nitrogen was used, the bicyclo systems **203** (two stereoisomers) with a bridgehead nitrogen were produced (Scheme 43). However, no intramolecular cycloaddition could be observed in the absence of an activating group in the alkene moiety.

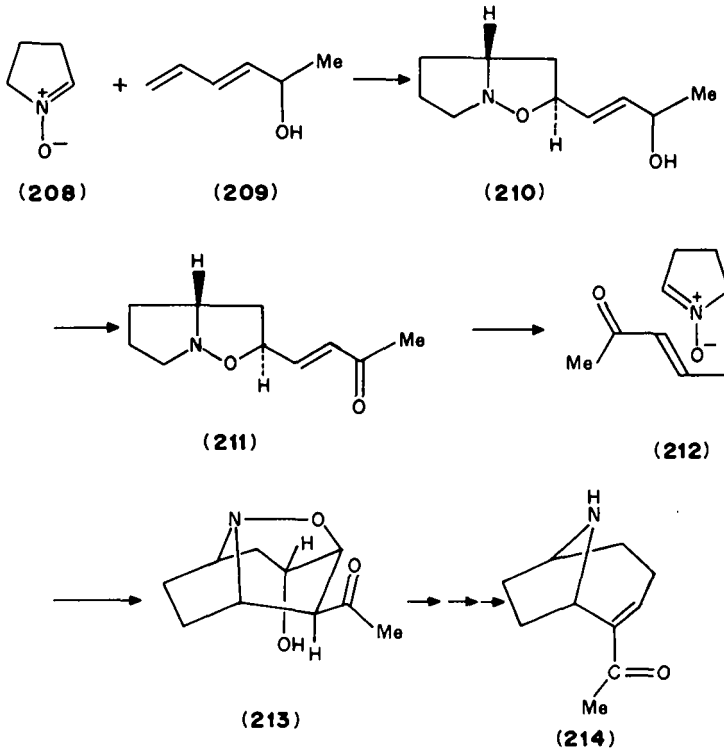
More recently, thermolysis of 3-phenyl- and 3-unsubstituted-2-alkenoyl-1-methylaziridines has been investigated[74]. 3-Unsubstituted 2-alkenoylaziridines **204a** and



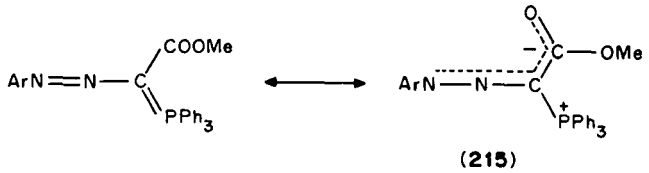
SCHEME 40

205a were unchanged even when heated at temperatures up to 200 °C for several hours, whereas 2-phenyl derivatives **204b**, **204c**, **205b** and **205c** yielded bicyclo adducts at temperatures as low as 80 °C after a few hours. Thus, aziridines **205b** and **205c** when treated at 80 °C for 10 h (or 95 °C for 2.5–3.5 h) gave a single *cis*-fused [6.5]cycloadduct **206**, and **204b** and **204c** gave again a *cis*-fused bicycloadduct **207** (Scheme 44): though the azomethine ylides bearing an aryl at one carbon and an acyl at the other are inert to unactivated alkenes, the intramolecular version overcomes this difficulty. Exclusive formation of **206** and **207** indicates the selective participation of *anti* ylides (S shape) in the stereospecific cycloaddition.

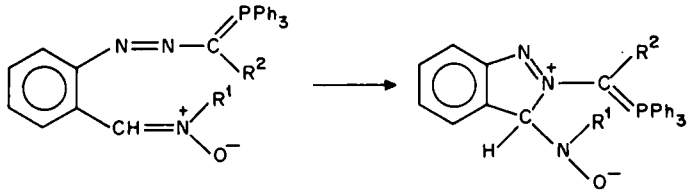
Ring opening of the aziridines **208** bearing an ester group as the only C-substituent is so difficult under the usual conditions that a technique of flash vacuum pyrolysis (FVP) has been applied[75]. Mostly *cis*-fused [6.5] and [5.5]bicyclic lactones **209** and **210** were obtained from *E*-**208** and *Z*-**208**, respectively. Interesting is a rare example for the formation of a *trans*-fused [6.5]lactone **211** together with **210** in a 1:1 ratio from *Z*-**208** (R = COMe, $n = 2$) (Scheme 45). The intramolecular version of the reaction led again to the formation of pyrrolidines even with alkenes lacking electron-withdrawing substituents.



SCHEME 41

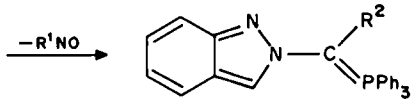


The cycloadditions of nitrones with activated alkynes provide 4-isoxazolines which readily ring open into highly stabilized azomethine ylides[76]. This concept can be utilized in an intramolecular cycloaddition[77]. Thus, nitrones **212** underwent cycloaddition with dimethyl acetylenedicarboxylate to give internal cycloadducts **216** as the final products. It is evident that the reaction proceeds via an intramolecular cycloaddition of azomethine ylides **215** generated from a ring-opening of intermediary aziridines **214** which are produced from an isomerization of initial cycloadducts **213**. In some cases isoxazoline **213** and azomethine ylide **215** were isolated. It is quite interesting that highly stabilized azomethine ylides such as **215** show sufficient reactivity toward the furan ring. Thus, nitrone **217** reacted similarly with the acetylene to give intramolecular cycloadducts **218** (Scheme 46).

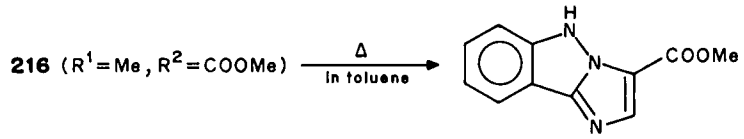


(216) (217)

R^1 = Me, R^2 = COOMe ; R^1 = CH_3, R^2 = $COCH_3$;
R^1 = Ph, R^2 = $COCH_3$; R^1 = Ph, R^2 = *p*-tosyl

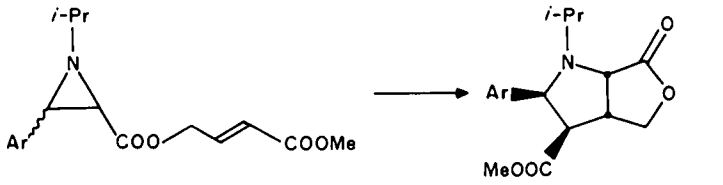


(218)

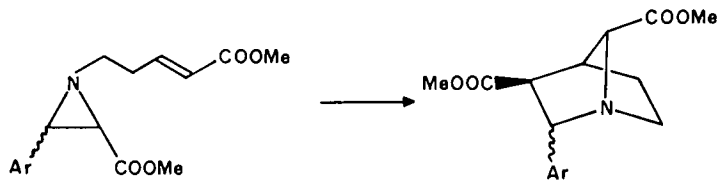


(219)

SCHEME 42

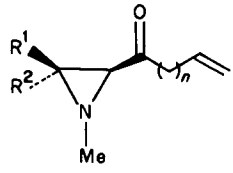


(200) (201)



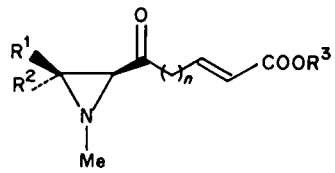
(202) (203)

SCHEME 43



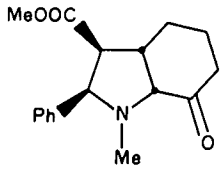
(204)

(a) $R^1=R^2=H, n=2,3$
(b) $R^1=Ph, R^2=H, n=3$
(c) $R^1=H, R^2=Ph, n=3$

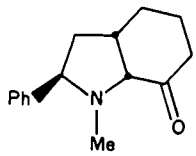


(205)

(a) $R^1=R^2=H, R^3=Et, n=2,3$
(b) $R^1=Ph, R^2=H, R^3=Me, n=3$
(c) $R^1=H, R^2=Ph, R^3=Me, n=3$

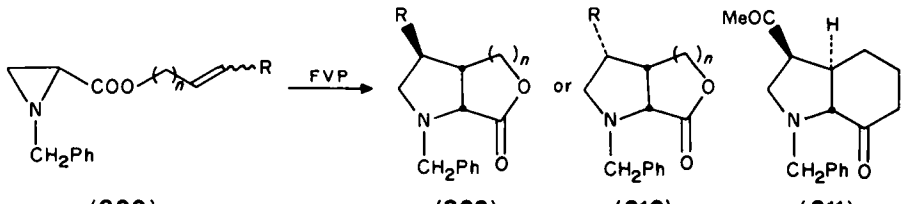


(206)



(207)

SCHEME 44



(208)
R = H, COMe
$n = 1,2$

(209) from *E*-208

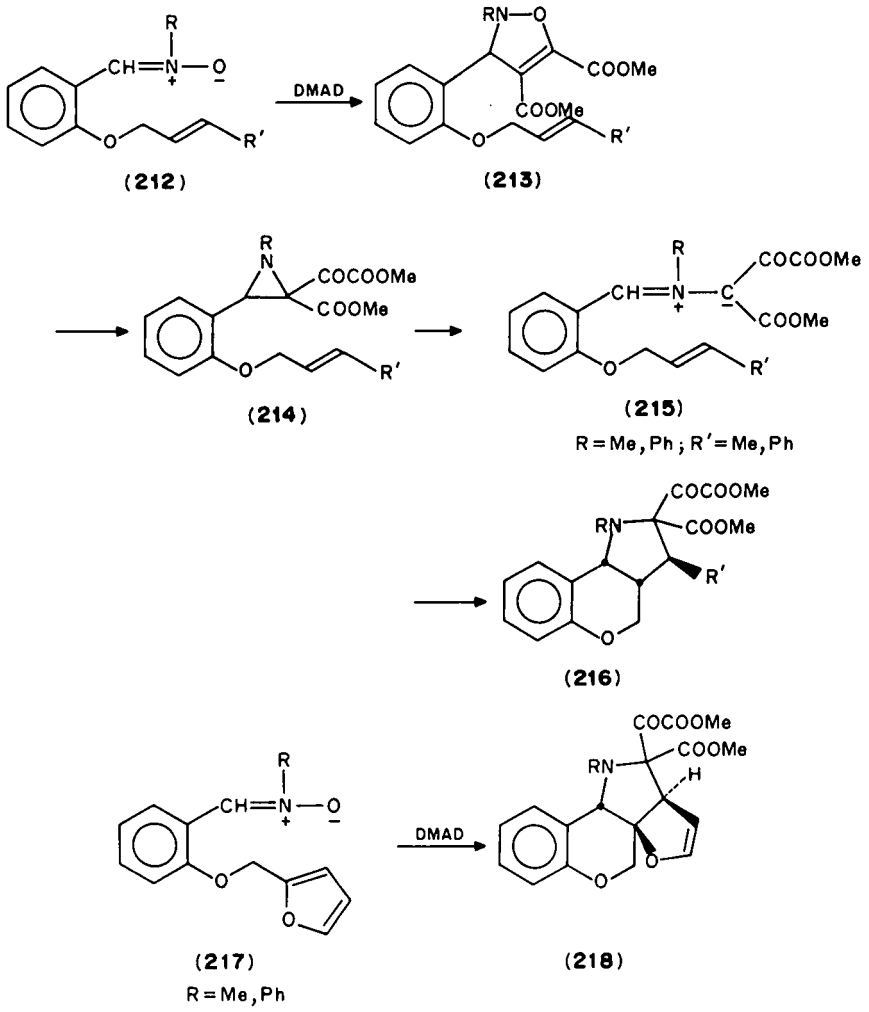
(210) from *Z*-208

(211)

SCHEME 45

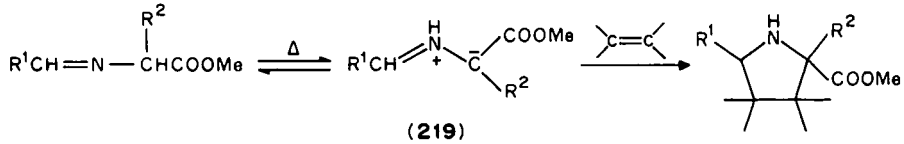
B. Imine–Azomethine Ylide Tautomerism

Several new routes to generation of azomethine ylides have been recently developed. One of them is the imine–azomethine ylide tautomerism method. The first evidence for the existence of acyclic N-unsubstituted azomethine ylides as tautomers of imines was provided by Grigg and coworkers[78]. When imines of α-amino esters are heated in benzene or toluene in the presence of alkenes or alkynes, pyrrolidine- or pyrroline-2-carboxylates are isolated in high yields. These heterocycles correspond to the products produced by the



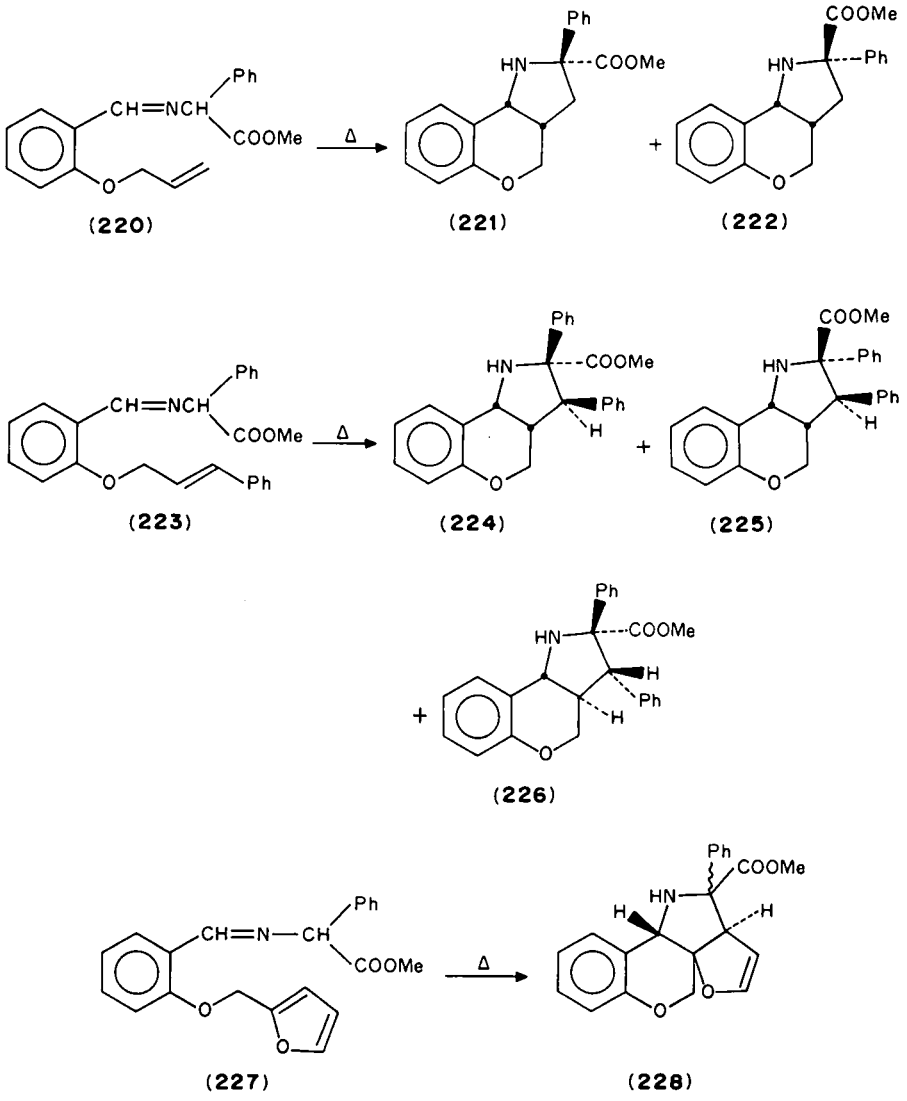
SCHEME 46

1,3-dipolar cycloadditions of N-unsubstituted azomethine ylides, indicating the thermal equilibrium between the imine esters and the azomethine ylides **219**.



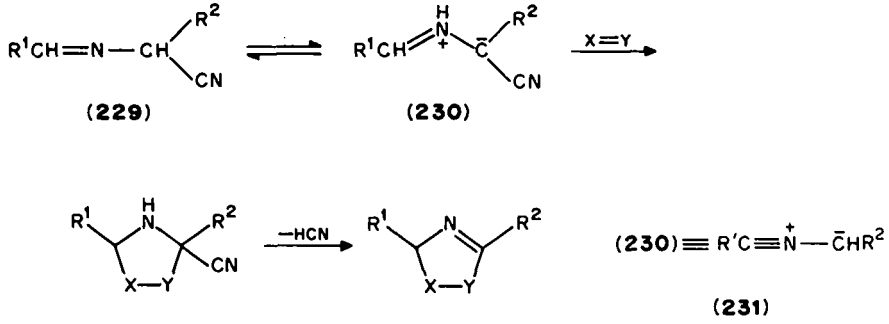
Azomethine ylides generated by a thermal tautomerization of aryl imines of phenylglycine ester react intramolecularly with alkynes[79,80] or alkenes[80,81] to give ring-fused

cycloadducts. Grigg and coworkers[82] have reported in detail the above intramolecular cycloadditions. Heating imine **220** bearing an allyloxy group in refluxing xylene afforded a 3:2 mixture of two stereoisomeric cycloadducts **221** and **222**[82]. On the other hand, intramolecular trapping of the same dipole with a cinnamyloxy group gave rise to a mixture of three stereoisomeric cycloadducts **224**, **225** and **226** in 31, 32 and 13% yields, respectively[81], showing a low stereoselectivity with respect to the ylide geometry (Scheme 47). Internal cycloaddition of the imine group in **227** to its furan dipolarophile gave **228**, albeit in poor yield[22].



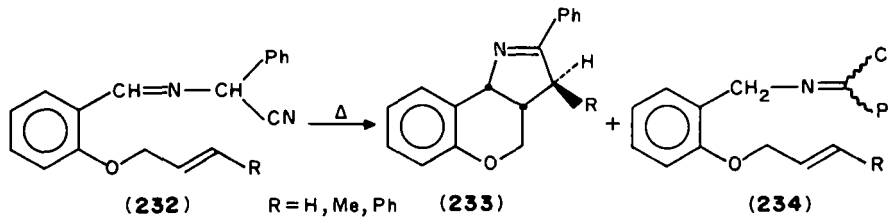
SCHEME 47

Thermal tautomerization of imines **229** derived from α-aminoalkane nitriles generates N-unsubstituted azomethine ylides **230**, which can be formally regarded as synthetic equivalents of nitrile ylides **231** owing to elimination of hydrogen cyanide from initial cycloadducts[83] (Scheme 48).



SCHEME 48

The azomethine ylides generated from imines of α-amino nitriles are intramolecularly trapped[84]. For example, heating imines **232** bearing an alkenyl dipolarophile in refluxing xylene afforded fused pyrrolines **233**, together with the isomeric imines **234** (a mixture of two stereoisomers) (Scheme 49).

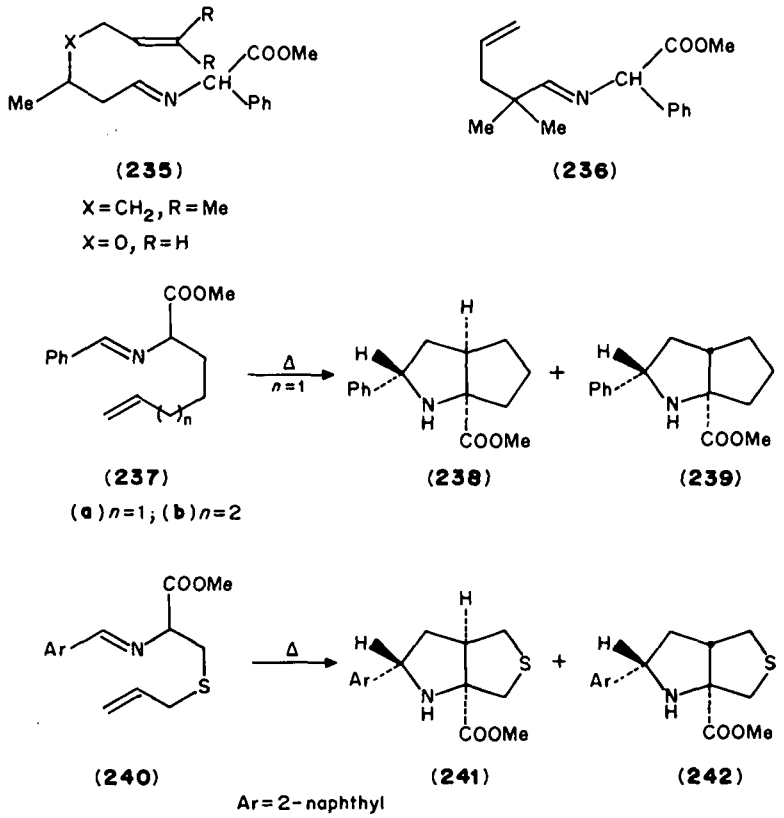


SCHEME 49

Imines such as **235** and **236** in which incorporated the dipolarophile into aliphatic aldehyde precursor did not form intramolecular cycloadducts. However, incorporation of the dipolarophile into an amino acid moiety proved more successful[82]. Heating the pentenyl glycine imine **237a** in refluxing xylene afforded an 87:13 mixture (81%) of cycloadducts, **238** (major) and **239** (minor), whereas the hexenyl glycine imine **237b** failed to undergo intramolecular cycloaddition. Under similar conditions imine **240** underwent intramolecular cycloaddition to give a mixture of the *cis*-fused **241** (92%) and the *trans*-fused cycloadduct **242** (8%) (Scheme 50).

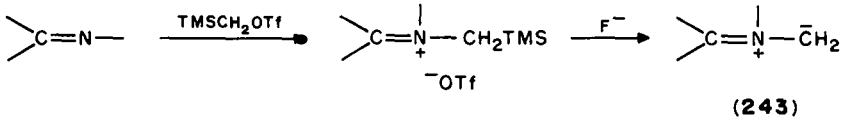
C. Desilylation of Silylmethyliminium Salts

In 1979 Vedejs and Martinez reported a new concept for the generation of nitrogen, sulfur and phosphorus ylides[85]. Their method consists of initial alkylation of the hetero atom of amines, imines, sulfides or phosphines with trimethylsilyl triflate, and subsequent desilylation of the resulting salts with a fluoride ion. For the generation of azomethine ylides, imines are treated first with the triflate to form the corresponding iminium triflates,



SCHEME 50

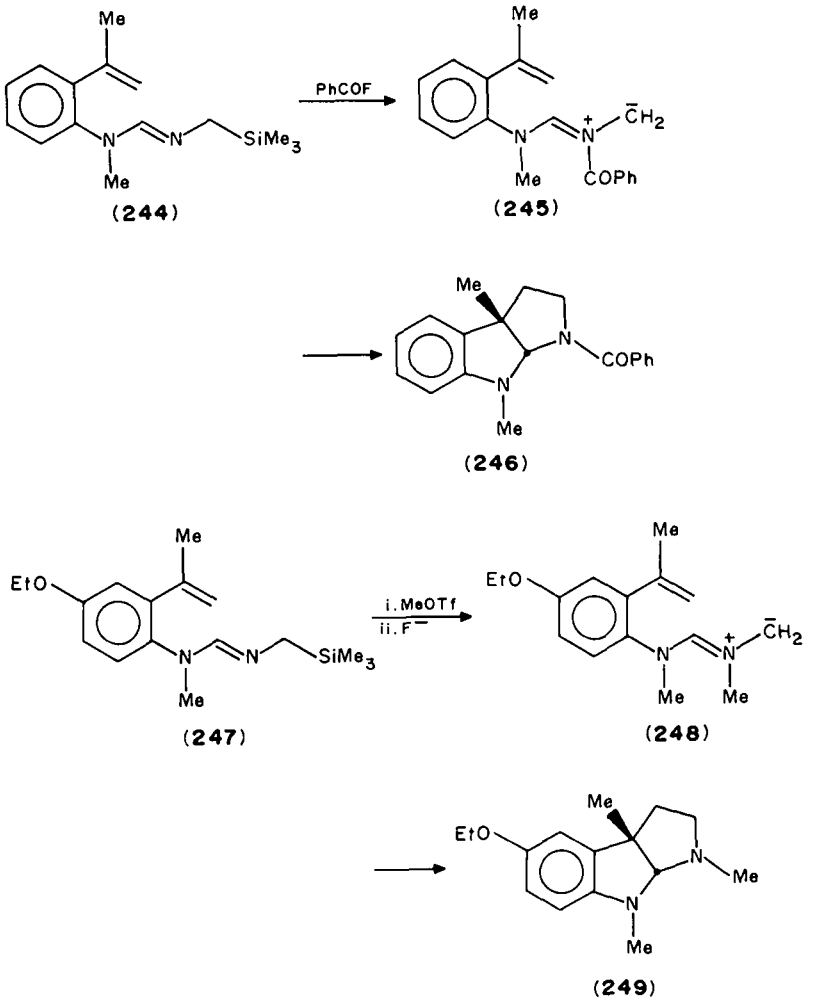
and then with fluoride ion to generate the nonstabilized azomethine ylides **243** (Scheme 51). A number of nonstabilized azomethine ylides have been generated by the Vedejs method, using imines, imidates, thioimidates and oximes.



SCHEME 51

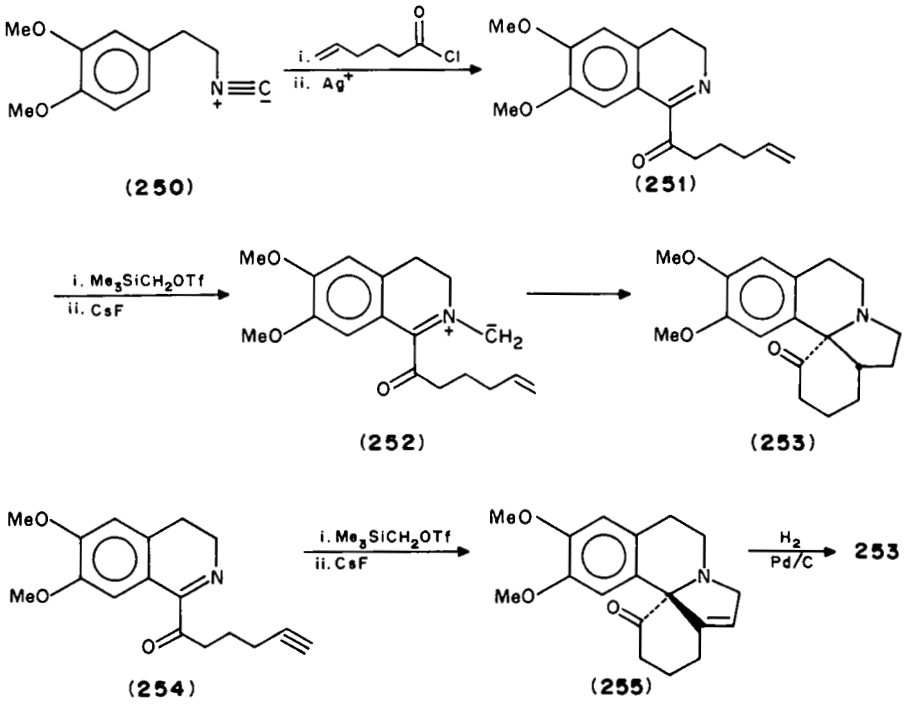
Livinghouse and Smith[86] found that silylformamidines and silylformimidates reacted with acyl fluoride to generate directly N-acylimidate methylides, which have been successfully trapped with dipolarophiles. This methodology was applied to an intramolecular version. The reaction of silylformamidine **244** with benzoyl fluoride in acetonitrile at 45 °C afforded the tricyclic aminal **246** via the nonstabilized azomethine ylide **245** in good yield[86,87]. A stereospecific synthesis of (±)-eserethole **249** embodies the

first example of an intramolecular cycloaddition of a formamidine ylide to an unactivated alkene as a central feature. Thus, formamidine **247** in several steps generated azomethine ylide **248**, which gave **249** in 70% overall yield[87,88] (Scheme 52).



SCHEME 52

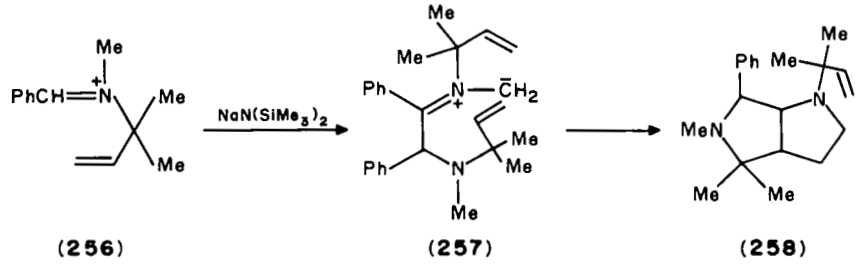
The desilylation route has been used to construct the erythrinane skeleton[89]. Thus, reaction of 2-(3,4-dimethoxyphenyl)ethyl isocyanide **250** with 5-hexenoyl chloride and subsequent cyclization produced 3,4-dihydroisoquinoline **251**. N-Silylmethylation of **251** and subsequent desilylation gave 4-oxo-15,16-dimethoxyerythrinane **253** via an azomethine ylide **252**. A similar reaction of the dihydroisoquinoline **254** bearing an alkynyl moiety afforded an intramolecular cycloadduct **255**, which was then catalytically hydrogenated to **253** (Scheme 53).



SCHEME 53

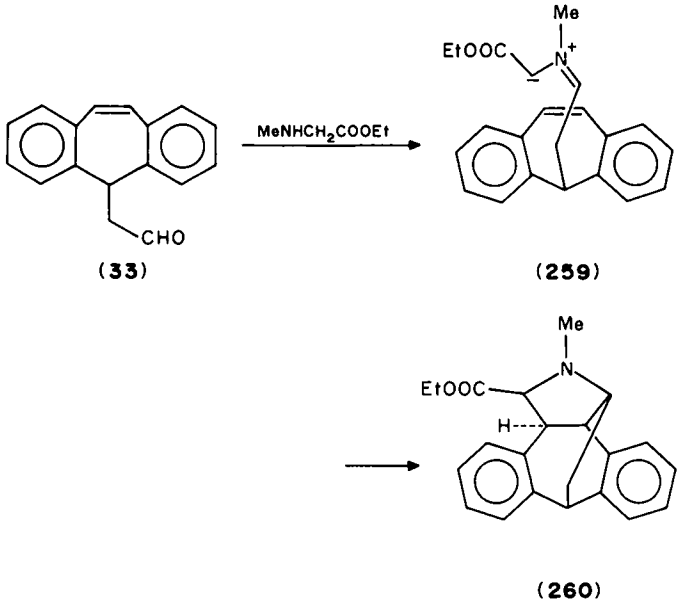
D. Deprotonation of Iminium Salts

A direct generation of azomethine ylides would be N-alkylation of imines and subsequent α-deprotonation. The involvement of intermediary azomethine ylides was speculated in the reaction of ketiminium and aldiminium salts with sodium bis(trimethylsilylamide)[90]. This reaction sequence was applied to an N-allylaldiminium salt **256**[91]. Thus, the reaction of **256** with sodium bis(trimethylsilylamide) afforded dimer **258**, whose formation was suggested to arise via the internal cycloaddition of a transient azomethine ylide **257** (Scheme 54). This is the first example of an intramolecular azomethine ylide cycloaddition.



SCHEME 54

The simplest deprotonation method for the generation of azomethine ylides consists of the condensation of N-substituted α-amino esters with carbonyl compounds. This procedure is especially useful for intramolecular cycloadditions because the substrates are simply prepared *in situ* by reacting the carbonyl compounds (or secondary amines) bearing a trapping chain with secondary amines (or carbonyl compounds). This idea was first demonstrated by Confalone and Huie[25]. The aldehyde **33** reacted with ethyl sarcosinate and the resulting azomethine ylide **259** was trapped by the internal alkene to give **260** in good yield (Scheme 55).

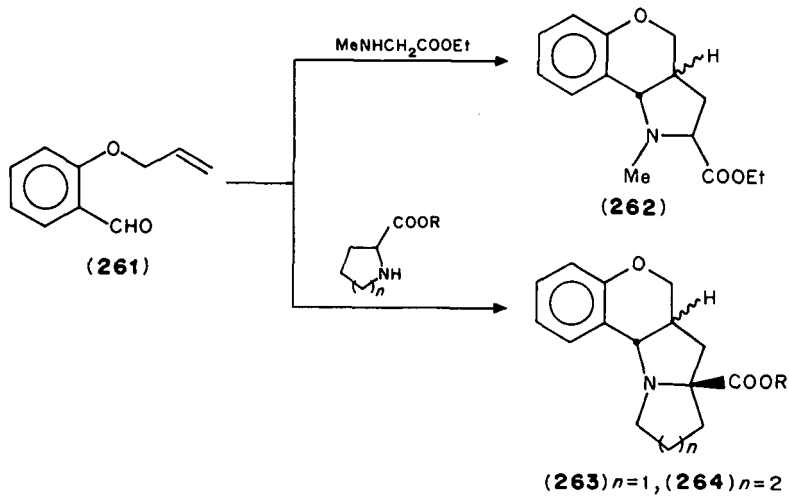


SCHEME 55

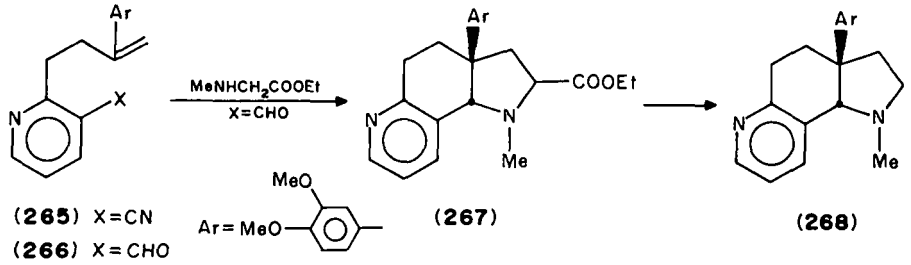
Advantages of this method include the possibility of wide structural variations from the single precursor as well as high yields. Starting from 2-(allyloxy)benzaldehyde **261**, intramolecular cycloadducts **262** (97%, *cis/trans* = 10), **263** (R = Me, 98%, *cis/trans* = 2.5) and **264** (R = Et, 99%, *cis/trans* = 11.5) were obtained by treating with ethyl sarcosinate, methyl prolinate and ethyl pipecolinate, respectively[92] (Scheme 56).

This method was successfully applied to the total synthesis of the sceletium alkaloid A_4[92]. Deprotonation of 3-cyano-2-methylpyridine with lithium hexamethyldisilazane and subsequent alkylation with 3-bromo-2-(3, 4-dimethoxyphenyl)propene gave cyano alkene **265**, which was converted into the desired aldehyde **266** by Dibal reduction. Heating **266** with the sarcosinate gave the tricyclic adduct **267**, which was then converted into (±)-sceletium alkaloid A_4 **268** (Scheme 57).

Further applications for the preparation of [5.5] and [6.5]ring-fused systems using functionalized azomethine ylides have been reported[93]. Aldehydes **269** condensed with N-alkyl glycinates to yield the *cis*-fused pyrrolidines **271** through an intramolecular cycloaddition of the presumed intermediate azomethine ylides **270** (Scheme 58). The successful cyclization of these functionalized olefin aldehydes overcomes some limitations



SCHEME 56



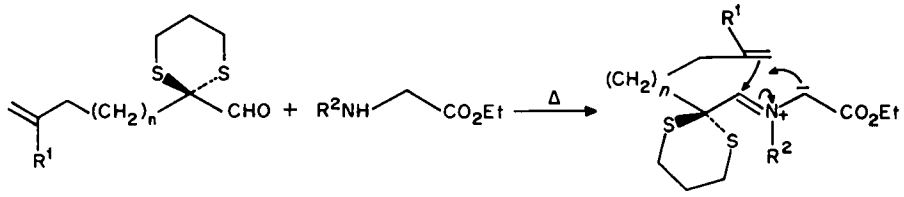
SCHEME 57

in the parent cases, because the cycloaddition failed for 6-heptenal and 6-phenyl-6-heptenal.

Condensation of allenic aldehyde **272** with ethyl sarcosinate was found to give a mixture of two cycloadducts, **273** (19%) and **274** (28%) (Scheme 59). The observed regiochemistry favors the isomer **274**, and the route provides a ready access to the lycorenine alkaloid system.

E. Decarboxylative Condensation of α-Amino Acids with Carbonyl Compounds

Decarboxylative condensation of α-amino acids with carbonyl compounds provides a very useful route to the generation of nonstabilized azomethine ylides[94]. Internal trapping of azomethine ylides generated from this procedure has been reported. Heating 2-(allyloxy)naphthalene-1-carboxaldehyde **275** with phenylglycine[95] or sarcosine[96] in DMF gave the corresponding *cis*-fused cycloadduct **277** or **279**, respectively. Similarly, the reaction of *o*-(allyloxy)benzaldehyde **261** with proline afforded two stereoisomeric cycloadducts **281**. It is evident that cycloadducts **277**, **279** and **281** arise via an



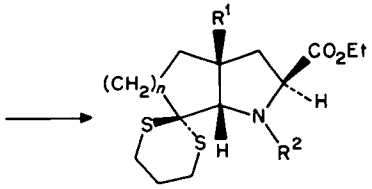
(269)

(a) $n=1, R^1=H$

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

(c) $n=2, R^1=Ph$

(270)



(a) $n=1, R^1=H, R^2=Me$ (80%)

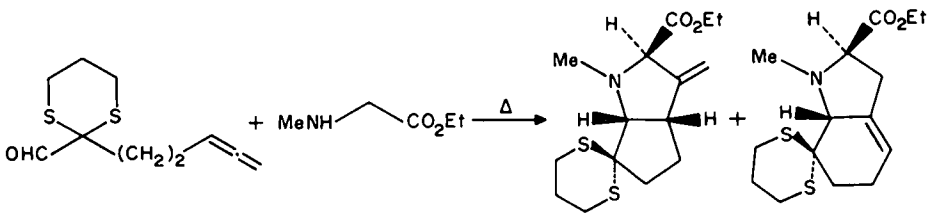
(b) $n=2, R^1=H, R^2=Me$ (68%)

(c) $n=2, R^1=H, R^2=CH_2Ph$ (70%)

(d) $n=2, R^1=Ph, R^2=Me$ (51%)

(271)

SCHEME 58



(272) (273) (274)

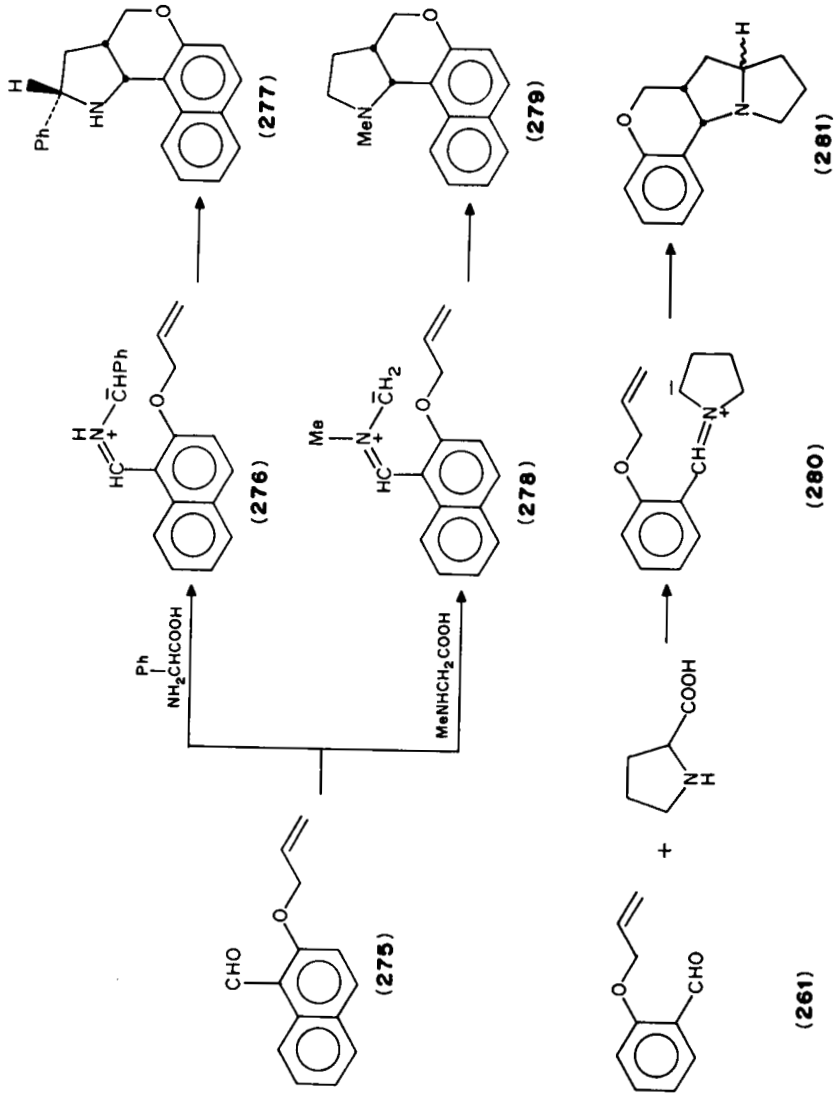
SCHEME 59

intramolecular cycloaddition of intermediary azomethine ylides **276**, **278** and **280**, respectively (Scheme 60).

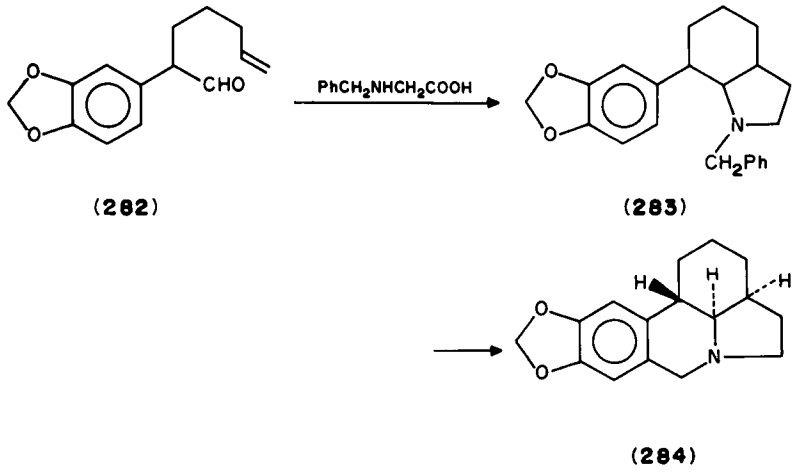
This procedure succeeded in a short and stereospecific synthesis of (±)-α-lycorane[97]. Thus, heating the aldehyde **282** with N-benzylglycine in toluene gave a single isomer of the intramolecular cycloadduct **283**. Debenzylation of **283** by catalytic hydrogenation, followed by cyclization with formaldehyde, provides (±)-α-lycorane **284** (Scheme 61).

F. Mesoionic Δ^2-Oxazolium-5-oxides

The mesoionic Δ^2-oxazolium-5-oxides, referred to as munchnones, are well known to behave as cyclic azomethine ylides, and their bimolecular cycloadditions have been investigated in detail[98]. It has been reported by Padwa and coworkers that munchnones

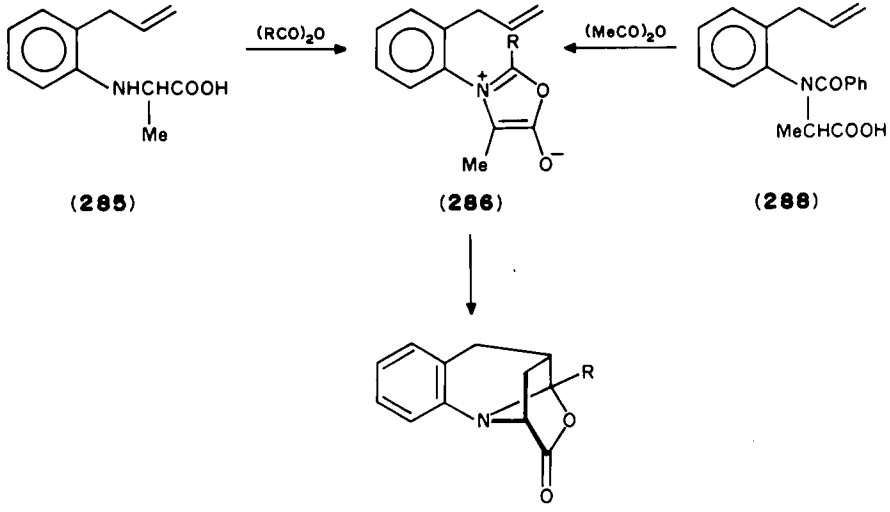


SCHEME 60



(282) (283) (284)

SCHEME 61



SCHEME 62

bearing a suitably located dipolarophilic function undergo smooth intramolecular cycloaddition to form novel heterocycles[99,100].

Treatment of N-(*o*-allylphenyl)alanine **285** with acetic anhydride at 55 °C gave cycloadduct **287** (R = Me) in 54% yield. Similarly, treatment of **285** with benzoic anhydride afforded an 81% yield of cycloadduct **287** (R = Ph), which was also obtained from the reaction of N-benzoyl-N-(*o*-allylphenyl)alanine **288** with acetic anhydride. These are intramolecular cycloadditions of an unstable munchnone intermediate **286** to an unactivated allylic double bond. Cycloaddition of the munchnone derived from N-(*o*-allylphenyl)-2-phenylglycine **289** and acetic anhydride gave a mixture of two regioiosmeric cycloadducts **290** (R = Me) and **291** (R = Me) in 62 and 10% yields, respectively. Opposite regioselectivity was encountered in the intramolecular cycloaddition of the munchnone derived from heating **289** with benzoic anhydride. In this case **290** (R = Ph) and **291** (R = Ph) were formed in a 1:2 ratio[99,100] (Scheme 62).

All attempts to detect intramolecular cycloaddition of munchnone **293** derived from N-methyl-N-(*o*-allylbenzoyl)-2-phenylglycine **292** failed. However, munchnones **295** derived from the treatment of homologous unsaturated phenylglycines **294** with acetic anhydride have been found to undergo an intramolecular cycloaddition[100]. Treatment of **294** (R = Ph) with acetic anhydride gave a 17% yield of tricyclic compound **299** (R = Ph), which corresponds to the compound with loss of carbon dioxide and hydrogen from a primary cycloadduct **296** (R = Ph). In the reaction of **294** (R = Me) with acetic anhydride, 4,5-dihydrobenzindole **299** (R = Me) and 3-acetyltetrahydrobenzindole **300** were formed in low yields, respectively. The compound **300** was suggested to form by the acetylation of the enamine functionality of the intermediate tetrahydrobenzindole **298** (Scheme 63).

IV. DIAZOALKANES

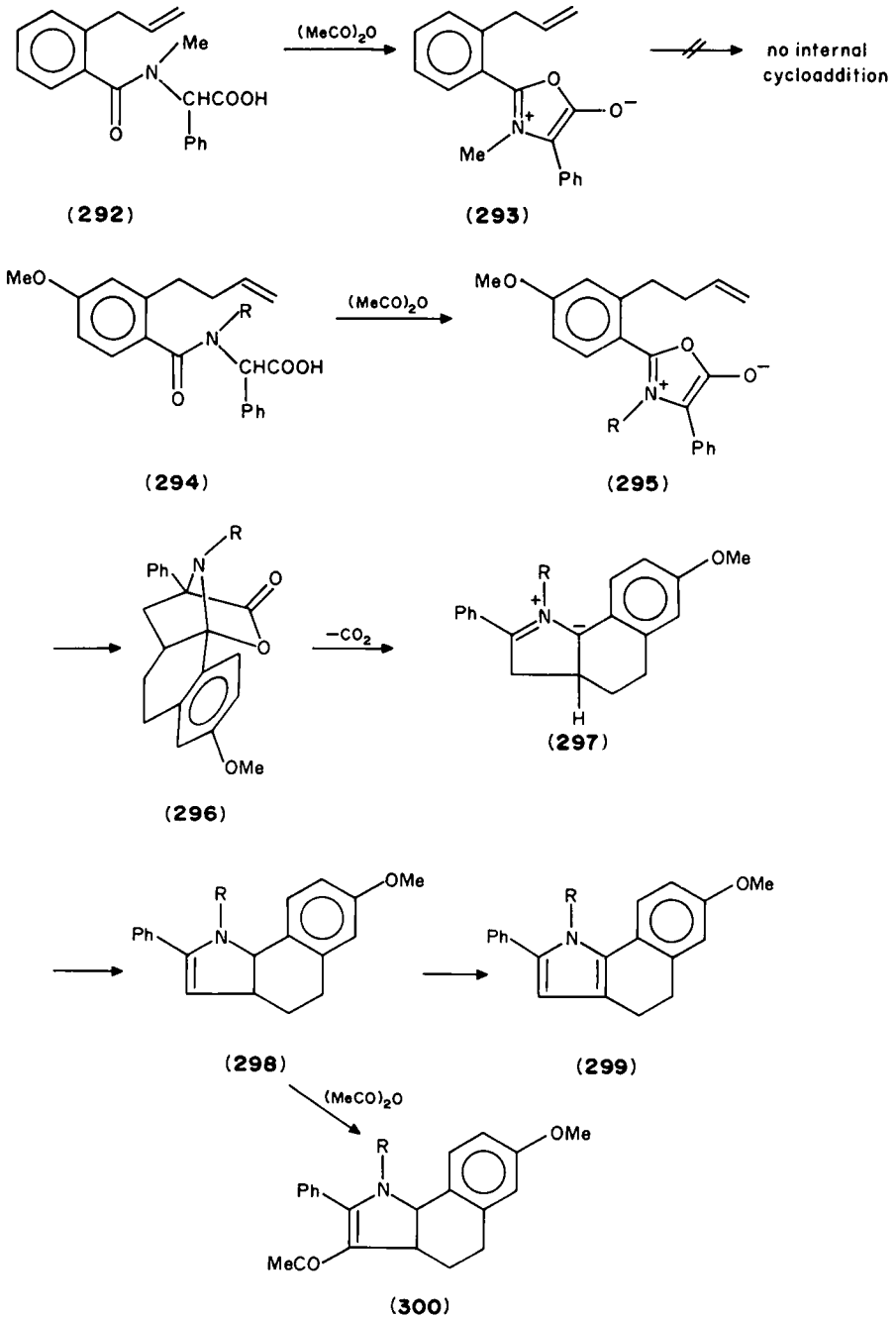
About 100 years ago, ethyl diazoacetate and diazomethane were already found to undergo cycloaddition with carbon–carbon multiple bond systems[101,102]. Many papers dealing with bimolecular cycloaddition of diazoalkanes have since appeared[103], but the intramolecular versions were reported only in the 1960s[104–106] and have not received much attention.

A. 3-Butenyl- and 4-Pentenyl-substituted Diazomethane Systems

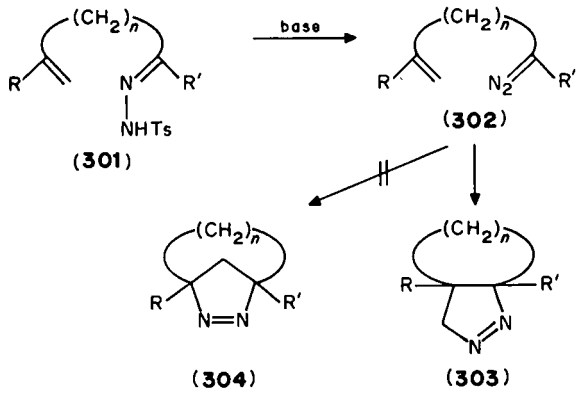
An early investigation indicated that thermal intramolecular cycloaddition of diazoalkanes of type **302**, generated from the tosylhydrazones **301**, leads to the formation of bicyclo[*n*.3.0]azoalkanes **303** rather than bicyclo[*n*.2.1]azoalkanes **304**[105], and the results were confirmed by recent works[107,108] (Scheme 64).

Wilson and coworkers have found a facile acid-catalyzed method[107] in which the tosylhydrazones **301** ($n = 2, 3$) undergo intramolecular cyclization to give the corresponding bicyclo[*n*.2.1]azoalkanes **304** ($n = 2, 3$) (Scheme 65). The less strained [3.2.1]system is formed with the greater ease, and in either system the intramolecular cyclization is favored by more nucleophilic alkenes (Table 1). Boron trifluoride etherate was proved to be the most generally applicable acid. In the reaction of the tosylhydrazone **301d**, the azoalkane **304d** was formed along with the intermolecular condensation product **305**. On the other hand, the reaction of **301f** under various conditions has been found to produce no azoalkane **304f**, but instead afforded two intermolecular condensation products **306** and **307**.

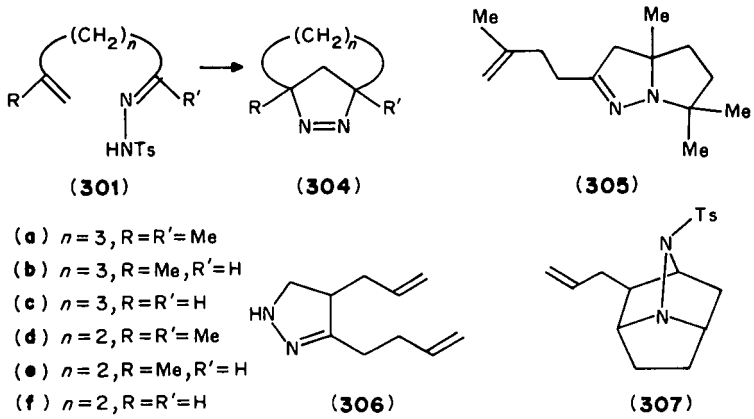
The formation of products was rationalized in terms of intervention of the initially formed imminium salt **308** which undergoes an internal cyclization with loss of proton to


(MeCO)2O
no internal cycloaddition
(292)
(293)
(294)
(295)
(296)
−CO2
(297)
(298)
(299)
(300)

SCHEME 63



SCHEME 64

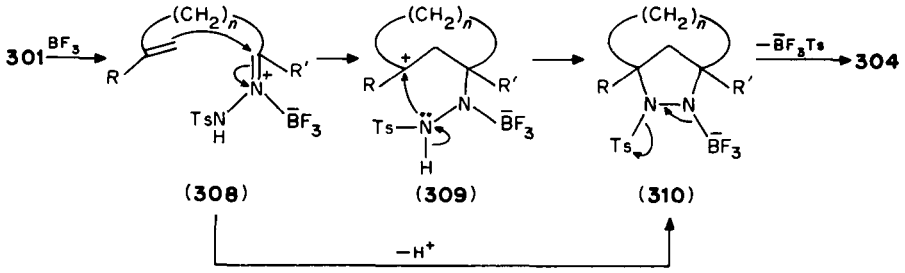


SCHEME 65

TABLE 1

	Conditions	Product (%)
301a	$Et_2O \cdot BF_3$, CH_2Cl_2, 0 °C–RT, 2.5 h	**304a** (87)
	$AlCl_3$, C_6H_6, RT, 2 h	(65)
	TsOH, C_6H_6, 65 °C, 2.5 h	(45–50)
	H_2SO_4, C_6H_6, 60 °C, 1 h	(15)
301b	$Et_2O \cdot BF_3$, CH_2Cl_2, 0 °C, 0.5 h	**304b** (46)
301c	$Et_2O \cdot BF_3$, CH_2Cl_2, 0 °C–RT, 24 h	**304c** (14)
301d	$Et_2O \cdot BF_3$, C_6H_6, reflux, 6 h	**304d** (42), **305** (39)
301e	$Et_2O \cdot BF_3$, CH_2Cl_2, reflux, 18 h	**304e** (55)
301f	$Et_2O \cdot BF_3$, variety of conditions	**304f** (0), **306** (36) **307** (38)

yield **310** by a stepwise (**308** → **309** → **310**) or concerted (**308** → **310**) mechanism (Scheme 66).



SCHEME 66

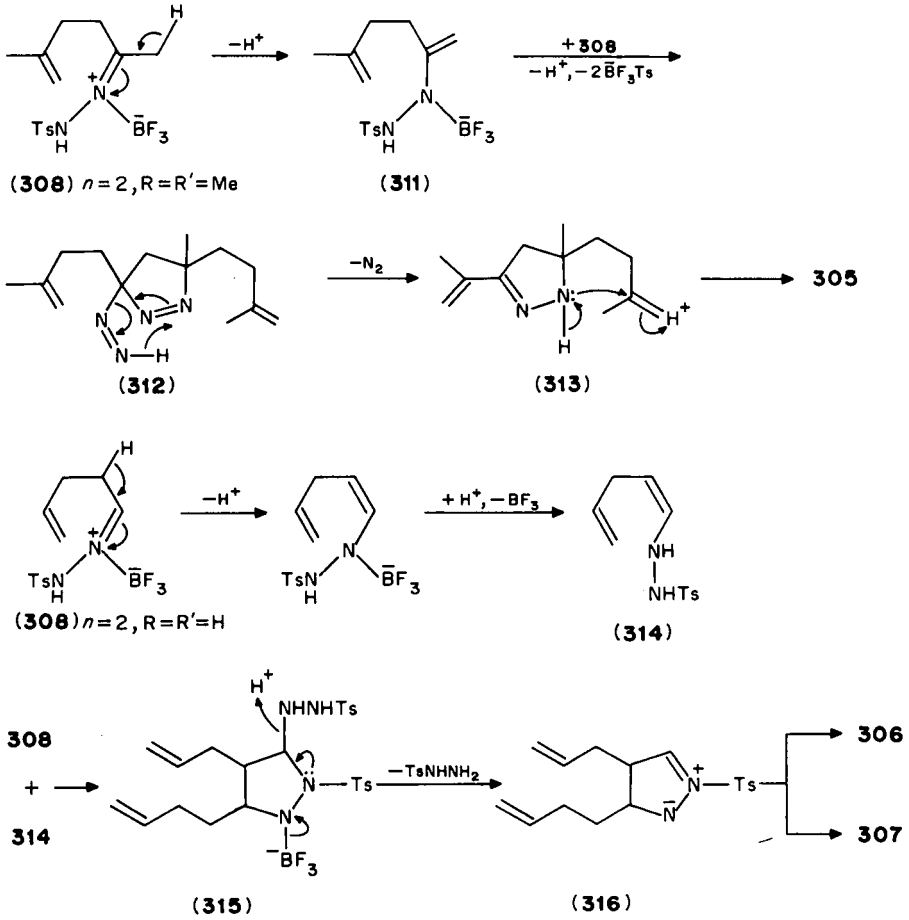
The formation of **305** in the reaction of **301d** was explained by the initial reaction between **308** and an enamine intermediate **311**, generated from **308** with loss of proton from a methyl group, followed by elimination of nitrogen and subsequent cyclization (**308** → **311** → **312** → **313** → **305**). On the other hand, a cyclic azomethine imine dipole **316** is involved as a key intermediate in the reaction of **301f**. Thus, the condensation between **308** and an enamine **314**, generated from **308**, results in the diaza heterocycle **315** in which the alkenic side-chains are on adjacent carbon atoms. The elimination of tosylhydrazine from **315** yields azomethine imine **316** which undergoes loss of toluenesulfinic acid followed by aromatization to give **306**, or an intramolecular dipolar cycloaddition to give the tricyclic hydrazine **307** (Scheme 67).

This acid-mediated intramolecular cyclization constitutes a new mode of tosylhydrazone chemistry which should complement the more conventional chemistry of tosylhydrazone under basic conditions.

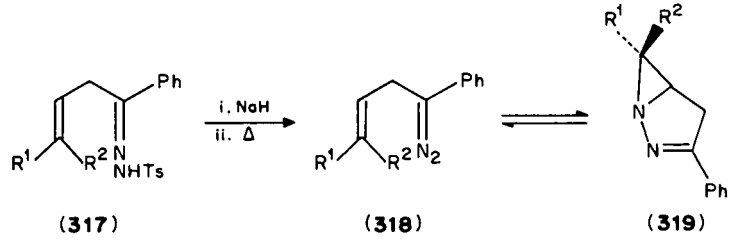
B. 2-Allyl-substituted Diazomethane Systems

Mukai[109,110] and Padwa[111,112] have independently demonstrated that 2-allyl-substituted diazomethanes undergo a formal nitrene-type 1,1-cycloaddition to give 1,2-diazabicyclo[3.1.0]hex-2-enes instead of the usual 1,3-dipolar cycloaddition to give 2,3-diazabicyclo[3.1.0]hex-2-enes.

Mukai and coworkers investigated thermolysis of the sodium salts of 2-allyl-substituted tosylhydrazones **317**[109,110]. Heating the sodium salt of (*E*)-1,4-diphenyl-3-buten-1-ene tosylhydrazone **317a** in refluxing carbon tetrachloride for 1 h afforded a 1.9:1 mixture of the diazomethane **318a** and exo-3,6-diphenyl-1,2-diazabicyclo[3.1.0]hex-2-ene **319a**, and after 10 days the ratio **318a**/**319a** was observed to be 0.4. Further example indicated that these substituted diazoalkanes undergo intramolecular 1,1-cycloaddition to furnish stereoselective products, 1,2-diazabicyclo[3.1.0]hexenes. Thus, diazomethane **318b** generated from the sodium salt of (*E*)-1-phenyl-3-penten-1-one tosylhydrazone **317b** was found to cyclize rapidly and, upon standing for 1 h at room temperature, afforded 72% yield of *exo*-1,2-diazabicyclohexene **319b** as a sole isomer. Heating the sodium salt of (*Z*)-isomer **317c** in refluxing carbon tetrachloride for 1 h gave diazomethane **318c** and *endo*-1,2-diazabicyclohexene **319c** in the ratio 1.5:1, and ^{1}H NMR analysis of the crude reaction mixture after 4 days revealed the formation of **319c** in 51% yield. The ratio **319b**/**319c** determined by HLC analysis was 1/84.4, indicating the occurrence of 98.8% high stereoselective 1,1-cycloaddition (Scheme 68). Thermal reversibility between aziridine **319** and diazomethane **318** was also observed. When aziridines were heated in refluxing carbon



SCHEME 67



(a) R^1=Ph, R^2=H; (b) R^1=Me, R^2=H; (c) R^1=H, R^2=Me; (d) R^1=R^2=Me

SCHEME 68

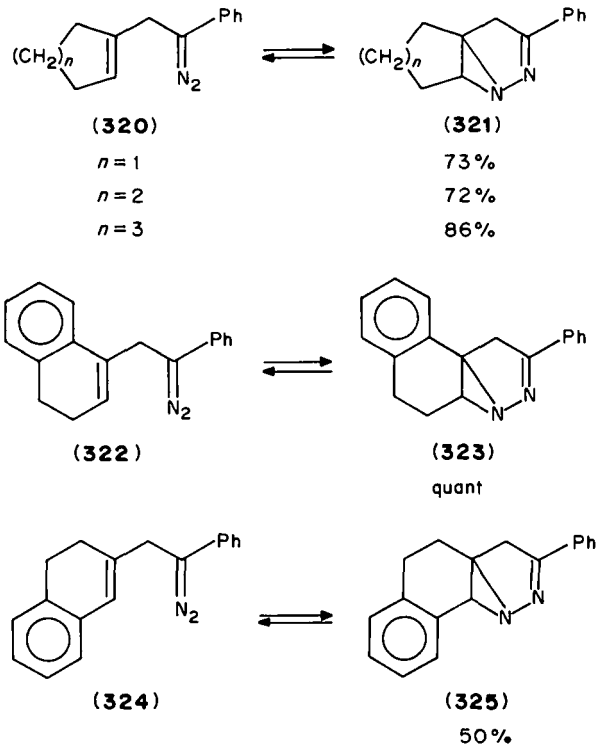
TABLE 2

	318 :	319
From **319a**	2.3	1
319b	1	4.8
319c	1.9	1
319d	1	2

tetrachloride for 1 h, an equilibrium mixture of the corresponding aziridine **319** and diazomethane **318** was formed (Table 2).

Thermolysis of the sodium salts of tosylhydrazones **317** in benzene at 80 °C was found to give similar results[111,112]. The stereospecificity of the 1, 1-cycloaddition is similar to that involved in the intramolecular carbene-type addition of nitrile ylides[113] and nitrile imines[114].

Inspection of molecular models of the allyl-substituted diazomethane system indicates that the normal two-plane orientation approach of the diazo group and allyl π system is impossible due to geometric restrictions of the system. Consequently the normal mode of 1, 3-dipolar addition does not occur here. Instead, attack of the terminal nitrogen atom of the diazo group on the neighboring double bond occurs to generate the 1,2-

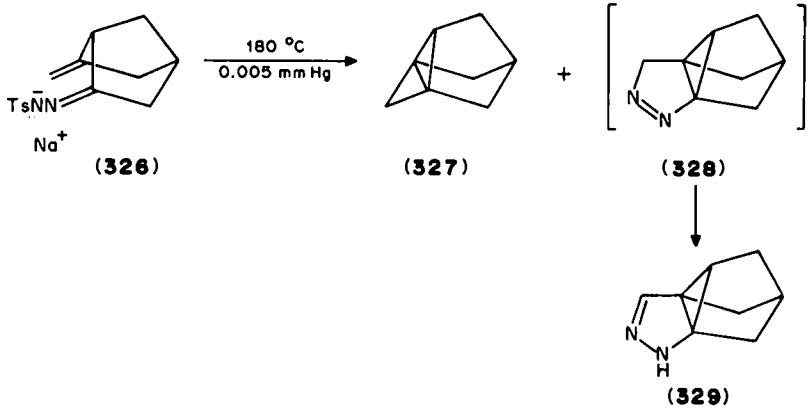


SCHEME 69

diazabicyclohexene ring system. The fact that 1,1-cycloaddition is limited to the phenyldiazo derivatives has been rationalized by theoretical studies in terms of the potential nitrene character of the terminal nitrogen atom of phenyldiazomethane. The energies and shapes of HOMO of the delocalized π system and the orthogonal, unoccupied, 2π orbital are such that phenyldiazomethane could undergo concerted 1,1-cycloaddition to electron-rich alkenes provided steric requirements are favorable for the process[115].

Similar 1,1-cycloadditions were observed to occur with diazoalkanes **320**, **322** and **324** which were generated from the corresponding sodium salts of tosylhydrazones[109] (Scheme 69).

Pyrolysis of the dry sodium salt **326** of 6-methylene-2-norbornane tosylhydrazone at 180 °C in vacuo produced 50% yield of a 2:1 mixture of 2,6-methano-2,6-dehydronorbornane **327** and the dihydro-1*H*-pyrazole derivative **329**[116]. The heterocycle **329** is a diaza[3.3.1]propellene derived from tautomerization of the initially formed intramolecular 1,3-dipolar cycloadduct **328** of the diazoalkane intermediate (Scheme 70).

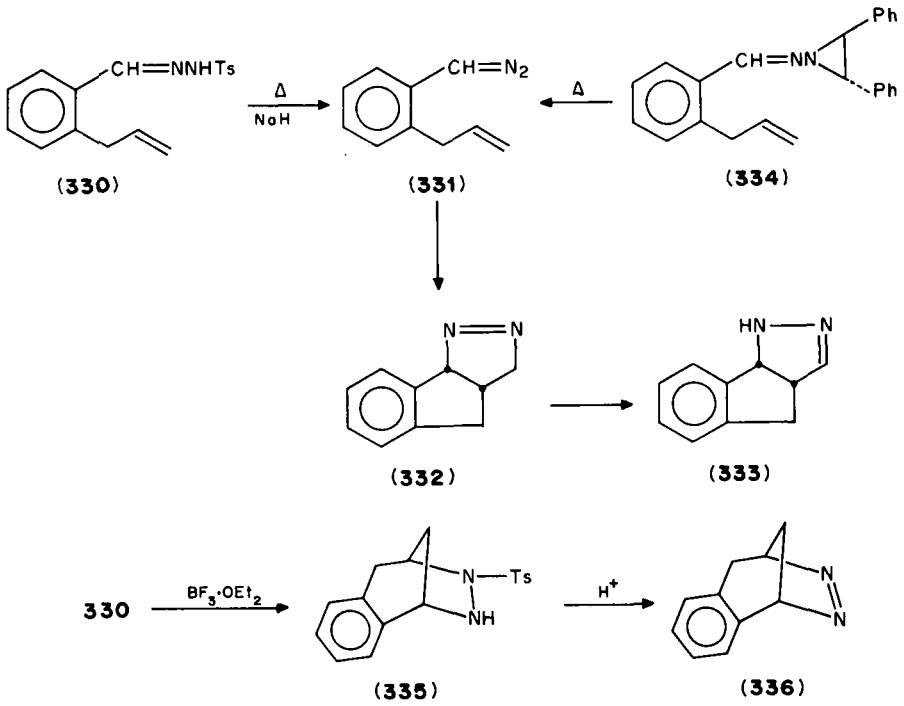


SCHEME 70

C. *o*-(Alkenyl)phenyldiazomethane Systems

o-Allylbenzaldehyde tosylhydrazone **330** was found to exhibit hebavior similar to hydrazones of type **301** ($n = 3$)[108]. Thermolysis of the sodium salt of **330** at 120 °C gave *cis*-tetrahydroindenopyrazole **333** (51%), apparently formed by intramolecular dipolar cycloaddition of the initially generated diazoalkane **331** followed by a proton transfer of the transient cycloadduct **332**. This sequence was supported by thermolysis of aziridinyl imine **334** as a masked diazoalkane which resulted in the isolation of the cycloadduct **332** in 75% yield. In contrast to the thermal result, treatment of tosylhydrazone **330** with boron trifluoride etherate followed by silica gel chromatography gave 4,5-dihydro-1,4-methano-1*H*-2,3-benzodiazepine **336** as the exclusive product in an excellent yield. Examination of the crude reaction mixture before column chromatography clearly showed the presence of **335** as an isolable intermediate (Scheme 71).

A high degree of regio- and stereospecificity was observed in thermal cycloaddition of *o*-(2-butenyl)phenyldiazomethanes. Thus, thermolysis of the sodium salt of (*E*)-butenylbenzaldehyde tosylhydrazone **337** or of (*E*)-butenylphenylmethyleneaziridinamine **338** at 80 °C afforded the same single product, *exo*-tetrahydro-3-methylindenopyrazole **339**. Similarly, thermolysis of (*Z*)-aziridinamine **340** gave the *endo*-methyl-substituted

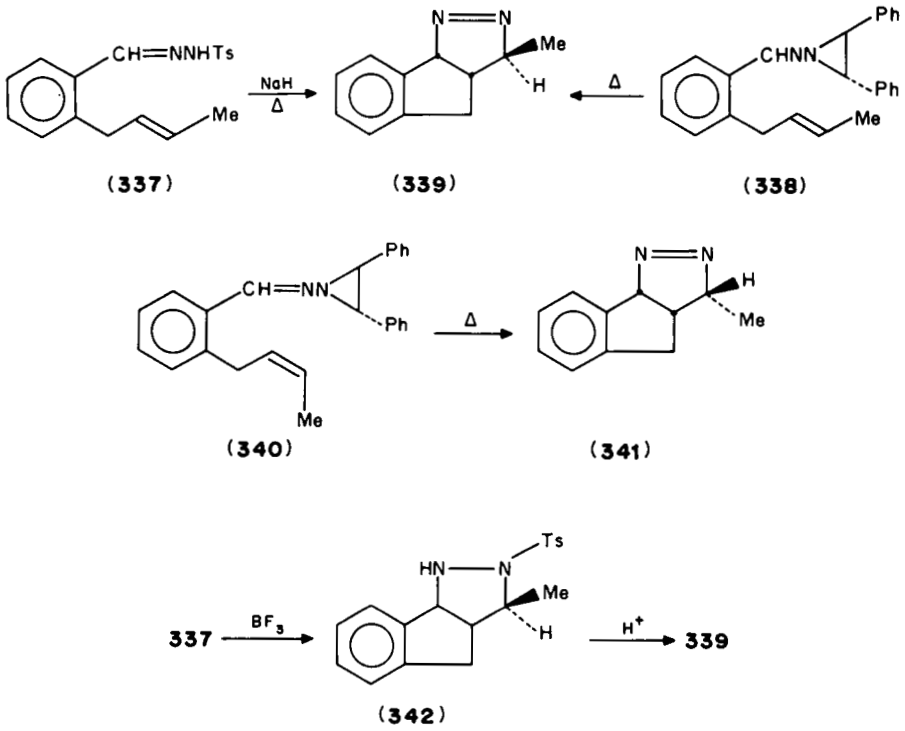


SCHEME 71

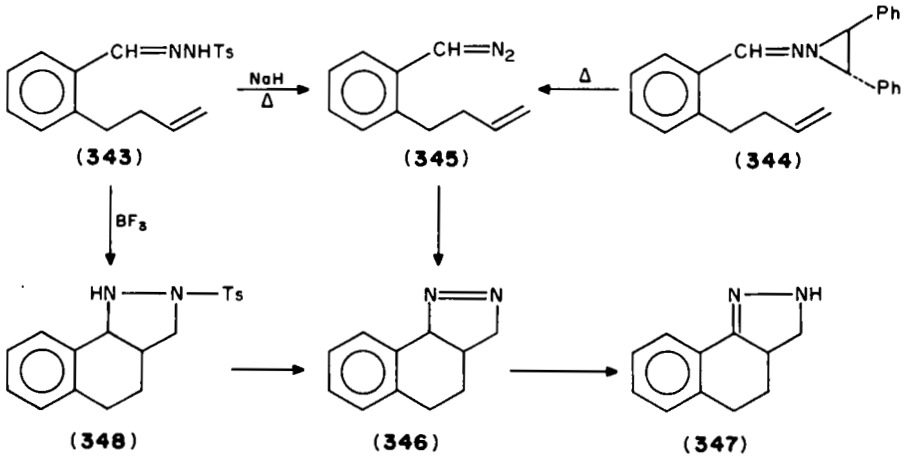
pyrazoline **341** as the sole product. It has been found that treatment of tosylhydrazone **337** with boron trifluoride etherate gave rise to hexahydroindenopyrazole **342** which was readily converted into **339**[108] (Scheme 72). This result clearly indicates that attachment of a methyl substituent on the double bond has a pronounced effect on the regiochemistry of the Lewis acid-induced cyclization of the *o*-allyl-substituted tosylhydrazone system.

o-(3-Butenyl)phenyldiazomethane **345**, generated either from **343** or from azirinamine **344**, undergoes similar cycloaddition to that of *o*-allylphenyldiazomethane system **330** or **337** to give **347** via **346**. Treatment of tosylhydrazone **343** with boron trifluoride etherate resulted in the formation of **348** which, on heating, produced **346** (Scheme 73). In this case, as in the case of tosylhydrazone **337**, none of the alternative 7,8-diazabenzobicyclo [4.2.1]hexene regioisomer can be detected.

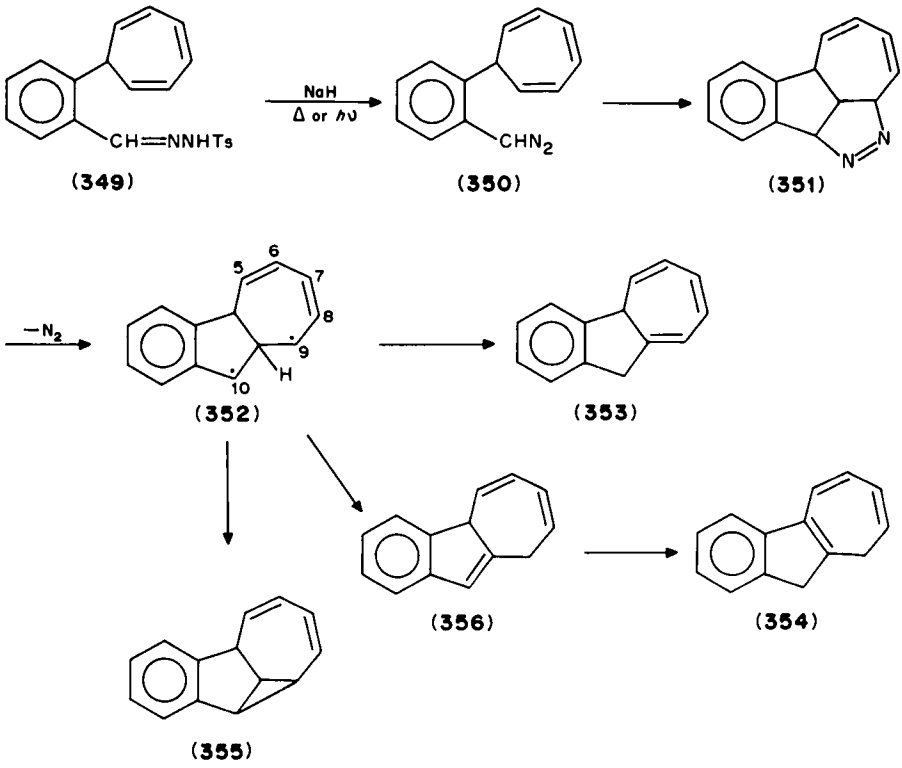
The thermal or photochemical decompositions of the sodium salt of 2-(7′-cyclohepta-1′,3′,5′-trienyl)benzaldehyde tosylhydrazone **349** yield three isomeric hydrocarbons 4*a*, 10-dihydrobenz[*a*]azulene **353**, 9,10-dihydrobenz[*a*]azulene **354** and 8,9-benzotricyclo[5.3.0.0^{2,10}]deca-3,5,8-triene **355**[117] (Scheme 74, Table 3). The most likely mechanism for the decomposition of **349** involves the intermediacy of pyrazoline **351**, formed by an intramolecular cycloaddition of the initially generated diazo compound **350** onto the proximate cycloheptatriene π bond. Loss of nitrogen from pyrazoline **351** would give diradical **352**, which can readily give rise to the cyclopropane derivative **355**. Formation of **353** can occur by intramolecular hydrogen transfer from C-9a to C-10, while C-9a→C-9 hydrogen transfer would give compound **356**, which, as a substituted indene derivative, would be expected to isomerize under the reaction conditions to the conjugated isomer **354**. An attempt was made to detect the intermediates



SCHEME 72



SCHEME 73



SCHEME 74

350 and **351** by warming the tosylhydrazone **349** with sodium methoxide in pyridine at 60 °C, but only hydrocarbons **353–355** were detected.

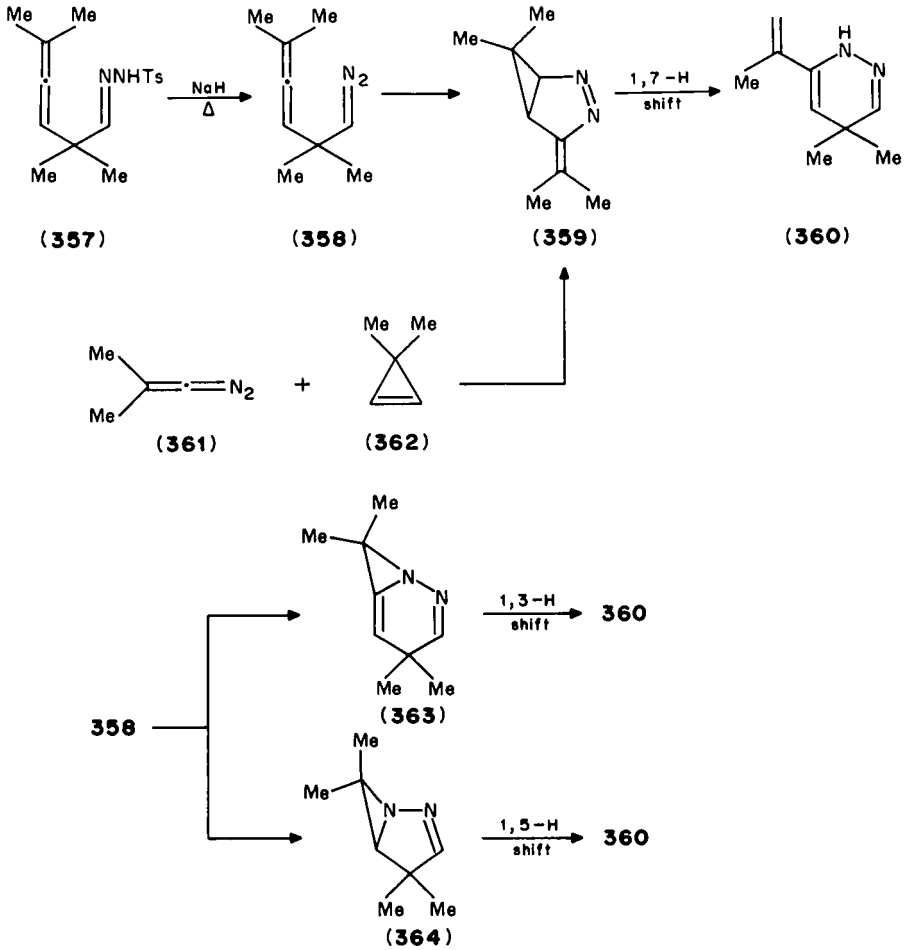
TABLE 3

Conditions for decomposition of Na salt of **349**	Product ratio **353** : **354** : **355**		
diglyme, 120 °C	1	1.5	5
benzene, 100 °C	1	1.6	3.2
pyridine, 60 °C	1	4.8	6.5
THF, *hv*, 0 °C	2.3	1	2.9

D. Other Diazoalkane Systems

Pyrolysis of the sodium salt of the allenic tosylhydrazone **357** in boiling benzene gave a 48% yield of 4,4-dimethyl-6-isopropenyl-1, 4-dihydropyridazine **360**, which was also formed in the reaction of diazoethene **361** with 3,3-dimethylcyclopropene **362**[118]. The formation of **360** is rationalized in terms of intervention of an intramolecular 1,3-dipolar

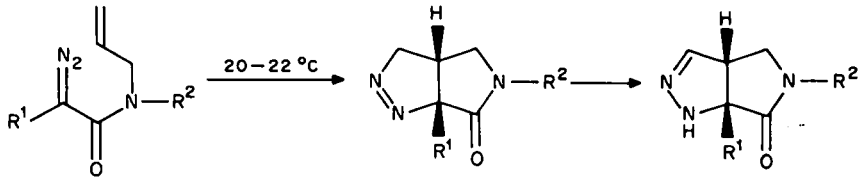
cycloadduct **359** formed from the allenic diazoalkane **358**, followed by 1,7-sigmatropic hydrogen shift, rather than the intervention of 1,1-cycloadduct **363** or **364** (Scheme 75).



SCHEME 75

The allyldiazoacetamides **365** and *N*-allyldiazomalonamide esters **366** were found to be unstable at 20 °C and undergo an intramolecular cycloaddition to give the corresponding *cis*-hexahydropyrrolo[3,4-*c*]pyrazoles **367** and **368**; the rate of intramolecular cycloaddition of the system **366** is substantially faster[119] (Scheme 76). The cycloadducts **367** and **368** undergo ready base-catalyzed isomerization to **369** and **370**, respectively. However, the diallyldiazoketone **371** and secondary *N*-allylmalonamide ester **372** are stable and failed to furnish intramolecular cycloadducts.

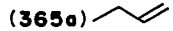
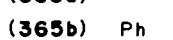
An early work provided an interesting example of an intramolecular diazoalkane cycloaddition followed by a cycloreversion in the thermolysis of the sodium salt of α-phenyl-α-tropylacetoaldehyde tosylhydrazone[120].

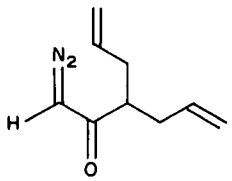


(365) R^1=H
(366) R^1=COOEt

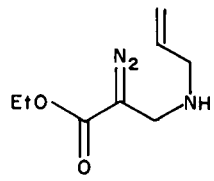
(367) R^1=H
(368) R^1=COOEt

(369) R^1=H
(370) R^1=COOEt

	R^2		Yield (%)
(365a)		30 days	(367a) 65% isolated as **369a**
(365b)	Ph	5 months	(367b) 80%
(366a)	Me	24 h	(368a) 90%
(366b)		< 12 h	(368b) 72% isolated as **370b**



(371)



(372)

SCHEME 76

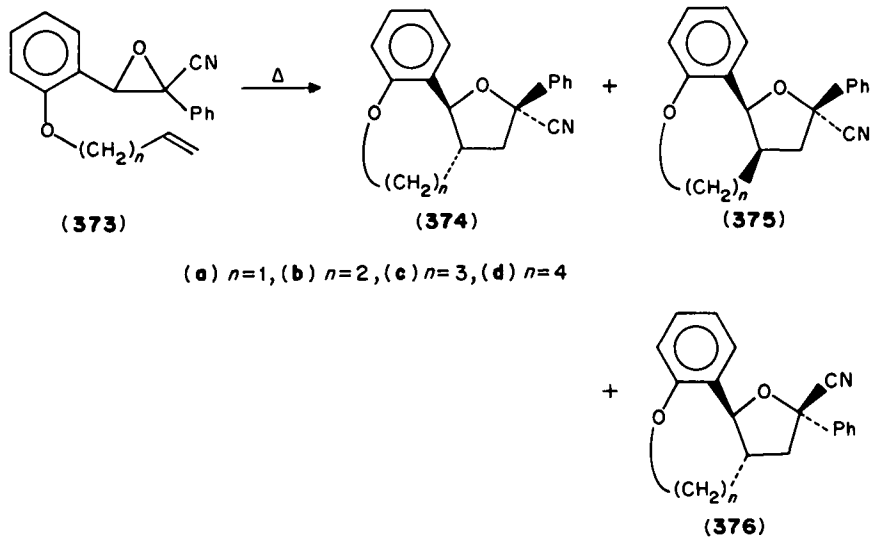
V. CARBONYL YLIDES

A. Ring Opening of Oxiranes

Thermal or photochemical cleavage of the oxirane carbon–carbon bond generates carbonyl ylides. The thermal cycloaddition of 2-cyano-*trans*-stilbene oxide with alkynic and alkenic dipolarophiles gives stereospecific cycloadducts to the carbonyl ylide generated via a controtatory ring-opening[121,122], while photocycloaddition of stilbene oxides with electron-deficient alkenes can be rationalized by the assumption that the electronically excited oxirane undergoes carbon–carbon fission to give carbonyl ylides via a disrotatory ring-opening[123].

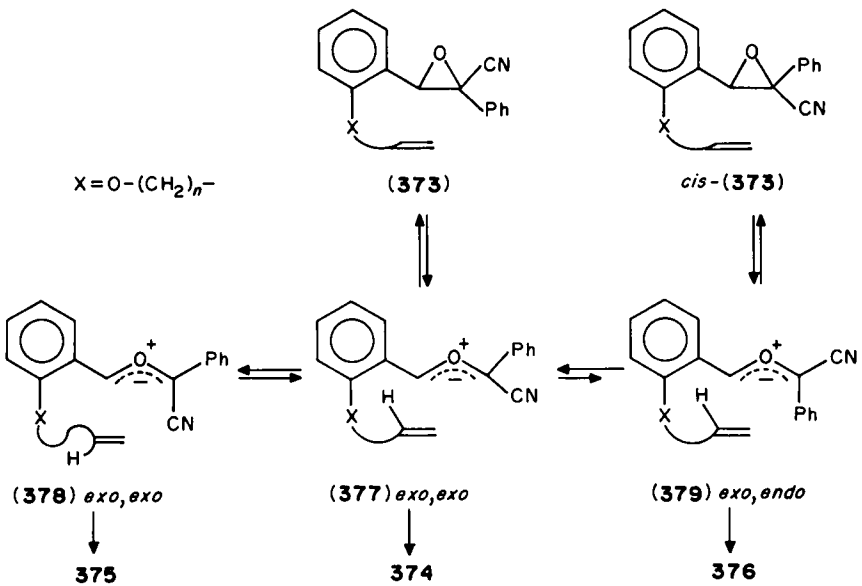
The intramolecular trapping of carbonyl ylides by multiple bonds has been reported for the first time by Eberbach and coworkers[124]. Heating ene-oxirane **373a** at 175 °C gave a 2:1 mixture of intramolecular cycloadducts **374a** and **375a**. Under the same conditions, the homolog **373b** gave only the *trans* diastereomer **374b**[124,125]. The higher homologs **373c** and **373d** underwent an intramolecular cycloaddition at higher temperature, but a mixture of three stereoisomers **374**, **375** and **376** was obtained in low yield[125] (Scheme 77, Table 4). A small amount of *cis*-oxirane, *cis*-**373**, was found in the recovered oxirane fraction.

The formation of **374** and **375** was attributed to an initial thermal ring-opening of the oxirane ring to *exo,exo*-carbonyl ylides **377** and **378**, followed by intramolecular cycloaddition. The energetically more favorable transition state **377** leads to the major product **374**. Low selectivity is observed in the reaction above 200 °C, owing to the



SCHEME 77

intervention of the *exo, endo*-ylide **379** generated by the rotation of the carbon–oxygen bond in **377** (Scheme 78).



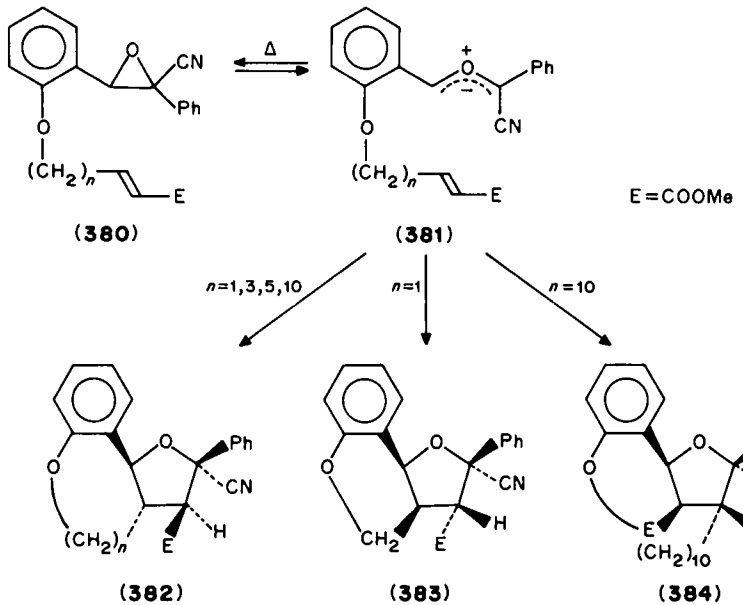
SCHEME 78

Several additional examples have been reported by Eberbach and coworkers[126–128]. The intramolecular cycloadditions of carbonyl ylides with ester-activated C=C bonds

TABLE 4

	Conditions	Yield (%)	374 :	375 :	376
373a	175 °C/8 h	75	66	34	—
373b	175 °C/8 h	66	100	—	—
373c	240 °C/8 h	21	88	1	11
373d	240 °C/8 h	11	86	1	13

were studied[125,126]. Whereas the annelated adduct **382** and/or **383** were formed in the case of ene-oxiranes **380a–380c** ($n = 1, 3, 5$), thermolysis of **380d** ($n = 10$) leads predominantly to the bridged compound **384** (Scheme 79, Table 5).

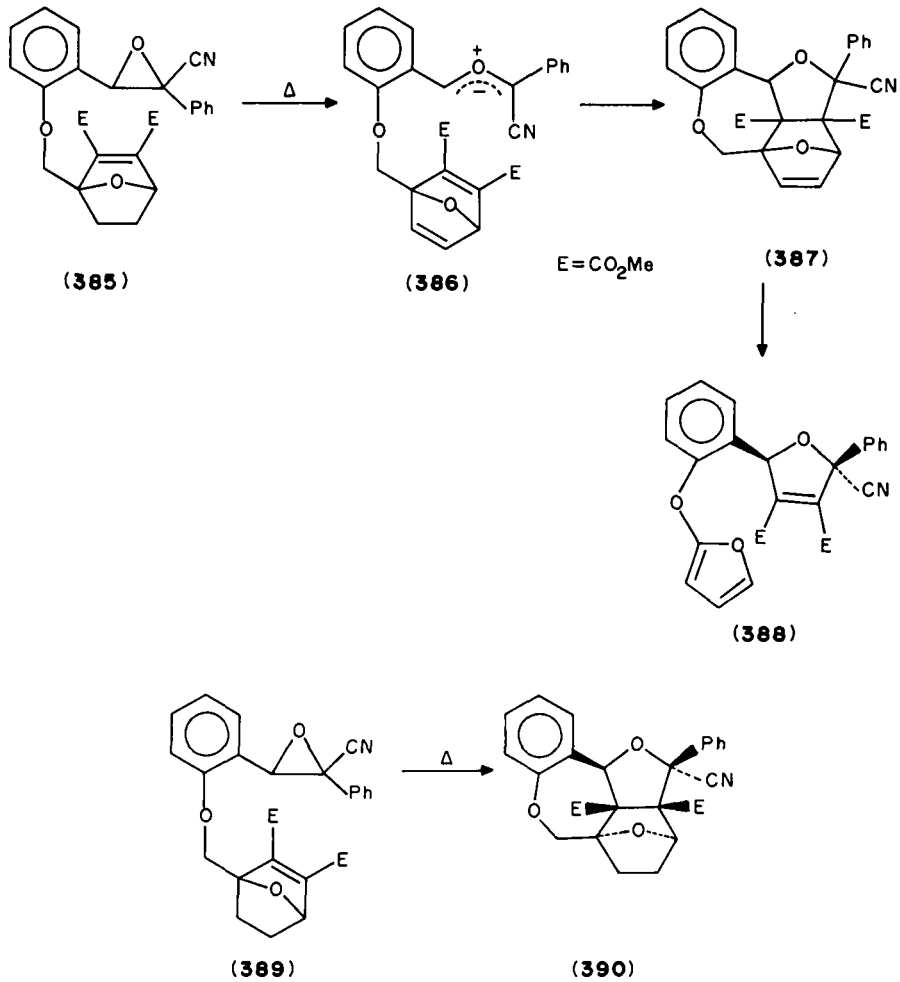


SCHEME 79

Heating at 120 °C the specifically designed ene-oxirane **385** gave the 2,5-dihydrofuran derivative **388**[127]. As the mechanism of this interesting conversion, ring-opening to carbonyl ylide **386**, followed by formation of the intramolecular cycloadduct **387**, and

TABLE 5

	Conditions	Yield (%)	382 :	383 :	384
380a ($n = 1$)	170 °C/5 h	97	89	11	—
380b ($n = 3$)	215 °C/7 h	57	100	—	—
380c ($n = 5$)	240 °C/8 h	73	100	—	—
380d ($n = 10$)	230 °C/0.5 h	75	9	—	91



SCHEME 80

rapid cycloreversion leading to **388** was proposed (Scheme 80). The latter process is precluded in the case of the dihydro derivative **389** which, in fact, reacts under comparable conditions and with equally good yield to give **390** as a thermally stable and sterically pure compound. In the presence of dimethyl acetylene dicarboxylate as external dipolarophile, bimolecular cycloadditions do not compete with the intramolecular cycloaddition.

The formation of large-size ring systems with up to 34 ring members has been achieved by intramolecular cycloaddition reactions of carbonyl ylides generated from the thermal ring-opening of ene-oxiranes **391**–**394**[125,128] (Scheme 81).

On the other hand, thermolysis of *cis*-enyne-substituted oxiranes (e.g. **402**) predominantly afforded 2-vinylfurans. The formation of 2-vinylfurans **406** from oxiranes **402** was rationalized in terms of the intermediacy of seven-membered cycloallenes **404** produced from electrocyclization of conjugated carbonyl ylides **403** (Scheme 82). The thermal ring

expansion reaction of sterically fixed and benzo-annelated epoxyhexadienes has also been reported[131].

B. From Diazoketones

The intramolecular trapping of carbonyl ylides generated from diazoketones has recently been reported by two groups. The rhodium-catalyzed decomposition of diazoketone **407** afforded oxatricyclononanone **410** as the major product[132]. The formation of **410** involves an intramolecular cyclization step between the ketocarbenoid and the oxygen atom of the ester carbonyl to give a resonance stabilized five-membered carbonyl ylide intermediate **409**. The ylide dipole can then be trapped internally by the alkenic double bond to give **410** (Scheme 83).

The catalytic decomposition of the bis-diazoketone **411** was also investigated and was found to give **414**[132]. The formation of **414** represents a unique case where two diazoketone moieties in the same molecule under the influence of the same catalyst react in different ways: one by addition to the double bond to give intermediate **412** (route a) and the other by carbonyl ylide formation to give the second intermediate **413** (route b). Intramolecular trapping of this ylide **413** affords the product **414** (Scheme 84).

Treatment of diazoacetophenones **415** with rhodium acetate resulted in an initial cyclization to generate a six-ring carbonyl ylide **416**, which undergoes intramolecular cycloaddition to give the product **417**. The catalytic decomposition of diazoamide **418** in an analogous reaction gave **419**[133] (Scheme 85).

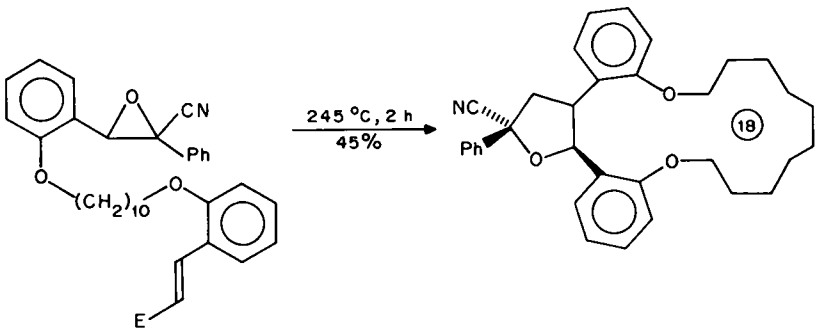
C. 3-Oxidopyrylium Ylides

3-Oxidopyridinium betaines **420** have been shown to react as cyclic azomethine ylides in 1,3-dipolar cycloaddition reactions[134]. Recently, Hendrickson and Farina reported the trapping of 3-oxidopyrylium betaine **421**, the O-analogue of **420**, reacting as a cyclic carbonyl ylide by reaction with certain dipolarophiles[135].

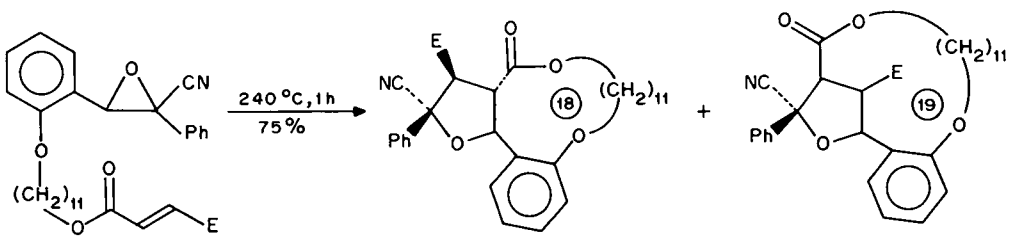
Intramolecular versions using 3-oxidopyrylium ylides bearing unsaturated side-chains have been investigated by Sammes and coworkers[136]. On heating the pyranulose acetate **422a** bearing a pentenyl group at 150 °C in acetonitrile (sealed tube) the enone **424a** was formed as a major product (61%), rationalized in terms of an intramolecular *exo*-cycloaddition of the isolated double bond to the presumed oxidopyrylium intermediate **423**. Heating the hexenyl homologue **422b** under similar conditions also gave a good yield of cycloadduct **424b**. It has been found that the more convenient treatment of **422a** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) at room temperature also afforded the cycloadduct **424a** in 75% yield. Pyrolysis of pyranone **425** at 150 °C in acetonitrile containing a catalytic amount of acetic acid was found to give the cycloadduct **426** in 52% yield (Scheme 86). Thus, these intramolecular cycloadditions appear to be general, giving access to a variety of substituted perhydroazulenes.

The above methodology was applied to the total synthesis of (±)-β-bulnesene[137,138], (±)-cryptofauronol[138], (±)-fauronyl acetate[137] and (±)-valeranone[137].

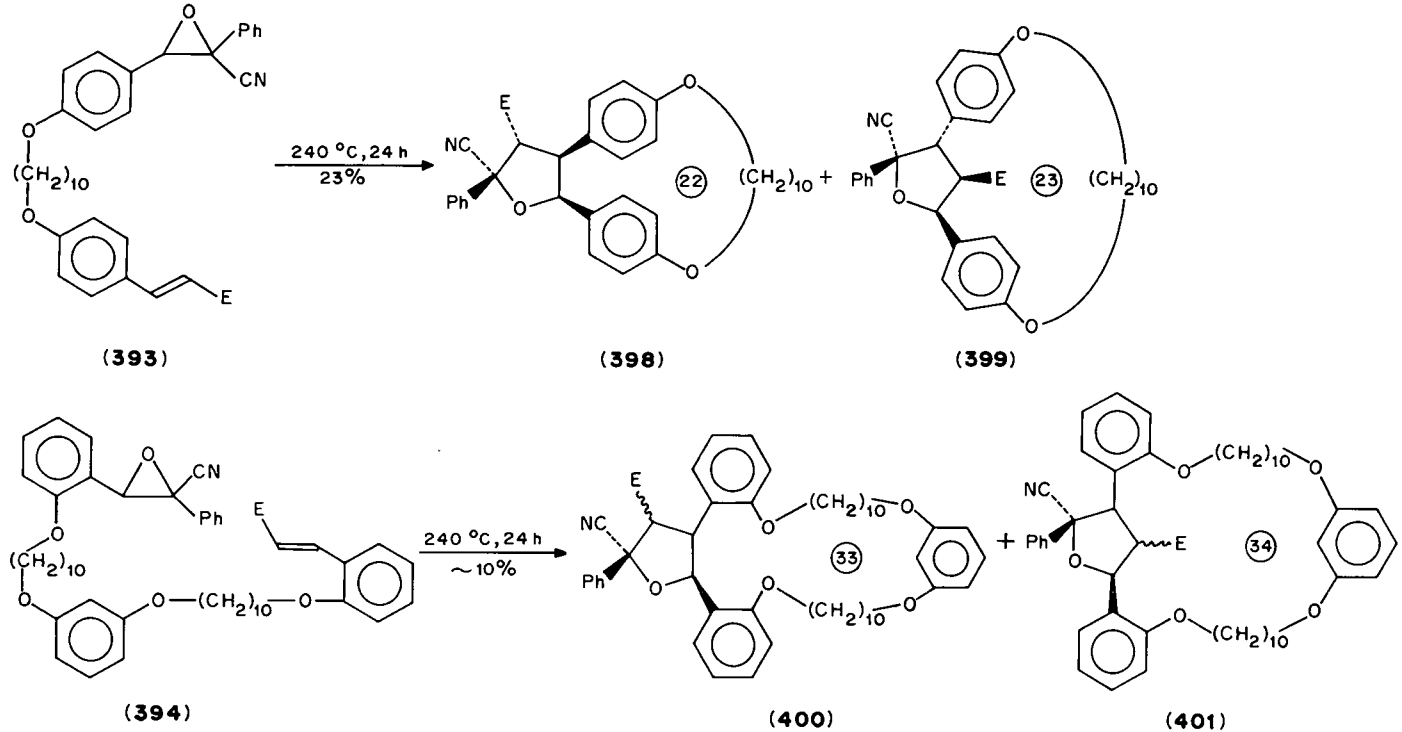
Heating the pyranulose acetate **427** at 150 °C afforded 75% yield of a mixture of stereoisomeric perhydroazulene cycloadducts **430** and **431** (1:5). The formation of **431** as major product can be explained by considering steric interactions in the transition state leading to the isomeric adduct **430**. Steric repulsion between the methyl substituent and aromatic ring in the 3-oxidopyrylium intermediate **428** leading to **430** would tend to disfavor this mode of addition with respect to its isomer **429** leading to **431**. A mixture of 8-methyl epimers, **430** and **431**, was elaborated to a mixture of (±)-β-bulnesene **432** and (±)-4-epi-β-bulnesene **433** (17:83)[137,138]. In order to control the relative geometry of the pendent 4-methyl group in **432**, a method involving the stereoselective reduction of an



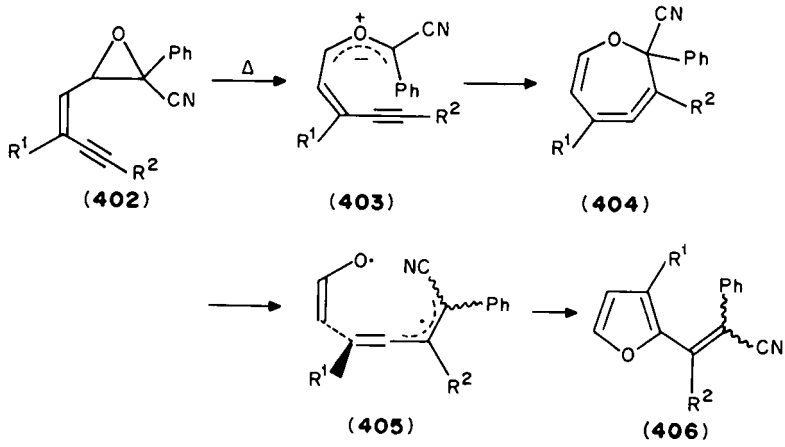
(391) (395)



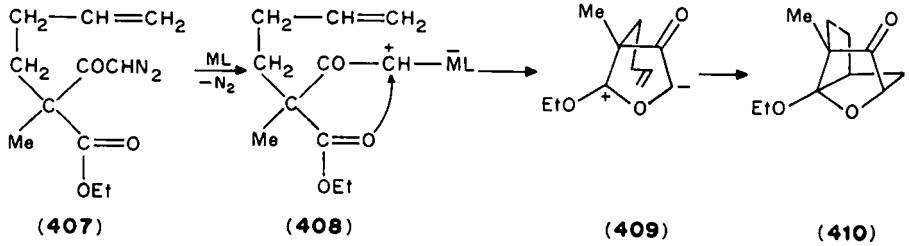
(392) (396) (397)



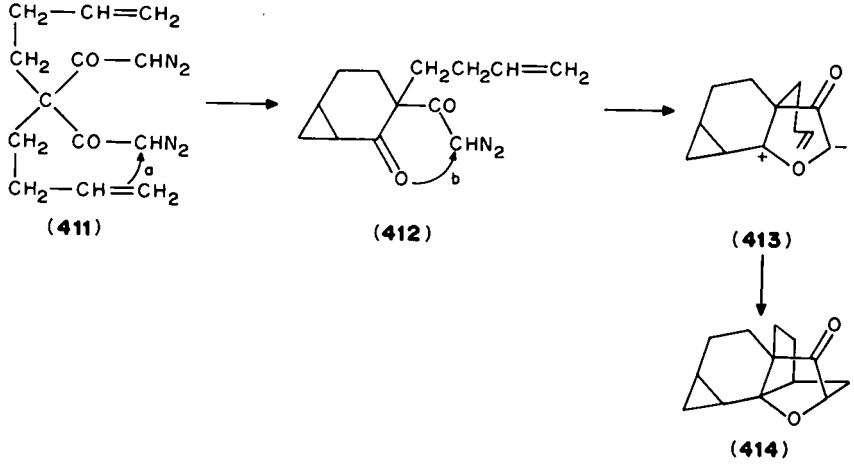
SCHEME 81



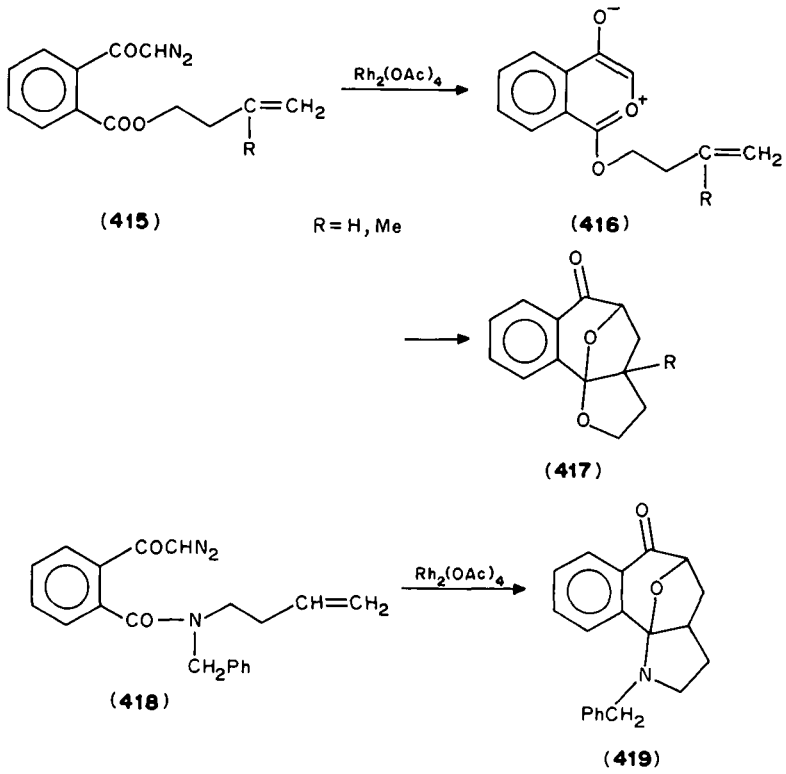
SCHEME 82



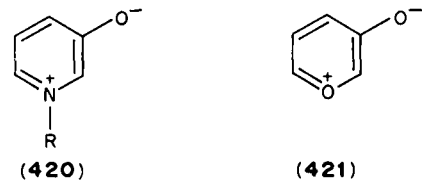
SCHEME 83



SCHEME 84

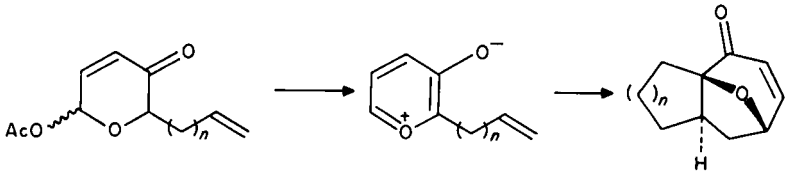


SCHEME 85



exocyclic methylene group was employed[138]. Thus, on heating at 150 °C or treatment of DBN at room temperature the pyranulose acetate **434** gave solely the intramolecular cycloadduct **435** in 61 or 65% yield. Hydrogenation of **435** over palladium on charcoal gave **430**, which could be transformed into the target compound **432**.

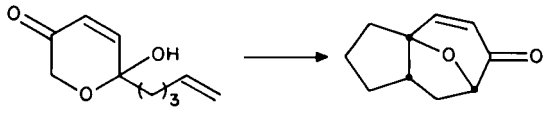
Cleagave of the epoxy-bridge can also be effected by a skeletal rearrangement to the *cis*-decalin system. This methodology was applied to the synthesis of (±)-cryptofauronol, (±)-fauronyl acetate and (±)-valeranone[137]. Thermolysis of the pyranulose **436** at 150 °C afforded the single cycloadduct **437** in 62% yield. Reaction of the adduct **437** with isopropylmagnesium iodide afforded the alcohol **438** as a single isomer. By treatment with titanium tetrachloride at 0 °C the alcohol **438** was smoothly converted into (±)-cryptofauronol **439**. Heating **439** with acetic anhydride in the presence of sodium acetate gave (±)-fauronyl acetate **440**, which was converted into (±)-valeranone **441** (Scheme 88).



(422a) $n=3$
(422b) $n=4$

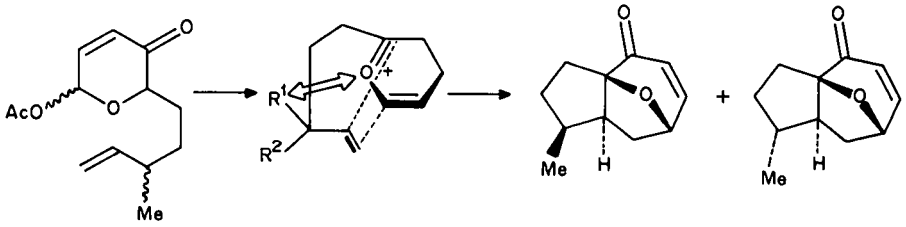
(423)

(424a) $n=1$
(424b) $n=2$



(425) (426)

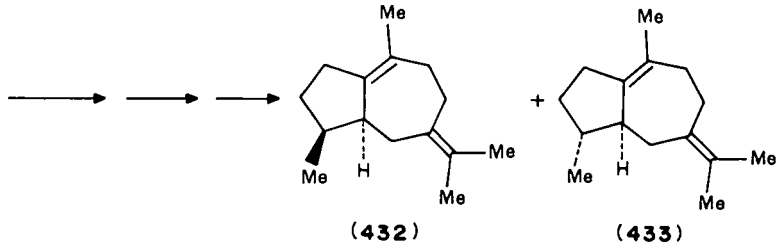
SCHEME 86



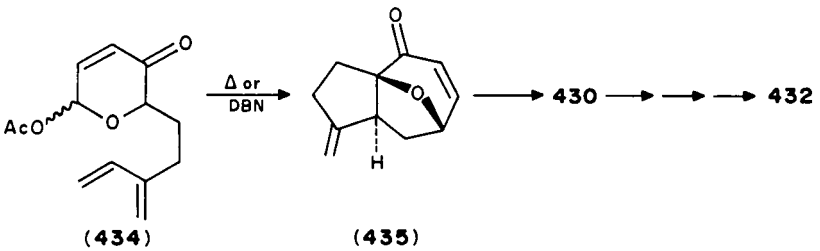
(427)

(428) $R^1=Me, R^2=H$
(429) $R^1=H, R^2=Me$

(430) (431)

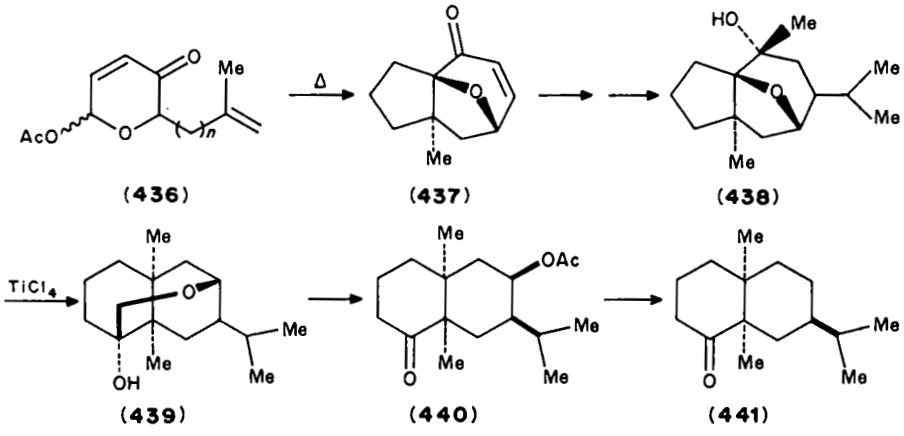


(432) (433)



(434) (435)

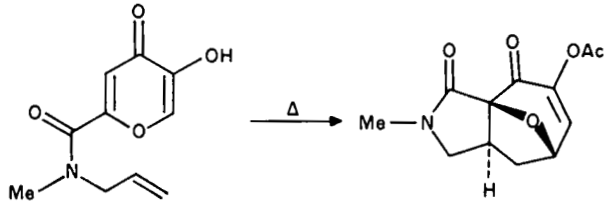
SCHEME 87



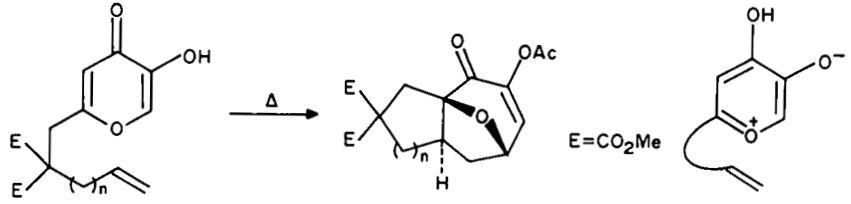
(436) (437) (438)

(439) (440) (441)

SCHEME 88

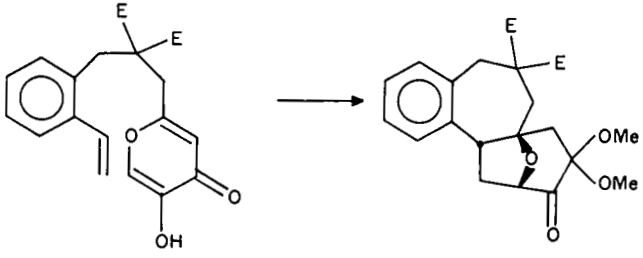


(442) (443)



(444) (445) (448)

(a) $n=1$; (b) $n=2$; (c) $n=3$



(446) (447)

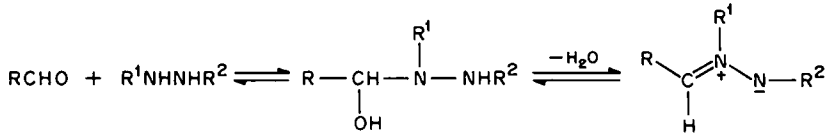
SCHEME 89

The closely related intramolecular cycloaddition of 2-(ω-alkenyl)-5-hydroxy-4-pyranones has also been reported[139]. Pyrolysis of amide **442** derived from comenic acid, in refluxing benzene followed by acetylation, gave the acetylated cycloadduct **443** in 55% yield. On thermolysis followed by acetylation, 2-alkenyl-5-hydroxy-4-pyranones **444a** and **444b** afforded cycloadducts **445a** and **445b**, respectively, but a higher homologue **444c** failed to give the expected adduct under a variety of conditions. Although pyrolysis of 5-hydroxy-4-pyranone **446** slowly led to complete decomposition, treatment of **446** with methanesulfonic acid in refluxing methanol gave ketal **447** in 87% yield. It is evident that a 3-oxidopyrylium ylide of type **448** in involved in these reactions (Scheme 89).

VI. AZOMETHINE IMINES

A. From the Reaction of Aldehydes with *N,N'*-Disubstituted Hydrazines

The condensation of aldehydes with *N,N'*-disubstituted hydrazines is a convenient procedure for the generation of azomethine imines (Scheme 90).



SCHEME 90

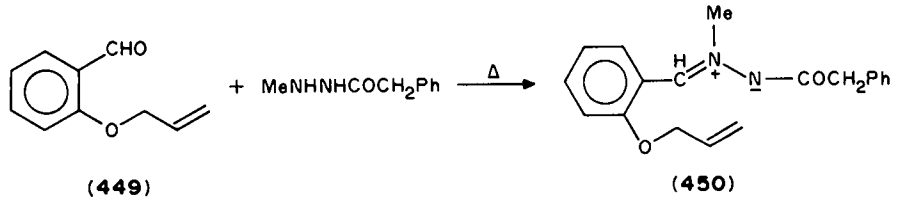
Huisgen and coworkers have shown that the 1,3-dipoles generated by this method are readily trapped with alkenic dipolarophiles to give pyrazolidines[10b]. Oppolzer reported the first example for the intramolecular cycloaddition of azomethine imines generated in this fashion[140,141]. When unsaturated aldehydes are used, the reaction first gives the 1,3-dipole and is then followed by an intramolecular cycloaddition[140]. For example, *o*-allyloxybenzaldehyde **449** was heated with *N*-methyl-*N'*-phenylacetylhydrazine in refluxing toluene to give *cis*-fused **451** and *trans*-fused cycloadduct **452**, both through an intramolecular cycloaddition of the transient azomethine imine **450**, in 84 and 8% yields, respectively. The reaction of aldehydes **453** with the same hydrazine to give tetracyclic pyrazolidines **454** and/or **455** follows an analogous course (Scheme 91).

An intramolecular azomethine imine cycloaddition to a furan ring has been also reported[22]. *o*-(2-Furylmethyloxy)benzaldehyde **456** reacted with a hydrazine in refluxing toluene to give the intramolecular cycloadduct **457** in 60% yield (Scheme 92).

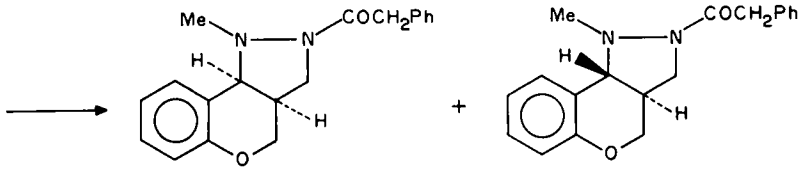
The reaction of hydrazines bearing an alkenic function with aldehydes was employed in a further variation[141] (Scheme 93). The reaction of *N*-acetyl-*N'*-(3-butenyl)hydrazine **458** or its pentenyl homologue **459** with paraformaldehyde in refluxing xylene afforded 1,7-diazabicyclo[2.2.1]heptane **460** or 1,7-diazabicyclo[3.2.1]octane **461**, respectively. In the reaction of hydrazine **459** with benzaldehyde under similar conditions, however, a mixture of 1,7-diazabicyclic systems, **462** and **463**, and 1,8-diazabicyclic systems, **464** and **465**, were obtained.

Recently, an analogous procedure was used for the synthesis of novel heterocycles. The reaction of aldehyde **33**[25] or **466**[142] with an acylhydrazine afforded the intramolecular azomethine imine cycloadduct **467** or **468**, respectively (Scheme 94).

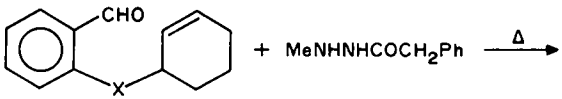
As a synthetic approach to saxitoxin, the intramolecular cycloaddition of azomethine imines generated from hydrazide **469** was investigated by Jacobi and coworkers[143]. Although **469** did not react with benzaldehyde, it did with benzaldehyde diethyl acetal, at 80 °C, in DMF containing a catalytic amount of *p*-toluenesulfonic acid to give the



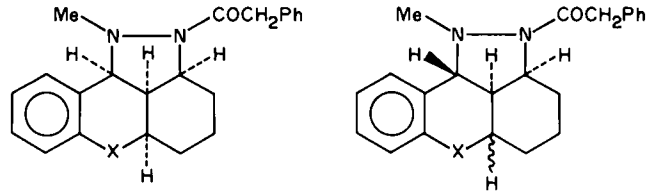
(449) (450)



(451) (452)



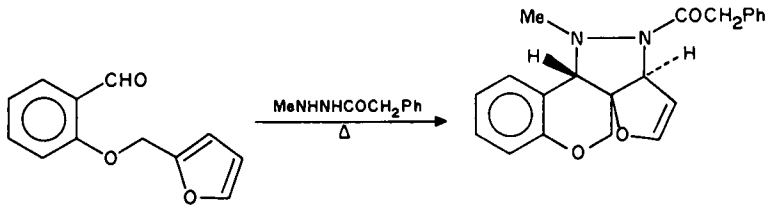
(453)



(454) (455)

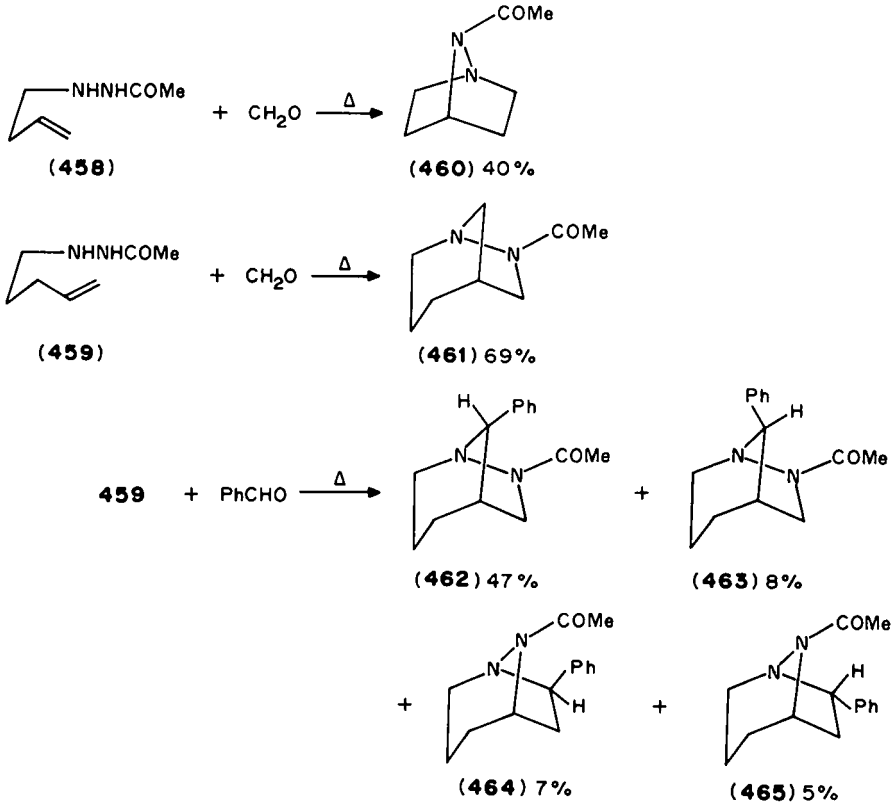
X=O	38%	31%
X=NCHO	48%	—

SCHEME 91

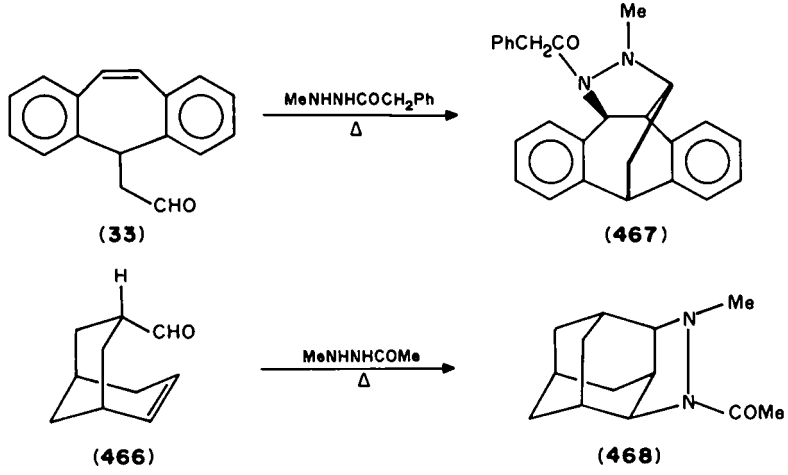


(456) (457)

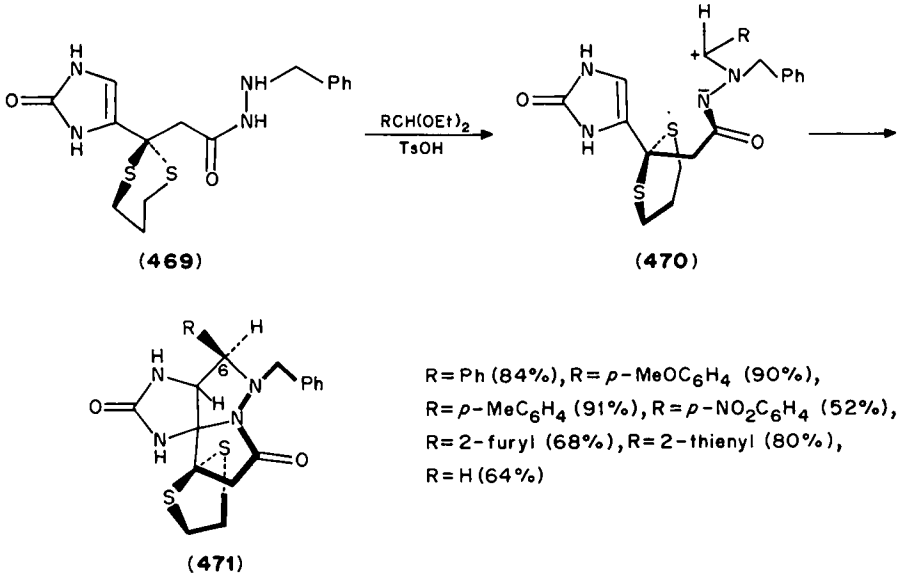
SCHEME 92



SCHEME 93



SCHEME 94



(469) (470) (471)

SCHEME 95

cycloadduct **471** in good yield. Similarly, the reaction with various aldehyde acetals afforded the corresponding cycloadducts **471** (Scheme 95). This reaction proceeds via an intramolecular cycloaddition of azomethine imine **470**. It is interesting to note that in no case could a measurable quantitity of an adduct having the α-configuration at C-6 be detected. The high stereoselectivity was rationalized on the basis of severe nonbonded interaction in the transition state to the epimer having the α-configuration at C-6.

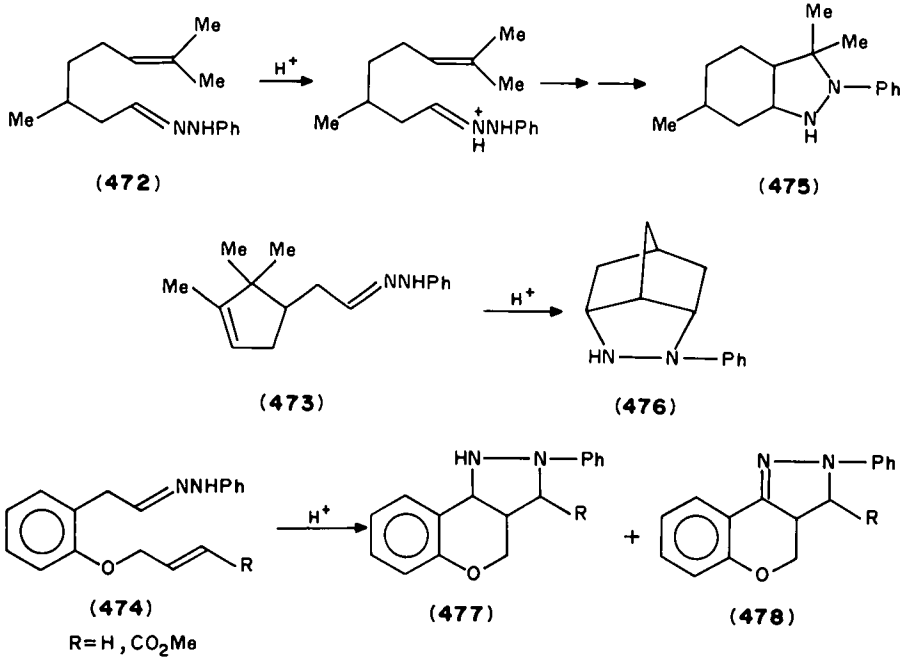
B. From Hydrazones

Hydrazones are ambident nucleophiles which can react with electrophiles at either carbon or nitrogen. Recent investigations show that monosubstituted hydrazones undergo 1,3-dipolar cycloadditions via the azomethine imine tautomer[144] and acid-catalyzed $[3^+ + 2]$cycloadditions[145].

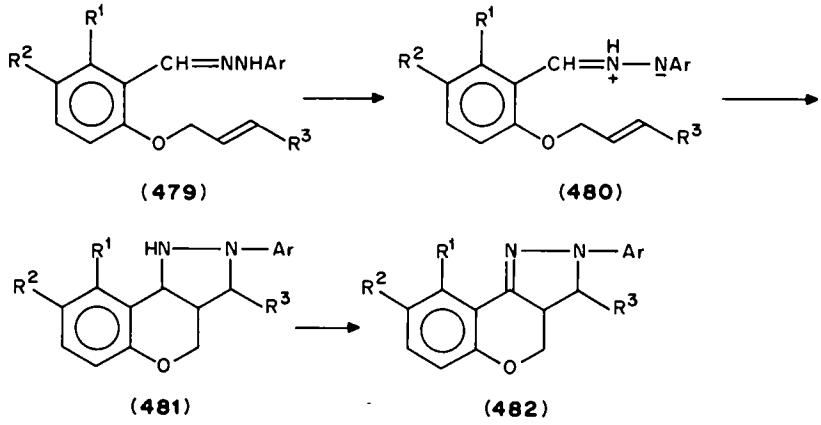
Few examples of intramolecular versions using these methodologies have been reported. In acidic media alkenyl phenylhydrazones **472–474** undergo intramolecular cycloaddition to produce fused pyrazolidines **475–477** in excellent yields, respectively. In the case of **474**, the dehydrogenated product **478** was also formed (Scheme 96). The reaction proceeds via a $[3^+ + 2]$cationic cycloaddition of a protonated hydrazonium intermediate.

Heating 2-(3-aryl-2-propenyloxy)benzaldehyde arylhydrazones **479** at 150 °C in xylene afforded ring-fused pyrazolines **482** in poor to good yields. This reaction presumably proceeds via an intramolecular cycloaddition of the azomethine imine tautomer **480**, and the resulting pyrazolidine **481** is dehydrogenated to **482** under the reaction conditions[147] (Scheme 97). If the cyclization of **482** was carried out in solvents containing traces of acid, the $[3^+ + 2]$cycloaddition proceeds much faster than the azomethine imine cycloaddition.

Recently, intramolecular $[3^+ + 2]$cycloadditions using *N*-substituted and *N,N*-disubstituted aldehyde hydrazones have been reported[148]. The reaction of two molar

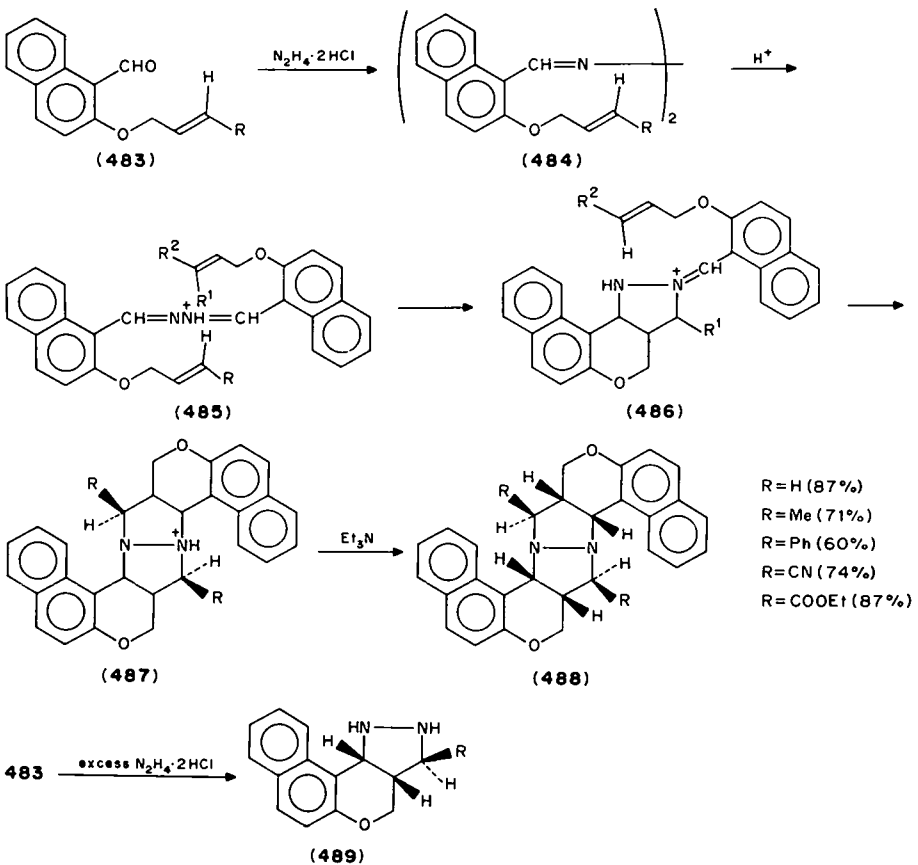


SCHEME 96



SCHEME 97

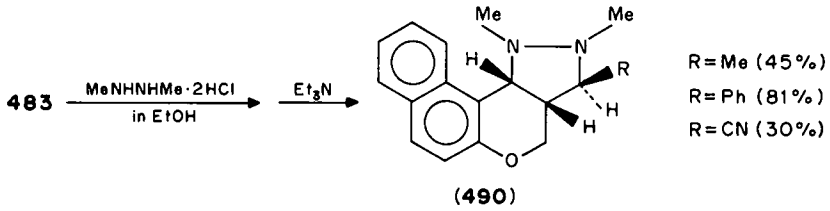
equiv of 2-(allyloxy)-1-naphthaldehyde **483** with hydrazine dihydrochloride, and subsequent treatment of the mixture with triethylamine, led to intramolecular [3$^+$ + 2]criss-cross cycloadducts **488**. On the other hand, a similar series of reactions using a large excess of the dihydrochloride gave the mono[3$^+$ + 2]cycloadducts **487** (Scheme 98).


CHO
H
R
(483)
$N_2H_4 \cdot 2HCl$
CH=N
H
R
2
(484)
H^+
R^2
O
H
HN
N
CH
R^1
(485)
(486)
R
H
N
NH
(487)
Et_3N
(488)
R=H (87%)
R=Me (71%)
R=Ph (60%)
R=CN (74%)
R=COOEt (87%)
483
excess $N_2H_4 \cdot 2HCl$
HN
NH
(489)

SCHEME 98

The formation of **488** in the former reaction was explained by the consecutive reactions involving the formation of azine **484** and protonated dipole **485**, and subsequent double cycloadditions giving **487** via **486**. In fact, the criss-cross cycloadduct **488** (R = H) was prepared in a similar yield by treatment of azine **484** (R = H) with a stoichiometric amount of conc. hydrochloric acid.

Acid-catalyzed reaction of **483** with *N,N'*-dimethylhydrazine also afforded 1,2-dimethyl-substituted fused pyrazolidines **490** (Scheme 99).

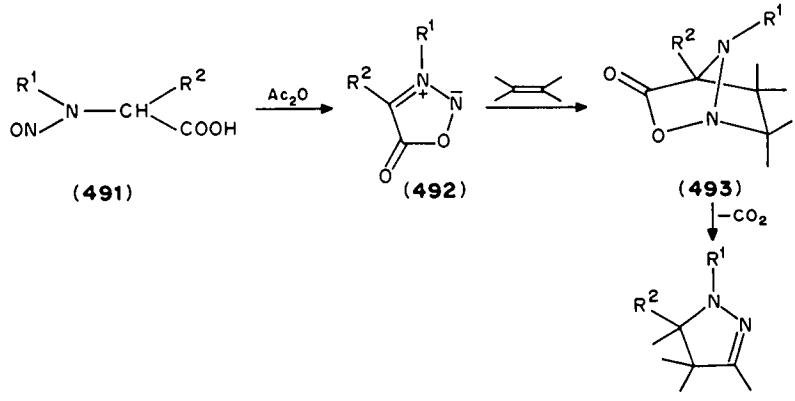


(490)

SCHEME 99

C. Sydnones

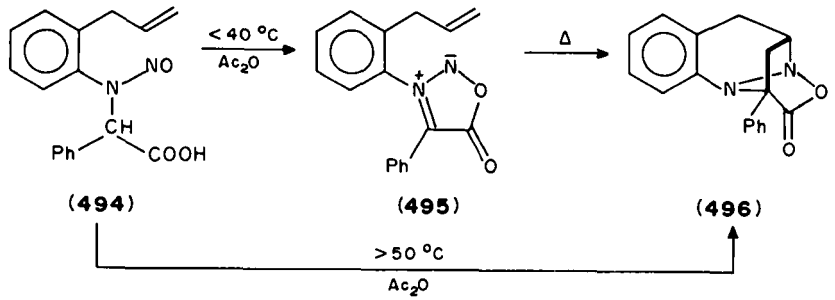
Anhydro-5-hydroxy-1,2,3-oxadiazolium hydroxide systems, commonly referred to as sydnones, were prepared initially in 1935[149]. The most direct method for the preparation of sydnones **492** involves cyclodehydration of *N*-nitroso-α-alkylamino acids **491** with acetic anhydride. They behave as cyclic azomethine imines, and react with alkenic or alkynic dipolarophiles to produce 2-pyrazolines or pyrazoles, respectively. The reaction involves the formation of an initial cycloadduct **493** followed by loss of carbon dioxide and subsequent tautomerization or aromatization (Scheme 100).



(491) **(492)** **(493)**

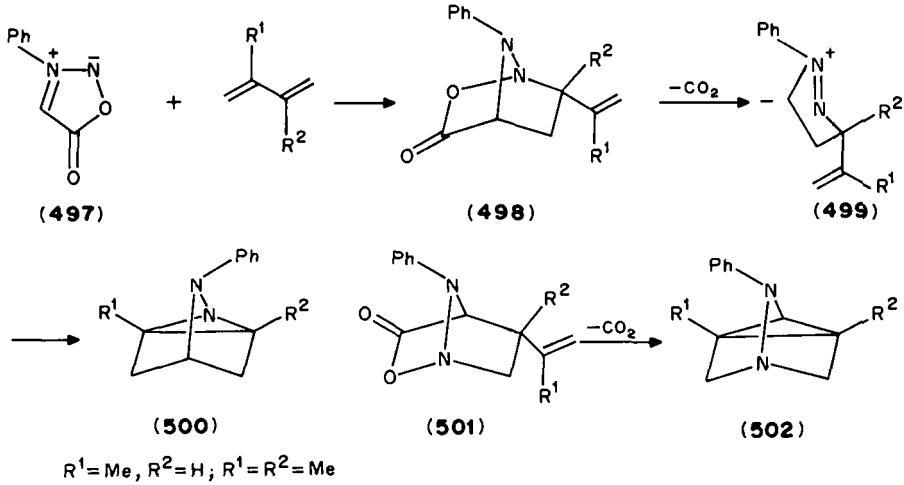
SCHEME 100

Some examples for the intramolecular cycloaddition of sydnone systems have been reported. The reaction of nitrosoamino acid **494** with acetic anhydride below 40 °C produced the sydnone derivative **495**, which could be converted into the unique 1,2,3-oxadiazolidin-5-one **496** whose structure has been proved by X-ray analysis[150,151] (Scheme 101).



SCHEME 101

Inter- and intramolecular cycloaddition sequence has been found in the reaction of 3-phenylsydnone **497** with isoprene and 2, 3-dimethylbutadiene[152]. Heating of a solution of **497** and of the diene in ethyl acetate gave 1, 7-diazatricycloheptane **500** together with the bimolecular cycloadduct. The formation of **500** was rationalized by a regioselective cycloadditon leading to **498**, followed by loss of carbon dioxide and subsequent intramolecular cycloaddition of azomethine imine **499** (Scheme 102). The product **502** originating from the alternative intermediate **501** could not be found in the reaction mixture. This regioselectivity is in the same line as the reaction of **497** with stilbene[10b], and is also compatible with frontier MO theory[7]. A related double 1, 3-dipolar cycloaddition of **497** with 1, 5-cyclooctadiene has also been reported[153].



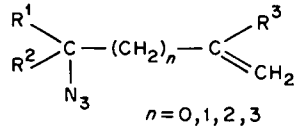
SCHEME 102

VII. AZIDES

The intermolecular cycloadditions of azides to a wide range of multiple bonds have been investigated[2,3,10].

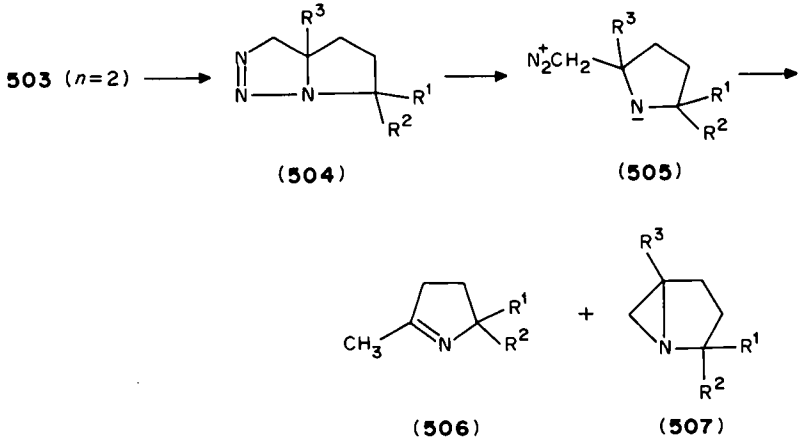
A. Acyclic Alkenyl Azide Systems

Logothetis studied systematically the thermal decomposition of alkenyl azides **503**[154]. Azides **503** ($n = 2, 3$) isomerized quantitatively into triazolines at room temperature in two months. Thermolysis of these triazolines gave the same products as did that of the parent



(503)

azides **503**, namely cyclic imines and bicyclic aziridines were formed. For example, heating azide **503** ($n = 2, R^1 = R^2 = R^3 = H$) to 120°C afforded a 72% yield of cyclic imine **506** ($R^1 = R^2 = H$) and bicyclic aziridine **507** ($R^1 = R^2 = R^3 = H$) (ratio 7:1). In the thermolysis of **503** ($n = 2$, $R^1 = R^2 = Me$, $R^3 = H$) at 80 °C in cyclohexane, the ratio of **506** ($R^1 = R^2 = Me$) to **507** ($R^1 = R^2 = Me$, $R^3 = H$) was 22:1, with a total yield of 70% (Scheme 103). A nitrene intermediate was completely excluded in these reactions. Allyl azide **503** ($n = 0$) and 4-azido-1-pentene **503** ($n = 1$) cannot undergo internal cycloaddition to give a triazoline like **504** because of the high degree of strain in such a structure.



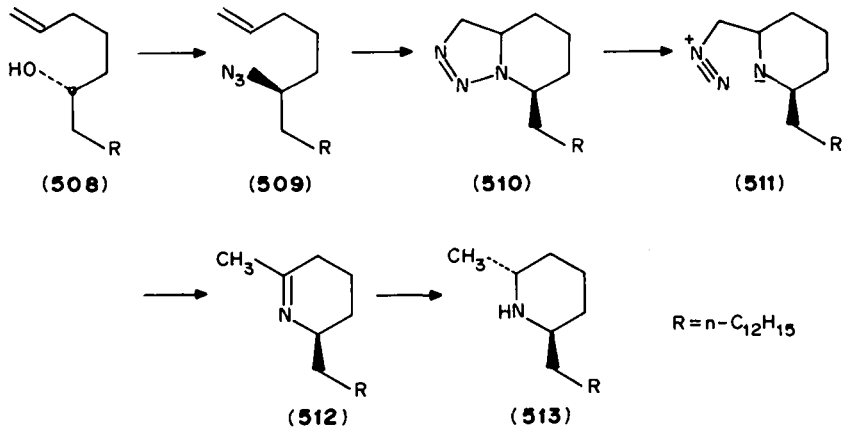
SCHEME 103

Recently, an enantioselective route to solenopsin B **513** has been developed[155] (Scheme 104). The key transformation in this synthesis is the thermolytic cyclization of an alkenyl azide. Although thermolysis of the alkenyl azide **509**, prepared by Mitsunobu coupling[156] of secondary alcohol **508**, in *o*-dichlorobenzene at 165 °C afforded the cyclic imine **512** through the path **510** → **511**, the yield of **512** was low, presumably due to its inherent instability. However, direct hydride reduction of the crude thermolysis products gave (*R*, *R*)-solenopsin B **513** in 71% isolated yield from azide **509**.

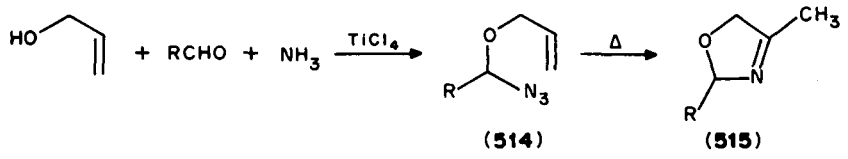
B. Allyl α-Azidoalkyl Ether Systems

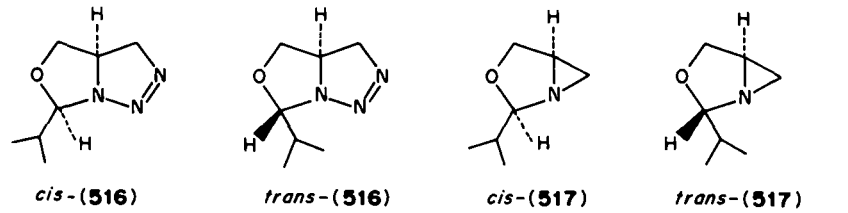
Hassner and coworkers[157] developed a new route to the preparation of α-azido ethers from aldehyde, an alcohol and hydrazoic acid using titanium tetrachloride as the catalyst.

It has been found that the thermolysis of allyl α-azidoalkyl ethers **514**, prepared using allyl alcohol in the above method, provided a novel synthesis of 2,5-dihydroxazoles **515**[158] (Scheme 105).



SCHEME 104





SCHEME 105

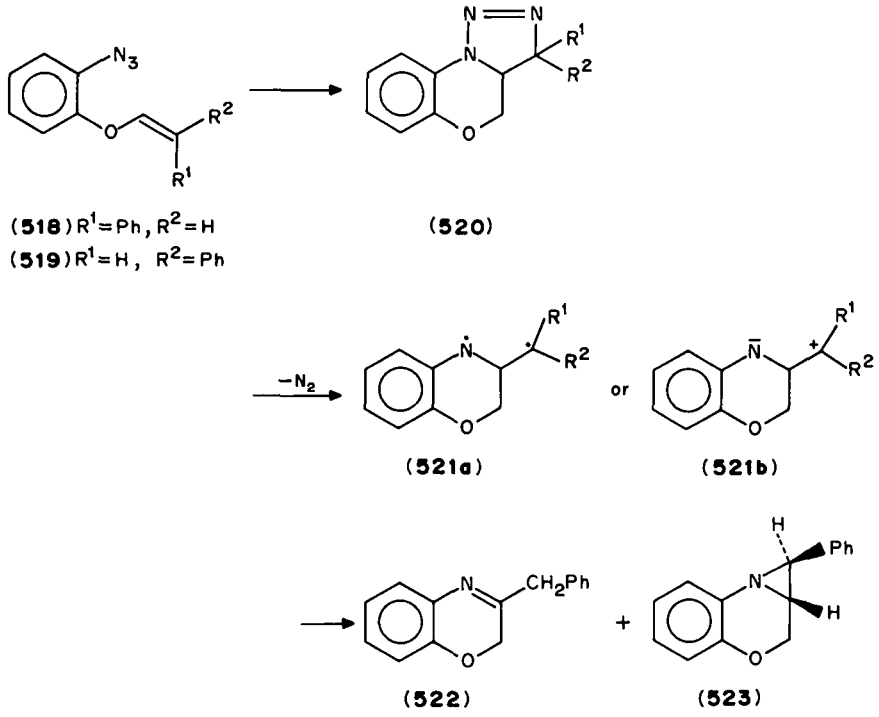
In order to determine whether oxazolines **515** are formed via an independent nitrene pathway or via triazolines, the thermolysis of azide **514** (R = *i*-Pr) was followed by ^{1}H NMR at 70 °C. Formation of both oxazoline **515** (R = *i*-Pr) and triazoline **516** was observed at partial conversion, but after 3 h of heating only the oxazoline **515** was present. On the other hand, if a mixture of oxazoline **515** and triazoline **516** after 50% conversion was chromatographed (silica gel), only the oxazoline **515** and the fused aziridine **517** (*cis* and *trans* mixture) were isolated in addition to starting material. Furthermore, the conversion of azide **514** (R = *i*-Pr) to triazoline **516** (2.9:1 of *trans* and *cis* isomers), without

appreciable presence of **515** or **517**, was accomplished by heating at 50 °C in $CDCl_3$ for 1 h (^1H NMR). Thus, the overall pathway for the conversion of azido ether **514** to oxazoline **515** involves first formation of internal cycloadduct **516**, which thermolyzes to **515** or is converted on silica gel to aziridine **517**.

C. Aryl Azide Systems

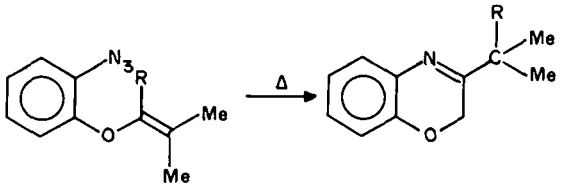
Intramolecular cycloadditions of aryl azides bearing unsaturated *ortho* substituents gave ring-fused products[159].

Thermolysis of *o*-(allyloxy)phenyl azides at 110–120 °C gave benzoxazines, dihydroazirinobenzoxazines or 3-alkenylbenzomorpholines[160]. For example, heating the *cis* and *trans* isomers of *o*-(γ-phenylallyloxy)phenyl azide (**518** and **518**) gave the same products, **522** and **523**, in the same ratio; this implies a common intermediate, either a radical **521a** or zwitterion **521b** derived by homolytic or heterolytic fragmentation of the initially formed triazoline intermediate **520** (Scheme 106).



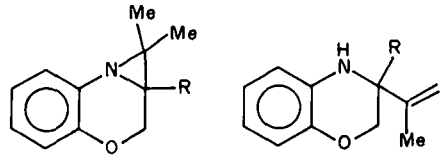
SCHEME 106

Thermolysis of azide **524** produced the expected imine **525** and aziridine **526** (each R = H), accompanied by an alkenylbenzomorpholine **527** (R = H); the ratio was 31:61:8. On the other hand, azide **528** bearing an additional methyl group was thermolyzed under similar conditions to give the benzomorpholine **527** (R = Me) as the sole product (Scheme 107). Formation of **527** requires a 1,4-hydrogen shift from a methyl in an intermediate like **521** ($R^1 = R^2 = Me$)[160].



(524) R=H
(528) R=Me

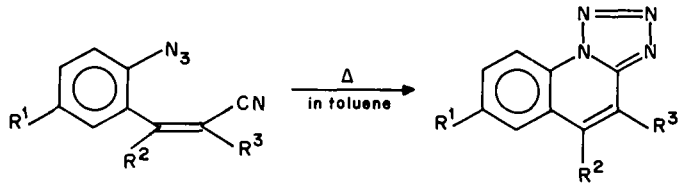
(525)



(526) (527)

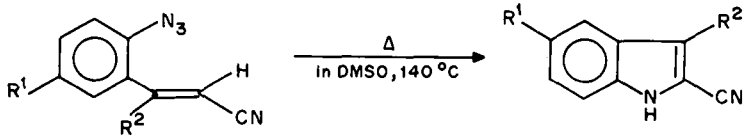
SCHEME 107

Treatment of (*Z*)-*o*-azidocinnamonitriles **529** in refluxing toluene converted them rapidly (< 30 min) to tetrazoquinolines **530** in high yields, which clearly involves an intramolecular cycloaddition of the azido group onto the neighboring cyano group. Although (*E*)-isomers **531** were stable under the above conditions, they decomposed at 140 °C in DMSO within 2 h to 2-cyanoindoles **532** as the only characterizable products[161] (Scheme 108). This reaction may involve loss of nitrogen from the azido group and



(529) (530)

$R^1=R^2=R^3=H$; $R^1=Cl$, $R^2=Ph$, $R^3=H$; $R^1=R^2=H$, $R^3=Me$



(531) (532)

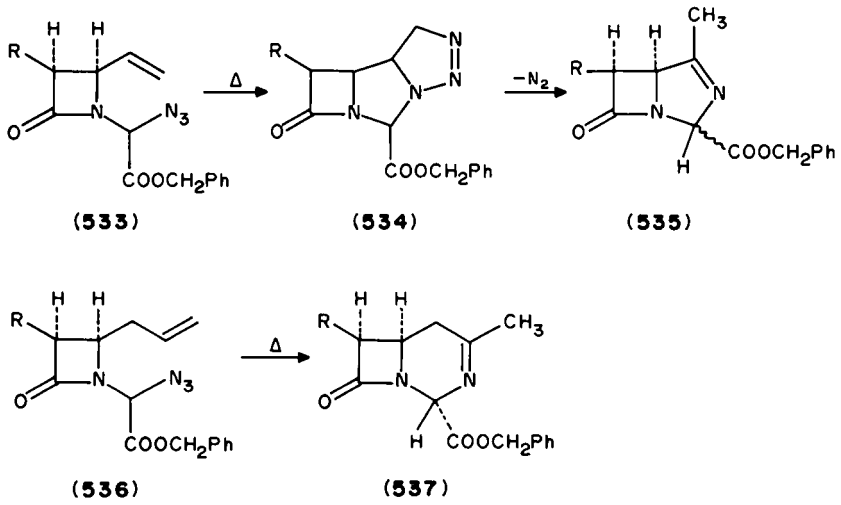
$R^1=R^2=H$; $R^1=Cl$, $R^2=Ph$; $R^1=H$, $R^2=Me$

SCHEME 108

subsequent addition of the resulting nitrene to the carbon–carbon double bond. On the other hand, studies of the thermal reaction of 2-nitrophenyl azide[162], 2-acylphenyl azide[162] and 2-(2-pyridyl)phenyl azide[163] indicate a concerted mechanism without formation of intermediate nitrenes. A similar mechanism may be involved in the cyclization of **531**.

D. Synthesis of Fused β-Lactams

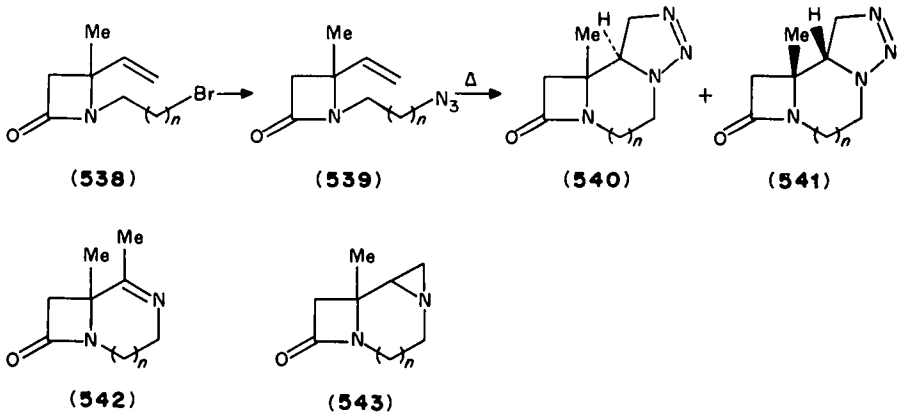
Synthesis of fused β-lactams by intramolecular azide cycloaddition reactions has been demonstrated. When 4-vinylazetidinone azides **533** were heated in refluxing toluene, a mixture of diasteromeric imines **535** was isolated. The intermediate triazoline **534** was assumed to undergo readily loss of nitrogen to form the isolated products[164,165]. A closely related transformation was also observed to occur with the homologous 4-allyl-azetidinone system (**536** → **537**) (Scheme 109).



SCHEME 109

Initial tricyclic triazolines could be isolated in the thermal cycloaddition of 4-vinylazetidinone azides of type **539**[166]. The azides **539** ($n = 1, 2, 3$) were prepared quantitatively by the reaction of the corresponding bromide **538** with polymeric azide reagent[167] at room temperature. On heating in benzene, azide **539** ($n = 1$) gave exclusively *cis*-fused tricyclic β-lactam **540** ($n = 1$). In the thermal reaction of **539** ($n = 2$) both *cis* and *trans* isomeric triazolines **540** and **541** (each $n = 2$) were formed in a ratio of 9:1. As the ring size increases ($n = 3$), the stereoselectivity is reduced (Scheme 110).

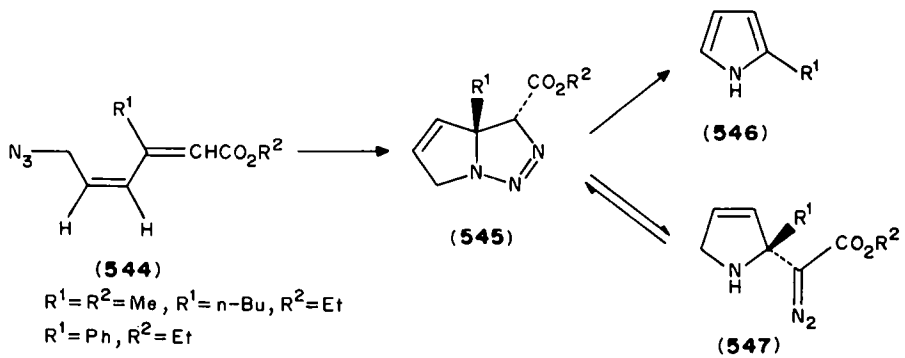
Although thermolysis or photolysis of triazolines **540** and **541** resulted in a mixture of aziridine, imine and polymeric material, a smooth chemoselective transformation of these triazolines was achieved by treatment with silica gel. The fused six-membered ring **540** ($n = 1$) gave exclusively imine **542** ($n = 1$), while the fused seven-membered ring **540** and **541** (each $n = 2$) led to a 7:3 mixture of imine **542** and aziridine **543** (each $n = 2$). The fused eight-membered ring **540** ($n = 3$) was converted to aziridine **543** ($n = 3$) only, and **541** ($n = 3$) furnished an isomeric aziridine. The ease of decomposition of the fused triazolines depended upon ring size, the order being $n = 1 > 2 > 3$.



SCHEME 110

E. Azidodiene Systems

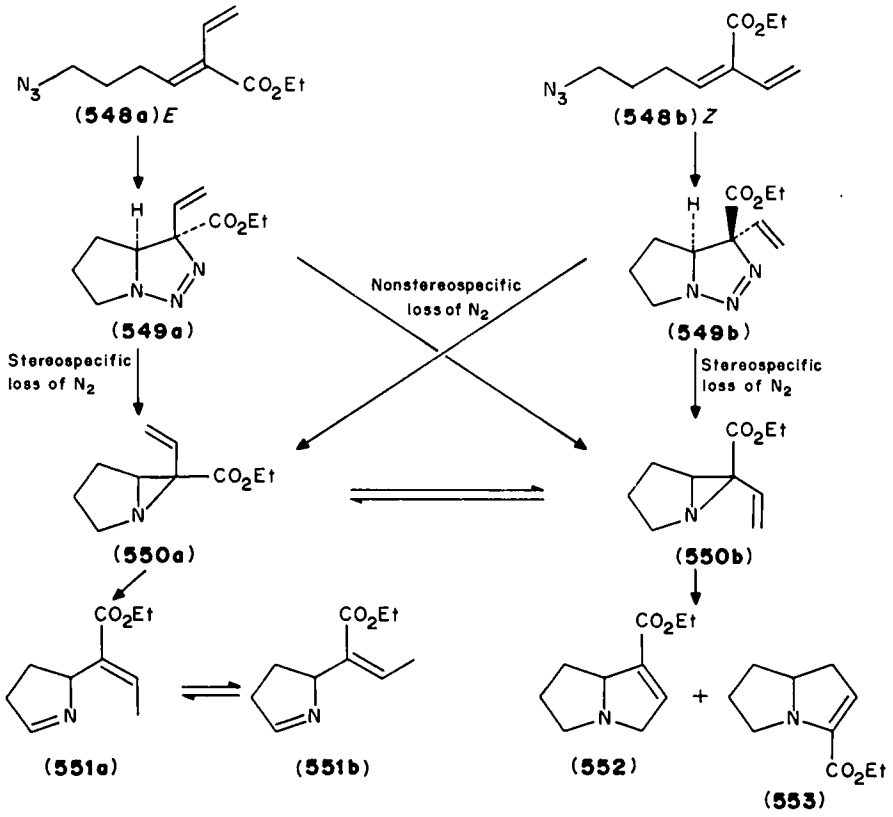
Intramolecular cycloadditions of several azidodienes have been studied. 3-Substituted 6-azidohexa-2,4-dienoate esters **544** undergo intramolecular cycloaddition to form 3*a*, 6-dihydro-3*H*-pyrrolotriazoles **545** at rates which depend upon the stereochemistry and substituent of the azide **544**[168]. The adducts **545** are unstable and decompose to 2-substituted pyrroles **546**, at rates which are both substituent and solvent dependent. Under certain circumstances, the initial cycloadducts **545** are converted to the open-chain valence tautomers, α-diazo-2,5-dihydropyrrole-2-acetate esters **547** (Scheme 111). The observed regiochemistry is in accord with that commonly found and predicted for cycloadditions of azides to electron-deficient dipolarophiles[7].



SCHEME 111

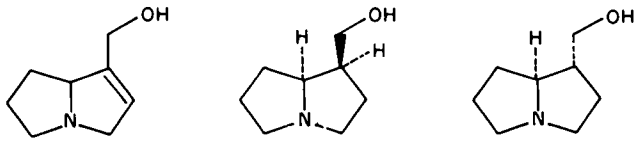
Thermolysis of the azidodiene **548** was simultaneously reported by two groups[169,170] and elaborated later[171]. On standing at 0 °C for 1 week azide **548** (mixture of *E* and *Z* isomers) was transformed to triazoline **549**, which was too sensitive to isolate in pure form, together with vinylaziridine **550** and imine **551** (> 80:10:10). Refluxing **548** in THF or benzene caused smooth conversion to imine **551**, which was contaminated by tetrahydro-

pyrrolizines **552** and **553** (85:4:10 or 88:3:9). Flash pyrolysis of **548** at 550 °C also gave a mixture of **551**, **552** and **553** (51:9:40) (Scheme 112).

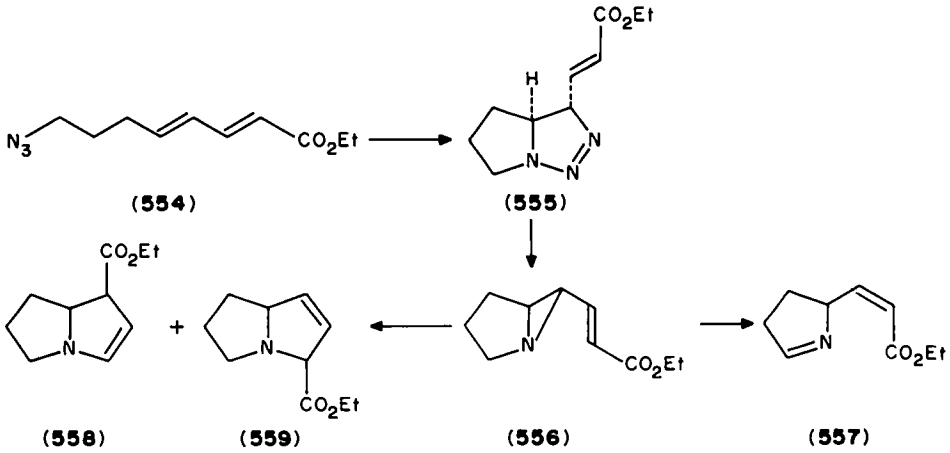


SCHEME 112

The mechanism suggested for thermolysis of azide **548** involves the formation of vinylaziridine **550** produced from initial cycloadduct **549** with stereospecific or non-stereospecific loss of nitrogen. Vinylaziridine **550** then undergoes a 1,5-homodienyl shift to imine **551a**, which in turn isomerizes to **551b** via a zwitterion, or opens to different diradical or zwitterionic intermediates leading to tetrahydropyrrolizines **552** and **553**. Vinylaziridine **550b** (*exo* isomer) was completely rearranged to **552** upon refluxing in acetone containing LiI or in DME containing NaI[171]. The preparation of **552** constitutes a formal total stereospecific synthesis of (±)-supinidine, (±)-isoretronecanol and (±)-trachelanthamidine.



Thermolysis of azidodiene **554** has also been investigated[171]. Refluxing azide **554** in toluene gave an excellent yield of vinylaziridine **556**, obtained via the cycloadduct **555**, together with a small amount of imine **557**. Flash pyrolysis of **554** at 450 °C provided a mixture of aziridine **556**, and tetrahydropyrrolizines **558** and **559** (*ca* 67:27: < 6). The pyrolysis of **556** under the same conditions produced **558** and **559** (90: < 5) (Scheme 113).



SCHEME 113

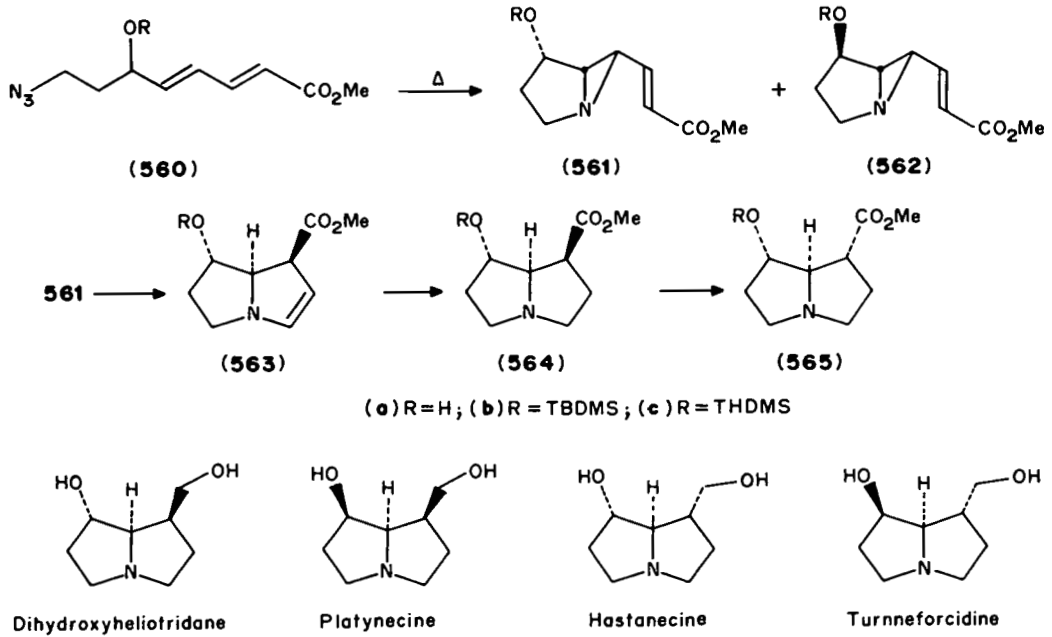
Thermolysis has been extended to azidodienes of type **560**[172] (Scheme 114). The azidodiene **560a** refluxed in toluene for 16 h gave 49% yield of a mixture of vinylaziridines **561a** and **562a** (64:36). Identical conditions applied to the *tert*-butyldimethylsilyl (TBDMS) ether **560b** afforded vinylaziridines **561b** and **562b** (12 h) with an improved yield (70%) and with improved diastereoselectivity (85:15). The presence of the bulky silyl group favors the cycloaddition to take place from the reface of the diene, to a further extent than the directing effect of the hydroxyl group. The thexydimethylsilyl (THDMS)-protected azide **560c** gave, with complete control of stereochemistry, only the vinylaziridine **561c**.

Flash pyrolysis of vinylaziridine **561** at 480 °C afforded tetrahydropyrrolizine **563**, which was subsequently hydrogenated to the saturated **564**. Isomerization of the ester function in **564** gave ester **565**. Thus, the synthesis of **564** and **565** represents a formal total synthesis of dihydroxyheliotridane, platynecine, hastanecine and turnneforcidine (Scheme 114).

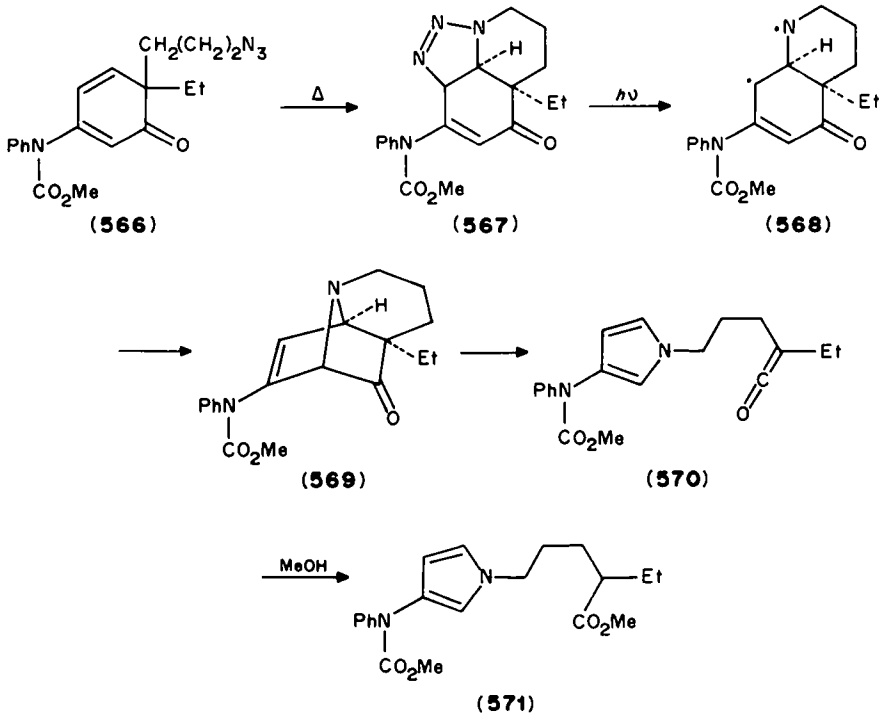
An interesting sequence of reactions leading to a pyrrole has been reported[173]. Azidodienone **566** underwent intramolecular azide–alkene cycloaddition in refluxing benzene to give triazoline **567**. Brief irradiation of **567** in methanol gave the pyrrole carboxylic ester **571** in quantitative yield. The mechanism suggested for the phototransformation involves homolytic extrusion of nitrogen from **567** to generate diradical **568**, which by recombination gives the bridged intermediate **569**. The latter is formally an intramolecular pyrrole-ketene Diels–Alder adduct and its retro-Diels–Alder reaction would lead to the pyrrole ketene **570**, which in turn gives the methyl ester **571** by the reaction with methanol (Scheme 115).

F. Azidoenone Systems

Intramolecular cycloadditions of several azidoenones have also appeared in the literature. In connection with the intramolecular cycloaddition of an azide across the 5, 6-


OR
N3
CO2Me
Δ
RO
N
CO2Me
+
RO
N
CO2Me
(560)
(561)
(562)
561
RO
H
CO2Me
N
(563)
(564)
(565)
(a) R=H; (b) R=TBDMS; (c) R=THDMS
HO
H
OH
N
Dihydroxyheliotridane
Platynecine
Hastanecine
Turnneforcidine

SCHEME 114

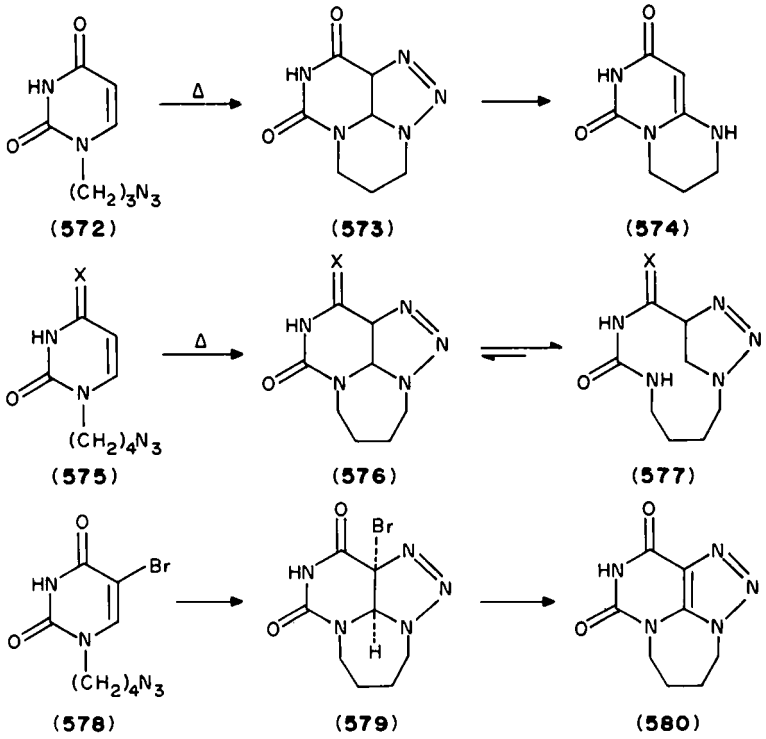


SCHEME 115

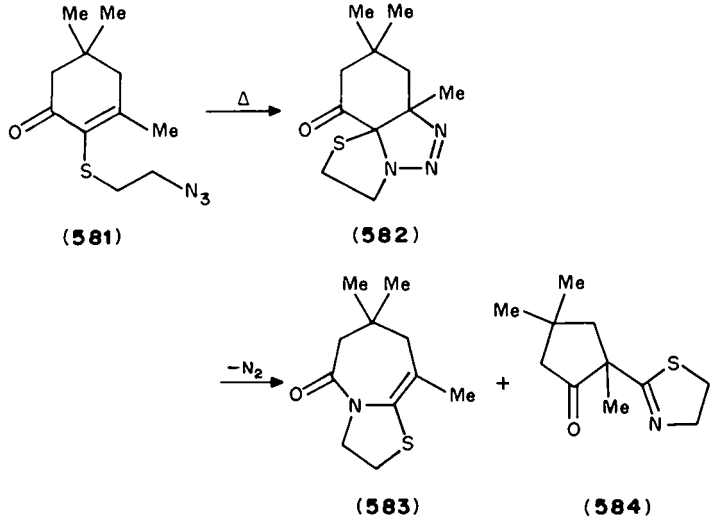
double bond of pyrimidine nucleosides[174], thermolysis of 1-(3-azidopropyl)uracil **572** and 1-(4-azidobutyl)pyrimidines **575** has been investigated[175]. **572** in refluxing toluene gave 1,N^6-trimethylene-6-aminouracil **574** in high yield, which can be rationalized by loss of nitrogen from an initially formed tricyclic triazoline **573**. Heating uracils **575** (X = O, S) in toluene, however, gave the N^1—C_6 cleaved addition products **577** (X = O, S) in good yields. A similar thermal reaction of bromouracil **578** afforded 3,9-tetramethylene-8-azaxanthine **580** produced by *cis* elimination of hydrogen bromide from an initial cycloadduct **579** (Scheme 116). The compound **580** was not obtained by heating **577** with DDQ.

Azidoenone **581** thermolyzed in refluxing xylene to a mixture of **583** and **584** (1:1) in 85% yield[176], suggested to proceed via the triazoline **582**, which in turn undergoes competitive acyl migration with loss of nitrogen to give both **583** and **584** (Scheme 117).

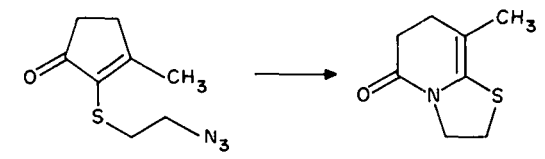
Additional examples for successive intramolecular cycloaddition–nitrogen extrusion reactions are also given. In the case of azidocyclopentenone **585**, ring contraction to a cyclobutanone did not compete with ring expansion to dihydropyridone **586**. In contrast to **581**, thermolysis of fused-ring azidocyclohexenone **587** gave ring expansion product **588** (Scheme 118). The exclusive formation of **588** and none of the ring-contracted compound **590** may be a result of a preferred orientation for azide–alkene cycloaddition to give triazoline **589** rather than a *cis*-fused decalone ring system. Carbonyl migration with expulsion of nitrogen from **587** would be expected to produce a ring-contracted compound with a relatively strained *trans* ring fusion (e.g. **590**).



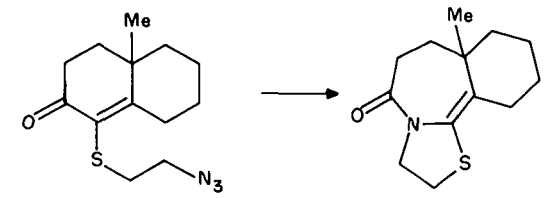
SCHEME 116



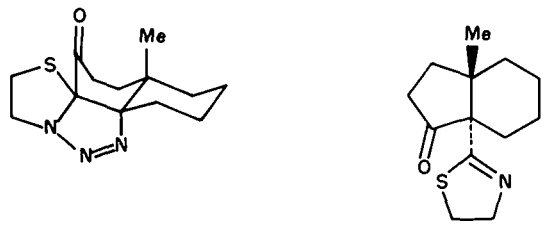
SCHEME 117



(585) (586)



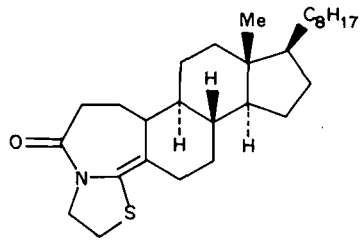
(587) (588)



(589) (590)

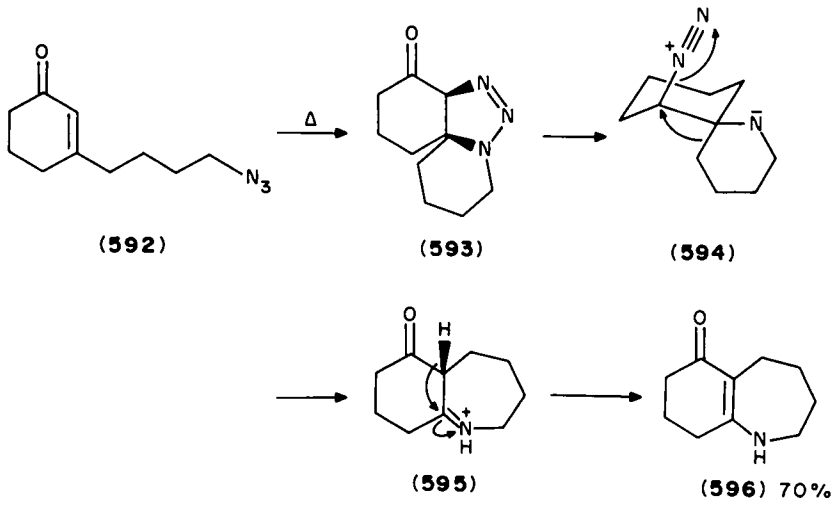
SCHEME 118

Furthermore, 4β,5β-epoxycholestan-3-one was converted to the steroid derivative **591**, suggesting that this methodology will be useful in the construction of a variety of A-aza-A-homosteroidal analogues.



(591)

Azidocyclohexenones undergo smooth intramolecular cycloaddition to give products of various types via the rearrangement of intermediary triazolines with loss of nitrogen depending upon the structures of the azides as well as upon the reaction conditions[177]. For example, azidoenone **592** in refluxing toluene gave enaminone **596**. Presumably, intramolecular cycloaddition of **592** would give triazoline **593**, which gives **596** via a decomposition followed by a 1,2-alkyl shift (**594** → **595**) (Scheme 119).



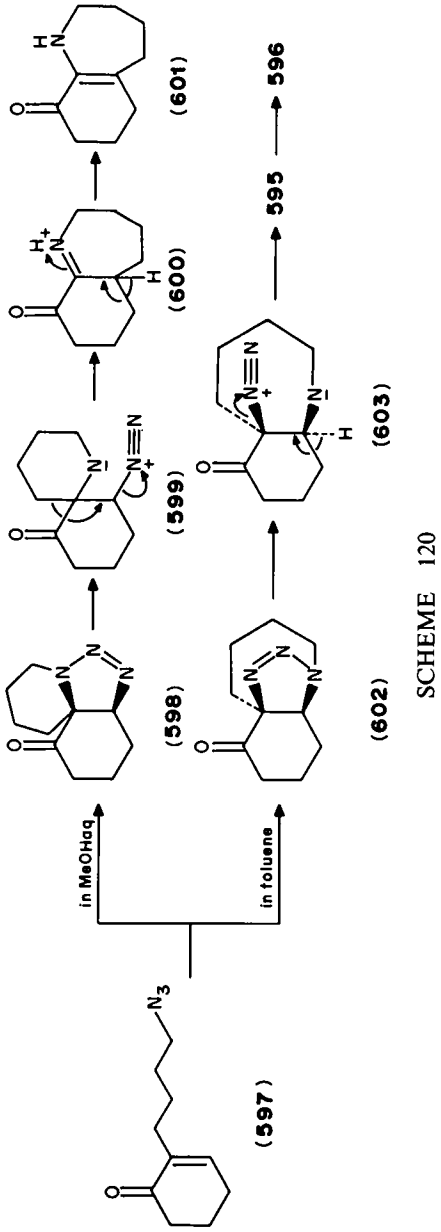
SCHEME 119

Heating azidoenone **597** in aqueous methanol gave the isomeric enaminone **601** in 20% yield; while heating azide **597** in toluene, enaminone **596** was obtained as the major product (39%). In aqueous methanol, triazoline **598** was probably formed as an intermediate which could rearrange into **601** via a 1,2-alkyl shift in the intermediate **599**. On the other hand, in toluene a reversal of the regiochemistry of the cycloaddition afforded triazoline **602**, which decomposed to give the product **596** (**602** → **603** → **595** → **596**) (Scheme 120).

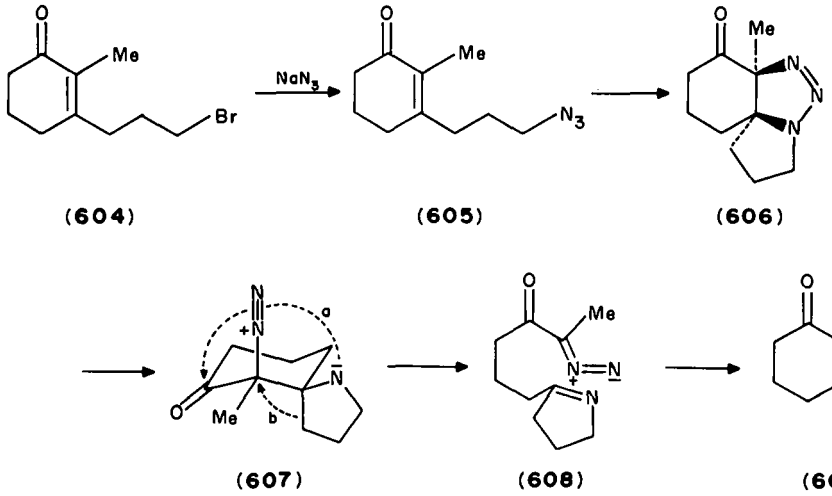
Treatment of enone bromide **604** with sodium azide in dry DMF at 80 °C afforded the aziridine **609** (57%). Apparently no rearrangement similar to those in Schemes 119 and 120 had occurred. In this case, a triazoline like **606** might undergo a 1,3-dipolar cycloreversion[178] via the intermediate **607** to give diazo imine **608**, which by intramolecular carbenoid insertion would give **609**. It is conceivable that the methyl group in **607** would occupy an equitorial position and prevent it from attacking the carbonyl group (arrow a). Furthermore, the 1,2-alkyl shift (arrow b) might also be retarded by the methyl group (Scheme 121).

According to the same method[179] the azide **611**, which was prepared from the tosylate **610** and sodium azide in DMF, decomposed in refluxing xylene to give aziridine **612**. The latter was reduced by chromous chloride to give spiro aminoketone **613**, which was alkylated to give Godleski's intermediate **614** for the synthesis of (±)-desamylperhydrohistrionicotoxin **615** (Scheme 122).

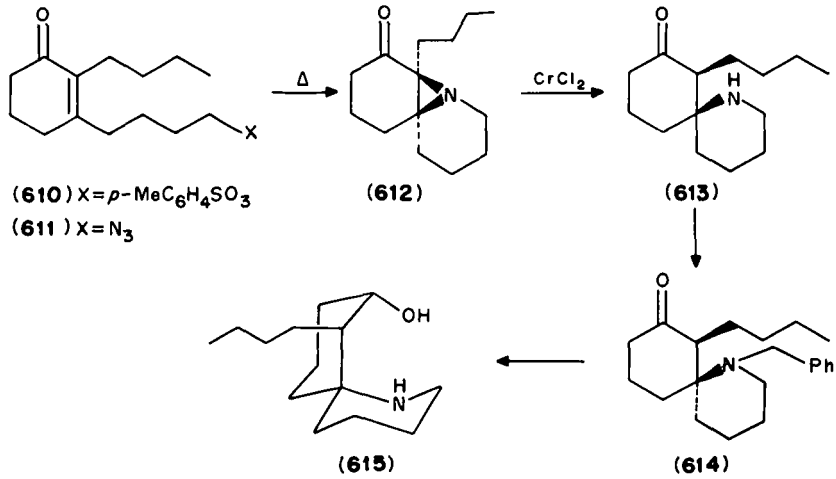
An interesting intramolecular cycloaddition to oxyallyl zwitterions generated by photorearrangement has been reported[180,181]. 4-(Azidoalkyl)-2,5-cyclohexadienones **616–621** were irradiated in benzene with a 366-nm light source. The azide **616** gave the phenols **624** and **625**, while **617** afforded bicyclohexenone azide **622** ($R^1 = R^4 = H$, $R^2 = OMe$, $R^3 = CO_2Me$, $X = CH_2$); no evidence for the formation of an azide cycloadduct was obtained. In the photorearrangement, however, the azides **618–622** gave the corresponding bridged triazenes **626–629**, derived from intramolecular cycloaddition of oxyallyl zwitterions **623** (Scheme 123).



SCHEME 120



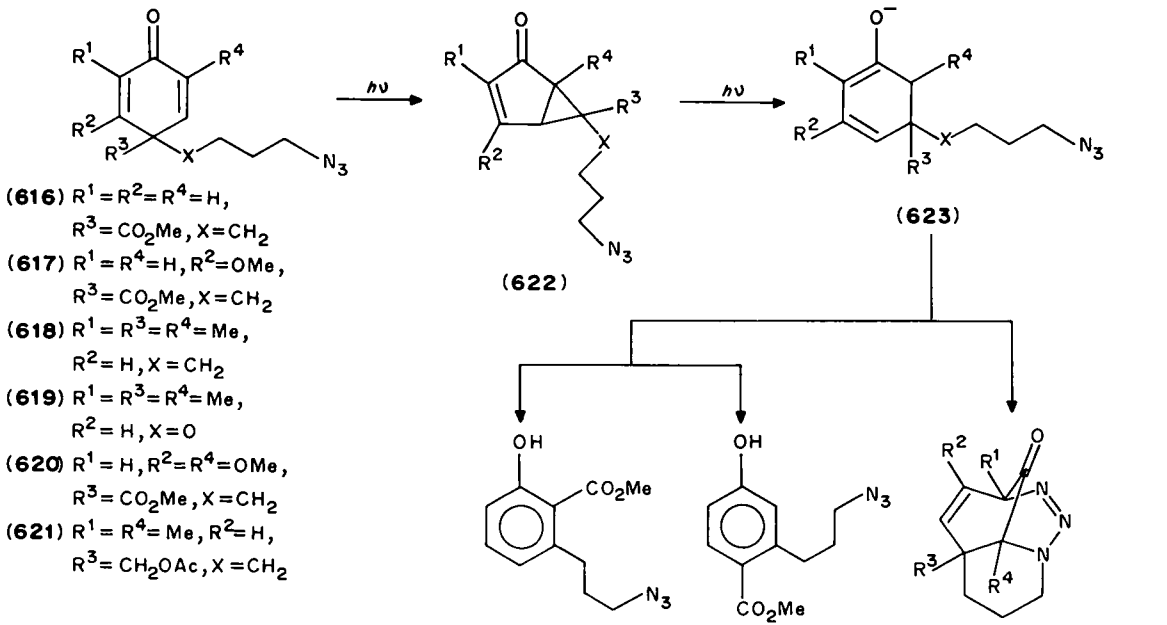
SCHEME 121



SCHEME 122

G. Other Alkenyl Azide Systems

Decomposition of allyl azidocinnamate **630** in refluxing toluene gave four products: indole **634** (10%), benzazepine **635** (20%), tricyclic aziridines **636** (35–40%) and **637** (30–35%)[182]. The yields of thermolysis products were temperature dependent: when the azide **630** was decomposed at higher temperatures in boiling xylene or decalin, the yields of **634** and **637** increased with increasing temperature whereas those of **635** and **636** decreased correspondingly (Scheme 124). Formation of all products has been suggested on the basis of a temperature-dependent competition between cycloaddition and decomposition of the



(**616**) $R^1 = R^2 = R^4 = H$, $R^3 = CO_2Me$, $X = CH_2$

(**617**) $R^1 = R^4 = H$, $R^2 = OMe$, $R^3 = CO_2Me$, $X = CH_2$

(**618**) $R^1 = R^3 = R^4 = Me$, $R^2 = H$, $X = CH_2$

(**619**) $R^1 = R^3 = R^4 = Me$, $R^2 = H$, $X = O$

(**620**) $R^1 = H$, $R^2 = R^4 = OMe$, $R^3 = CO_2Me$, $X = CH_2$

(**621**) $R^1 = R^4 = Me$, $R^2 = H$, $R^3 = CH_2OAc$, $X = CH_2$

(**626**) $R^1 = R^3 = R^4 = Me$, $R^2 = H$, $X = CH_2$ (64%)

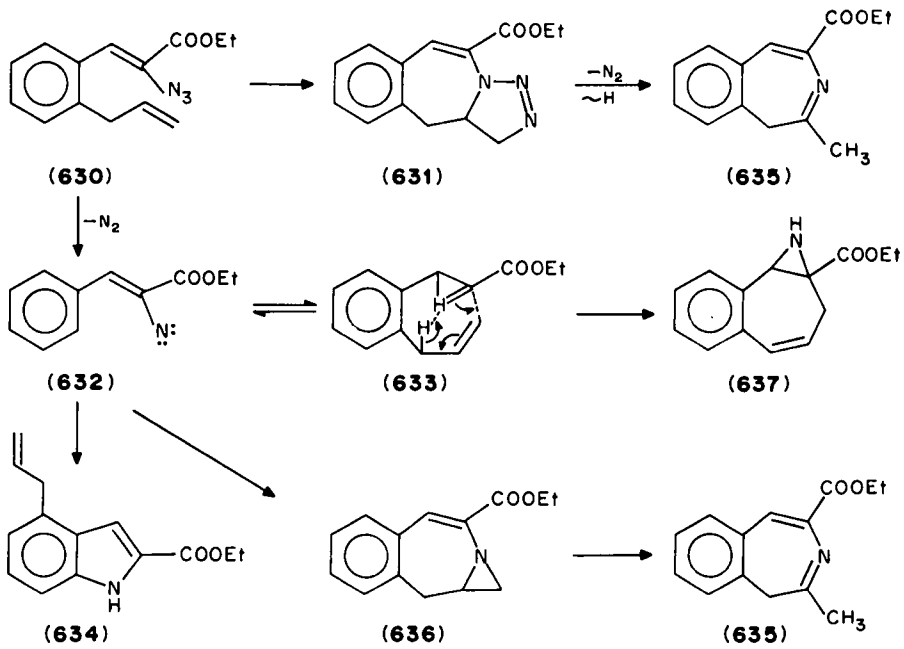
(**627**) $R^1 = R^3 = R^4 = Me$, $R^2 = H$, $X = O$ (75%)

(**628**) $R^1 = H$, $R^2 = R^4 = OMe$, $R^3 = CO_2Me$, $X = CH_2$

(**629**) $R^1 = R^4 = Me$, $R^2 = H$, $R^3 = CH_2OAc$, $X = CH_2$

SCHEME 123

azido group; intramolecular cycloaddition to the double bond gives a triazoline **631**, while loss of nitrogen leads to the nitrene–azirine equilibrium (**632** → **633**). The latter path is the minor one at lower temperature but is favored with increasing reaction temperature. Loss of nitrogen from the triazoline **631**, accompanied by 1, 2-hydrogen shift, gives benzazepine **635**. The nitrene **632** can cyclize to indole **634** or add to the allyl double bond to give aziridine **636**, which can in turn also rearrange to **635**. The azirine **633** can undergo an intramolecular ene reaction to give aziridine **637**.

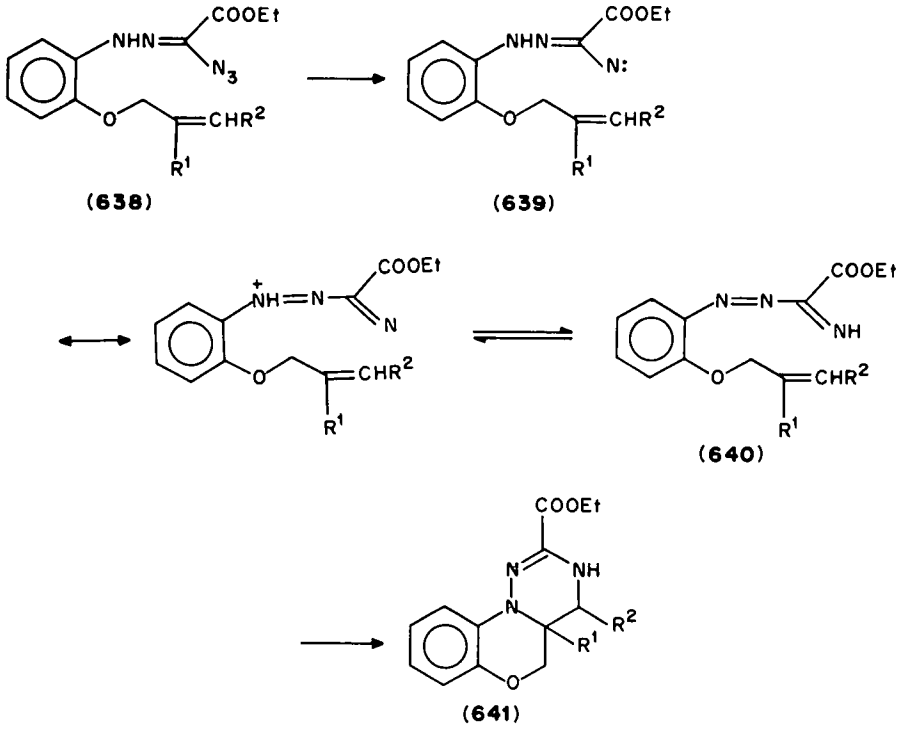


SCHEME 124

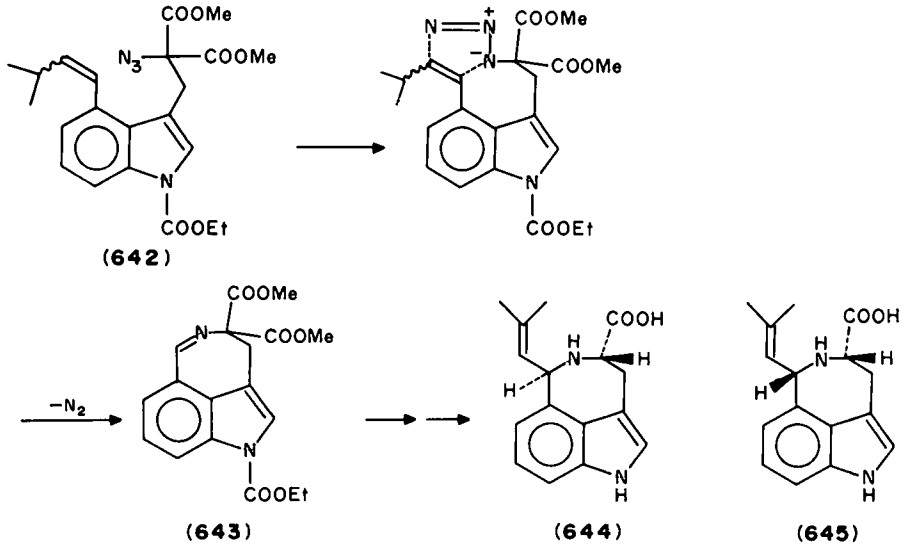
Thermolysis of 1-azidohydrazones **638** afforded benzoxazines **641** in good yields[183]. This was interpreted as involving the preliminary loss of nitrogen to generate the nitrene **639**, which reacts intramolecularly (as such or in the tautomeric form **640**) by 1,4-cycloaddition with the neighboring methylene bond (Scheme 125).

The intramolecular cycloaddition of azide to alkene has been explored as a possible route to the ergot products, the claviciptic acids[184]. On heating the azide **642** in *o*-dichlorobenzene at 190–195 °C for 8 h, the imine **643** was formed as the exclusive product. The intermediate triazoline could not be detected, but presumably is formed and extrudes nitrogen to yield a diradical that rearranges to **643**. The imine **643** was subsequently converted into claviciptic acids **644** and **645** (Scheme 126).

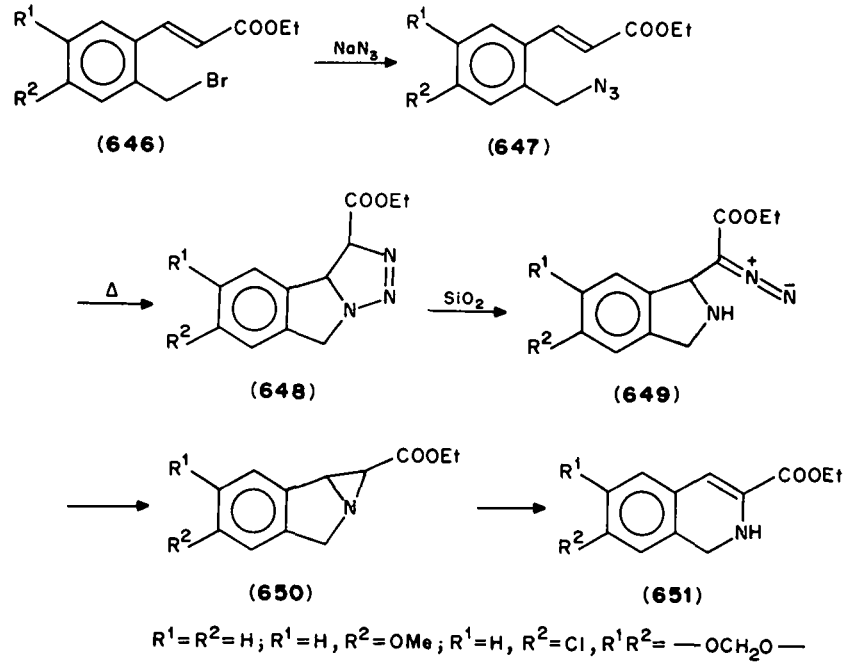
A new entry into 1, 2-dihydroisoquinolines has been recently reported[185]. Reaction of ethyl (*E*)-3-[2-(bromomethyl)phenyl]-2-propenoate **646** with sodium azide afforded azides **647**, which underwent internal cycloaddition to give triazolines **648**. Rearrangement of **648** on silica gel gave diazo compounds **649**, which with rhodium acetate afforded substituted 1, 2-dihydroisoquinolines **651** via aziridines **650** in good overall yields (Scheme 127).



SCHEME 125



SCHEME 126



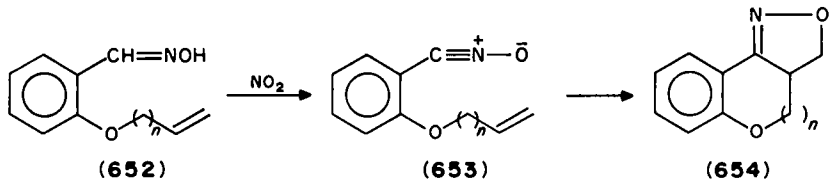
SCHEME 127

VIII. NITRILE OXIDES

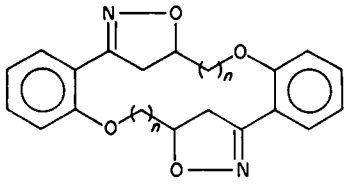
A. Benzonitrile Oxides Bearing an Alkenyl Function

The first example of the intramolecular nitrile oxide cycloaddition (INOC) reaction appeared in 1975. Oxidation of 2-allyloxybenzaldehyde oxime **652** ($n = 1$) with nitrogen dioxide gave 42% of the fused-ring compound **654** ($n = 1$) derived from an INOC reaction of the intermediary nitrile oxide **653** ($n = 1$)[186]. Since nitrile oxides generally undergo bimolecular 1,3-dipolar cycloaddition with terminal alkenes to give 5-substituted 2-isoxazolines[187], the formation of **654** ($n = 1$) indicates that geometric factors can force the reaction to occur in the opposite manner from that normally encountered. It has also been investigated whether the intramolecular reaction proceeds as the chain length between the dipole and dipolarophile function is increased. A similar oxidation of aldoxime **652** ($n = 2$) afforded a low yield (17%) of the cycloadduct **654** ($n = 2$), and a 2% yield of an intermolecular dimeric cycloadduct **655** ($n = 2$). With the next higher homologues **652** ($n = 3$ and 4), however, no intramolecular cycloadducts were detected, but instead the corresponding dimers **655** [$n = 3$ (13%) and $n = 4$ (19%)] were obtained together with much resinous material (Scheme 128).

As part of an investigation of intramolecular 1,3-dipolar cycloadditions to furan rings, *o*-(2-furylmethyloxy)benzonitrile oxide **657** was selected[22]. The reaction of the latter, generated from *o*-(2-furylmethyloxy)benzaldoxime **656** by Lee's method[189], proceeded smoothly to produce the expected cycloadduct **658** and bisadduct **659** in 83 and 10% yields, respectively (Scheme 129). Clearly **659** was derived from a further cycloaddition of **657** to **658**.

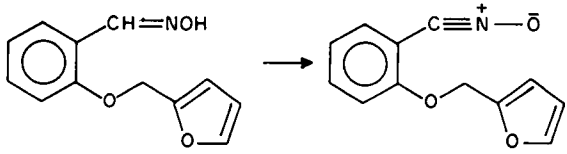


(652) (653) (654)

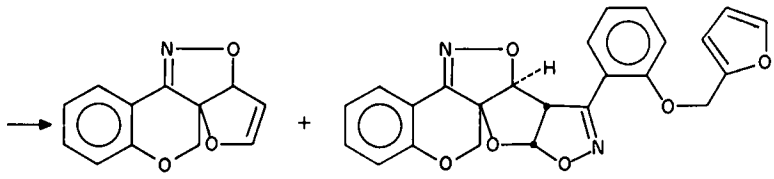


(655)

SCHEME 128



(656) (657)



(658) (659)

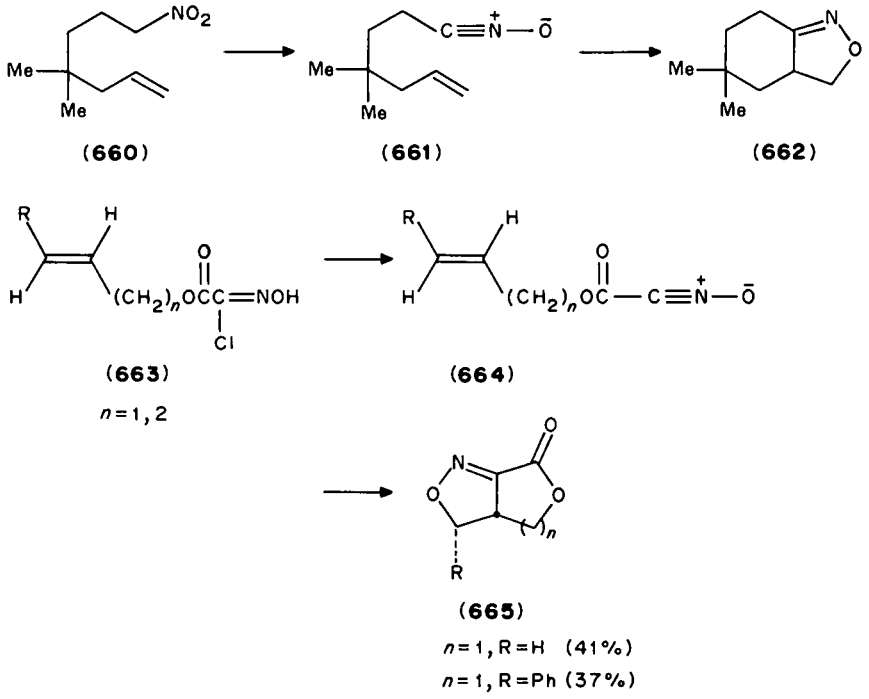
SCHEME 129

B. Acyclic Alkenyl Nitrile Oxide Systems

Since isoxazolines, generally synthesized via the cycloaddition of nitrile oxides to alkenes, can be transformed to γ-amino alcohols, β-hydroxy ketones (and thus α,β-unsaturated ketones, allylic alcohols, 1,3-diols and 1,3-dienes), β-hydroxy nitriles, acids and esters, and α,β- and β,γ-unsaturated oximes, INOC reactions, particularly of aliphatic nitrile oxides, have been often studied in recent years.

Treatment of 4,4-dimethyl-7-nitro-1-heptene **660** with phenyl isocyanate in the presence of triethylamine (Mukaiyama's method[190]) generated the nitrile oxide **661**, which underwent an internal cycloaddition to produce the fused isoxazoline **662** as the exclusive

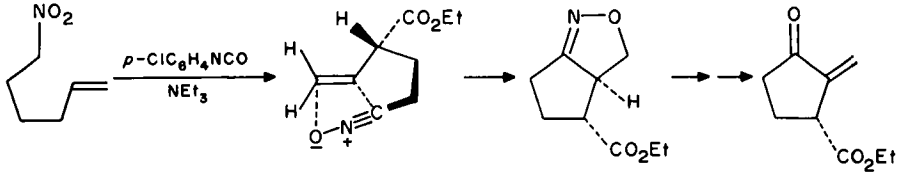
product in 91% isolated yield[191]. Nitrile oxides **664** ($n = 1$), generated from the corresponding 1-chlorooximes **663** ($n = 1$) and triethylamine, gave stereospecific cycloadducts **665** ($n = 1$)[192] (Scheme 130). However, treatment of oxime **663** ($n = 2$, $R = H$) with triethylamine under the same conditions resulted in tarry mixtures from which no products could be isolated and characterized. Although it is reasonable to assume that the propensity to intramolecular cycloaddition might decrease with increasing distance between the reacting groups, the lack of an intramolecular path in the case of **663** ($n = 2$) is somewhat surprising, considering the formation of an intramolecular cycloadduct from the related compound having an alkynyl dipolarophile[192].



SCHEME 130

The INOC reaction has been used for the construction of cyclopentanoids such as the methylenecyclopentanone sarkomycin[193]. Thus, nitroalkene **666** was converted to the corresponding nitrile oxide **667**, which was intercepted by the tethered alkene to give a single isoxazoline **668** in 55% yield. The stereochemistry of **668** is presumed to arise from reaction through a transition state that minimizes $A^{1,3}$ strain. Isoxazoline **668** was then converted into the antitumor agent sarkomycin (Scheme 131).

Kozikowski and Stein[194] have also reported a formal total synthesis of the prostaglandin $F_{2\alpha}$ based on the INOC reaction. Conversion of each of separable alcohols available from debenzylation of **670** to the corresponding aldehyde and thence to its oxime afforded the nitrile oxide precursors **671** and **672**. From **672** the isoxazoline **676** could be obtained in good yield. An examination of molecular models reveals that the required parallel plane approach of dipole and dipolarophile can be achieved only for the conformation of **675**, when overlaying of the dipole/dipolarophile orbitals requires no



(666) (667) (668) (669)

SCHEME 131

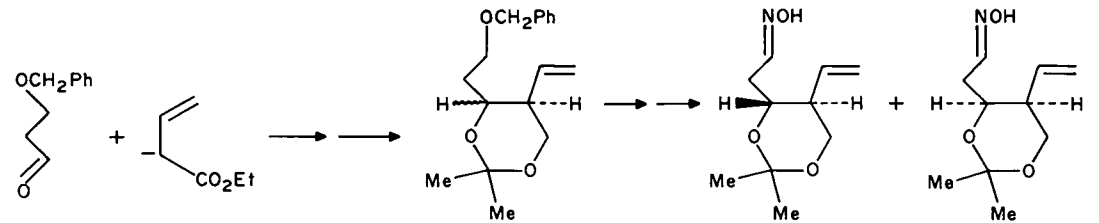
significant distortion of the dioxane ring. The oxime **671** gave the nitrile oxide **673** and, after cyclization, the isoxazoline **674**. The latter was eventually converted into **678**, which is the intermediate prepared by Stork[195] for the synthesis of prostaglandin $F_{2\alpha}$ (Scheme 132).

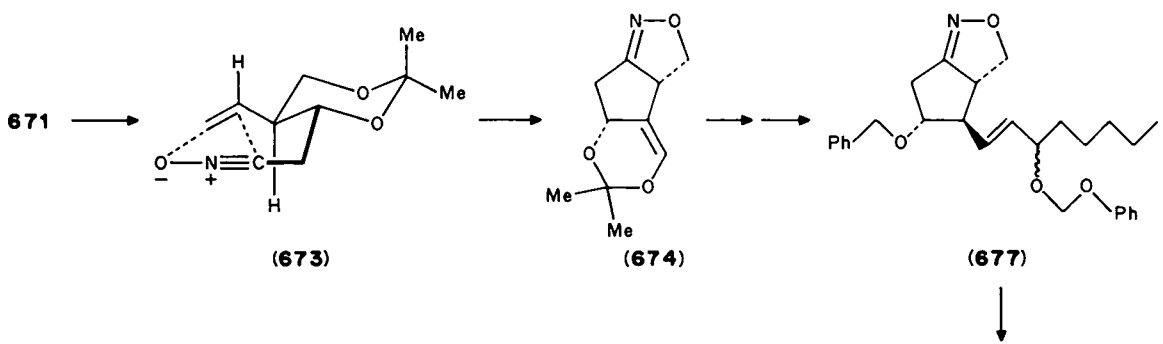
A conceptually different approach to aldol adducts that involves cycloaddition, rather than carbonyl condensation, in the key carbon–carbon bond-forming reaction has also been reported[196]. The two-step sequence involves the formation of isoxazolines followed by Raney nickel cleavage to produce β-hydroxy ketones. Since 1, 3-dipolar cycloadditions of nitrile oxides are well known to be 100% stereospecific[197], this cycloaddition–reduction sequence gives a unique possibility for the diastereospecific formation of β-hydroxy ketones. Examples using INOC reaction are shown below. Nitrile oxides **681**, produced from (*Z*)- and (*E*)-nitroalkenes **680** by Mukaiyama's method[190], underwent readily intramolecular cycloaddition to give stereospecific fused isoxazolines **682** in high yields. Raney nickel catalyzed reduction of **682** afforded β-hydroxy ketones **683**, which are formally the products of a diastereoselective aldol condensation between two ketones (Scheme 133).

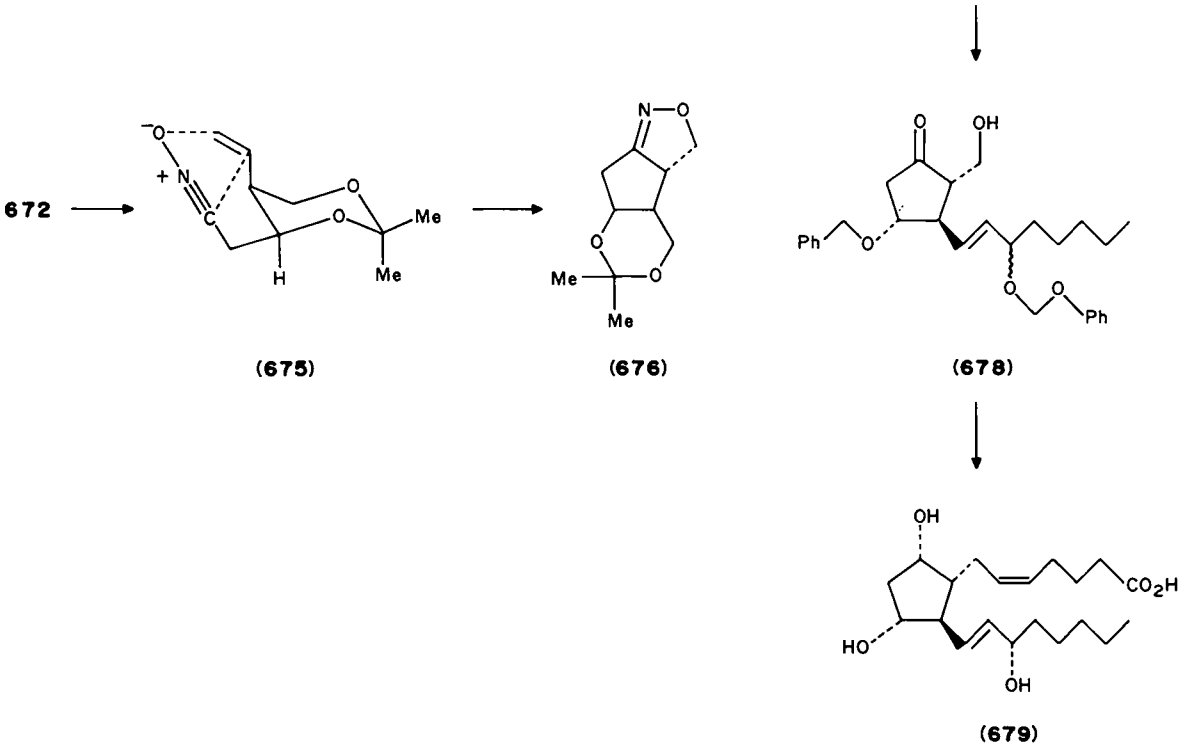
Kozikowski and Chen revealed that it is possible to achieve high diastereoface selectivity in INOC reactions, as long as an allylic asymmetric center is present within the non-isoxazoline ring being formed[198]. Subjection of *Z*-nitroalkene **684** to phenyl isocyanate/triethylamine[190] led to the formation of cycloadduct **686** as a single isomer. On the other hand, a similar treatment of *E*-nitroalkene **689** gave a 3:1 mixture of two cycloadducts **691** (major) and **693** (minor). These results were explained in terms of $A^{1,3}$ strain present in the transition state for cycloaddition. For the *Z*-alkene **684**, an examination of Dreiding models indicated that one mode of cycloaddition **687** leading to a stereoisomeric cycloadduct **688** would involve a severe methyl–methyl interaction, whereas the other **685** leading to **686** contains a less serious methyl–hydrogen interaction. For the *E*-alkene **689**, the two possible transition states are **690** and **692**. A hydrogen–hydrogen interaction is found in **690** leading to **691**, whereas a more serious methyl–hydrogen interaction is present in **692** leading to **693**. Since these steric interactions are much less serious than a methyl–methyl interaction, the *E*-alkene **689** gave a mixture of two stereoisomeric isoxazolines **691** and **693** (Scheme 134).

Recently, INOC reactions on *Z* and *E* chiral alkenes have been studied in order to evaluate the influence of the double bond configuration on the stereochemical outcome of the process[199]. Treatment of alkenyl oximes **694–697**, derived from lactaldehyde or glyceraldehyde, with sodium hypochlorite gave the nitrile oxides, which were trapped *in situ* by intramolecular cycloaddition to give the corresponding isoxazolines **698–701** as mixtures of diastereoisomers (Scheme 135).

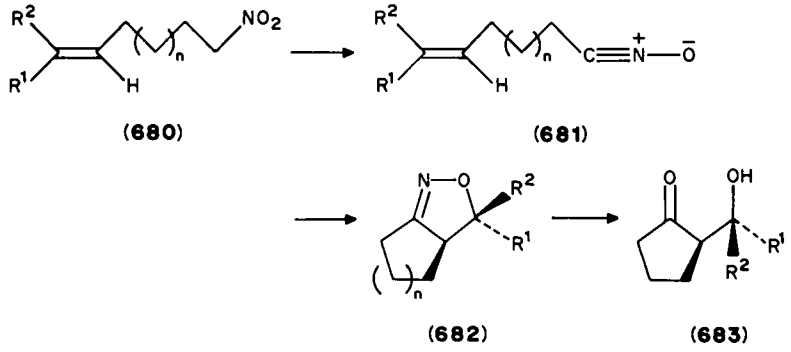
From (*Z*)-alkenyl oximes C-4/C-5 *syn* products and (*E*)-alkenyl oximes C-4/C-5 *anti* products were obtained, while the relative stereochemistry at C-5/C-5′ of the predominant isomers was found to be *anti* in all cases. On the basis of the experimental results as well as of theoretical calculations (MM2) of the cycloaddition transition structures, the following conclusions were introduced. With the (*Z*)-alkenes, the 'small' group of the allylic


OCH2Ph
CO2Et
OCH2Ph
NOH
NOH
Me
Me
Me
Me
Me
Me
H
H
H
H
H
H
O
O
O
O
O
O
(670)
(671)
(672)

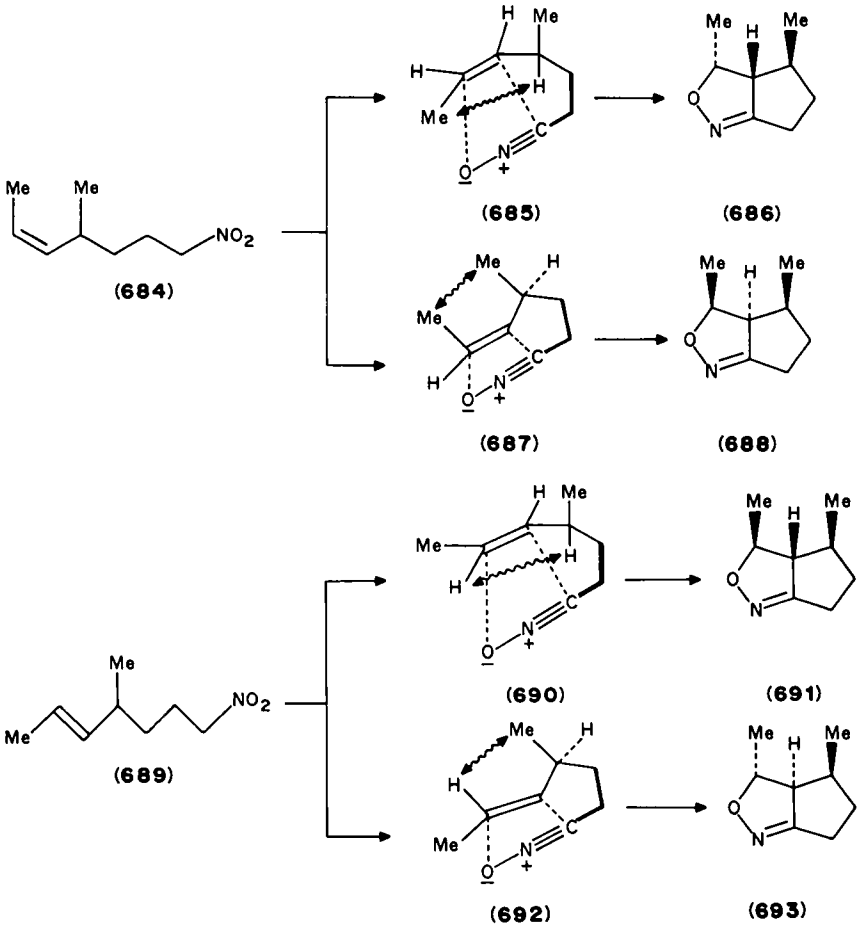

671
Me
Me
H
H
O
O
O
O
N
C
N
O
O
Me
Me
Me
Ph
O
O
O
Ph
(673)
(674)
(677)



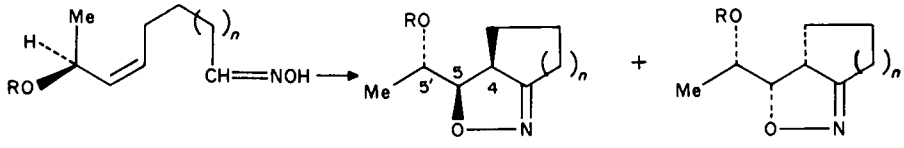
SCHEME 132



SCHEME 133

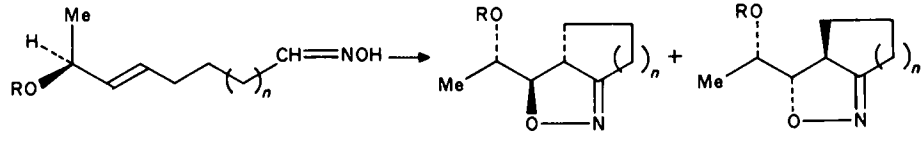


SCHEME 134



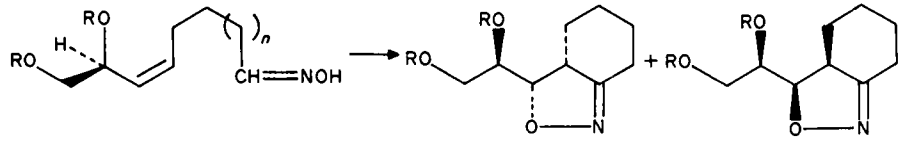
(694) *Z* **(698a)** **(698b)**

$n=1$ **698a / 698b** = 75/25; $n=2$ **698a / 698b** = 80/20



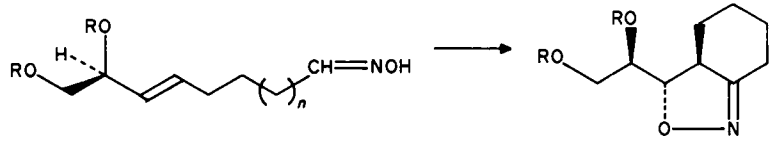
(695) *E* **(699a)** **(699b)**

$n=1$ **699a / 699b** = 58/42; $n=2$ **699a / 699b** = 60/40



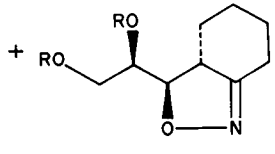
(696) *Z* **(700a)** **(700b)**

$n=2$ **700a / 700b** = 83/17



(697) *E* **(701a)**

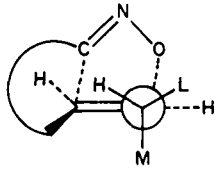
$n=2$ **701a / 701b** = 86/14



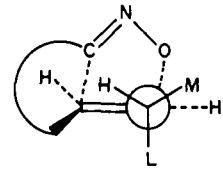
(701b)

SCHEME 135

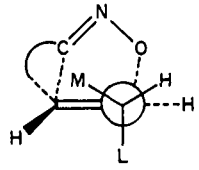
stereocenter prefers the most crowded inside position, the 'medium' the *anti*, and the 'large' the outside, with respect to the forming C—O bond. For example, the transition state **702** (M = OR, L = Me) leading to **698a** is more favourable than **703** leading to **698b**, because a repulsion between the oxygens of alkoxyl group (M) and of the oncoming nitrile oxide involves **703**: the factors controlling the stereoselectivity are mainly steric.



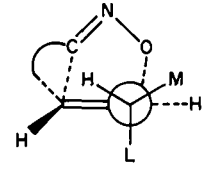
(702)



(703)



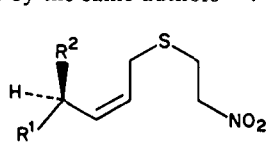
(704)



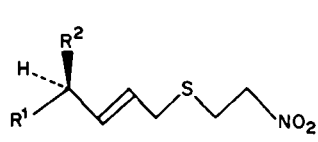
(705)

On the other hand, with the less sterically requiring (*E*)-alkenes, the 'large' substituent prefers the *anti* position, the 'medium' the inside (inside alkoxy effect[200]), and the 'small' the outside. For example, the transition state **704** (M = OR, L = Me) leading to **699a** is more favourable than **705** leading to **699b**, as previously proposed for intermolecular reactions[201]. The higher selectivity shown by the (*E*)-allyl ether (e.g. **697**) derived from glyceraldehyde compared to the one [e.g. **683** (*n* = 2)] derived from lactaldehyde (86/14 vs 60/40) could be interpreted in terms of electronic factors.

Similar INOC reactions using (*Z*)-**706** and (*E*)-alkenyl nitrosulfides **707** have been investigated by the same authors[202].



(706)

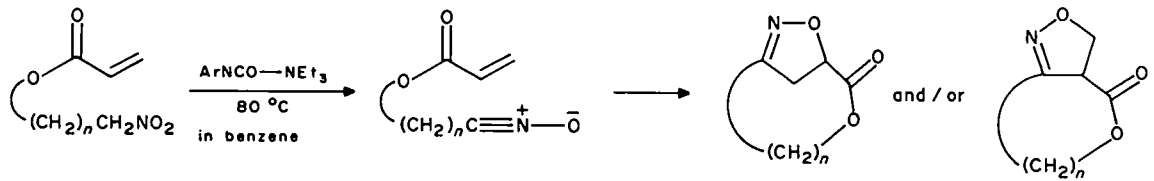


(707)

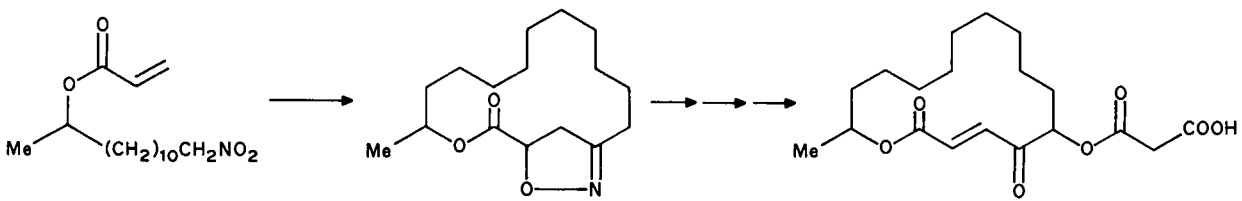
C. Macrocyclization Using INOC Reactions

A successful application of an INOC strategy for macrocyclization has been reported by two groups[203,204].

Treatment of ω-nitroalkyl acrylates **708** with *p*-chlorophenyl isocyanate-triethylamine in refluxing benzene gave the corresponding nitrile oxides **709**, which were trapped *in situ* with the internal double bond to produce fused macrocyclic lactones **710** and/or **711**. Although **708** (*n* = 5) gave only the nine-membered lactone **711** (*n* = 5), longer-chain nitroalkyl acrylates **708** (*n* = 8, 10 or 11) afforded 14-, 16- or 17-membered lactones **710** as a major or exclusive product[203]. This indicates that the regiochemistry associated with the



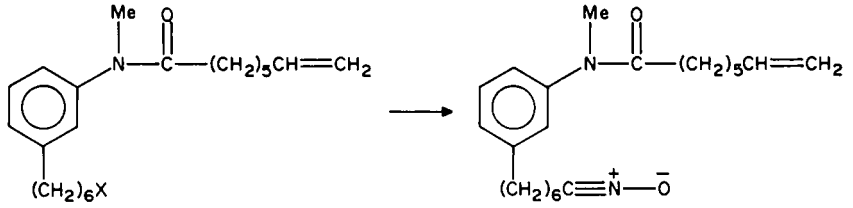
(708)	(709)	(710)	(711)
$n=5$		—	44%
$n=8$		68%	14%
$n=10$		64%	10%
$n=11$		67%	—



(712) (713) (714) A26771B

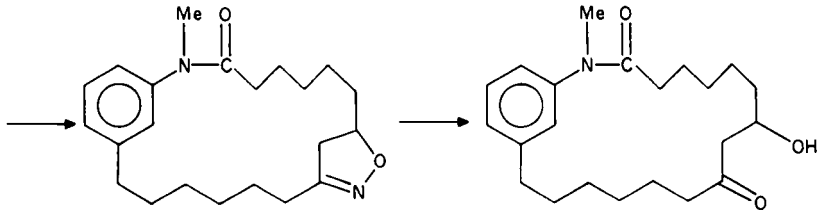
SCHEME 136

intramolecular cycloaddition reaction is strongly affected by the ring size of the forming lactones. Cyclization of the nitroalkyl acrylate **712** at 60–65 °C for 36 h afforded the isoxazoline **713** (50%), which was elaborated to (±)-A26771B **714**[203] (Scheme 136).

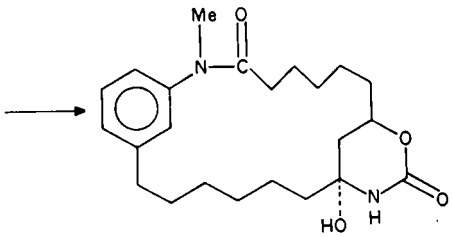


(715) X=CH=NOH
(716) X=CH_2NO_2

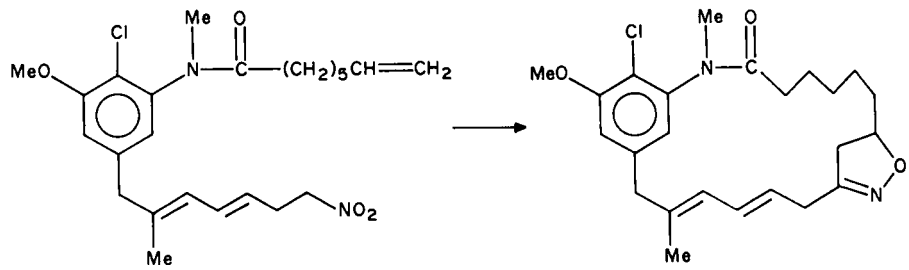
(717)



(718) **(719)**



(720)



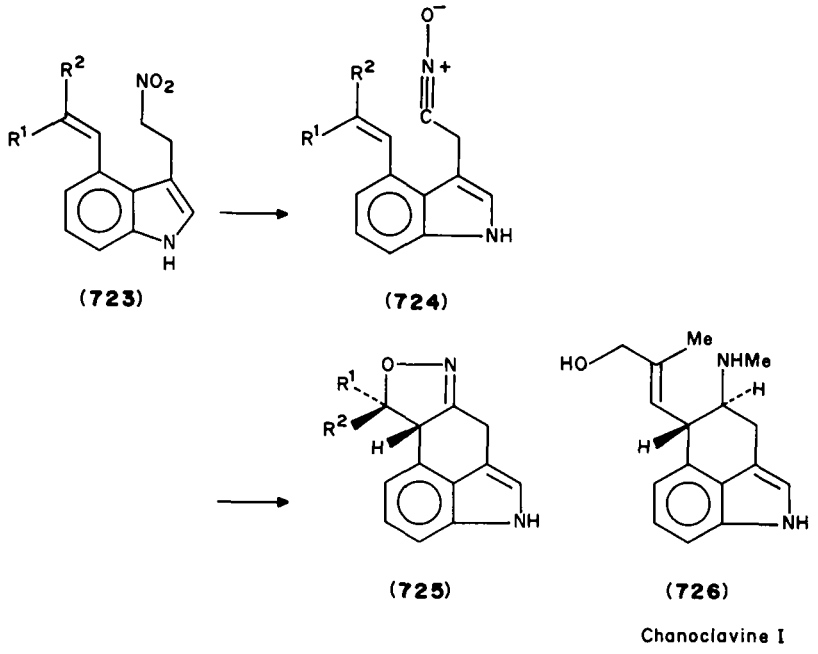
(721) **(722)**

SCHEME 137

Recently, the macrocyclization of an alkenic nitrile oxide to the ansamacrolide skeleton has been demonstrated[204]. Treatment of the alkenyl oxime **715** with sodium hypochlorite–BuN_4OH generated the nitrile oxide **717**, which gave 51% yield of the 19-membered cycloadduct **718**. The nitroalkene **716** was found to be an excellent precursor for the macrocyclization. In a highly diluted toluene solution treatment of **716** with *p*-chlorophenyl isocyanate-triethylamine at 80 °C afforded 82% yield of cycloadduct **718**. Hydrolytic reduction of **718** gave *β*-hydroxy ketone **719**, which then converted to **720**, embodying the 'carbon backbone' of maytansine. Furthermore, the highly functionalized nitrotriene **721** was found to smoothly cyclize to the desired macrocyclic isoxazoline **722** (Scheme 137).

D. INOC Reaction Using Indole Nitroalkenes

Kozikowski and coworkers accomplished total synthesis of the ergot alkaloids chanoclavine I[205] and Paliclavine[206] by using INOC reaction as the key step. Indole nitroalkenes **723** (by Mukaiyama's procedure[190]) afforded high yields, (70–90%) of isoxazolines **725** which correspond to internal cycloadducts of transient nitrile oxides **724**[205] (Scheme 138). No side-products resulting from reaction of the dipole with the electron-rich indole nucleus were detected. The isoxazoline **725c** was eventually converted into chanoclavine I **726** in a subsequent series of steps.

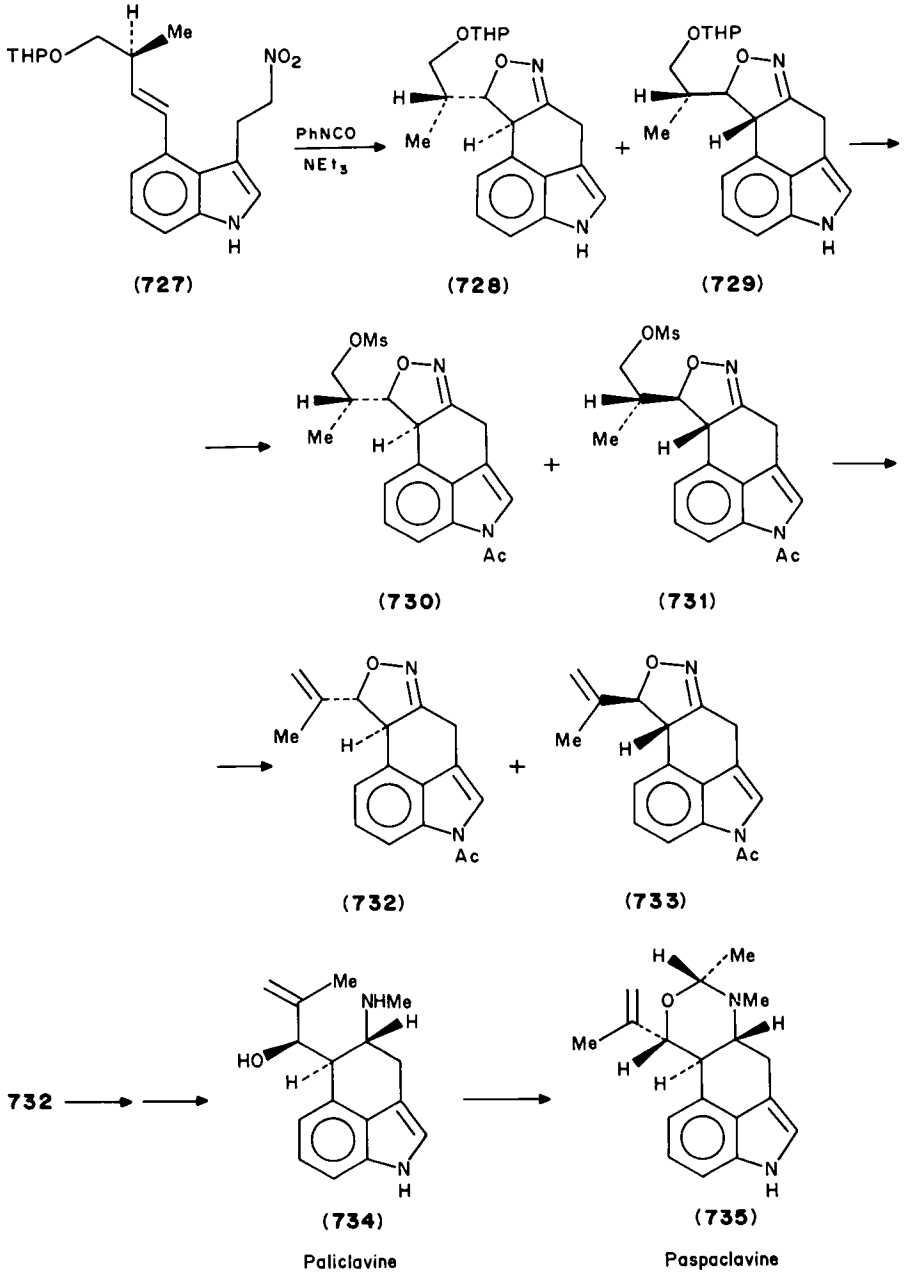


(a) $R^1=R^2=H$; (b) $R^1=OMe$, $R^2=H$; (c) $R^1=H$, $R^2=CH_2OAc$

SCHEME 138

On subjecting indole **727** to phenyl isocyanate-triethylamine, the desired INOC reaction occurred in high yield to afford isoxazolines **728** and **729** as an unseparable 1.1:1

mixture of diastereomers. *N*-Acetylation of this mixture followed by removal of the THP group and subsequent mesylation gave a separable mixture of the diastereomeric products



(727) (728) (729) (730) (731) (732) (733) (734) (735)

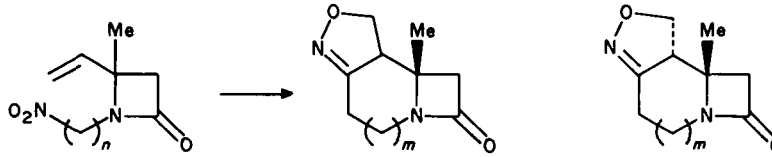
Paliclavine Paspaclavine

SCHEME 139

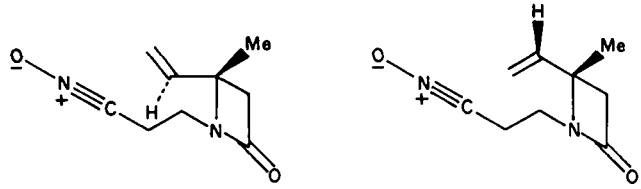
730 and 731, which were converted into 732 and 733, respectively. The compound 732 possessing the correct stereochemistry was eventually converted into 734 and then into (±)-paspaclavine 735[206] (Scheme 139).

E. Synthesis of Fused β-Lactams

The INOC reaction has also been applied to the synthesis of fused β-lactams[166]. The nitroalkene 736 ($n = 3$) (by Mukaiyama's procedure[190]) gave exclusive formation of the *cis*-fused tricyclic isoxazoline β-lactam 737. On the other hand, the INOC reaction starting with nitroalkene 736 ($n = 4$) produced preferentially the *trans* isomer 739 (738:739 = 40:60) (Scheme 140). However, attempts to effect the INOC cyclization on 736 ($n = 2$ and 5) did not lead to the expected five- and eight-membered ring annelation products. Thus, ring closure to eight-membered rings is more favorable for the intramolecular azide cycloaddition [539 → 540 + 541 (each $n = 3$)] than for the INOC reaction. The *cis* stereoselectivity during ring closure to the fused six-membered ring system 737, as well as 540 ($n = 1$), is attributed to a preference for a chair-like transition state 740 over a boat-like transition state 741. Models indicate that 740 also provides better orbital overlap of the dipole and dipolarophile than does 741. As the size of the newly formed ring increases from six to eight, the greater conformational flexibility permits the formation of *trans* isomers.



(736) (737) $m=1$ (738) $m=2$ (739) $m=2$

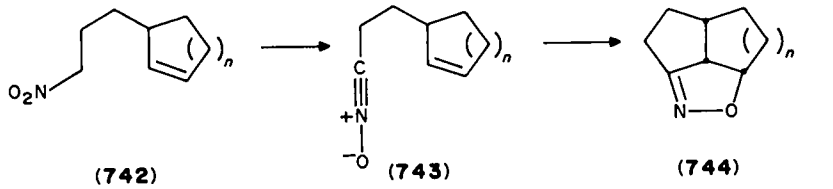


(740) (741)

SCHEME 140

F. Ring Annelation Using Cycloalkenyl Nitrile Oxides

Ring annelations by the INOC reaction with nitro cycloalkenes 742 of varying ring sizes have been reported[207]. Treatment of 742 with phenyl isocyanate-triethylamine generated the corresponding nitrile oxides 743, which were trapped with the internal double bond to produce the desired tricyclic isoxazolines 744 in excellent yields (Scheme 141). The tricyclic isoxazolines 744 can be transformed to β-hydroxy ketones and enones. For example, hydrogenolysis of 744 ($n = 2$) followed by hydrolysis gave the β-hydroxy ketone 745 (95%), which was then converted into enone 746 in 69% isolated yield.

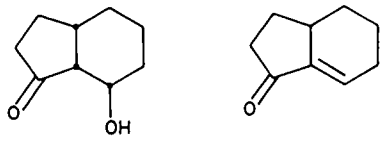


(742) (743) (744)

$n=1\sim4$

$n=1$(91%), $n=2$(96%)

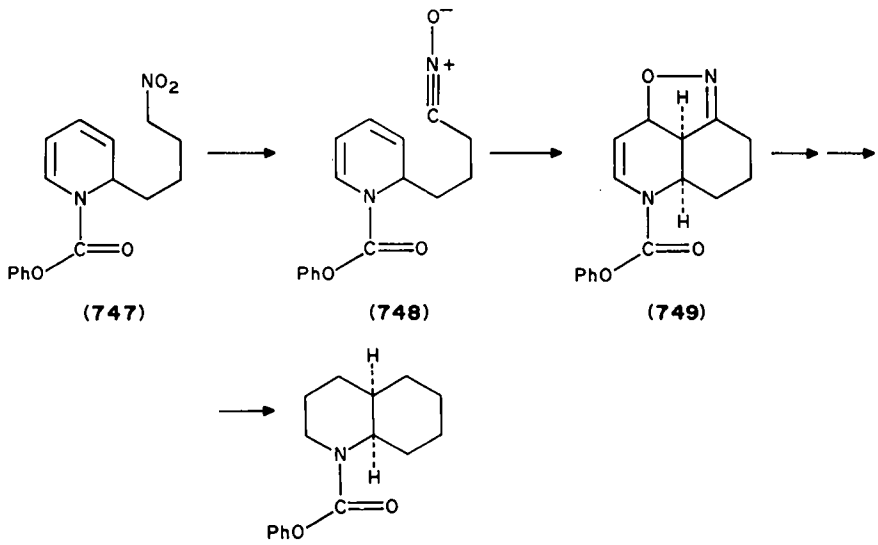
$n=3$(91%), $n=4$(81%)



(745) (746)

SCHEME 141

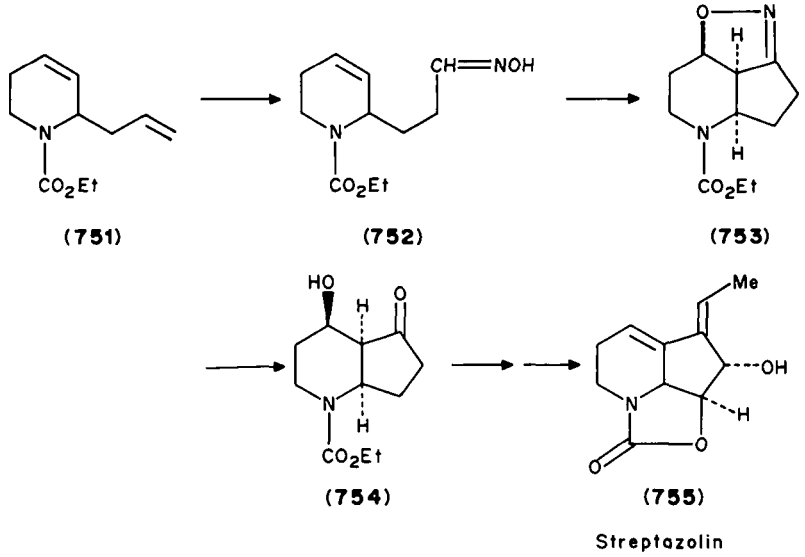
The first example of an intramolecular 1,3-dipolar cycloaddition to a dihydropyridine system has appeared[208]. Mukaiyama's procedure[190] with the nitrobutyl-substituted dihydropyridine **747** gave a single *cis*-fused isoxazoline **749** by stereospecific *syn* addition of the intermediary nitrile oxide **748** in 68% yield. Subsequent elaboration of **749** provided the *cis*-decahydroquinoline ring system **750** (Scheme 142).



(747) (748) (749) (750)

SCHEME 142

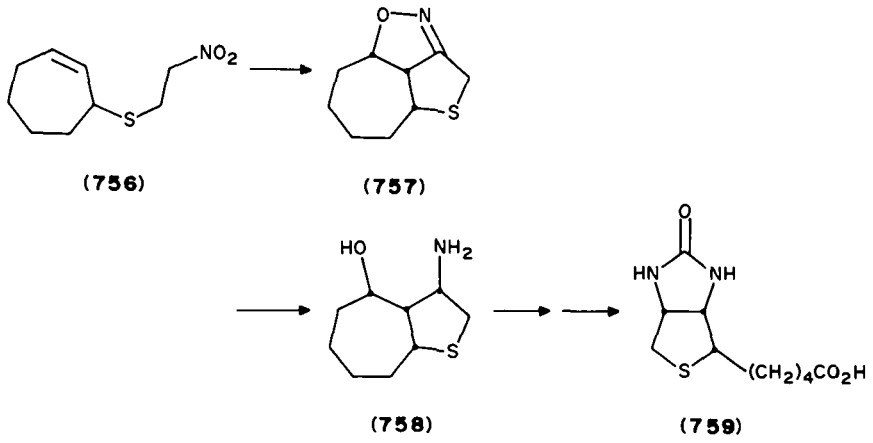
The INOC reaction for crafting the skeleton of the structurally unique antimicrobial agent, streptazoline, has been reported[209,210]. The required nitrile oxide precursor, oxime **752** (prepared from 2-allyltetrahydropyridine **751**), with sodium hypochlorite afforded stereospecifically the isoxazoline **753** (90%). Hydrogenolysis then provided the azahydrindanone **754**, an appropriately functionalized precursor to streptazolin **755** (Scheme 143).



(751) (752) (753) (754) (755) Streptazolin

SCHEME 143

Confalone and coworkers have also utilized the INOC reaction in the stereospecific synthesis of the key amino alcohol **758**, which was converted in five steps to (±)-biotin **759**[211]. Treatment of nitro cycloheptane **756** with phenyl isocyanate-triethylamine led

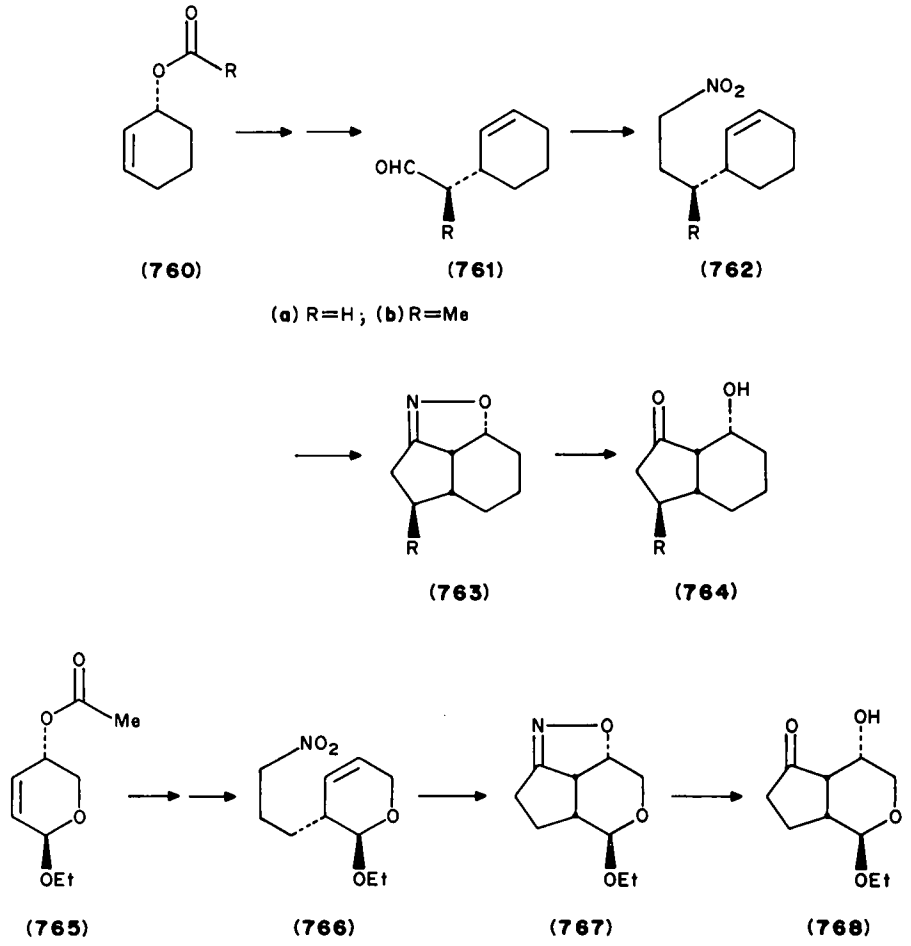


(756) (757) (758) (759)

SCHEME 144

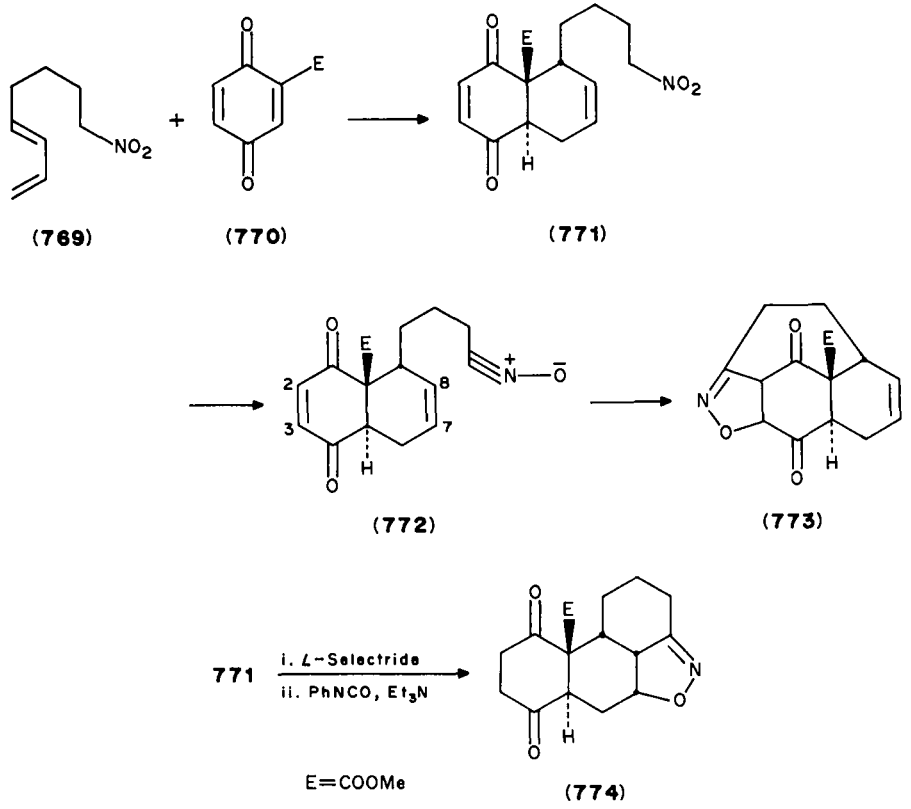
directly to the tricyclic isoxazoline **757**, which was then transformed into the target biotin **759** (Scheme 144).

A new method for annelation of a ring onto an existing allylic alcohol[212] involves the combination of Claisen rearrangement and INOC reaction. The ester enolate Claisen rearrangement[213] of cyclohexenol acetate **760a** or propionate **760b**, followed by methylation and subsequent reduction, gave the aldehyde **761**. The requisite nitro compound **762a** or **762b** was prepared by Wollenberg homologation[207] of the corresponding aldehyde **761**. Nitrile oxide generation and intramolecular cycloaddition using Mukaiyama's conditions[190] proceeded smoothly to give the tricyclic isoxazoline **763a** or **763b** in 70 or 74% yield, respectively. Reduction of **763** gave the corresponding β-hydroxy ketone **764** as a single stereoisomer. This sequence was also applied to glycal **765**, which was prepared from D-xylal. Cycloaddition of nitroalkene **766** under similar conditions afforded cycloadduct **767**, which was again reduced to β-hydroxy ketone **768** as a single stereoisomer (Scheme 145).



SCHEME 145

Kozikowski and coworkers have developed a new method for polycyclic construction through the Diels–Alder INOC reaction sequence[214]. For example, the nitro diene **769** reacted with methoxycarbonyl-*p*-benzoquinone **770** to give the Diels–Alder adduct **771** (90%), and subsequent INOC reaction of **772**, generated by Mukaiyama's procedure[190], provided 58% yield of the cycloadduct **773** as a single isomer. The formation of the eight-membered cycloadduct **773** in preference to a less strained six-membered ring presumably reflects the heightened reactivity of the C_2–C_3 double bond. On the other hand, the tetracycle **774** was formed in 47% overall yield by the reduction of **771** with L-Selectride followed by an INOC reaction (Scheme 146).

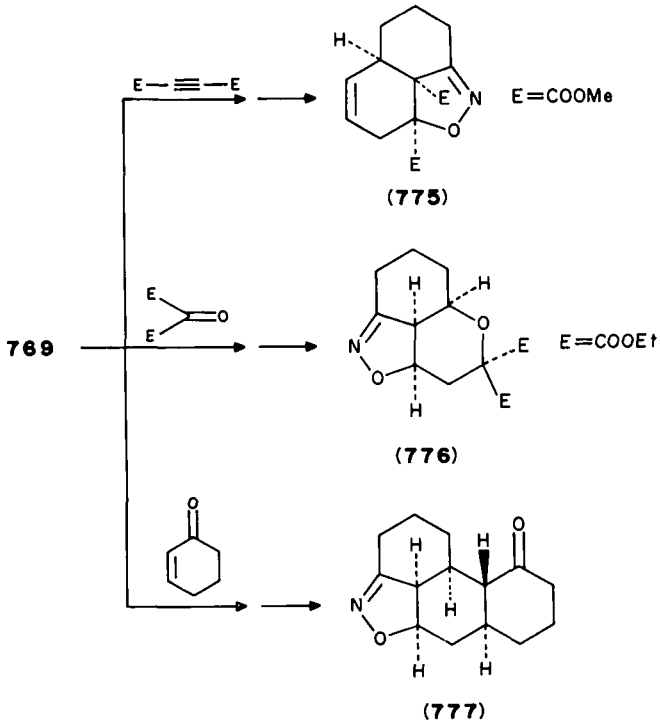


SCHEME 146

Some other examples of the Diels–Alder INOC triannelation process are given in Scheme 147, showing the versatility of this methodology for gaining access to a multiple ring system in a stereospecific manner.

IX. NITRILE IMINES

Nitrile imines can be obtained by the treatment of hydrazonyl halides with base[215], the thermal or photochemical decomposition of tetrazoles[216], the photolysis of sydnones[217], or thermal elimination of carbon dioxide from 1,3,4-oxadiazolin-5-ones[218]. During the



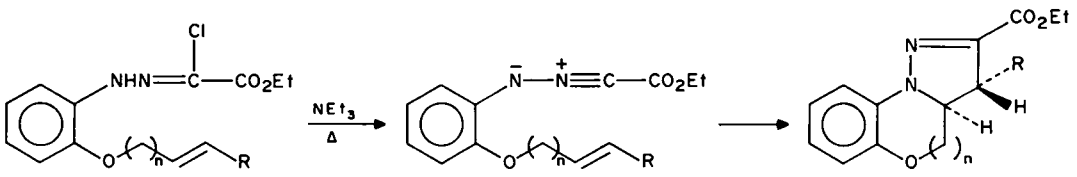
SCHEME 147

past few years a large number of studies dealing with the intramolecular 1,3-dipolar cycloaddition reactions of nitrile imines have been reported.

A. Dehydrochlorination of Hydrazonyl Chlorides

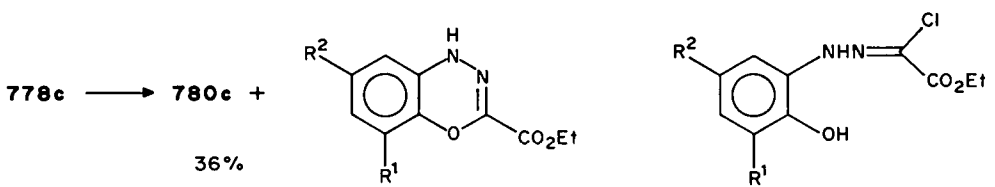
Treatment of 2-(*o*-allyloxy)phenyl- or 2-(*o*-butenyloxy)phenyl-substituted hydrazonyl chloride **778a** or **778b** with triethylamine in boiling benzene or toluene afforded 85 or 45% yield of 3,3*a*-dihydro-4*H*-pyrazolobenzoxazine **780a** or tetrahydropyrazolobenzoxazepine **780b**, whose structure corresponds to the intramolecular cycloadduct of the initially formed nitrile imine **779**, respectively. However, the closely related system **778c**, upon refluxing in toluene in the presence of triethylamine, gives a mixture of the intramolecular cycloadduct **780c** and two isomeric benzoxazines **781** and **782** (Scheme 148)[219].

The structure of **780c** reveals *cis* stereospecificity, which is in line with findings for intermolecular cycloaddition of nitrile imines with 1,2-disubstituted alkenes[4]. The by-products **781** and **782** could arise from the preliminary Claisen-type rearrangement of **778c** to the isomeric phenols **783**. Owing to the presence of triethylamine, the corresponding phonoxide ion should be actually present, from which the products **781** and **782** may be formed through intramolecular nucleophilic displacement of the halogen. Hydrazonyl chlorides of type **778** ($n = 1$) in boiling xylene in the absence of a base gave a mixture of several products including compounds of type **783** which, upon treatment with triethylamine, were readily converted into **781** and **782**[220].



(778) (779) (780)

(a) $n=1$, R=H; (b) $n=2$, R=H; (c) $n=1$, R=Ph

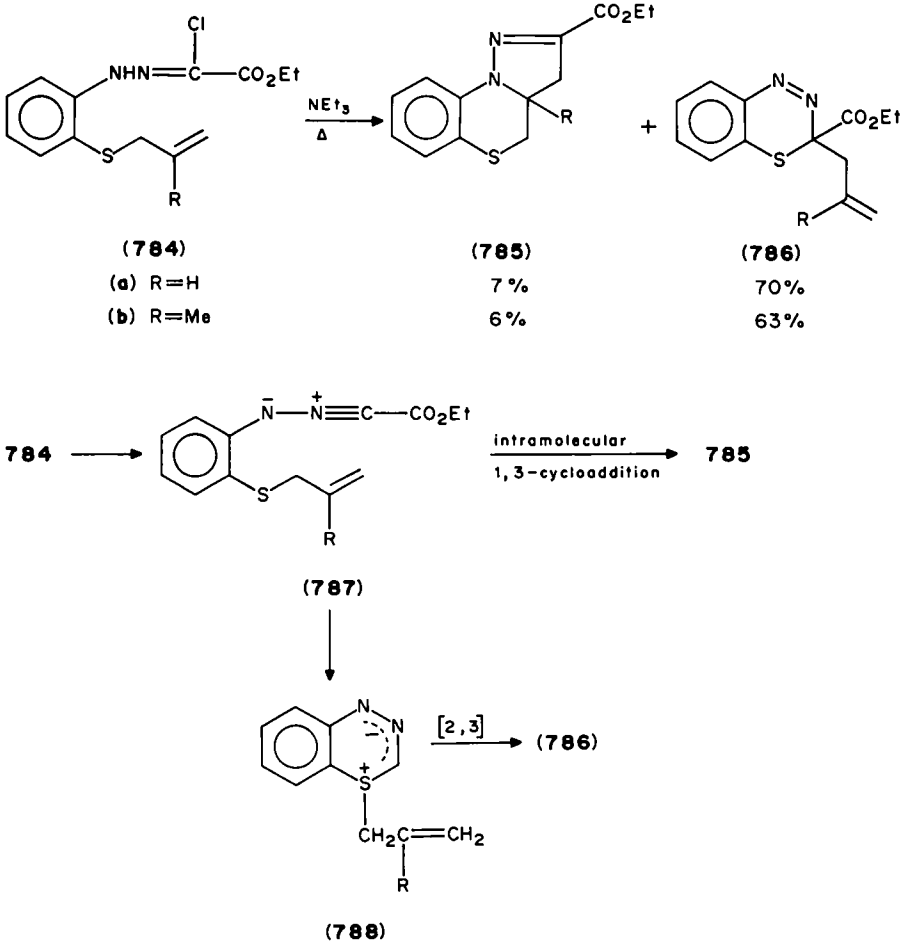


(781) R^1=CH(Ph)CH=CH_2, R^2=H 10%

(782) R^1=H, R^2=CH_2CH=CHPh 12%

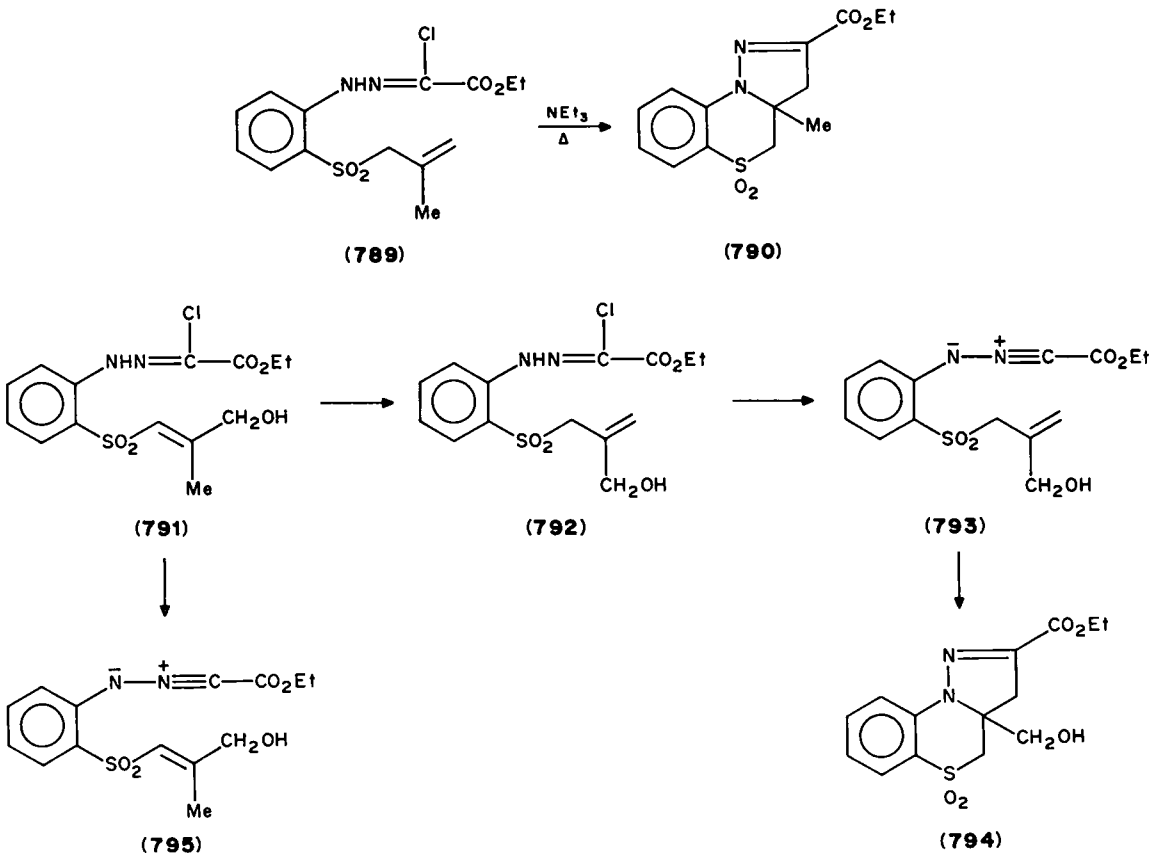
SCHEME 148

Treatment of S-analogues **784** with triethylamine in boiling benzene afforded 4, 1, 2-benzothiadiazines **786** as the major products, together with a small amount of the expected intramolecular cycloadducts **785**[221]. This can be rationalized by the mechanisim given in Scheme 149, involving formation of the nitrile imine **787** followed by intramolecular attack of sulfur on the electron-deficient carbon of the 1, 3-dipole generating the cyclic sulfur ylide **788**. The latter is transformed to **786** by a [2, 3]sigmatropic rearrangement of the allyl group.



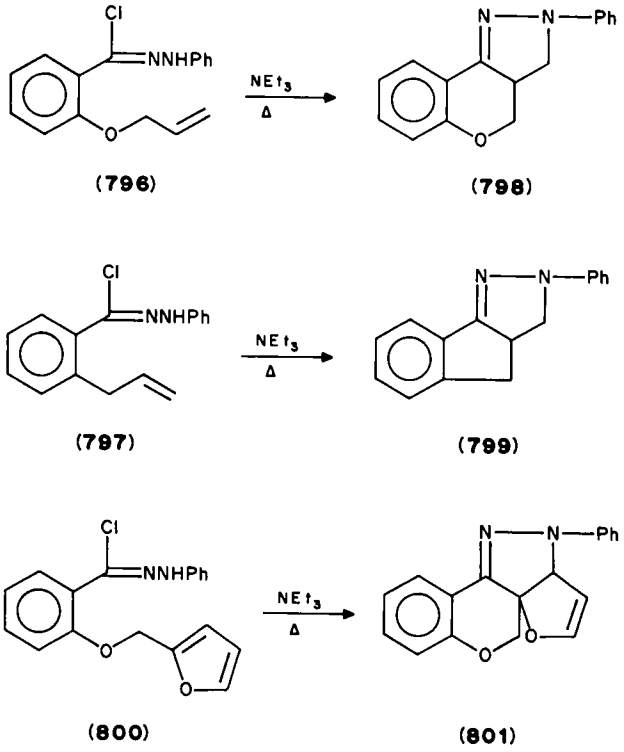
SCHEME 149

Under similar conditions the sulfonyl analogue **789** gave the intramolecular cycloadduct **790** in 40% yield. Hydrazonyl chloride **791**, however, gave the structurally related **794** as the major product in 24% yield, interpreted by the sequence **791** → **792** → **793** → **794** (Scheme 150)[222]. It is noteworthy that the nitrile imine species **795**, which is likely to be present to some extent in the reaction medium, does not undergo intramolecular cycloaddition.


Cl
NHN=C—CO2Et
SO2
Me
NEt3
Δ
CO2Et
N
N
Me
S
O2
CH2OH
(789)
(790)
(791)
(792)
(793)
(794)
(795)

SCHEME 150

The base-induced reaction of hydrazonyl chlorides **796** and **797** under similar conditions gave tetrahydrobenzopyranopyrazole **798** and tetrahydroindenopyrazole **799** in 61 and 60% yields, respectively[223]. An intramolecular cycloaddition of a nitrile imine to a furan ring has been also reported[22]. Treatment of hydrazonyl chloride **800** with triethylamine afforded a cycloadduct **801** in 44% yield (Scheme 151).

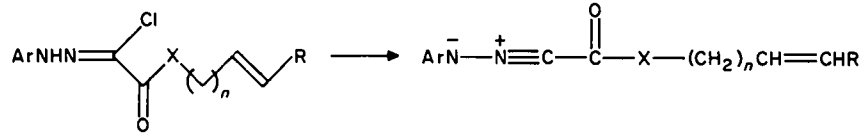


SCHEME 151

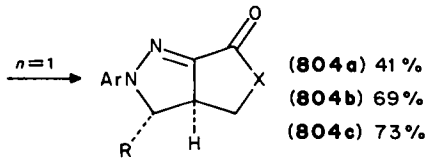
The base-induced reaction of hydrazonyl chlorides of type **802** ($n = 1$) under similar conditions gave bicycle pyrazolines **804**, clearly by intramolecular cycloaddition of the nitrile imines **803** ($n = 1$)[219,224]. (Scheme 152). However, this reaction did not occur with **802** (X = 0, $n = 2, 3$) bearing a longer unsaturated chain. Since the alkenic function of the latter is electronically similar to that of **778b**, the lack of intramolecular cycloaddition may be attributable to unfavorable molecular geometries for the intramolecular approach of the reactive centers.

B. Decomposition of Tetrazoles

Irradiation of 2-(4-pentenyl)-5-aryl-substituted tetrazoles, **805** and **806**, with UV light results in the loss of nitrogen and the formation of nitrile imines **807**, which undergo intramolecular cycloaddition to bicyclopyrazolines **808** and **809**[223,225] (Scheme 153 and Table 6).



(802) (803)



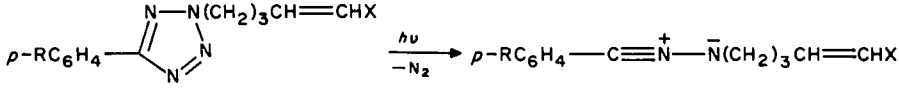
(804a) 41 %
(804b) 69 %
(804c) 73 %

(804)

Ar = *p*-ClC_6H_4

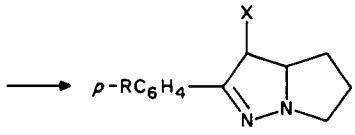
(a) R=H, X=NH; (b) R=H, X=O; (c) R=Ph, X=O

SCHEME 152



(805) R=H
(806) X=H

(807)



(808) R=H
(809) X=H

805, 808
(a) X=H; (b) X=CO_2Me
(c) X=CN; (d) X=COMe

806, 809
(a) R=Me, (b) R=OMe
(c) R=NMe_2, (d) R=Cl
(e) R=CO_2Me, (f) R=CN
(g) R=NO_2

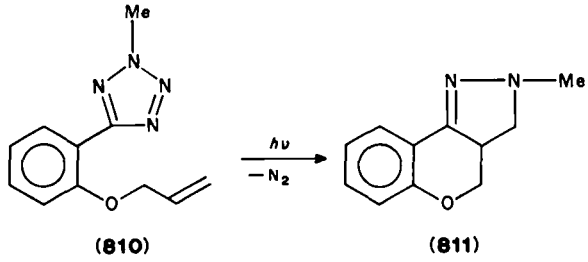
SCHEME 153

The primary photochemical process occurs from the n–π excited singlet state. A kinetic investigation, involving Stern–Volmer plots and relative reactivity studies, shows that there is a marked leveling of the rate profile associated with these internal cycloadditions when compared with their bimolecular counterparts[225]. The cyclozation of the nitrile imine **807** derived from **805b** was faster (6.3 times) than that of the dipole derived from **805a**. This is to be expected, since nitrile imine cycloadditions are HOMO-controlled

TABLE 6

	Irradiation time (h)	Product (%)
805a	2	**808a** (98)
805b	2	**808b** (88)
805c	2	**808c** (71)
805d	2	**808d** (48)
806a	2	**809a** (88)
806b	2	**809b** (76)
806c	2	**809c** (65)
806d	2	**809d** (87)
806e	20	**809e** (17), **806e** (51)
806f	20	**809f** (28), **806f** (33)
806g	20	**809g** (0), **806g** (79)

processes when electron-deficient alkenes are used. What is surprising, however, is that the rate difference is so small, because the rate constants associated with bimolecular cycloadditions of nitrile imines usually range over many powers of $10^{6,7}$. The larger entropy term associated with the intramolecular cycloaddition will tend to compress the rate scale.



(810) **(811)**

SCHEME 154

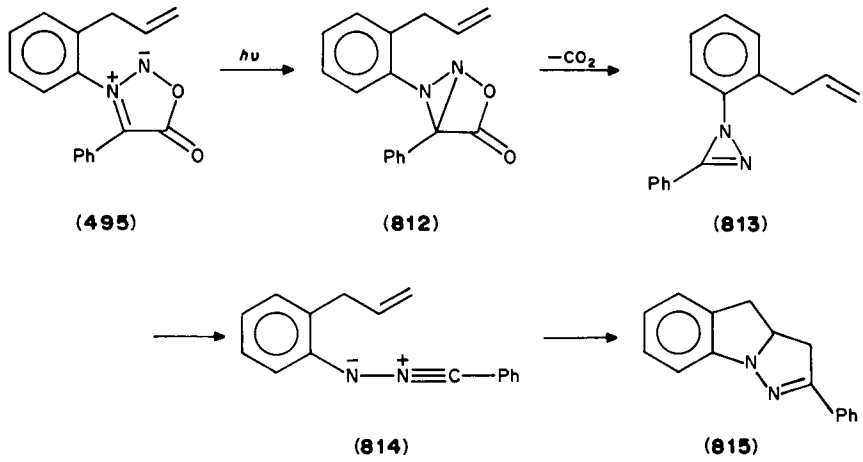
Irradiation of tetrazole **810** in benzene afforded 88% yield of **811** (Scheme 154)[223], whose structure is closely similar to **798** derived from the base-induced reaction of hydrazonyl chloride **796**.

C. Photolysis of a Sydnone

As shown in Scheme 101, thermal reaction of sydnone derivative **495** gives the intramolecular azomethine imine cycloadduct **496**. In contrast, irradiation of **495** in benzene produced dihydro-3*H*-pyrazoloindole **815** in 30% yield[150], which probably arises by intramolecular cycloaddition of nitrile imine **814**. The conversion of **495** to **815** is thought to proceed via intermediate **812**, which loses carbon dioxide to yield the highly strained intermediate **813**, in turn giving the nitrile imine **814** through a ring opening (Scheme 155).

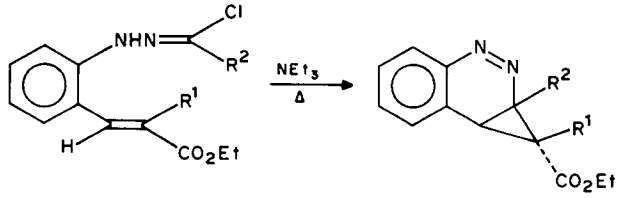
D. Cycloaddition of *o*-Vinylphenyl-substituted Nitrile Imines

1,1-Cycloaddition of nitrile imines to π bonds occurs when the p orbitals of the dipolarophile have been constrained to attack perpendicularly to the nitrile imine plane.



SCHEME 155

Treatment of *o*-vinylphenyl-substituted hydrazonyl chlorides **816** with triethylamine in boiling benzene afforded cyclopropacinnolines **817** in 54–72% yields[226] (Scheme 156).

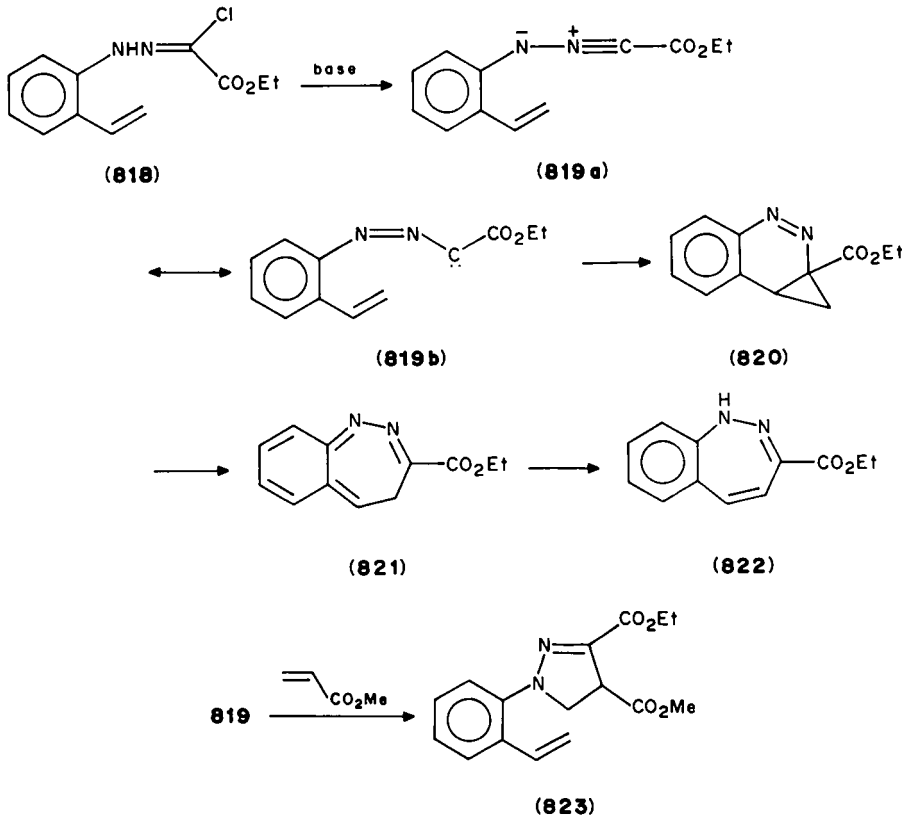


R^1=Me, R^2=COMe; R^1=Me, R^2=COPh

R^1=Ph, R^2=COMe; R^1=Ph, R^2=SO_2Ph

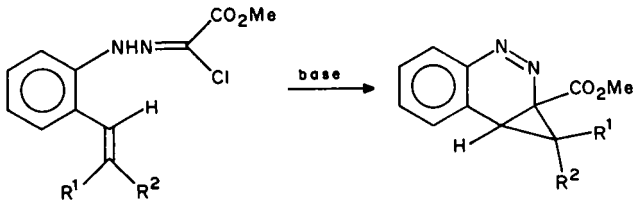
SCHEME 156

Padwa and Nahm have reported intramolecular 1, 1-cycloaddition of nitrile imines as a route to benzodiazepines and cyclopropacinnolines[227]. Treatment of hydrazonyl chloride **818** with triethylamine in benzene under reflux gave 91% yield of 1*H*-1, 2-benzodiazepine **822**, whereas **818**, on treatment with silver carbonate at room temperature, yielded 92% of 1*H*-cyclopropacinnoline **820**, which rearranged at 80 °C to **822**. The thermal rearrangement of **820** to **822** is readily explicable in terms of an electrocyclic ring opening of **820** to **821** followed by a 1,5-sigmatropic shift (Scheme 157). The formation of **820** (and/or **822**) could be markedly suppressed when **818** was treated with base in the presence of excess methyl acrylate; the bimolecular 1, 3-cycloadduct **823** was obtained as the major product. Clearly, the nitrile imine **819** is an intermediate in this reaction and **820** arises by intramolecular 1, 1-cycloaddition of **819b**.



SCHEME 157

The base-induced reaction of the *cis* and *trans* methyl-substituted chlorohydrazones **824** and **825** was also investigated[227]. Treatment of **824** with silver carbonate at room temperature gave the *endo*-cyclopropacinnoline **826** as the exclusive product. Similarly, chlorohydrazone **825** afforded the *exo*-cyclopropacinnoline **827** as the sole product



(824) R^1=Me, R^2=H **(826)** R^1=Me, R^2=H

(825) R^1=H, R^2=Me **(827)** R^1=H, R^2=Me

SCHEME 158

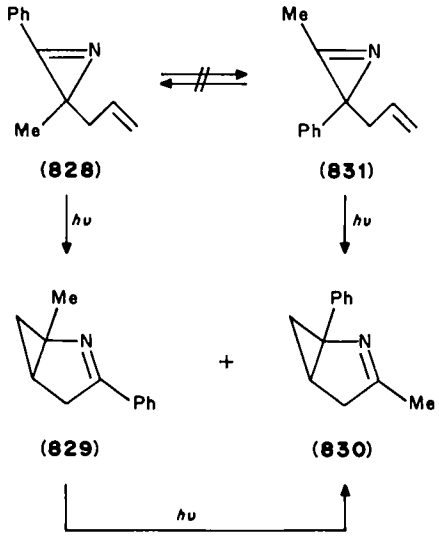
(Scheme 158). These results indicate that complete retention of stereochemistry about the π system has occurred in the cycloaddition reaction.

X. NITRILE YLIDES

Nitrile ylides can be generally obtained by the treatment of imidoyl chlorides with base[1–3], the thermal or photochemical extrusion of alkyl phosphite from 2,3-dihydro-1,4-Δ^5-oxazaphospholes[228] or photolysis of 2*H*-azirines[229,230]. The last route offers the greatest opportunity for structural variation. Padwa and coworkers have found interesting features of intramolecular cycloaddition reactions of nitrile ylides.

A. 2-Allyl-substituted-2*H*-azirine Systems

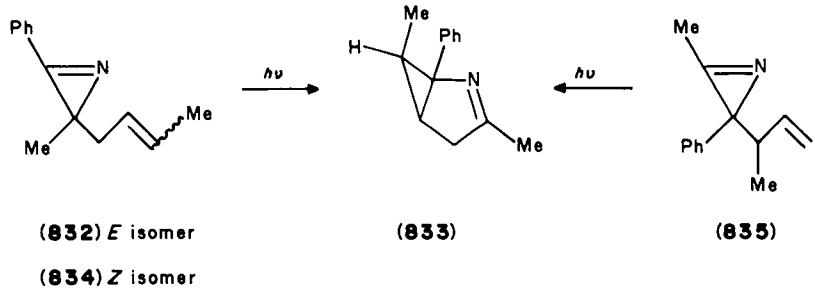
Padwa and Carlsen studied the first example for the 1,1-cycloaddition of nitrile ylides during an investigation of photochemistry of 2-allyl-substituted-2*H*-azirines[231]. When a cyclohexane solution of 2-allyl-2*H*-azirine **828** was irradiated with light of wavelength > 250 nm, a rapid and clean conversion to 1-phenyl-3-methyl-2-azabicyclo[3.1.0]hex-2-ene **830** was observed, although at 20% conversion a 1:1 mixture of **830** and the isomeric 1-methyl-3-phenylazabicyclohexene **829** was formed. It has also been found that irradiation of the isomeric 2*H*-azirine **831** gave a quantitative yield of **830**, and a control experiment showed no interconversion between **828** and **831** (Scheme 159). Moreover, photolysis of **828** and **831** in the presence of added dipolarophiles resulted in the trapping of a nitrile ylide and gave bimolecular cycloadducts.



SCHEME 159

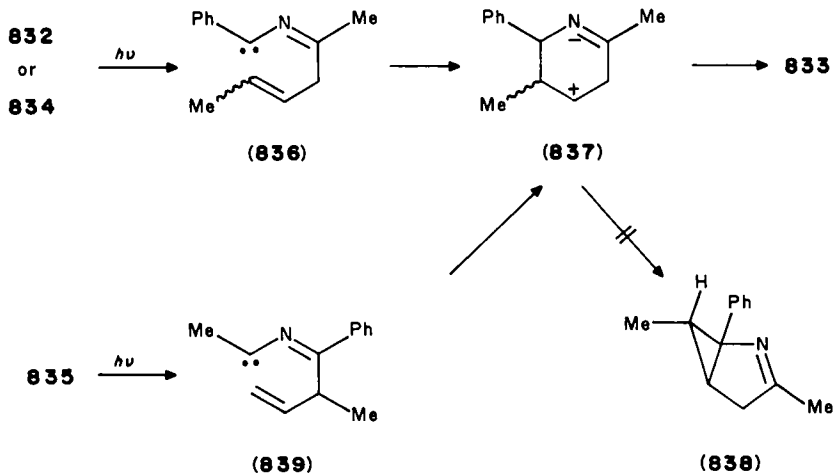
Irradiation of (*E*)-2-(2-butenyl)-2*H*-azirine **832** gave rise to *endo*-3,6-dimethyl-1-phenylazabicyclohexene **833**, whose formation corresponds to a complete inversion of stereochemistry about the π system in the cycloaddition process. Upon irradiation, the *Z*-isomer **834** or 2-phenyl-2-(1-methylallyl)-3-methyl-2*H*-azirine **835** gave also the same

azabicyclohexene **833** (Scheme 160). Photoisomerization about the carbon–carbon double bond of **832** or **834** did not occur during the irradiation.



SCHEME 160

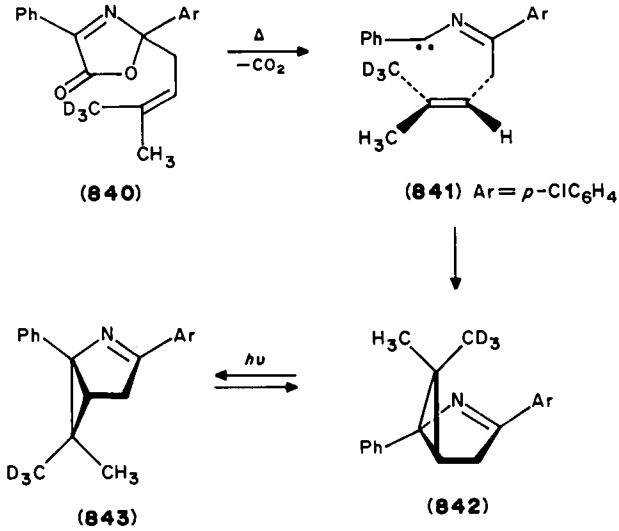
Padwa and coworkers proposed a bent (carbene-like) nitrile ylide intermediate as the most reasonable path to account for these cycloadditions. For example, photolysis of 2*H*-azirine **832** or **834** generates a bent nitrile ylide **836**, followed by attack of the carbene carbon on the terminal position of the neighboring double bond leading to a six-membered-ring intermediate **837**. Collapse of **837** to the thermodynamically more favored *exo* isomer **838** results in a severe torsional barrier in ring closure. On the other hand, collapse of **837** to the thermodynamically less favored *endo* isomer **833** moves the phenyl and methyl groups farther apart and accounts for the formation of a less stable product. Photolysis of 2*H*-azirine **835** gives the same trimethylene intermediate **837** via a bent nitrile ylide **839** (Scheme 161).



SCHEME 161

Singlet carbenes undergo concerted 1,1-cycloadditions with alkenes. The expected retention of configuration at the alkenic double bond was observed by Fischer and Steglich[232]. Thermolysis of 3-oxazolin-5-one **840** generates the nitrile ylide **841**, formulated as a carbene. The (*Z*)-CD_3 label of **841** winds on the *endo* side of the

azabicyclohexene **842** after the 1,1-cycloaddition. Irradiation of **842** establishes an equilibrium with **843**, probably via a six-membered-ring trimethylene intermediate (Scheme 162). Thus, earlier claims that the carbene 1,1-cycloaddition takes a stepwise and nonstereospecific course[231,233] may be superseded by the new evidence.



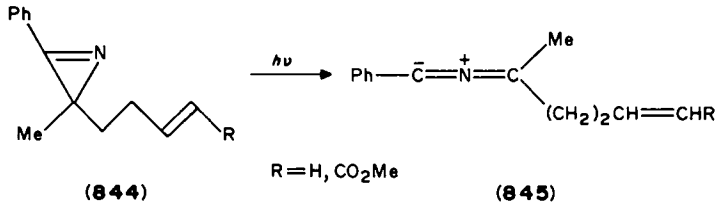
(840) **(841)** Ar = *p*-ClC$_6$H$_4$

(843) **(842)**

SCHEME 162

B. 2-(4-Pentenyl)-2*H*-azirine Systems

Although photolysis of 2-(3-butenyl)-2*H*-azirine **844** in the presence of added dipolarophile afforded the corresponding bimolecular cycloadduct of nitrile ylide **845**, irradiation of **844** in the absence of external dipolarophile gave no intramolecular 1,1- and/or 1,3-cycloadducts; but instead a polymer or a complex mixture of products was formed[234] (Scheme 163).

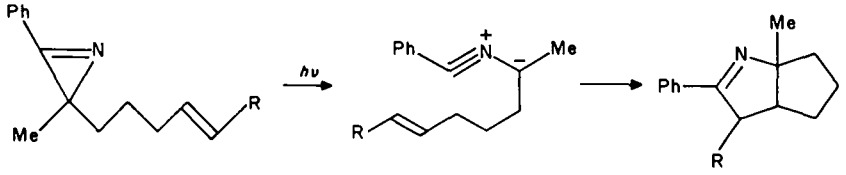


(844) **(845)**

SCHEME 163

Upon irradiation, however, the next higher homologous 4-pentenyl-substituted 2*H*-azirines gave intramolecular 1,3-cycloadducts. Thus, 2-(4-pentenyl)-2*H*-azirines **846–848** in benzene afforded high yields of hexahydrocyclopentapyrroles **850–852**, whose structures correspond to the intramolecular 1,3-cycloadducts of initially formed nitrile ylides **849**[234] (Scheme 164). Neither the 1,1-cycloadduct **853** nor the regioisomeric 1,3-cycloadduct were detected. As the dipole of HO-dipolarophile LU orbitals control

regioselectivity with nitrile ylides, the exclusive formation of **850–852** rather than **854** is unusual. A similar inconsistency was found on irradiation of 2*H*-azirine-2-butyraldehyde **855** leading to **856** (70%)[234] (Scheme 165).



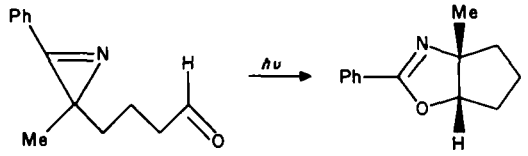
(846) R=H
(847) R=CO_2Me
(848) R=CN

(849)

(850) R=H 81%
(851) R=CO_2Me 97%
(852) R=CN 93%

(853) **(854)**

SCHEME 164



(855) **(856)**

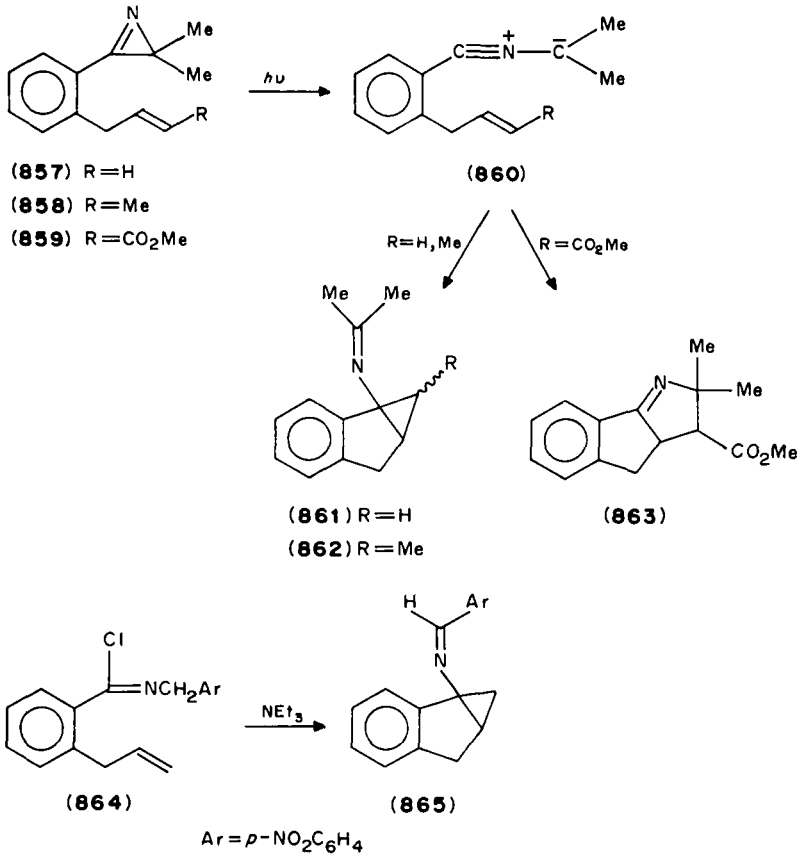
SCHEME 165

C. *o*-Alkenylphenyl-substituted 2*H*-Azirine Systems

Spatial requirements and the role of substituents in controlling the mode of intramolecular cycloaddition of nitrile ylides have been investigated using photolysis of a number of *o*-alkenylphenyl-substituted 2*H*-azirine systems[235,236].

Irradiation of *o*-allylphenyl-substituted 2*H*-azirines **857** and **858** afforded quantitative yields of 1,1-cycloadducts **861** and **862** (a 1:4 mixture of *endo* and *exo* isomers), whereas 2*H*-azirine **859** gave only 1,3-cycloadduct **863** in 85% yield[235] (Scheme 166). Since the bimolecular 1,3-dipolar cycloaddition of nitrile ylides to α,β-unsaturated carboxylic esters is many powers of 10 faster than that to 1-alkenes, in the case of nitrile ylide **860** generated from **859** the 1,3-cycloaddition leading to **863** dominates.

A similar 1,1-cycloaddition reaction was observed with the related *o*-allylphenyl-substituted imidoyl chloride (**864** → **865**).



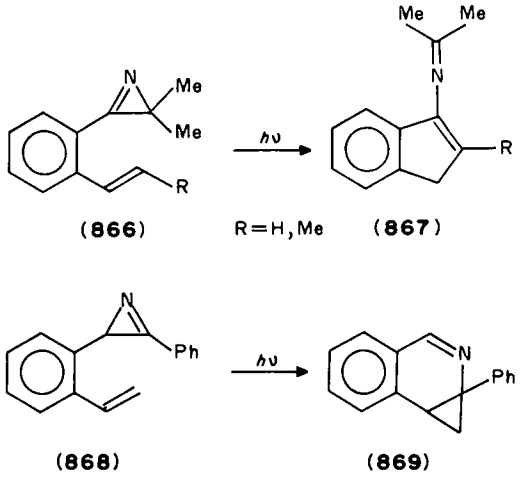
SCHEME 166

Photolysis of 3-(*o*-vinylphenyl)-2*H*-azirine **866** gave the indene derivatives **867** in high yields. Upon irradiation of 2-(*o*-vinylphenyl)-2*H*-azirine **868**, however, a 1, 1-cycloadduct **869** was formed as the exclusive product[235] (Scheme 167). This indicates that the nitrile ylide produced may undergo carbene-type addition to a vinyl group, as long as there are no considerable bond distortions involved in the transition state for the internal cycloadditions.

Since *o*-(3-butenylphenyl)-2*H*-azirines have a methylene chain which is of sufficient length to allow the dipole and dipolarophile to approach each other in parallel, intramolecular 1, 3-cycloaddition may be expected to occur. In fact, photolysis of *o*-(3-butenylphenyl)-2*H*-azirine **870** gave the expected 1, 3-cycloadduct **871** as the exclusive product. A related intramolecular 1, 3-cycloaddition was found to occur upon irradiation of azirinyl aldehyde **872** leading to **873**[235] (Scheme 168).

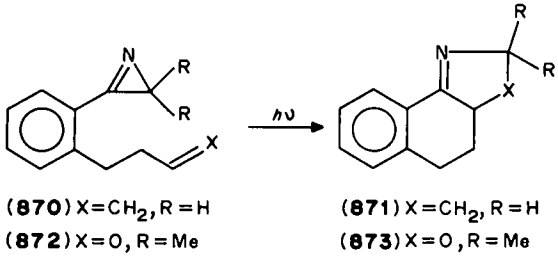
On irradiation, *o*-allyloxyphenyl-substituted 2*H*-azirines undergo intramolecular 1, 3- and/or 1, 1-cycloaddition, depending on the substituent groups attached to the 2-position of the azirine ring[236].

Photolysis of 2*H*-azirine **874** (R = R′ = H) gave only **876**, the product of intramolecular 1, 3-cycloaddition of the nitrile ylide **875**. In contrast, the dimethyl-substituted 2*H*-azirine



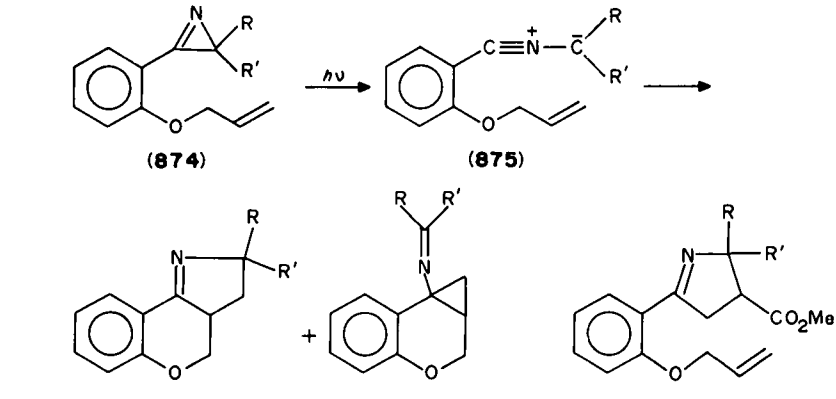
SCHEME 167

874 (R = R′ = Me), upon irradiation, produced only the 1,1-cycloadduct, N-cyclopropylazomethine **877**. The monomethyl-substituted 2*H*-azirine **874** (R = Me, R′ = H) undergoes both 1,3- and 1,1-cycloaddition (Scheme 169). When the irradiation was carried out in the presence of methyl acrylate, the intermolecular formation of **878** was the preferred pathway. These results indicate that the two-plane orientation complex for the 1,3-dipolar cycloaddition (**875** → **876**) is suffering from geometric restraints. The distorted transition state demands a higher activation enthalpy, and the carbenic 1,1-addition with its lower spatial requirements becomes competitive. The dependence of the product ratio on the degree of methyl substitution of **875** may be associated with steric factors.

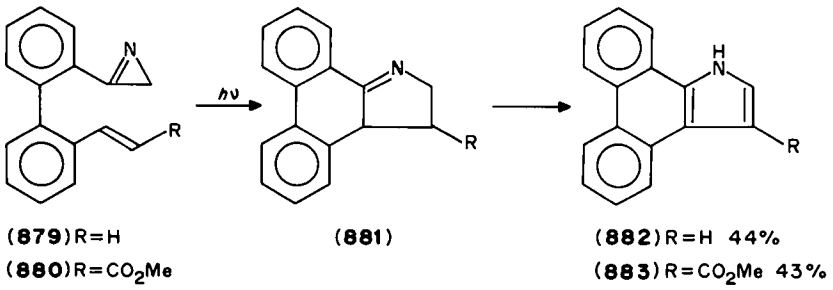


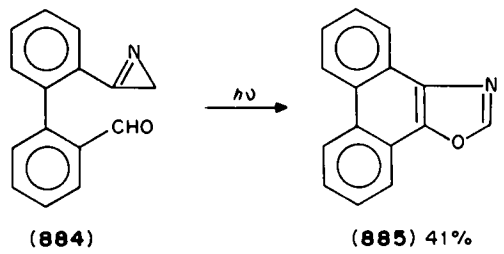
SCHEME 168

Photolysis of vinylbiphenyl-substituted 2*H*-azirine systems was also reported[237]. Such 2*H*-azirines **879** and **880** in benzene gave phenanthropyrroles **882** and **883** in moderate yields, respectively, by 1,3-cycloaddition of the initially formed nitrile ylide to the double bond, followed by air oxidation (**881** → **882**, or **883**). A similar 1,3-cycloaddition was observed with azirinyl-biphenylcarboxaldehyde **884** leading to phenanthroxazole **885** (Scheme 170). The regioselectivity encountered in the photolysis of **880** and **884** is similar to that normally observed in the photolysis of 2*H*-azirines with methyl acrylate and benzaldehyde[228,238].



SCHEME 169

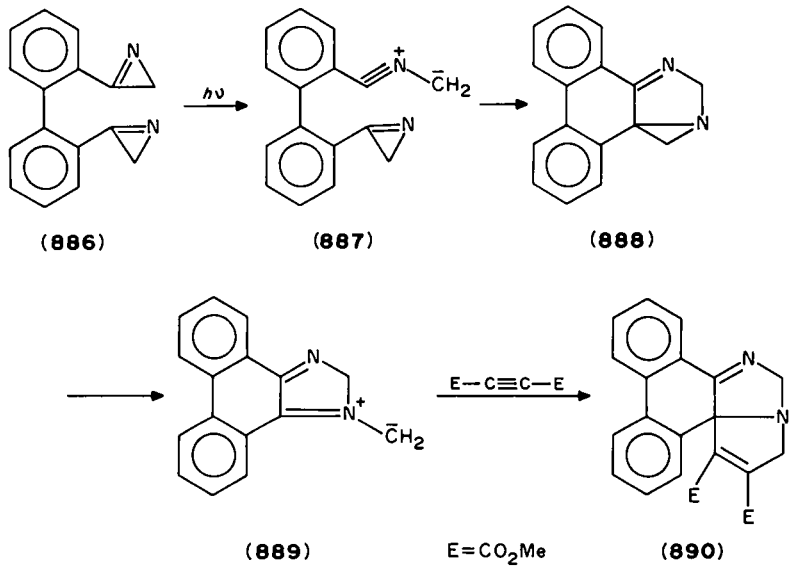




SCHEME 170

Irradiation of (biphenylene)bis[2*H*-azirine] **886** in benzene resulted in the formation of a complex mixture of products. However, irradiation of **886** with an electron-deficient dipolarophile was found to afford a cycloadduct derived from a transient

diazabicyclo[3.1.0]hexene intermediate[237], and thus **886** with dimethyl acetylenedicarboxylate afforded **890**. The formation of **890** was rationalized by the assumption that the initially generated nitrile ylide **887** undergoes cycloaddition across the carbon–nitrogen double bond of the adjacent azirine ring to give a transient diazabicyclohexene **888**. The bimolecular cycloaddition of the azomethine ylide **889**, generated by ring opening of the aziridine **888**, to the acetylene, gives the final cycloadduct **890** (Scheme 171).



(886) (887) (888) (889) (890)

SCHEME 171

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The Chemistry of Double-bonded Functional Groups
Edited by S. Patai

CHAPTER **8**

The ene reaction

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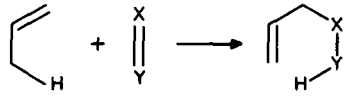
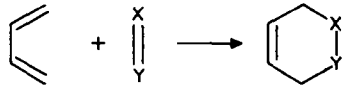
I. INTRODUCTION

The ene reaction (equation 1) is the 'indirect substituting addition' of an unsaturated compound X=Y to an olefin with an allylic hydrogen atom, which is transferred in the process. The reaction is so named because of its formal resemblance to the Diels–Alder reaction, the 'diene synthesis' (equation 2), and the two components are named 'ene' and 'enophile' to conform to 'diene' and 'dienophile'. Since Alder's pioneering paper of 1943[1] there has been increasing recognition of the wide scope and synthetic importance of the ene reaction, of its reverse, the 'retro-ene reaction', of catalyzed and intramolecular processes and reactions of compounds containing hetero atoms. Much attention has been paid in recent years to developing methods for controlling the steric course of these reactions.



(1)

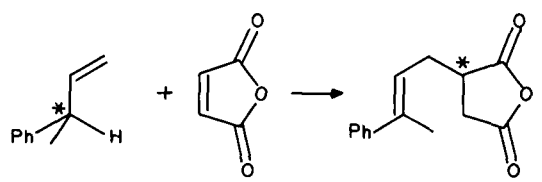


(2)

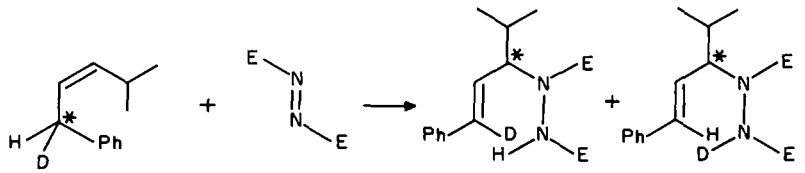
This account should be read as a sequel to Hoffmann's excellent review of 1969[2], covering all aspects of the ene reaction, and that by Oppolzer and Snieckus[3] on intramolecular ene reactions. Other general accounts[4] should be noted.

There is an unending stream of articles on the mechanism of ene reactions. It should be stated at the outset that no unifying mechanism exists to embrace all the variants of the reaction. It is generally accepted that most ene reactions are concerted, that is, there are no intermediate dipolar or diradical species of relatively long life, in which only one bond has been made; however, the exact timing at which the new bond has been made and the hydrogen atom transferred depends on the nature of the components. In the ene reaction there is a reorganization of six electrons; it can be classified as a $[2\pi_s + 2\pi_s + 2\sigma_s]$ process; such a suprafacial–suprafacial approach of the partners is allowed by the rules of orbital symmetry[5].

The concerted nature of the ene reaction is supported by the finding[6] that *R*-(−)-3-phenyl-1-butene reacts with maleic anhydride to yield an optically active product (equation 3), in which chirality has been transferred from one carbon atom to another. Optically active *S-cis*-1-deuterio-4-methyl-1-phenyl-2-pentene and dimethyl azodicarboxylate gave a mixture of *R* and *S* adducts by abstraction of either hydrogen or deuterium from the chiral benzylic centre (equation 4). The ratio (3.1:1) of the enantiomers produced matched the isotope effect ($k_H/k_D + 3.3$); hence the reaction 'met all the requirements of a concerted process'[7].



(3)

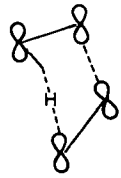


(4)

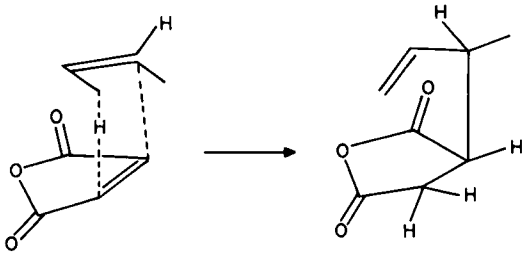
E = CO_2Me

The geometry of the transition state (1) in the propene–ethylene reaction has been calculated using STO-3G and 3-21G basis sets[8]. It is as predicted[2], except that the angle round the hydrogen atom is compressed to 156°. Numerous molecular orbital calculations

on the ene reaction have been reported[9]; most indicate a concerted process with carbon-to-carbon bonding preceding the transfer of hydrogen. As in the Diels–Alder reaction, an *endo* transition state is favoured. This was demonstrated by the preferred formation of the *threo* isomer in the addition of maleic anhydride to *cis*-2-butene (equation 5)[10].



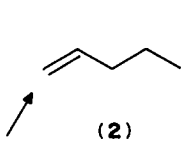
(1)



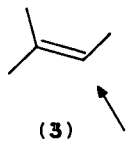
(5)

II. THE ENE COMPONENT

The prototype of the ene reaction, that of propene with ethylene (equation 1, X=Y = CH_2=CH_2), has not been observed but the reverse, the fragmentation of 1-pentene, occurs at elevated temperatures[4a]. Simple olefins, especially terminal olefins, react with maleic anhydride at 230 °C; with esters of azodicarboxylic acids the addition takes place at room temperature during several days[1]. All ene reactions are of this type, involving an electron-rich ene and an electron-poor enophile. The process is dominated by the interaction of the HOMO of the former with the LUMO of the latter[11]. A study of the addition of the electron-deficient diethyl azodicarboxylate with the five isomeric pentenes has shown[12] that the least substituted carbon atom is attacked preferentially (see, for

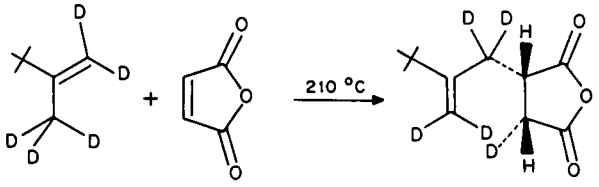


(2)



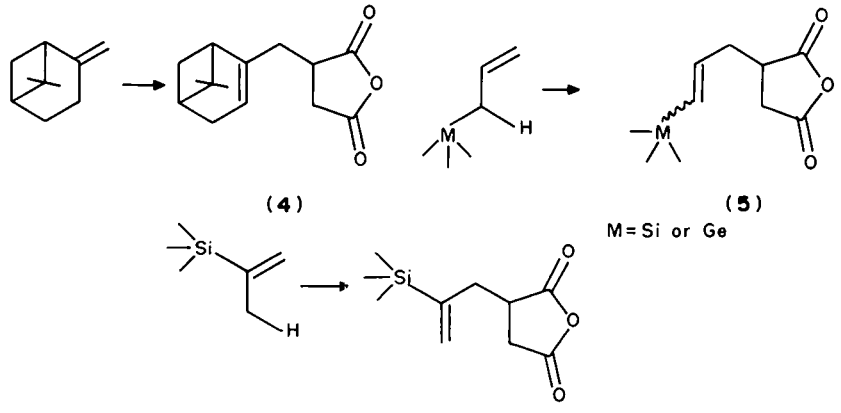
(3)

instance, **2** and **3**). The complex mixture of geometrically isomeric and diastereomeric products obtained from maleic anhydride and each of the nine linear isomers of decene were analysed by high-field. ^{13}C NMR spectroscopy. It was found that the regioselectivity of the reaction was strongly influenced by the size of the alkyl groups flanking the double bond but *cis/trans*- and diastereoselectivity were not[13]. *cis*-Addition to the enophile has been established by deuterium labelling (equation 6); the geometry of the product is consistent with a concerted suprafacial–suprafacial process but a biradical or zwitterionic intermediate, in which *cis*-hydrogen transfer is kinetically preferred, is not excluded[14].

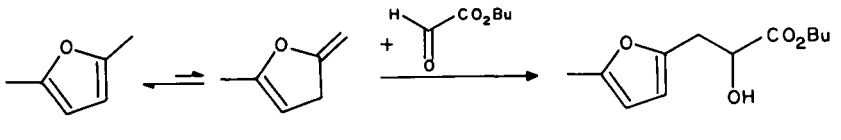


(6)

Methylenecycloalkanes add maleic anhydride at *ca* 200 °C, β-pinene yielding compound **4**. At high pressures (40 kbar) the reaction takes place at room temperature[15]. Allyltrimethyl-silane or -germane and maleic anhydride form the adducts **5** as 1:1 mixtures of *cis* and *trans* isomers; 2-trimethylsilylpropene yields compound **6**[16]. The addition of



butyl glyoxylate to 2, 5-dimethylfuran at 25 °C/8 kbar proceeds by way of an intermediate methylenedihydrofuran (equation 7)[17]. The stable dihydrofuran **7** similarly yields furan derivatives with tetracyanoethylene and other reactive enophiles[18]. 3, 7, 7-Trimethyl-4-



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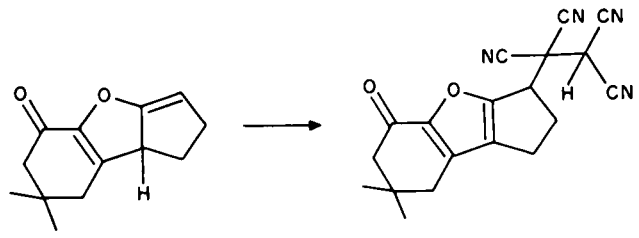
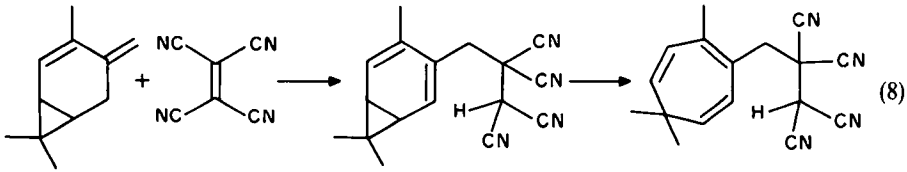
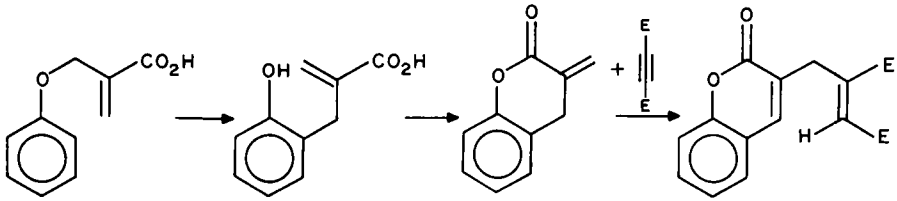


methylenebicyclo[4.1.0]hept-2-ene adds tetracyanoethylene in hot benzene to afford a cycloheptatriene by valence tautomerization of an intermediate norcaradiene (equation 8)[19]. Heating 2-carboxyallyl phenyl ether with dimethyl acetylenedicarboxylate yields a coumarin derivative by sequential Claisen rearrangement, lactonization and ene addition (equation 9)[20].

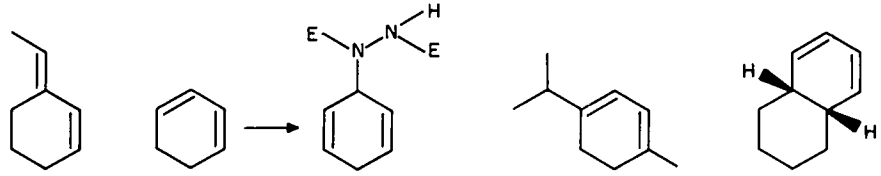


(8)

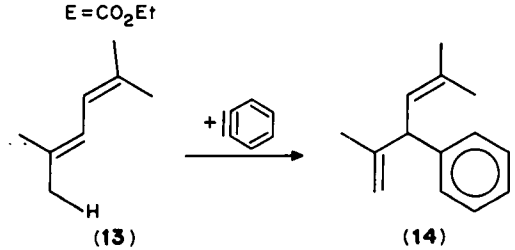


E=CO2Me (9)

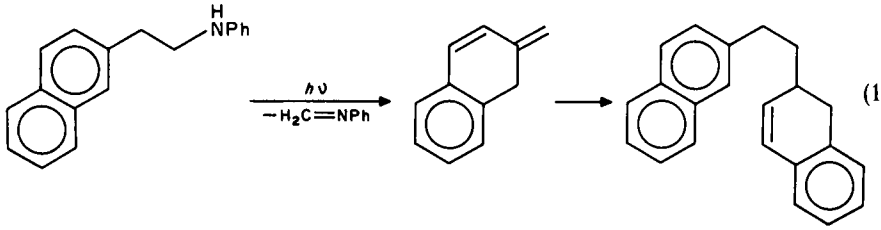
Transoid 1,3-dienes, such as 3-ethylidenecyclohex-1-ene (**8**), cannot form Diels–Alder adducts; instead they undergo ene reactions. It has been found that even the cisoid 1,3-cyclohexadiene **9** affords 80% of the ene product **10** on treatment with diethyl azodicarboxylate, together with only 20% of the Diels–Alder adduct; the cisoid dienes **11** and **12** undergo solely the ene reaction[21]. 2,5-Dimethylhexa-2,4-diene exists in the transoid conformation **13**; consequently it reacts with benzyne to yield the ene product **14**[22].



(8) (9) (10) (11) (12)



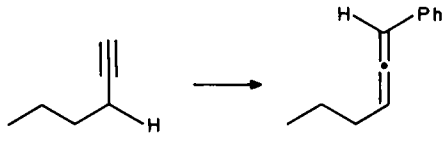
(13) (14)



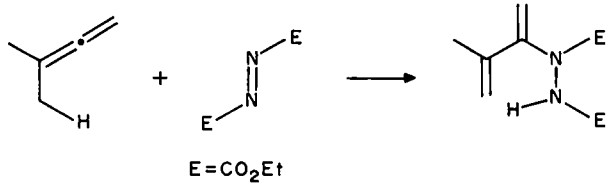
(10)

Irradiation of *N*-(2-β-naphthylethyl)aniline generates 2-methylene-1,2-dihydronaphthalene, which dimerizes spontaneously by an ene process (equation 10)[23].

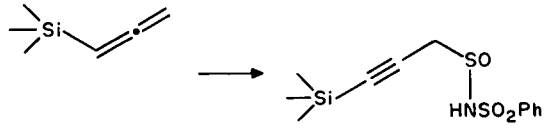
Acetylenes undergo the ene reaction only reluctantly: the action of benzyne on 1-hexyne yields less than 4% of the adduct **15**[2]. Alkylallenes are attacked at the central carbon atom, as expected, to form 1,3-dienes (see, for example, equation 11)[24]. It has been reported,



(15)

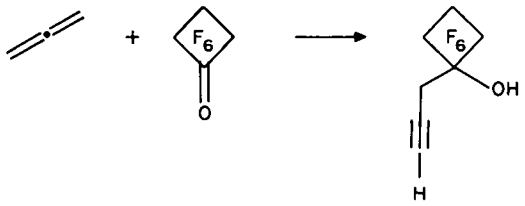


(11)



(16)

however, that trimethylsilylallene furnishes the adduct **16** in the reaction with *N*-sulphinylbenzenesulphonamide, $O{=}S{=}NSO_2Ph$, hydrogen being transferred from an olefinic carbon atom[25]. Similarly, allene itself adds the powerful enophile hexafluorocyclobutanone below room temperature to produce an acetylene derivative (equation 12); primary and secondary isotope effects for this reaction, using 1,1- and 1,3-dideuterioallene, indicate a concerted process with a dipolar transition state[26].



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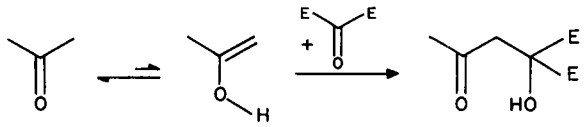
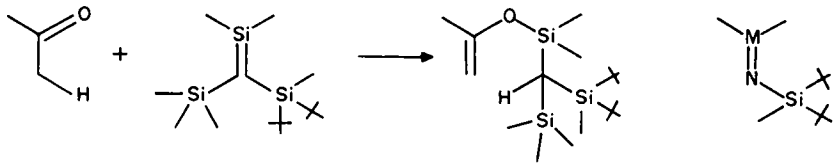


(13)

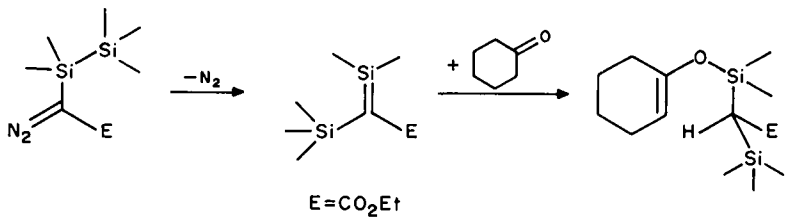
$E = CO_2Et$

Enols may function as ene components. This is particularly important for intramolecular reactions (see Section IV.C). Diethyl oxomalonate (mesoxalic ester) adds to acetone at 120 °C in the absence of catalysts (equation 13). The polarity of the solvent has little influence on the rate of this reaction; the effect of pressure points to a concerted process with a product-like transition state[27].



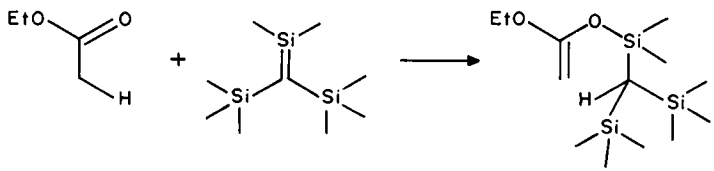
(17) (18) (19)

M = Si or Ge



(14)

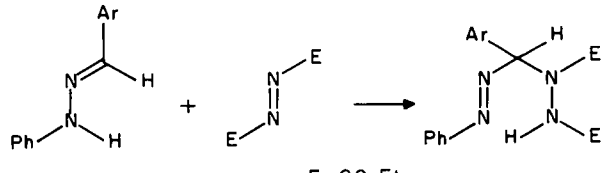
$E = CO_2Et$



(15)

The addition of highly reactive silaalkenes and silaimines and their germanium analogues to carbonyl compounds at the oxygen atom are ene reactions in a formal sense. The stable silaethene **17** yields the silyl enol ether **18** with acetone[28]. Unstable silaethenes

are trapped as 'ene-adducts' in the presence of ketones (equation 14)[29] or ethyl acetate (equation 15)[30]; similar reactions have been reported for the imines **19**[30].



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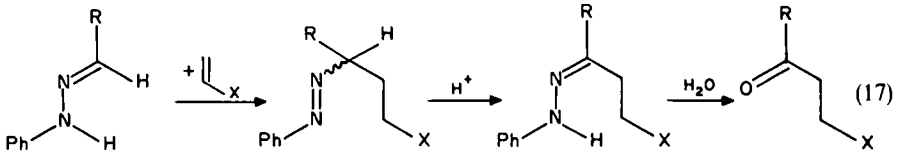


(17)

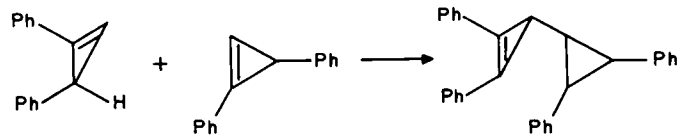
X=CN or CO_2Me

The reaction of diethyl azodicarboxylate with phenylhydrazones of aromatic aldehydes was discovered some time ago[31]. The products, 1-phenylazo-1-hydrazinoalkanes, arise by an ene reaction (equation 16). Phenylhydrazones of aliphatic aldehydes add acrylonitrile or methyl acrylate to give mixtures of geometrically isomeric azo compounds[32], which tautomerize to hydrazones on treatment with trifluoroacetic acid. Hydrolysis affords γ-keto nitriles or γ-keto acids (equation 17)[33].

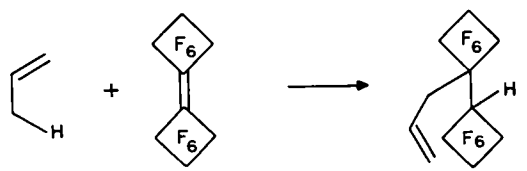
III. THE ENOPHILE

A. Olefins and Acetylenes

Simple alkenes do not function as enophiles. The strained double bond in cyclopropenes causes these compounds to dimerize in an ene process. Thus 1,3-diphenylcyclopropene is stable only in solution at −78 °C; at higher temperatures it forms the dimer **20**[34]. Angle strain is also responsible for the ability of perfluorobicyclobutylidene to add propene at 100 °C (equation 18)[35].

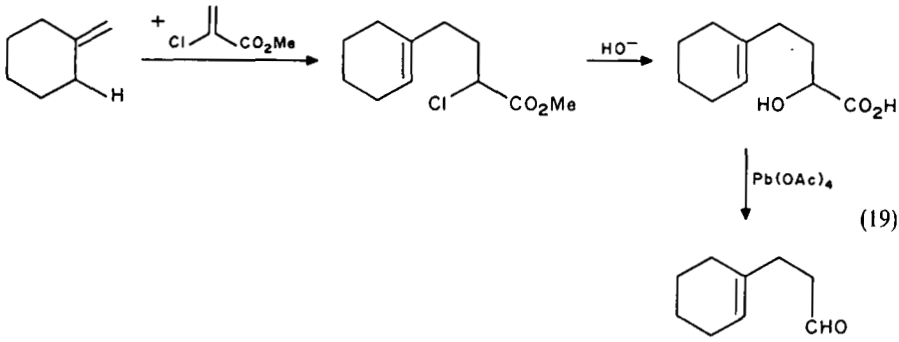


(**20**)

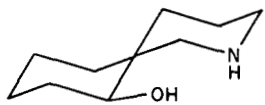


(18)

Typical olefinic enophiles contain electron-withdrawing groups as in maleic anhydride, tetracyanoethylene, methyl acrylate and acrylonitrile. The reactions are carried out by prolonged heating (about 20 h) in suitable solvents at 180–220 °C. Common acetylenic enophiles are dimethyl acetylenedicarboxylate, dicyanoacetylene and esters of propiolic acid. Benzyne is particularly powerful, reacting even with toluene[2]. Methyl α-chloroacrylate functions as a synthetic equivalent of ketene in the sequence shown in equation 19. This reaction was used in the synthesis[36] of the alkaloid (±)-nitramine **21**. The stereoselective introduction of the side-chain into the pregnene derivative **22** by methyl acrylate was the key step in the synthesis[37] of chenodeoxycholic acid **23**. Trimethyl



(19)



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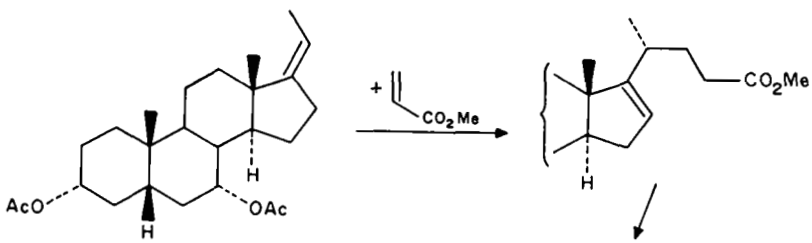
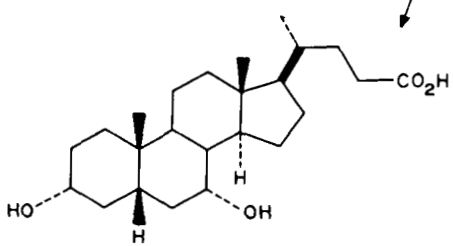
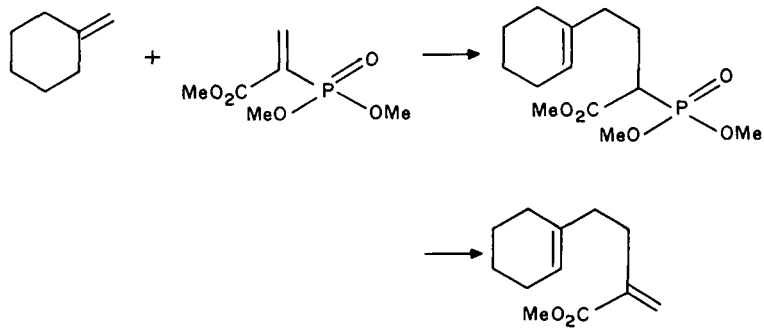


(22)



(23)

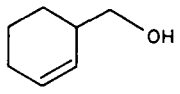
2-phosphonoacrylate is a useful enophile since it yields products which undergo the Witting reaction, e.g. the adduct with methylenecyclohexane on treatment with sodium hydride, followed by paraformaldehyde, gives a 1,5-diene (equation 20)[38].



(20)

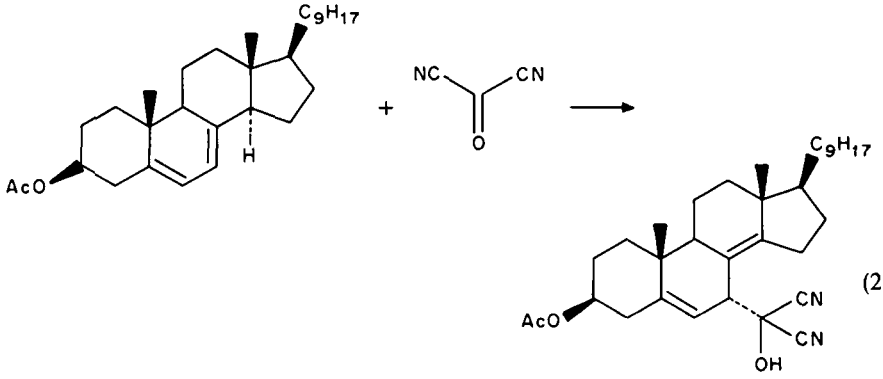
B. Carbonyl Compounds

The ene reaction of carbonyl compounds as enophiles is related to the Prins reaction[39], the acid-catalysed addition of aldehydes to olefins[40], which proceeds by way of carbonium ions. Ene-type products are sometimes formed, for instance the alcohol **24** (2.8%), when cyclohexene is treated with formaldehyde and aqueous sulphuric acid.



(**24**)

Thermal ene reactions of simple aldehydes and ketones appear to be unknown, but activated carbonyl compounds, such as trichloroacetaldehyde, ethyl glyoxylate and diethyl oxomalonate, react at 120–200 °C. Carbonyl cyanide is especially reactive, adding to olefins at room temperature[41]. With ergosteryl acetate it undergoes an ene reaction (equation 21) rather than Diels–Alder addition[42]. The action of hexafluoroacetone on 3-phenylpropene led to **25**, with 2-phenylpropene a mixture of **26** and the bis-adduct **27** was obtained, while 1-phenylpropene did not react[43].



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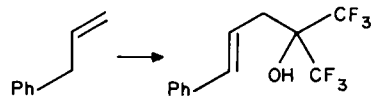

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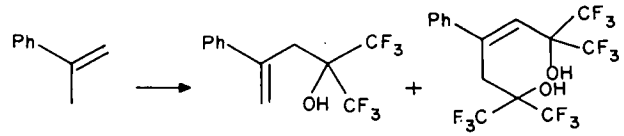

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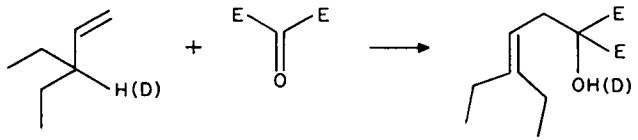
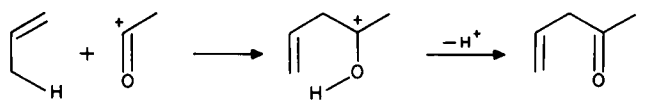


(22)

$E = CO_2Et$

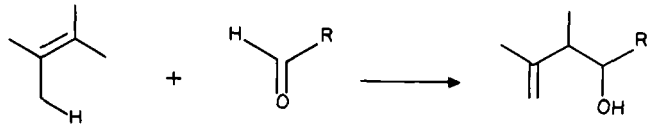
The thermal ene reaction of diethyl oxomalonate with 3-ethyl-1-pentene and its 3-deuterio analogue (equation 22) shows a primary isotope effect of only 2.16, consistent with a concerted process, in which, however, the C—H and O—H bonds are not broken and formed simultaneously[44]. Activation volumes and pressure dependence of the rates of the reactions of the same ester with various alkenes likewise support a concerted mechanism with a product-like transition state, in which the transfer of hydrogen occurs in a non-linear fashion[45]. The same conclusion was based on the temperature independence of the primary kinetic isotope effect k_H/k_D in the reaction of diethyl oxomalonate with allylbenzene and the deuterio analogue $PhCHDCH{=}CH_2$[46].

Acetyl hexachloroantimonate is an effective enophile; the reactions are conducted at low temperatures in the presence of a hindered base, such as ethyldiisopropylamine (equation 23)[47].



(23)

Lewis acids catalyse ene reactions of carbonyl compounds, because the LUMO of the enophile is lowered by complexation just as it is by the presence of electron-withdrawing groups. Alkylaluminium chlorides are particularly useful because they act as proton scavengers: the alcohols produced form non-acidic aluminium alkoxides and alkanes, so that proton-promoted rearrangements are prevented[48]. In the presence of dimethylaluminium chloride, mthylenecyclohexane, 3-methyl-2-butene and even 2,3-dimethyl-2-butene add aliphatic aldehydes at room temperature (equation 24)[49]. The action of aliphatic aldehydes on *E*- and *Z*-3-methyl-2-pentene, **28** and **29**, in the presence of dimethylaluminium chloride at 0 °C leads in each case to mixtures of *erythro* and *threo*



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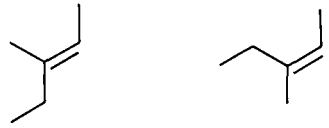
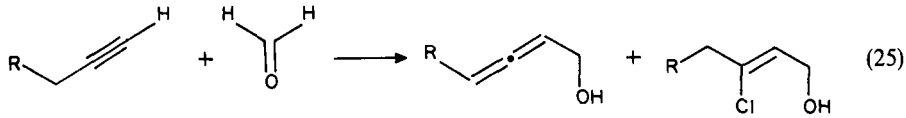


(28) (29)



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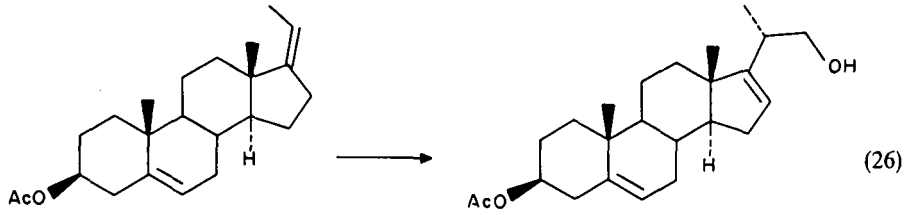
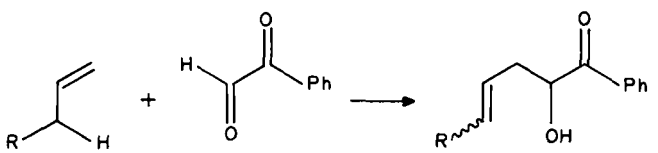


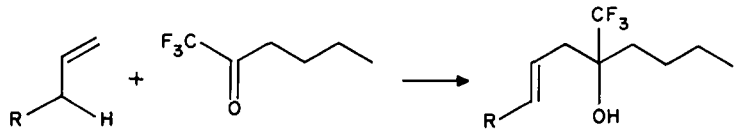
(26)

compounds and double-bond isomers[50]. Under these conditions formaldehyde reacts with terminal alkynes to yield α-allenic alcohols by an ene reaction, together with 'Friedel–Crafts products', chloroallyl alcohols (equation 25)[51]. A stereoselective introduction of a steroid side-chain to give the natural configuration at C(20) was achieved in a reaction with paraformaldehyde and boron trifluoride at 0 °C (equation 26)[52]. Whereas phenylglyoxal adds to various 1-alkenes in the presence of tin(IV) chloride to give ene products as mixtures of geometrical isomers (equation 27)[53], the aluminium trichloride-catalysed reaction of 1, 1, 1-trifluorohexan-2-one with terminal alkenes is stereospecific, affording only *trans* products (equation 28)[54]. The diastereoselectivity of the addition of trichloroacetaldehyde to β-pinene in the presence of Lewis acids was found to depend on the catalyst: with boron trifluoride a 1:1 mixture of the epimers 11 *R*-(**30**) and 11*S*-(**30**) was obtained, while with titanium(IV) chloride only the 11-*S*-isomer was formed[55].



(27)

R = Et, Bu or C_6H_{13}



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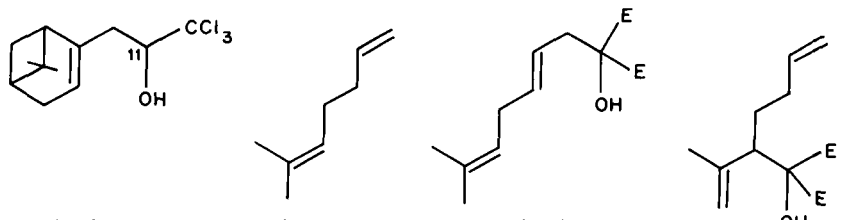
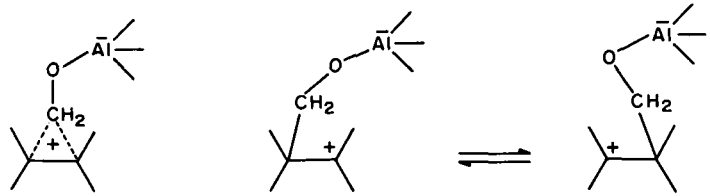


(30) (31) (32) (33)

E = CO_2Et

Catalysed ene reactions may exhibit a different regiochemistry from their thermal counterparts. For example, diethyl oxomalonate adds to the diene **31** to yield a mixture of **32** and **33**. In the thermal reaction at 180 °C these are produced in the proportion 11:1; by contrast, if the reaction is conducted in the presence of tin(IV) chloride at room temperature, the ratio is reversed to 1:30[56].

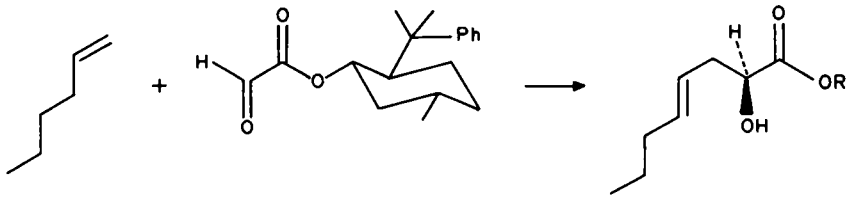
There is mounting evidence that thermal and catalysed ene reactions of carbonyl compounds proceed by different mechanisms. Intramolecular isotope effects (hydrogen versus deuterium) in the thermal reaction of $PhCHDCMe{=}CH_2$ with diethyl oxomalonate and intermolecular isotope effects ($PhCH_2CMe{=}CH_2$ versus $PhCD_2CMe{=}CH_2$) are high ($k_H/k_D = 3.1–3.6$), indicating a one-step process. In the tin(IV) chloride–catalysed reactions both effects are reduced to *ca* 1.1, which suggests that, while a concerted course prevails, C—H and C—D bond breaking have only slightly progressed at the transition state; a dipolar intermediate seems to be excluded[57]. In a related study of catalysed additions of formaldehydes to various olefins it was concluded that the reactions proceed via an intermediate **34**, which can be regarded as a π complex or its kinetic equivalent, a pair of rapidly equilibrating zwitterions **35a** and **35b**, where there is no free rotation, so that regio- and stereoselectivity are observed[58]. It has been suggested that such an intermediate can 'partition between reversal, equilibration of geometrical species and conversion to product'[59].



(34) (35a) (35b)

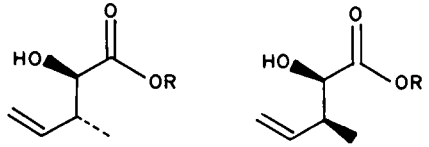
Asymmetric induction is achieved when chiral esters of glyoxylic acid are employed in catalysed additions to olefins. The reaction of (−)-8-phenylmenthyl glyoxylate with 1-hexene affords a single disastereomer (equation 29)[60]. A 1,2-disubstituted alkene gives a

product with two chiral centres: *trans*-2-butene and phenylmenthyl glyoxylate yielded a mixture of *erythro* and *threo* esters (**36** and **37**, respectively) in the ratio 15:1[61]. The glyoxylates of optically active *trans*-2-phenylcyclohexanol[62] and *trans*-2-(1-phenylethyl)cyclohexanol[63] are especially effective in diastereospecific ene syntheses.



(29)

R = 8-phenylmenthyl

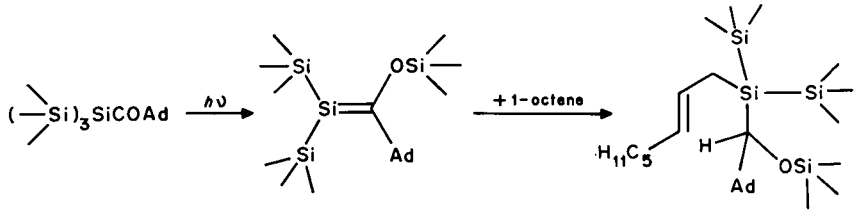


(36) (37)

R = 8-phenylmenthyl

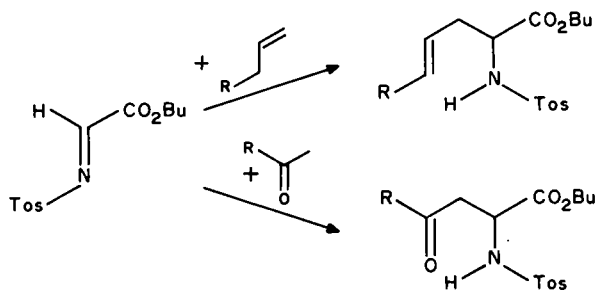
C. Other Systems of the Type C=X and C≡X[64]

Silenes, generated by irradiation of acyltris(trimethylsilyl)silanes, react readily with simple alkenes to form ene adducts (e.g. equation 30)[65].



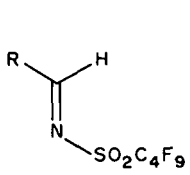
(30)

Ad = 1-adamantyl



(31)

N-Sulphonylimines, which are further activated by the presence of electron-withdrawing groups on the carbon atom, such as *N*-nonafluorobutanesulphonylimines (**38**; R = CCl_3 or CO_2Bu)[66] or butyl *N*-(*p*-toluenesulphonyl)iminoacetate, readily add to olefins[67] and to the enol tautomers of ketones[68] (equation 31). The reaction of the corresponding ethyl ester with cyclohexene is stereospecific, giving only compound **39**; with *trans*-2-butene, a 9:1 mixture of the diastereomers **40** and **41** is obtained[69]. Asymmetric induction has been observed in the Lewis acid-catalysed reaction of (−)-menthyl *N*-(*p*-toluenesulphonyl)iminoacetate with isobutene. The configuration of the chiral carbon atom in the product **42** depends on the nature of the catalyst and on conditions. Tin(IV) chloride and titanium(IV) chloride favour formation of the *S* isomer, aluminium chloride the *R* isomer, while in the presence of boron trifluoride an excess of either may be formed. The stereochemical outcome of these reactions is determined by the conformation of the enophile–Lewis acid complex[70].



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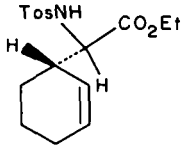
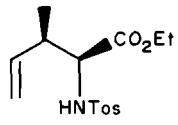


(39)



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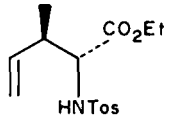

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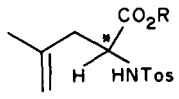
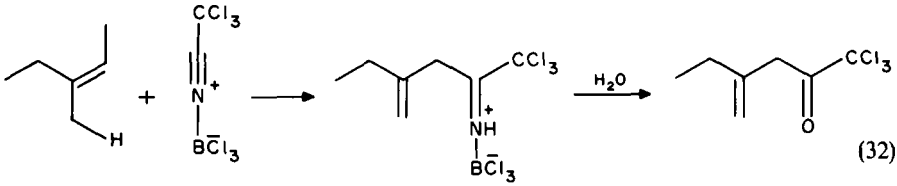


(42)

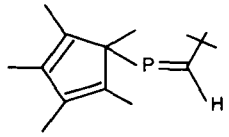
R = menthyl

The first examples of nitriles functioning as enophiles concern mono- and trichloroacetonitrile, which readily add to alkenes in the presence of boron trichloride. The products yield ketones on hydrolysis (equation 32)[71]. The phosphaalkyne P≡CBu^t reacts



(32)

with 1,2,3,4,5-pentamethylcyclopentadiene to give the adduct **43**, in which the phosphavinyl group undergoes rapid [1.5]sigmatropic shifts at room temperature since only one signal is observed for the five ring-methyl substituents in the ^1H NMR spectrum. At −70 °C the signal is split into three[72].



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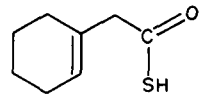
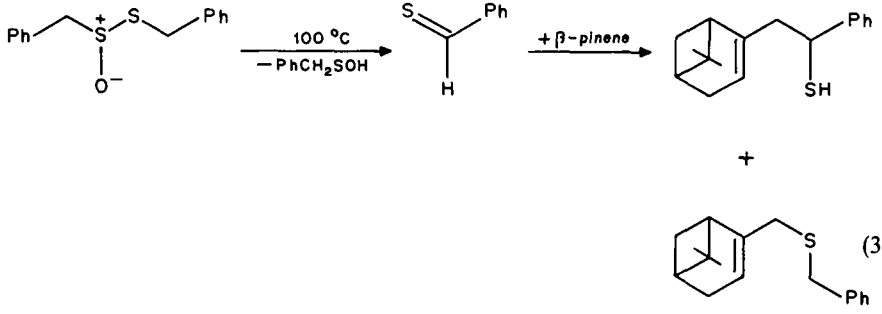


(44)

Thioaldehydes are highly reactive enophiles. The transient thiobenzaldehyde, generated by heating *S*-benzyl phenylmethanethiosulphinate, adds to β-pinene in two senses, at carbon or at sulphur (equation 33)[73]. Addition of carbonyl sulphide, COS, to methylenecyclohexane in the presence of dimethylaluminium chloride affords solely the thioic acid **44**[74]. β-Pinene, 2-phenylpropene and other 1-alkenes readily add to methyl cyanodithioformate at the sulphur atom (equation 34), but more highly substituted or endocyclic olefins give very poor yields[75]. The reaction of ethyl α-chloro-α-(phenylthio)acetate with 1-pentene and other terminal olefins in the presence of tin(IV) chloride at −78 °C proceeds via the cation shown in equation 35; the products are mixtures of geometrical isomers[76].



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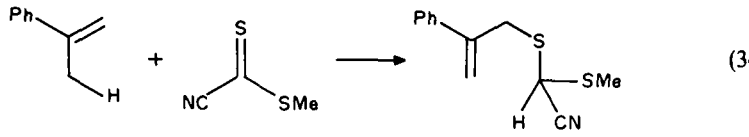

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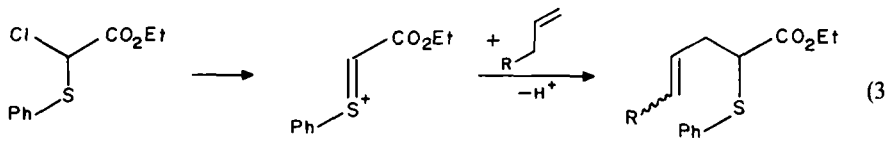


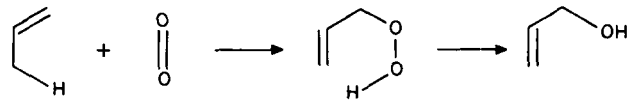
(35)

D. Singlet Oxygen[77]

The most powerful enophile is singlet oxygen, $^1O_2$, the first excited state of molecular oxygen, which is involved in the dye-sensitized photooxygenation of unsaturated

compounds. The resulting allyl hydroperoxides (equation 36) are somewhat unstable; they can be smoothly reduced to allyl alcohols by triphenylphosphine, organic phosphites, sodium borohydride or lithium aluminium hydride. This is usually done when it is desired to identify the primary products of the photooxygenation.

All types of alkenes react readily with singlet oxygen, regardless whether the carbon atom attacked is primary, secondary or tertiary. 2-Methyl-2-pentene, for instance, yields a mixture of tertiary and secondary hydroperoxides (equation 37)[78]. Oxygenation at the disubstituted carbon atom of 3-methyl-2-pentene is preferred (equation 38)[79]. This is the opposite of the regiochemistry observed in the reactions discussed in Section II. 1-Propenylcyclopropanes give mixtures of hydroperoxides, in which the strained cyclopropylidene isomer predominates (equation 39)[80].



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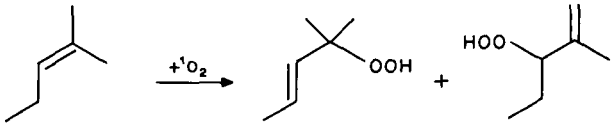

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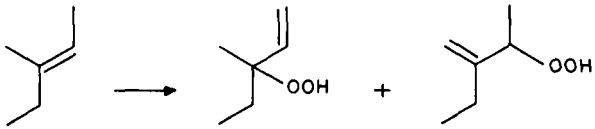

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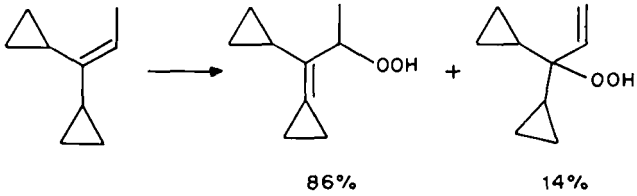
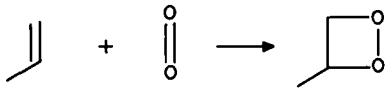


(39)

Allyl peroxides are often accompanied by dioxetanes, which are formed by a [2 + 2]cycloaddition (equation 40). These may be the major products, as in the photooxy-

genation of indenes, where only small amounts of ene adducts are produced (equation 41)[81]. In the case of 1, 3-dienes, hydroperoxides are formed side by side with Diels–Alder adducts, 'endoperoxides' (equation 42). Photooxygenation of 1-vinylcycloalkenes of ring sizes 5–10 and 12 produces mixtures of two types of hydroperoxide, together with endoperoxides (equation (43)[82]. 2, 5-Dimethyl-2, 4-hexadiene is oxidized to a mixture of an endoperoxide and two ene products, **45** and **46**. The latter arises by a 'vinylogous ene reaction' by way of the proposed intermediate singlet diradical **47**[83].



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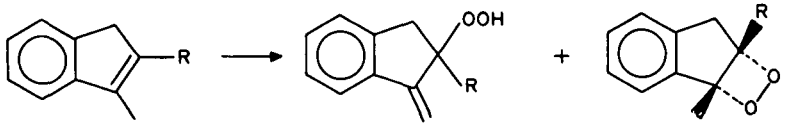

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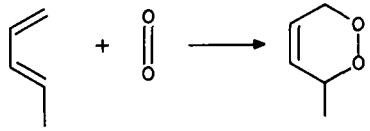

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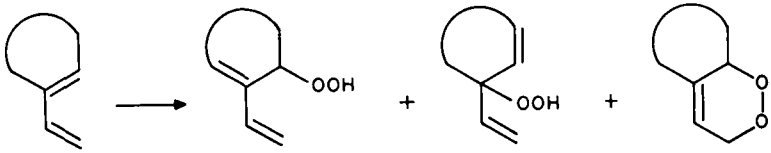

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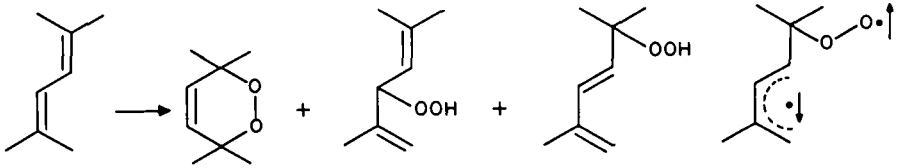
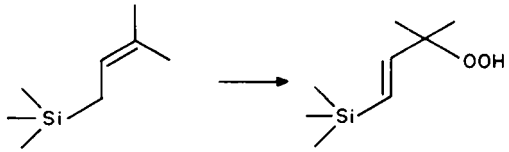


(45) (46) (47)

Allylsilanes, e.g. **48**, undergo a normal ene reaction with singlet oxygen[84]. 3-Trimethylsilyl-1-propene affords a mixture of *cis* and *trans* hydroperoxides in the ratio

78:22 (equation 44), in contrast to the reaction of the carbon analogue, which yields the *trans* product **49** almost exclusively[85].

The action of triphenyl phosphite ozonide on tetramethylethylene and its hexadeuterio analogues gives the products of ene reactions; however, free singlet oxygen is not involved[86].



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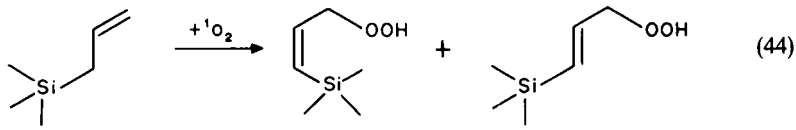

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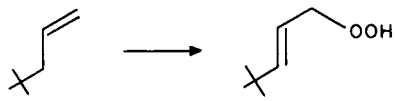
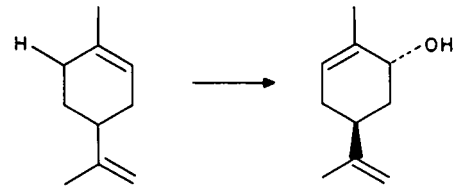
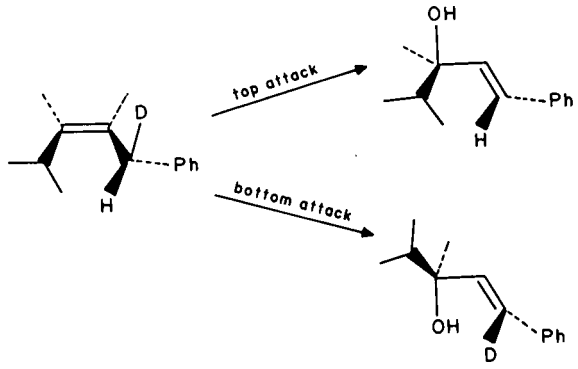


(49)

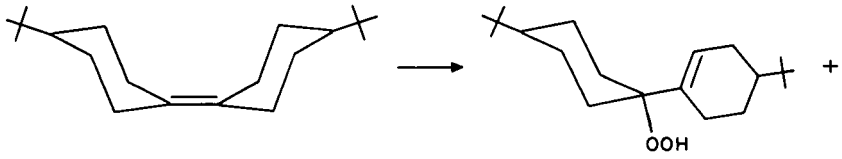
The mechanism of the singlet oxygen ene reaction has been studied intensively[87]. The reaction is stereospecific; thus optically active limonene gave, after reduction, optically active *trans* carveol (equation 45)[88]. Furthermore, the reaction is suprafacial with respect to the ene component; that is, carbon–oxygen bonding and hydrogen abstraction take place on the same side. This was demonstrated in the photooxygenation of the chiral deuteriated compound of equation 46, which after reduction gave a 1:1 mixture of *R* and *S* alcohols[89]. Yet a completely concerted process is ruled out by the finding that, although 4,4′-di-*t*-butyldicyclohexylidene has properly aligned carbon–hydrogen bonds only on one side of the double bond, it is attacked from both the top and the bottom to give a mixture of hydroperoxides (equation 47), which requires the intervention of an intermediate[90]. The nature of this intermediate is hotly debated. The extremes are a zwitterion (**50**)[91,92] or a perepoxide (**51**)[93]. The formation of the intermediate may be preceded by some loosely associated complex. It has been suggested that in the complex the LUMO of singlet oxygen interacts with the HOMO of the ene component, which has contributions from both the olefinic π-orbital and the CH_3 pseudo-π-orbitals (**52**); this explains why oxygen normally reacts at the more substituted side and the results of isotope studies on the photooxygenation of the hexenes **53** and **54**, which show that only *cis*-placed groups are competitive. The complex is formed irreversibly. It subsequently gives a perepoxide or it moves into bond-making and bond-breaking or it could form a dipolar intermediate in special cases[89a].

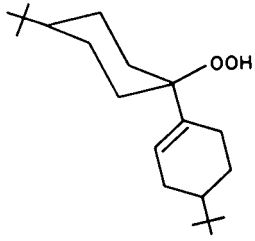


(45)

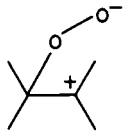


(46)

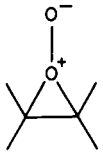




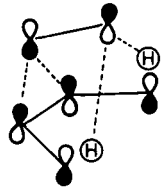
(47)



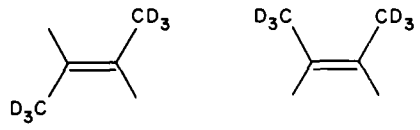
(50)



(51)



(52)

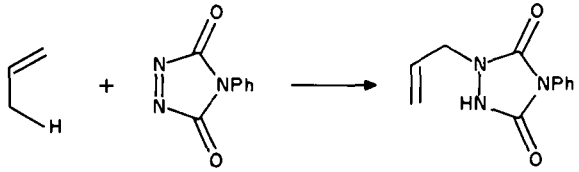


(53) (54)

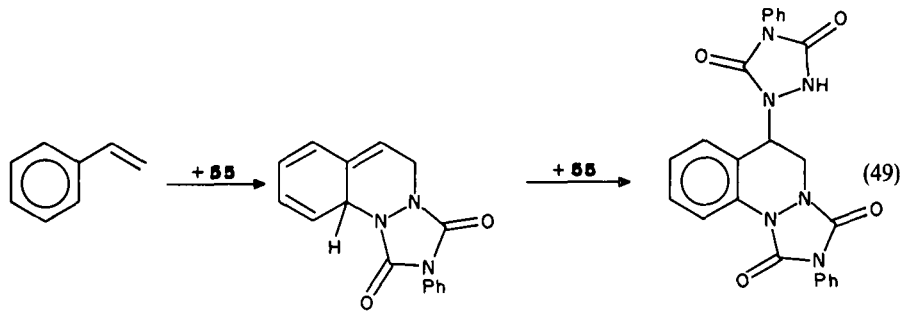
k_H/k_D 1.41 1.0

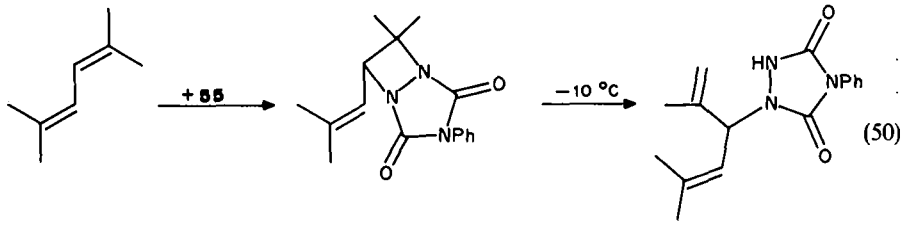
E. Azo Compounds

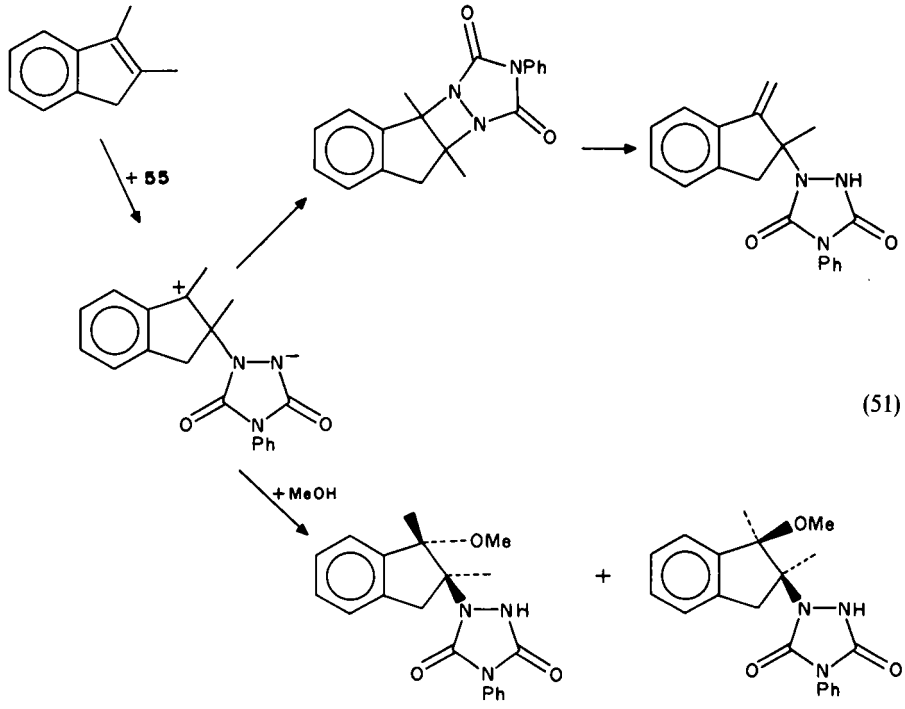
It was mentioned previously that esters of azodicarboxylic acid are effective enophiles, adding to simple alkenes slowly at room temperature[1]. They are far surpassed in reactivity by 4-phenyl-1, 2, 4-triazoline-3, 5-dione (**55**), which is almost as powerful as singlet oxygen. As it is consumed, its intensely red colour is discharged (equation 48). The triazolinedione reacts with styrene at room temperature to yield a di-adduct, which arises by ene addition to an intermediate Diels–Alder product (equation 49)[94]. Addition to 2, 5-dimethyl-2, 4-hexadiene gives mainly the adduct shown in equation 50; low-temperature NMR spectroscopy showed the intermediacy of a short-lived diazetidine[95]. An intermediate [2 + 2]adduct is also observed in the reaction of **55** with 2, 3-dimethylindene. The intermediate rearranges to an ene product on standing. The reaction takes place via a zwitterion, which can be trapped as a mixture of *E*- and *Z*-methyl ethers in the presence of methanol (equation 51)[96].



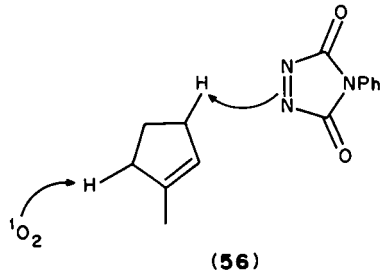
(55) (48)



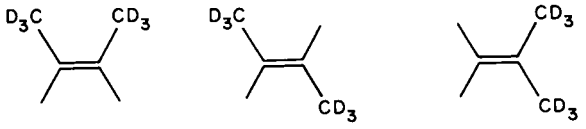




(51)

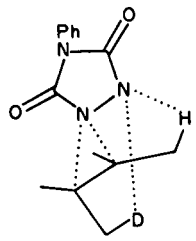


(56)

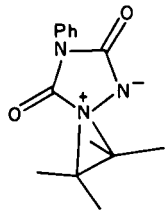


(57)	(58)	(59)
k_H/k_D 1	3.8	5.6

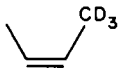
N-Phenyltriazolinedione usually mimics singlet oxygen but there are subtle differences. Whereas the former preferentially abstracts a hydrogen atom at C(3) in 1-methylcyclopentene, the reverse holds for oxygen, hydrogen being removed from C(5) (see **56**)[97]. Isotope effects in the reaction of 4-methyl- or 4-phenyl-triazolinedione with the three hexadeuteriated 2-butenes **57–59** are as shown. It is concluded[97] that there is an intermediate in which little or no breaking of the allylic carbon–hydrogen bond has occurred. The conversion to products gives an isotope effect only when methyl and trideuteriomethyl groups are on the same side of the double bond, which is consistent with the structure **60** (cf. **52**), which is virtually an aziridinium imide (**61**), analogous to the perepoxide (**51**). However, a similar study employing the trideuterio-2-butenes, **62–64**, revealed small but significant isotope effects for the *trans* isomer **63** and for the *gem* compound **64**, indicating that the intermediate aziridinium imide **61** or the complex **60** can either revert to starting materials or open to a zwitterion[98].



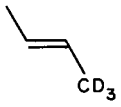
(**60**)



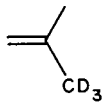
(**61**)



(**62**)



(**63**)

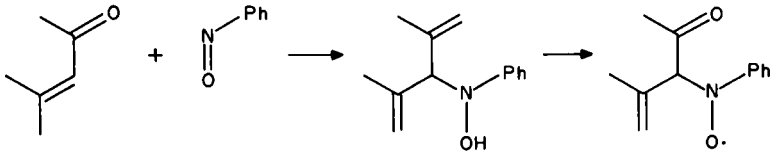


(**64**)

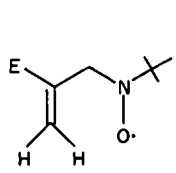
k_H/k_D 5.36 1.29 1.25

F. Other Enophiles

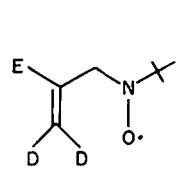
The reaction of aliphatic and aromatic nitroso compounds with alkenes gives hydroxylamines, which are oxidized to stable nitroxyl (aminoxyl) radicals by an excess of the nitroso compound (equation 52)[99]. The electron spin resonance spectra of the radicals **65** and **66**, produced from 2-methyl-2-nitrosopropane and methyl methacrylate and its 3,3-dideuterium analogue, have been reported[100] and the hyperfine splitting constants of the nitroxyl radicals formed from 2,4,6-trichloronitrosobenzene and 1-octene, 1-nonene and other olefins have been measured[101].



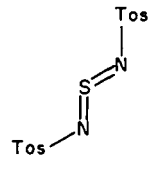
(52)



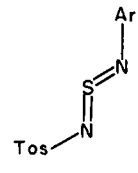
(65)



(66)



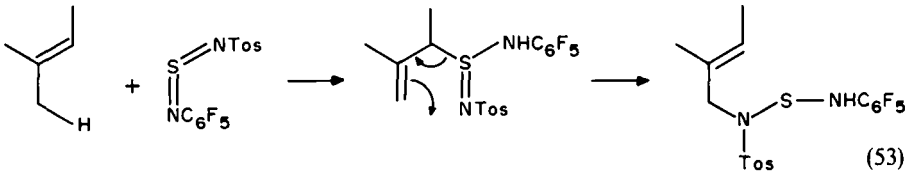
(67)



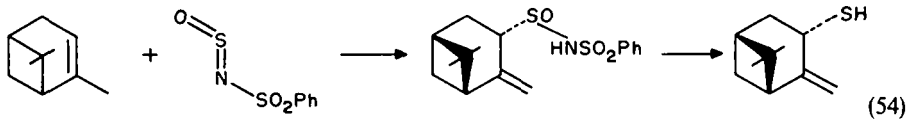
(68)

E = CO_2Me

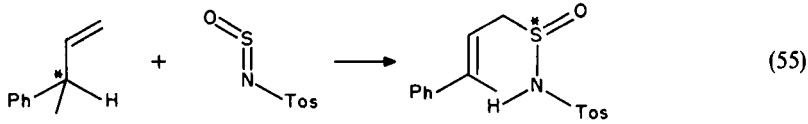
Ene additions to nitrogen–sulphur double bonds readily take place with *NN'*-di(*p*-toluenesulphonyl)sulphurdiimide (**67**) and *N*-aryl-*N'*-(*p*-toluenesulphonyl)sulphurdiimide (**68**). The pentafluorophenyl compound (**68**; Ar = C_6F_5) reacts with 2-methyl-2-butene exclusively at the ArN=S bond; the product is formed by a subsequent [2.3]sigmatropic shift (equation 53)[102]. *N*-Sulphinylarenesulphonamides, $ArSO_2N{=}S{=}O$, are 'super-enophiles'. They react with terpenes, e.g. α-pinene, at O °C to give adducts, which can be reduced to thiols by lithium aluminium hydride (equation 54)[103]. The *p*-toluenesulphonyl derivative adds to optically active 3-phenyl-1-butene to afford an optically active product,



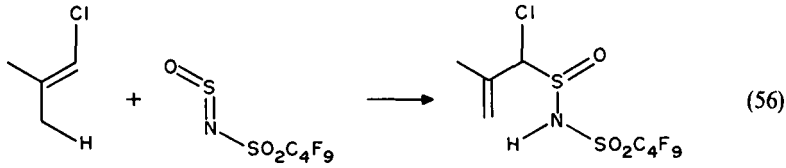
(53)



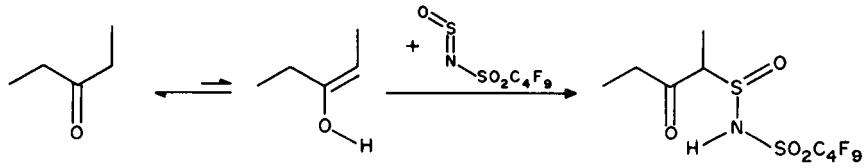
(54)



(55)

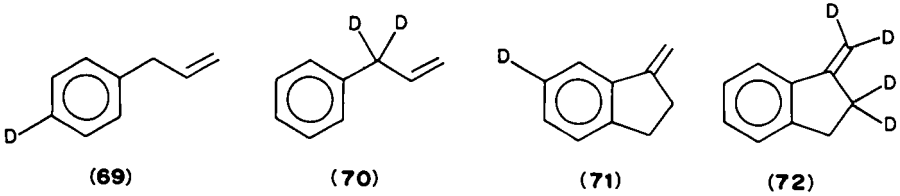


(56)

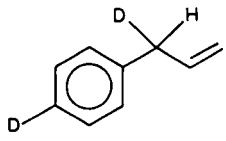


(57)

chirality having been transferred from carbon to sulphur (equation 55)[104]. *N*-Sulphinylnonafluorobutanesulphonamide is at least a thousand times more reactive than the previously mentioned sulphinyl compounds, adding even to electron-deficient olefins (equation 56)[105]. It also reacts with enolizable ketones within minutes at room temperature to yield products of an enol addition (equation 57)[106]. The reaction of *N*-sulphinyl-*p*-toluenesulphonamide with the deuterioallylbenzene $PhCHDCH{=}CH_2$ shows an isotope effect, which is independent of temperature over the range -10 to $+30\,^{\circ}C$, from which a non-linear transfer of hydrogen is postulated[107]. A study of intermolecular isotope effects in competition experiments using mixtures of **69** with **70**, and of **71** with **72**, and the intramolecular H/D isotope effect in **73** in reactions with the enophiles $TosN{=}S{=}O$, $C_4F_9SO_2N{=}CHCCl_3$, $TosN{=}CHCl_3$, 4-phenyl-1,2,4-triazoline-3,5-dione and pentafluoronitrosobenzene revealed that the last-mentioned was exceptional, in that it alone exhibited only the intramolecular isotope effect with **73**; the others showed effects in all three reactions, with **69/70**, **71/72** and **73**. It was concluded that all the enophiles reacted by a two-step mechanism, but that the rate-determining step was different in the case of the nitroso compound[108].

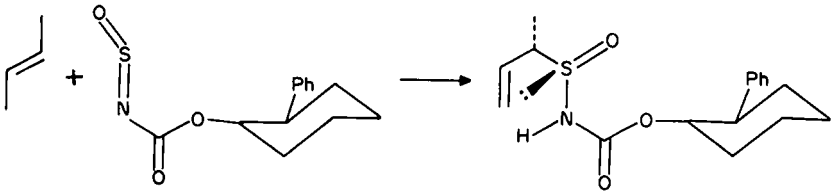


(69) **(70)** **(71)** **(72)**



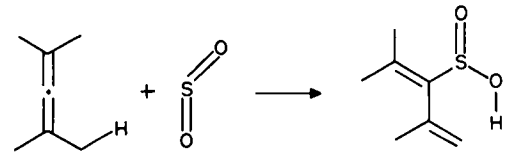
(73)

Asymmetric induction at both carbon and sulphur occurs in the tin(IV) chloride-catalysed addition of alkenes to optically active *trans*-2-phenylcyclohexyl *N*-sulphinylcarbamate; *trans*-2-butene, for instance, yields the *R*-sulphur *S*-carbon product (equation 58)[109].

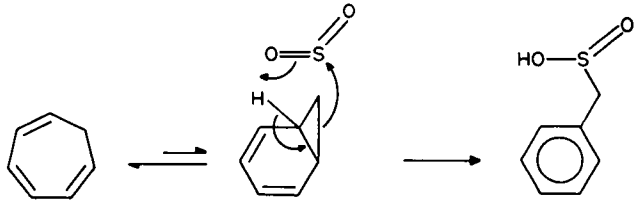


(58)

Sulphur dioxide functions as an enophile. It forms the stable sulphinic acid **74** by reaction with tetramethylallene at room temperature[110]. Phenylmethanesulphinic acid is produced from cycloheptatriene and sulphur dioxide in an ene-like process (equation 59)[111].

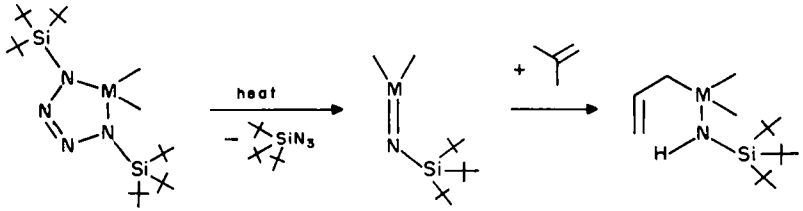


(74)



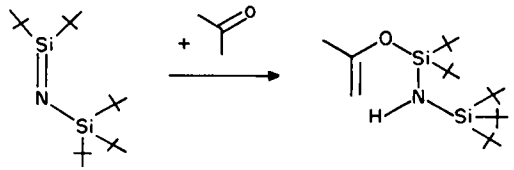
(59)

When highly labile imino-silanes and -germanes are generated in the presence of isobutene, they are trapped as ene adducts (equation 60)[112]. The stable iminosilane **75** reacts with isobutene even at $-100\,°C$; with acetone it yields[113] the enol ether **76**.



M = Si or Ge

(60)

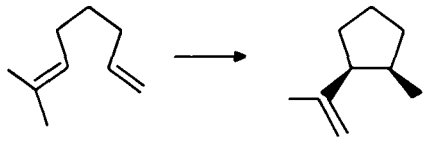


(75) **(76)**

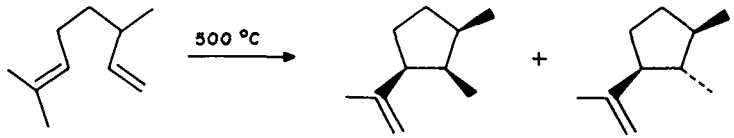
IV. INTRAMOLECULAR ENE REACTIONS[3,114]

A. Olefin–Olefin and Olefin–Acetylene Additions

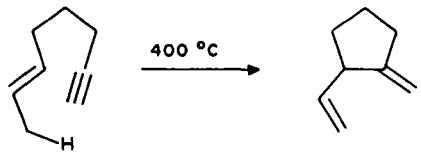
Early instances of intramolecular ene reactions are the high-temperature cyclization of 7-methyl-1, 6-octadiene to *cis*-1-methyl-2-(propen-2-yl)cyclopentane (equation 61)[115], the



(61)



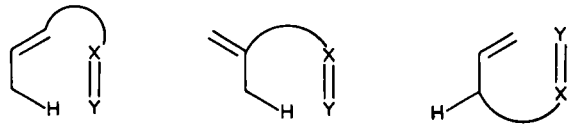
(62)



(63)

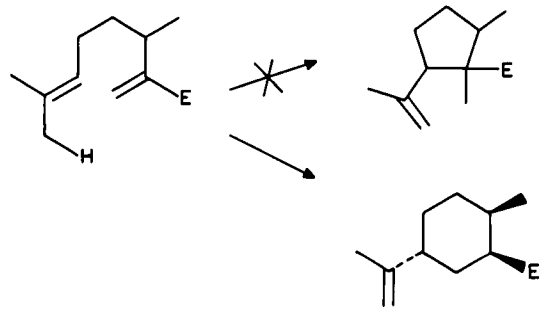
similar ring closure of 3,7-dimethyl-1,6-octadiene to a mixture of *cis*- and *trans*-cyclopentane derivatives (equation 62)[116] and the formation of 1-methylene-2-vinylcyclopentane from 6-octen-1-yne (equation 63)[117]. These examples illustrate the entropy advantages of intramolecular processes: even unactivated double and triple bonds can accept the ene component.

The intramolecular ene reaction has been classified[3] as three types according to the attachment of the linking chain to the terminal atom of the ene component, the central atom or the allylic terminal.



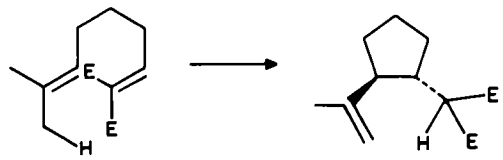
Type I Type II Type III

It was pointed out[118] that for each of these types there are two modes of reaction, since bond formation can take place at either of the termini of the enophile. For instance, the 1,6-octadiene derivative shown in equation 64 can cyclize in two ways to yield either a cyclopentane or a cyclohexane. The reaction, when carried out in the presence of ethylaluminium dichloride, yielded only the cyclohexane product as a result of the electronic effect of the complexed ester group[118]; in the absence of such an effect the formation of a five-membered ring is favoured (cf. equation 64). Placement of an electron-withdrawing group at the other end of the enophilic double bond brings about formation of a cyclopentane (equation 65). The reaction is stereoselective, affording mainly the *trans* product shown[119]. A similar *trans* selectivity operates in the thermal or zinc bromide-promoted cyclization of the next higher homologue (equation 66)[120].



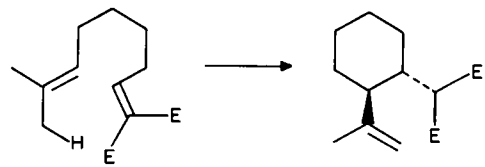
(64)

E=CO2Me

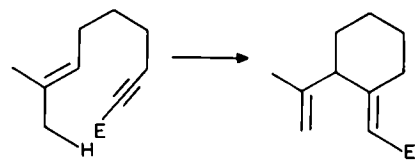


(65)

E=CO2Et

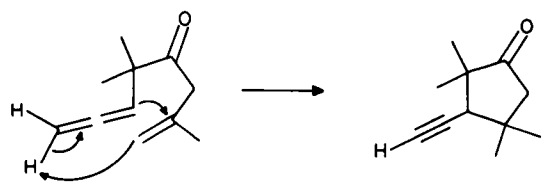


(66)

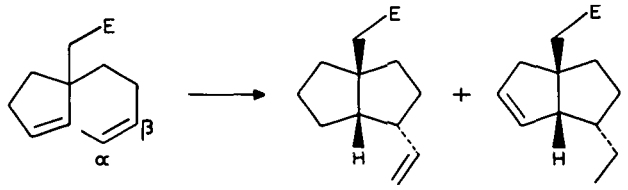


(67)

E=CO2Me



(68)

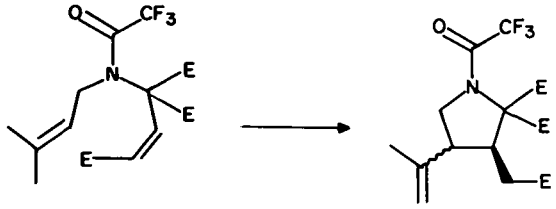


(69)

E=CO$_2$Et

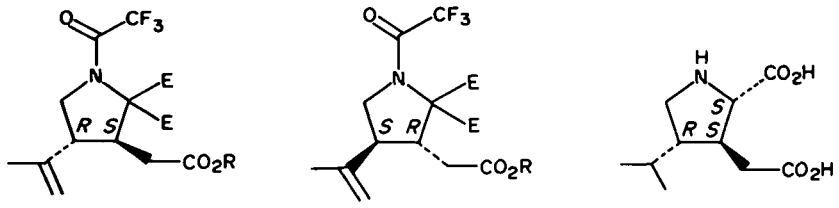
1,7-Enynes cyclize to 1-methylene-2-vinylcyclohexanes (equation 67)[121]. An allene functions as the ene in the formation[122] of the acetylenic cyclopentanone shown in equation 68. The ring closure of the 1,6-diene of equation 69 yields a mixture of two bicyclooctanes, which are derived from two modes of reaction. The former is produced by a cyclization in which the α,β-double bond is part of the ene component; in the formation of the second this bond functions as the enophile. If a trimethylsilyl substituent is present at C(α), only the first type of product is formed[123].

The stereoselectivity of intramolecular ene reactions may depend on conditions: the cyclization depicted in equation 70, when catalysed by diethyaluminium chloride, afforded solely a *trans* product, whereas thermolysis gave a 3:1 mixture of *trans* and *cis* isomers[124]. High dia- and enantio-stereoselectivity was observed when the corresponding chiral 8-phenylmenthyl ester was treated with diethylaluminium chloride at − 35 °C: the product mixture contained 95 parts of *R,S-trans* and 5 parts of *S,R-trans* isomers, 77 and **78**. The reaction was used for the synthesis[125] of the natural α-allokainic acid **79**.



(70)

E=CO$_2$Et



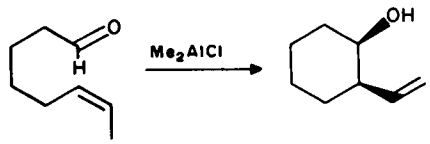
(77) **(78)** **(79)**

E=CO$_2$Et, R=8-phenylmenthyl

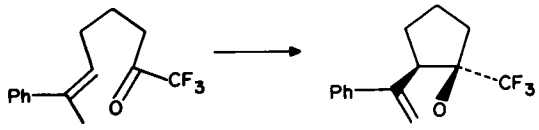
B. Intramolecular Reactions of Carbonyl Compounds

The Lewis acid-catalysed ene reactions of carbonyl compounds described in Section III.B have been applied advantageously to intramolecular processes, where high

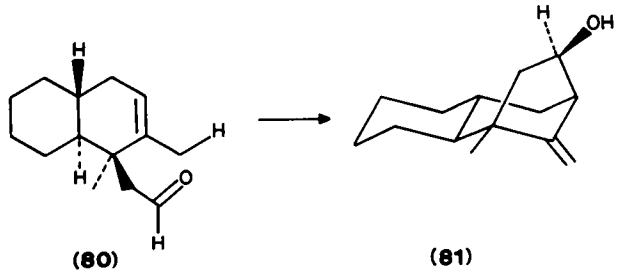
stereoselectivity is often observed. Cyclization[126] of *Z*-6-octenal affords solely the *cis* product shown in equation 71. There is also *cis* selectivity in the ring closure of an unsaturated trifluoromethyl ketone (equation 72)[127]. The bridged decalin **81** is produced by the tin(IV) chloride-catalysed cyclization of the γ,δ-unsaturated aldehyde **80**[128]. The mildly acidic oxidizing agent pyridinium chlorochromate, $C_5H_5\overset{+}{N}H\ ClCrO_3^-$, oxidizes alcohols to carbonyl compounds; in the case of citronellol, the oxidation is followed by cyclization and further oxidation, yielding pulegone (equation 73)[129].

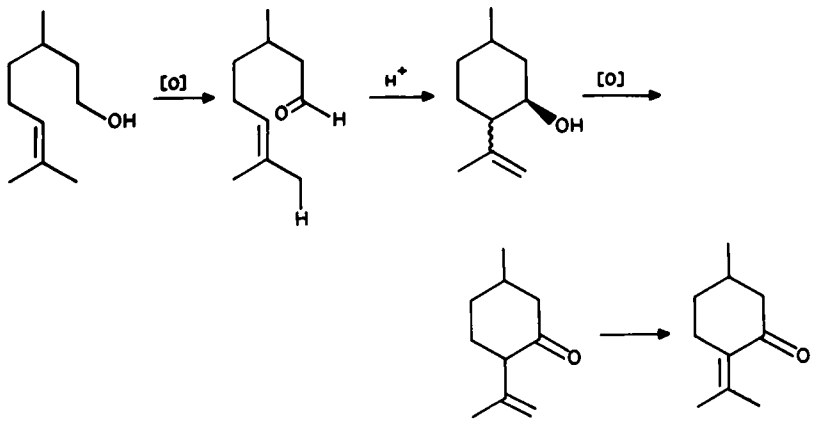


(71)

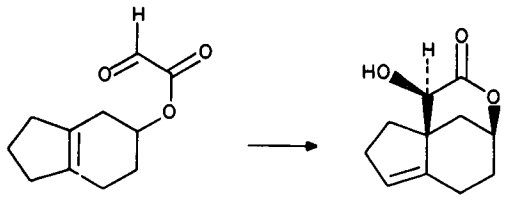


(72)

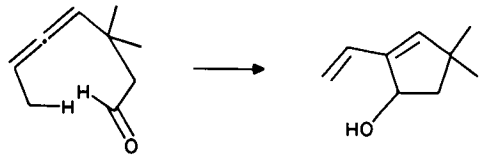




(73)



(82)

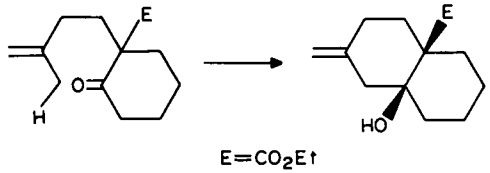


(83)

S-(+) S-(−)

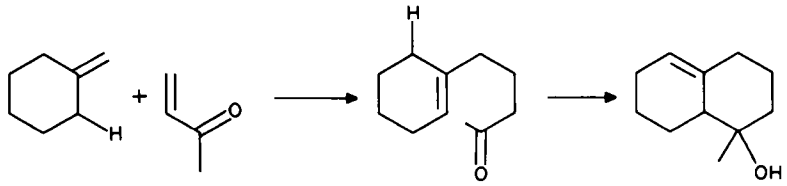
The intramolecular tin(IV) chloride-catalysed ene reaction of the glyoxylic ester **82** is stereospecific[130]. Transfer of chirality from one carbon atom to another occurs in the thermal cyclization[131] of the optically active allenic aldehyde **83**.

All the intramolecular ene reactions described so far are of Type I, although the reaction leading to **81** may be classified as either of Type I or II since there are two chains linking the ene to the enophile. Those belonging to the second and third types are much rarer; nearly all the following examples represent additions to carbonyl enophiles. 2-Ethoxycarbonyl-2-(3-methylbut-3-en-1-yl)cyclohexanone readily cyclizes in the presence of dimethylaluminium chloride (equation 74)[132]. In a new annulation procedure, alkylidenecycloalkanes are treated with α,β-unsaturated carbonyl compounds and dimethylaluminium chloride at room temperature to give bicyclic alcohols (equation 75). The process involves two successive ene reactions; the first is intermolecular and the second intramolecular of Type II[133]. Another Type II ring closure, which proceeds with high stereoselectivity, is shown in equation 76[134]. The allenic aldehyde **84** cyclizes in two ways. The thermal reaction affords a mixture containing equal amounts of the cyclohexanols **85** and **86**, formed, respectively, by Type II and Type III processes, while in the presence of dimethylaluminium chloride only the Type II product **85** is obtained[134]. The transannular cyclization in the following sequence of reactions may be classified as belonging to either Type I or Type II (equation 77)[135].

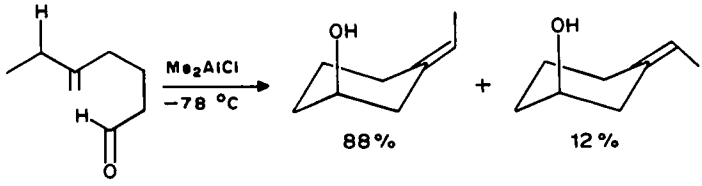


(74)

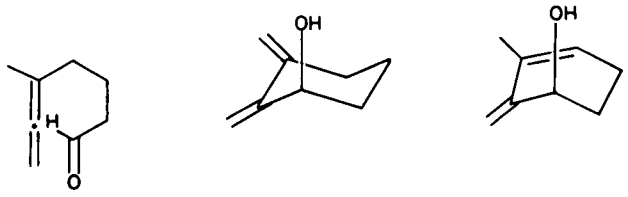
E=CO_2Et



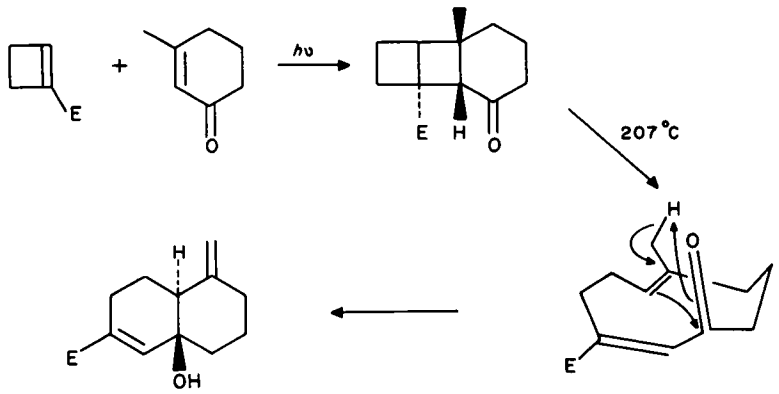
(75)



(76)



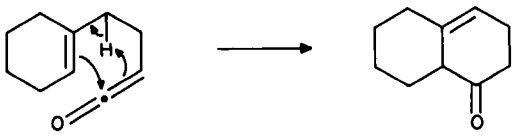
(84) (85) (86)



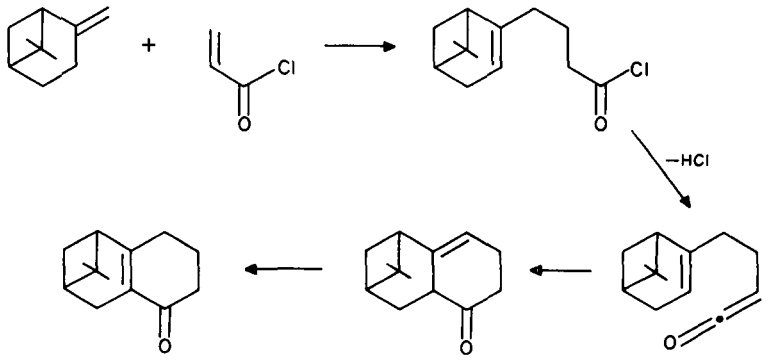
(77)

E = CO_2Me

We conclude this section with two examples of Type III reactions of ketenes. The thermal ring closure of the cyclohexene derivative **87** gives the octalenone **88**[136]. A more elaborate reaction of this type is shown in equation 78. The ene adduct of acryloyl chloride to β-pinene is converted into a ketene by the action of hot tributylamine; the ketene cyclizes spontaneously and the final product is formed by base-catalysed prototropy[137].



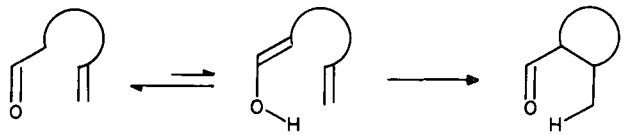
(87) (88)



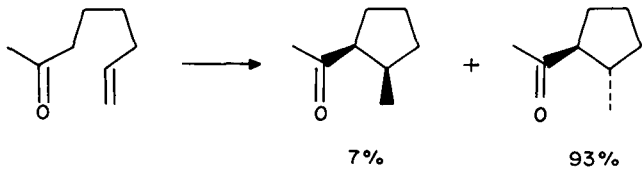
(78)

C. Enol–Olefin Reactions

The thermal cyclization of ω-olefinic carbonyl compounds (equation 79) has been extensively investigated by Conia and his associates, who suggest that the initial enolization is catalyzed by the glass of the reaction vessel; the subsequent ring closure is an intramolecular ene reaction[138]. Oct-7-en-2-one reacts at 350 °C to yield a mixture of geometrically isomeric 1-acetyl-2-methylcyclopentanes (equation 80); the *trans* isomer is formed preferentially as it is thermodynamically favoured[139]. The next higher homologue affords equal amounts of *cis*- and *trans*-1-acetyl-2-methylcyclohexane; the nine-membered ring analogues are formed in poor yields from dodec-11-en-2-one (equation 81)[140]. Cyclization of the acetylenic ketone oct-7-yn-2-one takes place at 260 °C; the primary product isomerizes to a mixture of acetylcyclopentenes (equation 82)[141]. 2-Methyloct-7-en-3-one affords 2, 2, 3-trimethylcyclohexanone in a Type II process by way of the more substituted enol (equation 83)[142]. 2-(Pent-4-en-1-yl)cyclohexanone cyclizes thermally to the spiro compound **89**[143]; 4-(but-3-en-1-yl)cyclohexanone gives the bridges ketone **90** in almost quantitative yield (equation 84)[144]. A derivative of bicyclo[2.2.1]heptane is produced in good yield from 1-acetyl-3-allylcyclopentane (equation 85); 1-acetyl-3-allylcyclohexane reacts analogously[139].



(79)



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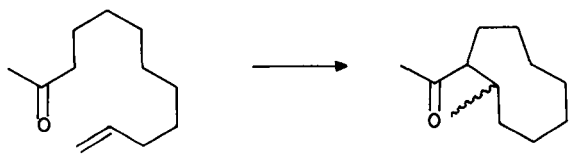
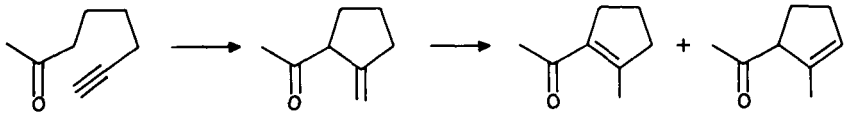
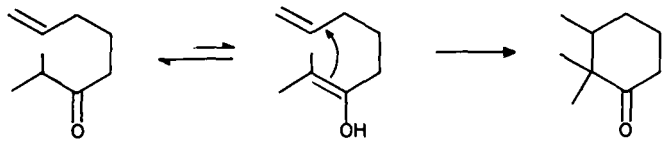


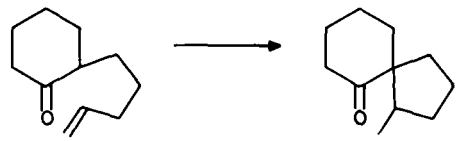
(81)



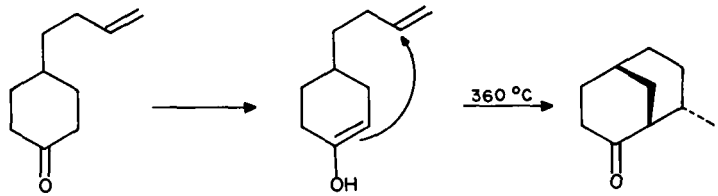
(82)



(83)

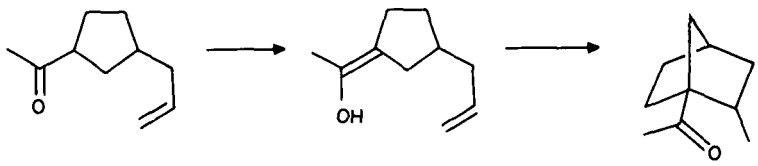


(89)



(84)

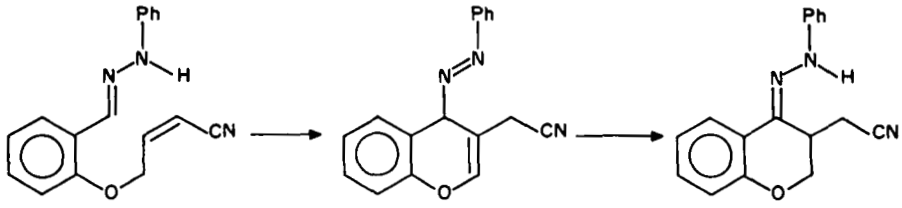
(90)



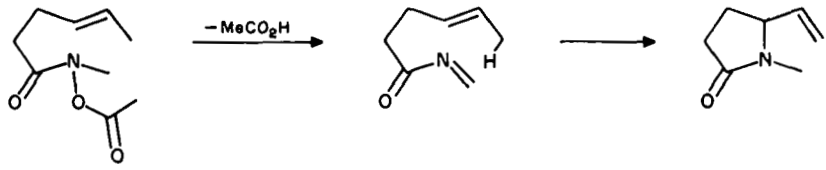
(85)

D. Other Intramolecular Additions

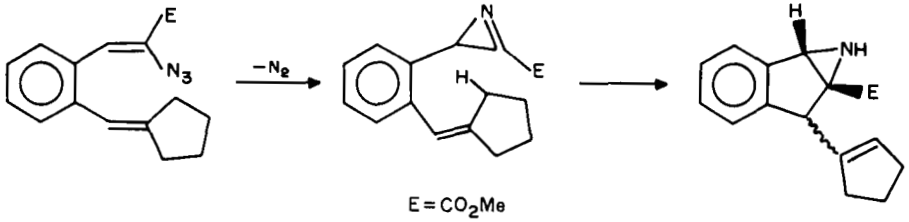
The 3-cyanoallyl ether of salicylaldehyde phenylhydrazone is transformed into a derivative of chromanone (equation 86)[145]. Flash-vacuum pyrolysis of the complex diacylhydroxylamine of equation 87 generates a transient *N*-acylimine, which cyclizes spontaneously[146]. Another intramolecular addition to imines occurs when methyl α-azido-*o*-(cycloalkylidenemethyl)cinnamates are heated in boiling toluene (equation 88)[147].



(86)

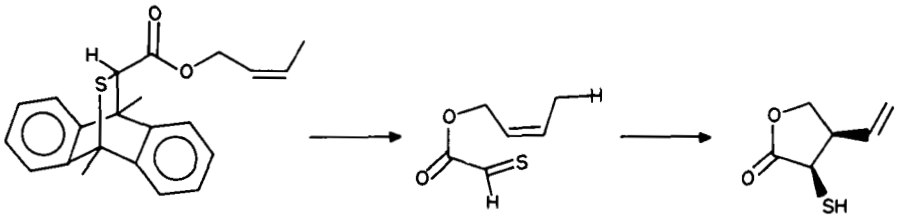


(87)



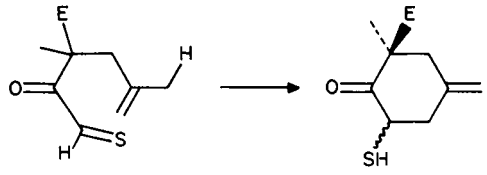
(88)

Heating the bridged dihydroanthracene **91** yields 9,10-dimethylanthracene and a thioaldehyde by a retro-Diels–Alder reaction; the thioaldehyde cyclizes spontaneously to a γ-lactone in a stereospecific fashion (equation 89)[148]. An intramolecular ene reaction of a thioaldehyde, which leads to a mixture of diastereomeric cyclohexanones, is shown in equation 90[149]. Acyl-nitroso compounds, which are generated by heating their adducts to 9,10-dimethylanthracene, are very reactive dienophiles and enophiles; an intramolecular ene addition of such a species (equation 91) was the key step in the synthesis of (±)-mesembrine[150].



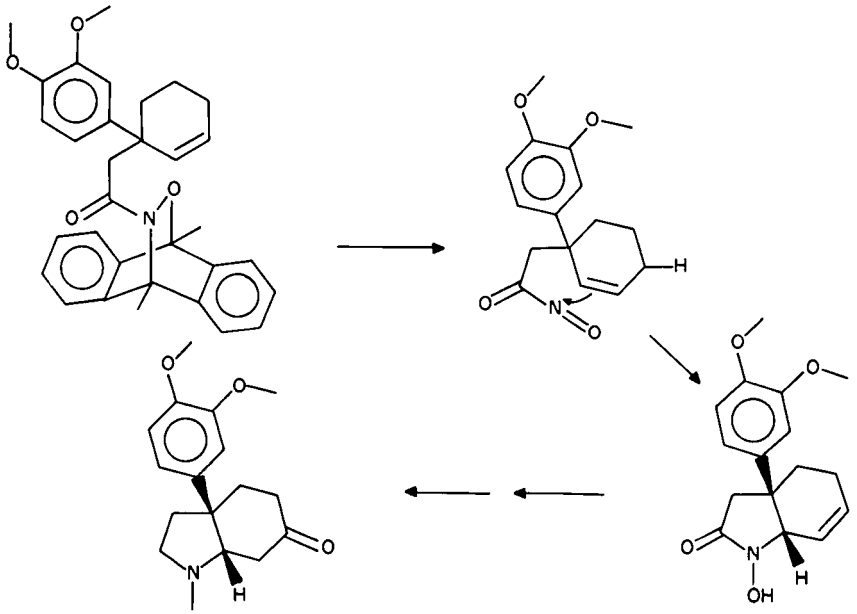
(**91**)

(89)



(90)

$E = CO_2Et$

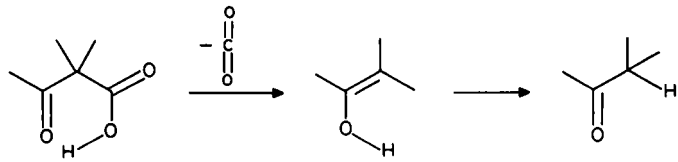


(±) = mesembrine (91)

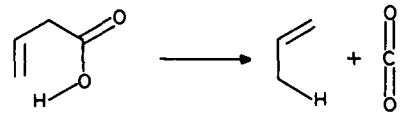
V. RETRO-ENE REACTIONS

A. Olefins and Imines[2]

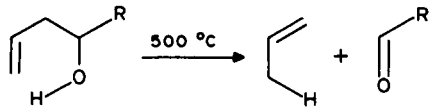
The best-known retro-ene reaction is the thermal decarboxylation of β-keto acids (equation 92); β,γ-unsaturated acids lose carbon dioxide at ca 250 °C (equation 93)[151], while the decomposition of γ,δ-unsaturated alcohols into olefins and carbonyl compounds requires much higher temperatures (equation 94). Carbon dioxide-laser irradiation of 3-buten-1-ol (R = H) gives propene and formaldehyde[152].



(92)

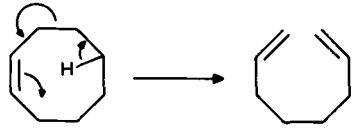


(93)

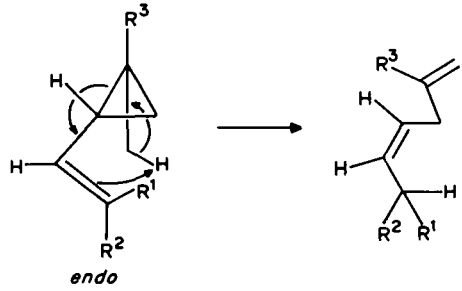


(94)

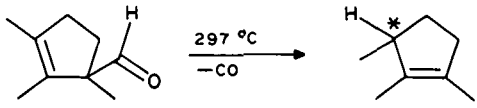
Retro-ene reactions in all-carbon systems have been little studied except intramolecular variants[2], e.g. the ring opening of cyclooctene to 1,7-octadiene (equation 95)[4a]. The kinetics of the gas-phase pyrolysis of various vinylcyclopropanes to yield *cis*- or *trans*-1,4-pentadienes show a clear preference for *endo* transition states in this reaction (equation 96).[153]. The suprafacial nature of the retro-ene reaction was demonstrated in the thermal decarbonylation of *R*-(+)-lauronelal (**92**), which yielded *R*-(+)-1,2,3-trimethylcyclopentene stereospecifically; hence the aldehyde hydrogen atom is delivered to the γ-carbon atom on the same face from which carbon monoxide is expelled (equation 97)[154]. The decomposition of the non-enolizable aldehyde 2,2-dimethyl-3-butenal (**93**) was considered[155] to be 'highly concerted' since no cross-over products were formed in the thermolysis of a mixture of the deuterio derivatives **94** and **95**.



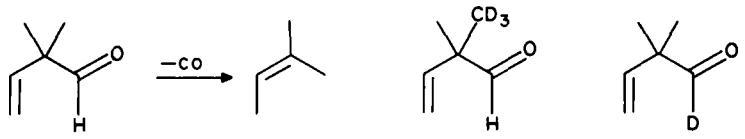
(95)



(96)

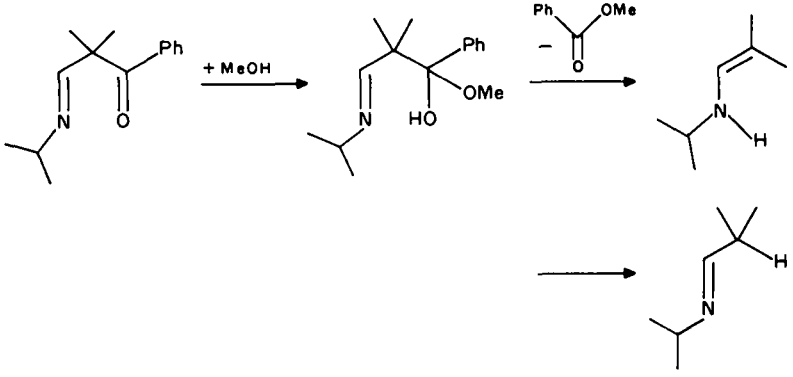


(92) (97)

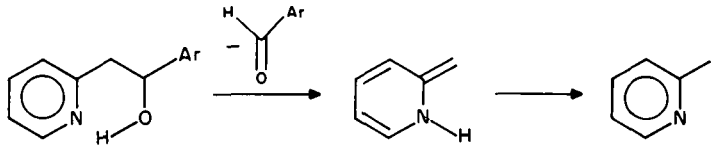


(93) (94) (95)

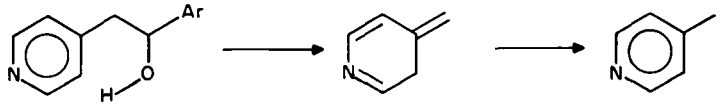
The imino ketone shown in equation 98 decomposes in boiling methanol to a mixture of methyl benzoate and isobutyraldehyde *N*-isopropylimine by a retro-ene reaction of an intermediate hemiacetal[156]. Thermolysis of various 1-aryl-2-(2-pyridyl)ethanols at 170 °C yields aryl aldehydes and α-picoline by prototropy of the primary products of the fragmentation (equation 99); the 4-pyridyl isomers react more slowly, presumably by way of 4-methylene-3,4-dihydropyridines (equation 100), while 3-pyridine compounds are stable at this temperature[157]. Enol esters are attacked by aqueous hydroxylamine at room temperature to yield hydroxamic acids and oximes (equation 101)[158]; the reaction was used for the selective cleavage of enol ester groups in sugar derivatives, e.g. **96**.



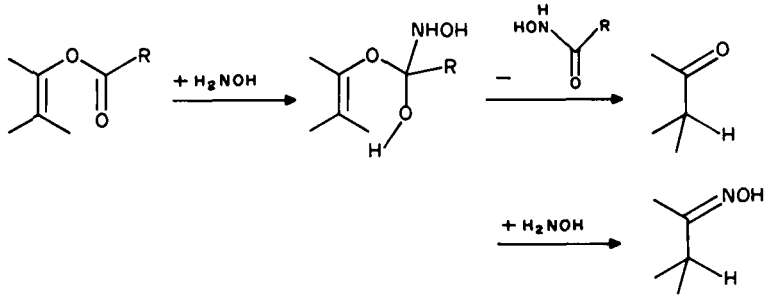
(98)



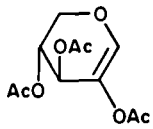
(99)



(100)



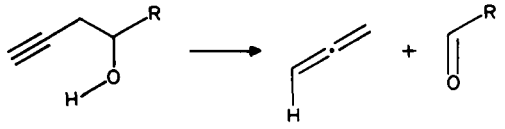
(101)



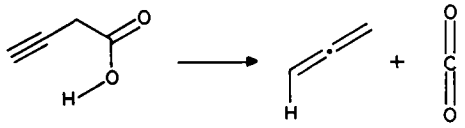
(96)

B. Acetylenes and Allenes[159]

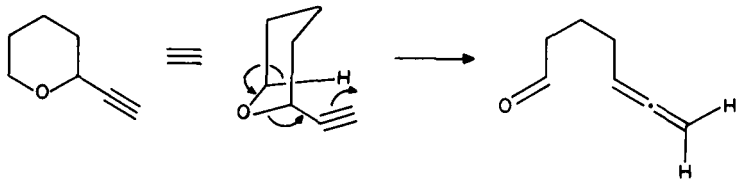
γ,δ-Acetylenic alcohols, like their olefinic counterparts (see equation 94), undergo thermal cleavage (equation 102). Laser-induced fragmentation of 3-butyn-1-ol yields allene and formaldehyde[152]. In an investigation of the rates of the vapour-phase thermolysis of a series of variously substituted γ,δ-acetylenic and γ,δ-olefinic alcohols, it was found that in all comparable cases the acetylenic compound fragmented faster than the olefinic, although reaching the transition state for reaction 102 requires considerable angle distortion. The enhanced rate was explained by reference to the geometry of the transition state. A planar structure, permitting maximum overlap of all the participating orbitals, is only possible for the acetylenes[160]. β,γ-Acetylenic acids likewise suffer cleavage more readily than the corresponding olefinic acids (equation 103)[161]. The requirement for a planar transition state in the retro-ene cleavage of acetylenic compounds is supported by the contrasting behaviour of 2-ethynyltetrahydropyran and 2-ethynyltetrahydrofuran. The former underwent ring opening at 470 °C (equation 104), whereas the latter was stable at this temperature. A planar arrangement is possible in the case of the tetrahydropyran derivative, though at the expense of considerable strain in the heterocyclic ring; in the tetrahydrofuran analogue such a transition state cannot be attained[162].



(102)

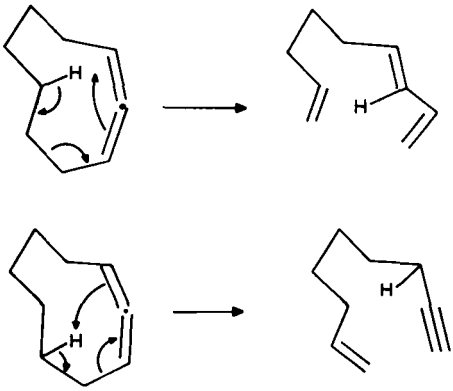


(103)



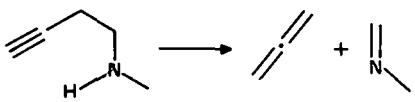
(104)

The bent cyclic allenes cyclonona-1,2-diene and cyclodeca-1,2-diene on flow-vacuum pyrolysis at 500–650 °C give mixtures of trienes and enynes, which are formed by two modes of cleavage (equation 105)[163].

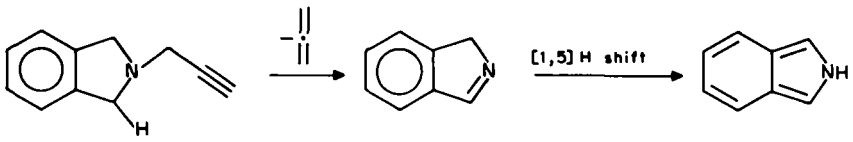


(105)

4-Methylamino-1-butynes undergo a retro-ene reaction at 460 °C (equation 106). As in the case of unsaturated alcohols, these reactions are faster than those of their olefinic counterparts[164]. Flash-vacuum pyrolysis of *N*-propargylisoindoline is a useful method for preparing isoindole (equation 107); the intermediate imine was not detected[165].



(106)

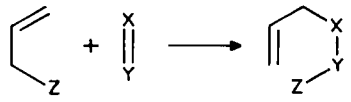


(107)

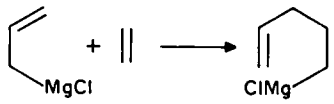
VI. METALLO-ENE REACTIONS AND OTHER ANALOGUES OF THE ENE REACTION

A number of cases are known in which the migrating hydrogen atom in the ene reaction is replaced by some other group (equation 108). The most thoroughly studied process of this kind is the addition of alkenes to allyllic magnesium halides or bis(allyl)zinc compounds, the '*metallo-ene reaction*' (equation 109)[166]. The reactivity of enophiles increases in the

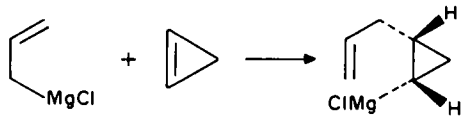
order 1-alkenes < styrene < 1,3-butadiene < ethylene. Cyclopropene yields solely products of *cis* addition (equation 110)[166].



(108)

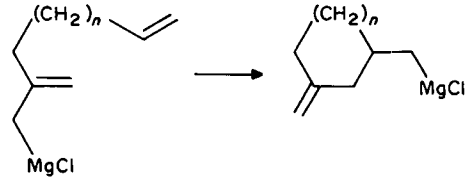


(109)



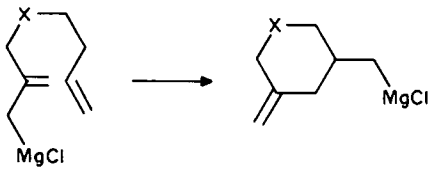
(110)

There is an increasing number of reports of intramolecular metallo-ene reactions. The magnesium compounds shown in equation 111 undergo a Type II ring closure at 80–130 °C to afford methylenecycloalkanes of ring size 5–7[167]. Methylenetetrahydropyrans and methylenepiperidines are similarly produced (equation 112)[168]. The cyclization depicted in equation 113 was a key step in the synthesis of (±)-chokol-A (**97**); the ring closure is highly regio- and stereoselective[169].



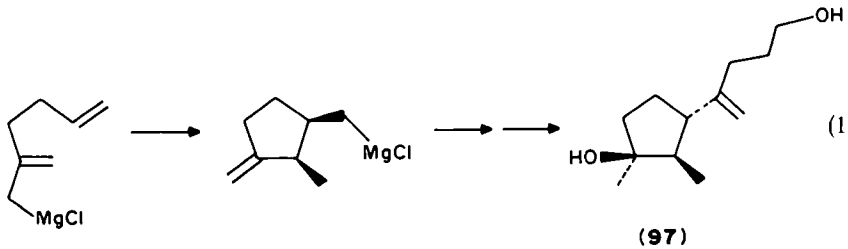
(111)

$n = 1, 2$ or 3



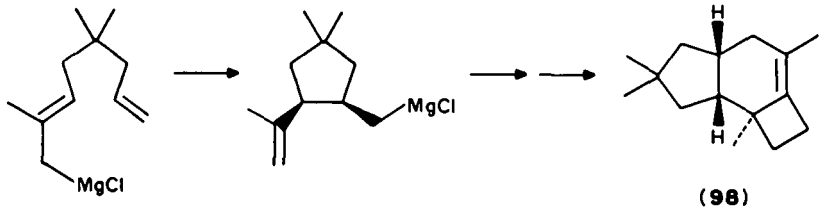
(112)

X = O or NMe



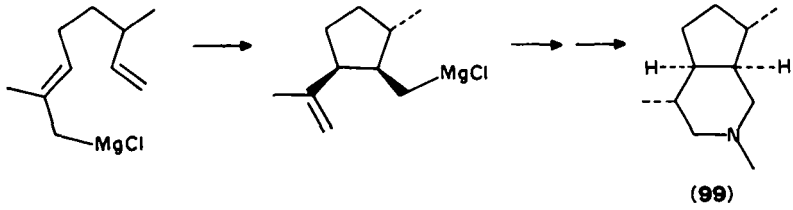
(113)

(97)



(98)

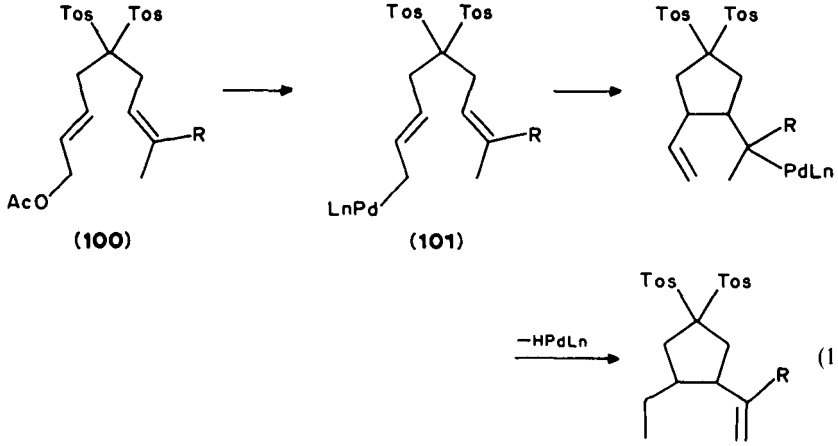
(114)



(99)

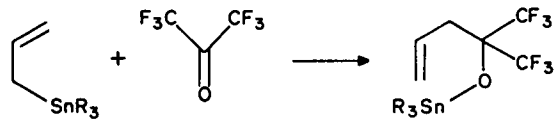
(115)

Intramolecular metallo-ene reactions of Type I are illustrated in equations 114 and 115. The first reaction was used for the synthesis of (±)-6-protoilludene (**98**)[170], the second for α-skytanthine (**99**)[171]. The disulphones (**100**; R = H or Me) form palladium complexes (**101**; L = ligand) by the combined action of bis(dibenzylideneacetone)palladium and triphenylphosphine; the complexes cyclize in acetic acid to yield derivatives of cyclopentanone (equation 116)[172].

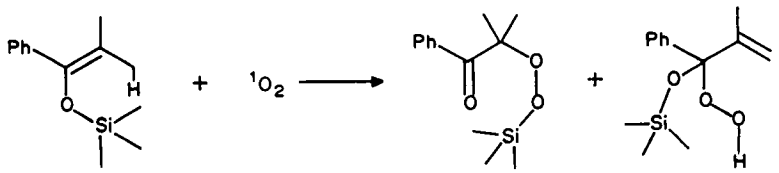


(116)

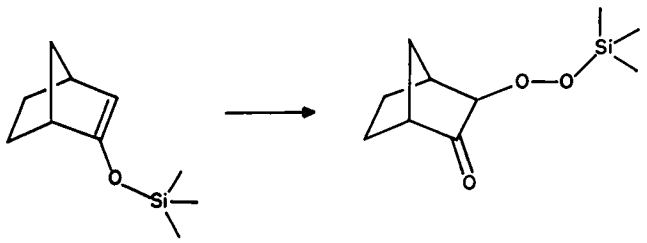
Allylstannanes add to hexafluoroacetone to yield products in which the stannyl group has migrated (equation 117)[173]. A trimethylsilyl group is transferred in competition with hydrogen in the photooxygenation of 2-methyl-1-trimethylsilyloxy-1-phenylpropene to yield two products (equation 118)[174] Trimethylsilyloxynorbornene reacts stereospecifically with singlet oxygen at low temperatures (equation 119)[175].



(117)

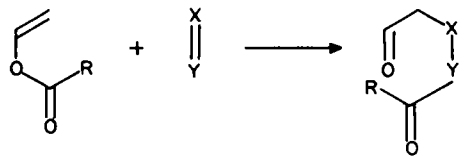


(118)

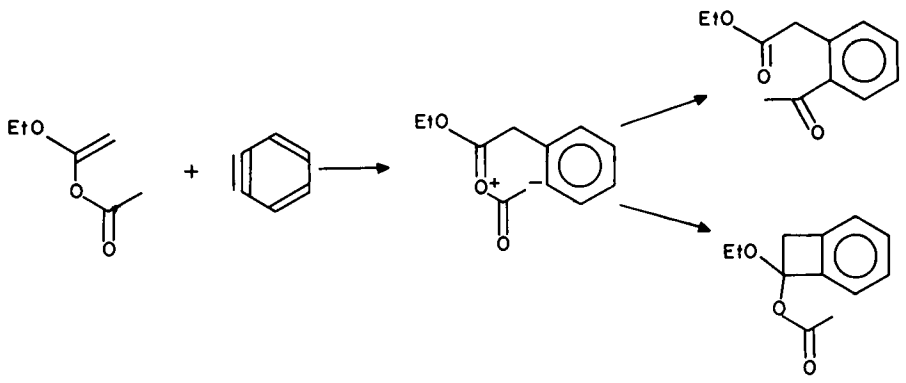


(119)

This chapter closes with a description of addition reactions of enol esters with various unsaturated compounds, in which acyl groups are transferred (equation 120). 1-Ethoxyvinyl acetate and benzyne yield a mixture of the 'acyl-ene' product and a benzocyclobutene (equation 121)[176]; the formation of the latter is good evidence for a

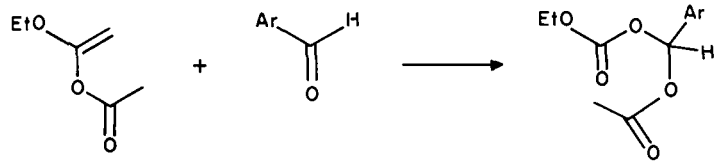


(120)

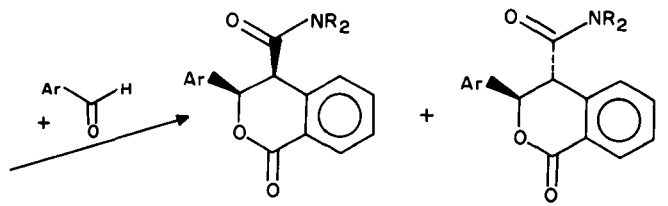


(121)

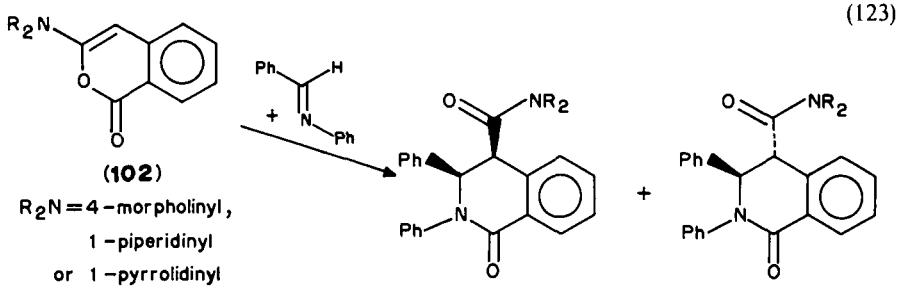
dipolar intermediate. Aromatic aldehydes also react with 1-ethoxyvinyl acetate (equation 122)[177]. 3-Dialkylamino-1*H*-2-benzopyran-1-ones (**102**) are especially reactive, adding readily to aromatic aldehydes, imines and *trans*-β-nitrostyrene to afford mixtures of geometrical isomers (equations 123–125). Novel heterocycles were obtained from nitrosobenzene and carbon disulphide (equations 126 and 127). These reactions required the polar solvents acetonitrile or acetic acid, which is consistent with the formation of a dipolar intermediate[178].



(122)



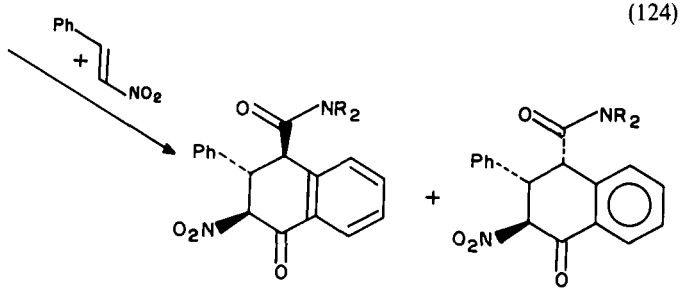
(123)



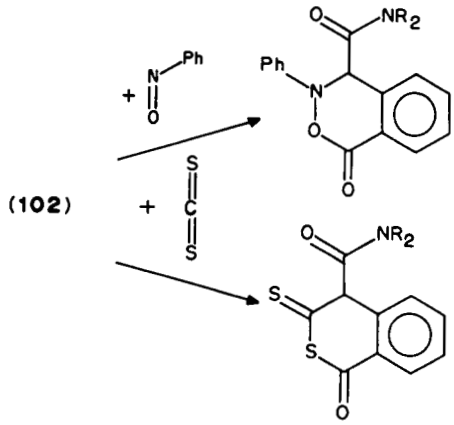
(102)

R_2N = 4-morpholinyl, 1-piperidinyl or 1-pyrrolidinyl

(124)



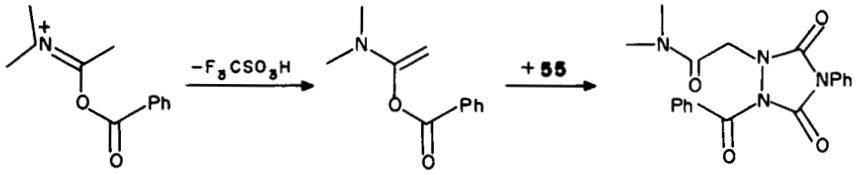
(125)



(126)

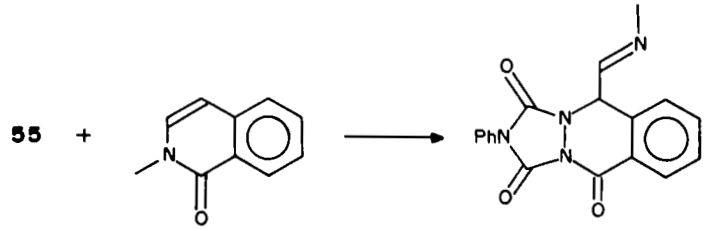
(127)

The benzoyloxyiminium salt **103** is obtained from *N*, *N*-dimethylacetamide and benzoyl chloride in the presence of silver trifluoromethanesulphonate. Treatment with triethylamine gives the unisolable acyloxyenamine **104**, which can be trapped as the adduct **105** if the deprotonation is carried out in the presence of 4-phenyl-1, 2, 4-triazoline-3, 5-dione (**55**)[179].



(**103**) $F_3CSO_3^-$ (**104**) (**105**)

The addition of the triazolinedione to *N*-methylisoquinoline-1-one (equation 128) is a variant of the acyl-ene reaction, in which the migrating acyl group is originally attached to a nitrogen atom[180].



(128)

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The Chemistry of Double-bonded Functional Groups
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CHAPTER 9

Radiation chemistry of double-bonded compounds

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I. INTRODUCTION

Radiation chemistry is the study of the chemical effects produced in a system by the absorption of ionizing radiation. This definition includes the chemical effects due to radiation from radioactive sources, high-energy charged particles and short-wavelength (less than about 400 Å)[1] electromagnetic radiation from accelerators. The principal characteristic of high-energy radiation is that it causes ionization in all materials. This makes a distinction between radiation chemistry and photochemistry[2,3]. Photochemistry deals with longer-wavelength electromagnetic radiations which have lower energy (less than about 30 eV). This relatively low energy leads in many cases only to the excitation of the molecules and does not produce ions. Usually, the energy of the particles and photons applied in radiation chemistry is much higher. The whole energy is not absorbed by a single molecule, as in photochemistry, but rather distributed over several molecules, along the track of the ionizing particle or photon. The high-energy photons and particles are not selective and may ionize, excite or dissociate any molecule lying in their path, while in photochemistry only some compounds may interact with the radiation, in accordance with the energy of the photons.

The high-energy photons or particles lose energy in successive events and produce ions and primary electrons which in turn form several secondary electrons with lower energies[4]. The chemical effects of ionizing radiation occur almost exclusively through the secondary electrons most of which have less than 100 eV. These electrons will cause ionization and excitation of the surrounding molecules and will lose energy until they reach thermal energies. In many solvents these thermal electrons polarize the solvent and are bound to it in a stable quantum state; these electrons are called solvated electrons.

The study of radiation chemistry might be divided, from the experimental point of view, into two parts. The first is the study of unstable intermediates which have short lifetimes and thus cannot be studied by the usual methods of chemistry. The second part is the study of the final products of the radiolysis which are measured by common chemical techniques.

One way to make the short-lived intermediates amenable to study is to increase their lifetime, usually by irradiation in the solid state and at very low temperature. Then, the intermediates can be measured at the end of the irradiation by optical absorption spectroscopy or ESR.

Another method of making the lifetime longer in the liquid phase is by adding compounds which, upon addition of radicals, produce long-lived radicals; this method is called spin trapping[5].

More common in the liquid phase is pulse radiolysis[6]. In this technique, electron accelerators which can deliver intense pulses of electrons lasting a very short time (ns up to μs) are used. Each single pulse can produce concentrations of intermediates which are high enough to be studied by various methods such as light absorption spectroscopy or electrical conductivity.

The yields of radiolysis products are always expressed by the G value, which is defined as the number of particles (molecules, radicals, ions) produced or consumed per 100 eV of energy absorbed in the system.

The units for the absorbed energy (dose) are the rad, defined by $1\,\text{rad} = 100\,\text{erg}\,\text{g}^{-1} = 6.243 \times 10^{13}\,\text{eV}\,\text{g}^{-1}$, and the Gray (Gy) defined by $1\,\text{Gy} = 100\,\text{rad}$.

II. RADIATION CHEMISTRY OF CARBONYL COMPOUNDS

Freeman in a chapter on radiation chemistry of ketones and aldehydes in a previous book in this series[7] summarized the main basic studies on radiolysis of carbonyl compounds and gave examples of the studies for liquid acetone and cyclopentanone. We will extend this material by reviewing the studies done after the preparation of the above review or omitted

in it, such as, for example, the pulse radiolysis of acetone and the radiation chemistry of aqueous or non-aqueous solutions of carbonyl compounds. However, due to the limited size of the present chapter only a selected part of the data found in the literature will be summarized here.

A. Initial Products in the Radiolysis of Aldehydes and Ketones at Low Temperatures—ESR Studies

Radiolysis of compounds at low temperatures produces the same initial products as at higher temperatures, but due to the lower temperatures and the solid phase at those temperatures the reactions of these species are considerably slowed and they can be measured by ESR. Mishra and Symons[8] studies the ESR spectra of irradiated solutions of formaldehyde in sulphuric acid and found a triplet with hyperfine coupling of $\approx 90\,G$ and assigned it to the formaldehyde radical cation $H_2CO^{\ddagger}$. Symons and Boon[9] investigated the ESR spectra of γ-irradiated dilute solutions of acetaldehyde, acetone and cyclohexanone in $CFCl_3$ at 77 K. They used $CFCl_3$ as a solvent since it was found earlier that freons are ideal solvents for radiolytic preparation of radical cation, due to their reactivity with the anions and unreactivity toward the cations. In the case of acetone they found $(CH_3)_2CO^{\ddagger}$ with γH of about $3G$. For the acetaldehyde solution they observed[10] an anisotropic doublet of quartets. The assigned a large proton coupling of $\sim 136\,G$ to the aldehydic proton and the small quartet structure to three equivalent methyl hydrogens. They explained the absence of a corresponding substructure from the methyl hydrogens of the acetone radical cation by postulating that $CH_3CHO^{\ddagger}$ differs from $(CH_3)_2CO^{\ddagger}$ in having a preferred conformation for the methyl group with a large coupling to one of the methyl hydrogens in the molecular plane. However, Snow and Williams[10] studied the ESR spectrum of a γ-irradiated $CFCl_3$ solution of acetaldehyde-h_4 (all hydrogen) and of acetaldehyde-2,2,2-d_3 (CD_3CHO) at 88 K and obtained very similar patterns for $CH_3CHO^{\ddagger}$ and $CD_3CHO^{\ddagger}$, the only difference being the much better line resolution for $CD_3CHO^{\ddagger}$. Consequently it can be concluded that the quartet structure of $CH_3CHO^{\ddagger}$ has no connection with the methyl group. Snow and Williams proposed that this ESR spectrum is due to superhyperfine interaction between the acetaldehyde radical cation and the halogen atoms of the solvent matrix. Symons and Boon[11] agree with this assignment.

Belevskii and coworkers[12] measured the ESR spectra of γ-irradiated Freon 11 and Freon 113 solutions of acetaldehyde and propanal at 77 K. They found that the first intermediate in the case of acetaldehyde is the radical cation $CH_3CHO^{\ddagger}$ which is converted by proton or H-atom transfer to the radicals $CH_3\dot{C}O$ and $CH_3\dot{C}HOH$ and the corresponding cations. Similarly for propanal the first intermediate is $CH_3CH_2CHO^{\ddagger}$ which is converted to $CH_3\dot{C}HCHO$ and $CH_3CH_2\dot{C}O$,

$$CH_3CHO^{\ddagger} + CH_3CHO \longrightarrow \begin{cases} \longrightarrow CH_3\dot{C}O + CH_3CHOH^{+} \\ \longrightarrow CH_3CO^{+} + CH_3\dot{C}HOH \end{cases} \qquad (1)$$

B. Initial Products in the Radiolysis of Liquid Acetone and Other Ketones; Pulse Radiolysis Studies

1. Spectra and identification

Several workers studied the pulse radiolysis of acetone[13–20]. Rodgers[17] found that pulse radiolysis of pure acetone leads to transient optical absorption spetra with two distinct bands, one near 500 nm and the other centred around 850 nm. He found that the decay of the 850 nm band has a slow and a fast component while the 500 nm absorption has only the slow step. Scavenger studies showed that the 500 nm band is due to the acetone anion and

the 850 nm band is due to the molecular cation. This conclusion agrees with the results of radiolysis at low temperature of acetone glasses by Shida and Hamill[22], who found similar spectral features. The formation of both cations and anions is known also from pulse radiolysis studies of acetone solutions of aromatic compounds, which also show the formation of anions and cations of many aromatic solutes[14,15,18,20].

The addition of water (or ethanol) to acetone causes the removal of both bands. This is explained as due to the reactions

$$(CH_3)_2CO^{+} + ROH \longrightarrow ROH_2^{+} + \cdot CH_2COCH_3 \quad (2)$$

$$(CH_3)_2CO^{-} + ROH \longrightarrow RO^{-} + (CH_3)_2\dot{C}OH \quad (3)$$

The relatively long half-life of the acetone cation in pure liquid acetone, 20 ns at 298 K[16], shows that the acetone cation reacts with acetone molecules with a rate constant $\leqslant 2.5 \times 10^6\ M^{-1}\,s^{-1}$, where the 'less-than' symbol allows for the possibility that the decay of the radical cation is by reaction with some impurity. This rate is much slower that the rate constant found for the reaction of the acetone cation-radical with acetone molecule in the gas phase by mass spectrometry studies[21-23]. These studies show that $(CH_3)_2CO^{+}$ reacts with acetone molecule practically in every collision, about $10^{11}\ M^{-1}\,s^{-1}$. Sieck and Ausloos[21] suggested that this difference shows that none of the absorptions found in the pulse radiolysis of pure liquid acetone can be ascribed to the acetone cations, since all these which do not undergo geminate recombination will react within 10^{-12} s. However, Rodgers[17] argued that the 850 nm absorption band according to scavenger studies belongs to a cation and as he could not think of another cation which would be responsible for the formation of aromatic cations (e.g. of pyrene, naphthalene, 2,6-dimethylnaphthalene) or oxidize halide ions[24] he concluded that this is the band of the acetone cation radical or acetone dimer-cation. Rodgers found[17] that the acetone cation radical abstracted an electron from aromatic molecules (e.g. pyrene) with rate constant about twice the diffusion-limited value and this is interpreted, as in the dichloroethane system, in terms of a higher mobility of positive holes through a homogeneous matrix by resonance charge transfer. At sufficiently high solute concentrations, aromatic cations may interact with neutral ground-state solute molecules forming a dimer cation. Robinson and Rodgers[16] found that the rate constant for the first-order decay of the acetone cation in pure liquid acetone increased with increasing temperature with an activation energy of 1.50 kcal mol^{-1}. This value is close to the activation energy of the viscosity of acetone[25], 2.21 kcal mol^{-1}, and hence it can be deduced that the bimolecular decay of acetone cations is governed by a diffusion-controlled process, the rate of which is about $3 \times 10^{10}\ M^{-1}\,s^{-1}$. This means that $(CH_3)_2CO^{+}$ reacts with a reactant M having a concentration of about 10^{-3} M (residual impurity),

$$(CH_3)_2CO^{+} + M \longrightarrow \text{products} \quad (4)$$

and the reaction between the acetone cation-radical and the acetone molecule

$$(CH_3)_2CO^{+} + (CH_3)_2CO \longrightarrow (CH_3)_2COH^{+} + \dot{C}H_2COCH_3 \quad (5)$$
$$\text{or } (CH_3COCH_3COCH_3)^{+} + \dot{C}H_3$$

is not a significant contributor to the cation decay.

The acetone anion ($\lambda_{max} = 550$ nm) formed presumably by a rapid electron capture

$$(CH_3)_2CO + e^{-} \longrightarrow (CH_3)_2CO^{-} \quad (6)$$

decays also in a first-order process but markedly more slowly, e.g. at ambient temperature $k = 6.4 \times 10^5\ s^{-1}$.

The assignment of the 550 nm band to the acetone radical anion was questionable, since pulse radiolysis of alkaline aqueous solutions of alcohols does not show this band[26,27].

Badger and Brocklehurst[28] suggested that the infra-red band is due to dimer cations of acetone rather than to the cation itself. Arai and coworkers[20] decided to measure the pulse radiolysis at low temperatures (77 K) when the lifetime of the ionic species is considerably longer and their optical absorptions are easily observed using microsecond pulse radiolysis. For clearer identification of the bands they studied also the pulse radiolysis of tetrahydrofuran solutions of acetone at low temperatures and the absorption spectra of γ-irradiated glassy butyl chloride solution of acetone. Irradiated pure butyl chloride at 77 K had an absorption band at 530 nm, while irradiated (77 K) butyl chloride solution of 0.5 M acetone had an absorption band at 740 nm, almost the same as that obtained with pulse-irradiated acetone saturated with N_2O (to trap the electrons and prevent the formation of the radical anions)[20]. Butyl chloride solutions of acetone at concentrations between 0.05 and 0.4 M exhibited bands at both 530 and 740 nm. The intensity of the band at 530 nm decreased and that at 740 nm increased with increasing concentration of acetone. No other bands were found in the range of 350 to 1200 nm and there is no increase of the intensity at 740 nm during the warming of the solutions. Thus it can be concluded that the 740 nm band (850 nm in Rodgers' studies)[17] is due to the molecular cations of acetone and not to the dimer.

The microsecond pulse irradiation of acetone at room temperature produces a weak absorption starting at about 600 nm and increasing to 330 nm. As the temperature is reduced the intensity of the spectrum increases and the decay becomes slower. At 193 K there is a peak at 500 nm and a long tail extending to 1000 nm. The addition of N_2O to acetone causes complete removal of the peak at 500 nm with formation of a spectrum with a peak at 740 nm[20]. The addition of 0.1 M triethylamine, a cation scavenger, removes 30–40% of the absorption at 500 nm but nothing at 300–400 nm. Thus it can be concluded that the absorption at 500 nm is due to at least two absorbing species. Addition of water almost completely removes the absorption at 500 nm and almost none at $\sim$350 nm. The difference between the spectra of acetone at 193 K with and without water gave a spectrum with an absorption band at about 500 nm. These findings indicate bands of an anionic species at 500 nm and a cationic one at 740 nm.

By comparing the absorbance at 500 nm for pure acetone with that at 720 nm (the band of the anthracene anion) for an acetone solution of 5×10^{-3} M anthracene containing 1 M triethyl amine and using the molar absorption coefficient of anthracene at 720 nm ($1 \times 10^4\ M^{-1}\ cm^{-1}$), they estimated[20] the molar absorption coefficient of acetone anion at 500 nm to be $5 \times 10^3\ M^{-1}\ cm^{-1}$.

It is well established[29,30] that the solvated electron is one of the main products in the radiolysis of tetrahydrofuran (THF). The hydrated electron is very reactive toward acetone and so it can be expected that molecular anions of acetone will be formed in the radiolysis of THF solutions of acetone in the early stages. Arai and collaborators[20] found that the absorption spectra obtained by pulse radiolysis of THF solutions containing from 6×10^{-4} to 7.4×10^{-1} M acetone all have a peak located at 500 nm independent of the acetone concentration. The intensity of the peak increases with increasing acetone concentration. Thus this is another proof for the identity of the 500 nm band as being due to the anion radical of acetone.

Acetone absorption observed in the pulse radiolysis of acetone at low temperature[20] has a peak below 330 nm. As this absorption is not influenced by either cation or anion scavengers, it is possibly due to neutral radical. This identification is supported by the finding that the decay of the absorption at 340 nm fits a second-order rate law.

The observation that the acetone cation decays much faster than the acetone anion means that the neutralization reaction between acetone anions and acetone cations does not occur to a significant extent in pure acetone at room temperature.

Arai's group[20] measured the absorptions of the molecular radical anions of several liquid ketones and found a general trend that the larger the side-chain the longer the

wavelength of the band of the molecular anions, but diisopropyl ketone is an exception. They could not correlate the absorption bands with physical parameters of the parent ketones.

Both acetone anions and cations are very reactive species, e.g. the cation reacts with CNS^- to give CNS radical with a rate constant of $1.1 \times 10^{11}\,M^{-1}s^{-1}$ and with Br^- to give Br atom with $k = 4.2 \times 10^{10}\,M^{-1}s^{-1}$ while the anion reacts with anthracene, pyrene and $CHCl_3$ with rate constants of 4.9×10^9, 1.3×10^{10} and $3.3 \times 10^8\,M^{-1}s^{-1}$, respectively[16].

While at room temperature the decay of the 850 nm band had both a fast and a slow component and the 550 nm band had only a slow component; at about 200 K both bands show fast and slow components[16]. The presence of 3% nitromethane (an anion scavenger) removed both components of the 550 nm band while both components of the 850 nm band were unaffected. Robinson and Rodgers[16] suggested that the components represent two different decay modes of the same ions decaying by either geminate interaction or as free ions; the distribution between the two depends on the initial distribution of thermalized secondary electrons in liquid acetone. A theoretical interpretation of ion decay[31] indicates that geminate decay should proceed with a $t^{1/2}$ dependence. Robinson and Rodgers[16] show that the optical density at both 860 and 550 nm are linearly dependent on $t^{1/2}$ for a 20 ns electron pulse in pure acetone at 185 K. The geminate decay of the cations and of the anions have coincident rate parameters which indicates that they are decaying together, unlike the free ions which have decay parameters a factor of fifty apart.

2. *Yields*

Arai and Dorfman[13] studied the yield of anions and excited states in acetone by pulse radiolyzing acetone solutions of anthracene and naphthalene and measuring the intensity of the absorption bands of naphthalene triplet and anthracene triplet and anion radical. They found for the acetone species, which leads to formation of triplet anthracene or naphthalene, a half-life of at least 5μs, that ruled out this precursor being singlet acetone which has a much shorter half-life. The precursor for the aromatic triplets can neither be a molecular anion, as the kinetics for the formation of the triplet and the decay of the anion are different. Arai and Dorfman[13] found G(triplet) $= 1.1 \pm 0.7$ from anthracene studies and 1.9 ± 1.0 from benzanthracene studies. The relatively large errors are due to uncertainties in the molar absorption coefficients of the triplets of the aromatic compounds. They found also G(anion) $= 1.7 \pm 0.6$. Most of the uncertainty in this case is due to the uncertainty of the G value of solvated electrons in ethanol.

It was found later that the absorption of anthracene at 720 nm is not due only to the anthracene anion as was assumed by Arai and Dorfman, but also to the anthracene cation which absorbs at the same wavelength. Arai and coworkers[15] assumed the same molar absorption for anthracene cations and anions and similarly the same for biphenyl cations and anions, and obtained G(cation + anion) $= 1.1$ from the biphenyl studies and G(cation + anion) $= 1.5$ from the acetone solution of anthracene. The yields of the excited triplet state of acetone using more accurate values for the molar absorption coefficients of the triplet aromatics give[15] 1.4 from anthracene studies, 1.3 from naphthalene studies and 1.7 from 1,2-benzanthracene studies, so $G(^3\text{acetone}) = 1.5 \pm 0.2$. The first singlet excited state of acetone has a higher energy than those of pyrene and anthracene, but less than those of biphenyl and naphthalene. It was found[15] that acetone solutions of pyrene or anthracene emit fluorescence of the solutes when subjected to the electron pulse while solutions of biphenyl or naphthalene did not. Thus it can be concluded that the first excited singlet state of the aromatic solute is formed by energy transfer from the first excited singlet state of acetone to the aromatic molecule. The yield of the first excited singlet state of acetone was found to be $G = 0.31$.

This method of formation of molecular triplet states by electron pulse radiolysis is used frequently for direct investigation of the reactions of molecular triplet states in solutions[32-34]. Barwise and coworkers[35] studied by this pulse radiolysis method the quenching or aromatic carbonyl triplets.

Chaudhri and Asmus[19] measured the yield of acetone radical anion $(CH_3)_2CO^{\cdot-}$ in radiolysis of pure acetone using conductivity measurements of pulse radiolysis and obtained $G = 1.2 \pm 0.2$. However, this value depends on the value assigned for the equivalent conductance of the anion $(CH_3)_2CO^{\cdot-}$. The authors assumed this value to be $105 \pm 20\,\Omega^{-1}\,cm^2\,equiv^{-1}$, but the true uncertainty might be higher.

Robinson and Rodgers[16] found that the yield of triplet acetone is $G = 1.0$ (by anthracene studies) and of the singlet acetone excited state is $G = 0.35$.

Addition of various ion scavengers to acetone solutions of anthracene reduces the yields of both excited singlet and triplet anthracene. This can be explained as due either to reaction of the ion scavenger with primary ions in spurs, which resulted in lower yields of excited acetone molecules produced by geminate recombination of the ions in the spurs, or to reaction of the added scavengers also with the excited states. The correct mechanism can be found by studying not only the decrease in the yield of the excited states of anthracene in acetone solution as a function of the scavenger concentration, but including also the study of the rate of formation of anthracene excited states. Let us look at the sequence of reactions induced by radiation in acetone solution of anthracene and a scavenger (S stands for the acetone solvent, A for anthracene and Q for the scavenger-quencher):

$$S^+ + S^- \longrightarrow {}^3S^* \tag{7}$$

$${}^3S^* \xrightarrow{k_\alpha} S \tag{8}$$

$${}^3S^* + A \xrightarrow{k_\beta} {}^3A^* + S \tag{9}$$

$${}^3S^* + Q \xrightarrow{k_\gamma} \text{Products} \tag{10}$$

If all three reactions are involved, the rate of triplet anthracene formation is given by

$$d[{}^3A^*]/dt = (k_\alpha + k_\beta[A] + k_\gamma[Q])[{}^3S^*] = \beta[{}^3S^*] \tag{11}$$

which leads to

$$[{}^3A^*]_t = [S_0]^*\{1 - \exp(-\beta t)\} \tag{12}$$

where β depends linearly on the concentration of Q. However, if reaction 10 is not included β is independent of [Q], and the rate of formation of excited anthracene should not depend on the addition of scavenger. Robinson and Rodgers[16] found that both H_2O (2.8 M) and ethanol (0.25 M) reduced the triplet yield of 10^{-4} M anthracene in acetone solution by a factor of two without affecting the rate of formation. However, 4.6×10^{-3} M nitromethane also reduced the yield of anthracene triplets by a factor of two, but this addition also causes an increase by a factor of two in the rate of formation of the anthracene excited states, indicating that nitromethane reacts not only with the precursors of the excited states but also with the excited acetone molecules.

C. Final Products of Radiolysis of Ketones

The main bond ruptured by γ-radiolysis of carbonyl compounds is the bond next to the carbonyl group. Thus acetone gives mainly hydrogen, CO and methane; diethyl ketone

yields mainly carbon monoxide and ethane, and propionaldehyde breaks down mainly to carbon monoxide, ethane and hydrogen. The γ-radiolysis of liquid acetone was reviewed by Freeman[7] and we will not deal much with it. Matsui and Imamura[36] studied the radiolysis of liquid aliphatic ketones (acetone, methyl ethyl ketone and diethyl ketone) with high linear energy transfer (LET) radiation using accelerated ^4He, ^{12}C and ^{14}N ions as the radiolysis inducing agents with LET up to 80 eV A^{-1}. The radiolytic yields of the main gaseous products, hydrogen and carbon monoxide, were found to increase appreciably with an increase in the LET up to about 50–70 eV $Å^{-1}$, where the radiolytic yield reaches a maximum. The increase with LET is much higher for $G(H_2)$ than $G(CO)$ and hence the ratio of the two yields $G(H_2)/G(CO)$ also increases substantially with an increase in the LET. In γ-radiolysis of acetone, methyl ethyl ketone and diethyl ketone, the addition of a radical scavenger, e.g. I_2, decreased the yields of H_2 and CO by not more than 20%[36–38], indicating that these products are formed in γ-radiolysis mainly in the γ-ray spurs. Therefore in the radiolysis with high LET radiations, as with high-energy charged particles, it is reasonable to assume that H_2 and CO are mainly formed within the dense ionization tracks, via 'molecular' mechanisms. Hydrogen is presumably produced by the abstraction reaction of the hot and/or thermal hydrogen atoms which are formed by fragmentation of the excited ketone molecules and excited ions. Excited acetone molecules can dissociate in one of the following reactions[39]:

$$CH_3COCH_3^* \longrightarrow \begin{cases} \longrightarrow CH_3CO\cdot + CH_3\cdot & \text{(a)} \\ \longrightarrow 2CH_3\cdot + CO & \text{(b)} \\ \longrightarrow CH_3COCH_2\cdot + H & \text{(c)} \end{cases} \qquad (13)$$

Higher temperatures favour more pathway (b) over pathway (a) due to the thermal decomposition of the acetyl radical,

$$CH_3CO\cdot \longrightarrow CH_3\cdot + CO \qquad (14)$$

which has a relatively high activation energy (18 kcal mol^{-1} [40]).

The increase in $G(H_2)$ and $G(CO)$ with an increase of the LET up to $\sim$ 70 eV $Å^{-1}$ can be explained as due to a larger percentage of 'molecular' reactions with increasing LET as described by the spur diffusion model, based on simple competition between the diffusion and reaction of radicals or excited ketone molecules formed in a LET-independent step. However, this model cannot explain the increase in the ratio of the two yields $G(H_2)/G(CO)$ with increasing LET. A probable explanation for this effect is the thermal-spike effect[41]. Burns and Barker[42] estimated the temperature rise in a spherical spur formed by γ-radiolysis (for which Magee found a 50–100 °C rise[43]) and in a cylindrical track and found substantial thermal rise for very high LET radiation. This temperature rise will accelerate the decomposition of alkyl radicals to form H radicals more than the decomposition of the carbonyl radicals due to the higher activation energies of the first process ($C_nH_{2n+1} \rightarrow C_nH_{2n} + H$; $\Delta E \sim 30$ kcal mol^{-1}). However, this explanation of Matsui and Imamura[36] seems improbable for acetone radiolysis, as the reaction $CH_3\cdot \rightarrow CH_2 + H$ is very unlikely to occur; a more probable progress is $2CH_3\cdot \rightarrow C_2H_4 + H_2$ or $CH_3CO\cdot + CH_3\cdot \rightarrow C_2H_4 + H_2 + CO$.

An alternative explanation is the possible formation of highly excited states formed only in the very high LET region. The latter states are decomposed differently from the lower excited states produced in the low LET region.

An interesting finding[36] is that when the product $G(CO) \times dE/dx$, where dE/dx is the linear energy loss (LET), is plotted vs. dE/dx, a saturation is observed above $dE/dx = 50$ eV $Å^{-1}$. This means that the number of CO molecules produced per 100 Å of radiation track reaches saturation. The plateau values for $G(CO) \times dE/dx$ are estimated to be 100 ± 20 molecules per 100 Å.

The number of CO molecules produced should obviously not exceed the number of

ketone molecules decomposed. In the γ-radiolysis of liquid acetone, some oxygen-containing compounds other than carbon monoxide are produced, and their yields are greatly reduced in the presence of a radical scavenger (I_2), indicating that these products are formed in the bulk. In the higher LET region, the yields of these compounds must decrease, and presumably carbon monoxide will be the main oxygen-containing product.

If this assumption is accepted, the number of CO molecules produced in the very high LET region can be said to be approximately equal to the number of ketone molecules decomposed. The nearly saturated curves of $G(CO) \times dE/dx$ vs. dE/dx thus indicate that the numbers of ketone molecules decomposed are limited above the given dE/dx values to about one molecule of ketone per Å of radiation track. The appearance of the maximum $G(CO)$ and $G(H_2)$ vs. dE/dx may be explained on the basis of a saturation phenomenon, which has not been observed for H_2.

Barker and Noble[44] studied the effect of addition of water (up to 0.4% v/v) on the γ-radiolysis of liquid acetone and found that the yields of hydrogen, methane and hexane-2, 5-dione were increased with the addition of water while the yields of carbon monoxide, ethyl methyl ketone and 4-hydroxy-4 methylpentan-2-one were decreased. These effects were explained in terms of ionic reactions, e.g.

$$Me_2C^+OH + H_2O \longrightarrow Me_2CO + H_3O^+ \quad (15)$$

$$Me_2CO^{\ddagger} + H_2O \longrightarrow MeCOCH_2\cdot + H_3O^+ \quad (16)$$

$$Me_2CO^{\mp} + H_2O \longrightarrow Me_2COH\cdot + OH^- \quad (17)$$

Matsui and Imamura[45] studied the effect of addition of H_2O on the radiolysis of liquid acetone both by γ irradiation and by high LET accelerated charged particles bombardment, using higher concentration of water, 2 and 5 wt%. The same yields of all products, within experimental error, were found for 2% and 5% H_2O either for the γ-radiolysis or for the heavy-ion radiolysis. For γ- and He-ion radiolysis Matsui and Imamura[45] used I_2 as a free-radical scavenger to obtain 'molecular' yields while for C and N ion radiolyses it was assumed that even in the absence of I_2, H_2 and CO are formed practically only by 'molecular' processes. In contrast to the results with pure acetone, no peaks of $G(H_2)$ and $G(CO)$ were observed with acetone + water, when G is plotted as a function of dE/dx. For low LET radiation γ-radiolysis the addition of water leads to different results than those obtained by Barker and Noble[44] with regard to carbon monoxide. While Barker and Noble[44] found that addition of 0.4% increases $G(H_2)$ by a factor of 1.27 and decreases CO by a factor of 1.22, Matsui and Imamura[45] found for γ-radiolysis that 2% water in the absence of I_2 increases both $G(H_2)$ and $G(CO)$ as well as CH_4 and C_2H_6 (Barker and Noble found an increase for CH_4 and a decrease for C_2H_6). However, the results in the absence of I_2 as a radical scavenger are due to both radical and 'molecular' processes and cannot be compared with those of heavy-ion radiolysis. In the presence of 1.3×10^{-3} M I_2, the 'molecular' yields of H_2 and CO in γ-radiolysis were decreased due to the addition of H_2O by a factor of about 2, while the yields of the saturated hydrocarbons (CH_4 and C_2H_6) were increased and those of the unsaturated hydrocarbons were practically unaffected. The lowering effect of H_2O on the 'molecular' $G(H_2)$ and $G(CO)$ decreases with increasing LET and, when $dE/dx > 70\,eV\,Å^{-1}$, for $G(H_2)$ the trend is opposite and already increasing with the addition of H_2O; for $G(CO)$ there is no effect and it remains unchanged within the experimental error.

The significant effects of water on the product yields and their LET dependence in the heavy-ion radiolysis was explained by Matsui and Imamura as due to energy transfer from the tracks by H_2O, which form a hydrogen-bonded network among the acetone molecules. The dependence of $G \times dE/dx$ on dE/dx for the pure ketones indicates that, above the critical LET, decomposition takes place only within the tracks which are of limited radii. The excessive energy deposited in the tracks above the critical LET caused the thermal

decomposition of free radicals with high activation energies, or promoted the formation of highly excited states of ketone molecules. Under these conditions some energy is wasted and does not form products, and therefore the yields are reduced with an increase in the LET above the critical value. If the hydrogen-bonded network formed by water added to acetone could serve to transfer the excessive energy from the track toward the bulk, the reaction zone in which acetone molecules can decompose would accordingly expand outside the track core. Thus, the excessive energy, which would be wasted within the limited volume of the track in pure acetone at LET above 50 eV $Å^{-1}$, may be consumed efficiently and the yields may be expected to increase continuously with an increase in LET.

D. Hot Atom Reactions of Acetone

Tsuneyoshi and coworkers[46] studied the reaction of acetone gas with hot atoms (Sb and Sn) produced by recoil due to nuclear reaction. The acetone gas pressure was varied in order to study the mechanism, and the yields of methyl compounds formed by the reaction of hot ^{46}Sb and ^{63}Zn with acetone gas were measured. ^{63}Zn was produced either by Ni(α, xn) or Cu(p, xn) reactions and it was found that the yields are linearly proportional to the pressures up to saturation pressures for both reactions. Comparing the two reactions, the slopes of the yields vs. pressures are inversely proportional to the average range of the ions. Thus it can be concluded that the yields are mainly due to hot atom thermal reactions.

E. Radiolysis of Aqueous Solutions of Carbonyl Compounds

Irradiation of dilute aqueous solutions results in the interaction of the ionizing radiation mainly with water molecules, as their number is much larger than the number of the solute molecules. The radiolysis of water produces hydrated electrons (e^-_{aq}, $G = 2.9$), hydrogen atoms ($G = 0.55$) and hydroxyl radicals ($G = 2.8$) which react with the molecules of the solutes. In addition, the radiolysis of aqueous solutions leads to formation of H_2O_2 ($G = 0.75$), gaseous hydrogen ($G = 0.45$) and hydronium ions (H_3O^+, $G = 2.9$).

The primary radicals can be interconverted or removed by use of specific scavengers, permitting some choice of the radicals reacting in the system and allowing the elucidation of the mechanism of the radiolysis. Thus, the hydrated electron can be converted into hydroxyl radical via

$$e^-_{aq} + N_2O + H^+ \longrightarrow N_2 + \dot{O}H \tag{18a}$$

and to the hydrogen atom

$$e^-_{aq} + H^+ \longrightarrow \dot{H} \tag{18b}$$

Therefore in aqueous N_2O saturated solutions $\dot{O}H$ radicals are the predominant species, while in acidic aqueous solution there are only H and $\dot{O}H$ radicals (a little excess of H atoms).

Hydrated electrons are obtained as predominant radicals by removing the $\dot{O}H$ radicals with *t*-butyl alcohol. The removal of both H and $\dot{O}H$ radicals is accomplished by isopropanol,

$$H(OH) + CH_3CHOHCH_3 \longrightarrow H_2(H_2O) + CH_3\dot{C}OHCH_3 \tag{19}$$

1. Radiolysis of air-free aqueous solution of acetone

The radiolysis of air-free aqueous acetone solutions was first studied by Fricke, Hart and Smith[47]. They found that at pH = 3 the yield of hydrogen as a function of acetone

concentration is a maximum-type curve. The decrease in the yield of H_2 with increasing concentration of acetone beyond the concentration of the maximum was explained by Allen and Scholes[48] as due to the competition of acetone and hydrogen ions on the hydrated electrons. Further studies based on competition kinetics[49] and pulse radiolysis[50] have confirmed that acetone is an excellent scavenger for hydrated electron. Riesz[51-53] studied the yields of various products from the γ-radiolysis of air-free aqueous acetone solutions in neutral and acid solutions over the concentration range of 10^{-3} to 1 M.

The major radiolysis products were identified as hydrogen, hydrogen peroxide, isopropyl alcohol, 2,5-hexanedione and hydroxyacetone. Smaller amounts of pinacol, diacetone alcohol, methane and ethane were also observed. The G values of hydrogen and of 2,5-hexanedione were independent of dose over the range 15–230 krad, while those of isopropyl alcohol, hydroxyacetone and hydrogen peroxide decreased with increasing dose. In both neutral and acid solutions a steady-state concentration, $[H_2O_2]_{ss}$ is reached with increasing dose. With increasing acetone concentration, $[H_2O_2]_{ss}$ decreases markedly in acid solutions but increases slightly in neutral solutions. Since the observed H_2O_2 yields, $G(H_2O_2)_{ss}$ were always lower than the molecular H_2O_2 yield, $G(H_2O_2)$, and since it was shown by control experiments that none of the observed radiolysis products react with H_2O_2 under the conditions of these experiments, it follows that H_2O_2 is removed by reaction with one or more radical intermediates.

In order to identify these intermediates, the effect of adding H_2O_2 to neutral acetone solutions before irradiation was studied. A large decrease of the isopropyl alcohol yield and an approximately equal increase of the 2,5-hexanedione yield occur in neutral solutions of 0.1 M acetone. As the H_2O_2 concentration falls to the stationary-state concentration, the slopes of the isopropyl alcohol and 2,5-hexanedione yields approach those obtained in the absence of added H_2O_2. These results show that H_2O_2 is removed by reaction with the radical precursor of isopropyl alcohol but not with the acetonyl radical which is the logical radical precursor of 2,5-hexanedione. In agreement with this inference, it was found that a plot of the sum of the yields of isopropyl alcohol plus the difference between observed and molecular H_2O_2 yields (ΔH_2O_2) is a linear function of the dose. In 10^{-2} M acetone at pH 1.2, the G value for hydrogen is 3.2 and no isopropyl alcohol can be observed. With increasing acetone concentration at this pH, the H_2 yield falls and the isopropyl alcohol yield rises, approaching the values for neutral solutions. This behaviour is consistent with the assumption that hydrated electrons react with acetone to form an anion radical which leads to isopropyl alcohol. In acid solutions the hydrogen ions compete with acetone for hydrated electrons, converting them to hydrogen atoms, which react principally to give H_2 and acetonyl radicals. If H_2O_2 is removed by the radical precursor of isopropyl alcohol which is produced by the reaction of e_{aq}^- with acetone, the steady-state H_2O_2 concentration at pH 1.2 should decrease with increasing acetone concentration. Riesz[53] found really that at acidic pH the steady-state concentration of H_2O_2, $[H_2O_2]_{SS}$, decreased with increasing acetone concentration. It also follows from the proposed competition that at a fixed acetone concentration the hydrogen yield should fall and that of isopropyl alcohol plus ΔH_2O_2 rise with increasing pH. This was proven to be true[53]. In dilute acetone solutions the 2,5-hexanedione yields are larger at pH 1.2 than at neutral pH; this difference disappears at higher acetone concentrations. Such a result is to be expected if acetonyl radicals are produced by the reaction of hydrogen atoms and hydroxyl radicals, but not of hydrated electrons, with acetone. At high acetone concentrations, the reaction of hydrated electrons with hydrogen ions to give hydrogen atoms is suppressed even in the acid solutions. The G value for pinacol from 0.2 M acetone solutions at pH 1.2 irradiated with a dose of 0.16 Mrad is approximately 0.05. No pinacol was found from neutral solutions. The value of G for diacetone alcohol from 0.1 M neutral acetone solutions is about 0.06 at a dose of 0.6 Mrad. These small yields do not contribute

significantly to the material balance, but they demonstrate the presence of the 2-hydroxy-2-propyl radical in these solutions.

The amounts of methane and ethane produced by radiation are directly proportional to dose and acetone concentration, and are independent of pH. The G values for 'direct' products, methane and ethane, from 1 M acetone solutions are 0.22 and 0.0039, respectively, similar to the values obtained for liquid acetone by Barker[54]. Riesz[53] explained his results by the following set of reactions:

$$
\begin{aligned}
&H_2O \longrightarrow e_{aq}^-,\ H_3O^+,\ H,\ \dot{O}H,\ H_2,\ H_2O_2 && \text{(a)}\\
&e_{aq}^- + H_3O^+ \longrightarrow H + 2H_2O && \text{(b)}\\
&e_{aq}^- + (CH_3)_2CO \longrightarrow (CH_3)_2CO^{\cdot -} + H_2O && \text{(c)}\\
&(CH_3)_2CO^{\cdot -} + H_3O^+ \longrightarrow (CH_3)_2\dot{C}OH + H_2O && \text{(d)}\\
&(CH_3)_2\dot{C}OH + H_2O_2 \longrightarrow (CH_3)_2CO + H_2O + \dot{O}H && \text{(e)}\\
&2(CH_3)_2\dot{C}OH \longrightarrow (CH_3)_2CHOH + (CH_3)_2CO && \text{(f)}\\
&(CH_3)_2\dot{C}OH + (CH_3)_2CO \longrightarrow (CH_3)_2CHOH + CH_3CO\dot{C}H_2 && \text{(g)}\\
&H + (CH_3)_2CO \longrightarrow H_2 + CH_3CO\dot{C}H_2 && \text{(h)}\\
&H + (CH_3)_2CO \longrightarrow (CH_3)_2\dot{C}OH \text{ or } (CH_3)_2CHO\cdot && \text{(i)}\\
&\dot{O}H + (CH_3)_2CO \longrightarrow CH_3CO\dot{C}H_2 + H_2O && \text{(j)}\\
&\dot{O}H + (CH_3)_2CO \longrightarrow (CH_3)_2C(OH)O\cdot && \text{(k)}\\
&(CH_3)_2C(OH)O\cdot + R\cdot \longrightarrow CH_3COCH_2OH + RH && \text{(l)}\\
&2CH_3CO\dot{C}H_2 \longrightarrow CH_3COCH_2CH_2COCH_3 && \text{(m)}\\
&CH_3CO\dot{C}H_2 + (CH_3)_2\dot{C}OH \longrightarrow CH_3COCH_2C(OH)(CH_3)_2 && \text{(n)}\\
&2(CH_3)_2\dot{C}OH \longrightarrow (CH_3)_2C(OH)C(OH)(CH_3)_2 && \text{(o)}\\
&CH_3COCH_2OH + R\cdot\text{—unidentified products} && \text{(p)}
\end{aligned}
\qquad (20)
$$

An essential feature of the mechanism, that hydrated electrons lead to a radical precursor of isopropyl alcohol (reaction c), is clearly demonstrated by the effect of adding n-propyl alcohol to neutral acetone solutions before radiolysis. Alcohols are known to be efficient scavengers for H and OH radicals, but to be very unreactive toward hydrated electrons. It was found that n-propyl alcohol almost completely suppresses the formation of 2, 5-hexanedione but does not decrease the isopropyl alcohol yield.

Isopropyl alcohol formation at low acetone concentration (10^{-2} M) occurs almost entirely by the disproportionation of 2-hydroxy-2-propyl radicals (reaction f), while at high acetone concentration (0.5 M) isopropyl alcohol is made by the reaction of 2-hydroxy-2-propyl radicals with acetone (reaction g). That reaction f contributes very predominantly in 0.1 M neutral acetone can be seen from the effect of adding H_2O_2 before radiolysis. Reactions g and e followed by j both lead to approximately the same number of acetonyl radicals in neutral solution, since only a very small reaction of the OH radicals is removed by reaction k.

Nelson[55] studied the products and the mechanism of reaction of radiolysis of aqueous (D_2O) acetone using CIDNP and FT-NMR. Nelson found in radiolysis of acetone in D_2O, by FT-NMR spectra, deuterated acetone and 2-propanol as major products and 2, 5-hexanedione and hydroxyacetone as minor radiolytic products. In some experiments carried out on the radiolysis of neutral aqueous acetone solutions, 1-methylethenol, the enol of acetone, was also observed. Riesz[53] presented kinetic arguments which suggested that hydroxyacetone is not formed from the reaction of OH· and the acetonyl radical. The CIDNP data suggest[55] that the enol of acetone is a major product of aqueous acetone radiolysis and hence its concentration might be much higher than the equilibrium

concentration of the enol, and hydroxyacetone can be formed by the addition of OH to the enol.

$$\begin{array}{l} \mathrm{OH} \\ | \\ \mathrm{CH_3C{=}CH_2} \end{array} + \mathrm{OH\cdot} \longrightarrow \begin{array}{l} \mathrm{OH} \\ | \\ \mathrm{CH_3\dot{C}{-}CH_2OH} \end{array} \xrightarrow[-\mathrm{H}]{} \mathrm{CH_3COCH_2OH} \qquad (20q)$$

2. Radiolysis of aqueous solutions of aldehydes

The products of radiolysis of aqueous formaldehyde were studied very early by Fricke and coworkers[47] and the study was extended by Marcovic and Sehested[56]. Fricke measured the hydrogen yield in a 10 mM formaldehyde solution at pH 1–11. For pH < 3, $G(H_2)$ is constant and its value suggests that the only reaction of H atoms is

$$\mathrm{H + CH_2O \longrightarrow H_2 + \dot{C}HO} \qquad (21)$$

or rather the reaction with the hydrate of formaldehyde

$$\mathrm{H + CH_2(OH)_2 \longrightarrow H_2 + \dot{C}H(OH)_2} \qquad (22)$$

At pH > 3 Fricke found a decrease of $G(H_2)$ which was explained later by the competition of H^+ and formaldehyde on the hydrated electron. Fricke found that the irradiation leads to a decrease in the pH, probably due to formation of formic acid by disproportionation of the formyl radicals.

$$\mathrm{2\dot{C}H(OH)_2 \longrightarrow HCOOH + CH_2(OH)_2} \qquad (23)$$

Formaldehyde is practically completely hydrated in water[57] and this is probably true also for the formyl radical which exists as $\mathrm{\dot{C}H(OH)_2}$ rather than ĊHO. Markovic and Sehested[56] measured the yield of formic acid in the radiolysis of aqueous solutions of formaldehyde by determining the change of the pH.

Both groups' results for $G(H_2)$ agree for pH $\leqslant 3$ for which it equals $G_{H_2} + G_H + G_{e_{aq}^-}$, where $G(H_2)$ is the experimental yield of molecular hydrogen and G_{H_2}; G_H and $G_{e_{aq}^-}$ are the primary yields of molecular hydrogen, atomic hydrogen and hydrated electrons in the radiolysis of pure water. However, for higher pH Markovic and Sehested found lower yields than Fricke's group. For pH = 6.8 it is equal within experimental error to $G_{H_2} + G_H = 0.55 + 0.45 = 1.0$. From the decrease of $G(H_2)$ with increasing pH ~ 3, the rate constant of the hydrated electron with $CH_2(OH)_2$ relative to its reaction with H^+ can be calculated. A more direct way is by following the e_{aq}^- absorption at 650 nm as was done[56] for 65 mM formaldehyde solution, argon saturated at pH 7, giving $k = 1 \times 10^7\ \mathrm{M^{-1}\,s^{-1}}$. Gordon and colaborators[58] measured earlier, under the same conditions, $k < 1 \times 10^7\ \mathrm{M^{-1}\,s^{-1}}$. This rate constant for the e_{aq}^- reaction is much lower than that for the reaction of e_{aq}^- with acetaldehyde for which a rate constant of $3.5 \times 10^9\ \mathrm{M^{-1}\,s^{-1}}$ was found[58]. This is due to the fact that while formaldehyde is completely hydrated, only about half of the acetaldehyde molecules are hydrated ($K = 1.06$[59]). The hydrated electron reacts very fast with the carbonyl group by addition to the carbonyl bond, but very slowly with alcohols, and formaldehyde in water has practically no carbonyl bond. Acetaldehyde reacts with e_{aq}^- almost as fast as acetone, $6.5 \times 10^9\ \mathrm{M^{-1}\,s^{-1}}$ [60]. Considering that acetaldehyde is only about 50% in the carbonyl form, the rate constant for acetaldehyde is almost the same as for acetone. Buxton and coworkers[60] corrected the value of Gordon[58] for the fraction of the diol form and obtained $5.4 \times 10^9\ \mathrm{M^{-1}\,s^{-1}}$. Duplatre and Jonah[61] found for the reaction $e_{aq}^- + \mathrm{CH_3CHO}$ a rate constant of $4.4 \times 10^9\ \mathrm{M^{-1}\,s^{-1}}$.

On the other hand, OH radicals react much faster with alcohols than with carbonyl groups and hence the rate constants for the reaction of OH with formaldehyde and

acetaldehyde (7×10^8 and 5×10^8) are about an order of magnitude larger than for the reaction with acetone ($7 \times 10^7\ M^{-1}\ s^{-1}$).

$$\dot{O}H + CH_2(OH)_2 \longrightarrow H_2O + \dot{C}H(OH)_2 \tag{24}$$

Markovic and Sehested[56] studied the yield of formic acid in N_2O-saturated aqueous solution of 20 mM formaldehyde at pH 5–6. (N_2O converts the e^-_{aq} to OH radicals.) The radiolytic yield was constant up to 50 krad giving $G(HCOOH) = 2.5$ for the highest dose rate used (1 μs pulse, highest dose 8 krad/pulse). This is lower than can be expected from reactions 21–24, for which

$$G(HCOOH) = 0.5 \times (G_H + G_{e^-_{aq}} + G_{OH}) = 3.0 \tag{25}$$

This discrepancy indicates that some of the formyl radicals combine rather than disproportionate and produce glyoxal (with $G = 0.5$).

$$2\dot{C}H_2OH \longrightarrow (CH_2OH)_2 \longrightarrow HC(O)—C(O)H \tag{26}$$

At the high dose rate obtained with electron accelerator pulses, a small amount of glyoxal was identified but was not determined quantitatively, and an approximate G(glyoxal) of 0.1 was estimated[56].

Decreasing the dose rate leads to an increase of $G(HCOOH)$ which means that HCOOH can be formed also by a reaction of the formyl radical with formaldehyde, probably by the reaction

$$\dot{C}H(OH)_2 + CH_2(OH)_2 \longrightarrow HCOOH + \dot{C}H_2OH + H_2 \tag{27}$$

For low dose rate (^{60}Co irradiation) $G(HCOOH) = 6.05$ (in accordance with reaction 27) and no glyoxal was found. From the dose-rate dependence of $G(HCOOH)$ Markovic and Sehested found $k_{27} = 5 \times 10^5\ M^{-1}\ s^{-1}$. The formic acid yield in argon-saturated solutions of formaldehyde at pH = 5 irradiated in the ^{60}Co system is $G(HCOOH) = 4.3$ instead of 6.05 as measured in N_2O-saturated solution, indicating that the radical formed in the reaction of e^-_{aq} with formaldehyde is different from formyl radicals and does not give formic acid in a subsequent reaction.

The rate of disappearance of the formyl radical in pulse radiolysis was studied (at 230 nm where the peak of the formyl radical was observed) and was found to be of second order, with $2k_{23}/\varepsilon = 2.02 \times 10^6$, where ε is the molar absorption of the formyl radical at this wavelength. Using $\varepsilon_{230} = 520\ M^{-1}\ cm^{-1}$ it was found that $2k_{23} = 1.06 \times 10^9\ M^{-1}\ s^{-1}$.

Kalyazin and coworkers[62] studied the yield of the various products in the radiolysis of an aqueous solution of acetaldehyde and the results are given in Table 1 for a dose of 234 krad. The relatively high yield of biacetyl $(CH_3CO)_2$ indicates that at room

TABLE 1. Radiolytic yields (G = molecules/100 eV) of various products in the γ-radiolysis of aqueous solutions of acetaldehyde at room temperature (dose = 234 krad)

Acetaldehyde concentration	Products				
(M)	CO	CH_4	$CH_3COCOCH_3$	C_2H_5OH	CH_3COOH
0.5	0.6	0.5	1.5	2.5	2
1.0	0.7	0.7	1.8	4	3.8
2.0	1.2	1.1	2.0	6	6.2
3.0	1.4	1.3	—	—	—
4.0	—	—	2.3	10	11

temperature the acetyl radical is quite stable in aqueous solution. At elevated temperature the acetyl radical will decompose to a larger extent and the values of $G(CO)$ and $G(CH_4)$ at 120 °C for 3 M acetaldehyde solution are approximately 9 and 6.5, respectively. These high yields indicate that acetaldehyde is decomposed via a chain mechanism:

$$H(OH) + CH_3CHO \longrightarrow H_2(H_2O) + CH_3CO\cdot$$

$$CH_3CO\cdot \longrightarrow CH_3\cdot + CO \tag{28}$$

$$CH_3\cdot + CH_3CHO \longrightarrow CH_4 + CH_3CO\cdot \tag{29}$$

This mechanism suggests the same yield for CH_4 and CO, however the yield of CO was found to be higher (at all concentrations and both at room temperature and at 120 °C). Ethane was not found[62] as one of the products so $CH_3\cdot$ cannot disappear by combination of two methyl radicals. The most probable extra route for CH_3 is by addition to the carbonyl bond as was found for other alkyl radicals[63].

$$CH_3\cdot + CH_3CHO \longrightarrow (CH_3)_2CHO\cdot \tag{30}$$

$$(CH_3)_2CHO\cdot + CH_3CHO \longrightarrow (CH_3)_2CHOH + CH_3CO\cdot \tag{31}$$

Ethanol and acetic acid are produced from the γ-radiolysis of the diol form (hydrated form) as was found for γ-radiolysis of formaldehyde[56,64]. The high yields are characteristic of chain processes

$$H(OH) + CH_3CH(OH)_2 \longrightarrow CH_3\dot{C}(OH)_2 + H_2(H_2O) \tag{32}$$

$$CH_3\dot{C}(OH)_2 + CH_3CH(OH)_2 \longrightarrow CH_3\dot{C}HOH + CH_3COOH + H_2O \tag{33}$$

$$CH_3\dot{C}HOH + CH_3CH(OH)_2 \longrightarrow CH_3CH_2OH + CH_3\dot{C}(OH)_2 \tag{34}$$

The $CH_3\dot{C}HOH$ radical is formed also from the hydrated electron reacting with the aldehyde form

$$CH_3CHO + e^-_{aq} \longrightarrow CH_3CHO^{\cdot -} \xrightarrow{H_2O} CH_3\dot{C}HOH + OH^- \tag{35}$$

Nelson[55] studied the pulse radiolysis of an aqueous solution of acetaldehyde using CIDNP/FT-NMR as a mechanistic probe. He found that the main radicals are $CH_3\dot{C}HOH$ and $CH_3\dot{C}(OH)_2$ while the contribution of the acetyl radical reaction to the products is more limited. They found an additional minor product, acetoin, which was identified only in neutral solutions.

3. *Radiolysis of oxygenated aqueous solutions of acetone*

Zagota and coworkers[65] studied the radiolysis, both by a ^{60}Co gamma source and by electron accelerator pulse radiolysis of aqueous solution, of acetone in the presence of O_2. The solution contains also N_2O(N_2O:O_2 4:1 v/v in the gaseous phase, but the concentration of N_2O in the aqueous phase is ten times higher owing to the higher solubility of N_2O in water). Most of the e^-_{aq} were converted to OH; the e^-_{aq} reacting with O_2 lead to the superoxide anion

$$e^-_{aq} + O_2 \longrightarrow O_2^{\cdot -} \tag{36}$$

At acidic pH, O_2^- reacts with H^+ to give the $H\dot{O}_2$ radical which has a pK_a of 4.7[66]. The OH radicals react with acetone as described previously, abstracting hydrogen atoms.

$$\cdot OH + CH_3COCH_3 \longrightarrow H_2O + \cdot CH_2COCH_3 \tag{37}$$

However in the presence of oxygen the acetonyl radicals react with oxygen, rather than

reacting between themselves or with other radicals, to give the corresponding acetonylperoxyl radicals.

$$\cdot CH_2COCH_3 + O_2 \longrightarrow \cdot O_2CH_2COCH_3 \tag{38}$$

As the reaction of H atoms with acetone is much slower than their reaction with oxygen (2×10^6 vs. $1.9 \times 10^{10}\,M^{-1}s^{-1}$ [60]), hydrogen atom forms the $HO_2\cdot$ radical which is fully dissociated to the superoxide anion radicals (O_2^-) in neutral and basic solutions.

The main products in the radiolysis of an oxygenated aqueous solution (saturated with N_2O/O_2, 4:1 v/v in the gas phase) of 10^{-3} M acetone are methylglyoxal ($G = 2.5$), hydroxyacetone (0.5), formaldehyde (1.6), acids (1.7), organic hydroperoxide (0.4), H_2O_2 (2.2) and CO_2 (0.5). The yield of organic hydroperoxides was much increased in 10^{-1} M acetone, but for this high acetone concentration the N_2O concentration was not sufficient to scavenge the hydrated electrons, hence G(organic hydroperoxide) = 1.3 and $G(H_2O_2) = 1.6$ were found.

Pulse radiolysis of oxygen-free solutions with conductometric measurements did *not* show[65] any formation of acid, thus excluding the addition of OH to the carbonyl double

$$\dot{O}H + CH_3COCH_3 \not\rightarrow CH_3CO(OH)CH_3 \rightarrow CH_3COOH + \dot{C}H_3 \tag{39}$$

bond, and leaving H-abstraction as the only reaction of the OH radical with acetone. Pulse radiolysis with conductometric measurements carried out in a N_2O/O_2-saturated solution of acetone (2×10^{-3} M, pH = 6.5) showed an immediate increase of conductivity with G(acid) = 0.4, which is attributed to the formation of H^+/O_2^- from $HO_2\cdot$.

In an N_2O/O_2-saturated basic solution of acetone, the conductivity of the solution was observed to decrease in two kinetically distinguishable steps. The faster one is attributed to the formation of methylglyoxal in the bimolecular decay of the acetonylperoxyl radical, and the slower decrease is ascribed to the OH^--induced hydrolysis of CO_2.

Acetonyl radical (formed in O_2-free solution) is a strong oxidizer like other β-oxoalkyl radicals and oxidizes *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (TMPD) with a rate constant of $1.2 \times 10^9\,M^{-1}s^{-1}$, while the acetonylperoxyl radical reacts with TMPD much slower, with a rate constant of $6 \times 10^7\,M^{-1}s^{-1}$.

Most of the products are formed by bimolecular reactions of two acetonylperoxyl radicals. It is not clear if the reaction proceeds through formation of an unstable tetroxide intermediate[67], which later decomposes unimolecularly with emission of an oxygen molecule, or if the two radicals lose an oxygen molecule in a concerted four-center reaction. However, this has no effect on the products. The possible reactions which can explain the observed products are shown in equations 40 and 41[65].

$$2CH_3COCH_2O_2\cdot \longrightarrow \begin{cases} \xrightarrow{a} O_2 + CH_3COCH_2OH + CH_3COCHO \\ \xrightarrow{b} 2CH_3COCHO + H_2O_2 \\ \xrightarrow{c} 2CH_2O + 2CH_3\dot{C}O + O_2 \\ \xrightarrow{d} 2CH_3COCH_2O\cdot + O_2 \end{cases} \tag{40}$$

$$2CH_3COCH_2O\cdot \longrightarrow \begin{cases} \xrightarrow{a} 2CH_2O + 2CH_3\dot{C}O \\ \xrightarrow{b} 2CH_3C\dot{O}HOH \xrightarrow{2O_2} 2HO_2\cdot + 2CH_3COCHO \\ \xrightarrow{c} (CH_3COCH_2O)_2 \\ \xrightarrow{d} CH_3COCH_2OH + CH_3COCHO \end{cases} \tag{41}$$

The acetyl radical CH_3CO reacts further:

$$\begin{aligned} CH_3CO\cdot + O_2 &\longrightarrow CH_3CO_3\cdot \\ 2CH_3CO_3\cdot &\longrightarrow O_2 + 2CO_2 + 2CH_3\cdot \end{aligned} \tag{42}$$

The major product of methyl radicals under oxygenated conditions is formaldehyde[68]. The organic peroxidic products are due both to reaction 41c as well as to reaction of $O_2^{\cdot-}$.

In $O_2^{\cdot-}$ saturated 10^{-1} M acetone solutions, solvated electrons are mainly scavenged by acetone. The resulting ketyl radical reacts rapidly with oxygen and subsequently eliminates $H\dot{O}_2/O_2$. Compared to N_2O/O_2-saturated solutions the acetonylperoxyl radical yield is halved while $O_2^{\cdot-}$ is now the most abundant species. Under such conditions 47% of the acetonylperoxyl radicals are converted into organic hydroperoxides.

4. *Radiolysis of aqueous solutions of acetylacetone (AA)*

Acetylacetone (2,4-pentanedione, AA) is an important substrate mainly due to its keto–enol tautomerism, which makes available for reaction both C=C and C=O double bonds. Broszkiewicz and coworkers[69] studied the pulse radiolysis of an aqueous solution of AA in which it exists in three different forms:

ketone	$CH_3COCH_2COCH_3$
enol	$CH_3COCH{=}COH{-}CH_3$
enolate	$CH_3COCH{=}C(O^-)CH_3 + H^+$

The pK_a value for the enol dissociation is 8.14[70], or 8.8 ± 0.2[69]. The results of optical absorbance and conductivity measurements lead to the following conclusions: (a) OH radicals do not react with the keto form of acetylacetone due to their faster reaction with the enol form and the fast keto–enol equilibrium. (b) OH radicals react with both the enol and the enolate with diffusion-controlled rates, and most of the OH radicals add to the C=C double bond. (c) OH reacts with enolates to produce OH^-.

ESR studies of *in situ* radiolyses of solutions at pH < 1 and at pH between 7 and 9 show a spectrum consisting of a septet of a doublet with hyperfine constants of 18.5 and 2.23 *G*, respectively, which was assigned[69] to the $CH_3COCHCOCH_3$ radical. The radical formed by the addition of the OH to the double bond was observed using a chemical method of formation of $OH(Ti^{+3} + H_2O_2)$[71] but was not observed in pulse radiolysis, possibly because of the higher concentration of the radicals produced by chemical generation.

5. *Radiolysis of aqueous solutions of aromatic ketones*

OH and H atom can both react with benzene rings to produce cyclohexadienyl radicals and also react with the non-cyclic parts of the molecules to form other radicals.

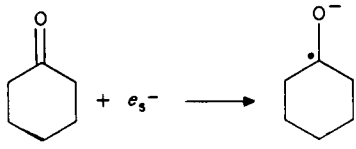
The pulse radiolysis irradiation of a deaerated aqueous alkaline solution of acetophenone (pH = 13) leads to the formation of an optical absorption spectrum with peaks at 315, 370 and 440 nm[72–74]. Using OH scavengers Adams and collaborators[72] showed that the absorption band with $\lambda_{max} = 370$ nm is due to the reaction of OH radicals with acetophenone. The bands with peaks at 315 and 440 nm are due to reactions of the hydrated electron and were ascribed[73] to the ketyl ion-radical. Hayon and coworkers[73] assumed that both these bands belong to the same short-lived intermediates. However, Pribush and Brusnetseva[74] found that the ratio $\varepsilon_{315}/\varepsilon_{440}$ derived from spectrophotometrical data differs from the same ratio obtained from the bimolecular decay of the absorption, indicating that these two peaks belong to different species. Other observations, e.g. in oxygenated solutions, also show[74] that two different intermediates are the origin of these two bands. The saturation of the solution with oxygen causes no changes in

the absorption spectrum within the range of 240–800 mn, immediately after the pulse. However, the tatio D_{315}/D_{440} decreases with increase in oxygen concentration. Also, the half-life of the optical absorption at 315 nm and 440 nm differs considerably. In 10^{-3} M solution of acetophenone, saturated with O_2 and containing 10^{-2} M of sodium formate, the reaction of a hydrated electron with acetophenone results in the formation of short-lived species with only one band at 440 nm, with a rate of formation of $1.6 \times 10^{10}\,M^{-1}\,s^{-1}$, while the rate of formation of the 315 nm absorbing species is only $2–4 \times 10^{9}\,M^{-1}\,s^{-1}$. Pribush and Brusnetseva[74] suggested, according to the molecular diagrams, that e_{aq}^- will react faster with carbons of the carbonyl group than with aromatic ones and hence propose that the 440 nm absorbing radical is due to interaction of e_{aq}^- with the carbonyl group while the reaction with the aromatic ring leads to formation of the intermediate absorbing at 315 nm.

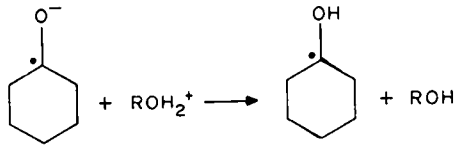
The pulse radiolysis studies of a deaerated aqueous acidic solution of acetophenone (pH = 2) leads to two absorption peaks at 340 and 370 nm[74]. The optical band with λ_{max} at 370 nm belongs to the OH adduct with acetophenone, while that at 340 nm is due to reaction of hydrogen atoms with the aromatic ring (both products are cyclohexadienyl radicals).

F. Radiolysis of Isopropanol Solutions of Ketones

Several works were conducted on the radiolysis of ketones in 2-propanol solutions[75–84]. The radiolysis of 2-propanol lead to the formation of solvated electron (e_s^-), H atoms, $\dot{C}H_3$, $\dot{C}H(CH_3)_2CH_3\dot{C}HOH$, $(CH_3)_2\dot{C}OH$ and $(CH_3)_2CHO\cdot$ and several studies were performed on the reactions of these species with benzophenone, cyclohexanone and furanyl ketones. The γ-radiolysis of pure 2-propanol gave as final products hydrogen, methane, acetone, acetaldehyde and 2,3-dimethyl-2,3 butanediol (pinacol)[85]. Addition of ketones modifies the yields of all these compounds and simultaneously gives rise to additional products. In the case of cyclohexanone these are cyclohexanol, 2-cyclohexanonyl cyclohexanone and 3-(2-hydroxy-2-propyl) cyclohexanone[78]. Alipour and coworkers[78] measured the radiolytic yields of all the main products for various mixtures from pure 2-propanol to neat cyclohexanone. Similar studies were carried out also for various substituted cyclohexanones. Scavenger studies show that the radioreduction of both cyclohexanone and benzophenone is due to the reaction of solvated electrons (equations 43–45).



(43)



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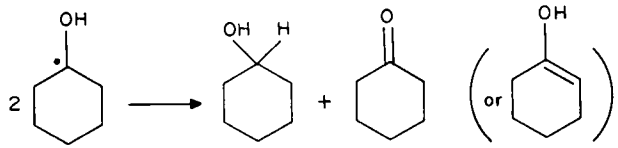
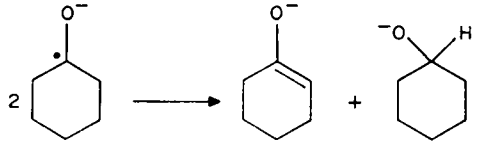


(45)

The presence of the hydroxycyclohexyl radical was confirmed by radical trapping with 1-hexane[78]. The decay curves of the solvated electron yield a rate constant for the reaction of the solvated electron with cyclohexanone of $4.5 \times 10^9\ M^{-1}\ s^{-1}$, only slightly lower than in aqueous solution[86,87] ($7.8 \times 10^9\ M^{-1}\ s^{-1}$). This rate constant is almost equal to the diffusion rate constant in isopropanol ($4.6 \times 10^9\ M^{-1}\ s^{-1}$). The yield of cyclohexanol should be half that of the solvated electron. As $G(e_s^-)$ is usually lower than 4, G(cyclohexanol) should be $\leqslant 2$. This is the case for dilute solutions with concentrations of cyclohexanone below 0.1 M. Since the yield of cyclohexanol is above 2 for higher cyclohexanone concentrations, another reaction leading also to cyclohexanol should be considered, and the efficiency of this reaction should increase with the concentration of the ketone. Aripour[78] suggested the sequence of reactions 46 and 47 of the radical anions of cyclohexane, formed from its reaction with e_s^-.



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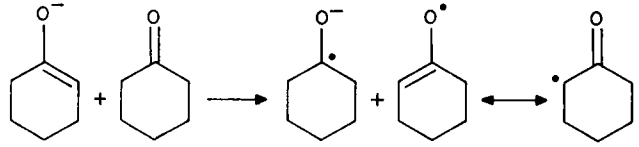

(47)

(A)

The total stoichiometry of both reactions shows that each radical-anion forms one alcoholate when there is sufficient ketone concentration. The dimerization of radical (A) explains the formation of the diketones, observed experimentally.

G. Formation of Aldehydes and Ketones from Small Molecules by Radiolysis

Sugimoto[88] studied the γ-ray and electron-beam induced reaction of carbon monoxide and hydrogen and found several types of products, the main products being formaldehyde and acetaldehyde. The amounts of the aldehydes increased almost linearly with increasing dose. The amounts obtained in γ-radiation per unit dose are much smaller than in the electron-beam experiments. This result might be due to the fact that the dose rate in the electron-beam irradiation was 4500 times larger than in the γ-radiation. For glyoxal, almost identical conversion-dose curves were obtained for electron beam and γ-irradiation, and a similar result was obtained for biacetyl. On measuring the yield of the products as a function of the composition of the CO–H_2 mixture it was found that acetaldehyde and biacetyl have a maximum G value at CO content of 50 mol% (G values of 0.8 and 0.004, respectively) while the maximum G value for formaldehyde is at about 15 mol% CO ($G = 1.3$). The yields of formaldehyde and acetaldehyde decrease with increasing irradiation temperature, possibly due to thermal decomposition of the products or of the intermediates yielding these products. The amount of propionaldehyde increases with increasing temperature. Addition of small amounts (0.011 mol%) of ammonia decreases the yield of all aldehydes, indicating that they are formed via ionic precursors[89].

Dyer and Moore[90] studied the radiolysis of mixtures of gases based on carbon dioxide together with CO (0.25 to 2.0 v/v), methane (60–760 vpm), hydrogen (380–1400 vpm) and water ($\sim$50 vpm). These mixtures are important due to the use of CO_2-based gas

mixtures as coolants in advanced gas-cooled nuclear reactors and the radiolysis reactions occurring in them. The main products are ethane, ethene, propane and propene, but small amounts of acetaldehyde and acetone together with C-4 alkanes and alkenes were also formed. At low dose a comparatively large amount of acetaldehyde was found, however in several other experiments in different conditions it was not found. Acetone was detected in most experiments. The presence of both acetaldehyde and acetone was substantially increased by the presence of graphite. The authors suggest that this is probably due to the graphite entering into the production process, perhaps via a surface oxide.

III. RADIATION CHEMISTRY OF ALKENES

The data on the radiation chemistry of alkenes is vast and a book on the radiation chemistry of hydrocarbons[91] includes almost 150 pages on the radiation chemistry of alkenes and cycloalkenes, without treating the radiation-induced polymerization of alkenes or the radiation chemistry of aqueous solution of alkenes. Due to the limited scope of this chapter on the one hand and the wish to also include some aspects of polymerization and the radiation chemistry of aqueous solution on the other, only a small part of the available scientific information is given in this chapter. However, the main subjects are treated and the main references cited.

A. Initial Processes

Platzman[92,93] in his theory of the initial processes in radiolysis assumed that when a polyatomic molecule AB is receiving energy of radiation, this energy may be utilized in two ways: (a) in a direct ionization with probability δ, or (b) in the formation of a molecule in a super-excited state (a term introduced by Platzman to indicate a molecule whose energy content is larger than that required for ionization) with probability $(1-\delta)$. This super-excited state can give either pre-ionization or dissociation, Platzman[92] suggested that the probability δ is much less than unity and there is real formation of super-excited states. Hatano[94] calculated the yield of the super-excited molecules and the consequent dissociation (values of g_d, number of dissociations per 100 eV energy absorbed) for some hydrocarbons. He used the optical approximation introduced by Platzman[93] assuming that the yield g_d is proportional to the square of the dipole-matrix element M_d calculated from the optical spectra:

$$AB \longrightarrow AB^+ + e^- \tag{48}$$

$$AB \longrightarrow AB^{**} \tag{49}$$

$$AB^{**} \longrightarrow \begin{cases} AB^+ + e^- \\ A\cdot + B\cdot \end{cases} \tag{50}$$

$$M_d^2 = \int_I^\infty [1-\eta(E)]\frac{R}{E}\frac{df}{dE}\,dE \tag{51}$$

where E is the excitation energy, R the Rydberg energy, I the ionization energy, df/dE the differential oscillator strength and $\eta(E)$ is the probability of ionization upon excitation at energy E. Table 2 summarizes the data for the W values, the average energy required for the formation of an ion-pair[95,96], and the g_d values for several olefins.

In the gaseous phase about one half of the absorbed energy leads to product of excited states while the other half results in the formation of ions. The ion yield in the radiolysis of gaseous unsaturated hydrocarbons is almost constant and independent of the number of carbon atoms or the structure of the alkene and is about the same for monoalkenes and

TABLE 2. Values of W and g_d for various alkenes

Alkene	W (eV)	g_d
C_2H_4	26.1 ± 0.2	1.0
C_3H_6	24.8 ± 0.2	0.8
$1\text{-}C_4H_8$	24.2 ± 0.4	0.7

dienes (4.0–4.3[95–99]). This is about the same value as for alkanes. The situation is different concerning the free-ion yield in the liquid phase (G_{fi})[100,101], which varies considerably with the molecular structure of the alkene. Thus, for instance, G_{fi} for 2, 2-dimethyl-2-butene is 0.44 compared to 0.10 for its isomer 1-hexene, and G_{fi} for *cis*-2-butene is 0.23 whereas for the *trans* isomer it is only 0.08. The yield of the free ion increases with increase in temperature. The value of G_{fi} is lower for alkenes than for alkanes (probably due to reactions with the double bond), but G_{fi} for alkenes is higher than for the corresponding alkynes.

Under the effect of ionizing radiation, alkenes are excited electronically to various levels. The excited states of lowest energies are the spin-forbidden triplet states (~ 4 eV for monoalkenes and ~ 3 eV for dienes). These states are formed directly in very low yield but they are formed more in indirect processes due to the high cross-section for intersystem-crossing. Okazaki and coworkers[102] calculated theoretically the yield of singlet and triplet excitation of monoalkenes by ionizing radiation and found that the yield of singlet excited states is 2.3 for all monoalkenes except for ethylene, for which the yield is about 5.0. The yield of the triplet excitation is about 1.5–1.7 for all monoalkenes.

B. Initial Intermediates

Fessenden and Schuler[103,104] studied the ESR spectra of γ-irradiated ethylene in the liquid phase at various temperatures between the melting point (-169 °C) and the boiling point (-104 °C). At low temperature the ESR spectrum fits that of ethyl radicals together with vinyl radicals. At higher temperatures (-133 °C) the lines of the vinyl radical disappear and nine lines typical of n-alkyl radicals appear. They are ascribed to 3-butenyl radicals formed by a very fast addition reaction of the vinyl radicals to ethylene,

$$CH_2{=}CH\cdot + CH_2{=}CH_2 \longrightarrow CH_2{=}CH{-}CH_2{-}CH_2\cdot \qquad (52)$$

At medium temperatures in which both the vinyl and 3-butenyl radicals were observed, they were found to be complementary—the sum of their yields was constant. Studies of the temperature dependence of the relative concentration of these two radicals lead to an activation energy of 3.35 kcal mol^{-1} for reaction 52.

For olefins with allylic hydrogens the main intermediates are those due to elimination of allylic hydrogen atoms. Thus ESR studies of low temperature–prolonged irradiation of cyclopentene show absorptions due to cyclopentyl, cyclopentenyl and cyclopentadienyl radicals with the lines of cyclopentenyl radicals predominating[105,106]. Thus the allylic radical is an important free radical in most irradiated alkenes other than ethylene.

Holroyd and Klein[106] found that in propylene about 45% of the radicals are allyl whereas in 2-butenes and in cyclohexene about two thirds of the radicals are allylic. Also, other studies by ESR spectroscopy found the major contribution of allylic-type radicals in radiolysis of alkenes[107].

Besides the radicals formed by H-atom elimination there are the radicals formed by the addition of these H atoms to double bonds. Thus, in ethylene the main radical besides vinyl is ethyl and similarly cyclohexyl radical in cyclohexene and propyl radical in propylene[106].

However, the main source of the H-adduct radical is not the addition of thermal hydrogen atoms to the double bond as can be seen, for example, from the ratio of isopropyl radical to n-propyl radical in the radiolysis of liquid propylene. In irradiated propylene $G(i\text{-}C_3H_7\cdot)/G(n\text{-}C_3H_7\cdot)$ is 2.7 compared to the 10:1 isopropyl/n-propyl radical ratio for thermal hydrogen addition to liquid propylene[108].

Another process which can lead to H-adduct radicals is an ion–molecule reaction followed by neutralization and de-excitation[109–111], e.g. for isobutene,

$$C_4H_8^{\ddagger} + C_4H_8 \longrightarrow C_4H_9^{+} + C_4H_7\cdot \tag{53}$$

$$C_4H_9^{+} + e^{-} \longrightarrow C_4H_9^{*} \tag{54}$$

The excited butyl radical can either be de-excited or decomposed to give ethylene + ethyl radical. This suggestion agrees with the observation that the yield of C_4H_7 is larger than that of C_4H_9.

Muto and coworkers[112] studied the radicals formed in radiolysis of ethylene in xenon matrices at 4.2 K by ESR. At this low temperature they found H atoms and vinyl and ethyl radicals. Upon warming to about 45 K they found that the hydrogen atoms are detrapped and react to give ethyl radicals. At 4.2 K the ratio of vinyl-to-ethyl radicals is 3.0. The efficiency of H addition to C_2H_4 upon warming was found to be about 55%.

Fukaya and collaborators[113] irradiated tiglic acid [$CH_2CH{=}C(CH_3)COOH$] and found by ESR spectrometry that nearly equal amounts of allylic and hydrogen addition radicals are formed. The hydrogen atoms are eliminated from the β methyl group and are added to the β carbon atom. For many unsaturated carboxylic acids it was found that the hydrogen atoms formed originate in the carboxyl group[114–116] and it is the carboxylic hydrogen which is added to the double bond. However, the situation is different in tiglic acid due to the β-methyl group[117]. In the case of unbranched alkene carboxylic acids the radicals RCOO· are formed[118] by the deprotonation of primary cations or vinyl-type radicals, however these radicals were not found in the radiolysis or tiglic acid.

Shida and Hamill[119] showed that alkenes formed radical cations in γ-irradiated alkyl chloride or alkane glasses. They observed broad optical absorption bands in the range 600–800 nm ('red bands') which were attributed to monomer radical cations of the alkenes. It was assumed that the positive charge generated by ionization migrates through the matrix (RX) and is trapped by the alkene (S) to give radical cation ($S^{\ddagger}$),

$$RX^{\ddagger} + S \longrightarrow RX + S^{\ddagger} \tag{55}$$

Badger and Brocklehurst[120] performed similar experiments with cyclohexene. They questioned this assignment of monomer radical cations and discussed the possible dimer radical cation formation as the cause of these 'red bands',

$$S^{\ddagger} + S \longrightarrow S_2^{\ddagger}$$

Cserep and collaborators[121] found similar red-band spectra after electron-pulse irradiation of liquid alkanes containing olefins. They tried to separate between monomer cation radicals and dimer cation radicals by the time profiles of the transient absorptions. They found in pulse radiolysis studies of glassy solutions over a wide temperature range that monomer radical-cations were produced within a 10 ns pulse whereas dimer radical-cations were not detected even at 50 μs after the pulse. Mehnert and coworkers[122] studied the electron pulse irradiation of cyclohexane or n-heptane solutions containing CCl_4 as an electron scavenger and alkenes as solute. The experimental results indicated that at least three different cationic transients are present: alkane radical cations and alkene monomer and dimer radical cations. The observed 280 nm bands were assigned to the π–π^* transition of the alkene monomer radical cation, whereas the red bands were attributed to charge resonance transition occurring in the alkene dimer radical cations[122,123]. The

assignment of the alkene monomer radical cation was based on the following arguments:

(1) The absorptions grew synchronously with the decay of the alkane radical cations.

(2) Even in glassy solutions a remaining solute absorption part was observed, which was formed during a 10ns electron pulse.

(3) An absorption band at 280 nm is in agreement with quantum-mechanical predictions of a strong π–π^* transition.

(4) The ion-cyclotron-resonance photodissociation spectrum of the *cis*-2-pentene radical cation showed a band of a similar position and structure.

The red bands were attributed to the dimer radical cations due to the following arguments:

(1) For all eleven alkenes used in this study a time gap was found between the disappearance of the alkane radical cation absorption and the growth of the red-band absorption.

(2) The rise time of the growing red-band absorption decreased with increasing alkene concentration.

(3) The growth of the red-band absorption became slower and its lifetime longer with decreasing temperatures. This absorption was not formed in glassy matrices within the time range of the experiment, indicating that diffusive motion is essential for its formation.

(4) Quantum-chemical calculations predict charge resonance bands with strong oscillator strength in the range 600–800 nm if a 'sandwich'-like structure is assumed for the cation and the neutral molecule of the dimer.

From the decay of the alkane radical cation absorption and the growth of the monomer alkene radical cation absorption, Mehnert and coworkers[122] concluded that alkene radical cations can be formed by charge transfer from mobile holes to alkene molecules with a rate constant of about $10^9\,M^{-1}\,s^{-1}$. The alkene monomer radical cations are added in a nearly diffusion-controlled manner to alkene molecules to form the alkene dimer radical-cations. These dimers undergo further reactions, e.g. with other alkene molecules, however these processes are 2–4 orders of magnitude slower than those of the dimer radical cation formation.

Similar monomer and dimer radical cations were observed also for some dienes (1,4-cyclo-hexadiene, 1,3-cyclopentadiene, 1,3-cyclohexadiene and 1,5-cyclooctadiene) when butyl chloride-diene solutions were pulse irradiated. Cserep's group resolved the overlapping spectra of the monomer and dimer radical cations of the various dienes and measured the rate constant of the formation of both cationic species[123].

C. Yields of Final Decomposition Products

The radiolytic yields of H_2 in alkene radiolysis are much smaller than in the case of alkanes, due to the high effectiveness of the double bond as a hydrogen atom scavenger. The radiolytic yields of hydrogen in the radiolysis of n-1-alkenes increase monotonically with the number of carbon atoms[124]. The difference between two consecutive compounds in the n-1-alkene homologue series is quite small [$\Delta G(H_2) \sim 0.05$–0.06]. However, the yields of hydrogen in the radiolyses of cycloalkenes do not show any regularity with the molecular weight. Table 3 shows that higher values of $G(H_2)$ occur for cycloalkenes for

TABLE 3. Radiolytic yields of hydrogen in the radiolysis of liquid n-1-alkenes and cycloalkenes[125,126]

Number of carbon atoms	4	5	6	7	8	10	12	13
n-1-Alkene	0.65	0.83	0.90	—	0.98	0.98		
Cycloalkene	0.55	1.20	1.19	0.98	0.85	1.02	1.60	1.65

which the rings are more stable, i.e. C_5, C_6 and then C_{12} and C_{13}. Cserep and Foldiak[126] showed (Figure 1) that $G(H_2)$ of the cycloalkenes is a decreasing monotonous function of the ring strain energies.

Large differences were found for $G(H_2)$ of various alkene isomers as can be seen in Table 4. Generally speaking, the splitting probability of a bond in a β-position with respect to the double bond is an order of magnitude higher than that of one in an α-position[127-131]. Cserep and Foldiak[132] found that $G(H_2)$ in the radiolysis of alkenes can be calculated additively assuming a specific hydrogen yield for each type of hydrogen atom (there are six types of hydrogen atom, allylic and non-allylic and for each primary, secondary and tertiary). They treated the vinylic hydrogens similarly to alkylic hydrogens, although they should be treated separately. Table 5 gives the specific contribution of each type of hydrogen atom and comparison of calculated $G(H_2)$ with the measured one. The specific contributions of the various bonds were calculated from the data of the straight-chain alkenes and Table 5 shows that there is good agreement between the calculated and experimental $G(H_2)$ values for straight-chain alkenes. However, the agreement is not so good for branched-chain alkenes, and the difference can be almost a factor of two. For

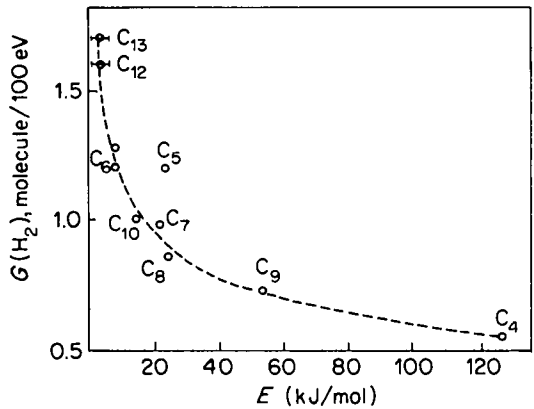

FIGURE 1. $G(H_2)$ values of cycloalkenes vs. the ring strain energies of the most stable isomers. Reproduced by permission of G. Foldiak

TABLE 4. Yields of the main products in the radiolytic decomposition of various alkene isomers[127,128]

Alkene	$G(H_2)$	$G(CH_4)$	$G(C_2)^a$
1-Hexene	0.90	0.03	0.25
2-Hexene	1.37	0.13	0.28
3-Hexene	1.64	0.23	0.47
1-Octene	0.98	0.02	0.13
2-Octene	1.42	0.06	0.11
3-Octene	1.63	0.08	0.14
4-Octene	1.61	0.06	0.24

[a] $G(C_2)$ is the total yield of the various two carbon molecules (ethane, ethylene and acetylene).

TABLE 5. Specific contribution of various C—H bonds of aliphatic alkenes in the additivity scheme of $G(H_2)$ for radiolysis of aliphatic alkenes[132] and comparison of calculated and experimental results

Type of bond	Allyl			Non-allyl		
	primary	secondary	tertiary	primary	secondary	tertiary
Specific contribution	0.172	0.359	0.520	0.011	0.026	0.210

	$G(H_2)$	
Alkene	measured	calculated
Propene	0.60, 0.80	0.59
1-Butene	0.74, 0.73	0.78
cis-2-Butene	1.02, 0.96	1.06
1-Pentene	0.83	0.88
1-Hexene	0.90	0.92
2-Hexene	1.37, 1.17	1.37
3-Hexene	1.64, 1.61	1.60
1-Heptene	0.94	0.96
1-Octene	0.98	1.00
2-Octene	1.42	1.45
3-Octene	1.63	1.68
4-Octene	1.61	1.68
1-Decene	1.10	1.08
5-Decene	1.70	1.78
1-Hexadecene	1.39	1.30
3-Methyl-1-butene	0.58	0.61
3, 3-Dimethyl-1-butene	0.37	0.12
2, 3, 3-Trimethyl-1-butene	0.62	0.63
2-Methyl-2-butene	1.10	0.56
2, 3-Dimethyl-2-butene	1.21	2.04
4-Methyl-1-pentene	0.95	1.04
2, 4-Dimethyl-1-pentene	0.75	1.55
2, 4, 4-Trimethyl-1-pentene	0.55	1.35
2, 4-Dimethyl-2-pentene	1.03	1.62
2, 4, 4-Trimethyl-2-pentene	0.61	1.14
2, 5-Dimethyl-2-hexene	1.17	2.06
trans-2-Methyl-3-hexene	1.30	1.35
trans-2, 5-Dimethyl-3-hexene	1.16	1.19
2, 2-Dimethyl-3-hexene	0.85	0.86
2-Methyl-1-hexene	1.25	1.41
3-Methyl-1-hexene	0.82	0.77
4-Methyl-1-hexene	1.13	1.13
5-Methyl-1-hexene	1.16	1.3

most of the compounds for which the measured and calculated $G(H_2)$ values do not agree, the measured value is lower than the calculated value and Cserep and Foldiak[132] explained it as due to steric hindrance. They found that the larger the deviation of the direction of the C—H bond from the position most favourable for the allyl interaction, the less is the hydrogen yield. A realization of this explanation can be found in Figure 2, which shows a model of 2, 3-dimethyl-2-butene. The free rotation of methyl groups on the same

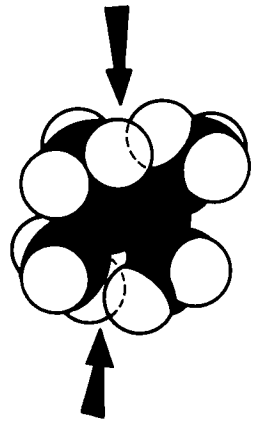

FIGURE 2. The model of 2,3-dimethylbut-2-ene molecule; arrows indicate the place of the steric hindrance of rotation. Reproduced by permission of G. Foldiak

side of the olefinic bond is hindered by each other and consequently the probability of formation of the favourable conformation leading to allyl interaction is decreased. However, this explanation for the disagreement does not explain the cases where the measured values are larger than the calculated ones (2-methyl-2-butene and 3, 3-dimethyl-1-butene). The bond additivity calculations are not in good agreement with the data on cycloalkenes. The $G(H_2)$ data for cycloalkenes are about the same as data of 1-alkenes for rings with a high strain and slightly higher for rings with low strains, while the bond additivity predicts much higher $G(H_2)$ values due to the four allylic hydrogens in cycloalkenes. For example, the scheme predicts $G(H_2)$ of 1.44 and 1.56 for cyclobutene and cyclohexene, respectively, while the measured values are 0.55 and 1.19. It seems that a more accurate additivity scheme will be one of group additivity rather than of bond additivity[133]. Foldiak and his coworkers[134,125] found that the specific bond contributions are a decreasing function of the bond dissociation energies of the respective C—H bonds as can be seen in Figure 3.

Hatano and Shida[135] studied the $G(H_2)$ for liquid butenes under γ-irradiation and found that the yield is independent of the temperature in the range -78 to 110 °C. They also studied the effect of scavengers on $G(H_2)$ in the radiolysis of ethylene, propene and cyclohexene and found that the hydrogen yield was not significantly influenced by either radical scavengers or ion (both positive ion and electron) scavengers. They concluded[135] that hydrogen is formed in radiolysis of alkenes directly from the excited molecules produced by the radiation and mainly from the superexcited molecules with energy higher than the ionization energy.

$$RH \longrightarrow RH^* \tag{56}$$

$$RH^* \longrightarrow H_2 + \text{alkadiene} \tag{57}$$

$$RH^* \longrightarrow H^* + R\cdot \text{ or } 2H^* + \text{other products} \tag{58}$$

$$H^* + RH \longrightarrow H_2 + R\cdot \tag{59}$$

H* means a hot hydrogen atom which is not scavenged by a radical scavenger. However, Kovacs and coworkers[136] observed a significant decrease in $G(H_2)$ in the radiolysis of cyclohexene when CCl_4, an electron scavenger, was added. Similarly, the addition of

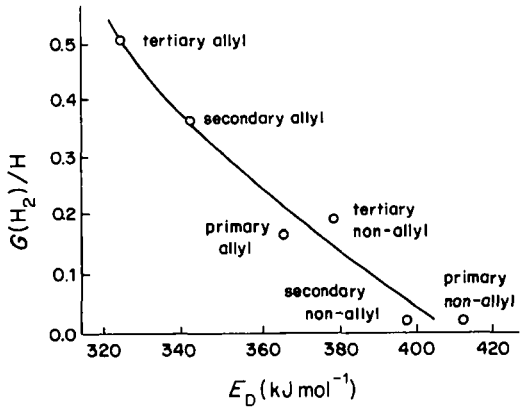

FIGURE 3. Specific hydrogen yield increments of aliphatic alkenes vs. bond dissociation energies of the respective C—H bond. Reproduced by permission of G. Foldiak

CCl_4 lowers $G(H_2)$ in the radiolysis of 2, 3, 3-trimethyl-1-butene[137]. Although CCl_4 might affect $G(H_2)$ due to excitation energy transfer, it is more probable that it affects the geminate ion–electron recombination, indicating that this process, which leads also to excited molecules, is important in the formation of hydrogen.

The hydrogen elimination will be maximal when the β-positioned C—H bond is perpendicular to the double bond, when the electron orbitals of the π bond and those of the allylic hydrogen have maximum overlap. Free rotation of the allylic CH_2 group of aliphatic alkenes—except for the case of hindrance by large substituents—makes such an orientation feasible. However, the cyclic structure of cycloalkenes allows only incomplete overlapping.

The yields of hydrogen in the radiolyses of dienes are generally much lower than for monoalkenes, probably due to higher scavenging capability of the two close double bonds. $G(H_2)$ is slightly larger for isolated dienes than for conjugated ones, probably due to the larger number of allylic hydrogens. However, the contributions of the allylic hydrogens are much smaller; e.g. hexa-1,5-diene has four allylic hydrogens which alone predict $G(H_2) = 1.44$, whereas the observed value is 0.45[138].

Table 6 gives the yields of methane, ethane, ethylene and acetylene for various alkenes[126,139]. Cserep and Foldiak[126] suggested that the factors influencing $G(H_2)$ in the radiolysis of alkenes have a similar effect on the formation of methane. $G(CH_4)$ depends on the number of methyl groups in the molecule and on the relative position of each methyl group and the π bond in the molecule. Thus comparing $G(CH_4)$ for the various substituted 3-hexenes, where there is no steric influence and the allyl interactions are not hindered, shows that $G(CH_4)$ increases with the number of methyl groups.

The methane yield from terminal alkenes is generally smaller than that from the corresponding inner alkenes (Table 4). This is likely to be due to the fact that, as a consequence of steric inhibition, the addition of a methyl radical is more probable at the end of the molecule than in an inner position. Foldiak[125] compared the $G(CH_4)$ of various hexene isomers and pointed out that, while the number of methyl groups is the same in 2- and 3-hexene, yet $G(CH_4)$ is higher for 3-hexene. He explained this as due to loosening of the terminal C—C bonds in the β-position with respect to the π bond.

TABLE 6. Yields of methane, ethane ethylene and acetylene in the radiolysis of various alkenes[126,139]

Alkene	Products			
	methane	ethane	ethylene	acetylene
1-Hexene	0.030	0.028	0.133	0.091
2-Hexene	0.132	0.107	0.122	0.049
3-Hexene	0.233	0.160	0.073	0.045
2-Methyl-3-hexene	0.270	0.057	0.032	0.035
2, 5-Dimethyl-3-hexene	0.410	0.010	0.008	0.040
2, 2-Dimethyl-3-hexene	0.550	0.080	0.040	0.045
4-Methyl-1-pentene	1.134	0.005	0.080	0.090
2, 4-Dimethyl-1-pentene	0.163	0.010	0.012	0.015
3, 3-Dimethyl-1-butene	0.244	0.026	0.105	0.130
2, 3, 3-Trimethyl-1-butene	0.255	0.023	0.010	0.012
2, 3-Dimethyl-2-butene	0.170	0.010	0.005	0.006
2,4-Dimethyl-2-pentene	0.330	0.010	0.006	0.008
2, 4, 4-Trimethyl-2-pentene	0.520	0.050	0.010	0.008
2, 5-Dimethyl-2-hexene	0.200	0.004	0.010	0.009

D. Yields of Larger Products

Much of the work on radiation chemistry of alkenes was done on the radiation-induced polymerization of alkenes. However, under the usual radiation conditions most unsaturated hydrocarbons do not form macromolecules and the reactions are terminated by dimers or at mostly oligomers. Polymerization will be treated in the next section and this paragraph will deal only with the formation of dimers. 50–80% of the dimers produced in radiolysis of straight-chain alkenes are monoalkenes. Straight-chain monoalkene dimers are usually formed with higher probability from terminal alkenes than from alkenes with an internal double bond. This has been explained by a unique bond formation between ions and the alkenic carbon. The formation of dimers can proceed either by a recombination of radicals, or by reaction of a radical with a monomer molecule or via an ionic mechanism. The formation of dimers in the radiolysis of alkenes with a terminal double bond occurs mainly by an ionic mechanism, while for inner alkenes (2-butene, 2- and 3-hexene) dimerization by radical combination is a more important route[140]. This difference is explained as due to the larger number of allylic hydrogens in inner alkenes, thus increasing the yield of radicals in these systems. Hunter and coworkers[141] irradiated thin films ($\sim$70 nm) of 1-hexene with electrons of varying energy. They found that the yield of the dimer as a function of the electron energy had a maximum at 4 eV and decreased nearly to zero at the ionization potential of 1-hexene (8–9 eV). At higher electron energy the yield rises again up to 50 eV, where the radiolytic yield is similar to that obtained in γ-radiolysis. The higher yield at energies below the ionization potential indicates that a major non-radical route of dimer formation is through triplet excited states.

E. Radiation-induced Polymerization of Alkenes

Radiation-induced polymerization of alkenes was studied for the first time in 1938 when Hopwood and Phillips[142] bombarded styrene with fast neutrons. In the very early days of radiation-induced polymerization it was suggested by S. C. Lind[1,2] that the mechanism is ionic. However, during the late forties and the fifties it was accepted that the mechanism is of free-radical chain propagation due to the following findings: (a) square-root dependence

of the polymerization rate on the dose rate; (b) an inverse square-root dependence of the average molecular weight on the dose rate; (c) inhibition of the polymerization by free-radical inhibitors; (d) increase of the rate with temperature in the same measure as was found for photo-reaction. However, Davison and coworkers[143] studied the radiation-induced polymerization of isobutene which could be carried out both with high-energy electrons and with ^{60}Co γ-rays. As this monomer cannot be polymerized by free-radical catalysts and is polymerized only by a cationic mechanism, it was clear that radiation could also initiate ionic polymerization. Further studies show that radiation-induced polymerization can propagate by radical, cationic or anionic mechanisms. In many cases two or three processes occur simultaneously. The relative importance of each mechanism depends on the chemical nature of the monomers, the solvents, the temperature and the type of concentration of additives.

Low temperature increases the importance of ionic polymerization. Halogenated solvents lead to domination of cationic polymerization, while anionic polymerization was found to take place when methyl methacrylate or acrylonitrile is irradiated in basic (amine or amide) solvents at low temperatures. The chlorinated solvents lengthen the life of the negative charges by converting the electrons into Cl^- while the amines act as positive ion stabilizers in which the positive charge is located on quartenary ammonium-type ions.

The mechanism by which the radiation-induced polymerization proceeds can be determined by three general methods: (a) by comparison of the characteristics of the radiation-induced polymerization with those of other catalytic methods of polymerization of the same monomer; (b) from the effect of external parameters, such as dose rate and temperature, on the rate of polymerization; (c) from the results of studies of the effect of various scavengers.

Polymerization induced by irradiation has been studied extensively and has been summarized by Chapiro[144], Williams[145,146] and Stannet and Silverman[147]. We cannot give here full details and will concentrate only on some examples.

1. Homogeneous bulk polymerization in the liquid phase

Several cases of radiation-induced bulk polymerization in the liquid phase were found to proceed by a free-radical mechanism and according to the well-known free-radical kinetics

$$R_p = k_p \left(\frac{R_i}{k_t}\right)^{1/2} [M] = k_i \cdot k_p [M] \cdot \tau_{ss} \tag{60}$$

where R_p is the rate of propagation, k_p is its rate constant, R_i is the rate of radical formation (initiation) which is proportional to the dose rate, k_t is the rate constant for the termination by reaction of two radicals, [M] is the concentration of the monomer and τ_{ss} is the mean lifetime of the free radicals in the stationary state. The most detailed study on free-radical radiation-induced polymerization was conducted for methyl methacrylate and vinyl acetate at or above room temperature[144]. The polymerization proceeds according to equation 60 as long as the conversion is low, involving only low changes of viscosity. Acrylonitrile polymerization proceeds also by a free-radical mechanism, however the kinetics does not obey equation 60 as the polymer is insoluble in acrylonitrile and thus this is not a homogeneous process. Styrene polymerized by radiation through a free-radical mechanism only when not extremely dry. Drying of styrene leads to increase in the rate of polymerization and the mechanism is changed to ionic propagation[148]. The yield of radicals in the radiolysis of vinylic monomers can be measured either by the rate of polymerization (i.e. by the measurement of the molecular weight) or by the consumption of DPPH (diphenylpicrylhydrazil—a radical scavenger). Table 7 shows that there is fair agreement between both measurements in independent studies.

TABLE 7. Radiation-induced free-radical bulk polymerization of vinyl monomers[145]

Monomer	Yield of radicals		Rate of polymerization ($M^{-1}s^{-1}$)		
	polymerization	G(-DPPH)	Temp(°C)	k_p	k_t
Vinyl acetate	12	6–9	25	1012	5.9×10^7
Methyl methacrylate	11.5	5.5–6.7	30	286	2.4×10^7
Acrylonitrile	1.2–5.6	5.0	60	1960	
Styrene	0.69	0.66	25	44	4.75×10^7

The larger value of both k_p and G(radicals), which is proportional to R_i, for the three aliphatic alkenes in Table 7 (vinyl acetate, acrylonitrile and methyl methacrylate) relative to styrene means that they are more readily polymerized by radiation through free-radical propagation. Other alkyl acrylates and methacrylates have similar large k_p values.

An interesting comparison of chemical initiation and radiation-induced polymerization concerns the activation energies of both processes. The activation energy for the overall rate of polymerization is given by the equation $E = E_p + \frac{1}{2}E_i - \frac{1}{2}E_t$ where E_p, E_i and E_t are the activation energies for the propagation, initiation and termination steps, respectively. The only difference between catalytic initiation and radiation is in the E_i term. Whereas for most catalytic initiations E_i is about 30 kcal mol^{-1}, initiation by radiation is temperature independent, i.e. $E_i = 0$. Thus $E = 22$ kcal mol^{-1} for chemical initiation compared to 7 kcal mol^{-1} for radiation-induced polymerization. This situation is reversed for the degree of polymerization for which the energy of activation is equal to $E_p - \frac{1}{2}E_i - \frac{1}{2}E_t$. Thus the activation energy for chemical initiation is approximately -8 kcal mol^{-1}, while in the radiation case it is $+7$ kcal mol^{-1}. Increasing the rate of polymerization (without changing the concentration of the chemical catalyst) by increasing the temperature leads to a *decrease* in the molecular weight while an increase of the temperature in radiation-induced polymerization will lead to a corresponding *increase* of the molecular weight.

Ionic polymerization is understood much less than the free-radical one and the results are less reproducible due to considerable variations caused by small concentration of impurities. Radiation-induced polymerization is a special case suitable for quantitative study of ionic polymerization, since high-energy radiation provides the only means of generating free ions in a medium of low dielectric constants, such as a hydrocarbon monomer. Due to lack of space, we will concentrate only on the bulk polymerization of styrene, α-methylstyrene and isobutene.

As mentioned previously, very small concentrations of water have an inhibiting effect on the rate of polymerization. This effect was explained[148,149] as due to reactions of the water to scavenge ions.

$$H_2O + AH^+ \longrightarrow H_3O^+ + A \tag{61}$$
$$H_3O^+ + Y^- \longrightarrow H_2O + HY$$

In these reactions the water scavenger is regenerated, and the water transfers protons from positive hydrocarbon ions to the negative ions and thus retards the rate of ionic polymerization.

Hirota and coworkers[150] found that *p*-benzoquinone, oxygen and nitrobenzene inhibit the radiation-induced polymerization of α-methyl styrene and consequently concluded that it is free-radical polymerization. Bates and coworkers[149] argued against the free-radical mechanism as it does not explain the inhibition by water. They suggested that the inhibition by water together with low molecular weights and high polymerization rates is consistent with a cationic mechanism involving a chain reaction through proton transfer

reactions. Various studies showed that the better the drying of α-methylstyrene, the higher was the yield of the polymer. Metz[151] employed silica gel for very careful drying of the monomer, and used vacuum baking of all glassware to remove all traces of water. He obtained G(-monomer) values of 7.8×10^4 and 5.1×10^5 at dose rates of 2.4×10^5 and 6.4×10^3 rad h^{-1}, respectively. Ammonia and amines at low concentrations[152] retarded strongly the radiation-induced polymerization of α-methylstyrene indicating that the mechanism involves cationic propagation, since bases cannot retard anionic processes. Other evidence for the cationic mechanism is: (a) the high efficiency of chain transfer occurs usually in proton transfer reactions and is unusual for anionic polymerization; (b) Uneo and collaborators[153] studied the radiation-induced copolymerization of α-methylstyrene–styrene mixtures and found that in dry systems the ratio of reactivities is the same as for cationic catalytic polymerization. For wet systems the reactivity ratio is typical to free-radical mechanism and the polymerization rate is much smaller.

Water terminates the propagating carbonium ion chain, but it also associates with the monomer which leads to complicated kinetics[154]. More specific scavengers are the amines, which interfere only with the chain propagation by termination due to proton transfer to them and hence they are commonly used for kinetics studies.

From the inverse dependence of G(-monomer) on the concentration of trimethylamine Hubmann and coworkers[152] calculated k_p assuming that the value of the rate constant for charge transfer is given by diffusion theory and using an assumed value of $G_i = 0.1$ for the yields of free ions. The result agrees quite well with another value obtained by the same group, based on measurements of absolute rates and ionic lifetimes[155].

Radiation-induced polymerization of styrene was found to be the same as for α-methylstyrene; it involved a slow free-radical mechanism in the presence of water and fast cationic propagation with extremely dry styrene[148,153].

Schneider[170] found previously in pulse radiolysis of styrene a monomer anion radical, formed through electron capture by a monomer radical, absorbing at 390 mμ. Beside the anion a second longer-lived species with an absorbing maximum at about 320 mμ appeared. This absorption was identified as the polymerizing styrene radical $\sim CH_2\dot{C}HC_6H_5$.

Recent picosecond pulse radiolysis of styrene[147] shows that the first reaction is, as usual in radiolysis, the ionization of the monomer to produce a cation and an electron which is captured by another monomer molecule to produce an anion. Within 10 ps the cation radical adds a monomer to become the cation dimer with an estimated rate constant of $8 \times 10^9 M^{-1} s^{-1}$. The dimer cation disappears by a first-order process with a lifetime of 20 ns. This is presumably the trimerization and thus the first step of the cationic polymerization. The calculated rate constant from this lifetime is $4 \times 10^8 M^{-1} s^{-1}$, in excellent agreement with the values estimated from a combination of conductivity and polymerization rate studies[155,157].

Many studies were conducted on the radiation-induced liquid-phase polymerization of isobutene, especially on the effects of various additives. Charlesby and coworkers[156] found that the yield of polymerization could be markedly enhanced by the addition of a fine suspension of inorganic oxides (mainly zinc oxide) to the monomer. The enhancement was explained by a heterogeneous mechanism, in which the electrons are captured by the solid, reducing geminate recombination and allowing the positive centre a larger lifetime to undergo propagation. Another evidence for this mechanism was the finding that G(monomer) increases considerably from 8×10^2 to 9.6×10^3 by addition of ZnO. This was explained as due to an increase in G_i from 0.2 to 2.9, ignoring any possible effects of the ZnO on the chain transfer. The molecular weight of the polyisobutene remains the same in both cases (about 5×10^5). Dalton and coworkers[157] used specially prepared preheated ZnO and obtained G(-monomer) up to 3×10^6, although the molecular weights still remained at the order of 10^6. If these values are simply explained as due to larger yield of

ions, it would mean an unreasonable value of several hundreds for G_i and the authors drew the obvious conclusion that the molecular weight is governed by chain transfer. Dalton and coworkers[157] neglect the idea that zinc oxide causes increased initiation and believe in electron trapping on ZnO, which may initiate the ionization of isobutene 'absorbed' on the surface of zinc oxide. In later papers[158]. Dalton and his coworkers found even higher G(-monomer), up to 10^7 at 390 rad h^{-1}, and higher molecular weights (up to 6.5×10^6) at -78 °C. They found inverse dependence of molecular weight on the temperature. A plot of log M (from viscosity) against $1/T$ gives an activation energy of 5.7 kcal mol^{-1}, which is probably the difference between the activation energies of the addition and the proton transfer steps in the ionic propagation of the monomer. Stannet and collaborators[159] found that without an additive, higher G(-monomer) values were generally obtained for very rigorously dried samples. This agrees with the findings that the most effective solids, such as zinc oxide, silica gel and alumina[160], are very good drying agents. Kristal'nyi and Medvedev[161] compared radiation-induced isobutene polymerization in the presence of ZnO or Al_2O_3 to polymerization of isobutene, which was pretreated with ZnO or Al_2O_3 but irradiated alone. They found the same results for both cases and their results are close to those of Dalton[158] and David and coworkers[160]. They found also that when 'wet' monomer is pretreated with zinc oxide, this leads to a large increase in G(-monomer). Water decreases the yield up to concentrations of about 10^{-3} mol%, but higher water concentrations do not have any more effect, indicating that the polymerization rate is retarded only by water dissolved in the monomer. Taylor and Williams[162] dried isobutene with vapours of sodium and potassium and obtained G(-monomer) of the order of 10^6–10^8 without any solid additive. The yield is about the same at -78 °C and at 0 °C, but the molecular weight is considerably lower at 0 °C (10^5 compared to 5×10^6 at -78 °C)[163].

To summarize, it seems reasonably clear that the effect of the additive is mainly due to removal of retarding water impurities.

2. *Polymerization in solution*

Radiation initiation for vinyl polymerization in solution is more complex than for bulk polymerization due to reactions with all components of the system, both solvents and solutes. For bulk polymerization it is easy to calculate the rate of initiation, R_i, from the G values, the dose rate and the physical constants of the monomer,

$$R_i = G_i \cdot \frac{I}{100\,N} \tag{62}$$

where G_i is the radiolytic yield of the initiating particles (free radicals or ions), I is the dose rate in eV $L^{-1} s^{-1}$ and N is the Avogadro number. In the case of solution the rate of initiation is a linear combination of the various components,

$$R_i = I/100N \times [\alpha_S(1\text{-}m) \cdot G_i(s) + \alpha_m \cdot m \cdot G_i(m)] \tag{63}$$

where α stands for the molar fraction of energy absorbed in each fraction (corresponding to its electron concentration), s represents the solvent and m is the mole fraction of the monomer.

If all the radicals (formed both from the monomer and solvent) react immediately with the monomer and the termination step is by the combination of growing chains, then a plot of the overall rate of initiation versus the mole fraction of the monomer, m, gives a straight line. If the plot curves, this indicates that energy transfer is taking place; curvature above the line shows sensitization and below the line indicates deactivation by the solvent. Chapiro[144] showed that the ratio of rates of polymerization in solution, R_p, and in bulk,

R_{po}, is given by the equation

$$\frac{R_p}{R_{po}} = \left[\frac{m}{m+(1-m)(V_s/V_m)}\right]^{3/2}\left[1+\frac{\alpha_s G_i(s)}{\alpha_m G_i(m)}\cdot\frac{1-m}{m}\right]^{1/2} \tag{64}$$

where V_s and V_m are the molar volumes of the solvent and monomer, respectively. Chapiro[144] drew the various curves of R_p/R_{po} as a function of $\phi_r = \phi_s/\phi_m$, where ϕ_s and ϕ_m are the molar yields of free-radical production from the solvent and monomer, respectively,

$$\phi_r = \frac{\alpha_s G_s(i)}{\alpha_m G_m(i)} \tag{65}$$

When $\phi_r = 1.0$ (as is the case of methyl methacrylate in ethyl acetate) the kinetics are similar to that obtained with catalyst-initiated polymerization systems for which there is no effect of the solvent on the initiation rate. For many cases R_p/R_{po} as a function of m can be fitted with a constant value of ϕ_r, however for some cases ϕ_r calculated from equations 64 and 65 for various values of m has different values. In these cases it is usually assumed that energy transfer processes are operative, i.e. excitation energy induced by the radiation in either the monomer or the solvent is transferred rapidly to other molecules.

$$M^* + S \longrightarrow S^+ + M^+ \xrightarrow{e^-} S\cdot + M \text{ or } S^* + M \longrightarrow M^* + S \longrightarrow M\cdot + S \tag{66}$$

Miller and Stannett[164] found energy transfer in the polymerization of a dibutyl disulphide solution of styrene. The value of ϕ_r decreases with increasing fraction of dibutyl disulphide, indicating that an energy transfer process is taking place, predominantly from the styrene to the disulphide. In order to account for the energy transfer another term was introduced into equation 64. This term, P_r, represents the relative probability of energy transfer from M to S versus transfer from S to M[144]:

$$R_p/R_{po} = \left[\frac{1}{m+(1-m)V_s/V_m}\right]^{3/2}\left[\frac{1+\phi_r\cdot P_r\dfrac{(1-m)}{m}}{1+P_r\dfrac{(1-m)}{m}}\right]^{1/2} m \tag{67}$$

While the energy transfer model is remarkably successful in analyzing the polymerization kinetics of vinyl monomer solutions, there may be other explanations with some monomer–solvent systems[165], e.g. in methanol-styrene studied by Huang and Chandramouli[166]. For neat styrene G(chains) = 0.7, for 5% methanol + styrene it increases to 5.7 and for higher methanol concentrations it levels off at G(chains) = 6.5. This is explained in the energy transfer model as due to excited styrene molecules which cannot produce styrene radicals but which can transfer energy to methanol and produce radicals of methanol. Silverman and coworkers[165] suggested an alternative model in which the methanol interferes with the geminate recombination of cations and anions and the reaction of these ions with methanol produces the initiators of the radical polymerization.

Pulse radiolysis studies were also done on styrene–methanol mixtures[167]. These studies suggest that methanol serves as a rapid proton donor to the anion radical, converting it to a neutral propagating free radical. The resulting methoxide anion could neutralize the cation radical, converting it to an additional free radical.

As a sample case we will discuss the radiolytic polymerization of ethylene in solution. Wiley and coworkers[168] studied the γ-ray-induced liquid-phase polymerization of ethylene in alkyl chloride solution. Although the reaction started in a homogeneous

solution, solid polymer particles soon formed a heterogeneous system. Under these conditions the growing polymer chains may be occluded in the solid particles and the termination can occur by primary radicals, small enough to diffuse into the particles and reach the growing chain ends. If the radicals are buried deeply enough they may remain unterminated. In both cases the polymerization rate is second order in the monomer concentration, in contrast to 'normal' polymerization kinetics in which the rate is first order in monomer concentration. In practical work depending on the importance of these effects the dependence of the rate on the monomer concentration would have an exponent ranging between 1 and 2. Wiley and coworkers[168] found that the rate of polymerization of ethylene in alkyl chloride solution was faster than in bulk under the same conditions. An induction period of about 1.5 h was found before solid polymer was formed in n-propyl, isopropyl and *t*-butyl chloride. After the induction period the rate of polymerization is constant and dependent on the ethylene concentration.

$$\log(\text{rate}) = \alpha + \beta \cdot \log[\text{monomer}] \tag{68}$$

β was found to be in the range 1–2 and depends on the system, temperature, etc. Reducing the oxygen content of the ethylene from 1000 to 60 ppm causes a considerable decrease in the induction period, indicating that the latter is at least partly due to scavenging by O_2 and is equivalent to the time required to consume the oxygen.

Oxygen is not only an inhibitor (causing an induction period) but also a retarder, decreasing the rate of the reaction after the induction period. Other radical scavengers also affect the system. Iodine causes both retardation and an induction period; the length of the induction period is proportional to the amount of the iodine. Diphenylamine causes no induction period but decreases the rate of polymerization. Such behaviour was observed earlier also in other free-radical reactions.

The fact that the solvent takes part in the polymerization is proved by the inclusion of about 0.9 chlorine atoms per polymer chain.

The activation energy for the polymerization in solution is slightly higher than in bulk: 7.4 and 5.0 kcal mol^{-1} in *t*-butyl chloride and n-propyl cloride, respectively, compared to 4.4 for the polymerization of liquid ethylene in bulk[169]. Wiley and coworkers suggested that the solvent increases the activation energy of the propagation step. The molecular weight was found to be approximately proportional to the one-third power of ethylene concentration. The molecular weight increased with rising temperature, probably due to termination of the growing chains by primary solvent radicals. The molecular weight as a function of the total dose is a maximum-type function; the initial increase is explained by consumption of impurities which lead to shorter chains, while the eventual decrease in the molecular weight is probably due to radiation degradation of the polymer.

F. Radiation Chemistry of Aqueous Solutions of Alkenes

Clay and coworkers[171,172] studied the products of γ-radiolysis of aqueous solutions of ethylene and propylene at various pressures. Irradiation in the absence of oxygen of ethylene-saturated water[172] yielded an oily polymer and a mixture of aldehydes, together with hydrogen peroxide. The yields of total aldehydes and hydrogen peroxide were linear with the radiation dose (up to ~ 100 krad): $G(H_2O_2) = 0.28 \pm 0.10$ and G(total aldehyde) $= 0.09 \pm 0.03$ at pH = 5 while at pH = 1.2 $G(H_2O_2) = 0.40 \pm 0.10$ and G(total aldehyde) $= 0.24 \pm 0.05$. The main aldehydes were acetaldehyde and butyraldehyde. Irradiation in the presence of oxygen yielded acetaldehyde, formaldehyde, glycolaldehyde and hydrogen peroxide, and smaller yields of unidentified organic peroxides. The yield of the last two products decreases slightly with increasing oxygen ratio (total ethylene + oxygen pressure = 1 atmosphere) the yields being 2.8 and 0.6 for H_2O_2 and ROOH at C_2H_2/O_2 ratio of 0.1 and 2.4 and 0.3 for a ratio of 9.0. The yields of the aldehydes increase with the partial

pressure of the oxygen. Henley and Schwartz[173] found a very high yield of acetaldehyde ($G \sim 60$) when water saturated with high pressures (above 8 atmospheres) of ethylene-oxygen was irradiated. However, Clay's group[172] irradiated a solution of oxygen-ethylene at a total pressure of 10 atmospheres (1:1 partial pressures) and found G(acetaldehyde + formaldehyde) = 1.3; other yields are $G(H_2O_2) = 2.6$ and G(glycolaldehyde) = 1.5. Clay's group[172] concluded that the increase in the ethylene does not lead to a chain reaction and has very little effect on the yield of the products. In the presence of oxygen [(ethylene)/(oxygen) = 3 in the gaseous phase of 1 atmosphere and 1:10 in the solution] the plot of yields vs. total dose is linear as long as the oxygen is not consumed considerably. In this linear part, the yield of the major products acetaldehyde and glycolaldehyde is almost equal at pH = 1.2. Formaldehyde yield is only 20% of these products. Increasing the pH decreases the yield of the organic products [G(organic products) = 5.9 at pH = 1.2 and 3.6 at pH = 5.5] and changes their nature, in that the yield of formaldehyde increases slightly while the yield of acetaldehyde decreases considerably and at pH 5.5 the major organic product is glycolaldehyde.

Both hydrated electrons and hydrogen atoms produce in the presence of oxygen $HO_2\cdot$ and $O_2^{\cdot-}$ according to the pH, and $HO_2\cdot$ like $\dot{O}H$ adds to olefinic double bonds.

Swallow[174] summarized the pulse radiolysis of aqueous solutions of vinylic monomers. $\dot{O}H$ radicals react rapidly with all vinylic monomers at rate constants of $1\text{–}3 \times 10^9\ M^{-1}s^{-1}$[175]. Hydrated electrons do not react rapidly with ethylene, and the rate constant is less than $2.5 \times 10^6\ M^{-1}s^{-1}$, but they react quite fast with conjugated dienes (e.g. with 1,3-butadiene the rate constant is $8 \times 10^9\ M^{-1}s^{-1}$) and with many substituted ethylenes.

The OH radical reacts by addition to the olefinic double bond, however with styrene or α-methylstyrene the observed major peak at 345–350 mμ[177] is consistent with that expected from an adduct of the hydroxyl radical at the benzene ring. Assuming the extinction coefficient of this adduct to be the same as those found for other OH adducts to benzene rings, it can be deduced that 90% of the OH radicals add to the ring in the case of styrene and 60% in the case of α-methylstyrene. Smaller peaks found in the case of styrene and of α-methylstyrene resemble those of other benzyl radicals and are attributed to the addition of OH to the olefinic double bond.

$$\cdot OH + CH_2{=}CHC_6H_5 \longrightarrow CH_2(OH)\dot{C}HC_6H_5 \qquad (69)$$

Hydrogen atoms are also added to the double bond while the reaction of hydrated electrons may in principle lead to the same products as H atoms or may lead to anions,

$$e_{aq}^- + A\cdot \longrightarrow \dot{A}H + OH^- \quad \text{or} \quad e_{aq}^- + A \longrightarrow A^{\cdot-} \qquad (70)$$

Chambers and coworkers[176] found that pulse radiolysis of neutral aqueous acrylamide formed species which absorb at 275 and 370 nm. The peak at 275 nm disappears when N_2O is added to the system, indicating that this species is due to the reaction of the hydrated electrons. The peak at 370 nm is almost unaffected by N_2O. The peak at 275 nm

$$CH_2{=}CH\overset{\displaystyle O}{\overset{\|}{C}}NH_2 + e_{aq}^- \longrightarrow CH_2{=}CH\overset{\displaystyle O^-}{\overset{\|}{C}}NH_2 \xrightarrow{H^+} CH_2{=}CH\overset{\displaystyle OH}{\overset{|}{C}}NH_2 \Leftrightarrow$$

$$\cdot CH_2CH{=}C(OH)NH_2$$

is also absent in sufficiently acidic solutions, also indicating that e_{aq}^- is the precursor of the species absorbing at 275 nm, and in acidic solution it reacts with H^+ to give hydrogen atoms. The absorption at 275 nm was found to be due to the radical formed by protonation of the anion obtained from the reaction of the hydrated electron with the carbonyl group. At high pH (11–12), where the protonation of the anion is slow, an absorption at 290 nm can be seen and is attributed to the anion. This radical absorbs at 275 nm and also at 370 nm. There is another species absorbing only at 370 nm and this is the adduct of the hydrogen atom $CH_3CHCONH_2$.

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The Chemistry of Double-bonded Functional Groups
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CHAPTER **10**

Asymmetric induction in additions to C=O and C=N bonds*

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Dedicated to the memory of my wife, Klara

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I. INTRODUCTION

A chemical process is said to involve asymmetric induction if it leads to the creation of a new chiral unit[1]. Such a process was considered initially to be an asymmetric synthesis if the new chiral unit contained an excess of molecules with one configuration over the other[2]. Therefore an inactive prochiral molecule had to be converted in an asymmetric synthesis into an optically active one[2]. Morrison and Mosher[3] have extended this definition of asymmetric synthesis and induction to reactions where stereoisomeric products (enantiomeric or diastereomeric) were found in unequal amounts. This was necessary, since most stereochemical studies have been carried out on racemic chiral compounds. In such compounds, an asymmetric induction of a new chiral unit relative to that present in the substrate will lead to an excess of one diastereoisomer, but this diastereoisomer can be optically inactive. This reaction will nevertheless give important information on the steric course of the reaction and on asymmetric induction.

Asymmetric induction was known for a long time. Thus, the extension of a sugar chain by the Kiliani[4] cyanohydrin synthesis involves an addition of hydrocyanic acid to a carbonyl group of a sugar and yields unequal amounts of the two diastereomers.

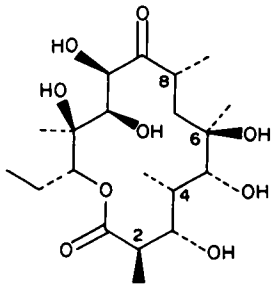
The systematic study of asymmetric syntheses, in view of the elucidation of the effects governing these reactions, started at the beginning of the fifties[5-7]. All these reactions involved additions to C=C and C=O bonds and the importance of steric effects was then revealed[8]. Later, stereoelectronic factors were also considered[9].

Asymmetric induction can be observed, when either the substrate or the reagent is chiral, or when both are chiral.

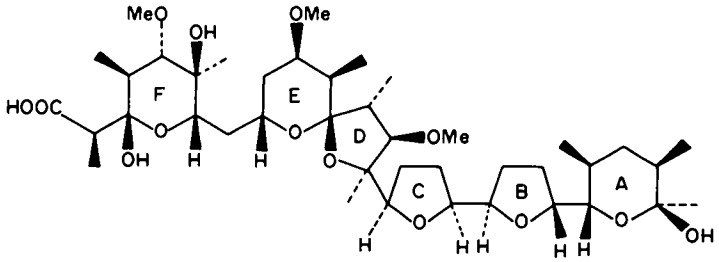
If neither the substrate nor the reagent are chiral, asymmetric induction can be accomplished (a) by the introduction of a chiral group (chiral template, chiral auxiliary or chiral adjuvant) into the substrate or reagent by covalent or ionic bonding, e.g. of a chiral alcohol to an achiral acid or a chiral acid to an achiral amine; (b) by adding an optically active complexing agent; (c) by carrying out the reaction in an optically active solvent; and (d) by using an optically active catalyst.

New synthetic challenges were recently concerned with the structure elucidation and preparation of natural compounds containing many stereogenic centers. (This is the correct nomenclature[10], but we shall use also, interchangeably, the term chiral center, since it is widely accepted.) Erythronolide A, the aglycon of the macrolide antibiotic erythromycin, has ten stereogenic centers **1** and the maximum amount of 1024 of stereoisomers are possible. An acylic aglycone **2** of the polyether antibiotic septamycin has 21 chiral centers, which means that more than two million stereomers are possible. The large number of possible stereoisomers makes impracticable syntheses involving separation of enantiomers, and demands methods for the direct preparation of single isomers with a minimal admixture of the opposite enantiomers or other diastereomers. Extensive research was carried out in the last fifteen years to develop such methods. Important achievements have been attained. Several books have been published[3,11-19] on this topic

and also a number of general reviews[20-27]. A number of more specialized reviews have been published and will be cited subsequently.



(1)



(2)

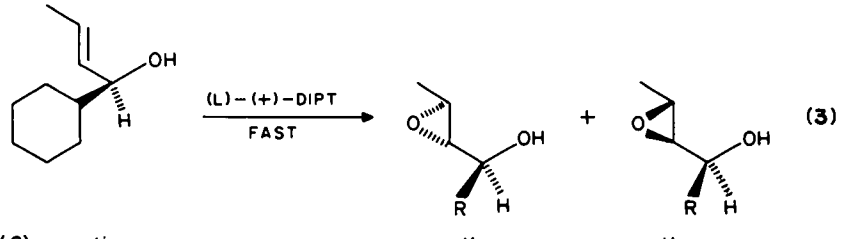
The functional groups to be treated in this review are the central ones in organic chemistry and the number of publications concerning asymmetric syntheses involving these groups is very large. We shall not give here a comprehensive review of all these reactions, but shall concentrate on methods that have led to considerable advances in these syntheses and to ideas that contributed to a better understanding of asymmetric induction. Work has often been done on parallel lines in several laboratories and our choice of the cited papers will sometimes be fortuitous or will reflect the preferences of this author. More recent work will be cited preferentially, since older work is summarized in an excellent manner by Morrison and Mosher[3] and reviews cited.

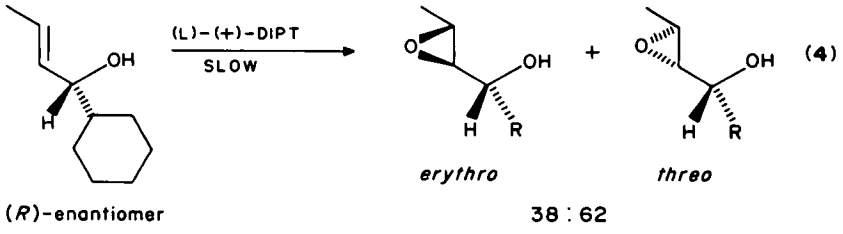
Significant developments did take place in several fields. The stereochemical concepts have been made more clear[10,28]. The term stereodifferentiating reactions[12] has been introduced generally with a prefix such as enantio- or diestereo-. However, the old term selective is still used preferentially with the prefixes enantio-, diastereo-, face-, group- or their combinations, e.g. enantiogroup or diastereoface selection. Examples of this use follow.

The enantioselectivity of reactions is now generally reported as percent of enantiomeric excess (% ee), where % ee = |%(*R*)−%(*S*)|.

The Sharpless asymmetric epoxidation reaction[29] is substrate selective and face selective (equations 3 and 4). The ratio in the rates of epoxidation[30] of (*S*)(*E*)-cyclohexylpropenyl and its (*R*)-enantiomer with *tert*-butyl hydroperoxide (TBHP), using L-(+)-diisopropyl tartrate (DIPT) as catalyst, is 104:1. The L-(+)-DIPT is also strongly face selective giving the *erythro* and *threo* products in a 98:2 ratio with the (*S*)-substrate (equation 3) but rather nonselective with the (*R*)-enantiomer (equation 4). A dramatic effectiveness of the kinetic resolution was observed, since after approximately 55% of the

reaction the recovered (*R*)-isomer had more than 96%ee. The % ee of the remaining enantiomer as a function of the percent of conversion and relative rates of the enantiomers was calculated by Sharpless[29] (Figure 1) and it appears that even small relative rate differences can provide a substance with high enantiomeric purity. The enantiomers RR′ and SS′ are obtained in unequal amounts due to the participation of the chiral catalyst C^R. The transition states for the formation of these two enantiomers can be written in a schematic form RC^RR' and SC^RS' and these transition states are not enantiotopic.

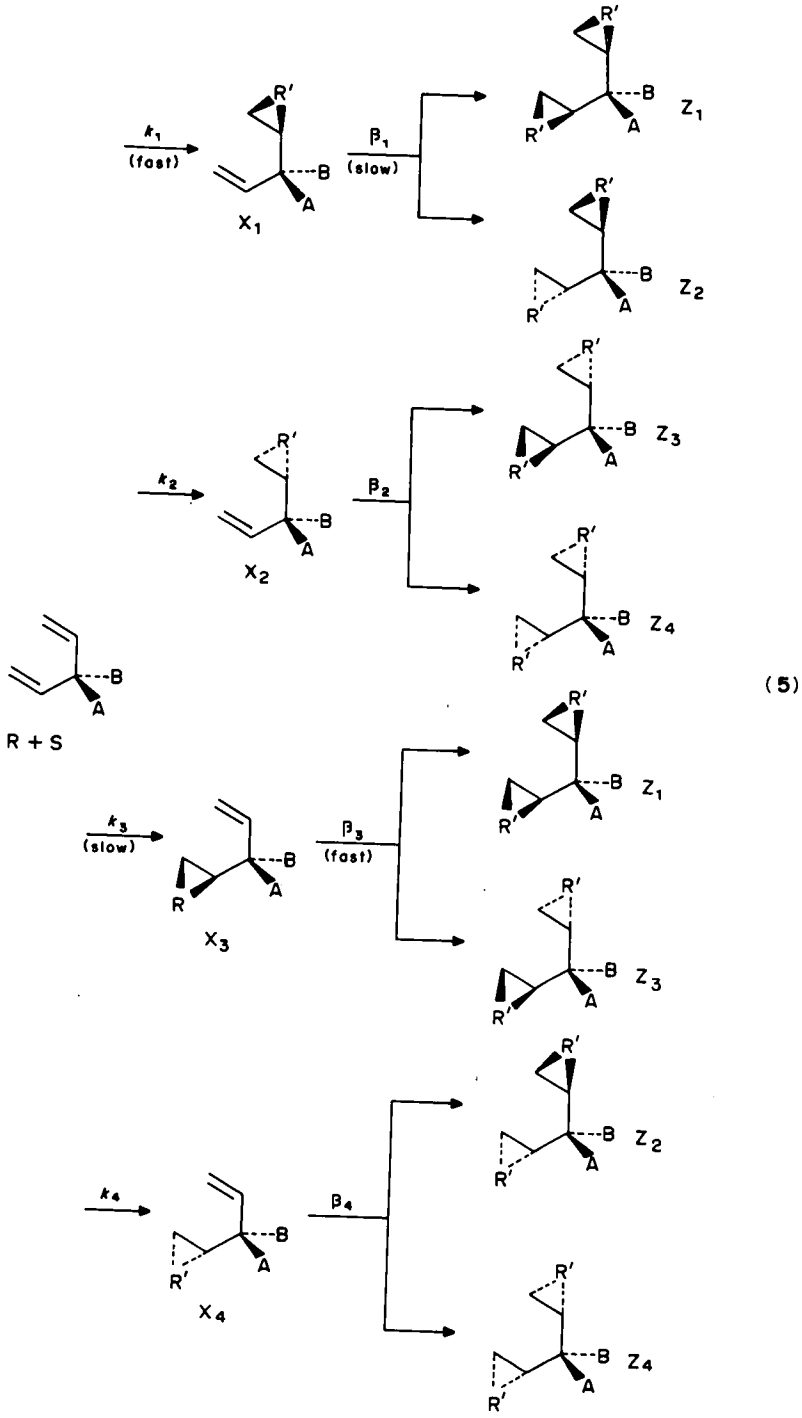




The high asymmetric induction brought about by chiral catalysts is one of the most dramatic developments in this field in recent years.

Mathematical methods for treatment of kinetic resolution and substrate-, group- and enantio-face differentiation have been developed recently[31-34,494]. Schreiber[34] has given a mathematical model for reactions that proceed with a combination of enantiotopic-, group- and diastereotopic-face selectivity. Asymmetric synthesis coupled with kinetic resolution leads to an increase in the enantiomeric excess of the primary products with time. The chemical model was the reaction 5 of a *meso* 3-substituted 1, 3-pentaediene with a chiral reagent that transfers an R′ group (chiral or nonchiral) to the diene. In the first step one of the enantiotopic vinyl groups is attached preferentially from one face to give X_1. The other isomers X_2, X_3, X_4 are formed in smaller amounts. Since the reagent is face selective, it will react preferentially with X_3 relative to X_1 to give Z_1 (X_3 is the enantiomer of X_1). The ratio of the enantiomers X_1/X_3 will therefore become arbitrarily large as the reaction goes to completion. This treatment was confirmed on a number of reactions[34].

An example of a reaction that proceeds with concomitant group and face differentiation leading to an efficient stereoselective functionalization, using an achiral reagent, was given recently by Kurth[35]. The heptadienoate **6** has two diastereotopic vinyl groups. All the four faces of the vinyl groups are also diastereotopic. The percentages of the products **7–10** show that the olefin selectivity was 147:1 and the face selectivity 30:1 in the kinetic iodolactonization. **7** and **9** vs. **8** and **10** reflect diastereotopic group selectivity; **7** and **8** vs. **9** and **10** *re* vs. *si* selectivity. The kinetic olefin selectivity can be rationalized by the lower energy of conformer **11** relative to **12**, due to less *gauche* interactions. These are the


R + S
k_1 (fast)
X_1
β_1 (slow)
Z_1
Z_2
k_2
X_2
β_2
Z_3
Z_4
k_3 (slow)
X_3
β_3 (fast)
Z_1
Z_3
k_4
X_4
β_4
Z_2
Z_4

(5)

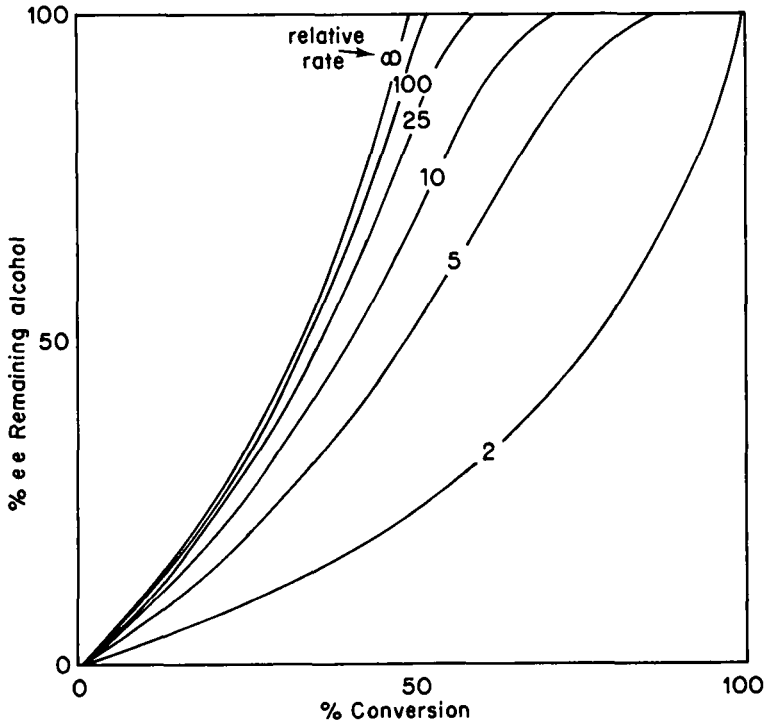


FIGURE 1. Dependence of enantiomeric excess on relative rate. Reprinted with permission from Martin *et al.*, *J. Am. Chem. Soc.*, **103**, 6237. Copyright (1981) American Chemical Society

conformations predisposed to cyclization. If the activation energies for the iodolactonization of both conformers are similar, the transition state energy for C_γ will be lower than for $C_{\gamma'}$ cyclization.

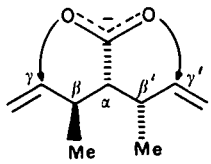
Other significant developments have been the synthesis of highly selective chiral reagents, the introduction of efficient chiral auxiliary groups based on natural compounds, and the use of various metals from both the main and transition groups. Chiral ligands have been introduced on the metals. These metals often participate in the formation of tight bi- and tri-cyclic intermediates and the transition state. The use of enzyme catalysis and microorganisms in asymmetric synthesis is increasing constantly. In some cases the use of small chiral molecules as catalysts in more advantageous than that of enzymes. This aspect of catalysis was discussed by Wynberg[490].

Finally, computational methods play an increasing role in the understanding of asymmetric synthesis by calculations of structures of transition states.

II. NUCLEOPHILIC ADDITIONS TO THE C=O BOND

A. Models of the Reaction

Cram[36,37] was the first to propose a model (**13**) that permitted one to correlate the steric course of a great number of additions to carbonyls containing a vicinal stereogenic

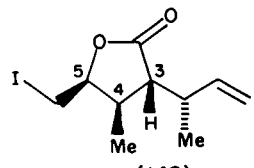


anti, syn

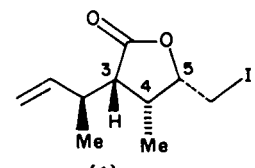
(6)

olefin

C_γ vs. $C_{\gamma'}$

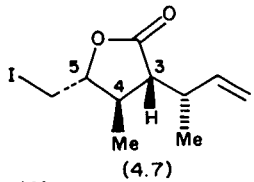


(7) (142)

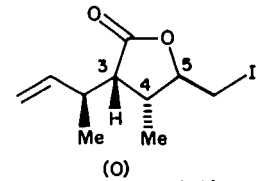


(1) **(8)**

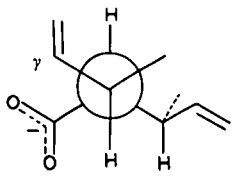
face re- vs. si-



(9) (4.7)

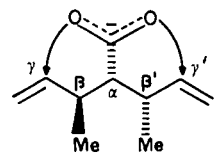


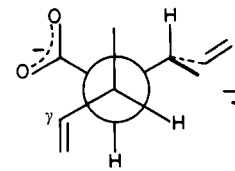
(0) **(10)**

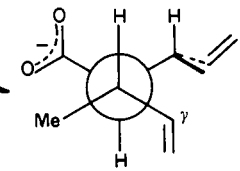


$(C_\beta—C_\alpha)$

(11)

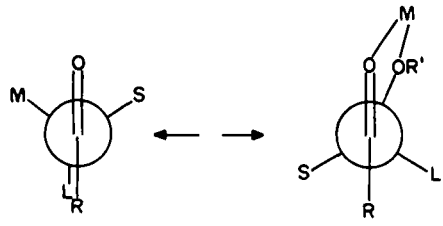


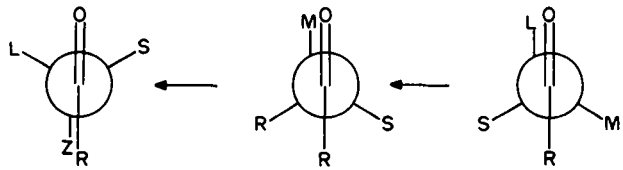




(12) $(C_{\beta'}—C_\alpha)$

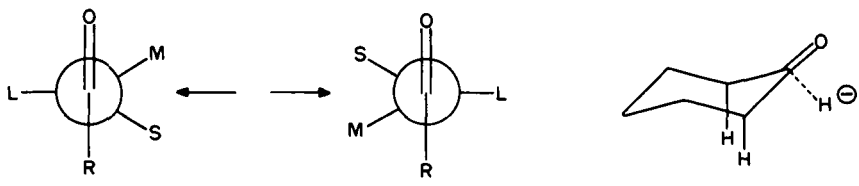
carbon[38]. This model is based on steric interactions and assumes that the largest group L on the vicinal stereogenic carbon is in an *anti* conformation to the oxygen of the carbonyl, and that the carbonyl is flanked by the medium M and small S groups. The predominant product will be obtained from the approach of the nucleophile from the less hindered side or the S side, as indicated by an arrow. This model is called the open chain model. The cyclic model **14** predicted the steric course of the preferential attack of ketones containing a hydroxyl or amino group α to the carbonyl. In nucleophilic reactions of these compounds, the conformation of the molecule was determined by the bridging of the oxygens of the carbonyl and hydroxyl by the metal cation of the nucleopile.



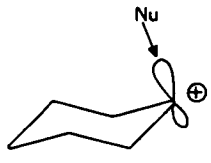


The dipolar model **15** was proposed by Cornforth[39] for compounds containing a polar group, e.g. chlorine, α to the carbonyl. The repulsion between the C=O and C—Cl (C—Z) dipoles will place them in an *anti* conformation. Karabatsos[40] suggested the model **16** instead of the open-chain model **13** on the basis of the known conformation of ketones. The minor product was supposed to be obtained from the minor conformer **17**.

The models considered were based on ground state conformations of ketones. Felkin and Cherest[41,42] proposed a model related to the structure of the transition state with staggered bonds **18**. They assumed that the major product was formed in a conformation, where the largest group L on the carbon α to the carbonyl will be *anti* to the approaching nucleophile. In this model the S group is near R and M near the oxygen of the carbonyl. The minor product was assumed to be formed via a transition state, where the S group is near the carbonyl oxygen **19**. The reluctance of unhindered cyclohexanones to undergo an equatorial attack by metal hydrides was attributed by Felkin to an eclipsing of the forming bond with the axial C—H bonds on the carbon vicinal to the carbonyl **20**.



Klein has observed that unhindered cyclohexanones are attacked axially by borane to yield predominantly equatorial alcohols[43], but methylenecyclohexanes preferentially react with borane from the equatorial direction[44]. Since the structures of the reagents were similar in both cases and the difference was in the character of the reactions, one being nucleophilic and the other electrophilic, the conclusion was that electronic effects intervened in the steric course of these reactions. Cyclohexanones and methylenecyclohexanes contain, in addition to the carbonyl and methylene groups respectively, only C—C and C—H bonds. It was concluded[45,46] that the C—C bonds interact preferentially with the functional groups, leading to a deformation or distortion of the frontier orbitals by a σ–π interaction. The LUMO was distorted in the axial direction **21** and nucleophilic reactions (Nu) preferred to occur from that direction, but the HOMO was distorted into the equatorial direction **22**, where electrophilic reactions (E) took place predominantly. This rationalization was extended to cyclohexyl cations and anions and to six-membered heterocycles. Later calculations have shown[47] that in endocyclic cyclohexene the frontier orbitals were slightly distorted both in the same axial directions **23**, reflecting the preferential axial attack of both nucleophiles and electrophiles on cyclohexens.



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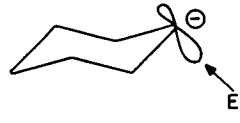

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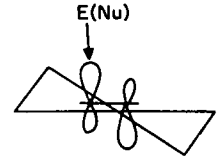
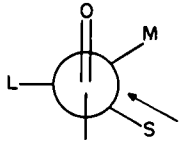


(23)

Nguyen Trong Anh and Eisenstein calculated[48] (STO-3G) the transition states of nucleophilic attack on a carbonyl group containing a vicinal stereogenic center and found that the Felkin models **18** and **19** are better representations of this transition state than those of Cram and Karabatsos. Moreover, the reason for the lower energy of **18** than of **19** was ascribed to the obtuse angle between the nucleophile and the C=O bond (**24** and **25**), by taking into account the trajectory deduced by Burgi and Dunitz[50] from the consideration of crystal structures of aminoketones and by calculations[51]. The preference of **24** over **25** arises from differential interactions of the nucleophile with the small S and medium M group.



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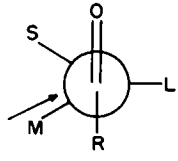
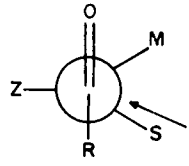


(25)



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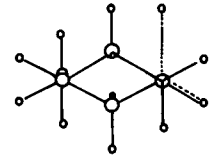


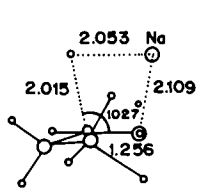
(27)

The reason for the attack of the nucleophile approximately *anti* to L is, according to Nguyen Anh, the stabilization of the transition state of this addition by the secondary interaction of the nucleophile with the antibonding σ^* orbital C—L. This orbital was calculated to be lower in energy than that of C—M or C—S. An *anti* overlap was also found to be preferred to a *syn* overlap.

The steric course of the reaction corresponding to the dipolar model is also due to the lower energy of the C—Z (e.g. C—Cl) antibonding orbital, and the transition state is **26** and not **15**.

The preferential axial attack of small nucleophiles on unhindered cyclohexanones was attributed to the distortion of the ring towards a more planar structure. In such a structure, the axial attack only[49] is in a direction antiperiplanar (**27**) to the axial C—H bonds, but the direction of an equatorial attack is not antiperiplanar to the C—H nor to the C—C bonds. A good overlap with the C—C or C—H *anti* bonds will not be allowed during equatorial attacks.

The group of Houk[52] investigated the effect of an allylic stereogenic center on the structure of the transition states in various reactions. Calculations were carried out with Gaussian 80 and 82 using the 3-21G basis set. The conclusion reached was that all the bonds to the atoms vicinal to the reacting center were staggered relative to the forming bond and one of the allylic bonds is *anti* to this bond. For calculations of larger systems the MM2 method[53] was used. The ratio of stereomers obtained experimentally reflected the differences in energy between the calculated transition states for their formation. The transition state of the reaction of sodium hydride with propionaldehyde[54] has a C—H bond antiperiplanar to the forming C—H bond and the methyl in an inside position in **28**. The conformation with the *anti* methyl group **29** is disfavored relative to **28** and the conformation with the outside methyl group **30** is the least stable for steric reasons: the *anti* methyl **29** destabilizes the electron-rich transition state because it is a better donor than a CH bond[347]. On the other side, the inside methyl in **28** stabilizes the transition state by electrostatic effects in nucleophilic reactions with ketones containing a secondary alkyl substituent at the α position. However, the transition state with one *anti* and one inside methyl is preferred to that with one inside and one outside methyl because, when alkyls are placed outside and inside, they cannot simultaneously achieve their preferred dihedral angles. The conclusion, that an *anti* hydrogen is preferred to a methyl, is contrary to the conclusions of Anh, that when the two alkyls of the secondary group differ in size, the larger group is *anti* to the nucleophile[348], according to the Felkin model. According to Houk, electronic effects favor placing a donor group inside or outside, with *anti* disfavored. Steric effects favor *anti* more than inside and inside more than outside positions. However, an attack of water on a carbonyl antiperiplanar to a methyl was estimated recently[55] to be at least 1.9 k cal mol^{-1} more favorable than such an attack *anti* to C—H (two C—C and one C—H bonds are on the carbon α to the carbonyl).



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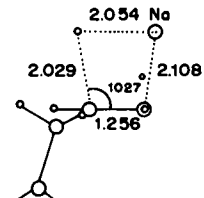

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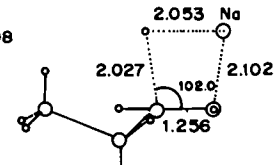
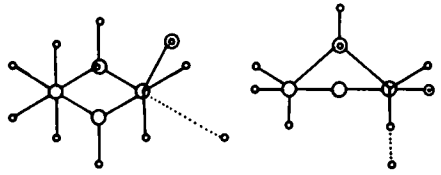


(30)

In the axial attack on cyclohexanone, the transition state can assume a structure without ring strain, but ring strain is introduced during an equatorial attack. The axial selectivity is enhanced in cyclohexenones[56–58], since in its transition state the torsional repulsions are minimized but these repulsions are increased in an equatorial attack. This can be seen on Newman projection of transition states[57] for equatorial hydride attack on cyclohexanone **31** and cyclohexenone **32**.

An entirely different approach was taken by Cieplak[59] to explain the preferential axial attack on cyclohexanones. This was attributed to the two-electron two-orbital interaction that stabilizes the transition state. However, instead of the stabilizing interaction of the HOMO of the nucleophile with the LUMO of the *anti* C—H bond, as assumed



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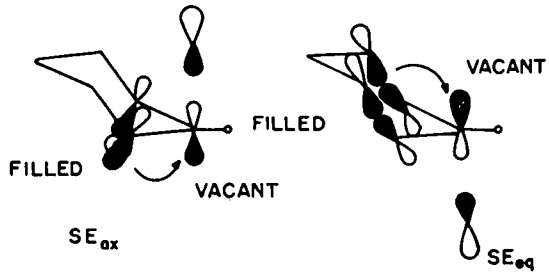
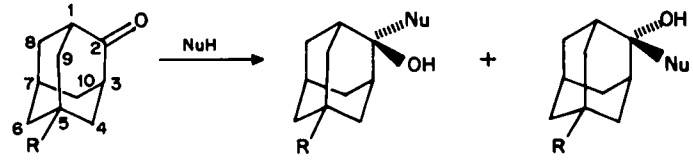


(33)

previously[39], this preference is now assumed to arise through the larger stabilization energy $SE(\sigma,\sigma^*)$ from the delocalization of the electrons of the α C—H bonds into the σ^* antibonding orbital of the bond forming between the nucleophile and the carbon of the carbonyl. This stabilization is larger than the corresponding stabilization energy by the C—C bonds (33). The C—H bonds were considered to be better electron donors than C—C bonds.

There are several recent investigations that support the Cieplak hypothesis. Le Noble[60] eliminated the steric effects in nucleophilic additions by studying these reactions with 5-substituted adamantanones **34**. The reduction of adamantanones **34**, where R were phenyl



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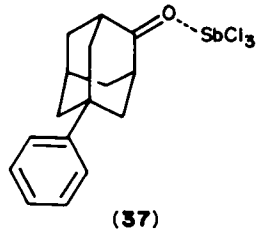
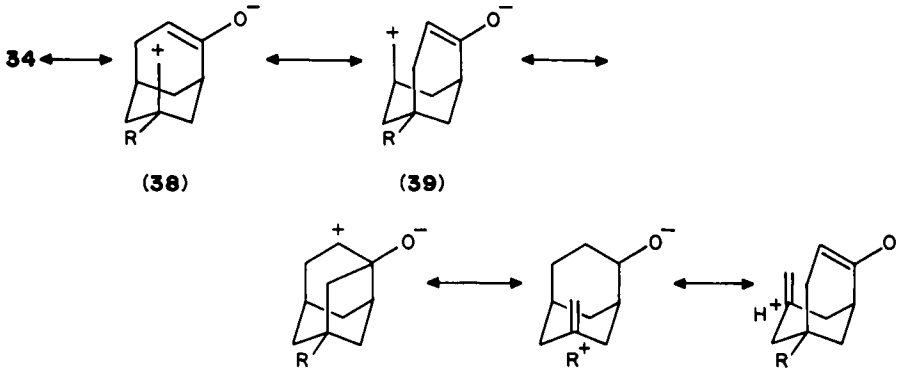


(37)

groups containing *para* substituents, with sodium borohydride yielded a mixture of *Z*- (**35**) and *E*-alcohols (**36**). The ratio of these alcohols depends on the R group. Electron-withdrawing groups favor *syn* approach of the nucleophile and electron-donating groups, *anti* approach. A plot of the $\log Z/E$ vs. σ_p gives a straight line with $\Delta\rho = -0.39$. The favored approach is *anti* to the more electron-rich C—C bond carrying the electron-donor group.



If hyperconjugation is effective in the transition state, it should also be manifest in a complex of adamantanone with a Lewis acid. This was indeed found by Laube[61] for the complex 5-phenyladamantan-2-one pentachloroantimony **37**. In the crystal structure of **37** the carbonyl bond and all the C_α—C_β bonds are lengthened relative to that of adamantanone, and the C_1—C_2, C_3—C_2 and C_7—C_8 bonds but not C_5—C_9 bonds are shortened. This is in agreement with the resonance structures **38–43** for hyperconjugation. ^{13}C NMR spectra of **27** and **24** also support this hyperconjugation in solution.

Despite these important investigations there is no unanimity[62] on the determining factor in these additions. Carbanions having electron-withdrawing groups such as carboxylates[63] or cyano[58,65,66] groups were found to prefer axial attack on cyclohexanones. This was attributed by Cieplak[59] to the lowering of the energy of σ^* and therefore a better interaction with the C—H σ orbital. On the other hand, this course of the reaction was assumed to be due to the hardness of the nucleophile and to electrostatic interactions whereas soft reagents were considered to prefer equatorial attack, because bond formation is important in their reactions[57].

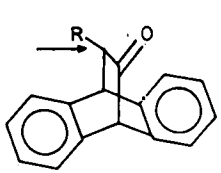
The exclusive axial attack[58] on 2-phenyl-1, 3-dioxan-5-ones and the equatorial attack on 1, 3-dithian-5-ones[59] was attributed[59] to the better donation by C—C than by C—O bonds and again to the better electron donation by C—S relative to C—C bonds. These directive effects have on the other side been attributed to torsion interactions[54].

Long-range effects by polar groups on the steric course of reaction of cyclohexanones were known[70–73]. Orbital overlap interpretations have been proposed[59] even for substituents at the 4 position of cyclohexanones, but kinetic measurements point to dipolar interactions[73].

The hydride attack on 3-alkyl bicyclo[2.2.2]octan-2-ones **43** *syn* to the alkyl group[74] was explained[59] by the better C—H than C—C electron donation to the σ^* orbital and, on the other hand, the C—C bond was thought to be the better electron donor and this was assumed to be the cause for the repulsive interaction with the nucleophile[54].

An experimental test was proposed to distinguish between the models to predict nucleophilic addition stereochemistries[491]. This attack does take place, according to

Cieplak[59], preferentially *anti* to the best electron-donor bond in the order C—S > C—H > C—C > C—N > C—O. Houk, however, has put the emphasis[52,54,57,492] on Felkin's[41] hypothesis of torsional effects. Benzocycloheptenone, that exists predominantly in the chair form **44**, was considered[491] to give the answer to the question, what is the directing effect in the steric course of nucleophilic addition to ketones. In cyclohexanones **45** axial attack involves less torsion strain than equatorial attack, but is also at the same time *anti* to C—H, whereas equatorial attack is *anti* to C—C. Both models predict the same result. In benzocycloheptenones the Cieplak model predicts that the axial attack is preferred. The model of Felkin–Houk **46**, however, predicts preferential equatorial attack and this is what was found.



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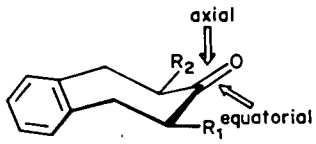

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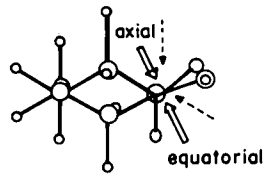

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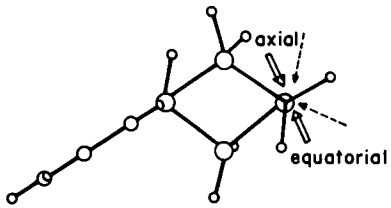
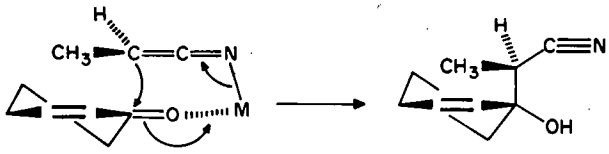


(46)

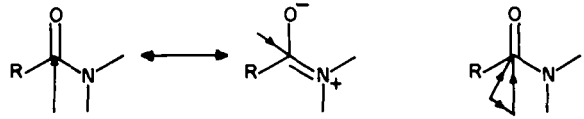
Further work of Trost[493] on the addition of metelated propionitrile to cyclohexenones showed again the increased axial selectivity of these compounds relative to that in cyclohexanones despite the presence of one axial antiperiplanar C—H bond in the first and two such bonds in the latter compounds. This is probably due to the preferred chair-like transition state in the axial attack and to orbital deformation effects. Furthermore, a 6/1 ratio of the two isomers, epimeric at the carbon bearing the methyl group, with **47** as the major diestereomer, was produced. The transition state **48** shows how the presence of a double bond and the absence of an axial C—H at the 3 position offers an empty pocket for the methyl group.



(48) (47)

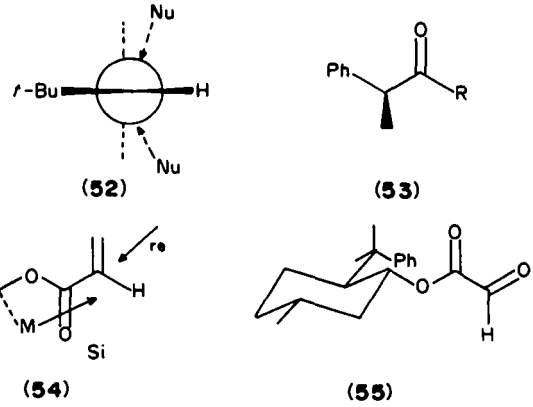
The trajectory followed by a nucleophile[51] in the course of addition to a carbonyl was discussed by Baldwin in a series of papers, describing rules for preferred approach to π systems[75–77]. A so-called approach vector analysis described the angle of approach of a nucleophile to a carbonyl resonating with another group as a resultant of two vectors, each representing the angle of approach to one of the resonating functional groups. The lengths

of the vectors were taken according to the weights of the resonance forms. The method is shown for the resonating form of an amide (**49** and **50**) and the resultant angle (**51**). The trajectory of approach of a nucleophile to an unsymmetrical π-electrophilic center was treated theoretically[78,79] and the interactions with the π, π^*, σ and σ^* frontier orbitals were considered.



(49) (50) (51)

Heathcock[80] carried out MNDO calculations[81] on the trajectory of approach of a hydride to pivaladehyde. A large deviation away from the *t*-butyl group was found from the plane perpendicular to the plane of the carbonyl and containing the C—O bond **52** (the oxygen points to the rear). Such a deviation can explain the observations[41] that asymmetric induction increases in **53** as the size of R increases, since a larger R will bring the trajectory of the nucleophile closer to the chiral group.



(52) (53)

(54) (55)

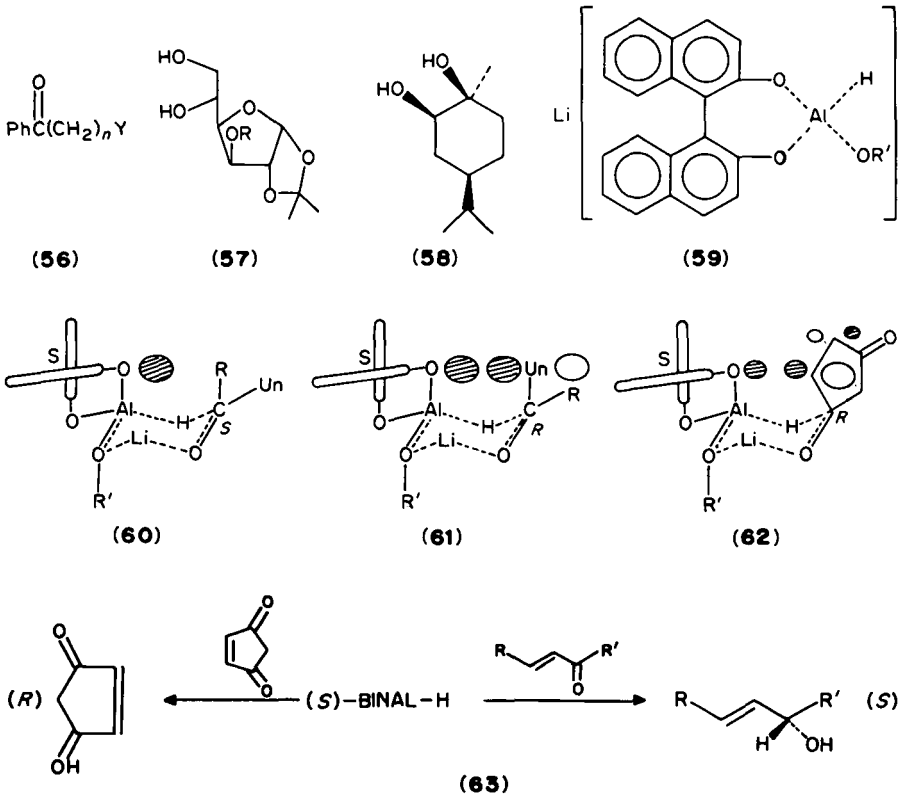
The steric course of nucleophilic additions to chiral glyoxylates has been rationalized by Prelog[82] by a model (**54**), where the carbonyls were disposed *anti* to each other and the largest group L of the chiral alcohol unit *anti* to the ester carbonyl. In this conformation the aldehyde group was presumed to be attacked preferentially from above. This conformation **54** was not consistent with X-ray crystal structures of these esters[83]. The asymmetric induction in these esters should depend on the difference in the size of S and M, but not on L. However, a very strong dependence on L was found[84,85]. Another model (**55**) was proposed in the case of the 8-phenylmenthol ester with the hydrogen S *syn* to the ester carbonyl and the two carbonyls *syn* to each other due to chelation by the organometallic nucleophile. The asymmetric induction depends according to this model on the size difference between L and M.

B. Reductions of the Carbonyl Group

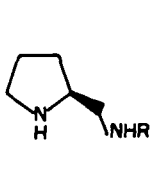
1. Reduction with aluminum hydrides[3,21,25,86,87]

Lithium aluminum hydride (LAH) can be modified by the reaction with chiral alcohols. One or more alkoxy substituents can be introduced on aluminum. The problem

with these derivatives is that they undergo disproportionation[88] to give mixtures of several compounds before and during the reduction. The interpretation of the course of the reduction is therefore difficult. The reduction of ketones with (−)-menthol–LAH gives carbinols with low enantiomeric excess[89]. A better asymmetric induction was obtained[90] for the same reaction with **56**, where $n = 1–3$, Y = OMe, NR_2. A still better result was obtained for the reduction of **56** with the monosaccharide **57** derivative of LAH[91], but simple ketones gave low enantiomeric excess (less than 10%). Pinanediol **58** was also used[92] to modify LAH, but met with little success. A reagent prepared from **57** (R = $PhCH_2$), ethanol and LAH was the most successful, reducing acetophenone[93] with 70% ee. The best diol modifier was a derivative of the chiral (*S*)-binaphthol that gave with LAH and an additional molecule of ethanol an efficient reagent[94] **59** called (*S*)-Binal-H. More than 90% ee have been reported for the reduction of ketones with this reagent[95]. The transition state for the reduction[96] of RC(O)Un, where Un is an unsaturated group, with this reagent is **60** leading to the (*S*)-alcohol. The other arrangement of the group **61** is less stable because of the n-π repulsion. However, the unsaturated group will be *syn* to oxygen when a 1,4-unsaturated diketone is reduced (**62**), due to the stabilizing two-electron interaction of the n lone pair with the π^* orbital. The divergent course of reduction is shown in equation 63.



Modification of LAH with monoamines gave poor results, but secondary diamines such as the proline derivatives **64** investigated by Mukaiyama[97,98] proved to be efficient and gave high ee.



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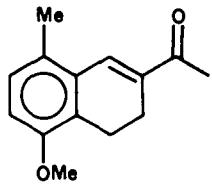

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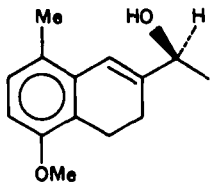

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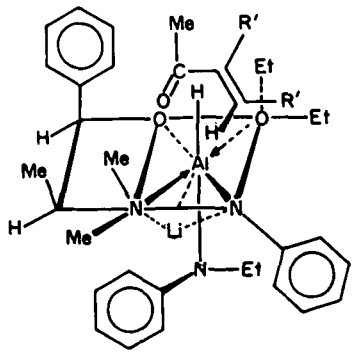
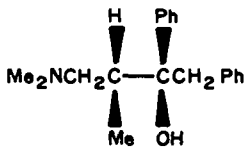


(67)

Aminoalcohols[99], such as quinine, quinidine or ephedrine, were also used as chiral auxiliaries for LAH modification and gave moderate asymmetric induction. A chiral complex[100], prepared by reacting LAH with (−)-*N*-methylephedrine and *N*-ethylaniline, reduced 65 to 66 with 92% ee. The structure **67** was assigned to this reagent.

Darvon alcohol **68** gave good results[101], as a LAH modifier. Reduction of acetophenone with this reagent directly after its preparation gave (*R*)-(+)-methylphenylcarbinol with 75% ee. However, after longer standing, this reagent yielded the (*S*)-enantiomer in 66% ee.

Morrison[102] investigated the effect of several groups in the molecule on the asymmetric induction and found that each of them in e.g. **69** contributes to this effect.



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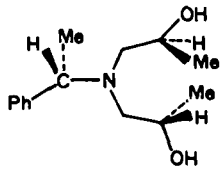

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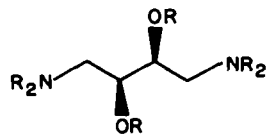


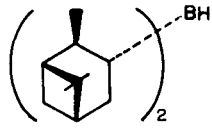
(70) DDB

Seebach[103] used a series of 1,4-bis-dialkylamine-2,3-butanediol derivatives **70** (DDB) prepared from tartaric acid as LAH modifiers, but their asymmetric induction was only moderate.

All these modified LAH compounds, except BINAL-H, are not characterized fully, their structure is uncertain and various equilibria take place probably in solution. The mechanisms proposed in the literature for their reactions are highly speculative.

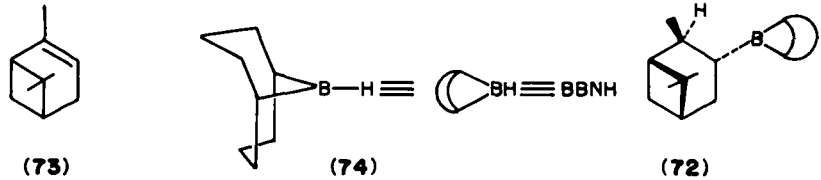
2. Reduction with boron compounds[104]

The high asymmetric induction brought about during the hydroborations of olefins[105] with (+)- and (−)-diisopinocamphenylborane $(Ipc)_2BH$ (**71**) led to a disappointment when only a modest asymmetric induction was observed for the reduction of ketones with this reagent[106,107]. The reason for this is probably the different mechanism of the reduction of ketones, that is not a one-step concerted addition of the borane[43] to the C=O bond.

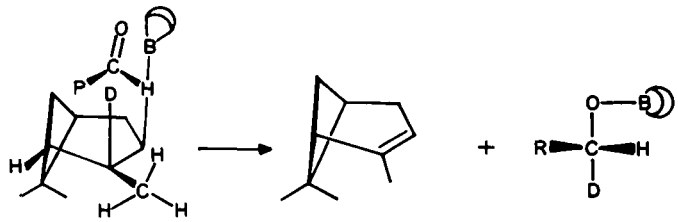


(71)

The attempts to modify boranes and borohydrides have started only in the 1980s and led to the preparation of efficient reagents. The breakthrough in the field of boranes was made by Midland by the preparation[108–110] of B-3-pinanyl-9-BBN (or B-Ipc-9-BBN or Alpine borane) **72** by the reaction of (+)- or (−)-α-pinene **73** with 9-borabicyclo[3.3.1]-nonane[111] (9-BBNH) **74**. This reagent reduced 1-deutero-aldehydes with almost 100% ee. The reason for this selectivity is the concerted mechanism of the reaction[108,109], where a β-hydride from the carbon is transferred to the aldehyde (equation 75). Ketones are not reduced effeciently, since the reaction with them is sluggish and heating brings about the reverse reaction of **72** to pinene and BBNH, and BBNH then reduces the ketone nonselectively. This difficulty has been circumvented in two ways: (a) by carrying out the reaction with the neat **72** and not in a solution to make the reaction faster[112], or (b) by carrying out the reduction under high pressure[113]. However, α-diketones and α-ketoesters[114] give close to 100% ee while alkynyl ketones[110,115] and α-bromoketones[116] are reduced with very high enantioselectivity (85–98% ee) even in normal conditions.



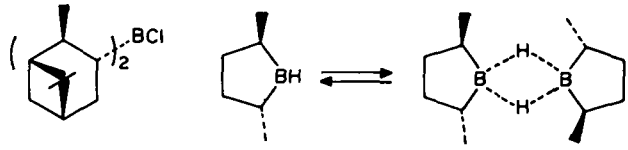
(73) **(74)** **(72)**



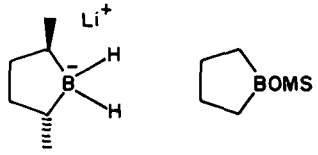
(75)

Another highly enantioselective reagent is diisopinocampheylchloroborane **76** Ipc_2BCl that is apparently the best reagent for asymmetric reduction of arylalkyl[117] and α-tertiary

alkyl ketones[118]. *Tert*-butyl methyl ketone is reduced with 91% ee and acetophenone with 98% ee.

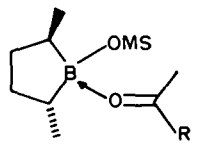


(76) (*R,R*)-(77) (78)



(79) (80)

The most efficient reagents for the asymmetric reduction of (hindered and unhindered) dialkyl ketones are (*S,S*)- or (*R,R*)-dimethylborolane[119] **77** or its dimer **78**. (*R*)-alcohols are obtained when (*R,R*)-**77** is used. Reduction of methyl branched-alkyl ketones yields practically one pure enantiomer. Even methyl unbranched-alkyl ketones are reduced with 80% ee. This high asymmetric induction was surprising, considering that terminal olefins undergo hydroboration with the same reagent with insignificant asymmetric induction[119]. An investigation[120] of the kinetics of the reaction and MO computations led to the proposal of a mechanism for the reaction. It was observed that, during the preparation of **78** from **79** with some excess of methanesulfonic acid, the dimethylborolanyl mesylate **80** was formed, and that **80** catalyzed the reduction. In its absence lower asymmetric induction was observed. A complex between **80** and the ketone was proposed as an intermediate **81** with boron *anti* to the larger alkyl. This complex was attacked by another molecule **77** via the transition state **82**, leading to the (*R*)-product calculated to be 1.2 kcal mol^{-1} more stable than the one leading to the (*S*)-isomer.



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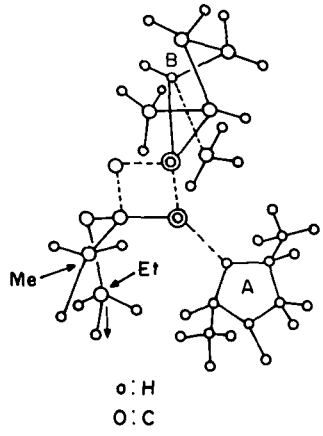

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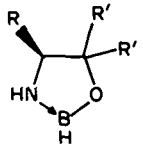

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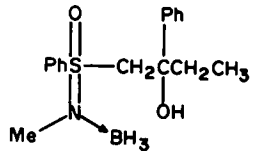


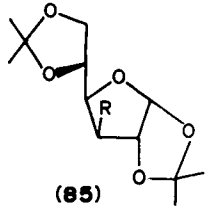
(84)

Complexes of borane with chiral aminoalcohols[121,122], e.g. **83**, gave up to 90% ee in the reduction of aliphatic ketones. A complex of borane **84** with a β-hydroxysulfoximine[123] gave also 82% ee.

The asymmetric reduction of ketones with borohydrides has met also with considerable success. Sodium borohydride and a chiral ammonium salt containing a hydroxyl group gave 39% ee in the reduction of acetophenone[124] in a phase transfer reaction.

(*S*,*S'*)-Dibenzoylcystine catalyzes the asymmetric reduction of aliphatic ketones by lithium borohydride[125] with 80–90% ee.

Sodium borohydride reacts[126] with 1,2′,5,6′-di-*O*-isopropylidene-α-D-glucofuranose **85** (R = OH) and isobutyric acid to give a reagent that reduces aromatic ketones with 18–64% ee, but aliphatic ketones with 12% ee. A better reagent[127] is obtained when **85** reacts with the sodium zinc borohydride to give **86**. This complex reduces aryl alkyl ketones with 40–68% ee and aliphatic ketones with 37% ee.



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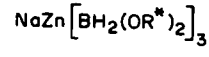
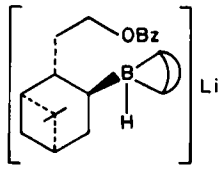


$R^* = 85$

(86)

Another derivative of **85** was prepared by Brown[129] by the reaction of **85** (R = OH) with BBNH to give 85 (R = OBBN). The introduction of a hydride on the boron by potassium hydride gave K 9-O-DIPGF-9-BBN (≡ K 9-O(1,2; 5,6-di-O-isopropylidene-α-glucofuranosyl-9-boratabicyclo-[3.3.1]nonane), that is a good reagent for the reduction of hindered aliphatic ketones.

Midland[128] prepared the "NB-Enantride" reagent **87** by hydroboration of benzyl nopol ether with BBNH and the introduction of a hydride by *tert*-butyllithium. This reagent reduced acetophenone with 70% ee. Brown[129] has made a comparison between the efficiancies of asymmetric inductions of many of these compounds.



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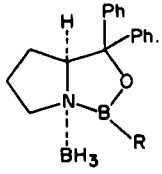

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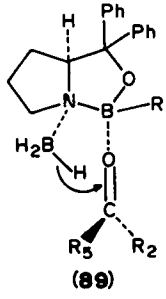


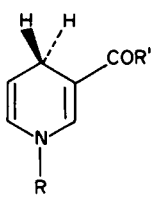
(89)

In most cases studied there is little knowledge about the transition state structure for these reductions. Corey[130] has built rigid oxaborolidines **88** (R = H and R = CH_3) containing a boron as a Lewis acid and another one as a hydride donor. The transition state proposed for the reduction of ketones is **89**.

3. *Reduction with chiral dihydropyridine reagents*[131,132]

The alcohol dehydrogenases require nicotinamide adenine dinucleotide (NADH) as a cofactor in their oxidation–reduction reactions. The stereoselectivities achieved in these reactions are high. It was therefore very attractive for chemists to examine the possibility of using simplified NADH models in asymmetric synthesis. It was also hoped that the investigation of the reductions using various models could throw light on the reasons for the opposite steric course of reduction by various enzyme catalyzed reactions.

The nonenzymatic asymmetric reduction was achieved using an optically active 1,4-dihydronicotinamide derivative (NAH) **90**, where R was an alkyl or benzyl group and R' a menthyl, amino acid or dipeptide group. Optical yields up to 47% ee have been achieved. Also chiral derivatives of the Hantsch ester **91** have been investigated. A metal salt is generally needed to accomplish these reductions. Magnesium and zinc salts have been used. An interesting dependence[133] of the asymmetric induction on the relative concentration of the magnesium salt and the NAH concentration was found. Increasing the relative amount of the salt increased the enantioselectivity, but large amounts of it could decrease this selectivity. There was also a favorable effect of the oxidized form[134] of NAH attributed to formation of a complex between the reduced and oxidized form, where one face of NAH was shielded. Another way of shielding one face of NAH was to prepare compounds containing two NAH groups[135] with C_2 symmetry **92** or by introducing a methyl group[136] at the 4 position of NAH (**93**). Finally, a bridge between the 3 and 5 positions[137] seems also to increase the enantioselectivity of the NAH. High asymmetric induction was found for the cyclic NAH derivative and a transition state **95** explaining it was proposed[137]. The effect of Mg in bridging the carbonyl and the amide groups is emphasized.



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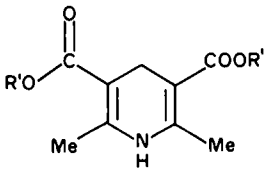

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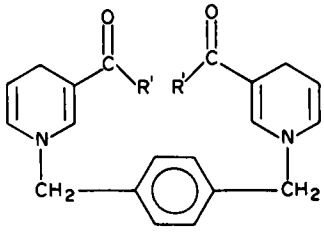

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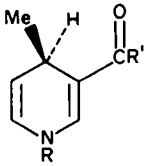

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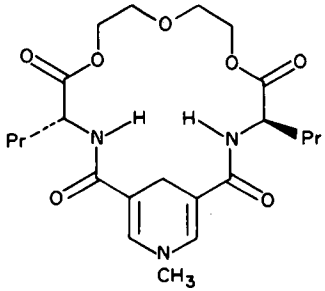

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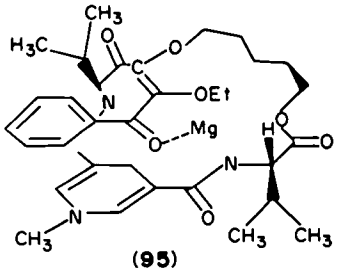
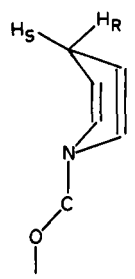


(95)

No generally valid mechanism and an understanding of the stereoselectivity has been achieved. Moreover, these reductions are limited to ketones activated by other carbonyl groups or by electronegative substituents. More advanced models are therefore expected.

The enzyme-mediated hydrogen transfer from NAH to carbonyl groups belong to two categories: one where the H_S and the other where the H_R is transferred. The side opposite to the transferred hydrogen is assumed to be blocked by the enzyme. An interesting hypothesis[138] was proposed to explain the different steric course taken by the two categories of the enzymes. The H_S is transferred from a *syn* conformation (C—H_S to the C—O bond of ribose) and H_R from a *trans* conformation **97**. It is always the pseudoaxial H that is transferred for stereoelectronic reasons. The *anti* conformation is the weaker reducing agent. The different reducing powers of the two conformations are adapted to the reactivity of the carbonyl to be reduced. The enzymes of the two categories have developed to impose either the **96** or the **97** conformation, according to the functions they have to perform.



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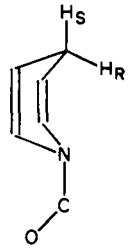


(97)

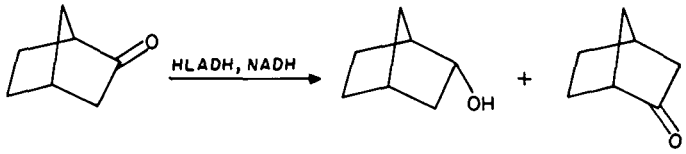
4. Enzyme-catalyzed reductions[139–147]

The ability of enzymes to induce stereospecific transformations in symmetrical substances is of particular importance in asymmetric synthesis and has led recently to a widespread use of their catalytic action in chemical processes. The stereochemical specificities of many enzymes and microorganisms are well documented and permit one to predict the configuration of the products or reactions. Prelog's[148,149] rule permits one to predict the stereochemical course of reductions, e.g. by yeast, where a re face attack of the hydride on a ketone will give an (*S*)-alcohol (equation 98) (the priorities are O > L > S; L is the large and S the small group).

(98)

An example of the enantiomeric specificity of the horse liver alcohol dehydrogenase (HLADH) is the specific reduction[150] of one enantiomer of norbornanone (reaction 99). The *trans*- and *cis*-2,7-decalinediones have been reduced using the same enzyme[151,152] with enantiogroup and diastereoface selectivity (equation 100), with a de (diastereomeric excess) and ee in excess of 98%.

Microorganisms have also been used directly in chemical processes as sources of enzymes. The relative advantages of the two methods have been discussed[146,153]. The



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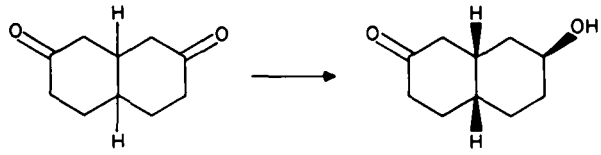
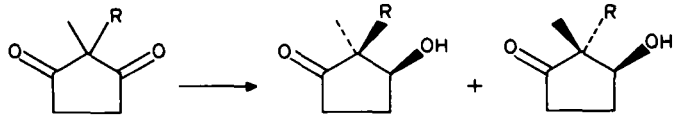


(100)

reduction of cyclopentanediones using common bakers' yeast[151] was also face and group selective (equation 101).

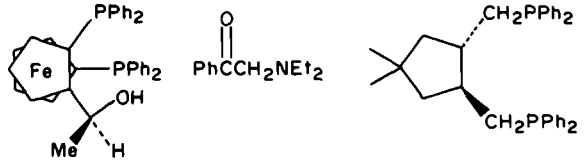


(101)

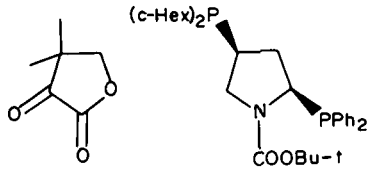
$R=CH_2CH_2CH_3$	100%	0%
$R=CH_2CH=CH_2$	90%	10%

5. Reduction of ketones by catalytic hydrogenation[21,25,154]

Homogeneous hydrogenation, catalyzed by chiral transition metal complexes[155], does not proceed with high asymmetric induction, except for compounds containing an additional functional group that can coordinate with the metal, such as a keto, hydroxy, amino, ester or a double bond. Cationic rhodium catalysts containing a chiral ligand are generally used. The reduction of pyruvic to lactic acid using a complex of rhodium containing (R)-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethanol (BPPFOH)[156] **102** as a ligand proceeded with 83% ee, and that of acetophenone with 40% ee. Higher asymmetric induction was obtained in the reduction of **103** using[157] a rhodium DIOP [2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane] catalyst **104**. Ketopantolactone **105** was reduced[158,159] in the presence of BCPM [(2S,4S-N-t-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine **106** with 90%ee. The BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] ruthenium catalysts[160] reached in many cases practically 100% optical yield in the reduction

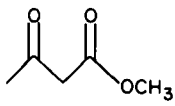


(102) (103) (104)



(105) (106)

of several keto-esters and amides. These catalysts are derivatives of BINAP = 2,2'-bis(diphenylphosphino)1, 1'-dinaphthyl and of an unknown structure. They are derivatives of Ru(II) containing halogens, have the empirical formula RuX_2(BINAP), and are different from the BINAP complexes that are used to catalyze the hydrogenation of C=C double bonds. Ketoester **107** is reduced by $RuCl_2$[(*R*)-BINAP] to (*R*)-**108** and by $RuCl_2$[(*S*)-BINAP] to (*S*)-**108** both with higher than 99% ee. The racemic **109** is reduced by $RuBr_2$[(*R*)-BINAP] to approximately an equal amount of the *syn* **110** and *anti* **111** products with 96% ee. Functional groups other than the ester function such as hydroxy, alkoxy, siloxy, keto, dialkylamino groups also promote the selective reduction by the ruthenium catalyst.



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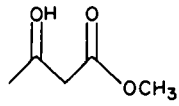

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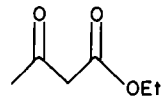

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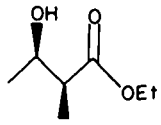

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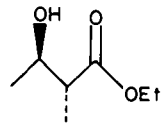


(111)

Heterogeneous hydrogenation in the presence of catalysts modified by a chiral compound can also lead to products with very high enantiomeric purity. Methyl acetoacetate was reduced by Raney nickel modified by (*R*, *R*)-tartaric acid to methyl (*R*)-3-hydroxybutyrate[161] with 83% ee. Hydrogenation of compounds containing a chiral auxiliary group on solid catalysts was also used as a method for asymmetric induction of carbinol formation[162]. The hydrogenation of (−)-menthyl or (+)-bornyl esters of benzoylformic acid using Raney nickel, PtO_2 or alkali-treated Pd/C led to an excess of (−)menthyl (−)mandelate or (+)-bornyl (+)mandelate respectively, but acid treated catalysts gave (−)menthyl (+)mandelate or (+)-bornyl (−)mandelate respectively.

Another route for the asymmetric reduction of ketones is catalytic hydrosilylation[163]. In this reaction a Si—H is oxidatively added to a transition metal complex. The silyl group and the hydrogenation are then consecutively transferred to the carbonyl group that was coordinated to the metal. The net reaction 112 can be catalyzed by a chiral catalyst. The preferred catalysts are cationic rhodium complexes of general formulae L_2*Rh(S)Cl, $[L_2$*$RhH_2S_2]^+ClO_4^-$, $[L_2^*Rh(OD)]^+ClO_4^-$. In the case of reaction 112[164] the catalyst was $[BMPPRhH_2S_2]^+ClO_4^-$, where BMPP is chiral benzylmethylphenylphosphine and S is the solvent. This reaction proceeded with 61% ee, but enantiomeric excesses of up to

85% can be obtained as a function of the substrate, catalyst and silane. Thus reaction 112 proceeded with only 28% ee, when trimethylsilane was used.

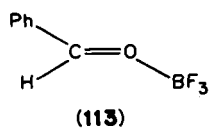
$$\mathrm{PhC(=O)Bu\text{-}}t + \mathrm{PhMe_2SiH} \rightarrow \mathrm{Ph^*CH(OSiMe_2Ph)Bu\text{-}}t \rightarrow \mathrm{PhCH(OH)Bu\text{-}}t \qquad (112)$$

The asymmetric reduction discussed until now was concerned mainly with induction by chiral catalysts; *substrate-dependent asymmetric reduction* will be discussed together with asymmetric induction in organometal additions (Section II.C.4).

C. Nucleophilic Additions of Organometal Compounds

1. Coordination to a metal

The main role of the metal is to be associated with the nucleophile and sometimes with the oxygen of the carbonyl and other groups in the substrate during the reaction. However, electron-deficient metal centers as in $TiCl_4$, $SnCl_4$ or BF_3 may act as catalysts without direct association with the nucleophile. Complexes of carbonyl compounds with such metal centers have been assumed for a long time, but only recently has the structure of a complex between benzaldehyde and BF_3 been established by X-ray crystallography[165]; see **113**. The boron trifluoride is complexed to the oxygen *anti* to the phenyl group. The B–O–C–C fragment lies in a common plane. The *anti* arrangement persists also in solution (NMR). The structure **113** is more like an imine than a ketone and can have a profound effect on the steric course of reactions; this will be discussed in the section on hetero Diels–Alder reactions.



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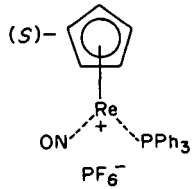

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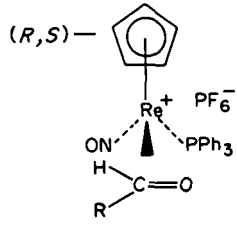

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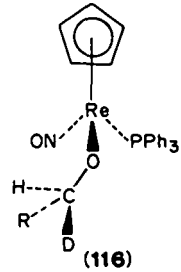
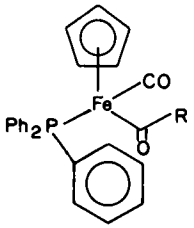


(116)

A different way of coordination of a carbonyl compound with a metal is by forming an η^2-coordination. This is of particular interest when the metal center itself is stereogenic and not only by the presence of chiral ligands. Such a complex can be expected to induce asymmetric reactions. A chiral pyramidal rhenium cation **114** was found[166] that coordinates with one face of an aldehyde in such a way as to minimize the steric interactions (**115**). Addition of a deuteride ion yields the (*R*, *R*)-product **116**, that is hydrolyzed to the chiral (*R*)-carbinol.

The carbonyl compound can be linked to the metal not only by coordination but also through a C—M σ bond. If the metal is a stereogenic center, the two faces of the carbonyl are diastereotopic, e.g. in the iron complexes[167] **117**. In this complex the triphenylphosphine group shields sterically one face of the carbonyl and diastereoselection is observed. The conformations[168] of this and similar compounds have been shown to depart from the ideal staggered form **118** and to be rather **119**.

A different kind of complexation that does not involve directly the carbonyl group, but renders its faces diastereotopic and determines the steric course of the reaction with the



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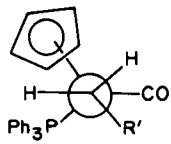

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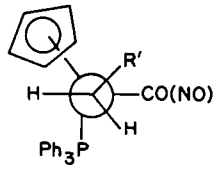
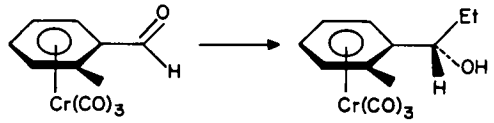
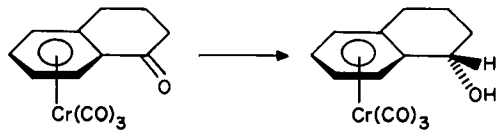


(119)

nucleophile, is that found in chromium tricarbonyl complexes of arylcarbonyl compounds. Complex **120** undergoes[169] a reaction with ethylmagnesium bromide to give **121** (one diastereomer only). Similarly **122** is reduced by sodium borohydride from one side only[170] to yield **123**. Analogous reactions are known[171]. The steric course of the reaction is determined by the interaction of the chromium with the hydroxyl group[172].



(120) (121)



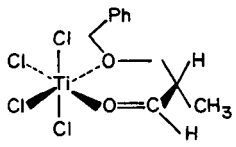
(122) (123)

2. Metal bridging

The cyclic model **14** of Cram assumed chelaion via a metal cation between the carbonyl and another group appropriately located in the molecule. The nucleophile attacked then from the less hindered side of the ring. Until recently, there was no independent confirmation of the existence of such a chelate, except the product of the reaction. If the product corresponded to the model 13 it was called the Cram (or the Felkin) product. If it did not it was assumed to proceed via a chelate **14**, provided a coordinating group was present in the molecule. It is of course possible that the different product did arise for reasons different than chelation. Many authors therefore use the term Cram or anti-Cram for products corresponding or not corresponding to model **13**. We shall also use these terms.

NMR evidence was found for a complex formation[173] between $TiCl_4$ and 2-benzyloxymethylpropanal **124** and 3-benzyloxybutanal **125**. It is of interest that the methyl group in **125** assumed a pseudoaxial conformation due to relief of $A^{1,3}$-like interactions[127], but an equatorial one in **124**. This explains the high level of diastereofacial selectivity in the reactions of **125**.

An NMR investigation of the reaction[174] of $MeTiCl_3$ with 2-benzyloxy-3-butanone revealed the formation of two chelates **126** and **127**. Both of these complexes reacted



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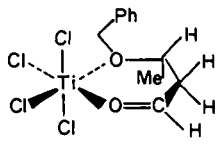

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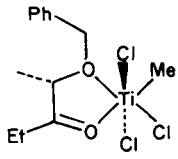

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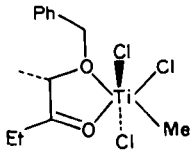

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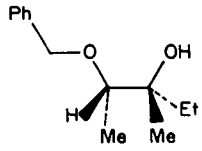
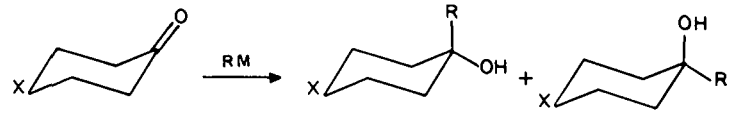


(128)

further and gave after hydrolysis **128**. This reaction was second order, proving that the methyl did not migrate intramolecularly but came from another molecule. This intermolecular transfer of the methyl was also confirmed by labelling experiments.

3. *Effect of ligands*

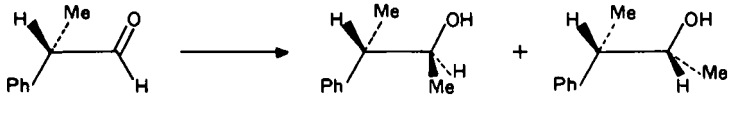
The nature of the ligands affects the course of the reaction profoundly. However, the precise structure of the organometallic species taking part in the reaction is most often unknown, due to ligand addition or exchange or to secondary reactions that take place before a catalytic cycle starts. With organometallic compounds that react stoichiometrically and do not undergo fast ligand exchange, the reacting species is generally known. This is the case in the reactions of boranes and borohydrides. We have previously discussed the enantioface reduction by these chiral compounds. The steric factor is very important in these reductions and the bulk of the ligand finds its expression in the diastereoselective reduction of ketones with borohydrides carrying ligands of different size. If the sodium borohydride reduction[175] of 4-*t*-butylcyclohexanone **129** yields 88% of the equatorial alcohol **130** (R = H) due to the stereoelectronically preferred axial attack, the same reduction with lithium tri-*sec*-butylborohydride[176] (L-Selectride) gives in excess of 99% of the axial alcohol **131** (R = H) in the product, because of the large bulk of the ligands on boron. Similarly[38] the reaction of **129** with methyllithium, butyllithium and lithium acetylide yields 35%, 25% and 88% of **130** (R = alkyl), respectively, the remainder being **131**.



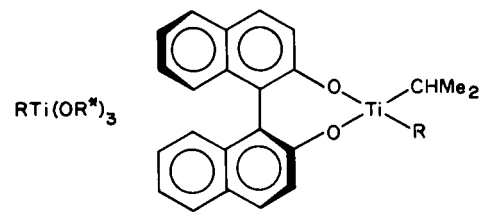
(129) (130) (131)

Other organometallic compounds[177] behave also in the same manner. Organotitanium[178–182] compounds are of particular interest, since the ligands can be varied and thus the bulk of the compound changed. In the reaction of **132** with MeLi, MeMgBr, $MeTiCl_3$ and $MeTi(OCHMe_2)_3$ the ratio of **133**/**134** was respectively[181,183] 65/35, 66/34,

81/19 and 88/12. Enantioselective addition can also be performed by using chirally modified titanium reagents[184], e.g. **135** where R*—OH is a chiral alcohol. The best reagent is of the BINAL type **136**. The asymmetric induction with these reagents is within 30–70% ee.

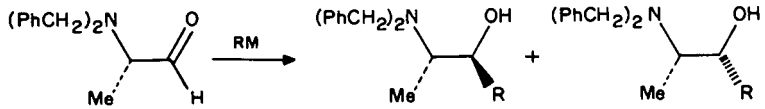


(132) **(133)** **(134)**



(135) **(136)**

The ligands on the metal can have another effect in addition to their bulk effect and asymmetric induction. Electronegative ligands on the metal increase its electron deficiency and its coordinating power[185]. Table 1 shows[185] that **137** reacts with methylmetal compounds to give either the Cram (**138**) or anti-Cram product (**139**). Even magnesium compounds, that generally do form chelates, give the Cram product, but $MeTiCl_3$ or tin tetrachloride are electron deficient enough to form a chelate. This does not happen in the reaction of $MeTi(OPr\text{-}i)_3$, since the electron donation from the oxygen n-orbitals to the metal decreases its coordinating ability.



(137) **(138)** **(139)**

A combination of a high propensity of monomeric aluminum compounds for complex formation, particularly with oxygen (oxygenophilicity), and their low reactivity with ketones lead to effects opposite to those observed with reactive organometallics carrying bulky

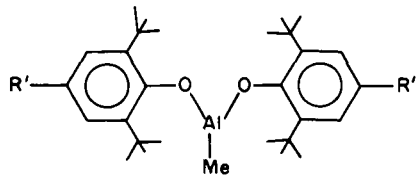
TABLE 1. Products of the reaction **137** $\xrightarrow[RM]{}$ **138** + **139**

RM	Ratio **138/139**	RM	**138/139**
MeMgI	5/95	$MeTiCl_3$	94/6
MeLi	9/91	$MeTi(NMe_2)_3$	4/96
PhMgBr	3/97	$AllSiMe_3/SnCl_4$	84/16
i-PrMgBr	3/97	$MeTi(OPr\text{-}i)_3$	3/97
Me_2CuLi	25/75		

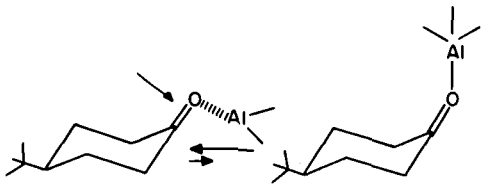
TABLE 2. Effect of MAD or MAT on RM reactions

Carbonyl compound	RM	Lewis acid	Yield (%)	Ratio
129	MeLi	none		**130/131** = 79:21
		MAD	84	1:99
		MAT	92	0.5:99.5
	EtMgBr	none	95	98:52
		MAD	91	0:100
144 (R = Ph)	MeMgI	none	64	**145/146** = 72:28
		MAT	96	7:93
	EtMgBr	none	78	84:16
		MAD	90	25:75
		MAT	98	20:80
	(−90 °C)	MAT	90	13:87

groups[186,187]. Methylaluminum bis(2, 6-di-*tert*-butyl-4-methylphenoxide) **140** (MAD) or methylaluminum bis(2, 4, 6-tri-*tert*-butylphenoxide) **141** (MAT) coordinate strongly with 4-*tert*-butylcyclohexanone but do not react with it. The bulky ligands on aluminum make the *exo* complex **142** more stable than the *endo* one **143**. Complex **142** then reacts with alkyllithium or magnesium compounds from the axial direction as indicated by the arrow (Table 2).

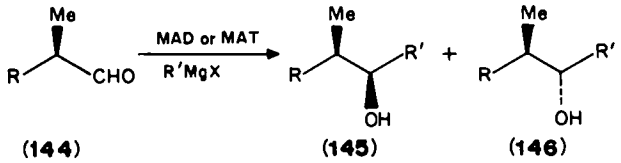


(140) R'=Me (MAD) **(141)** R'= *t*-Bu (MAT)

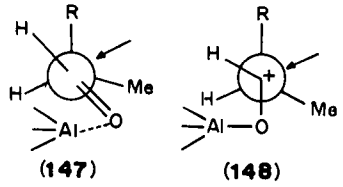


(142) **(143)**

The complexation of an α-substituted aldehyde by **140** or **141** leads to asymmetric induction for similar reasons[186,187,495]. The aldehyde **144** reacts with alkylmagnesium halides to give preferentially the Cram product **145**, but in the presence of MAD or MAT the anti-Cram product **146** is obtained preponderantly (Table 2). In the latter case, the formation of the complex **147** and attack of the Grignard reagent *anti* to Al was proposed (arrows in **147** and **148**).



(144) (145) (146)



(147) (148)

Strong complexation of the metal by external complexing agents, not taking part directly in the reaction of the organometallic compounds, can also affect asymmetric induction, although the reaction slowed down considerably[188,189], since the activation of the carbonyl due to coordination with the metal is weakened. Addition of crown ethers[190] to RLi or RMgX increases the ratio of Cram/anti-Cram products (Table 3). This is ascribed to the loosening of the bond between the metal and the reacting ligand due to complexation of the metal. The ligand acquires a more negative character and the angle of the nucleophilic attack is increased, according to the Felkin–Anh[98] model **24**. The difference in the energies of the transition states **24** and **25** is increased in favor of the Cram–Felkin product. Enhanced Cram selectivity was also observed[191] on addition of tetraalkylammonium bromides to alkyl-lithium or magnesium compounds, though the enhancement is not pronounced as in the presence of crown ethers. This effect was also attributed to the formation of 'naked' anions $R^-NR_4^+$.

Increased anti-Cram selectivity[190,191] was found in the reaction of cuprates in the presence of crown ethers or tetraalkylammonium bromides ('naked' cuprates). The increase of electron density on the reacting cuprate, due to the weakening of the bond with the lithium on complexation or its exchange with $^+NR_4$, promotes single electron transfer to the carbonyl compound. A ketyl anion-radical and alkyl radical are formed. It was argued that the increased charge on the oxygen makes this atom larger and therefore the

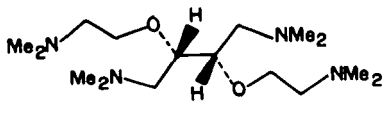
TABLE 3. Effect of crown ethers on RM reactions

Aldehyde	RM	Crown	Yield (%)	Cram/anti-Cram
144 (R = Ph)	BuLi	15—C—5	91	30:1
	BuLi	None	91	5:1
	MeLi	5—021	86	9:1
	MeLi	None	91	4:1
	EtMgBr	K—221	90	9:1
	EtMgBr	None	92	4:1
	Bu_2CuLi	K—21	80	1:5
	Bu_2CuLi	None	95	3:1
	$BuNBu_4$		93	8:1
	$EtNBu_4$		100	8:1
	Bu_2CuNBu_4		99	3:1

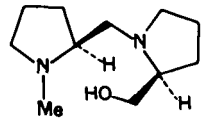
methyl prefers to be near the hydrogen and not the oxygen and, moreover, the direction of attack is perpendicular to the π orbital **148**.

The reduction of aliphatic ketones by dissolving metals, where the product-determining step is the protonation of the negatively charged carbon, proceeds preferentially from the side opposite to that from where ketone reduction by metal hydrides takes place[496]. These reactions support the view advocated by Klein[45,46] that nucleophilic and electrophilic attacks on double bonds, except those in endocyclic cyclohexenes[47], proceed from oppsite sides, due to electronic effects.

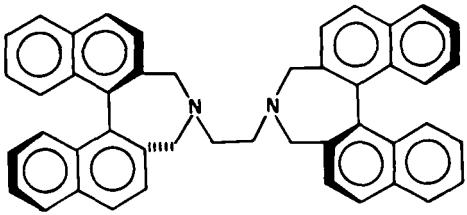
Enantioface selectivity in additions of organometallics to carbonyl compounds is promoted by chiral complexing agents[192]. Systematic investigations in the field were carried out by Seebach[193]. Most of the ligands were obtained from tartaric acid by various reactions, such as DDB (**65**) and DBE (**149**). In the presence of two equivalents of **149**, butyllithium adds to benzaldehyde to give the (*S*)-carbinol with 52% ee. A series of efficient chiral ligands based on proline was developed by Mukaiyama[97,98,194]. (2*S*,2′*S*)-2-Hydroxymethyl-1-(1-methylpyrrolidin-2-yl)-methylpyrrolidine **150** induced the reaction of alkyllithium compounds with aldehydes to proceed with 40–95% ee. The highest optical yields were obtained on lowering the temperature of the reaction and by choosing the appropriate solvent.



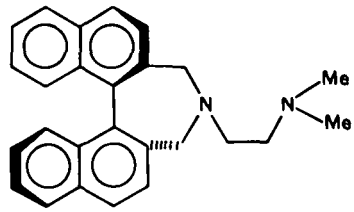
S-(**149**)



(**150**)



R,*R*-(**151**)

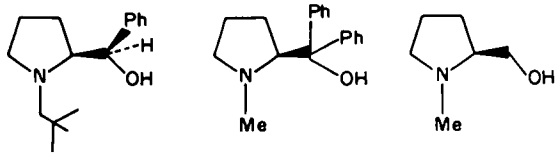


R-(**152**)

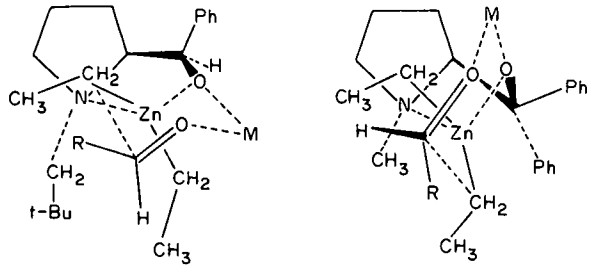
The ee of reactions of other organometallic compounds (of Mg, Zn, Cu) with aldehydes is enhanced when the lithium salt of **150** is used and not that with magnesium or zinc. Tricyclic rigid complexes chelated by lithium are evidently formed as intermediates. Chiral binaphthylamines[195] **151** and **152** induce enantioface selectivity in the addition of organolithium compounds to aldehydes (30–95% ee).

Enantioselective addition of organozinc compounds to aldehydes was studied recently, using complexes of camphorquinone dioximes[196–198,495] and ephedrine[200]. Catalytic-asymmetric induction.[199,201] in this reaction was also found[201]. Enantiomeric excess approaching 100% was found. Using *erythro* PNPM (PNPM = (1-R,2S)-Phenyl(1-neopentylpyrrolidin-2-yl)methanol) **153**-(*R*)-carbinol (100% ee) and, with (S)-(+)-DPMPM, ((S)-DPMPM = (S)-(+)-Diphenyl(1-methylpyrrolidin-2-yl)methanol] **154**-(S)-carbinol (97% ee) was obtained from diethylzinc and benzaldehyde. Steric compression enhances asymmetric induction, since **155** does not promote the formation of a chiral product. The two ligands **153** and **154** have similar structures but their catalytic activity is nevertheless complementary. The reactions were performed with the lithium alkoxides of

153 and **154** and the reacting complex is proposed to be **156** and **156a** for the additions using **153** and **154**, respectively.

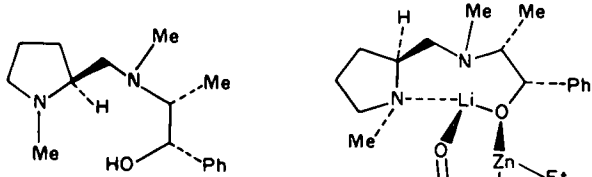


(153) **(154)** **(155)**



(156) **(156a)**

Chiral catalysts for the reaction of organozinc compounds with aldehydes have been described by Corey[202]. Compound **157** prepared from (*S*)-proline and (1*S*,2*R*)-(+)-ephedrine gave a lithium salt that catalyzed the reaction of diethylzinc with benzaldehyde to give (*S*)-(−)-1-phenylpropanol (95% ee). The reacting complex was assumed to be **158**, a tricyclic compound with the terminal rings *anti* to each other. Several other catalysts have also been prepared.



(157) **(158)**

It has been known for some time that if a ligand is not optically pure, the asymmetric induction exerted by it does not have to be proportional to the ee[203,204]. The reasons for this effect of partially resolved chiral auxiliaries on the extent of asymmetric induction have been discussed recently[204]. Departure from linearity between the ee of the chiral auxiliary and the extent of asymmetric induction in reactions of organometallic compounds carrying chiral ligands will be observed if more than one such ligand is associated with the metal. The distribution of the possible complexes in reaction 159 does not have to be statistical. The rates of the reactions of $A[M]L_RL_R$ and $A[M]L_SL_S$ will be equal, but that of $A[M]L_RL_S$ may be different. $A[M]L_RL_S$ will produce the racemate. If there is no *meso* complex $A[M]L_SL_R$ in solution or when this complex reacts with a rate equal to that of $A[M]L_RL_R$, there will be no departure from linearity. However, if the *meso* complex is more

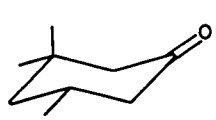
reactive than the optically active one, the optical yield will be less than according to the linear relationship, and vice verse; if the *meso* compound is less reactive, the optical yield will be higher.

$$A[M] + 2L^* \rightarrow A[M]L_RL_R + A[M]L_SL_S + A[M]L_RL_S \quad (159)$$

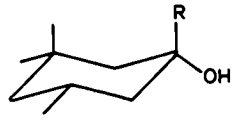
4. Substrate dependence

The stereochemical course of a reaction is controlled by steric or electronic interactions between the reagents or by a combination of both effects. The steric effects are more easy to predict and they can be generally made large enough to overrule electronic effects acting in the opposite direction. An understanding of the mechanism of the reaction is necessary to plan appropriate changes in the structure of the reagents to favor the desired course of the reaction. On the other hand, the effect of changing the structure or substituents of the substrate on the stereochemistry of the reaction contributes to the understanding of its mechanism.

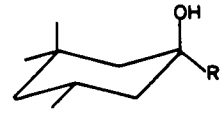
Lithium tri-*t*-butoxyaluminum hydride attacks[205] 4-*t*-butylcyclohexanone **129** from the electronically favored axial direction to give the trans 91% 4-*t*-butylcyclohexanol **130** (R = H) and 9% of the *cis* product **131** (R = H). However 3, 5, 5-trimethylcyclohexanone (**160**) gives with the same reagent only 11% of the alcohol **161** (R = H) and 89% of the less stable **162** (R = H). This is evidently a result of steric hindrance to the approach from the electronically favored axial direction as found[205] from the ratio of rates for axial attack on **129** and **160** that is 100/3, whereas this ratio for equatorial attack is only 2/1.



(160)

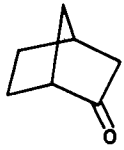


(161)

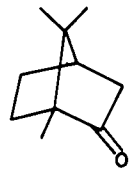


(162)

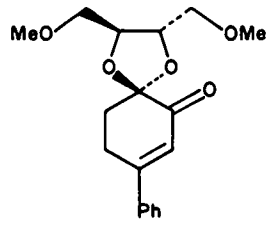
Norbornanone **163** is attacked by methyllithium from the *exo* direction, exclusively[38], but camphor **164** from the *endo* direction. A chiral auxiliary incorporated in a dicarbonyl compound[206] **165** induces a reduction by LAH on one face preferentially to yield **165** (92% ee).



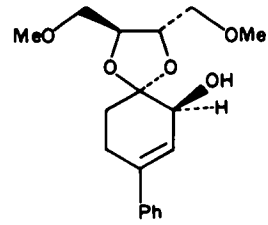
(163)



(164)



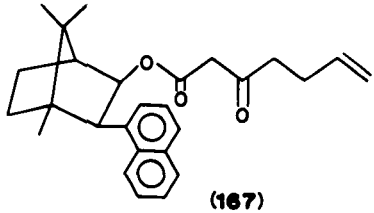
(165)



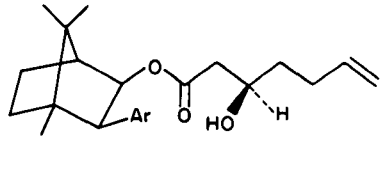
(166)

A combination of an auxiliary ligand blocking one face of a carbonyl group and appropriate reagents can induce[206] the formation of a carbinol with either configuration (*R*) or (*S*). An enantiomerically pure bornyl ester of a β-keto acid **167** carrying a naphthyl group is reduced by $Zn(BH_4)_2$, in the presence of the bidentate $ZnCl_2$, that bridges between the two carbonyls imposing the *syn* conformation, to give a ratio of 92/8 for **168/169** but this ratio is 4/96 in the presence of the monodentate diisobutylaluminum (2, 6-di-*t*-butyl-4-methylphenoxide) that is coordinating with one carbonyl only and imposes the *anti*

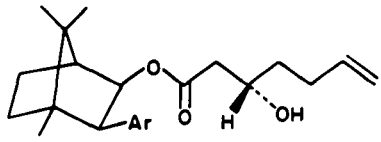
conformation on the two carbonyls. Hydrolysis gives the chiral hydroxacids and reduction the chiral diols.



(167)

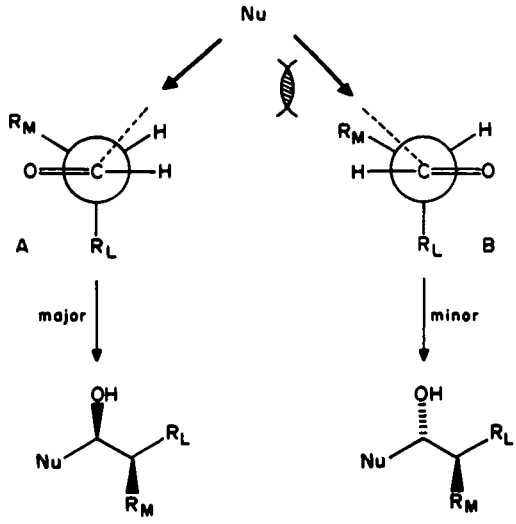


(168)



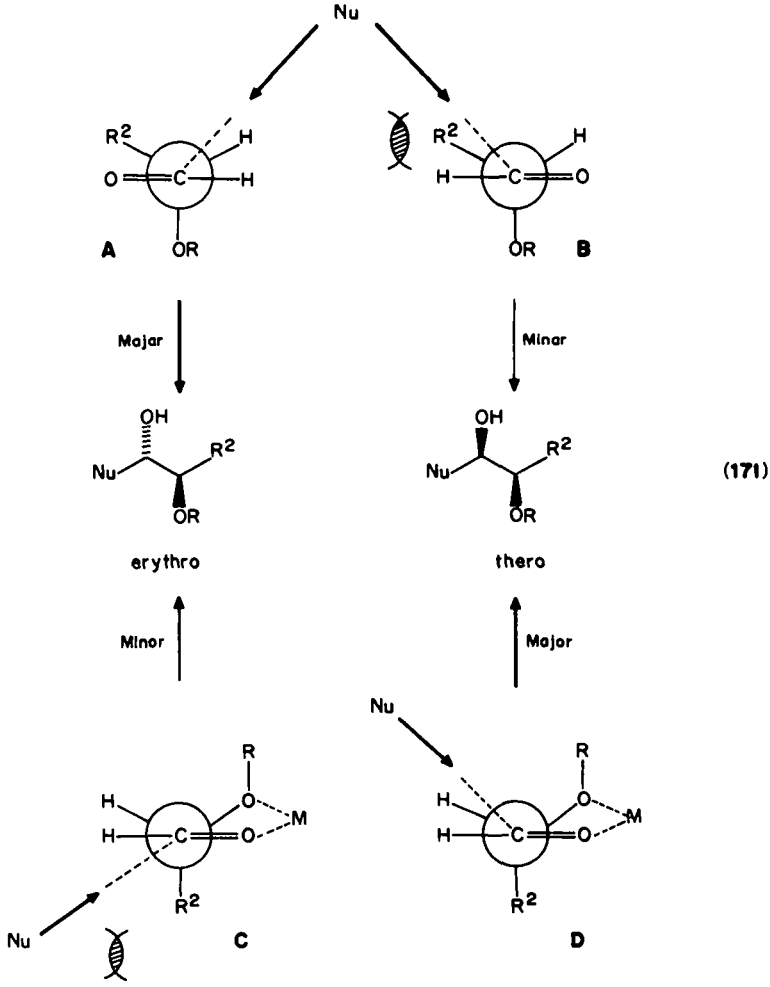
(169)

The addition of nucleophiles (Nu) to acyclic carbonyl compounds is represented according to the Felkin–Anh model in equation 170. The major product is obtained according to this model from the transition state A with the largest group (R_L) on the chiral carbon α to the carbonyl *anti* to the attacking nucleophile, and the medium group (R_M) near the oxygen of the carbonyl. These reactions are not very selective; the ratio of the major to the minor product of the reaction of 2-methylphenylacetaldehyde with methylmagnesium bromide is 70/30. Only with large nucleophiles does one obtain a better selectivity.



(170)

Good selectivities are achieved when the carbonyl compound contains a group that can coordinate with a metal and thus form a chelate containing also the carbonyl group. The products then correspond to the cyclic model of Cram. However, these products cannot always be predicted unequivocally. When the chiral carbon α to the carbonyl carries a hydroxyl group, the reaction may proceed according to the cyclic model and give the *threo* compound as the major product from the transition state D in equation 171. However, the C—O has a lower-energy σ^* orbital than C—C and will prefer to be *anti* to the nucleophile particularly when coordinated to a metal (transition state A). The *erythro* compound will in that case be obtained as the major product.



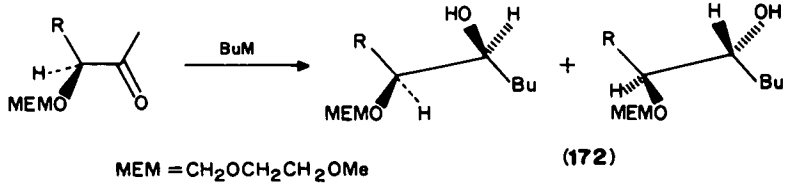
(171)

The problem of chelation versus nonchelation control of chiral α- and β-alkoxy carbonyl compounds was discussed by Reetz[209].

Before proceeding further we should say a few words about the stereochemical notation for compounds containing two chiral centers. In equation 171 the two diastereomers have

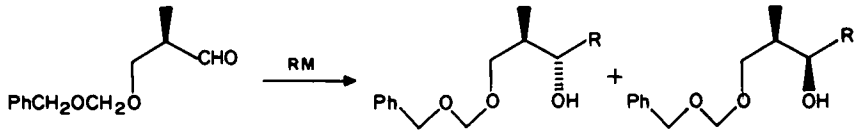
been named *threo* and *erythro*. However, it is not clear which of the products in equation 170 should be named *threo* and which *erythro*. This nomenclature is ambiguous. We shall therefore name these compounds *syn* and *anti* following Masamune[210]. The longest chain is written in an extended form and when the groups other than hydrogen in this conformation are on the same side of the plane containing the extended chain, the compound is *syn*, and when on opposite sides, *anti*. This nomenclature is not unambiguous, but it is easily visualized; thus, the major product in equation 170 is *syn* and the minor, *anti*. The most accurate nomenclature is that of Seebach and Prelog[211]. A compound is called *l* (*like*) when both chiral centers have the same configuration (*S*, *S*) or (*R*, *R*). If their configuration is different (*R*, *S*) it is called *u* (*unlike*). This notation can be visualized sometimes only after some effort. Two compounds having the functional groups *syn* according to the Masamune notation may have either the *l* or *u* notation in the Seebach–Prelog nomenclature, depending on the priorities of the various groups.

The reaction[212] of α-alkoxy ketones with butyllithium proceeds (equation 172) according to the open model to give the *syn/anti* or *threo/erythro* ratio of 0.7, but with butylmagnesium bromide this ratio is larger than 100 and a chelation-controlled mechanism is assumed. However, methyllithium and methylmagnesium bromide[213] reacting with β-alkoxyaldehydes (equation 173) give ratios of 0.7 and 1.0 respectively, corresponding to the open mechanism, and only dimethylcuprate is apparently reacting by the cyclic mechanism yielding the ratio of 30. The carbon carrying the ether group does

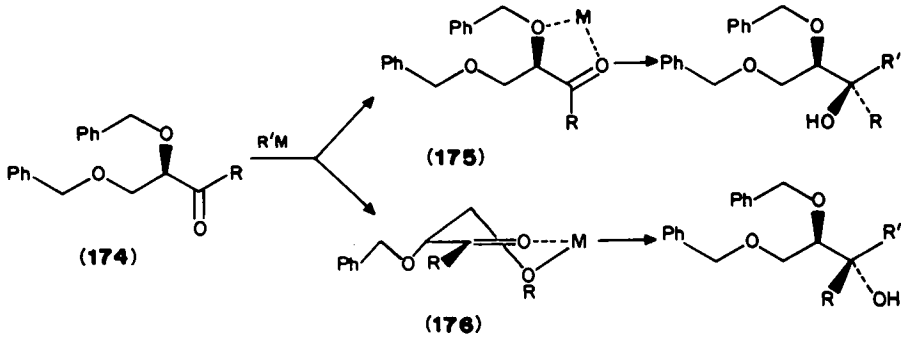


MEM = $CH_2OCH_2CH_2OMe$

(172)



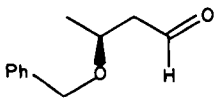
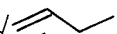
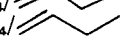
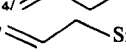
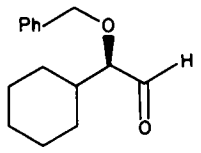
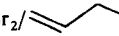
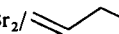
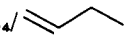
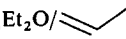
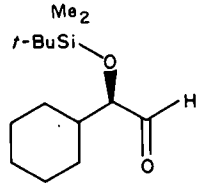
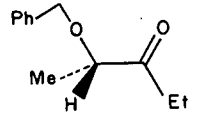
(173)



not have to be chiral, but the formation of the chelate imposes a conformation where the steric interactions are enhanced. A carbonyl compound containing an α- and β-alkoxy group **174** can in principle form a five- (**175**) or six-membered chelate ring (**176**). Each of them would lead to a different product in a reaction with a nucleophile. Addition[214] of $R'Cu \cdot MgBr_2$ gives the *syn* products, but that of lithium or magnesium compounds leads to the *anti* products. The latter are therefore produced perhaps from a six-membered chelate, but more likely via an open transition state. The steric course of reactions of 2, 3-*O*-isopropylideneglyceraldehyde, containing an α- and β-alkoxy substituent, have been studied[215] and reviewed[216].

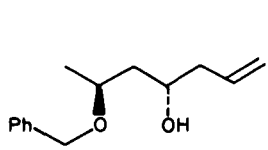
Control of the steric course of the addition to carbonyl groups by chelation or nonchelation can be established by changing the organometallic compound or the substituent on oxygen. Organolithium compounds are generally nonselective, and the drive for chelation increases generally in the series Mg < Zn < Cu < Ti. The largest extent of chelation control is achieved with $RTiCl_3$. Reactions, where catalysis by $TiCl_4$ or $SnCl_4$ is employed, are also chelation-controlled (Table 4). It is of interest that catalysis by $BF_3 \cdot Et_2O$ of the addition of allyltrimethylsilane to 3-benzyloxybutyraldehyde gives also preferentially the chelate-like controlled *anti* product[217] **177**. BF_3 is a monodentate ligand and chelation was considered improbable. It was therefore proposed[218] that, due to dipole repulsion, the complex with the aldehyde assumes conformation **178** or **179**, and attack on them from the less-hindered side gives the observed product. Very high diastereoface

TABLE 4. Stereochemistry of additions to alkoxyaldehydes

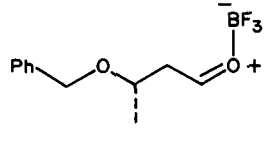
Substrate	Reagent	*syn/anti*[a]	Reference
	$MeTiCl_3$	10/90	217
	$TiCl_4$ / 	5/95	
	$SnCl_4$ / 	5/95	218
	BF_3 / 	15/85	
	$MgBr_2$ /  THF	20/80	219
	$MgBr_2$ /  CH_2Cl_2	250/1	
	$TiCl_4$ /  CH_2Cl_2	250/1	
	BF_3Et_2O / 	39/61	
	$MgBr_2$ /	21/79	
	$MeLi\text{-}TiCl_4$	99/1	220
	$MeMgCl$	1/99	
	$MeTi(OCHMe_2)_3$	1/99	

[a] *syn/anti* refers to the OR and OH groups.

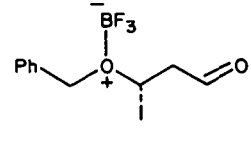
selectivity can be achieved[219] using $MgBr_2$ or $TiCl_4$ in CH_2Cl_2, but $BF_3 \cdot Et_2O$ in the studied case[218] yielded products according to the open model. Titanium compounds containing bulky electron-donating ligands such as $RTi(OCHMe_2)_2$ or $RTi(NR_2)_3$ do not form chelates and their reaction proceeds according to the open chain model[210]. No chelation-control is found in α- or β-silyl ethers with large groups on silicon[219].



(177)

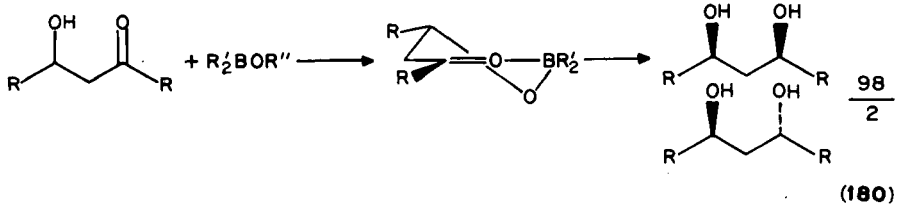


(178)



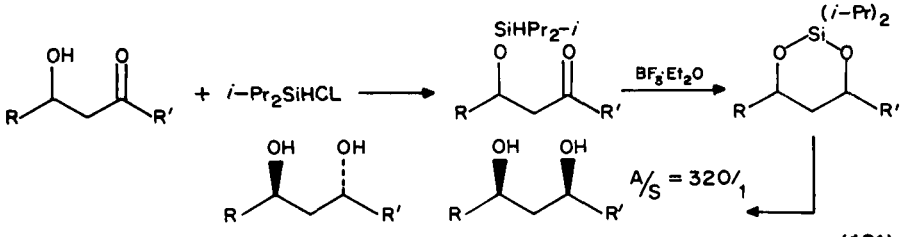
(179)

Complexation brought about by trialkylboranes[221], alkoxydialkylboranes[222] or aluminum compounds[223] on β-hydroxyketones directs reduction to yield preferentially *syn* diols (equation 180). However, intramolecular reductions by a silicon compound[224] (equation 181) or boron hydride[225] (equation 182) give predominantly the *anti* diols. Hydrogenation[226] of a 1,3-diketone using as a catalyst $Ru_2Cl_4[(R)\text{-BINAP}]_2(NEt_3)$, where BINAP is 2,2-bis(diphenylphosphino)-1,1'-biphenyl, yields 99% of the *anti* diol with 99% ee.



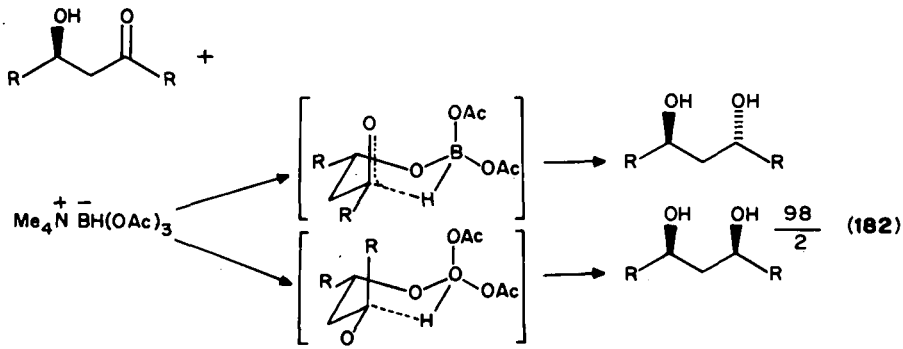
98 / 2

(180)



A/S = 320/1

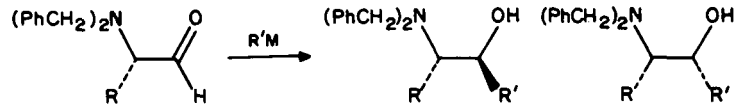
(181)



98 / 2

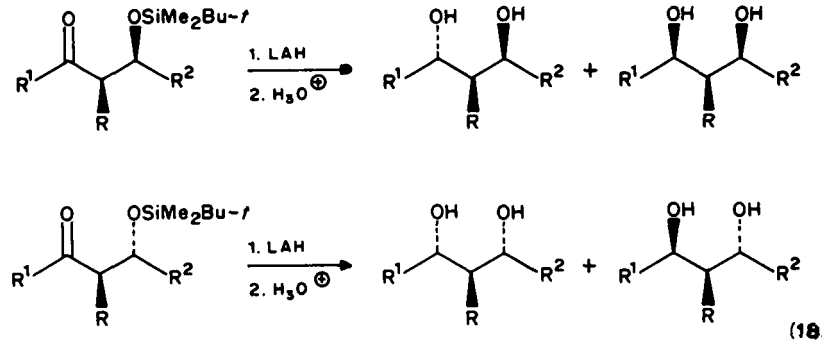
(182)

Zinc borohydride was used extensively to reduce selectively β-ketoacids, β-alkoxyketones, α,β-epoxyketones and α-hydroxyketones via a chelation-controlled reaction[227]. Chiral aminoaldehydes prepared from natural L-amino acids can also undergo chelation-controlled addition reactions[228] (equation 183) with $MeTiCl_3$ or with allyltrimethylsilane–$SnCl_4$, but not with magnesium or copper compounds. With smaller groups on nitrogen, cuprates also react via the cyclic mechanism.

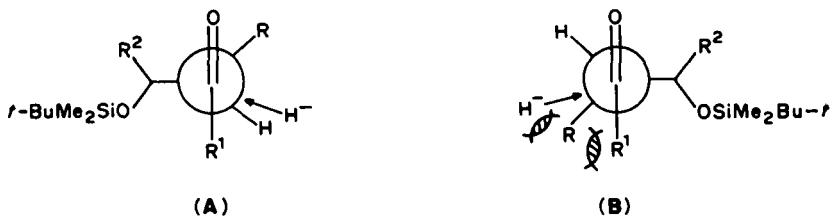


(183)

Tert-butyldimethylsilyl ethers of α-alkyl-β-hydroxyketones are reduced with high diastereofacial selectivity[349] (around 97/3) to give the formed hydroxyl *anti* to the allyl group independently of the configuration of the carbon carrying the siloxy group (equation 183a). Since the bulky siloxy group does not chelate, this selectivity was attributed to the much higher stabilization of the transition state A relative to that of B, according to the Felkin–Anh model.

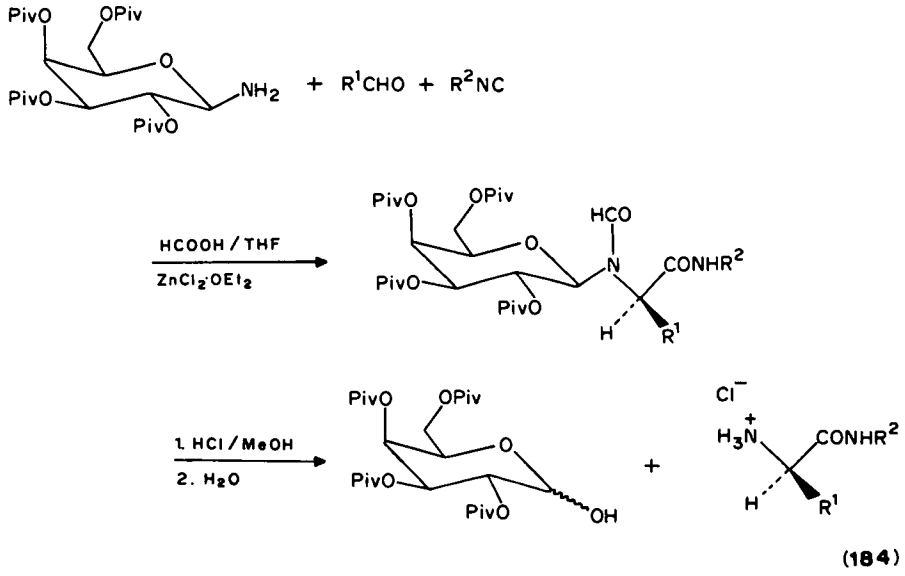


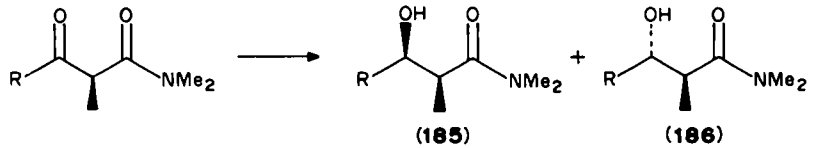
(183a)



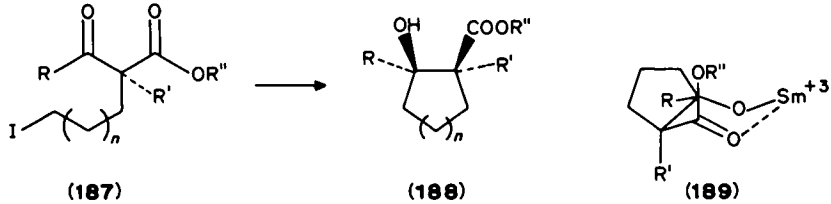
An asymmetric induction[207] by 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (equation 184) in the Ugi reactions[208] gives in one step a derivative of a (β-D,*R*)-amino acid in a ratio 96/4 to the other diastereomer. This derivative may be hydrolyzed to the chiral amino acid that may contain functional groups.

β-Ketoamides with a substituent at the 2 position are reduced[229] by $PhMe_2SiH$ to the *threo* (*syn*) isomer **185** in acidic conditions and to the *erythro* **186** in slightly basic conditions. In acidic conditions, there is apparently proton bridging between the two carbonyls and the ratio **185/186** is around 99/1. In the presence of F^- (delivered by TASF, tris(dimethylamino)sulfonium difluorotrimethylsiliconate) this ratio is 1/99 for R = aryl, but for R = alkyl it is 75/25.



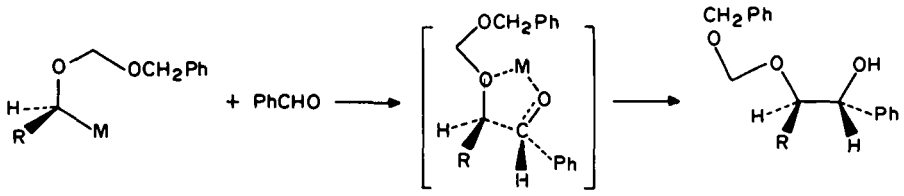


A cyclization reaction during an attack on a carbonyl may impose the stereochemistry of the product. A Barbier-type synthesis using the method of Kagan[230] with samarium diiodide yielded from 2-(ω-iodoalkyl)-β-ketoesters **187** a stereocontrolled cyclization[231] to *cis*-2-hydroxycycloalkanecarboxylates **188**. The stabilization of the product by chelation with Sm^{3+} (**189**) is apparently the reason for this preferential *cis* cyclization.



A less powerful chelation effect was found in a reaction[232] of a chiral lithium compound prepared from a chiral tin derivative, with benzaldehyde (equation 190). The major product (60% for R = Br; 92% for R = *t*-Bu[233]) was assumed to be formed via a chelated transition state. The use of the magnesium instead of the lithium counterion increased the stereoselectivity.

Formation of a ketal **191** with a chiral (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol induces asymmetric reductions by LAH to the (*R*)-carbinol **192**, but in the presence of $MgBr_2$ the (*S*)-isomer is obtained[234].



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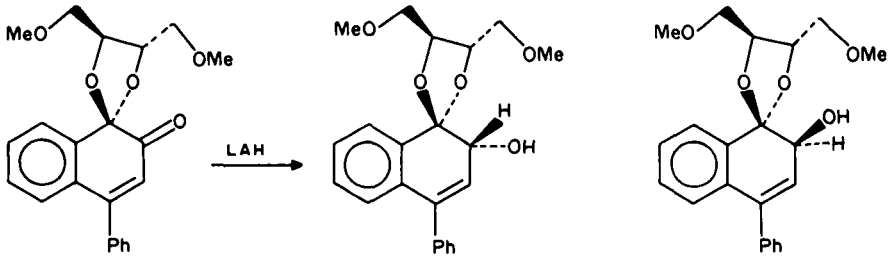
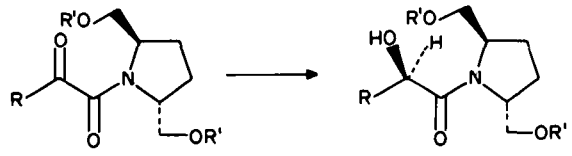


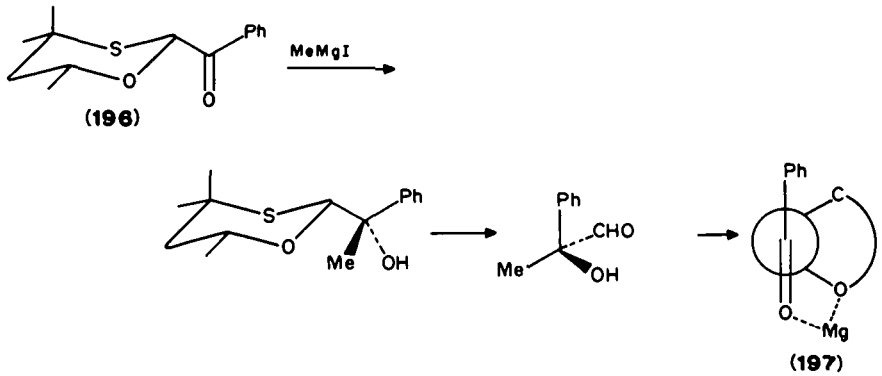
(191) (192) (193)

A ketoamide **194** prepared from a chiral amine is reduced[235] diastereoselectively to **195** by $LiBEt_3H$.



(194) (195)

A highly stereoselective atrolactic derivative synthesis was carried out by Eliel[236] starting with the chiral ketone **196**. This is chelation-controlled reaction, with the magnesium bridging the oxygen of the carbonyl and the oxathiane **197**.

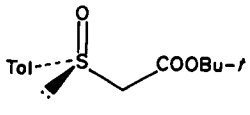


(196) (197)

D. Sulfur-containing Groups as Chiral Auxiliaries[192,258]

Sulfur-containing compounds play a very important role in synthesis. The advantage in using these compounds is that they stabilize negative charges α to sulfur and these anions undergo many reactions. Sulfur can be introduced readily into molecules and also removed easily after performing the desired reactions. Moreover, chiral sulfoxides can be prepared in addition to the Andersen method[237] also by asymmetric oxidation of sulfides with *t*-butylhydroperoxides in the presence of a modified Sharpless catalyst[238], by microbial oxidation[239] or oxidation by periodate, catalyzed by bovine serum albumin[240].

Sulfoxides are metalated at the α position. The metalated derivatives of chiral sulfoxides exhibit low selectivity in additions to carbonyl groups[241]. A better stereoface selectivity is achieved by the introduction of an additional sulfide group α to the carbanion[242]. Introduction of an ester group α to the carbanion enhanced the selectivity to 20–95% ee. The metalated compound was prepared[244] by reacting *t*-butylmagnesium chloride with the chiral *t*-butyl *p*-tolylsulfinylacetate **198**. The higher selectivity of the magnesium derivative of **198** in the reaction with carbonyl compounds was rationalized[243] by the bridged transition state **199**, where the carbonyl compound approaches the anion from the side of the lone pair on sulfur in such a way that the steric interactions are minimized[242].



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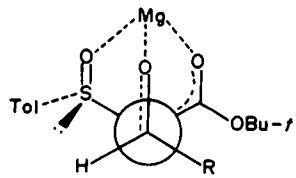
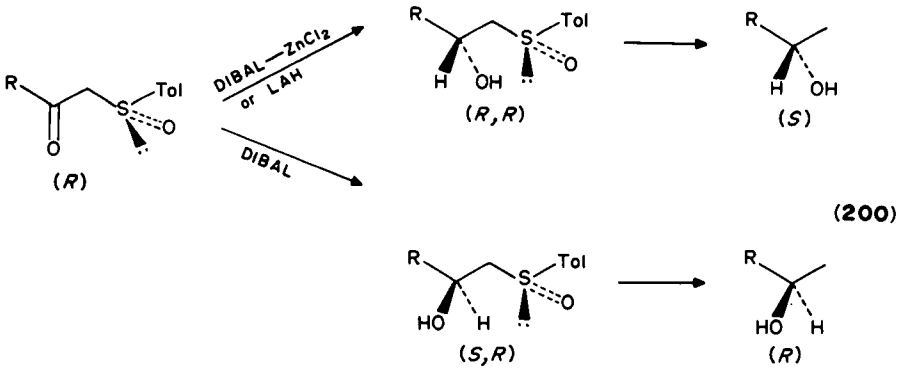
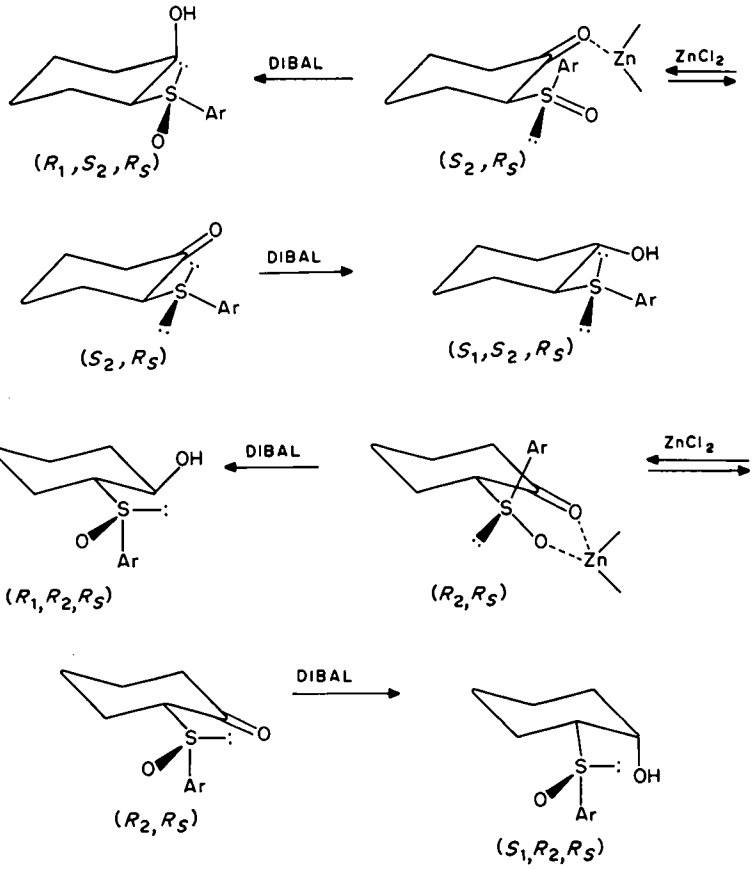


(199)

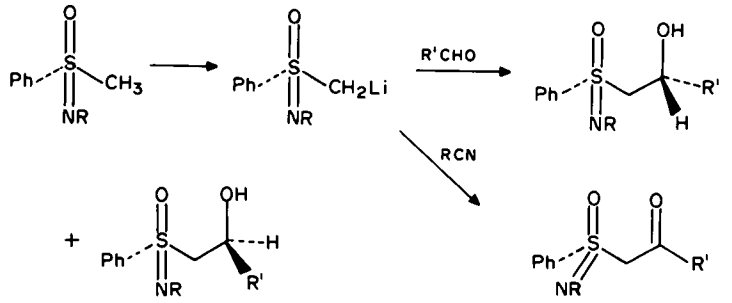
Optically active β-ketosulfoxides are convenient intermediate for the synthesis of both enantiomers of methylcarbinols (equation 200) with high ee by reduction with LAH or DIBAL[245] (diisobutylaluminum hydride) or DIBAL–$ZnCl_2$[246]. α,β-Unsaturated β-ketosulfoxides can be transformed in a similar manner into chiral allylic alcohols[247]. A similar course of reactions was observed in cyclic compounds[248], where the two epimers at the 2 position of the substituted cyclohexanone react in a different manner (equation 201).



(200)

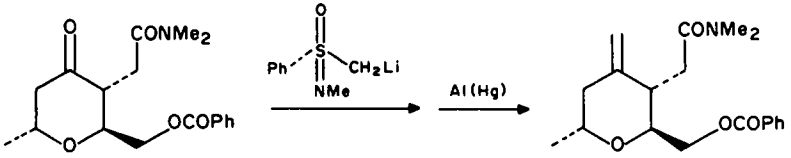


Chiral sulfoximines[249] are metalated at the α position and then react with carbonyl compounds[250] to give alcohols with up to 46% ee (equation 202). β-Ketosulfoximines can be reduced to chiral carbinols with sodium borohydride[251] or borane[252]. The asymmetric induction in the addition of metalated sulfoximines to aldehydes is enhanced by increasing the bulk of the substituent on the nitrogen, e.g. from the trimethylsilyl to the *t*-butydimethylsilyl group[253].



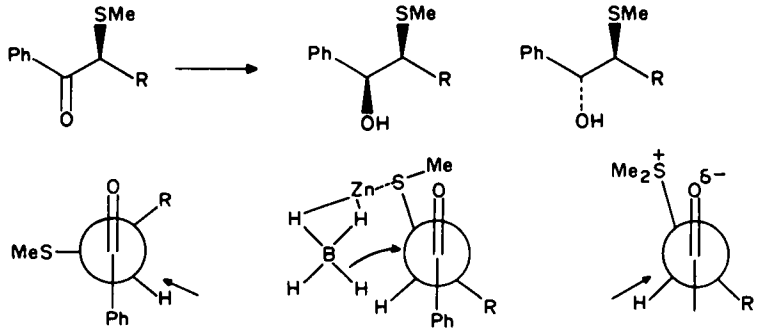
(202)

Two interesting applications of the addition of the metalated sulfoximines have been found. Since the product of this reaction reverts thermally to starting materials[254], one can carry out the reverse reaction after separation of the diastereomeric adducts and separate in this manner a racemic ketone into its enantiomers. Moreover, a reductive elimination carried out on the separated diastereomers of β-hydroxysulfoximines yields optically active olefins[255] (e.g. equation 203)[256].



(203)

A sulfide attached to a stereogenic atom α to a carbonyl induces the reduction[257] to give either the *syn* or the *anti* product with very high selectivity (a ratio of nearly 99/1 or 1/99; equation 204). The *syn* product is obtained in the reduction with L-Selectride according to the Felkin–Anh model **205**, but the *anti* isomer can be obtained with zinc borohydride via a chelated intermediate **206** or a dipolar interaction in the transition state **207**, when the sulfide is transformed into a sulfonium ion.



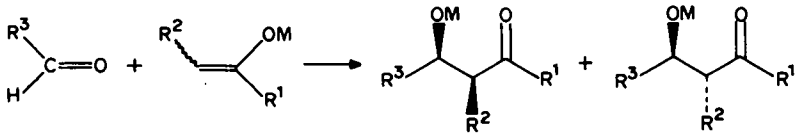
(204)

(205) (206) (207)

E. The Aldol Reaction

1. Simple diastereoselection

The aldol reaction 208 is one of the most important reactions in chemistry since, in addition to the formation of a C—C bond, two functional groups are introduced into the molecule. The introduced hydroxyl and carbonyl groups are in a 1,3- position relative to each other, an arrangement very important in biological processes and in natural compounds. This reaction takes place between a carbonyl compound and another molecule of a carbonyl compound (the same or a different one) in the form of an enol or enolate.



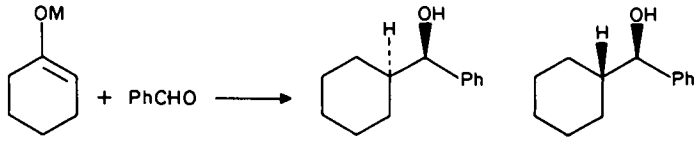
(208)

TABLE 5. Simple diastereoselection in the aldol reaction

Metal	Reaction	R^1	R^2	R^3	Enolate	T(°C)	Time	*syn/anti*	Ref.
1. ZnCl	**209**				*E*	14	5 min	17/82	266
2. ZnCl					*E*	5	5 min	33/67	266
3. Li					*E*	−72	5 s	48/52	267
4. MgCl	**208**	*t*-Bu	Me	Ph	*Z*			95/5	268
5. MgCl		*t*-Bu	Me	Ph	*Z*			5/95(equil.)	268
6. Li		Et	Me	*t*-Bu	*Z*			88/12	269
7. Li		Et	Me	*t*-Bu	*E*			48/52	269
8. $AlMe_2$		Me	Bu-*t*	Me	*E*			93/7	270
9. $AlMe_2$		Me	Bu-*t*	Me	*Z*			0/100	270
10. Li		H	Me	Ph	*Z*			50/50	267
11. Li		H	Me	Ph	*E*			65/35	267
12. Li		Et	Me	Ph	30/70			64/36	267
13. Li		Et	Me	Ph	66/34			77/23	267
14. Li		OMe	Me	Me	5/95			43/57	278
15. Li		$OC_6H_3Me_2$-2,6	Me	Ph				12/88	277
16. Li	**209**			Ph	*E*	−72		48/52	267
17. $B(c\text{-}C_5H_9)_2$				Ph	*E*	−78		32/68	281
18. $B(c\text{-}C_5H_9)(C_6H_{13})$				Ph	*E*	−78		4/96	281

The aldol reaction was investigated extensively in the last ten years, particularly with regard to its steric course. Numerous modifications of the basic procedure were introduced and new reagents developed to assure maximum control of the stereochemistry of its products. A number of excellent reviews[259–264] have been published. We shall therefore not deal with all the details of the reaction but discuss mainly mainly its basic features and recent developments.

When R^1 and R^2 are different from hydrogen, two stereogenic centers are introduced into the molecule and their relative configurations are either *syn* (*erythro*) or *anti* (*threo*). If an excess of one of the two racemic diastereomers is obtained, the reaction is said to exhibit simple diastereoselection. The ratio of the two diastereomers *S*/*A* (*syn*/*anti*) is generally different from unity and is referred to as diastereomeric selectivity (ds). The difference between the percentage of the two diastereomers in the product (their sum being 100%) is $|\%S\text{-}\%A|$ and is referred to as diastereomeric excess (de). This is then a diastereoselective process[265] and the product is often the less stable kinetically controlled one. However, formation of the thermodynamically controlled equilibration product is also possible (Table 5) since reaction **208** is reversible. Another way of equilibration is via the enolate of the product. The equilibration was observed by House[266] for magnesium and particularly zinc aldolates (equation 209) (Table 5). The equilibrium depends also on the metal and it is generally the *anti* isomer that is preferred thermodynamically. The reason is that there are less *gauche* interactions in the chelated aldolate of the *anti* **210** than in that of the *syn* **211** isomer.



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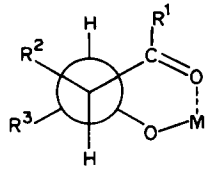

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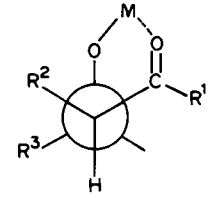
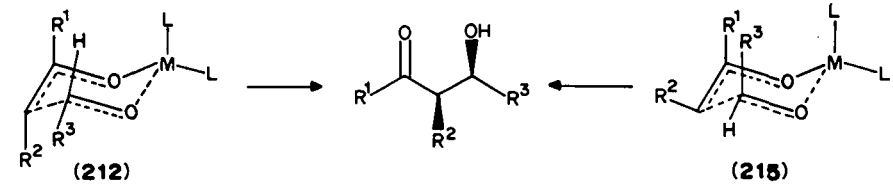


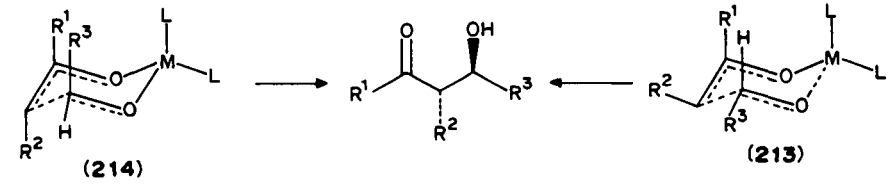
(211)

The stereochemistry of the kinetic product and its relation to that of the enolate was established for the first time by Dubois. The condensation[268] of the magnesium *Z*-enolate (R^1 = *t*-Bu) with benzaldehyde **212** gave preferentially the *syn* product, but equilibration led to the *anti* isomer (Table 5). Similarly, the lithium *Z*-enolate gave with pivalaldehyde[269] the *syn* product preferentially. However, the *E*-enolate showed no selectivity. The observed rough correlation between the enolate geometry and the aldol stereochemistry was explained by a cyclic chair-like transition state involving the metal, **212** for the *Z*- and **213** for the *E*-enolate, similar to the transition state proposed for the Ivanov reaction[270]. **212** leads to the *syn* and **213** to the *anti* product. Transition states **214** and **215**, starting from the *Z*- and *E*-enolates respectively, are destabilized relative to **212** and **213** and give the minor products. The R^1–R^3 and to a lesser extent the R^2–R^3 interactions determine the stability of these chair transition states. The transition states do not account for the lesser selectivity of the *E*- relative to the *Z*-enolates. Skewing[267,268] of the double

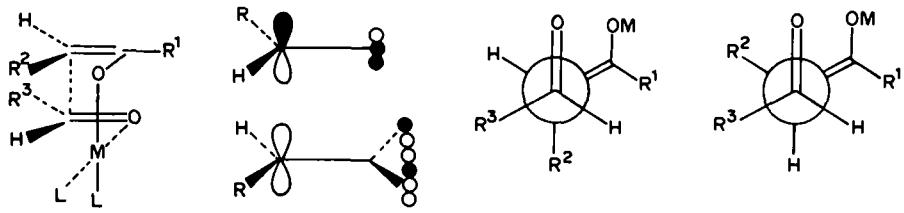
bonds of the carbonyl and enolate in the transition states to an angle 90° instead of 60°, or a greater R^2–R^3 interaction in **213** than in **215**, was proposed as explanations of this phenomenon. This last interaction accounts also for the predominant *syn* diastereoselection[271] for the *E*-enolate (entry 8, Table 5). This crossover in the selectivity[259] of the aldol condensation takes place also with the *Z*-enolate (entry 9) and is ascribed to a reaction via a boat transition state[259] **216**, that is more favorable energetically than via **212** for certain combinations of R^1, R^2 and R^3. In this conformation R^2 and R^3 are staggered and the R^1–R^3 eclipsing is minimized relative to that in **214**.



(212) (215)



(214) (213)



(216) (217) (218) (219)

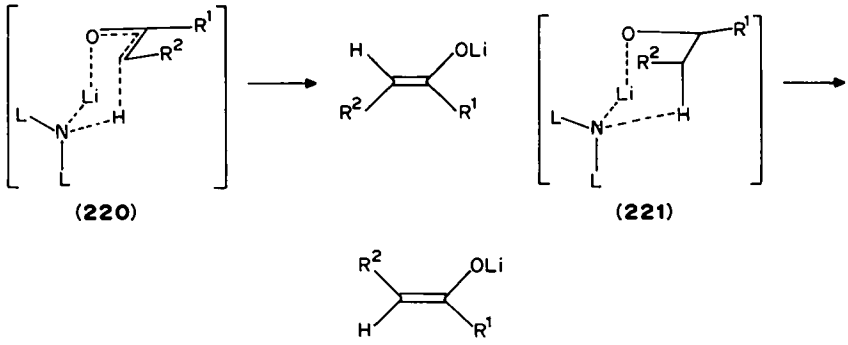
The *syn* selectivity of the *Z*-enolate and the *anti* of the *E*-enolate was ascribed[272] to the obtuse angle of attack on the carbonyl and the directionality of this attack in a plane deviating from the π plane away from R and towards H of the aldehyde. This conclusion was reached on the basis of MO calculations. The aldol reactions have a cyclic transition state determined on a HOMO–LUMO interaction, where the metal is not participating. This transition state is similar to that of a dipolar addition.

A more recent calculation of the transition state and the complex formation between the reactants in the aldol reaction between HCHO and CH_3CHO enolate, its Li and B salts has been carried out[497].

A HOMO–LUMO interaction as in **217** was proposed also by Mulzer[273] to rationalize the *anti* selectivity in the reaction of dianions of carboxylic acids with aldehydes. The stereoselectivity increased with increasing dissociation of the cation.

A topological rule applicable to a variety of processes, where acceptor π systems take part, has been presented by Seebach[274]. This rule assumes that the donor and acceptor are *gauche* to each other and all the bonds are staggered in the transition state. The donor C—D bond is in a *gauche* arrangement between the acceptor C—A and C—H bonds. The H atom on the donor component prefers to be *anti* with respect to the C—A bond. These rules applied to the aldol reaction have **218** as the model for the *E*- and **219** for the *Z*-enolate reaction.

The correlation between the enolate geometry and diastereoselection in the aldol reaction led to the development of a number of methods for the preparation of the *Z*- and *E*-enolates[213,275,276]. The course of the deprotonation is determined by the R^1–R^2 and R^2–L interactions in the transition states **220** and **221** in the reaction of the carbonyl compound with lithium amides[277]. Esters and thioesters of carbocyclic acids (R^1 = OCH_3, SCH_3) give with LDA (lithium dimethylamide) the *E*-enolates because of the predominant R^2–L interaction, but dialkylamides (R^1NR_2) yield the *Z*-enolates since the R^2–NR_2 $A^{1,3}$ interaction is stronger.



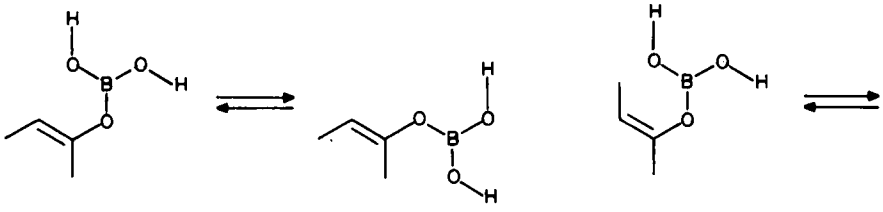
(220) **(221)**

The new methods for the preparation of *E*- and *Z*-enolates are not always very helpful, particularly when the enolates contain small R^1 and R^2 groups. In these cases (entries 10–14 Table 5) the aldol reaction is rather unselective. Bulky groups in the alcohol part of the ester enhance their *anti* selectivity. Amides and thioamides exhibit *syn* diastereoselection.

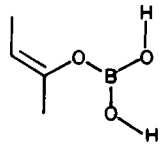
A drastic improvement in the selectivity of the reaction was obtained by the use of boron enolates[279,280]. The B—O and B—C bonds are much shorter than these bonds with the metals used before. The transition states in the boron enolates are tighter, the groups come closer to each other and their interactions are enhanced. Moreover, the ligands on boron can be changed very easily, thus modifying their interaction with the other groups in the transition state. The change of the *syn/anti* ratio as a function of the metal and the ligands is illustrated[281] in entries 16–18 of Table 5.

However, even with boron enolates, departures from the correlation of *E*-enolate and *anti* selectivity have been noted[282–286] and ascribed to boat-like transition states. Even acyclic *E*-enol borates may yield *syn* products with high selectivity, just as their *Z*-isomers. These stereocovergent reactions have been attributed[285] to the different conformations of the *Z*-and *E*-enol borates. Whereas the *Z*-enol borates can assume only the W conformation **223W**, their *E*-isomers have the freedom to assume also a U conformation **222U**. *Ab initio* STO-3G calculations show that **222U** is more stable by 1–2 kcal than **222W**, but **223W** is by 3–5 kcal more stable than **223U**. These calculations are confirmed by NOE effects (Nuclear Over hauser Effects) in the *E*-enol borate **224** between the positions indicated by the double arrow. The *Z*-enolate coordinates with the aldehyde *anti*

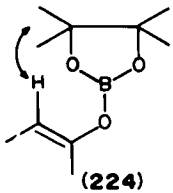
to the R group and the formed W complex **225** can adopt with little nuclear motion the geometry of the chair-like transition state **226**. The *E*-enolate adopts preferentially the U conformation in the complex **227** with the aldehyde and this geometry leads to the twist-boat transition state **228** that gives the *syn* product. The U conformation is also accessible to the *E*-enolate.



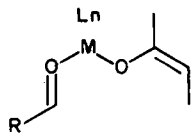
(222U) (222W) (223U)



(223W)



(224)



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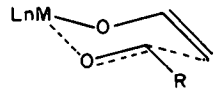

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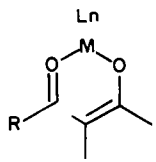

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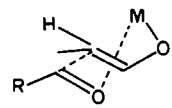
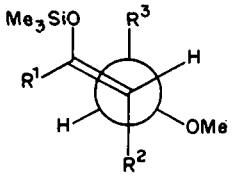


(228)

The Lewis acid catalyzed aldol reaction of enol silyl ethers does not give uniform results. The $TiCl_4$ catalyzed reaction is rather unselective, yielding more *anti* than *syn* products[287]. *Syn* product formation has been reported by Noyori[288] for the trimethylsilyl trifluoromethanesulfonate catalyzed reaction of acetals with enol silyl ethers, regardless of the geometry of the enolsilane. Open transition states have been proposed for the *Z*- (**229**) and *E*-enolsilane (**230**), the reacting species being $R^3C^+H(OMe)$. However, *anti* selectivity has been reported[289] for the BF_3 catalyzed reaction of *Z*- and *E*-enolsilanes with aldehydes and open transition states **231** and **232** have been proposed. The different results of Noyori and Heathcock may be a result of the possible *syn* arrangement of R and Me in RCH^+OMe.



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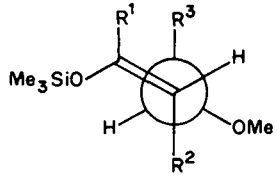

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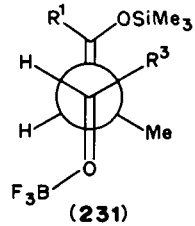

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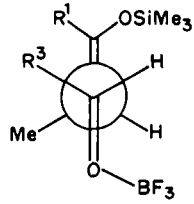
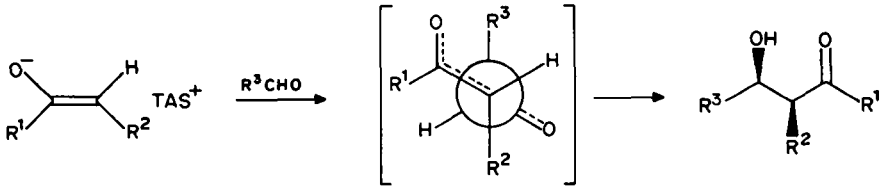


(232)

Excellent *syn* diestereoselection has been obtained by Reetz[290] in the reaction of *Z*-enolsilanes with α-alkoxy aldehydes. *Syn* selectivity was also observed byNoyori[291] in the reaction of 'naked' enolates prepared from enolsilanes by treatment with tris(dimethylamino)sulfonium difluoro trimethylsiliconate, regardless of the enolate geometry (equation 233). An open transition state was assumed, e.g. equation 233 for the *E*-enolate. Similar transition states have been proposed to explain the *syn* selectivity of enolstannanes[292].



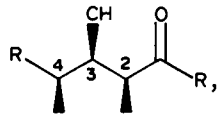
(233)

2. *Diastereofacial selectivity*

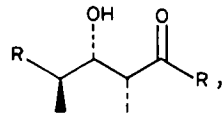
The reaction between two prochiral compounds was discussed in the preceding section. The faces in these compounds were enantiotopic and, although unequal amounts of diastereomers were formed, they were racemic.

A different situation obtains if one of the components of the reaction is optically active. The faces are then diastereotopic and the newly created centers may be asymmetric. Consider the reaction of a chiral aldehyde **238** containing an alkyl, e.g. methyl α to the carbonyl. In its reaction with a prochiral enolate one or more of the four isomers composing the triads **234–237** (containing three stereogenic center) with two methyl and one hydroxyl group can be formed. These are very important building blocks in natural compounds and the question is how to prepare them. Hoffmann[293] has presented an excellent discussion of this problem. Carbons 3 and 4 in **234–237** represent the carbonyl

and α carbon of the aldehyde **238** respectively. Carbon 4 is the only stereogenic carbon in the starting materials. The configuration of the two other stereogenic centers 2 and 3 in the products **234–237** depends on that of carbon 4. Such an induction is called a substrate-dependent one. The enantiomer of the aldehyde **238** can of course lead to one or more of the enantiomers of **234–237**. There are two factors that influence these configurations: (a) the 1,2-asymmetric induction in the stereoface selection in the addition to the aldehyde, or, in other words, the Cram or anti-Cram addition. This determines the configuration of carbon 3. The configuration at carbon 2 depends on the simple diastereoselection or its relative configuration to carbon 3 as discussed in the previous section..



(234)



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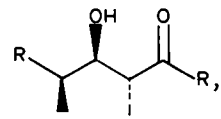

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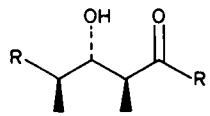

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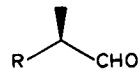
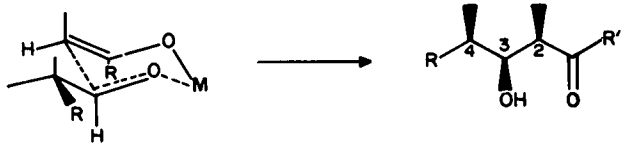


(238)

In a reaction of a prochiral aldehyde with an optically active enolate, the stereogenic center is in the enolate and it is this center that determines the steric course of the reaction. The stereoselection is called reagent dependent.

The relative configurations at centers 3 and 4 in the aldol depend on the face selectivity in the attack of the achiral enolate on the chiral aldehyde. Attack on the re face (equation 239) of the *Z*-enolate or that of the *E*-enolate on **238** yields the Cram product with *syn* 3,4-configuration. Attack on the si face of the aldehyde (equation 240) gives the *anti* 3,4-configuration or the anti-Cram product. The relative configuration at the 2 and 3 carbons determined by the chair-like transition state and is *syn* for the *Z*(O)- and *anti* for *E*(O)-enolate. The *Z*(O) and *E*(O) nomenclature was introduced by Masamune[294] to preserve the correlation between the configuration of the enolate and the configuration of the products, since it is the oxygen of the enolate that is linked to the metal and participates in the chair-like transition state. Thus **241** is a *Z*(O)-enolate and an *E*-enolate at the same time. Face selection following Cram's model is favored 3–4/1 relative to the anti-Cram selection, but chelation may change this to the opposite selectivity. The condensation of 2-phenylpropanal (**238**, R = Ph) with the enolates **242** gives the products **234–237** (R^1 = Ph) (Table 6). The Cram/anti- Cram face selection for $R^1 = t$-Bu[267] is 86/14 and for 2,6-dimethylphenoxy[295] it is 80/20. However, the simple aldol diastereoselection is complete in this cases.



(239)

(240)

(241) (242)

The aldol reactions with enolates containing no substituents at the α position are not selective[296]. The selectivity can be increased[297] by the introduction of a removable substituent or by using good chiral auxiliaries in the enolate.

Control of the stereochemistry of the aldol product using chiral enolates has met recently with great success. The chirality can be introduced into the enolate either by linking a chiral group to the metal or to the carbon. In the first case of the auxiliary group does not remain after the completion of the reaction, which may be an advantage.

Change in diastereoface selectivity **243/244** on introduction of a substituent in the α position of the enolate and exchange of the metal[298] is observed (Table 7). Less polar

TABLE 6. Face selection in the aldol reaction of lithium enolates

R^1	*Z/E*	% **234**	% **235**	% **236**	% **237**
t-Bu—	98/2	86	14	0	0
	2/98	0	0	80	20

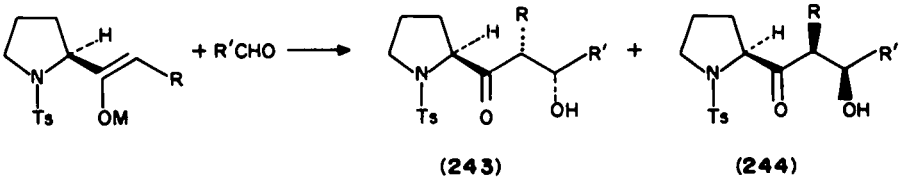
TABLE 7. Dependence of the diastereofacial selectivity in the aldol reaction on the metal and solvent

R	Metal	R^1	Solvent	**243/244**
H	Li	*i*-Pr	Ether	54/46
H	Bu_2B	*i*-Pr	Ether	72/28
Me	Li	*i*-Pr	THF	70/30
Me	Bu_2B	*i*-Pr	CH_2Cl_2	97/3

TABLE 8. Diestereofacial selectivity of enolates of α-alkoxy ketones as a function of the ligands on boron

BL_2 in **247**	R^1CHO	**248/249**
9-BBN	EtCHO	71/1
BBu_2	EtCHO	50/1
$B(c\text{-}C_3H_9)$	EtCHO	100/1

solvents enhance the diastereoselectivity. Two models have been proposed[281,298] for the transition states for the formation of the major (**245**) and minor (**246**) products. Enolates of chiral α-alkoxyketones [247] give good diastereoface selectivity[299] (Table 8).



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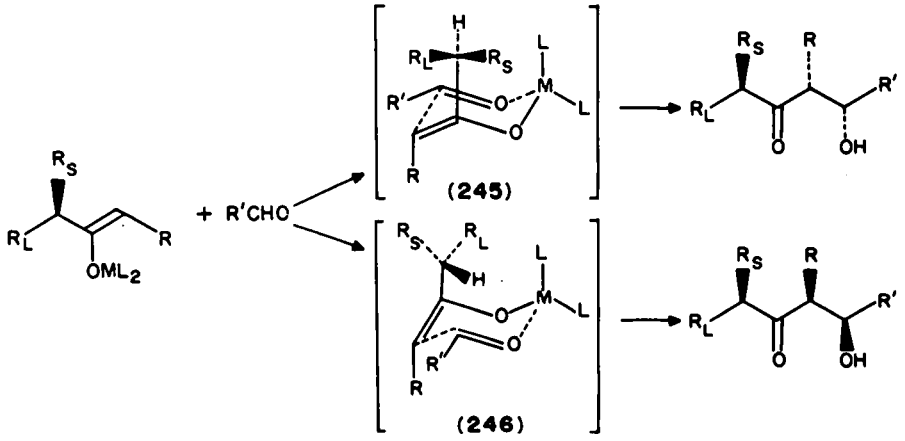
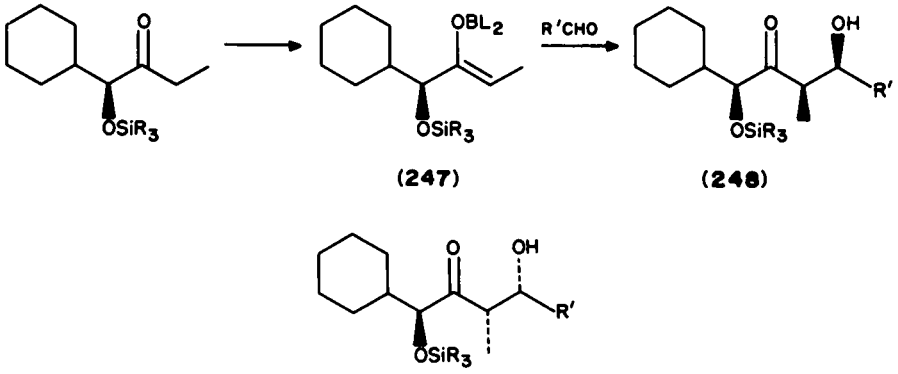


(245) (246)



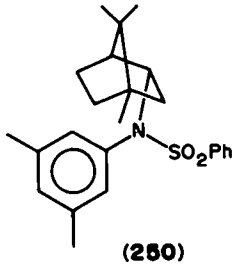
(247) (248)

(249)

The reaction of aldehydes with enolates of chiral esters is generally not selective. However, the Mukaiyama reaction[300] involving the Lewis acid catalyzed condensation of aldehydes with *O*-silylketene acetals is highly selective[301]. Camphor derivatives[302] such as **250** and **250a** shield one face of the enolsilane and induce the reaction at the unprotected face (Table 9).

TABLE 9. Face selectivity of enolates containing a camphor derivative as a chiral auxiliary group

R* in 251	M	R^1	252/253
250	Li	Et	73/27
250	$SiMe_2Bu$-*t*	Et	93/7
251	Li	Ph	38/62
251	$SiMe_2Bu$-*t*	Ph	6/94



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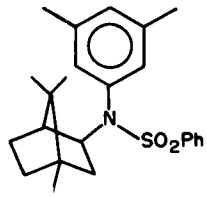

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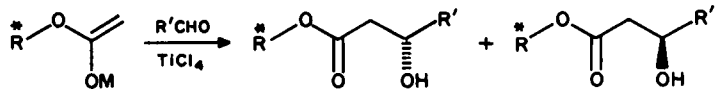
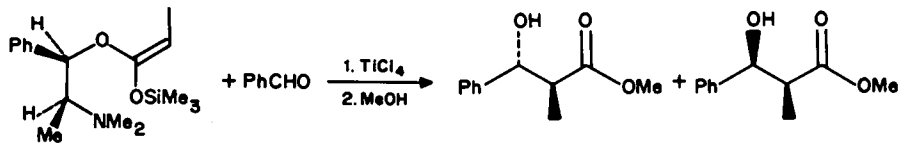


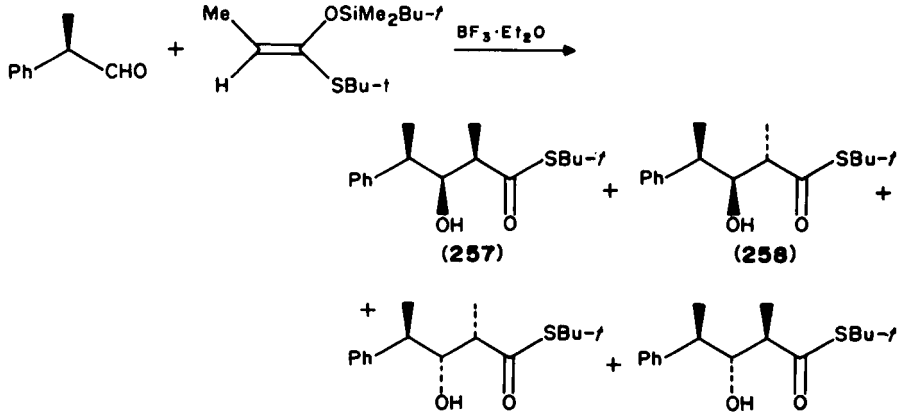
(251) (252) (253)

Anti diastereoselection was obtained[303–305] by using the *E*-silylketene acetals **254** derived from (1*R*,2*S*)-*N*-methylephedrine-*O*-propionate. Enantiomeric excess higher than 90% was obtained. Both enantiomers of the chiral inductor are commercially available inexpensive materials and can be recycled. The absolute configuration of the products is predictable. The $TiCl_4$ catalyzed reaction of **254** with benzaldehyde gave **255/256** in a 6/1 ratio and **255** with 94% ee. Addition of triphenylphosphine increased the face selectivity to an *anti/syn* ratio of 96/4. The aldehyde diastereoface selectivity is 3–5 6/1 but the enolate face selectivity is much higher. The **255**/ent-**255** ratio was 34/1 (ent-**255** is the enantiomer of **255**).

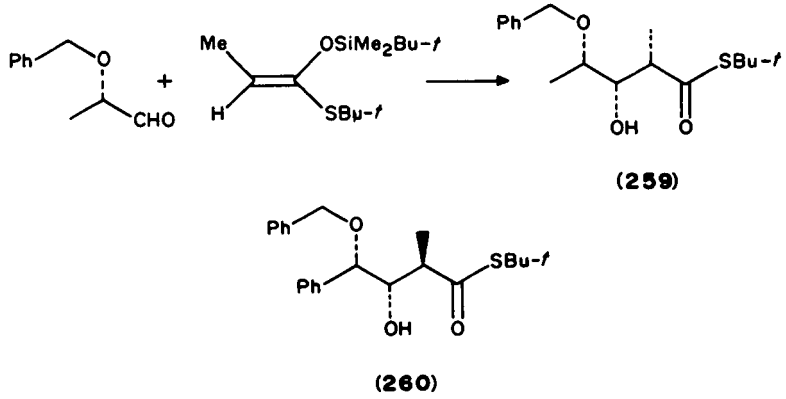


(254) (255) (256)

The boron trifluoride catalyzed reactions of thioester silylketene acetals with aldehydes[306] are stereoconvergent and give high *anti/syn* ratios (11/1 to 26/1). The **257/258** ratio for the reaction with 2-phenylpropanal is 7/91, the *anti/syn* 13/1 and the Cram/anti-Cram ratio is 49/1. With 2-benzyloxypropanal, the reaction is chelation-controlled to give a ratio of 95/5.



The reaction[307] of 2-phenylpropanal with enolates derived from dithioesters gives a 95/5 ratio of **261** and **262**.



Boron azaenolates **263** derived from achiral oxazolines and diisopinocampheylborane exhibit high *anti* selectivity[308] with 77–85% ee. On the other hand, the azaenolate **264**, derived from a chiral oxazoline, shows a very high *syn* selectivity (*syn/anti* = 98/2) with 30–70% ee.

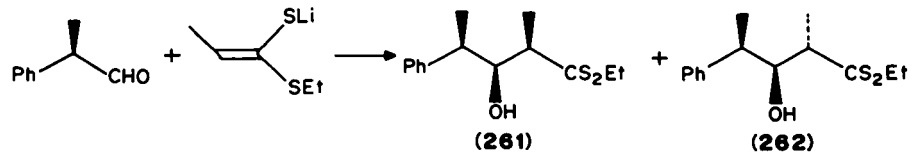
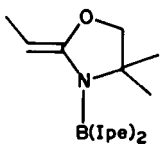


TABLE 10. Asymmetric induction using chiral imides

Imide	R^2	M	Product (%) 267	268	269	270
265; R = Me	n-Bu	B	0.7	99.3	—	—
265; R = SMe	Me	B	0.4	99.6	—	—
266; R = Me	n-Bu	B	> 99.8	< 0.2	—	—
266; R = Ph	Ph	B	> 99.8	< 0.2	—	—



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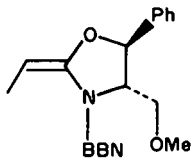

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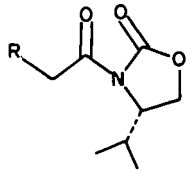

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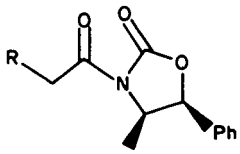
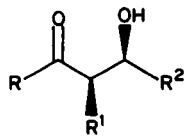


(266)

Very high asymmetric induction was achieved by Evans[308,309] using the imides **265** and **266** derived from (*S*)-valine and (1*S*,2*R*)-norephedrine, respectively. These compounds gave *Z*-enolates exclusively and their reaction with aldehydes R^2CHO can yield four aldols, **267**–**270**. The high selectivity of these reactions is recorded in Table 10 and is explained[289] by the preferential reaction of **271** out of the two conformations **271** and **272** of the enolates, due to the developing of steric interactions in the product **274** formed in the reaction of conformation **272**. In the conformation **271**, the attack occurs by addition to the less hindered re face.



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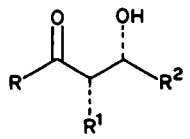

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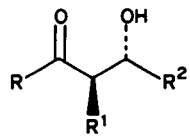

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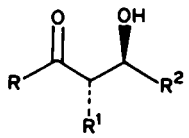

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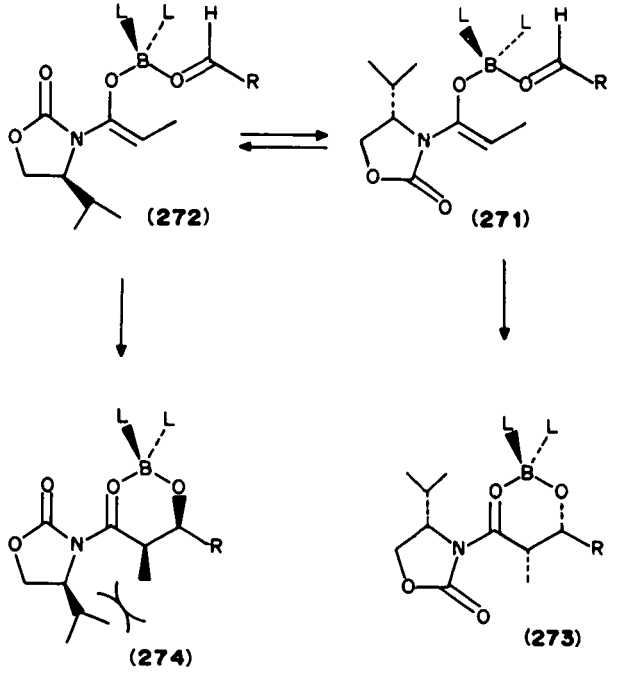
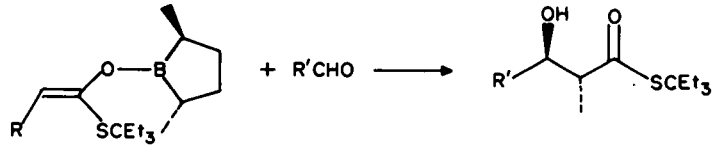
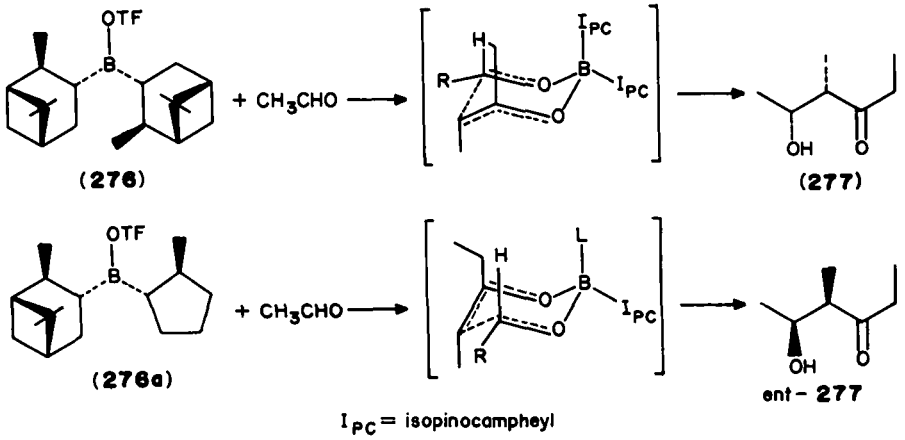


Enolates having the chiral group linked to the metal induce also face selectivity. The advantage in using this kind of binding of the chiral auxiliary group is that the product of the reaction does not contain the auxiliary group and no additional reactions are needed to remove it. An *E*(O)-enolate **275** of a thioester containing a chiral borolane group on the oxygen reacts[310] with aldehydes to give predominantly *anti* products (*anti*/*syn* = 30/1) with 95% ee. A somewhat lesser extent of asymmetric induction was observed by Reetz[311] using another chiral borolane.



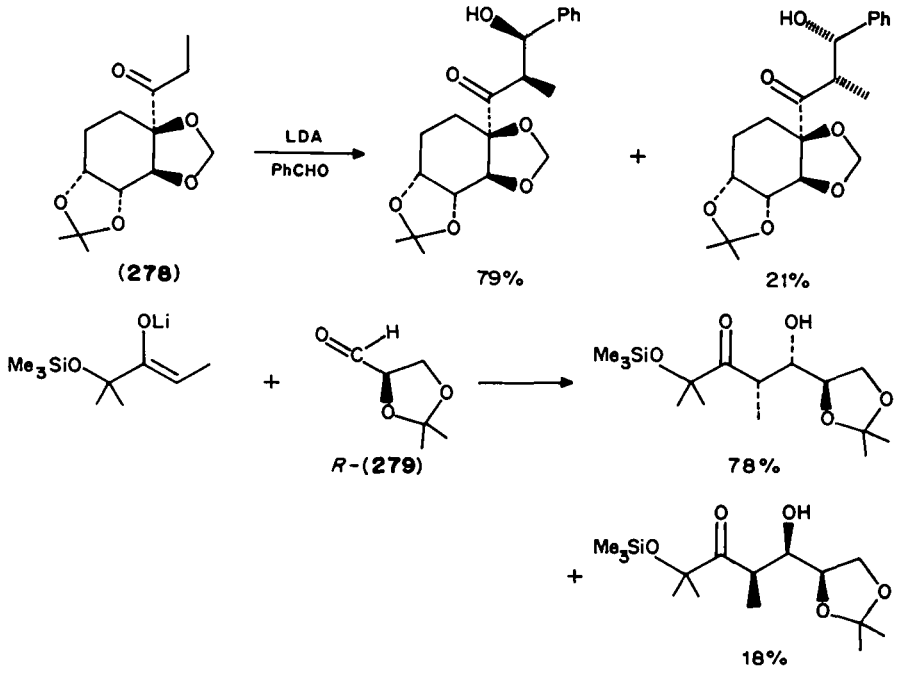
(275)

(−)-Diisopinocampheylboron triflate **276** gives with diethylketone in the presence of *i*-Pr_2NEt, the (*Z*)-enolate that yields[312] with acetaldehyde the *syn* product **277** with 82% ee, whereas a modified triflate **276a** yields mostly the enantiomer ent-**277** (52% ee) via a transition state with the Ipc group in an equatorial position and the other ligand on boron in an axial position.



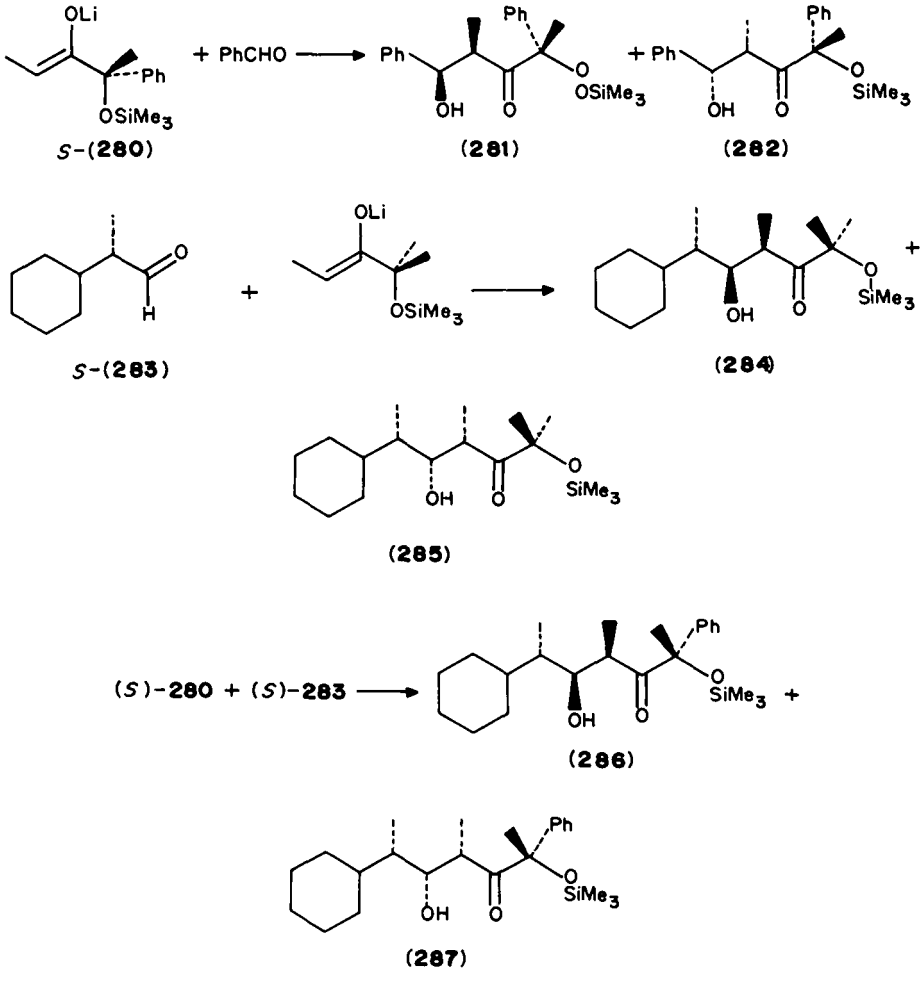
3. Double stereodifferentiation[313,314]

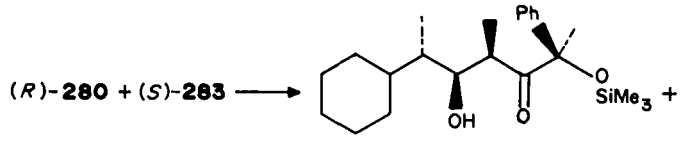
In the preceding section we dealt with reactions where one of the components was homochiral[314,315] (enantiomerically pure). The chiral aldehyde or enolate controlled the steric course of the reaction by its inherent diastereoface selectivity. When both the substrate and reagent are homochiral we have double stereodifferentiation. The inherent diastereoface selectivity of the substrate and reagent may reinforce one another (matched pair[314] or consonant double stereodifferentiation)[263] or oppose one another (mismatched pair or dissonant double stereodifferentiation).



As an example, the intrinsic diastereoface selectivity[316] of the enolate derived from the ketone **278** is 79/21, and that from the aldehyde **279** is 78/18. These two compounds are a mismatched pair, since their reaction yields products with opposite configurations of the hydroxyl and methyl bearing carbons and a mixture of aldol products in a 6:28:1 ratio. However, the reaction of **278** with (*S*)-**279** yields a single aldol product. They are therefore a matched pair.

Masamune[314] has studied extensively the phenomenon of double stereodifferentiation (double asymmetric synthesis). The homochiral enolate (*S*)-**280** reacts with benzaldehyde[317] to give the two *syn* products **281** and **282** in a 3.5:1 ratio. On the other hand, the homochiral aldehyde (*S*)-**283** reacts with an achiral enolate analogous to **280** to give the two *syn* products **284** and **285** in a 2.7:1 ratio. The configuration of **281** and **284** at the hydroxyl-bearing carbons are the same and therefore (*S*)-**280** and (*S*)-**283** are a matched pair. Indeed, the reaction between them yields **286** and **287** in a 8/1 ratio, close to the product of the ds of the substrate and reagent ($3.5 \times 2.7 = 9.5$). The reaction between (*S*)-**283** and (*R*)-**280** yields **288** and **289** in a 1/1.5 ratio, close to the quotient of the ds of the





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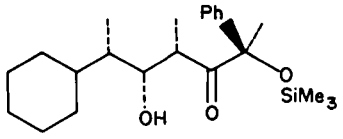
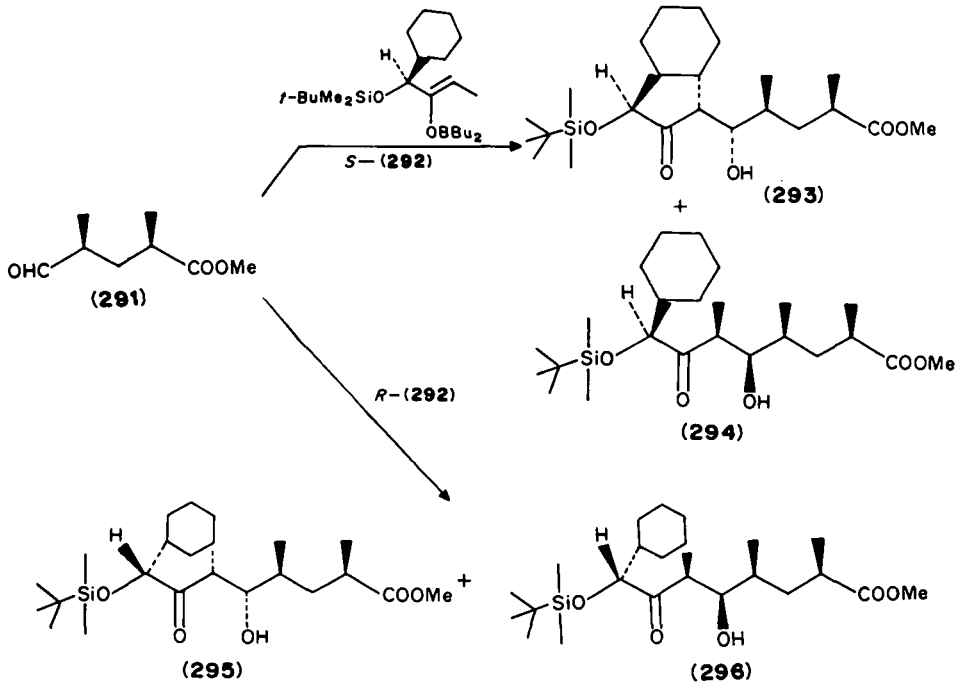


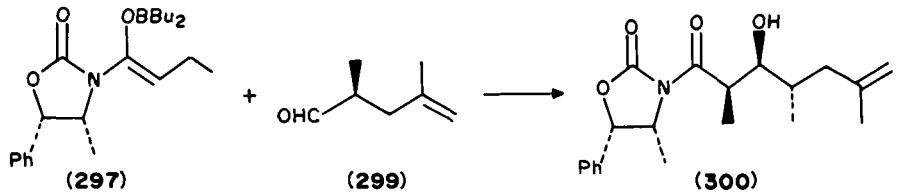
(289)

separate reagents (3.5/2.7 = 1.3) as expected for a mismatched pair. This multiplicativity correlation depends on the assumption that the single and double asymmetric reactions proceed through similar transition states[314]. If $\Delta\Delta G_1^*$, and $\Delta\Delta G_2^*$ represent the energy differences in the two diastereomeric transition states of the reaction used to determine the ds of each reactant, then ΔG^* (matched) and ΔG^* (mismatched) are given in equation 290, which is an expression of the multiplicativity rate. ΔG_{12}^* and ΔG_{12}^* are small peturbation terms

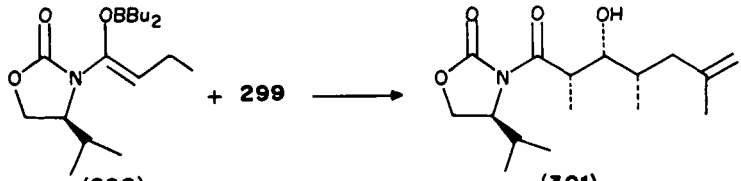
$$\begin{aligned}\Delta G^*(\text{matched}) &= \Delta\Delta G_1^{\ddagger} + \Delta\Delta_2^* + \Delta G_{12}^* \\ \Delta G^*(\text{mismatched}) &= \Delta\Delta G_1^* - \Delta\Delta G_2^{\ddagger} + \Delta G_{12}^{\ddagger}\end{aligned} \tag{290}$$



The slight excess of **289** relative to **288** shows that the larger ds of the enolate **280** determines the stereochemical outcome of the reaction. If the enolate shows sufficient diastereoface selectivity, it can override completely the modest diastereofacial selectivity of most aldehydes. The homochiral aldehyde **291** reacts with the enolate (*S*)-**292** to yield **293** and **294** in a 100/1 ratio, but the reaction of **291** with (*R*)-**292** gives **295** and **296** in a 1/30 ratio. An even larger effect is observed[318] in the reactions of the boron enolates **297** and **298** with **299**, that yield **300** and **301** respectively with ds larger than 99.75%.

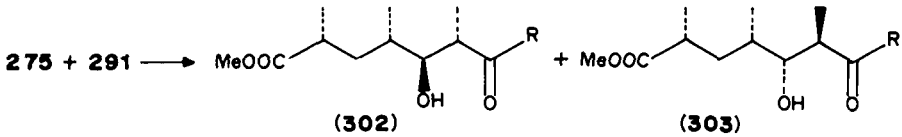


(297) (299) (300)



(298) (301)

The enolate **275** containing a chiral boron group undergoes also highly stereoselective reactions[319] with chiral aldehydes, e.g. **291** yields the products with *anti* (**302**) and *syn* (**303**) configurations at the 3,4 carbons in a ratio of 200/1, but the reaction of **275** with ent-**291** yields ent-**302** and ent-**303** in a 1/55 ratio. The pair **275**–**291** is a matched pair and **275**-ent–**292** a mismatched pair. Here the high diastereofacial selectivity of the enolate (*ca* 100/1) outweighs the modest opposite selectivity of the aldehyde to give the good 55/1 double asymmetric selectivity.



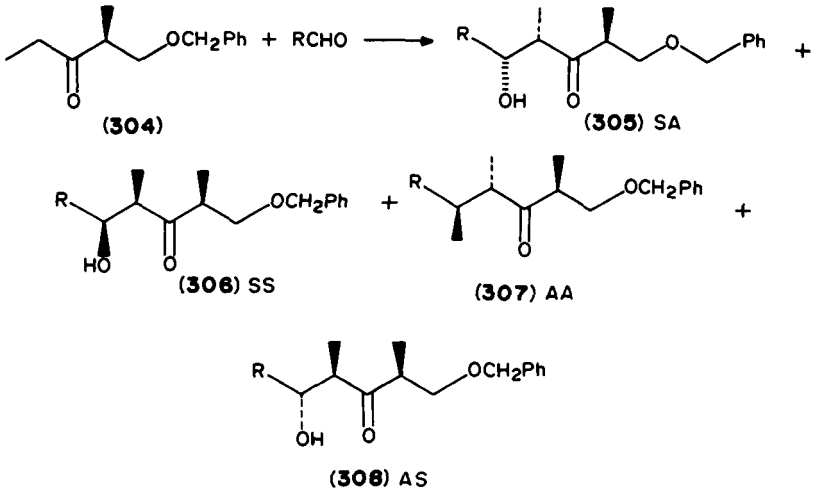
(302) (303)

Enhanced diastereoselection was observed in the reaction of enolates formed from chiral ethyl ketones and chiral boron groups[320,321] with achiral aldehydes. This is not really a double diastereodifferentiation despite the presence of two chiral units, since the aldehyde is achiral, but the chiral group on the metal can entirely change the inherent selectivity of the ketone. The homochiral ketone **304** forms an enolate with Bu_2BOTf–Et_3N. A subsequent reaction with an aldehyde RCHO gives four products **305**–**308**. The product distribution in the reaction of the enolate with an achiral boron group with methacrolein is recorded in Table 11. The bulk of the product consists of **307** and **308** (AA + AS). There is no discrimination between SA and SS and there is a preference for the *anti* products. However, when ent-**276** [(+)Ipc_2BOTf] is used for the enolate formation, there is a selective (*Z*)-enolate formation and the major product is SS. Moreover, this product is

TABLE 11. Asymmetric induction using chiral ketones and chiral boron groups

Reagent	Ketone (% ee)	Product composition				
		SA(% ee)	ss(% ee)	AA + AS	SA/SS	% yield
Bu_2BOTf (−78 °C)	**304**	41	48	11	1/1.2	76
Bu_2BOTf (0 °C)	**304**	2	4	94		57
ent-**276**	**304** (97)	7 (64)	93 (> 99)	< 2	1/13	74
ent-**276**	**304** (54)	28 (72)	72 (> 95)		1/2.6	51
276	**304** (97)	93 (99)	7 (64)		13/1	62
276	ent-**304** (84)	13 (9)	87 (99)		1/67	82

formed with 99% ee. The use of **276** led to the predominant formation of the SA product and the reaction of ent-**304** with the enolate formed with **276** gave mainly the SS product, again with 99% ee.



4. Reactions with other metal enolates

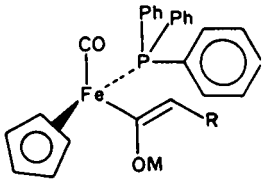
The enolates considered until now were of metals of the first, second and third groups and those of silicon. The enolates of tin[292], titanium[322] and zirconium[323] have also been studied and found to yield with aldehydes the *syn* products, independently of the *Z* or *E* geometry. Open transition states[292] such as **233** have been proposed to explain this phenomenon. Boat transition states have also been proposed[322]. The S/A selectivity of these reactions is around 85/15. The advantage of these reactions is that it is possible to obtain the *syn* products even when only *E*-enolates can be formed as in cyclic enolates.

Excellent *syn* selectivity and enantioselection was found for the dicyclopentadienylchlorozirconium enolates derived from prolinol amides[324]. Very good enantioface selectivity (99/1) was obtained using titanium enolates of α-silyloxy-esters[348].

Aldol reactions of tin enolates were found to give the *anti* products, and at higher temperatures the *syn* products[325]. The opposite steric course was also observed[326–329] in a crossed aldol reaction of divalent tin enolates.

α-Mercurioketones[330] undergo the aldol reaction with *syn* stereoselectivity. Rhodium-catalyzed reactions[331,332] of enolsilanes exhibit low enantioselection, when chiral rhodium catalysts are used[332]. Other α-metalloketone complexes[333] of transition metals undergo aldol reactions only on heating or irradiation, but the steric course of their reactions is not known yet.

An interesting group of α-metalloketones, containing an asymmetric iron center, was studied by Davies[334,335]. According to the rules formulated[336], the reaction of an acyliron complex with butyllithium leads to a *Z*-enolate with the C—O bond *anti* to the M—CO bond **309**. The reaction of this enolate with electrophiles proceeds from the direction opposite to the phenyl shielding one face. The lithium enolates do not react selectively and mixtures of *syn* and *anti* products are obtained. However, exchange in racemic **309** (R=H) of $AlEt_2$ for Li induces[337,338] a selective reaction with propional that leads to **310** and **311** (ratio 100/1). A boat-like transition state **312** was proposed for the formation of the major product[337,338].



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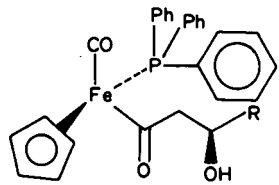
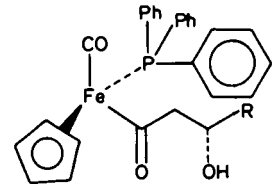


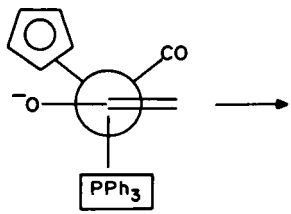
(310)



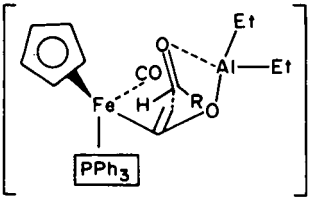
(311)

Tin enolates **309** (R=H, M=SnCl) give with propanal[337,338] preferentially **311** (ratio **310**/311 = 1/5.4). The aluminum enolate **309** (R = H, M = Al(*i*-Bu)$_2$) gives a 5.2/1 ratio of the same products. An open transition state was assumed for the reaction of the aluminum enolate and a cyclic chairlike one **313** for the tin enolate[339].

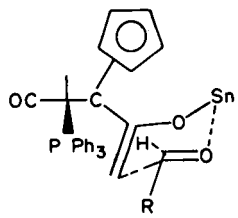
The reaction of **309** (R = Me, M = AlEt$_2$) with acetaldehyde[340,341] led to two diastereomers **314** and **316** in a 100/7 ratio. The copper enolate (R = Me, M = CuCl),



(309a)

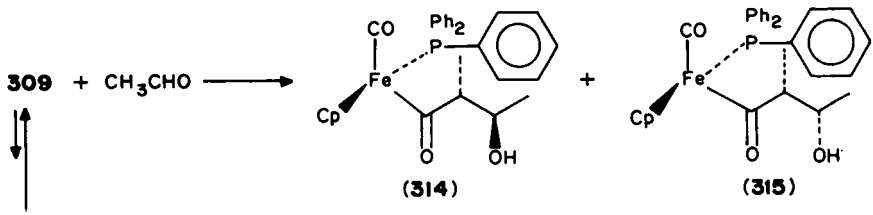


(312)

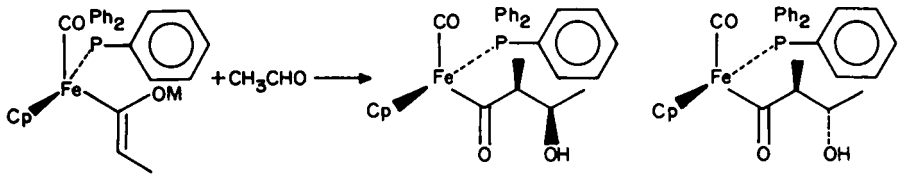


(313)

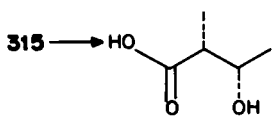
(≡ 309, R=H)



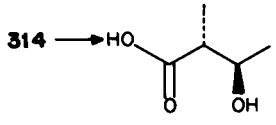
(314) (315)



(309b) (316) (316a)



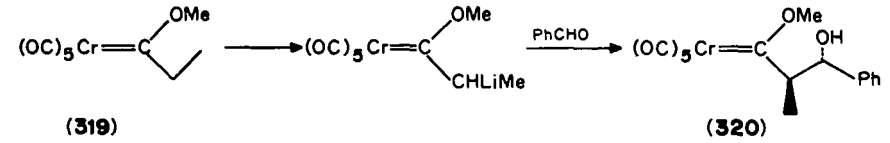
(318)



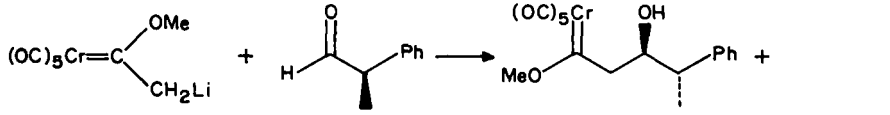
(317)

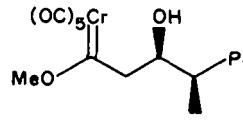
however, gave **314** and **315** in a 14/100 ratio. Complex **314** gave on decomplexation the *anti* (*threo*) **317** and decomplexation of **315** gave the *syn* (*erythro*) acid **318**. The high stereoselection between **314** and **316a** and that between **316** and **315** correspond to the enantioselectivities in asymmetric syntheses of the *anti* and *syn* α-methyl-β-hydroxyacids, respectively, and therefore high enantioselectivity is expected.

A different kind of enolate is obtained by metalation of a chromium alkoxy carbene complex[342], **319**. The metalated product yields with an aldehyde preponderantly the *anti* product **320** (A/S = 6/1). The primary lithium compound gives with the chiral 2-phenylpropanal the Cram product (1/8) **321**.

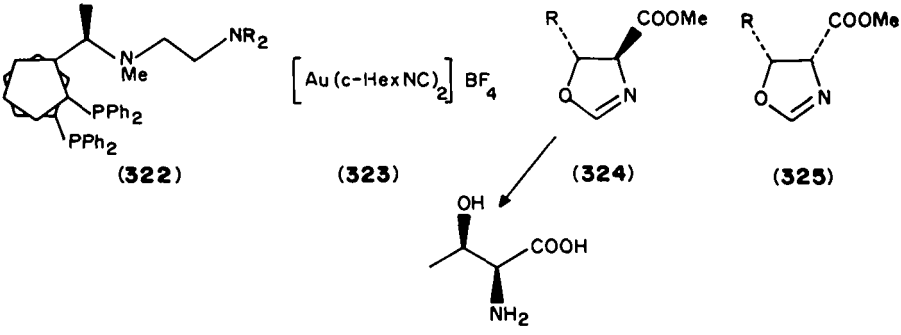


(319) (320)





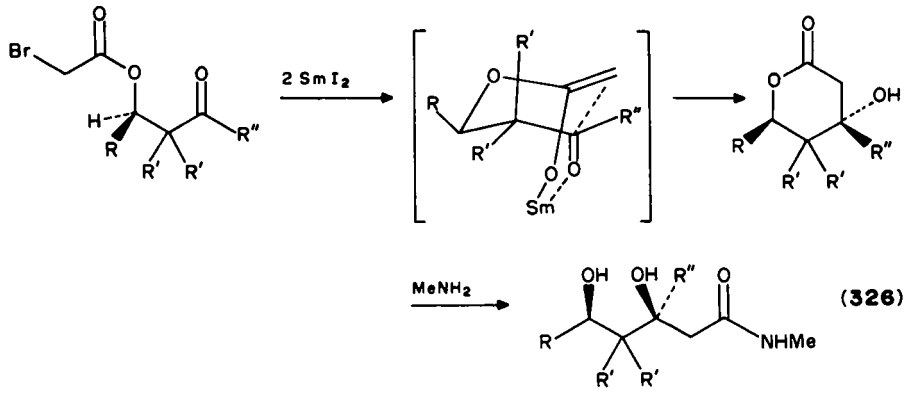
(321)



(322) (323) (324) (325)

An aldol reaction between an aldehyde and (*R*)-*N*-methyl-*N*-[2-(dialkylamino)-ethyl]-1-(*S*)-1,2-bis(disphenylphosphino)ferrocenyl]-ethylamine (**322**) complex with methyl isocyanoacetate is catalyzed[343–345] by a gold compound **323**. *Cis*- and *trans*-substituted oxazolines with up to 96% ee are obtained (*trans*/*cis* = 4/1), **324** and **325**. The optically active (4*S*, 5*R*)-**324** can be converted into L-threonine. Optically active β-hydroxy-α-aminoacids can thus be synthesized by a highly selective catalytic aldol reaction.

An intramolecular Reformatsky reaction, analogous to the aldol reaction, via a samarium enolate was found to be highly stereoselective[346] and led to a single diastereomer (equation 326).

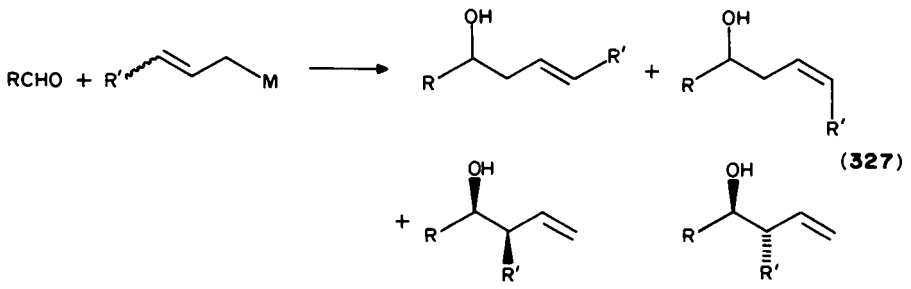


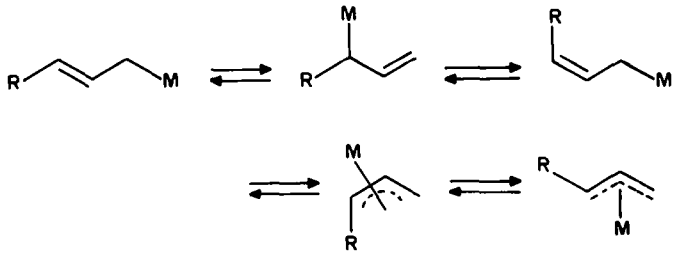
A chiral tricarbonylchromium complex of an aromatic aldehyde induced an enantioselective[350] Darzens reaction with 88% ee of the obtained epoxides.

F. Addition of Allylmetals to Carbonyl Compounds

1. Introduction

The reaction 327 of allylmetal compounds with carbonyl compounds can be considered a variant of the aldol reaction. The double bond of the homoallyl alcohol can be transformed into a carbonyl group, but other functional groups are also accessible from it. Of particular interest are substituted allylmetal compounds in this reaction 327 which can lead to four products. Substituted allylmetal compounds can exist in the form of mono- and triphapto fomrs (equation 328) and a variety of ionic species. The actual species in solution depends on the substituent, on the metal and the conditions such as solvent, temperature, etc. Derivatives of the first and second group of metals undergo fast metallotropic rearrangements and the products of their reactions are difficult to predict. There are some allylic lithium compounds where the metal is maintained in one position by a chelating substituent. Most of the recent investigations were concerned with the control of the stereo- and regioselectivity of the reaction 327 and derivatives of metals other than of the first and second group have been studied. Several reviews have been published[351–353].

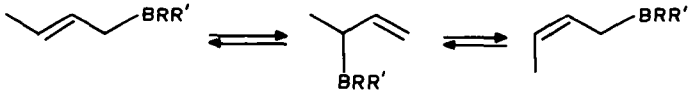




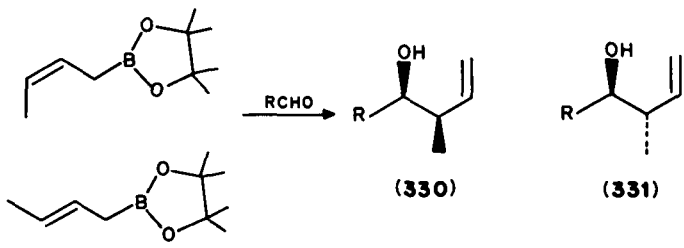
(328)

2. Allylboron compounds

The rate of the borotropic rearrangement 329 of allylborons depends on the nature of the other substituents on boron. Allyldialkylboranes rearrange faster than allylalkylborinates (R′ = OR″) and the latter faster than allylboronates (R = R′ = OR″). The first steric studies were therefore carried out by Hoffmann[354] on crotylboronates[355]. (*Z*)-Crotylboronates gave with aldehydes preferentially the *syn* product **330** (syn/anti ≈ 96/4), whereas the (*E*)-crotylboronates gave a *syn/anti* ratio of 7/93. Cyclic transition states were proposed for the reactions of the (*Z*)- and (*E*)-isomers respectively, analogous to those of the aldol reaction.

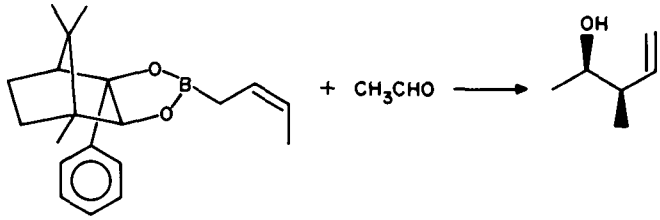


(329)



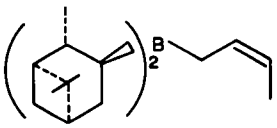
(330) (331)

This is a simple diastereoselection and the products obtained were racemic. Much effort has been devoted to the task of the direct preparation of the pure enantiomers by the use of chiral auxiliaries to control face selectivity. A (*Z*)-boronate **332** formed from a glycol derived from (+)-camphor[356,357] gave, with acetaldehyde, the *syn* product **333** in 90% yield and 60% ee, and the *E*-boronate gave the *anti* isomer with 52% ee.



(332) (333)

A much better enantioface selectivity was achieved by Brown[358] using (*Z*)-**334** and (*E*)-crotyldiisopinocampheylboranes **335** and prepared from methoxydiisopinocampheylborane derived from (−)-pinene and from crotyllithium (prepared by a modified procedure of Schlosser[355,359]). The use of (+)-α-pinene as starting material gave the isomeric (*Z*)- and (*E*)-crotyl boronates **336** and **337**. Reaction of **334–337** with acetaldehyde yielded the four possible isomers **338–341** correspondingly with 99% ds and 95% ee.



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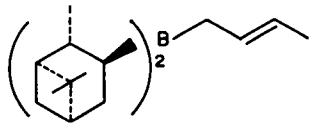

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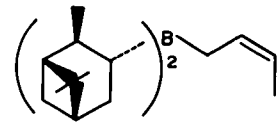
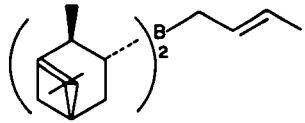


(336)



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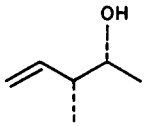

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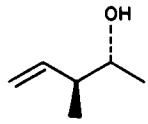
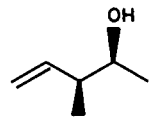
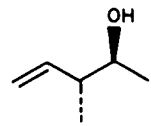


(339)

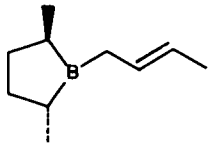


(340)



(341)

A similar enantioface selection was obtained by Masamune[367] using the chiral (*E*)-(*R*, *R*)-**342**, (*Z*)-(*R*, *R*)-**343** crotylborolanes and their enantiomers. The reaction of **342** with a number of aldehydes led to the predominant formation of the *anti* (**331** + ent-**331**) products (*anti*/*syn* ≈ 95/5), with **331** as the major isomer (96% ee). The (*Z*)-borolane **343** gave mostly the *syn* isomers (*syn*/*anti* ≈ 5/95) with **330** as the major products (86–97% ee).



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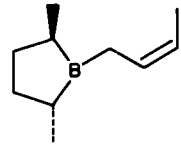
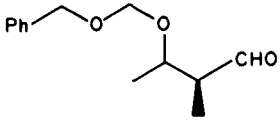
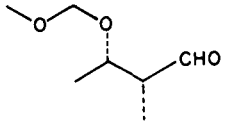


(343)

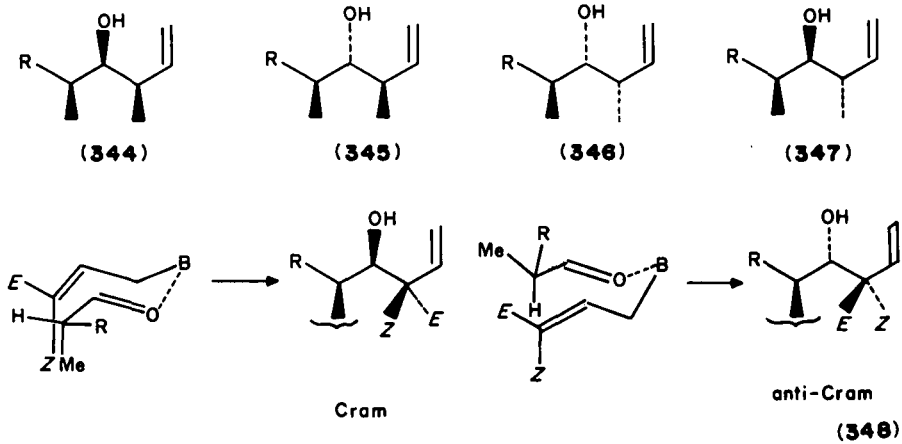
B-allyldiisopinocampheylborane reacts readily[360] with aldehydes to give homoallylic alcohols with 86–96 ee. Chiral isopropenylation of aldehydes was achieved using 3,3-dimethylallyldiisopinocampheylborane[361].

The stereoselective construction of the triads **344–347**, of interest to the synthesis of macrolides, is in principle possible by the reaction of crotylmetal compounds with α-substituted aldehydes. (*E*)-crotylboronates give a higher Cram selectivity in addition to α-chiral aldehyde than the allylboronates, whereas (*Z*)-crotylboronates lead to the preferential formation of anti-Cram diastereomers[351,362–365] (Table 12). The results show that the extent and direction of the asymmetric induction can be determined also by the

TABLE 12. The ratio of Cram/anti-Cram products[366]

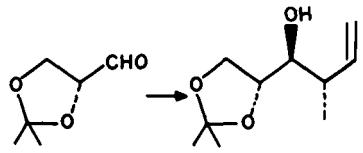
Aldehyde	Reagent		
	62/38	83/17	30/70
	61/39	89/11	22/78
	79/21	94/6	41/59

achiral reagent[366]. The models of the transition states explaining the effect are shown in equation 348. The (*E*)-crotylboronates give very good selectivities in favor of **347**, but the (*Z*)-isomers give only moderate selectivity in favor of **346**.

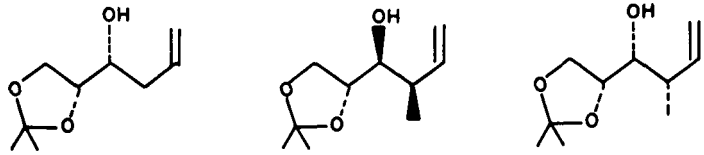


A greater extent of diastereoselection can be obtained by double stereodifferentiation. This method can also give access to the remaining triads **344** and **345**.

The reaction of the chiral borolane **342** with (*R*)-2,3-*O*-isopropylideneglyceraldehyde **349** led predominantly to **350** (96.1%), whereas **343** gave **352** (91.6%). Ent-**342** and ent-**343** afforded predominantly **351** (85.6%) and **353** (81.7%). **343** and **349** are a matched pair and the corrected ratio of the *syn*-alcohols **352**/**353** was 99/1, but ent-**343** and **349** are a mismatched pair with **352**/**353** = 1/5.7.

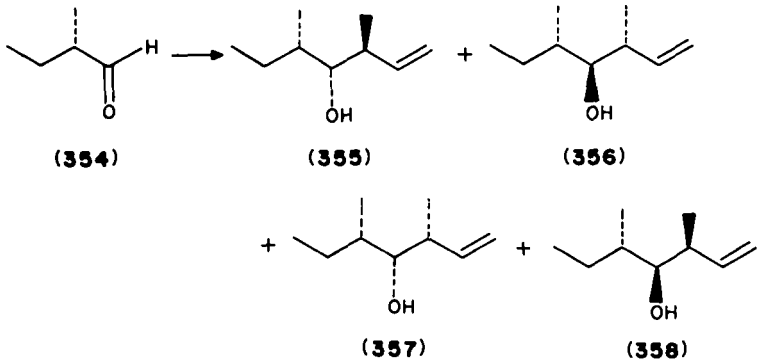


(349) (350)



(351) (352) (353)

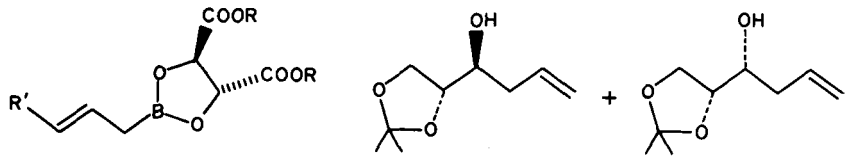
The crotyldiisopinocampheylboranes **334–337** have also been utilized[368] to induce diastereoface selection. The aldehydes **354** gave **337** the alcohols **355** and **356** in a 96/4 ratio, whereas **334** with the same aldehyde yielded the same products in a 9/91 ratio. The reaction of **336** and **335** afforded **357** and **358** in a 82/18 and 4/96 ratio, respectively. These reactions are highly selective and an appropriate selection of the chiral reagent can provide any desired isomer in this series.



(354) (355) (356)

(357) (358)

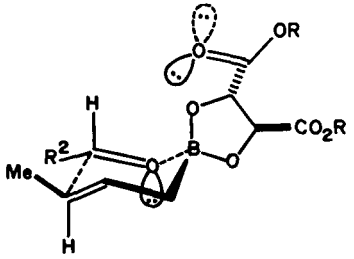
Tartrate ester based[369] allylboronates **359** (R′ = H), e.g. R = *i*-Pr, react with achiral aldehydes to give the homoallyl alcohols with 60–87% ee. The advantage of the boronates is their higher stereochemical stability. The reaction of **359** with chiral aldehydes such as **349** leads to **360** and **361** in a 96/4 ratio.



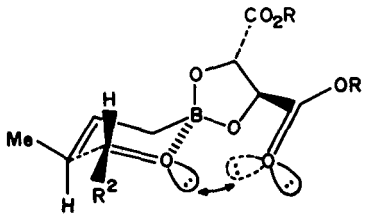
(359) (360) (361)

The diisopropyl tartrate-modified (*E*)-crotylboronate[362] **359** (R′ = Me; R = *i*-Pr) exhibits high diastereoface selectivity. Its reaction with **349** leads to **350**, **351** and **352** in a 87/9/4 ratio, but ent-**359** gave these products in a 2/96/2 ratio. Ent-**359** and **349** are therefore a matched pair.

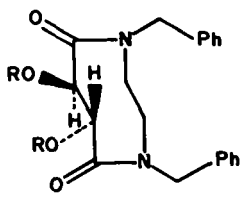
The asymmetric induction realized with **359** cannot be explained by simple steric interactions and has its origin in a stereoelectronic effect. The n/n electronic interaction involving the aldehydic oxygen atom and the *β* face ester carbonyl is less in transition state **362** than in **363**. The n/n interactions are even larger in the lactams **359a** (R = *β*-$CH_2CH{=}CH_2$) derived from tartaric acid, and a higher enantioselectivity in the reactions of these lactams[489] with aldehydes in observed (85–97% ee) than with **359** (R = H), since the conformations of this system are restricted (**362a**).



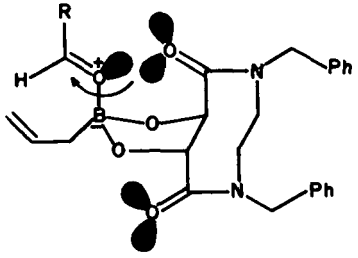
(**362**)



(**363**)



(**359a**)

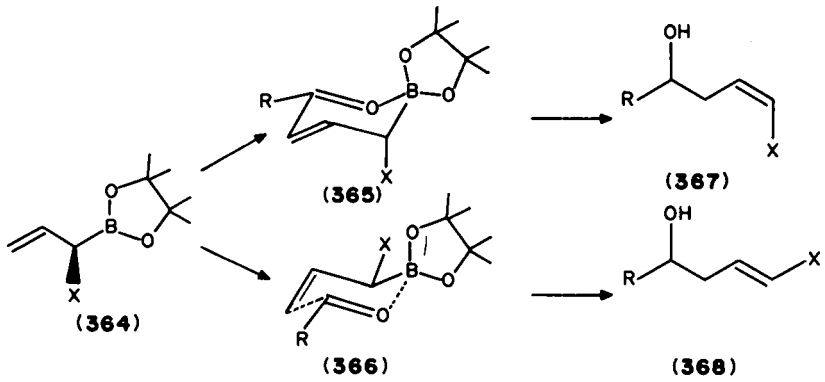


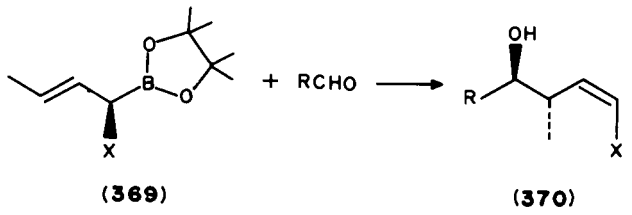
(**362a**)

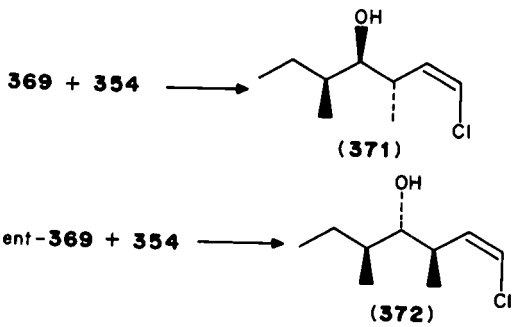
Chiral α-substituted allylboronates[370,371] **364** can, on reaction with aldehydes, transfer their chirality to the newly formed chiral center. Two transition states, **365** and **366**, are possible for this reaction, the first leading to **367** with a *Z* and the latter to **368** with an *E* double bond. The transition states can therefore be identified by the stereochemistry of the formed double bond even with racemic reagents. For X = Br the products **367** and **368** were formed in a 95/5 ratio for a number of aldehydes, although the transition state **365** for the formation of **367** contained an axial X group and **366** an equatorial one.

A study of a series of α-heterosubstituted allylboronates has shown that increasing the polarity of the C—X bond leads to a higher proportion of **367** in the product. The reason for the preferential axial bond to the heteroatom in the transition state is to minimize the π–σ^* interaction in an electrophilic attack of the carbonyl on the allylboronate. In the axial disposal of the C—X bond the angle between it and the π orbital is 90°.

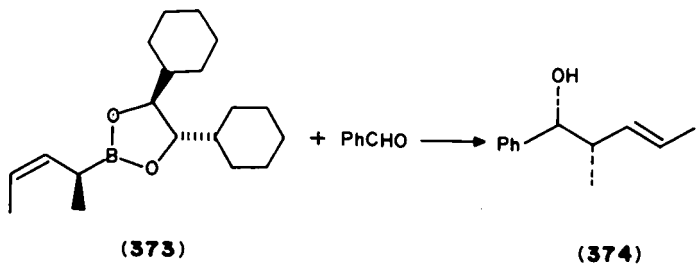
Homochiral α-substituted crotylboronates **369** have also been reacted with prochiral aldehydes, and products **370** with approximately 95% ee were obtained for X=Cl. The reaction[372,373] of **369** with **354** gave **371** with 98% ds, and that of ent-**369** with **354** yielded **372** with 90% ds.





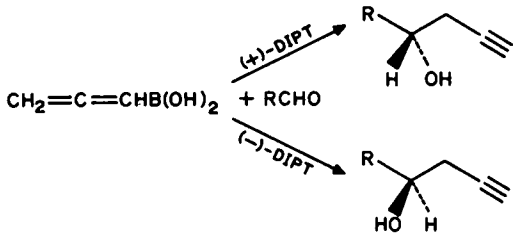


The homochiral α-methyl-(*Z*)-crotylboronate **373** gave[374], with benzaldehyde, the *syn* alcohol **374** with 99.5% ee.



A review of the effect of substituents on the stereochemistry of the reaction of crotylboronates with chiral aldehydes has led recently to the conclusion that Cornforth-type transition states **15** are favored in the reaction of alkoxy-substituted aldehydes[365,375].

The reaction of allenylboronic acid, esterified with chiral DIPT, with aldehydes[376] led to high enantioselectivity (94–99% ee) (equation 375). This result was ascribed to the screening effect of one of the ester groups **376**. A β-hydroxyaldehyde yielded with the allenylboronic acid an intermediate that reacted[377] intramolecularly with the carbonyl group with enantioselectivity larger than 99% ee (equation 377).



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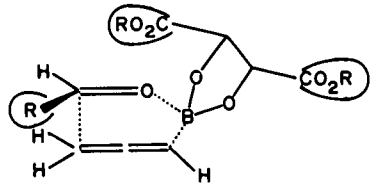

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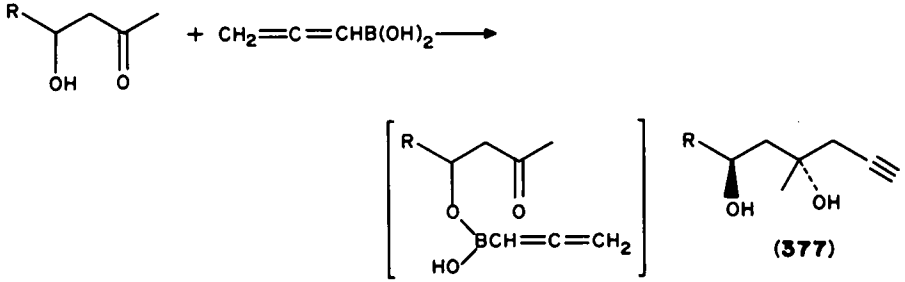
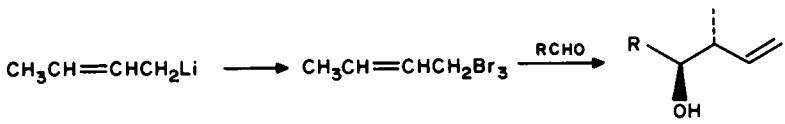


(377)

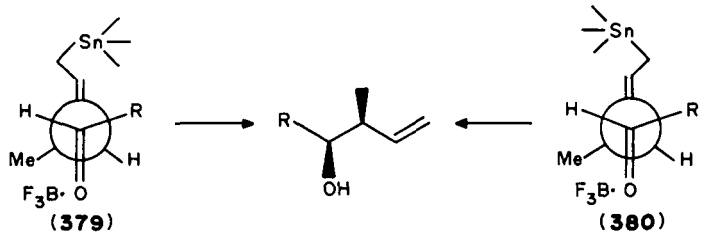
Crotylborates[378] give with aldehydes approximately 80% of the *anti* product, corresponding apparently to the percentage of the *E*-allyl compound (equation 378).



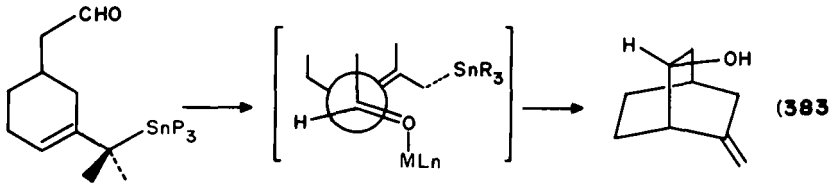
(378)

3. Allyltin and silicon compounds

Uncatalyzed reactions of allyltin compounds with aldehydes require higher temperatures and give the usual products corresponding to pericyclic reactions. (*E*)- and (*Z*)-allyltins yield the *anti* and *syn* products, respectively[379]. The pericyclic mechanism is supported by the acceleration of the reaction at higher pressures[387]. Lewis acid catalyzed reactions of these compounds proceed easily at lower temperatures, are convergent and give predominantly the *syn* products, without regard to the starting compounds[379a,380]. The Lewis acid catalyzed reaction exhibits enhanced Cram selectivity[379b]. The *syn* convergent product formation was rationalized by preferential antiperiplanar acyclic transition states, **379** for the (*Z*)- and **380** for the (*E*)-allyltin. The less favorable transition states are **381** and 382, respectively.



A synclinal transition state was proposed by Denmark[381] for these reactions, following Seebach's rule (equation 383), since some intramolecular reactions can be rationalized only by this transition state.



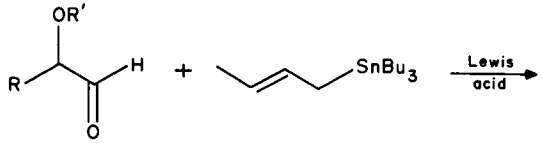
The reaction of an allyltin with a chiral α-hydroxyaldehyde (equation 384) may proceed by the chelated cyclic mechanism if the catalyst can coordinate with both oxygens[382] (Table 13). The chelation is also solvent dependent. The best conditions of chelating are to use dichloromethane as a solvent and $TiCl_4$ or $MgBr_2$ as a catalyst.

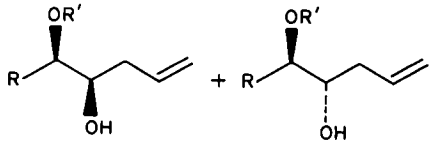
The 1,3-chirality transfer in homochiral allylic tin compounds permits one to prepare homochiral homoallyl alcohols[383] (equation 385).

Formation of the tin compound *in situ* from tin and the allyl halide leads to complete *anti* selection in the reaction of (*E*)-phenallyl chloride with aldehydes[384]. On the other

TABLE 13. Stereoselection in the reaction of allyltin compounds with α-alkoxy aldehydes (see equation 384)

R	R′	Lewis acid	Solvent	*syn/anti*
c-Hex	$PhCH_2$	$MgBr_2$	Et_2O	94/6
c-Hex	$PhCH_2$	$MgBr_2$	THF	20/80
c-Hex	$PhCH_2$	$MgBr_2$	CH_2Cl_2	250/1
c-Hex		$TiCl_4$	CH_2Cl_2	250/1
c-Hex		$BF_3 \cdot Et_2O$	CH_2Cl_2	39/61
c-Hex	*t*-$BuMe_2Si$	$BF_3 \cdot Et_2O$	CH_2Cl_2	9/91
c-Hex	*t*-$BuMe_2Si$	$MgBr_2$	CH_2Cl_2	21/79





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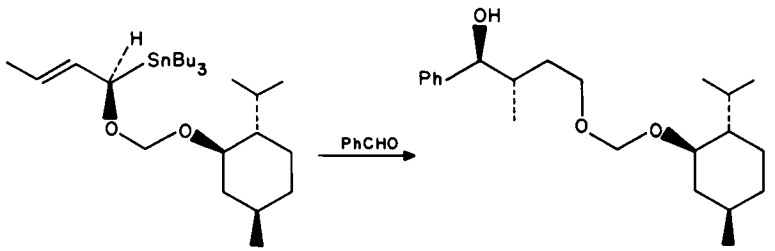

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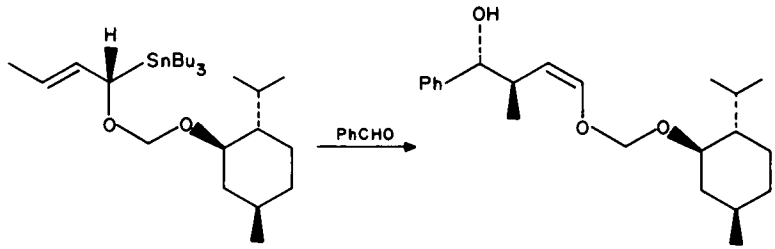
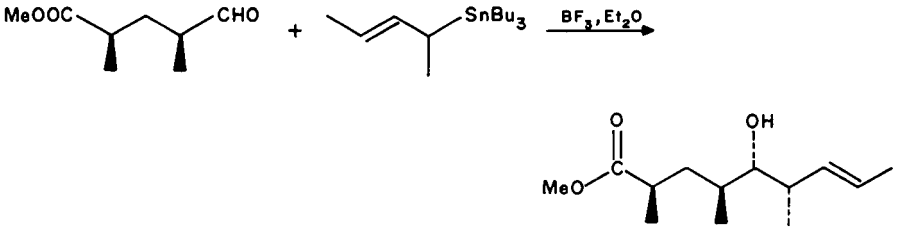


hand, reaction of (*E*)-crotyl chloride with aluminum and aldehydes yields mainly, but not exclusively, *syn* products[384].

Stereoconvergent *syn* product formation in the Lewis acid catalyzed reaction of

crotylsilanes with aldehydes (Sakurai reaction) was also observed[380,385], but (*E*)-crotyl silanes gave much higher *syn* selectivity (99/1) than their (*Z*)-isomers[385]. The reaction of homochiral silanes with aldehydes[386] proceeded by an S_E2 process with inversion to give **387** (99/1) and depended on the configuration of the double bond. The transition state was propoded as **388**.



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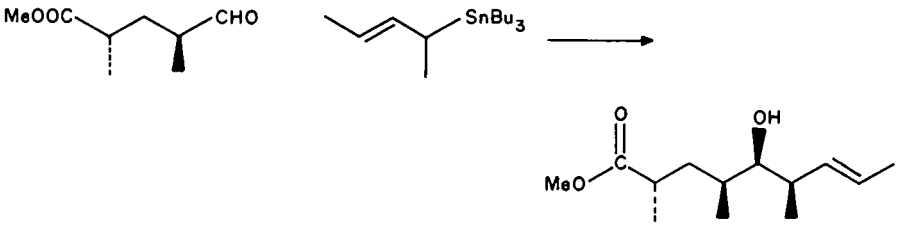

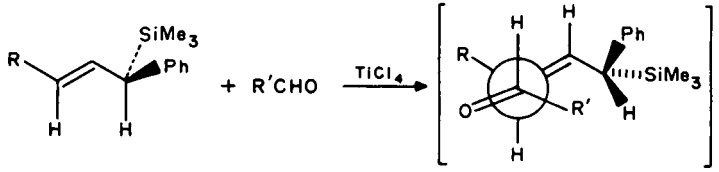

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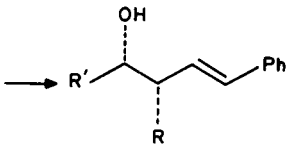

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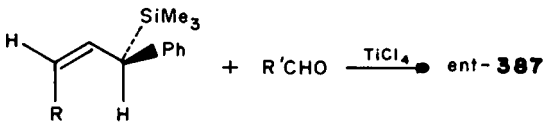
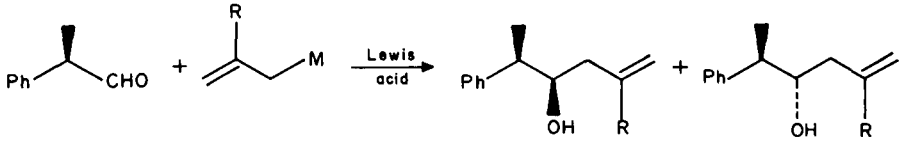


TABLE 14. Lewis acid catalyzed reaction of allylsilanes with α-substituted aldehydes

Reaction	Metal	Lewis acid	R in silane	*syn/anti*
389	Li	—	H	3/1
	t-BuMe$_2$Si	BF$_3$·Et$_2$O	H	10/1
	Me$_3$Si	BF$_3$·Et$_2$O	H	2/1
	Me$_3$Si	TiCl$_4$	H	1.6/1
	Me$_3$Si	BF$_3$·Et$_2$O	Me	7/1
390	SiMe$_3$	BF$_3$·Et$_2$O	H	1/1.5
	SiMe$_3$	SnCl$_4$	H	30/1
	SiMe$_3$	SnCl$_4$	Me	45/1

The Lewis acid catalyzed reaction of allyltrimethylsilanes with chiral α-alkyl aldehydes is somewhat less Cram-selective than that of lithium compounds[388,389], but the bulky *t*-butyldimethylallylsilane is more selective (equation 389 and Table 14). High selectivity is achieved in the Sakurai reaction of chiral β-alkoxyaldehydes (equation 390) using catalysts that can chelate the alkoxy with the carbonyl group ($SnCl_4$). The presence of a branching methyl group at the position 2 of the allylsilane has a similar effect.



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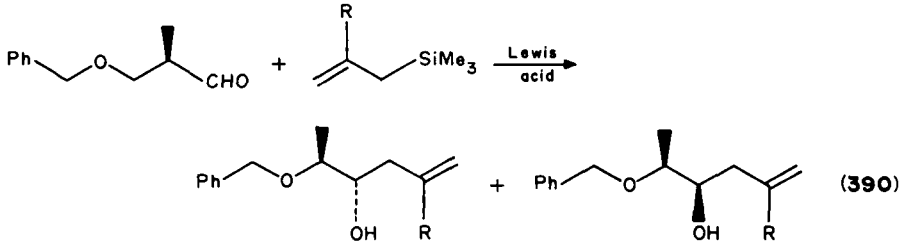


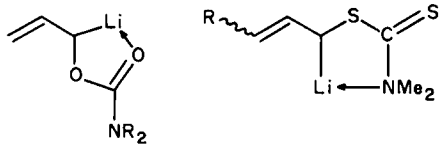
(390)

Similar observations have been made also by others[390,391].

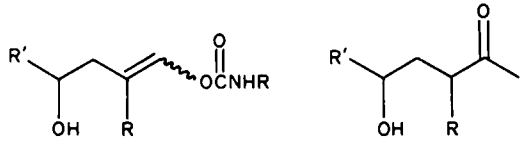
4. Other allylmetals

The metallotropic reaction of allyllithium compounds discussed in the introduction can be shifted to one side by the use of a substituent that can coordinate with lithium in one position. This was done with allylcarbamates that gave easily the α-lithiated[393] derivatives (**391**).

A similar metalation was obtained with dithiocarbamates[394] **392**. These compounds reacted with aldehydes predominantly at the γ-position, but the stereoselectivity was not good. Products with an oxygen function at the double bond **393** were obtained in the reaction of aldehydes and these could be transformed into carbonyl containing products **394**. The reaction was called therefore a homoaldol reaction[395].

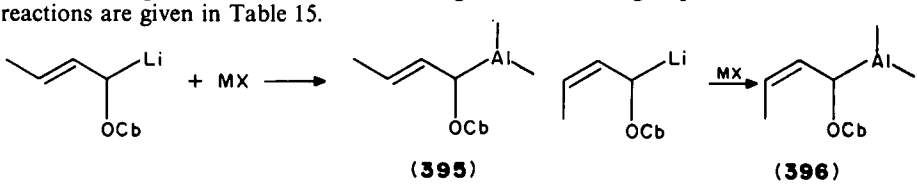


(391) (392)

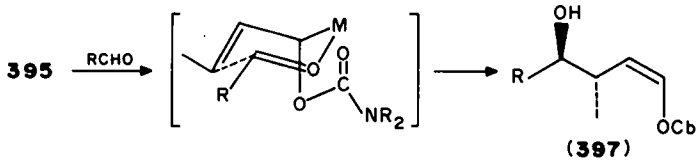


(393) (394)

In order to enhance the stereoselectivity of the reaction, other metals were substituted for lithium **395** (Cb = carbamate) and **396**. The (*E*)-crotyl derivative **395** is expected to give in the reaction with aldehydes the (*Z*)-*anti* product **397** and the (*Z*)-crotyl–(*E*)-*syn* product **398**. The other isomers, **399** and **400**, are also available from transition states with a different configuration of the carbon bearing the carbamate group. The results of the reactions are given in Table 15.



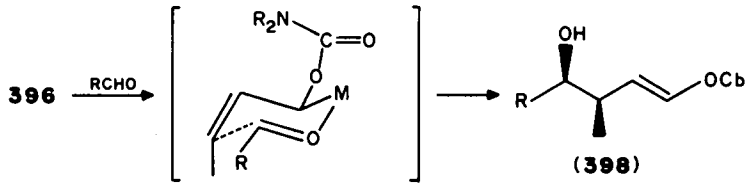
(395) (396)



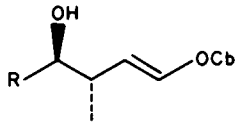
(397)

TABLE 15. Product dependence on the metal in the homoaldol reaction

Enolate	M	R	Products (%)				
			γ/α	**397**	**399**	**400**	**398**
395	Li	Me	80/20	55	0	45	0
	$(i\text{-Bu}_2)_2$Al	Me	91/9	15	78	< 1	8
	$(Et_2N)_3$Ti	Me	99/1	97	0	3	0
396	Li	Me	83/17	12	12	18	58
	$(i\text{-Bu})_2$Al	Me	99/1	2	8	3	87



(398)



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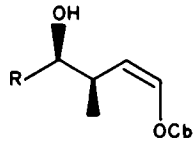
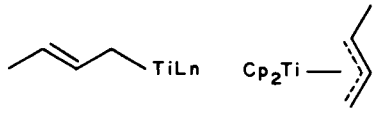


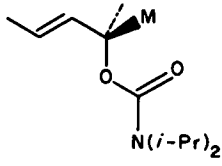
(400)

Titanium compounds were the best stereodifferentiating compounds. Croyl titanium compounds with a variety of ligands on titanium **401** [Ln = $(N(Et_2)_3$; $(OCHMe_3)_3$; Cp_2Br;] and also **401a** yielded the *anti* products with aldehydes[396,397]. The boron trifluoride catalyzed reaction gave the *syn* products preferentially[398].



(401) (401a)

A relatively, configurationally stable homochiral lithium derivative **402** (M = Li) was prepared[399,400] from an optically active carbamate of (*S*)-(*E*)-penten-2-ol **402** (M = H). The reaction of the lithium compound with $Ti(O\text{-}i\text{-}Pr)_4$ gave the titanium derivative **402** [M = $Ti(O\text{-}i\text{-}Pr)_3$] with retention of configuration and the latter yielded with 2-methylpropanal the *anti* product **403**. However, reaction of **402** (M = Li) with $ClTi(NMe_2)_3$ gave the titanium derivative **404** with inversion [M = $Ti(NMe_2)_3$], since reaction with the same aldehyde gave ent-**403**. The reagent possesses diastereoface selectivity to a high extent and can override the natural face selectivity of some aldehydes.



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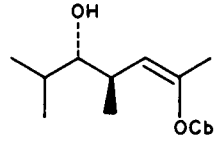

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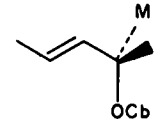
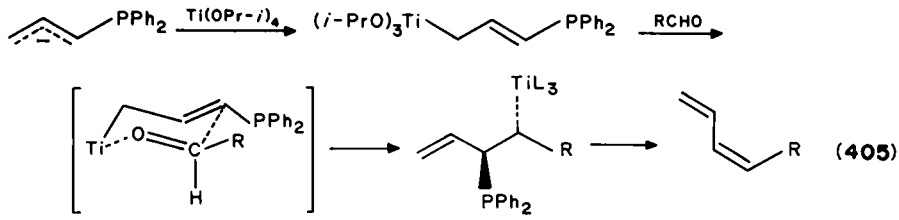
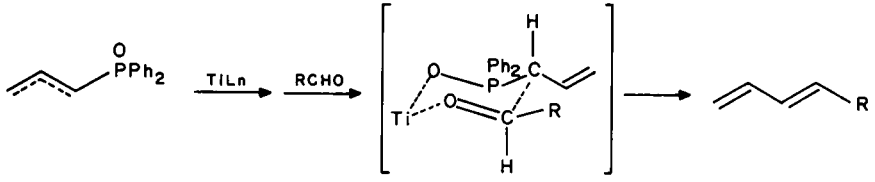


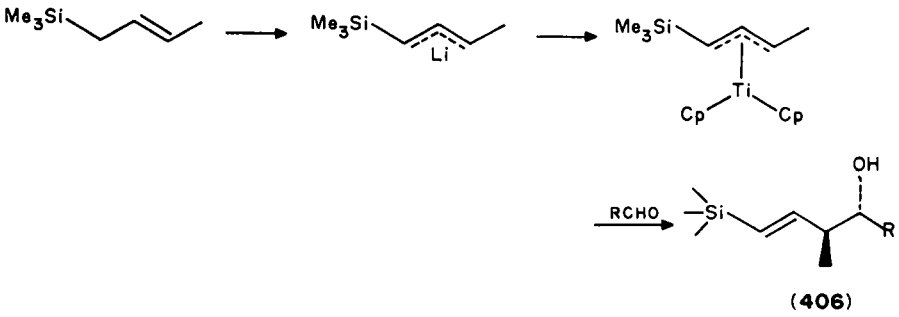
(404)

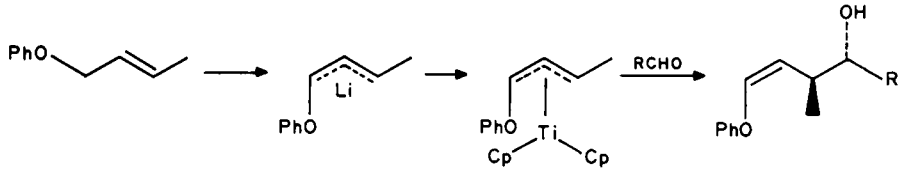
The product of the reaction of an allylic titanium compound containing a phosphine group (equation 405) is changed[401] on transforming the phosphine into a phosphine oxide. In the latter case, the oxygen on the phosphorous is part of the pericyclic transition state.

η^3-1,3-Substituted allyltitanium compounds[402] induce *anti* product formation (equation 406).

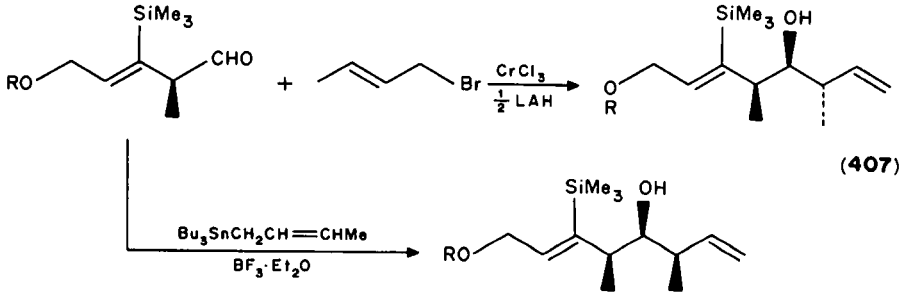








Crotylchromium reagents give with aldehydes the *anti* products[403,404]. The reaction is stereoconvergent, and it shows a high Cram selection[405] (equation 407).



A number of additional crotylmetal compounds (Hg, Cu, Zr, V) that yield generally *anti* products with aldehydes change the predominant product[406] to *syn* in the presence of $BF_3 \cdot Et_2O$.

III. NUCLEOPHILIC ADDITION TO THE C=N GROUP

A. Introduction

Nucleophilic additions to the double bond in imines are expected to be similar to additions to the carbonyl group. The steric and electronic differences between these two groups should find their expression in somewhat different reactivities. The imine group has a trisubstituted double bond and can be considered geometrically analogous to a ketone–Lewis acid complex. An iminium ion has a tetrasubstituted double bond and is geometrically similar to a C=C double bond, but is electronically very different from it. During reactions, the additional substituents could impose steric requirements different than those for the carbonyl group.

The imine group is a weaker electrophile than the carbonyl group and sulfonylimines; iminium salts or even aryliminium salts are used to enhance its reactivity with electrophiles.

During the reaction with nucleophiles, the imines are generally deprotonated and thus protected from addition of the nucleophile to the double bond.

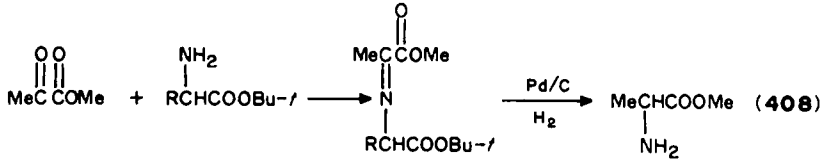
Alkyl-lithium and magnesium compounds react reluctantly even with not containing a hydrogen α to the $>C{=}N-$ group imines, but softer allyl metals and enolates do react satisfactorily.

The study of asymmetric induction in the addition to the C=N bond was neglected for a long time, but recent work has shown the potential usefulness of such studies.

B. Addition of Simple Nucleophiles

Early studies of the addition to the imine group[3] have been concerned mainly with the preparation of chiral amino acids. The Strecker synthesis, in which cyanide is added to an imine derived from a chiral benzylamine, gives after hydrolysis and hydrogenolysis amino acids in 22–58% ee[407]. A related reaction is the Ugi synthesis[207,208].

Hydrogenation of imines[408–410] obtained by asymmetric transamination leads to amino acids with high ee (equation 408).



(408)

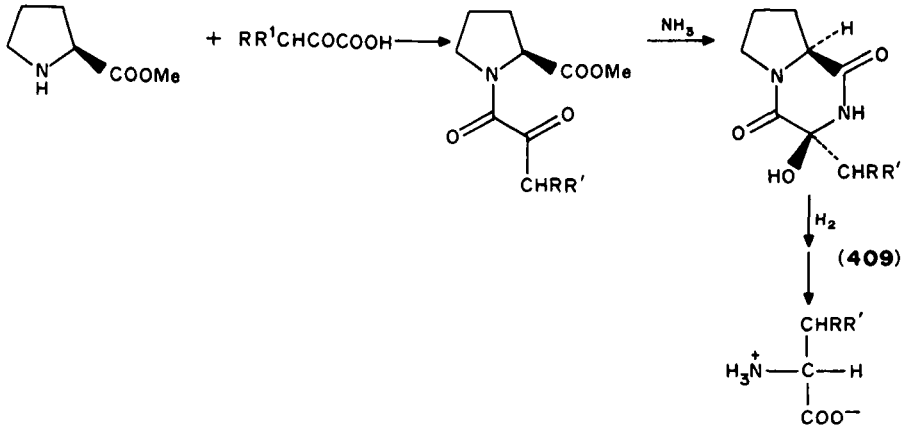
(*S*)-Proline was used[411] to synthesize chiral amino acids from ketoacids (equation 409).

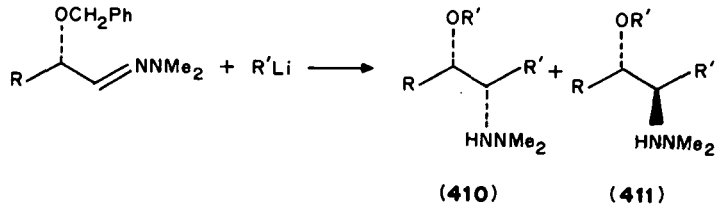
The addition of Grignard or alkylcadmium reagents[412] to benzylimine or α-methylbenzylimine of menthyl glyoxalate gave amino acids with up to 64% ee. However, a parasitic conjugate addition also take place in this reaction.

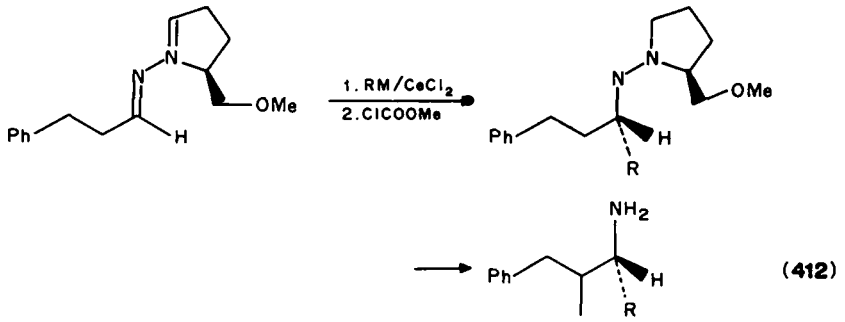
Alkyllithium compounds react with dimethylhydrazones of α-alkoxyaldehydes[413] to give predominantly (98/2) the *syn* product **410**. This product is apparently formed from a cyclic intermediate, since tritylllithium ($R' = Ph_3C$) gave the *anti* product **411** preferentially (**410/411** = 1/10) via an open-chain reaction.

(*S*)-1-amino-2-methoxymethylpyrolidine (SAMP) hydrazones react with alkyllithium

compounds[414] to give, after hydrogenolysis, chiral amines with 81–93% ee (equation 412).





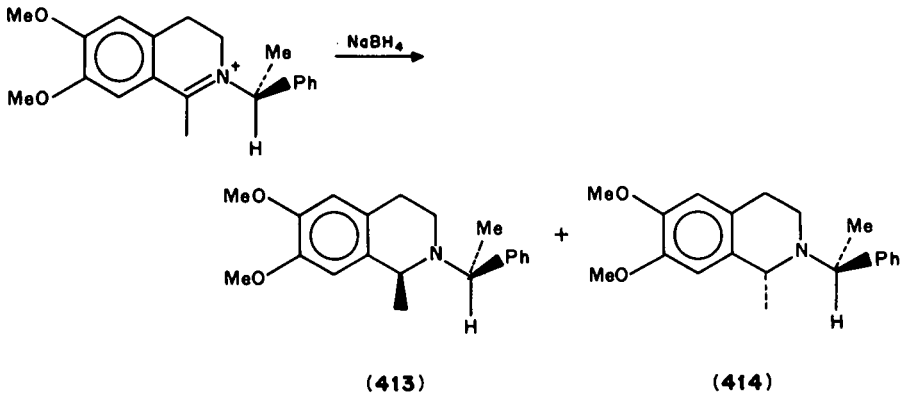


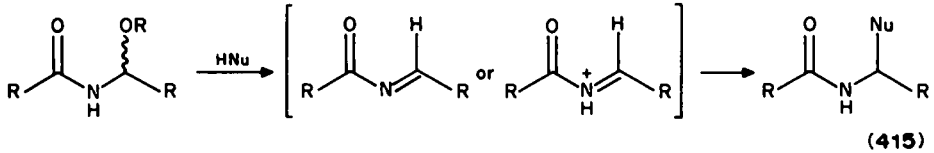
Organocerium reagents diminish the complications that arise from α-proton abstraction. They react with aldehyde–SAMP hydrazones[415] with a high extent of diastereoselection (93 –98% ds). The products of the reaction can be reduced to chiral amines.

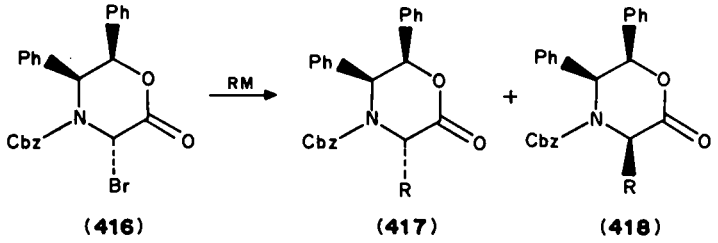
The reduction of chiral iminium ions is highly diastereoselective[416] (**413/414** = 93/7).

Amidoalkylation (equation 415) is a reaction of *N*-acyl *N*, *O*-acetals with nucleophiles[498]. This reaction is considered to proceed via *N*-acylimines or *N*-acyliminium ions. The reaction of **416** with alkyllithium yields **417** and **418** in a 5.6/1 ratio. Asymmetric induction to a higher extent was also achieved[499–501].

Acyclic acylimines **419** containing a powerful auxiliary chiral group[417] react also with high stereoselectivity[418] to give **420** and **421** in a 96/4 ratio. The preferential







formation of **420** provides evidence that the reaction proceeds through an *N*-acyl intermediate in the cisoid conformation **422**.

The BF_3 catalyzed addition of an alkylcopper derivative[419] to the chiral Schiff base **423** exhibits Cram selectivity yielding **424** and **425** in a 9/1 ratio.

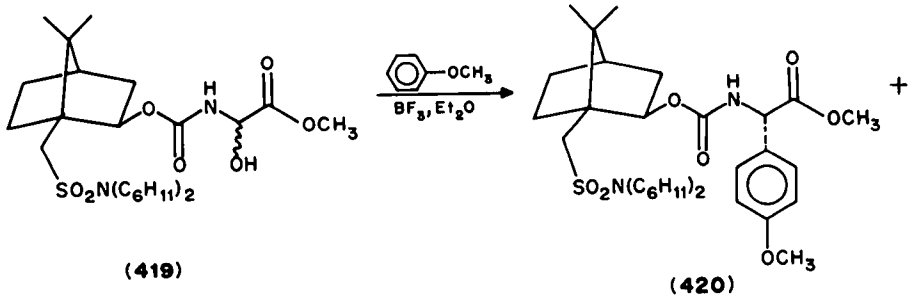
The reduction of ketoxime ethers[420] by BH_3 in the presence of (−)norephedrine yields (*S*)-amines from *anti* ketoximes and (*R*)-isomers from *syn* ketoximes, e.g. from phenyl-*p*-tolylmethylketoxime (equation 426).

The propensity of azetinone to undergo addition reactions was utilized to prepare an intermediate towards the synthesis of thienamycin[421]. Treatment of 4-phenylsulfonylazetidin-2-one **427** with thiophenol in benzene containing (−)-cinchonidine provided 4-phenylthioazetidin-2-one **428** (54% ee) that was converted in several steps into **429** from which thienamycin had already been prepared.

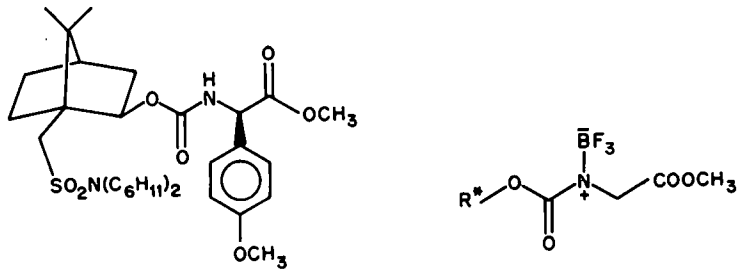
C. Addition of Enolates

The addition of enolates to imines, which is a variant of the aldol reaction, proceeds probably through similar pericyclic transition states[259]. These are represented in

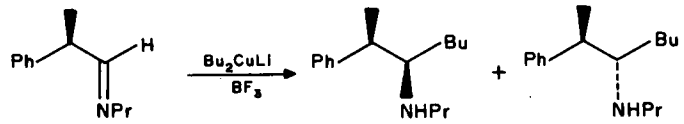
equation 430 for (*Z*)- and (*E*)-enolates and (*E*)-imines, where C stands for chair-like and B for boat-like transition states.



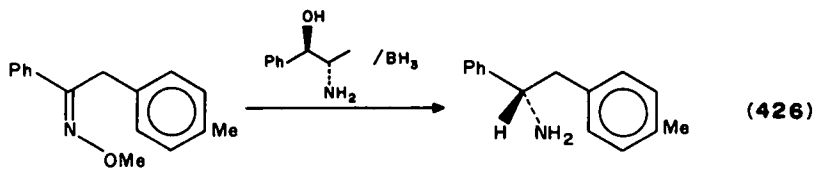
(419) (420)



(421) (422)



(423) (424) (425)



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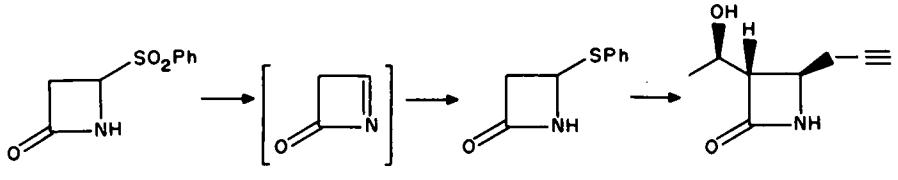
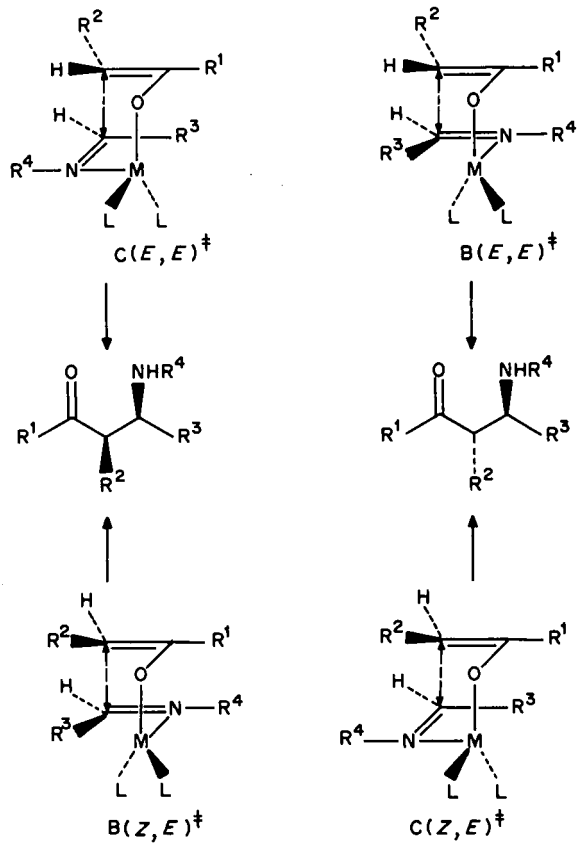


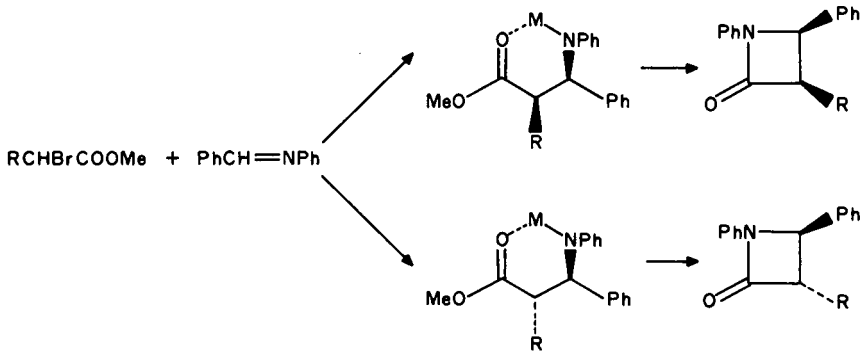
(427) (428) (429)



(430)

The imines generally have the (*E*)-geometry, but in most investigations stereochemically undefined enolates have been used. Solvent and temperature effects on the composition of the products of these reactions have been observed.

Gilman has found[422] that the Reformatsky reaction with imines (equation 431) yields lactams at the temperature of boiling toluene. Cyclization of the intermediate *syn*



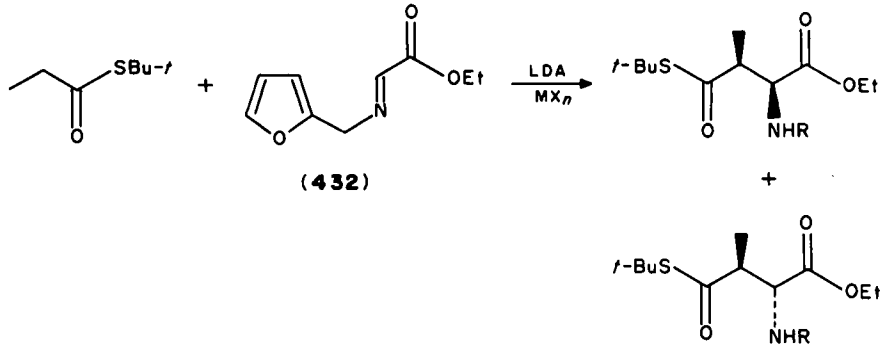
(431)

aminoester led to the *cis* lactam. A larger amount of *syn* than *anti* product was obtained in this reaction[423], but the aminoester formation was reversible[424] and warming the aldolate product led to more *anti* product and subsequently more *trans* lactam formation.

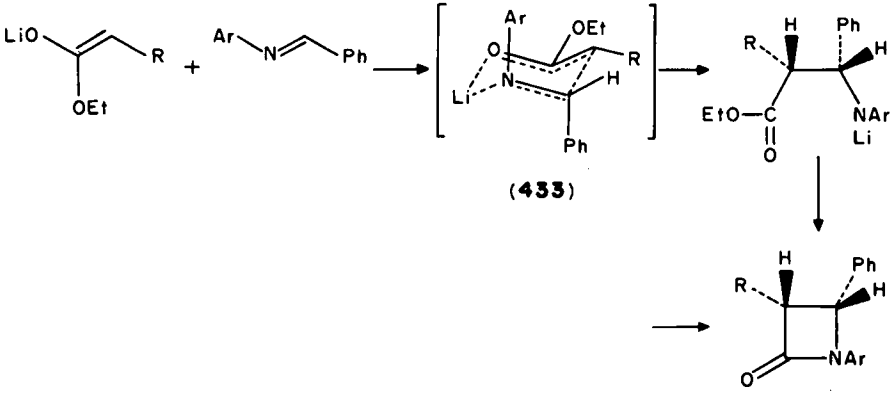
Condensation of amide enolates[425,426] with imines led to *anti* products. The *syn* products obtained from ester enolates and the *anti* products from amide enolates are in agreement with the chair-like transition state C(*E*,*E*) and C(*Z*,*E*) respectively in equation 430, since the propensity of *E*(O$^-$)-enolate formation from esters and *Z*(O)-enolates from amides was noted previously. The formation of *anti* lactams from *E*(O$^-$)-enolates of esters was confirmed for enolates prepared by proton abstraction from esters[427].

The formation of β-lactams in the reaction of enolates of esters with imines raised great interest in this reaction since β-lactams are components of many naturally occurring antibiotics, such as penicillins, cephalosporins, monobactons, thienamycin, etc.

Mukaiyama[428] has found that Li, Mg, Zn enolates of thioesters do not react with the iminoester **432** and that the best counterion is Sn(II). This enolate gives the *syn* and *anti* products in a 95/5 ratio.



Lithium *E*(O)-enolates of esters have been shown to yield *cis* lactams[429] probably via a pericyclic transition state **433** and subsequent cyclization. However, (*Z*)-enolates gave mixtures of *cis* and *trans* lactams.

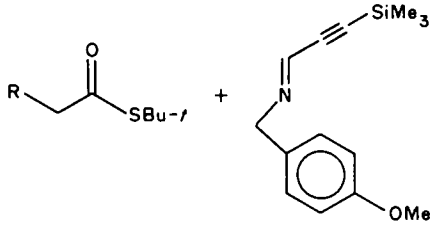


Boron[430] and aluminum[431] enolates from *S*-phenyl alkanethioates **435** condense with imine **434** in an *anti* selective manner[430], but with zirconium enolates preferentially in a *cis*

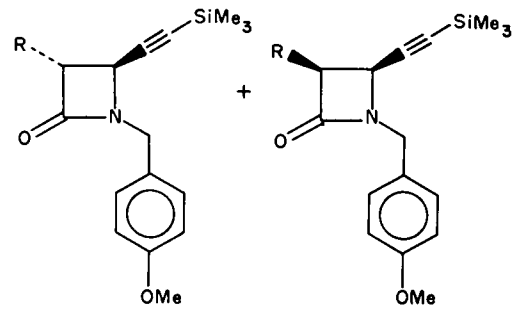
TABLE 16. Steric course of the condensation of Zr and Al enolates of alkanethioates with imine **434**

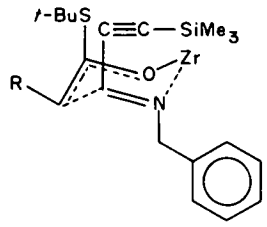
Metal in enolate of **435**	R	% Yield	*syn/anti*
Zr	Me	58	4/1
	Et	57	5/1
	i-Pr	43	21/1
Al	Me	78	4/1
	Et	80	3/1
	i-Pr	73	1/7

manner[431] (Table 16). The zirconium (*E*)-enolate reacts through a chair-like transition state **436** at − 78 °C, but the aluminum aldolate cyclizes at 250 °C, when retroaldolization can take place. It is of interest that in **436** and **433** the two substituents on the imine group assume axial conformations, and this determines the steric course of the reaction.



(435) **(434)**

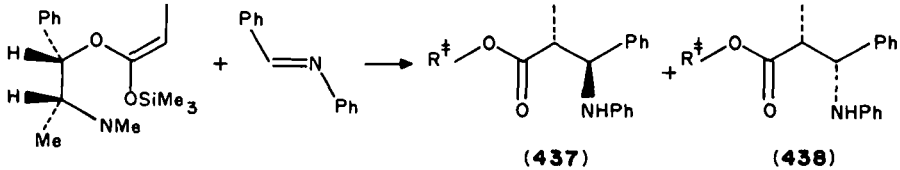




(436)

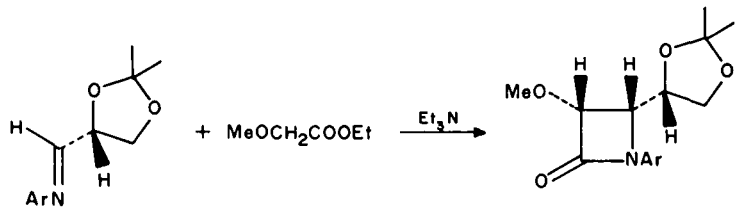
The silyl ketene acetals reaction with imines catalyzed by $TiCl_4$[432], trimethylsilyl trifluoromethanesulfonate[433] and ZnI_2[434] yields β-aminoesters with prevalent *anti* selection.

Asymmetric induction of the reaction[435] can be achieved by using a ketene silyl ester of (1*S*,2*R*)-*N*-methylephedrine. Catalysis by $TiCl_4$ of the reaction with benzaldehyde anil gives the *anti* and *syn* products **437** and **438** in a 10/1 ratio.

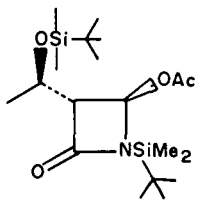


(437) **(438)**

The auxiliary chiral group can also be in the imine group[435]. The imine **439** formed from (*R*)-glyceraldehyde acetonide reacts with the enolate of ethyl methoxyacetate to yield the *cis* lactam **440**.

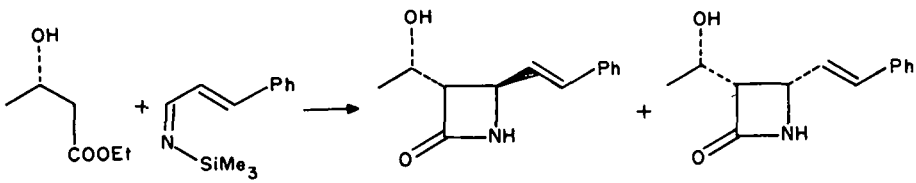


(439) **(440)**



(441)

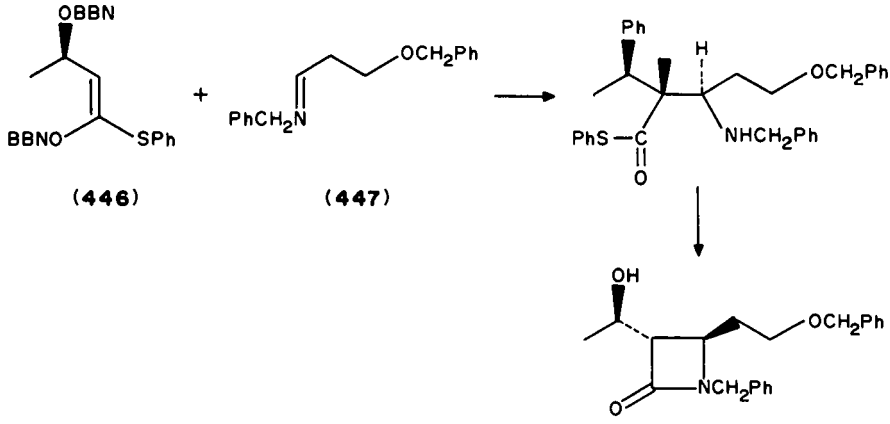
In many penem and carbapenem antibiotics an α-hydroxyethyl group is located at the 3 position of a β-lactam and **441**, which contains all the chiral centers in the correct configuration, constitutes one of the best synthos for the preparation of these antibiotics. This and similar other intermediates have been prepared by the reaction of imines with enolates[429–433,435–442]. The trianions of (*S*)- or (*R*)-3-hydroxybutyric acid or the dianion



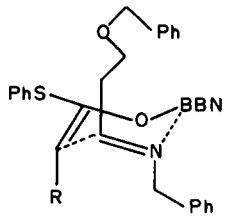
(442) **(443)** **(444)** **(445)**

enolate of the optically active ester were used as a reagent with a number of imines. Ethyl (*S*)-(−)-3-hydroxybutyrate **442** reacted[439] with *N*-trimethylsilylcinnamylidene imine **443** to give a mixture of 70/30 of (3*S*, 4*S*)- and (3*S*, 4*R*)-3-[(S)-1-hydroxyethyl]-4-styrylazetidin-2-one **444** and **445**. Both products could be transformed into **441**.

The desired *trans*-substituted β-lactam formation was achieved[430] by the use of *Z*(O)-vinyloxyborane **446** formed from 3(*R*)-hydroxybutyric acid in the reaction with the imine **447**. The steric course of the reaction of the vinyloxyborane with imines is opposite to that with aldehydes, and this may be attributed to (*E*)-geometry of the imines and the axial disposition of its substituents in the transition state **448**.



(446) (447)



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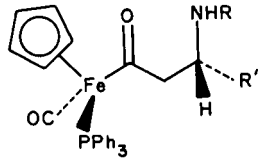

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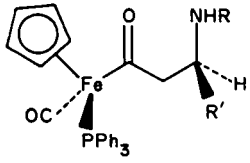
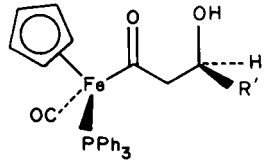


(450)



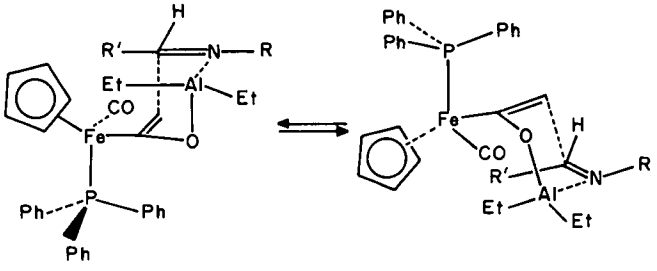
(451)

Asymmetric induction by a chiral metal center was also observed[442,443] in the reaction of enolates with imines. Aluminum enolates **309** (R = H, M = $AlEt_2$) having an iron chiral center react with imines to give **449** and **450** in a 20/1 ratio. This face selection was opposite to that found by the authors in the aldol condensation of **309** (R = H; M = $AlEt_2$), where

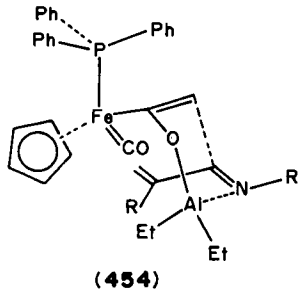
TABLE 17. Face selectivity in the reaction of chiral metal enolates (**309**) with imines

Imine	% Yield	**449/450**
(*E*)-PhCH=NPr	80	20/1
(*E*)-*i*-PrCH=NPr	68	20/1
(*E*)-PhCH=NC_6H_{13}	54	20/1
(*E*, *E*)-PhCH=CHCH=NPr	44	2.5/1
(*E*, *E*)-PhCH=CMeCH=NPr	53	11.5/1

also a lower degree of selectivity was found (1.7/1–8.2/1 for various aldehydes). The major product in the aldol condensation was **451**. The reaction of **309** with nitrones PhCH=N(O)Ph takes a steric course similar to that of the reaction with aldehydes. The condensation of a number of various imines and conjugated imines has been studied[443] (Table 17). The change in the ratio of **449** and **450** by changing the imine substituent in these reactions was rationalized as a competition between two chair-like transition states **452** and **453**. A boat-like transition state was dicounted. All the reactions of the enolates are assumed to take place away from the bulky phosphine group. The critical interactions take place between the imine R′ group linked to carbon and the cyclopentadienyl ligand. Transition state **452** is favored relative to **453**, since this interaction is less in **452**. However, an unsaturated group on the carbon makes this interaction in **452** and **453** closer in energy, since the =CH group is smaller than an alkyl group. This explains the lower selectivity in the reaction of **309** with unsaturated imines. Introduction of a branching in the unsaturated group makes it bulkier, as in **454** (corresponding to **453**), and the ratio of **449/450** increases.



(**452**) (**453**)



(**454**)

D. Reaction with Allylmetals

Yamamoto[444-447] has drawn attention to the different interactions in the reaction of allylmetal compounds with aldehydes and imines, due to the substituent on the nitrogen and the prevalent (*E*)-geometry in the imines. The Cram/anti-Cram selectivity in the reaction of allylmetal compounds with aldehydes is around 2/1, but with imines it is 3/1 and with allylboron compounds this ratio is close to 100/0 (Table 18). The reason for this selectivity[445,446] is the pseudoaxial disposition of the imine PhCHMe group in the transition states **462** and **463** leading to the products **455** and **456** respectively. In the corresponding reactions with aldehydes [464] the chiral group is in a pseudoequatorial location and its interaction with the ligands on the metal, even on boron, is minimal. Transition state **462** is much more favorable than **463**, since the ligands on the metal interact only with the hydrogen of the chiral group.

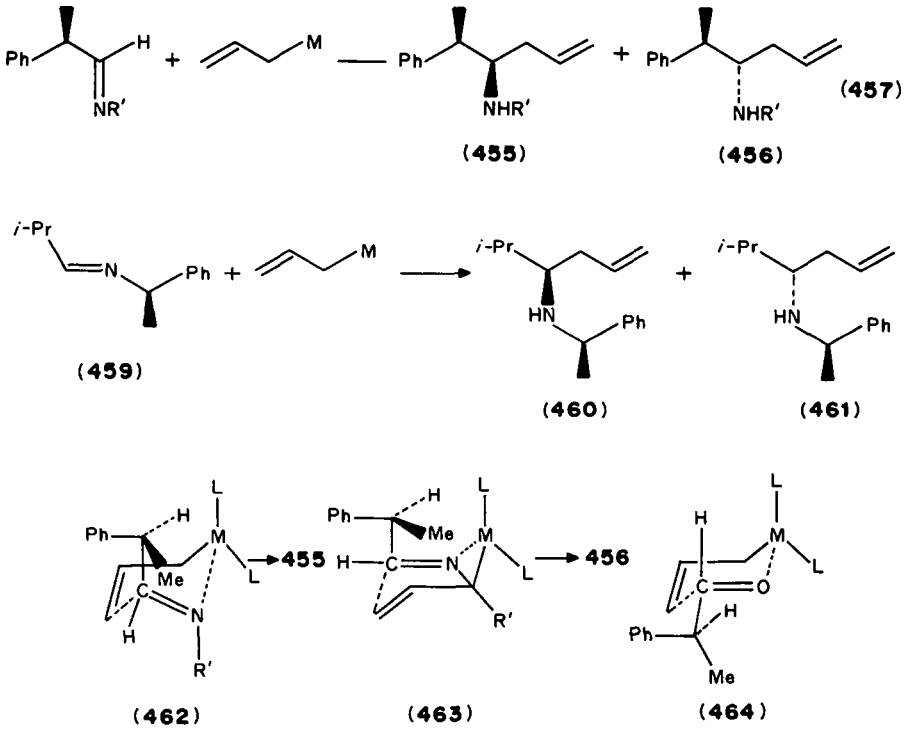
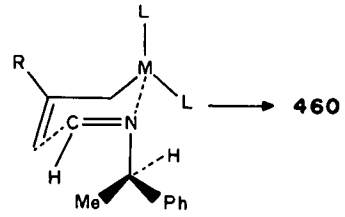


TABLE 18. Product dependence on the metal in the reaction of imines with allyl metals

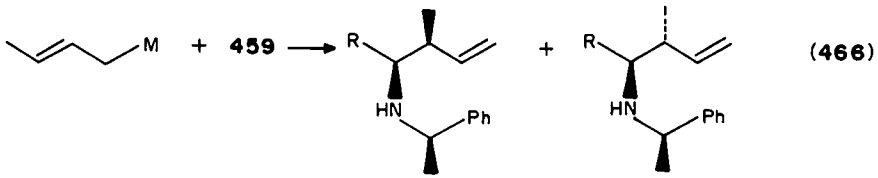
Reaction	M	RCH=NR'	Ratio of products	
457	M = MgCl	R' = *i*-Pr	**455/456**	70/30
457	M = 9-BBN	R' = *i*-Pr	**455/456**	100/0
457	M = $SnBu_3$	R' = *i*-Pr	**455/456**	92/8
458	M = 9-BBN	**459**	**460/461**	92/8
458	M = MgBr	**459**	**460/461**	80/20
466	M = 9-BBN	**459**	**467/468**	75/25

When the stereogenic center is linked to the nitrogen of the imine (reaction 458) a 1,2 axial–equatorial interaction of this center with the ligand on the metal develops (Table 18) and relatively high face selectivity is observed. The more favorable transition state is then **465**.



(465)

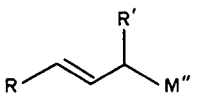
Crotyl organometallic compounds[446,447], even crotylboranes, exhibit selectivity in their reactions with 2-methylphenylacetaldehyde, but with **45a** a Cram selectivity of 100% is shown (Table 18). An α-alkoxy group in the imine **469** exerts a high 1,2-asymmetric induction (Table 19). Zn, Mg and Al allyl compounds give predominantly the chelation-determined product **470**, whereas Ti and B compounds afforded the nonchelation product



(466)

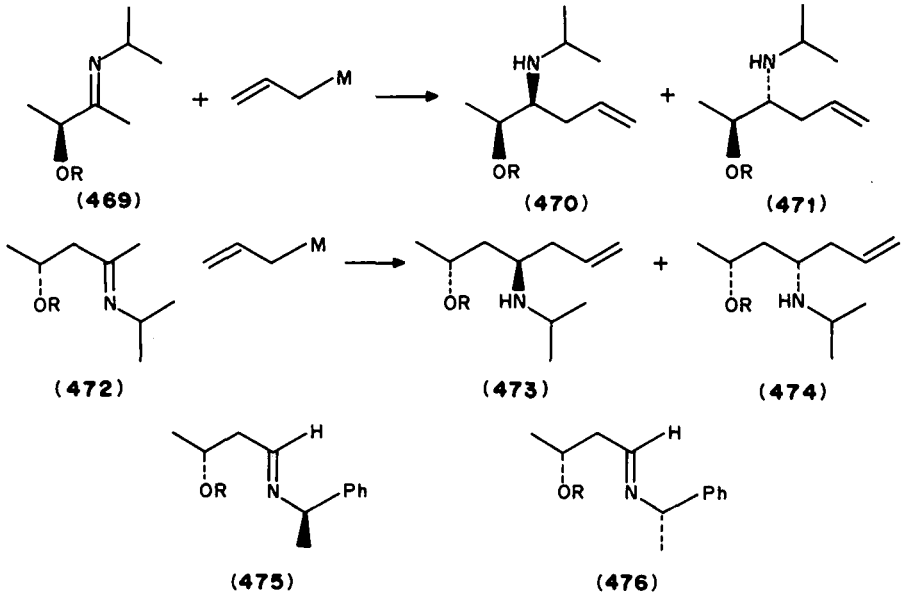
(467) **(468)**

TABLE 19. Product dependence of the reaction of imines with allylmetals on the α-substituent in the imine



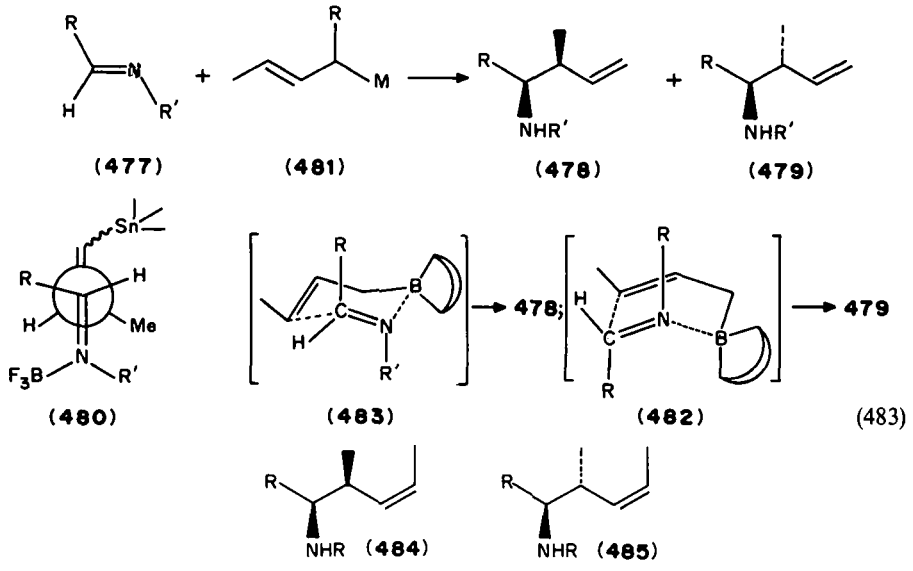
	Imine	Ratio of products	
MgBr, R = R′ = H	**469**	**470/471**	79/21
Ti(OPr-*i*)$_3$; R = R′ = H	**469**	**470/471**	23/77
9-BBN; R = R = H	**469**	**470/471**	> 99
MgCl; R = R = H	**472**	**473/474**	85/15
9-BBN; R = R′ = H	**472**	**473/474**	46/54
MgCl; R = Me; R′ = H	**477**, R = R′ = Ph	**478/479**	74/26
$SnBu_3/BF_3$; R = Me, R′ = H	**477**, R = R′ = Ph	**478/479**	75/25
9-BBN; R = Me, R′ = H	**477**, R = R′ = Ph	**478/479**	0/100
9-BBN; R = Me, R′ = H	**477**, R = R′ = Pr	**478/479**	75/25
9-BBN; R = Me, R′ = H	**477**, R = *i*-Pr, R′ = Pr	**478/479**	34/66
9-BBN; R = Me, R′ = H	**477**, R = R′ = *i*-Pr	**478/479**	30/70
9-BBN; R = R′ = Me	**477**, R = R′ = Ph	**484/485**	8/92
9-BBN; R = R′ = Me	**477**, R = Pr; R′ = *i*-Pr	**484/485**	100/0
9-BBN; R = R′ = Me	**477**, R = *i*-Pr; R′ = Pr	**484/485**	85/15

471. A less powerful effect was exerted by a β-alkoxy group in **472**. Introduction of an additional stereogenic center as in **475** and **476** modified appreciably the asymmetric induction.



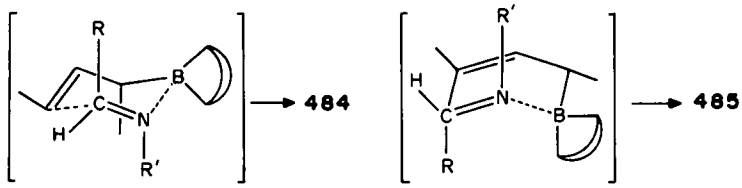
Imines without a stereogenic center **477** react with crotylmetal compounds[446] with good simple diastereoselection (Table 19).

The BF_3-catalyzed reaction of crotyltributyltin proceeds apparently as usual through the acyclic antiperiplanar transition state **480** for the formation of the predominant *syn*



(483)

product **478**. The crotylBBN reagent reacts preferentially through the pericyclic chair-like transition state **483**, but when R is large the boat-like transition state **482** predominates. These assumptions are considered to be supported by the composition of the products of the reaction of pent-3-en-3-ylBBN **481** (R = Me); (*Z*)-double bonds are formed in the products. The transition state **486** leading to **484** is considered to be more stabilized relative to **487** than **483** relative to **482**, although additional diaxial interactions with the methyl of **481** in **486** are presents.



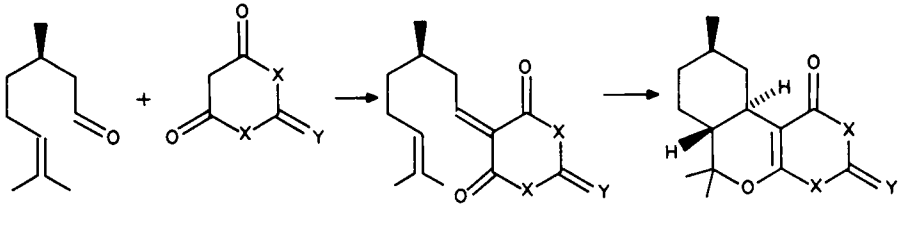
(**486**) (**487**)

IV. CYCLOADDITIONS OF COMPOUNDS CONTAINING A DOUBLE BOND TO A HETEROATOM

Diels–Alder reactions of compounds containing heteroatoms in the diene[448–450] or the dienophile have been known for some time. Only recently has attention been paid to the steric course of the reaction. These reactions can be subdivided into two groups: one, where the diene component contains the heteroatom, and the other, where the heteroatom is located in the dienophile. There is of course the possibility, observed long ago, where both the diene and dienophile contain heteroatoms as in the self-condensation of acrolein[451]. However, the last reactions take part more reluctantly owing to the different electronic requirements of the diene and dienophile.

A. Cycloadditions using Heterodienes[450]

The heterodienes are electron-poor compounds at the terminal carbons and have an inverse electron-demand to the usual Diels–Alder reactions, α,β-unsaturated ketones activated by electron-withdrawing groups[452] react rapidly at room temperature with simple olefins and show a remarkable selectivity in intramolecular cycloadditions. These activated unsaturated ketones containing an additional double bond are prepared easily from barbituric acids **488a** or Meldrum's acid **488b** by condensation with an aldehyde, such as (*R*)-citronellal **489**. The intermediate α, β-unsaturated ketone cycloadds readily to

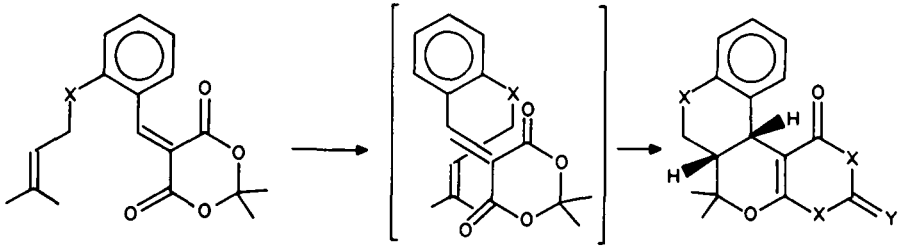


(**489**) (**488**) (**490**)

(**a**) X = NR; Y = O

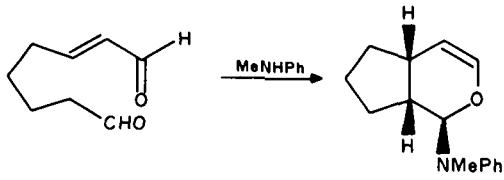
(**b**) X = O; Y = Me, Me

the intramolecular double bond[453] to give **490** with a *trans* junction between the rings and (*S*)-citronellal yields its enantiomer. The product is formed[454] with more than 98% de and 92% ee. The (*Z*)-heterodienes do not react well and isomerize to their (*E*)-isomers before undergoing cycloaddition[454–456]. Compounds containing aryls as a part of the chain between the two unsaturated groups give products containing a *cis* junction of the rings[457] (equation 491). This cycloaddition has been shown to be a concerted reaction by ^{13}C labelling, but it was also argued that it is not synchronous[454]. The transition state for the *trans*-product formation was assumed[454] to be *exo-E-anti* **492** and for the *cis* product *endo-E-syn* **493**. A pressure-induced diastereoselectivity in the intermolecular reaction of enamino ketones with enol ethers was observed recently[488].



(492) (493)

α,β-Unsaturated ketones and aldehydes cycloadd readily with electron-rich olefins such as enamines[458] and the intramolecular reaction is highly stereoselective (equation 494). The enamine is formed *in situ* and after several minutes the *cis* product is obtained. An alkyl group in an allylic position to an α,β-unsaturated aldehyde (equation 495) or to the enamine intermediate (equation 496) induces kinetically the formation of the shown



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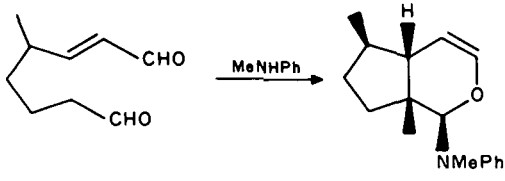
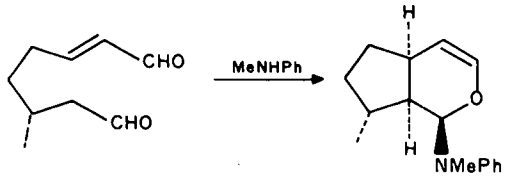


(495)

product (ratios of 4/1 and 14/1 to other isomers in equations 495 and 496, respectively) and this asymmetric induction is increased on equilibration to 25/1 for both reactions. The larger product selectivity in equation 496 relative to equation 495 was related to the difference in the energies of **498** and **497** (0.64 kcal mol^{-1}) relative to the difference in the energies of **500** and **499** (1.29 kcal mol^{-1}). The eclipsed rotamers **497′** and **499′** are conformations from which the major product was supposed to be formed, whereas **498′** and **500′** were considered as starting points for the minor products.



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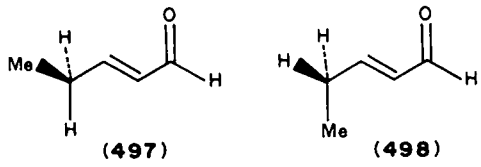
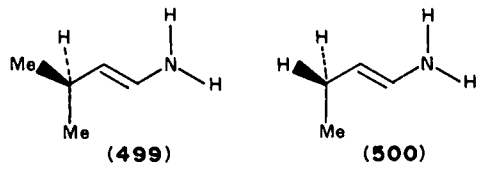
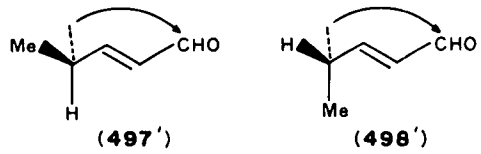
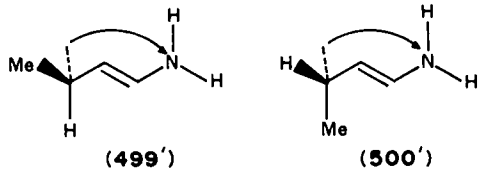


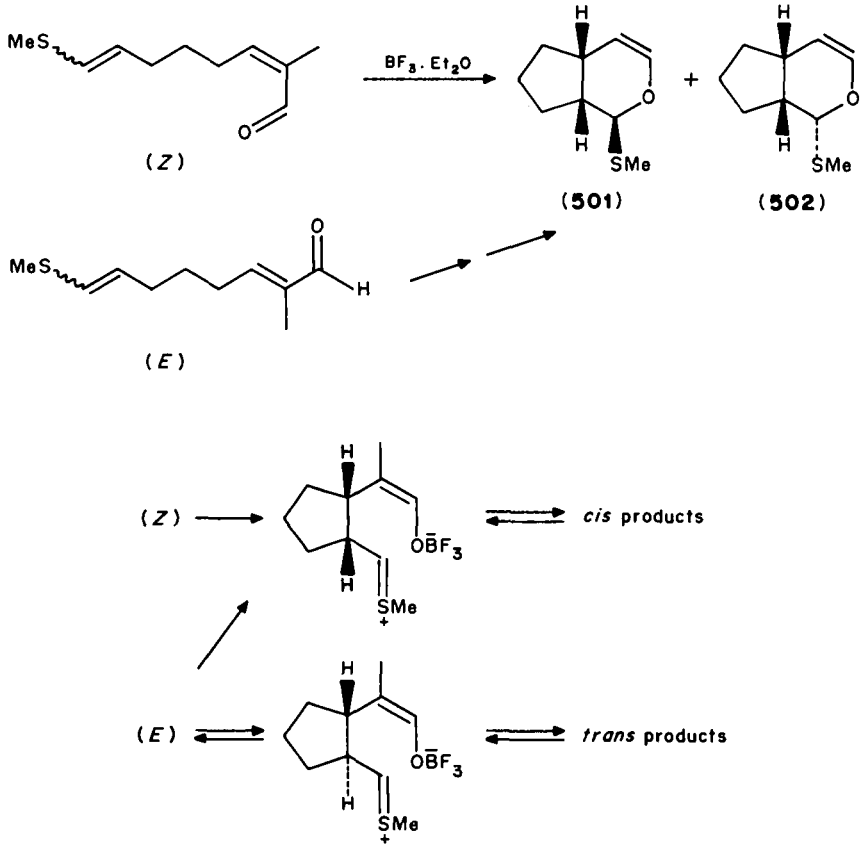






(*Z*)-α,β-unsaturated ketones also undergo intramolecular cycloadditions with vinyl sulfides with good stereoselectivity[459,460]. Here again, an increase in the ratio of the preferentially formed products **501** and **502** with reaction length was observed from 75/25 to 96/4. The (*E*)-isomers reacted less selectively, giving after short reaction periods much of the *trans* linked rings, but after longer reaction times the two *cis* products **501** and **502** were

formed in a 87/13 ratio. The course of the reaction was interpreted as proceeding via a two-step mechanism (equation 503).



α,β-Unsaturated nitroso compounds also undergo selective intramolecular cycloadditions[460]. Asymmetric induction was also formed in dipolar cycloadditions[502,503].

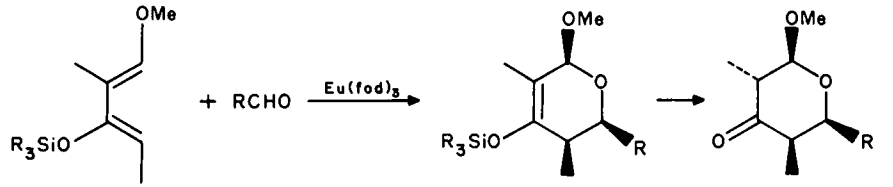
B. Cycloadditions using Hetero-dienophiles

Reviews of some of these reactions have been published[461–463]. The carbonyl group has to be activated by electron-withdrawing groups as in glyoxalates to be able to cycloadd to electron-rich dienes[464]. Simple aldehydes are activated by Lewis acids to undergo this reaction[465]. Heterocyclization was used for the synthesis of hexoses[466] and di- and trisaccharides[467].

Danishefsky[468–471] has carried out extensive investigations on the mechanism and stereochemistry of the Lewis acid catalyzed cycloaddition of aldehydes to electron-rich dienes.

The oxygenophilicity of the rare earth cations such as Eu(fod)$_3$ [= tris(6, 6, 7, 7, 8, 8, 8-heptafluoro-2, 2-dimethyl-3, 5-octadionato)europium] and their coordination to the oxygen of the aldehyde induce a hetero Diels–Alder reaction with dienes[468]. Carbon-branched pyranose rings can thus be prepared stereoselectively (equation 504).

1-Menthyloxydienes reacted with benzaldehyde[469] to give a slight excess of a 'D-pyranose' product, and a d-menthyloxydiene, a slight excess of a 'L-pyranose' product (equation 505). However, the use of the chiral catalyst Eu(hfc)$_3$ { = tris[3-(heptafluoropropyl)hydroxymethylene-d-camphoroto]europium} instead of Eu(fod)$_3$ as a catalyst brought about a reversal of the product obtained from 1-menthyloxydienes to 90% of the 'L-pyranose' type, whereas the d-menthyloxydiene with this catalyst did not change appreciably the composition of the product of the reaction despite the fact that the substrate and catalyst both directed the reaction towards L-pyranose.



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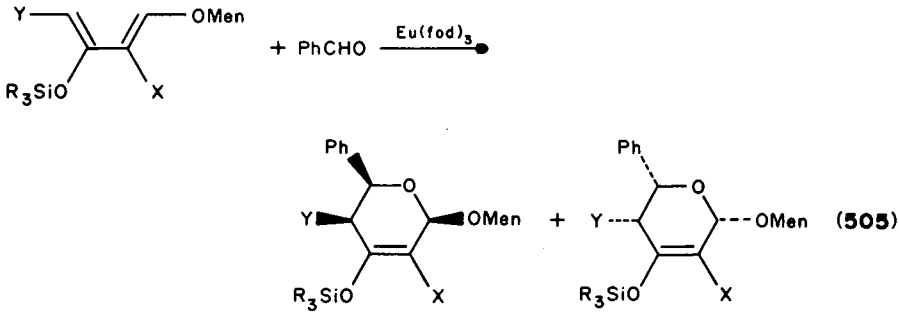
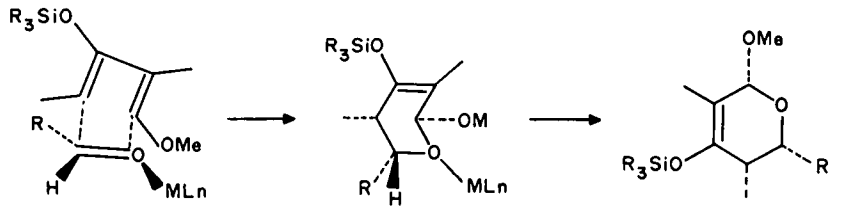
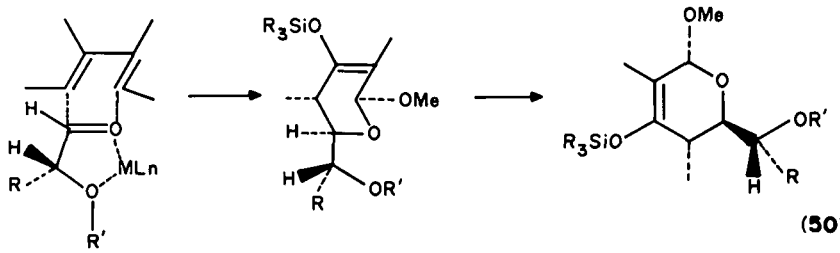


Subsequent research[470] has shown that the formations of the cyclic products did not proceed via the Mukayama variant of the aldol condensation, but are a result of a cycloaddition. The *cis* disposition of R and Me in equations 504 and 505 was caused by an *endo* addition (equation 506), due to the complex formation with the catalyst, where the metal with its ligands and solvation envelope is much bulkier than the R of the aldehyde and prefers to be *exo*, thus directing the R group to the *endo* position. The best Lewis catalyst for this purpose was zinc chloride in THF; $BF_3 \cdot Et_2O$ was apparently not a good cycloaddition catalyst or perhaps not bulky enough, since the *trans* product was obtained in its presence.



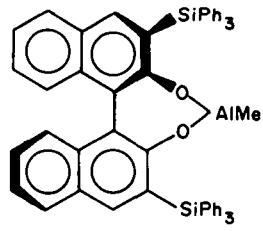
(506)

The *exo* coordination of the catalyst was supported by the results[471] of the reaction of α- and β-alkoxyaldehydes with the dienes. If the catalyst coordinates with the carbonyl *and* the alkoxy group, the R of the aldehyde will find itself in an *exo* position together with the catalyst (equation 507). The hydrogen will then be *endo*. Indeed, the α-alkoxyaldehyde gave with the diene a *trans* (Me, R) product exclusively in the presence of $MgBr_2$. This catalyst afforded with benzaldehyde and the same diene, in a reaction analogous to 506, the *cis/trans* ratio of 38/1.



(507)

It has been reported recently[504] that high asymmetric induction can be obtained in a hetero Diels–Alder reaction **507b** in the presence of trifluoroacetic acid (TFA), using a BINAL derivative **507a** as a catalyst.



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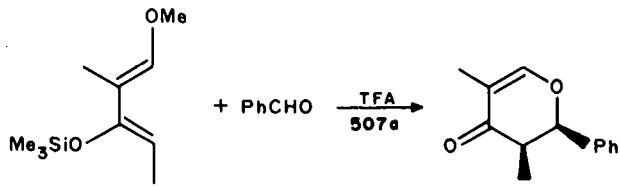
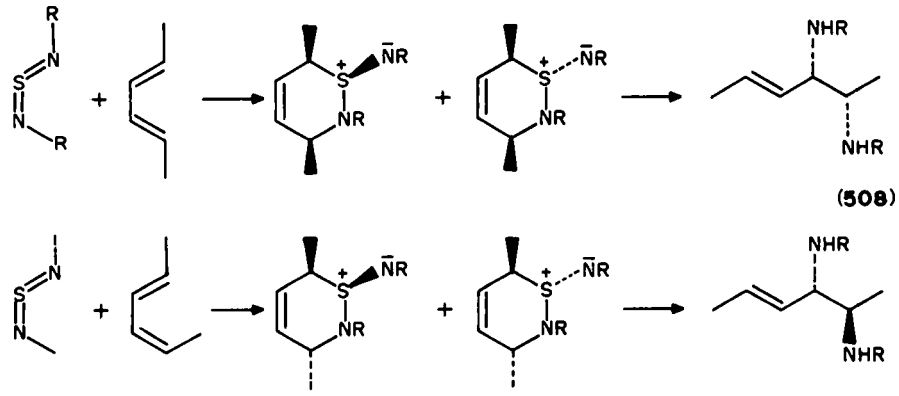


(507b)

Thioaldehydes with electron-acceptor substituents[472] cycloadd in the usual manner, i.e. *endo* and with the electron acceptor in the thioaldehyde *para* or *ortho* to the electron donor in the diene.

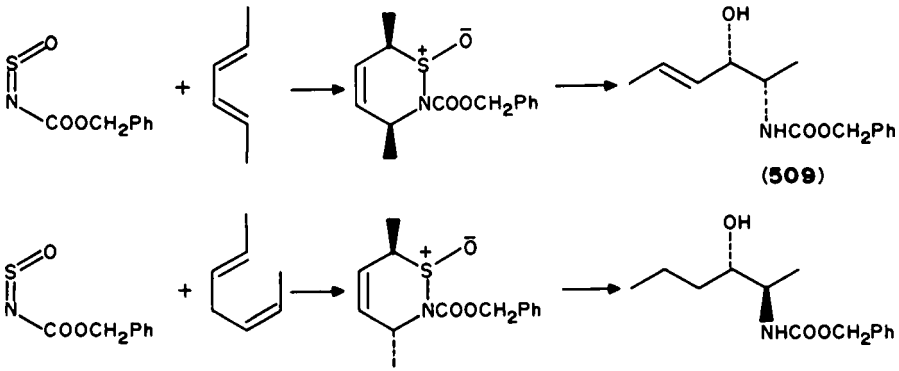
Bis(imides) of sulfur dioxide react with dienes[461] in Diels–Alder fashion. The stereochemistry of reaction 508 was studied[473].

E, *E*-2, 4-hexadiene gave two 3, 6-dihydrothiazin-1-imines with different configurations at sulfur but with the two methyls in a *cis* relationship. The two compounds could be transformed into *syn*-vicinal diamines. A similar reaction with *E*, *Z*-2, 4-hexadiene yielded two products with the methyls *trans* to each other that have been converted into *anti* diamines.



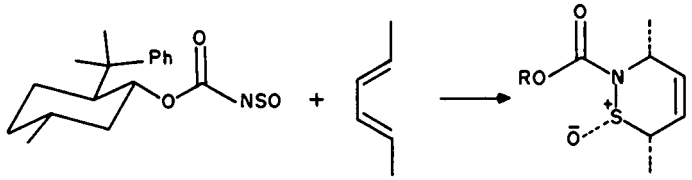
(508)

The reaction of benzyl *N*-sulfonylcarbamate[474,475] with the *E,E*- and *E,Z*-hexadienes gave products that were transformed into *syn* and *anti* aminoalcohols (equation 509).

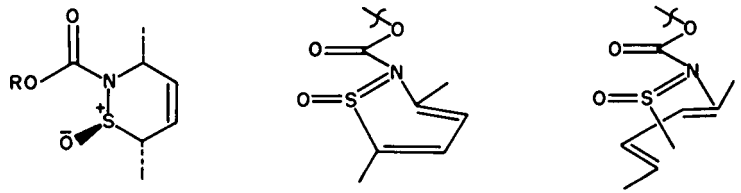


(509)

An asymmetric induction in the cycloaddition reaction with *N*-sulfonyl carbamate was observed[476] when the 8-phenylmenthol derivative **510** was used. A single isomer **511** was



(510) (511)



(512) (513) (514)

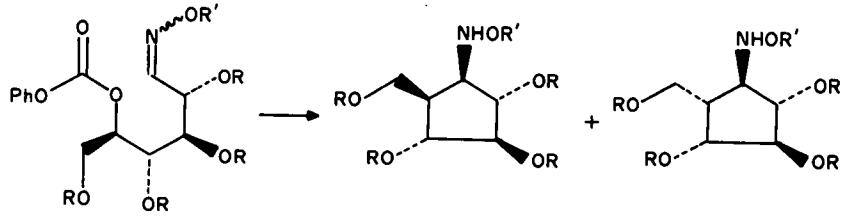
obtained in the reaction of **510** with the *E,E*-diene at room temperature using $SnCl_4$ as a catalyst. The thermal reaction without a catalyst afforded a mixture of isomers with **512** as the dominant product. The transition state for the formation of **511** was assumed to be *endo, syn* **513** and for the formation of **512** the *endo, anti* arrangement **514** was proposed.

V. RADICAL ADDITIONS TO THE C=O AND C=N GROUPS

Radical cyclizations are very important in synthesis in view of their tolerance of functionalty in the substrates[477-481].

Carbonyls had the reputation of being ineffective as radical acceptors. Recent investigations have shown by intramolecular competition that radical cyclizations of a 5-formyl-n-pentyl radical to give a cyclohexanol is preferred to cyclization of a 5-hexenyl radical[482,483]. The stereochemistry of this reaction was not studied.

The facile addition of free radicals to oxime ethers[484,485] led to the investigation of the intramolecular radical cyclization[486]. A low degree of asymmetric induction was found in this cyclization[486] and this was determined by conformational effects similar to those found for other radical cyclization[487]. The phenyl thionocarbamate **515** obtained from O-protected glucose hemiacetal undergoes a tributyltin hydride induced cyclization to give **516** and **517** in a 62/38 ratio.



(515) (516) (517)

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The Chemistry of Double-bonded Functional Groups
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CHAPTER **11**

Electrophilic additions to carbon–carbon double bonds

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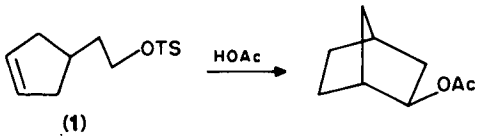
I. INTRODUCTION

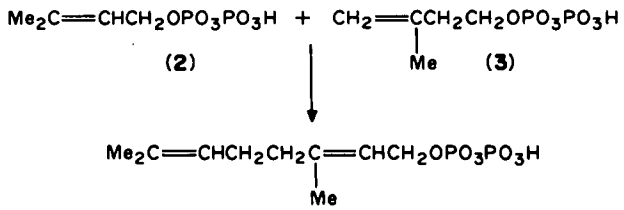
This chapter is concerned primarily with reviewing important developments since the previous edition of this review[1] on the reactions of alkenes with mineral and organic acids, halogens, peroxy acids, arene- and alkanesulfenyl halides, and arene- and alkaneselenenyl halides. Another purpose of this chapter is to examine these reactions in a slightly different way. Traditionally, these reactions are regarded as example of a large mechanistic class of organic reactions known as electrophilic additions. The definition of this type of reaction has been given numerous times[2–4]. The essential feature of this classification is that the alkene reacts with a reagent in such a way that the intermediate or transition state has carbocationic character. This definition of an electrophilic addition reaction focuses attention on the alkene; the carbon containing reactant. A different classification of this reaction can be obtained by focusing on the other reactant. In this way the reaction becomes a nucleophilic displacement reaction in which the alkene acts as the nucleophile.

This latter definition is rarely employed because an alkene is usually regarded as a poor nucleophile, particularly at a saturated carbon atom. Yet alkenes do act as nucleophiles towards carbon. For example, the acetolysis of 3-cyclopentenylethyl tosylate (1) to form norbornyl acetate[5] and the enzyme catalyzed reaction of 3,3-dimethylallyl

pyrophosphate (**2**) and 3-isopentenyl pyrophosphate (**3**) to form geranyl pyrophosphate[6] (equation 1) are examples of a double bond reacting as a nucleophile at a saturated carbon atom. In **1**, the double bond is close to the saturated carbon atom containing the leaving group while the enzyme places the double bond of **3** and the saturated carbon of **2** in close proximity. This enhances the nucleophilicity of the double bond.

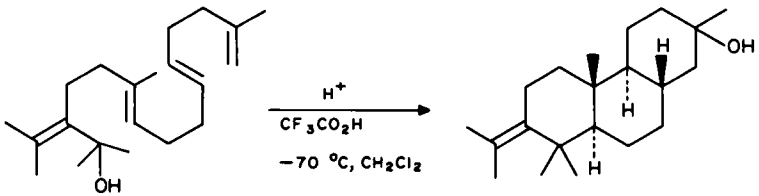


(1)



(1)

Further enhancement of the nucleophilicity of the double bond can be achieved when the reaction center is a carbocation. The cyclization reaction shown in equation **2**, one of many developed by W. S. Johnson[7], is another example of a double bond acting as a nucleophile.



(2)

It may appear to be a trivial matter to classify the reactions of alkenes with electrophiles as both an addition reaction to the alkene and as a nucleophilic displacement at the electrophile by the alkene. The advantage of recognizing this fact is that previous work and mechanistic conclusions reached in both classes can be applied to the problems of elucidating the mechanism of the reactions of alkenes. For example, the three limiting-case mechanisms shown in Figure 1 have been proposed for nucleophilic displacement

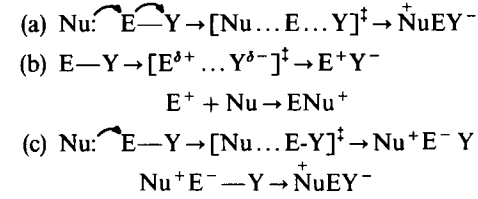


FIGURE 1. Three limiting-case mechanisms for nucleophilic displacement reactions. Nu = nucleophile, Y = leaving group, E = atom at which displacement occurs

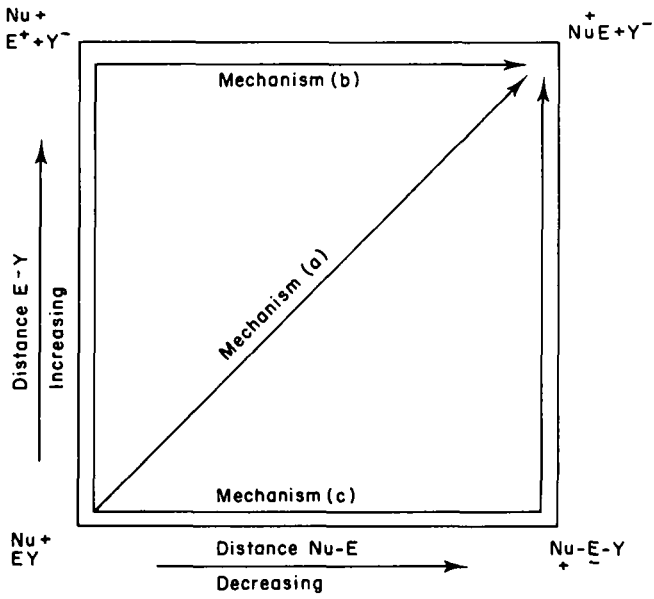


FIGURE 2. Jencks–More O'Farrell diagram for displacement reaction. Nu = nucleophile, Y = leaving group, E = atom where displacement occurs

reactions. Mechanism (a) is concerted, mechanism (b) involves an ionization of EY followed by reaction with the nucleophile and mechanism (c) involves addition followed by elimination. The rate-determining transition states of these three mechanisms differ only in the amount of bond making and breaking to the atom at which displacement occurs. Consequently all three can be placed on the same Jencks–More O'Farrell diagram as shown in Figure 2.

A great deal is known about the factors (types of groups bonded to E, type of leaving group, type of nucleophile, solvent and temperature) that affect the path of nucleophilic displacement, when E is a saturated carbon and Nu represents the usual carbon nucleophiles. In contrast, much less is known about the factors that affect the mechanism of the reaction when E is a halogen or sulfur and Nu is an alkene. The purpose of this chapter is to present the available data on electrophilic addition reactions in this format in an attempt to not only correlate various aspects of this mechanism in a different way but also to show where gaps exist in our knowledge of the mechanism of electrophilic addition reactions.

Let us start by examining displacement reactions at the simplest nucleus—the proton.

II. PROTON TRANSFER

Nucleophile displacement reactions at a proton are called proton transfer reactions. The general equation for such reactions is given in equation 3, where Nu represents a base (or nucleophile) and Y represents a leaving group.

$$\text{Nu:} \overset{\frown}{\text{H}}\text{—}\overset{\frown}{\text{Y}} \rightarrow \text{NuH}^+ + \text{Y}^- \qquad (3)$$

(a) $H_2O + CH_3CO_2H \rightarrow H_3O^+ + CH_3CO_2^-$

(b) $HO^- + CH_3NO_2 \rightarrow \bar{C}H_2NO_2 + H_2O$

(c) $BH^+ + Ph_2C{=}CH_2 \rightarrow Ph_2\overset{+}{C}CH_3 + B$

(4)

FIGURE 3. Three examples of proton transfer reactions

Specific examples, shown in Figure 3, represent the following types of reactions: (a) proton transfer from one electronegative atom such as oxygen to another electronegative atom such as nitrogen or oxygen, (b) proton transfer from a saturated carbon atom to an electronegative atom such as oxygen or nitrogen (sometimes the first step in an elimination reaction) to form a carbanion and (c) proton transfer from an electronegative atom such as oxygen, or a halogen, to an sp^2 carbon atom (usually called an electrophilic addition reaction) to form a carbocation intermediate (**4**). Notice that in reaction (b) in Figure 3 carbon acts as an acid while in reaction (c) carbon acts as a base.

Proton transfer between electronegative atoms is an important example of acid – base catalysis. This subject has been extensively studied. These studies will not be covered in detail here because of the many excellent books and reviews available on the subject[8–12]. However, it is instructive to recall the major details for comparison with the reactions of acids and alkenes. For additional details the reader is referred to References 8–12.

Eigen[8] defined a normal proton transfer as one whose rate in the thermodynamically favored direction in diffusion controlled. Consequently, normal proton transfer is very rapid as illustrated by entries 1–3 in Table 1. Such rapid proton transfer usually occurs between electronegative elements. Proton transfers involving carbon atoms are relatively slow, as illustrated by entries 4 and 5 in Table 1. Carbon acids and bases are sometimes called pseudoacids and pseudobases, because they lose and gain protons slowly in contrast to the more normal behavior of the rapidly reacting oxygen and nitrogen acids and bases[8].

The accepted mechanism of proton transfer is illustrated in equation 4.

$$AH + B^- \rightleftarrows \underset{I_1}{AH\cdots B^-} \rightleftarrows \underset{I_2}{A^-\cdots HB} \rightleftarrows A^- + HB \qquad (4)$$

The first step is diffusion-controlled encounter of the acid AH and base B^- to form the hydrogen-bonded complex I_1. The second step is the actual proton transfer to form another hydrogen-bonded complex I_2 followed by diffusion apart of A^- and BH. This mechanism has been successfully applied to proton transfer to and from carbon[15,16] as well as electronegative atoms.

TABLE 1. Rates of proton transfer

Reaction	k_2 ($M^{-1}s^{-1}$)	Ref.
$CH_3CO_2^- + H_3O^+ \rightleftarrows H_2O + CH_3CO_2H$	4.5×10^{10}	8
$NH_3 + H_3O^+ \rightleftarrows H_2O + NH_4^+$	4.3×10^{10}	8
$HO^- + NH_4^+ \rightleftarrows H_2O + NH_3$	3.4×10^{10}	8
$C_2H_5OCH{=}CH_2 + H_3O^+ \rightleftarrows H_2O + C_2H_5O\overset{+}{C}HCH_3$	1.8	13
$(CH_3)_2C{=}CH_2 + H_3O^+ \rightleftarrows H_2O + (CH_3)_2\overset{+}{C}CH_3$	3.7×10^{-4}	14

What factors are important in controlling the rate of proton transfer? The hydrogen-bonding ability of the proton donor and the proton acceptor is one factor. The acid and base must diffuse together to form a complex (I_1, in equation 4) before proton transfer can occur. One of the forces that holds this complex together is hydrogen bonding, particularly between strongly electronegative atoms. The stronger the hydrogen bond, the shorter the distance between the acid and base and the lower will be the energy barrier to proton transfer. Hydrogen bonding is never a significant factor in proton transfer to and from carbon, since carbon acids and bases are poor hydrogen donors and acceptors. This inability to form hydrogen bonds may be one reason for the slowness of proton transfer to and from carbon.

The delocalization of the electron pair that will receive the proton in the molecule is a second factor that may affect the rate of proton transfer. Oxygen or nitrogen bases generally have an electron pair that is localized on a single atom. In contrast, the electron pair of most carbon bases is delocalized. Such delocalization is usually accompanied by changes in bond angles and distances as well as a decrease in the charge density at the protonation site. Both of these serve to increase the energy barrier to proton transfer[12]. Accordingly, if the charge on a carbon base is localized on carbon, it should reprotonate as fast as an oxygen or nitrogen base. This in fact is the case. The negative charge on the carbanions derived from chloroform and terminal acetylenes are both localized on carbon and reprotonation of these bases is encounter controlled[17–19].

There is a problem with an explanation for the slow rate of transfer to carbon based on delocalization of its charge. The protonation of localized carbon bases in contrast to oxygen and nitrogen bases is a highly exothermic reaction. Some of the rapidity of proton transfer to a localized carbon base may be due to the extra driving force that exothermicity can provide.

Recently, Marcus theory[20–22], from which the relationship given in equation 5 can be derived, has been used to investigate this question. This relationship expresses the Gibbs energy of activation $\Delta G^{\ddagger}$ for the proton transfer step in terms of the standard Gibbs energy ΔG° and just one other parameter $\Delta G^{\ddagger}_0$. This latter term, usually called the intrinsic barrier, is the Gibbs energy of activation when the standard Gibbs energy is equal to zero. The value of this intrinsic barrier is useful for determining whether a reaction is intrinsically fast or slow.

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_0(1 + \Delta G^{\circ}/4\Delta G^{\ddagger}_0)^2 \tag{5}$$

A number of proton transfer reactions have been analyzed using this equation[23–25] and it has been found that the intrinsic barrier for proton transfer between electronegative atoms is generally much less then the intrinsic barrier for proton transfer to and from carbon atoms. This higher intrinsic barrier may be a consequence of the electronic and heavy atom reorganization which accompanies proton transfer to and from carbon. This is in accord with the mechanism given in equation 4. Step 1, diffusion of the acid and base, is rate determining for many proton transfer reactions between electronegative atoms because of the small intrinsic barrier. The relative large intrinsic barrier to proton transfer to and from carbon results in proton transfer (step 2) being the rate-determining step. As discussed in the previous edition of this review, proton transfer is also the rate-determining step in the reaction of alkenes and acids. Therefore the acid catalyzed hydration of alkenes and acid catalyzed additions of alcohols and carboxylic acids to alkenes all fit this general mechanistic class.

Previously reviewed data[1] support a structure of the rate-determining transition state of these acid catalyzed reactions in which proton transfer is far advanced. Recent linear free-energy relationships support such a transition state structure. For example, a good correlation has been found[26] between $\sum\rho_p^+$ and the rates of hydration of many alkenes of the type $RR'C{=}CH_2$ whose reactivities differ by more than 10^{20}. A large negative

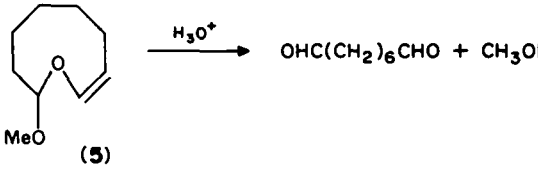
value (≈ -12) of ρ is obtained from this correlation, consistent with the close proximity of the substituents and the developing carbocationic center. These data are consistent with a structure of the transition state in which proton transfer is far advanced.

The effect of substituents on both the α and β carbons on their rates of hydration has been evaluated[27]. Substituents on the α carbon (equation 6) conjugate directly with the cationic center while those in the β position do not. Consequently, two different parameters are needed to evaluate the effect of these two different classes of substituent. For the α substituents, the values of σ_p^+ were used as in the case of the 1,1-disubstituted ethylenes. For the β substituents, two factors had to be taken into account. The first is the electronic effect of the group in the transition state expressed by σ_m^+. The second factor is the ground state stabilization of the alkene by the substituent which is expressed by the D parameters of Hine and Flachskam[28]. These factors are combined in equation 7. The satisfactory fit of the data by this derived equation permits the hydration data of both 1,1- and 1,2-disubstituted alkenes to be plotted on the same graph.

$$-\overset{+}{C}_\alpha-C_\beta- \tag{6}$$

$$\log k_2 = \rho[\sigma_p^+ + 0.60(\sigma_m^+ + 0.08D - 0.084)] + C \tag{7}$$

The acid catalyzed hydrolysis of vinyl ethers is another reaction whose mechanism involves rate-determining proton transfer from an acid to the double bond. A large amount of data supports such a mechanism[1]. The sole exception to this general mechanism was claimed for the acid catalyzed hydrolysis of 9-methoxy-1-oxacyclonon-2-ene (**5**) to suberaldehyde (equation 8)[29]. Reexamination of this reaction[30] has shown that **5** reacts in acid solution by initial hydrolysis of the acetal function to form **6** followed by ketonization (equation 9), not by protonation of the carbon–carbon double bond. Despite extensive search[31–35], no example is known of a mechanism involving reversible carbon protonation in the hydrolysis of vinyl ethers. All acid catalyzed hydrolyses of ketene acetals[36,37] and vinyl sulfides[38,39] studied so far also take place by a mechanism involving rate-determining and irreversible proton transfer.



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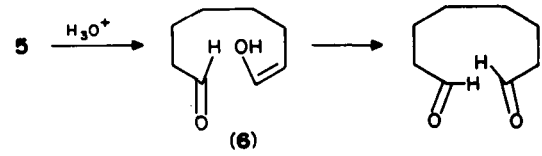
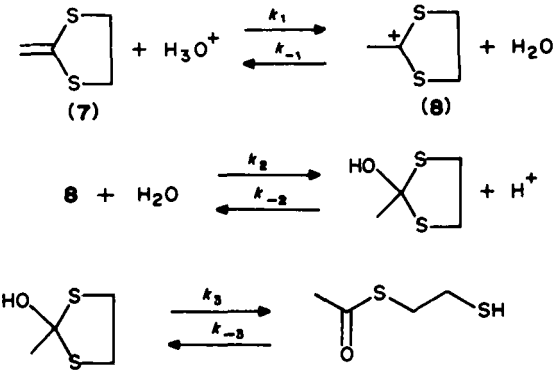


(9)

However, reversible or partially reversible protonation of a double bond has been established for the hydrolysis of a few compounds. An example is the hydrolysis of 2-methylene-1,3-dithiolane (**7**) whose mechanism has been shown to consist of three reversible consecutive reactions (Figure 4) involving 2-methyl-1,3-dithiolan-2-ylium ion (**8**) and 2-hydroxy-2-methyl-1,3-dithiolane as intermediates[40]. A kinetic study of the reactions of **7** as well as the isolated salt of **8** and the product *S*-(2-mercaptoethyl) thioacetate provides all six rate constants given in Figure 4. From these data, it is



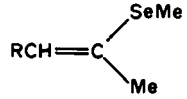
$k_1(M^{-1}s^{-1}) = 148, k_{-1}(s^{-1}) = 2.9, k_2(s^{-1}) = 21, k_{-2}(M^{-1}s^{-1}) = 39$
$k_3^A(M^{-1}s^{-1}) = 0.28$ and $k_3^B(M^{-1}s^{-1}) = 1.4 \times 10^{-3}$,

where

$$k_3 = k_3^A h_s + k_3^B/[H^+]$$
$$k_{-3}(M^{-1}s^{-1}) = 9 \times 10^{-5}$$

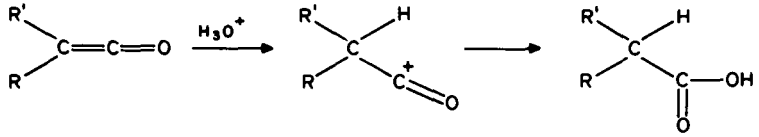
FIGURE 4. The mechanism of acid catalyzed hydrolysis of 2-methylene-1,3-dithiolane

concluded that above pH 3 the protonation of the starting material (7) is mainly rate determining at limiting zero-buffer concentration. As buffer concentration increases, the hydration of the ion **8** (step 2) becomes progressively rate determining. The last step becomes slow at pH below 2 while in strong acid ($H_0 < -1.5$) the reverse of the last step becomes important. Similar behavior has been reported for the acid catalyzed hydrolysis of enamines[41–43] and the methyl vinyl selenides[44] such as **9**.



(9)

The effect of pH on the rates of hydration of a number of ketenes in highly aqueous solutions has been reported[45,46]. The major effects of these substituents are both steric and electronic in nature. The results are consistent with a mechanism involving rate-determining proton transfer to the β carbon for the acid catalyzed reaction followed by rapid reaction of the acyl carbocation with water as shown in equation 10.

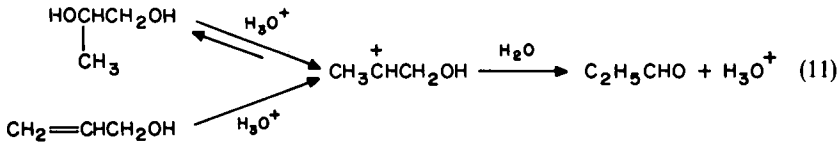


(10)

A carbocation is the first intermediate formed in the generally accepted mechanism of acid catalyzed hydration of alkenes. Recently, the existence of secondary carbocations as intermediates in solvolysis reactions has been questioned[47]. Since secondary carbocations

can be generated by hydration of certain alkenes, this reaction has been used as another method of determining if these ions can exist in aqueous solutions. The idea is that if the same carbocation intermediate is generated by either acid catalyzed hydration of alkenes or acid catalyzed dehydration of an alcohol, it must partition to products in the same way. If the same ions are not formed, then the product composition from the two precursors will be different. A number of workers have reported such studies.

Herlihy[48,49] measured the relative rates of partioning between regeneration of the substrate and pinacol rearrangement of optically active propane-1,2-diol in perchloric acid at 100 °C. These values agree with the product ratios obtained from the hydration of prop-2-en-1-ol under the same conditions if it is assumed that the regenerated substrate has undergone complete racemization (equation 11). These data are taken as evidence for a short-lived but free ion-dipole as the common intermediate in these two reactions.



(11)

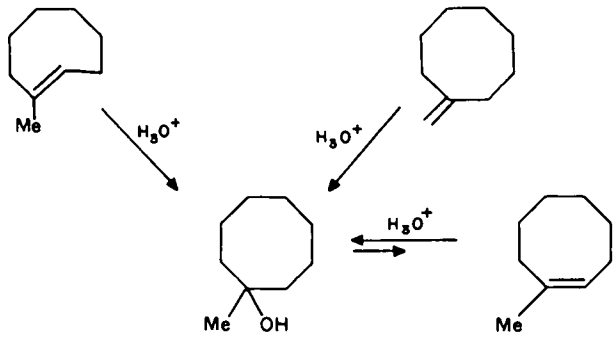
Jencks[50] reported that the acid catalyzed isomerization of the 4-methyl group of 1,1,1,2,3,3-hexadeuteriated 2-butanol between the 1- and 4-positions $CH_3CD_2CD(OH)CD_3 \rightarrow CH_3CD(OH)CD_2CD_3$, occurs faster than dehydration to 2-butene ($CH_3CD = CDCD_3$). The rate of this latter reaction was determined by measuring solvent hydrogen incorporation from water into the 3-position of 1,1,1,2,3,3-hexadeutirated 2-butanol in 0.55 M $HClO_4$. It can be concluded from these data that the reactions of 2-butanol are more complex than previously assumed and involve a significant amount of hydride migration. Taking this into account as well as the product yields of acid catalyzed hydration of 1-butene and the rate constants for isomerization and oxygen exchange of [4-^{14}C]-2-butanol available from the literature, Jencks has found that the partitioning ratios from 2-butanol and 1-butene are different. Consequently, it is concluded that these reactions do not proceed through a common intermediate. 'They must, therefore, occur largely or entirely by parallel concerted mechanisms through transition states that have a large amount of carbocation character and similar Gibbs energy'[50].

If there is no carbocation intermediate in the acid catalyzed reactions of 2-butanol, then it is unlikely that a carbocation would exist in the reaction of 1,2-propanediol. According to Jencks, however, the data of Herlihy are 'also consistent with concerted reactions of the two compounds through several different carbocation-like transition states of comparable energy that give the observed product ratios'.

What then determines if a carbocation exists as an intermediate in the acid catalyzed hydrations of alkenes? It has been suggested[51] that the lifetime of the intermediate is the criterion of choice. Thus if the lifetime of a species in the medium in which it is generated is less than the period of a molecular vibration, $\lambda = 10^{-13}$ s, then it is not a minimum on the energy surface of the reaction and it cannot be an intermediate. In such a case the reaction will have to occur by a concerted process. No direct information on the lifetimes of simple aliphatic carbocations in aqueous solution in available, but indirect order-of-magnitude estimates have been made.

Kresge[52] has measured the rate of reaction of 1-methyl-*cis*-cyclooctene, 1-methyl-*trans*-cyclooctene and methylenecyclooctane with aqueous perchloric acid at 25 °C (equation 12). The only products formed to any significant extent are 1-methylcyclooctanol and 1-methyl-*cis*-cyclooctene. Both the *trans* and *exo* alkenes give these two products in initially nonequilibrium proportions. This is taken to indicate the existence of

two conformationally different 1-methylcyclooctyl carbocations. The barrier to interconversion of these two ions and the barriers for hydration of either cation to the alcohol were estimated. From these estimates and the rate and equilibrium data determined experimentally, it was possible to construct an energy diagram of the 1-methylcyclooctyl system. An estimate of 10^{-10} s for the lifetime of a model tertiary aliphatic carbocation was made from these data. While this lifetime is much longer than a molecular vibration, it is very close to the rotational correlation time of liquid water, $\tau = 10^{-11}$ s. If the intermediate has a lifetime shorter than this, there will not be enough time for reorientation of the water molecule with which it will react. In that case, the reaction will occur by a preassociation mechanism in which the molecule of water gets into the proper reaction position before the carbocation is formed. Kresge has concluded that the lifetime of a tertiary aliphatic carbocation is just barely long enough for it to be a solvationally equilibrated reaction intermediate in dilute aqueous solution. Thus acid catalyzed hydrations of alkenes that form tertiary carbocations such as 2,3-dimethyl-2-butene occur by the usual stepwise mechanism.



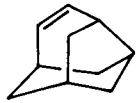
(12)

An estimate of the lifetime of a secondary carbocation in aqueous solution has been made by estimating the rate constant for the reaction of isopropyl cation with water[53]. This was done by extrapolating a σ constant correlation of rate data of the reaction of water with more stable alkoxy substituted cations. An estimated value of 5×10^{-12} s was obtained for the lifetime of the isopropyl cation in dilute aqueous solution. This places it into the category of a stable intermediate that is not fully solvationally equilibrated. However, the hydration of alkenes that form secondary carbocations is usually carried out in concentrated acids. In this environment the reaction of the cation with water is known to be slower and a lifetime of from 5×10^{-8} s to 5×10^{-9} s is estimated. Under these conditions a secondary carbocation, such as the one formed from *cis*-cyclooctene, is stable and solvationally equilibrated.

The work by Kresge and by Jencks represents a new and significant direction in investigating the reactivities of carbocations. Note that data gathered from reactions that are mechanistically in different classes (solvolysis reactions, acid catalyzed hydration of alkenes and acid catalyzed dehydration of alcohols) are used to gain an insight into the behavior of a particular intermediate, a carbocation. More data along these lines are anticipated.

Proton transfer to alkenes have been studied in other acidic media. The results of the reaction of neat trifluoroacetic acid (TFA) and alkenes have been interpreted in terms of rate-limiting proton transfer from TFA to the alkene[54,55]. Thus changing the solvent from aqueous acid to TFA does not change the mechanism. This conclusion is supported by a study of the kinetics of the reaction of protoadamantene (**10**) and norbornene (**11**) in H_2SO_4, $HClO_4$ and CF_3CO_2H[56]. Both alkenes have similar reactivities, rate depen-

dencies on acidity, solvent isotope effects, and activation parameters independent of the particular acid. Furthermore, a linear correlation of the reactivities of 12 alkenes (whose rates vary by 10^5) in TFA with their reactivity in aqueous acid is observed. No evidence for π complexes as kinetically significant intermediates was obtained despite claims to the contrary[57,58].



(10)

(11)

Results of reactions in other acidic media such as TFA in acetic acid[59], TFA in CCl_4[60] and sulfonic acids in acetic acid[54,49], while not as extensive, are consistent with the usual rate-determining proton transfer mechanism.

Additions of HCl and HBr to alkenes have been studied under a variety of conditions[1]. The order with respect to hydrogen halide in the rate law is sometimes first order, sometimes second order and other times of a complex order. The rate law first order in hydrogen halide apparently involves rate-determining proton transfer to form a carbocation. Mechanisms involving concerted additions, rate-limiting protonation from hydrogen halide dimers and equilibrium formation of π complexes have all been proposed as mechanisms for the reactions whose rate laws exhibit greater than first-order dependency on hydrogen halide concentrations. In none of these studies have there been claims of definitive evidence of π complexes as kinetically significant intermediates. Early work on HCl additions to alkenes has been critically reviewed[61].

The reaction of HCl and HBr to a number of alkenes in nonpolar solvents such as hexane, freons and CCl_4 at 195 K and 298 K has recently been reported[62]. The regiochemistry of the products, formed in quantitative yield, depends on the ratio of reagents and temperature. An excess of HBr forms mainly products with Markownikoff orientation while an excess of alkenes leads to products of *anti*-Markownikoff orientation as shown in Table 2 for the addition to 1-heptene in hexane. In both cases the product becomes more regioselective at lower temperatures. The authors concluded that the products are not formed by a free radical mechanism, because the product composition is unaffected by (i) changing the surface-to-volume ratio of the reaction vessel, (ii) carrying out the reaction in the presence of a free radical inhibitor or in the absence of peroxides.

It is proposed that molecular complexes between HBr (and HCl) and the alkene are the first formed intermediates. The IR spectra of mixtures of HBr (and HCl) and alkenes at low temperatures have been intrepreted as evidence for the formation of 1:1 and 2:1 HBr (HCl):alkene complexes[63,64]. Concerted rearrangement of atoms and bonds in the 2:1

TABLE 2. Effect of reagent concentration and temperature on product regiochemistry of addition of HBr to 1-heptene in hexane

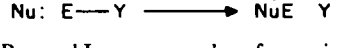
$[HBr]_0$ (M)	$[C_7H_{14}]$ (M)	T (K)	Product (%)	
			1-bromoheptane	2-bromoheptane
3	0.3	298	14	86
3	0.3	195	0	100
0.05	0.5	298	78	22
0.05	0.5	195	90	10

complex is proposed as the mechanism of formation of the Markownikoff products while rearrangement in a 1:2 HBr:alkene complex is proposed to explain products with *anti*-Markownikoff orientation[65]. Consistent with a mechanism involving a complex is the observation of a negative activation energy under certain conditions. While kinetic data consistent with this proposal are presented, the mechanistic explanation suffers from the very limited data on the effect of structure on rates and product composition. The fact that HCl and HBr are not dissociated in these nonpolar solvents and their tendency to self-associate no doubt contributes to this unusual behavior.

The mechanistic conclusions of acid catalyzed reactions of alkenes can be summarized as follows: In aqueous solutions of strong acids, where proton transfer occurs from the hydronium ion to the alkene, the evidence is overwhelming in favor of a mechanism involving rate-determining proton transfer to form a carbocation. There is no evidence in aqueous acidic solutions for the existence of a proton–alkene π complex. Exceptions to rate-determining proton transfer are found in acid catalyzed hydrations of alkenes with sulfur and/or selenium bonded to the vinyl carbons, in which case reaction of the cation with water can be rate determining under certain circumstances. Also, hydration of alkenes that form simple secondary carbocations may involve a concerted mechanism through a transition state that has a large amount of carbocation character. Reactions in nonaqueous acidic solution seem to occur by a similar mechanism, although the evidence in some cases is not conclusive. A molecular mechanism in which an alkene–HX donor–accepter complex is formed in the first step may be involved in some cases, particularly in very nonpolar solvents at low temperature. More evidence is needed in the later cases to establish this mechanism.

III. HALOGEN-CONTAINING REAGENTS

The general equation for the reaction of an alkene acting as a nucleophile at halogen of a halogen-containing reagent is given in equation 13. The atom E can be F, Cl, Br or I.



(13)

The reactions of F_2, Cl_2, Br_2 and I_2 are examples of cases in which E and Y are the same halogen atom. The reactions of interhalogens are described by this general equation when both Y and E are halogens but E is not identical to Y (e.g. ClF, BrCl, ICl). When Y is not a halogen but is still a good leaving group, the halogen-containing reagent is called a pseudohalogen (e.g. INO_3, ClSCN, BrN_3) A number of specific examples of reactions that may be considered as nucleophilic displacement reactions at halogens are shown in Figure 5.

While some of these reactions may occur via a concerted mechanism, the first step in the mechanism of the reaction of Cl_2, Br_2 and I_2 with alkenes is the formation of a 1:1 donor–acceptor complex. Evidence for this is primarily obtained from ultraviolet, infrared and Raman spectra of alkene–halogen mixtures.

A shifting of the double-bond stretching vibration to lower frequency concomitant with a shift towards higher frequencies of the C—H out-of-plane vibrations is observed in the infrared and Raman spectra of alkene–halogen solid mixtures at low temperature, where little or no reaction occurs[66–69]. In the case of symmetrical alkenes, the carbon–carbon double bond becomes infrared active. Also, the forbidden halogen–halogen stretching vibration becomes infrared active for many of the complexes and is observed at a lower frequency than that of the free halogen–halogen stretch.

In accord with the theory of Mulliken and Person[70], these complexes absorb in the ultraviolet or visible region of the spectrum. This new band is absent in the ultraviolet or visible spectrum of either the alkene or the halogen. Selected values of λ_{max} for these

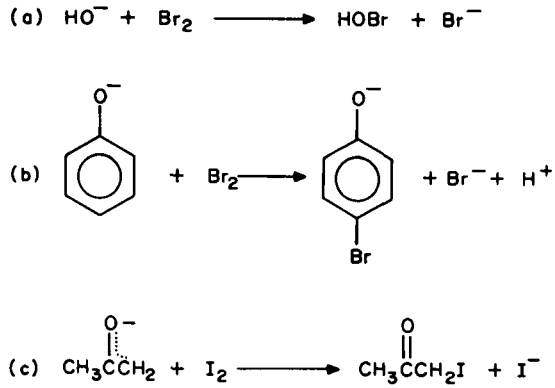


FIGURE 5. Examples of nucleophilic displacement reactions at halogens

TABLE 3. Literature values of the absorption band of selected alkene–halogen donor–acceptor complexes at 25 °C

Alkene	Iodine[a] λ_{max}	Bromine[b] λ_{max}	Chlorine[b] λ_{max}
$MeCH{=}CH_2$	270	267	246
$BuCH{=}CH_2$	275	270	248
Z-EtCH=CHMe	293	292	262
Z-PrCH=CHMe	294	294	264
Cyclohexene	295	294	263
$CH_2{=}CMePr$	293	—	—
$CH_2{=}CHEt_2$	290	—	—
$Me_2C{=}CHEt$	317	—	—
$Me_2C{=}CMe_2$	337	334	—

[a]Isooctane as solvent (Reference 71).
[b]Freon 112 or 113 as solvent (Reference 72).

charge-transfer bands of alkene complexes with a number of halogens and interhalogens are given in Table 3. The value of $1/\lambda_{max}$ for these complexes is found to be a linear function of the corresponding ionization potential of the alkenes[72]. This dependence is also explained by the theory of Mulliken and Person.

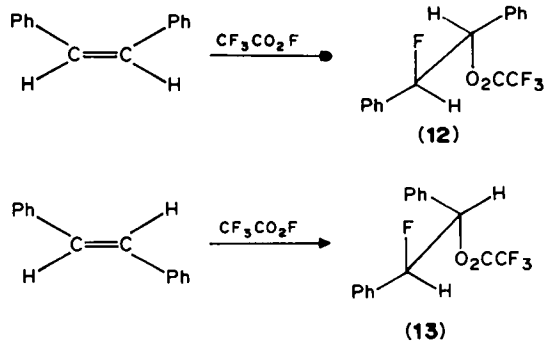
Let us examine the specific details of the reactions of alkenes with fluorine-, chlorine-, bromine- and iodine-containing compounds.

A. Fluorine-containing Compounds

The reactions of molecular fluorine with alkenes are very exothermic and are often quite violent. The major emphasis recently has been to develop new milder reagents to react with alkenes to form fluorine incorporated products. The reactions of two of these, XeF_2[73,74]. and CF_3OF[75,76], have recently been reviewed. Other new fluorinating reagents are CF_3CO_2F, CF_3CF_2OF, CH_3CO_2F, $CsSO_4F$, and aryliodine(III)difluorides($ArIF_2$). All

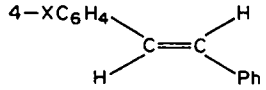
of these reagents can be formally regarded as molecular fluorine in which one atom has been replaced by another group.

Trifluoroacetyl hypofluorite (CF_3CO_2F), formed by passing nitrogen-diluted fluorine gas through a suspension of sodium trifluoroacetate in freon ($CFCl_3$) at $-75\,^{\circ}C$, reacts immediately with alkenes such as *E*- and *Z*-stilbene in CH_2Cl_2 to form stereospecifically the *syn* addition products *erythro*- and *threo*-1-fluoro-2-(trifluoroacetoxy)-1,2-diphenylethane (**12** and **13**) as shown in equation **14**[77].

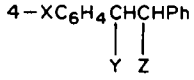


(14)

The regiochemistry of the reaction of CF_3CO_2F with unsymmetrical stilbenes **14** is á function of the electronic character of the group X. When X is a strong electron-withdrawing group, addition occurs in the Markownikoff sense forming **15** with Y = F and $Z = CF_3CO_2$. When X is a strong electron-donating group such as methoxy, the product orientation is reversed forming **15** with $Y = CF_3CO_2$ and Z = F. In this reaction an aromatic H is also replaced by fluorine. When X is a methoxy group, both *erythro* and *threo* isomers of **15** are formed. When X = Cl, the products are formed by stereospecific *syn* addition but nonregiospecific product composition is observed.

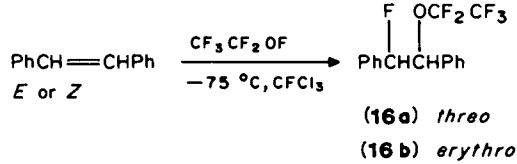


(14)



(15)

When a nitrogen-diluted stream of HF free fluorine gas is passed through a suspension of sodium trifluoroacetate in freon at $-75\,^{\circ}C$, instead of CF_3CO_2F, an oxidizing solution containing fluoroxypentafluoroethane (CF_3CF_2OF) is formed[78]. It also reacts with stilbenes as shown in equation 15. The product are formed by *syn* stereoselective addition. *E*-stilbene forms a 5:1 ratio of **16a/16b** while the *Z*-isomer forms a 1:5 ratio of **16a/16b**. Addition of CF_3CF_2OF to *E*-4-methoxystilbene (**14**, $X = OCH_3$) and *E*-4-(carbomethoxy)stilbene (**14**, $X = CO_2CH_3$) forms products of Markownikoff orientation (**15**, $X = OCH_3$, $Y = OCF_2CF_3$, Z = F and $X = CO_2CH_3$, Y = F, $Z = OCF_2CF_3$). In the



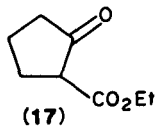
(16a) *threo*

(16b) *erythro*

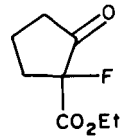
(15)

former case, addition is *syn* stereoselective while in the latter case addition is *syn* stereospecific. No difluoro products (**15**, X = OCH_3 or CO_2CH_3, Y = Z = F) are formed in contrast to the additions of CF_3OF where substantial amounts of such products are found[79].

Addition of acetyl hypofluorite (CH_3CO_2F) to *E*- and *Z*-stilbene and *E*- and *Z*-methyl (or ethyl) cinnamate has been reported[80]. Addition to the stilbenes is *syn* stereoselective while addition to the cinnamates is *syn* stereospecific. Acetyl hypofluorite is a milder fluorinating agent than fluorine gas, CF_3OF or CF_3F_2OF. Use has been made of this fact in the fluorination of 1,3-diones. For example, no fluorinated product is formed in the reaction of fluorine gas and 2-carboethoxycyclopentanone (**17**) or its enolate. The monofluoro derivative **18** is formed in only 13% yield in the reaction of **17** and CF_3CO_2F. In contrast, a yield of over 90% of **18** is obtained in the reaction of the enolate of **17** with CH_3CO_2F. In general, higher yields of monofluoro derivatives were obtained in the reaction of CH_3CO_2F with the enolates of 1,3-diones[81].

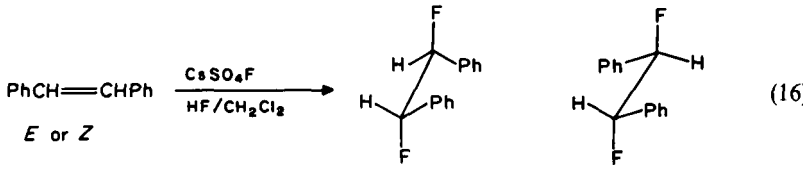


(**17**)

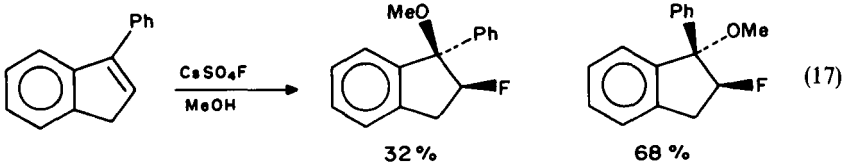


(**18**)

Another mild fluorinating agent is cesium fluoroxysulfate ($CsSO_4F$) which reacts with a variety of organic molecules, including alkenes[82]. The addition of $CsSO_4F$ to *E*-stilbene with HF in CH_2Cl_2 is stereoselective forming a 65:35 ratio of **19a**/**19b** while addition to the *Z*-isomer under the same conditions is nonstereospecific (equation 16). When the reaction is carried out in methanol as solvent, *vicinal* methoxy fluorides are formed as products. The products are formed in a regiospecific but stereoselective manner as shown by the addition to 1-phenylind-1-ene (equation 17)[83].



(**19a**) (**19b**) (16)



32% 68% (17)

The stereochemistry of the products of the reactions of various fluorinating reagents with *E*- and *Z*-stilbene are summarized in Table 4. Clearly, the stereoselectivity depends strongly on the nature of the fluorinating reagent. Trifluoroacetyl hypofluorite is the only reagent to form products by *syn* stereospecific addition. In contrast *anti*-stereoselective addition is found in the reaction of XeF_2. The stereoselectivity of the *vicinal* methoxy

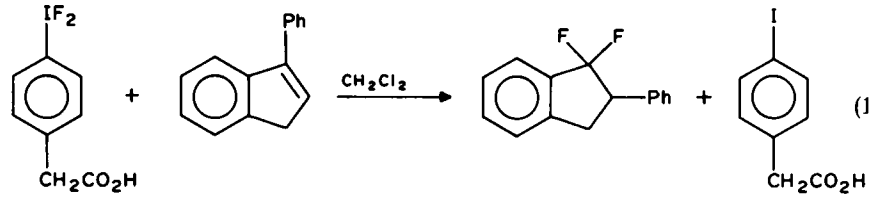
TABLE 4. Stereochemistry of the products of reaction of various fluorinating reagents with *E*- and *Z*-stibene

Alkene	Reagent	Experimental conditions	Y	Ratio **20**:**21**	Ref.
E	XeF_2	CH_2Cl_2/HF/20	F	38:68	84
E	CF_3OF	CH_3OH/-78	OCH_3	30:15	79
E	CH_3CO_2F	$CFCl_3/CH_2Cl_2$/-75	O_2CCH_3	54:7	80
E	CF_3CO_2F	$CFCl_3/CH_2Cl_2$/-75	O_2CCF_3	100:0	77
E	$CsSO_4F$	CH_2Cl_2/HF/20	F	65:35	83
E	$CsSO_4F$	CH_3OH/20	OCH_3	38:68	83
Z	XeF_2	CH_2Cl_2/HF/20	F	47:53	84
Z	CF_3OF	CH_3OH/-78	OCH_3	22:46	79
Z	CH_3CO_2F	$CFCl_3/CH_2Cl_2$/-75	O_2CCH_3	11:55	80
Z	CF_3CO_2F	$CFCl_3/CH_2Cl_2$/-75	O_2CCF_3	0:100	77
Z	$CsSO_4F$	CH_3OH/20	OCH_3	47:53	83
Z	$CsSO_4F$	CH_2Cl_2/HF/20	F	49:51	83
Z	F_2	$CFCl_3$/-78	F	16:84	85

20 = Threo PhCHFCHYPh **21** = Erythro PhCHFCHYPh

fluorides formed in the reactions of $CsSO_4F$ and CF_3OF are similar, but the latter reaction also forms *vicinal* difluorides and *vicinal* trifluoromethoxy fluorides.

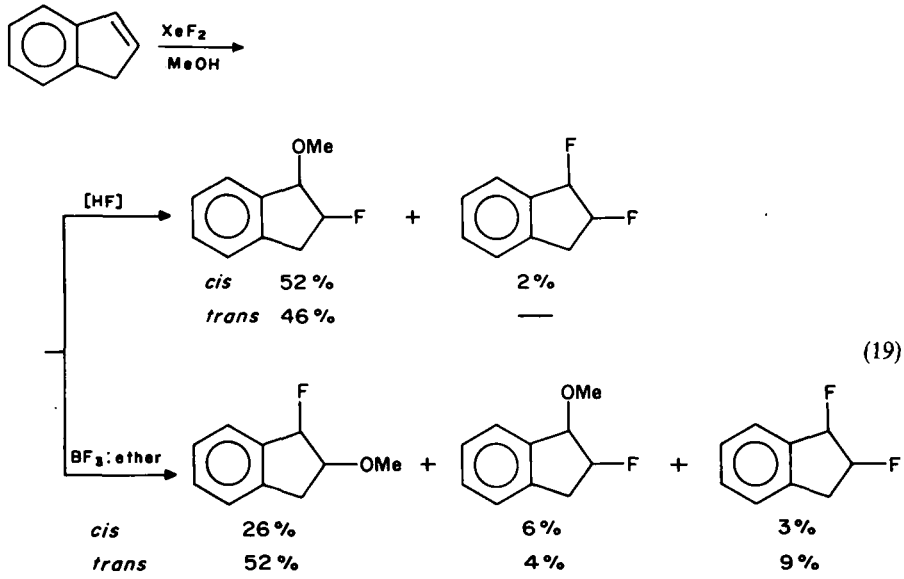
The ionic reaction of aryliodine(difluoride ($ArIF_2$) with alkenes in CH_2Cl_2 (usually in the presence of traces of HF) forms difluoro adducts. Competitive rate data provide evidence for the ionic nature of this reaction. Thus 1, 1-(4′, 4′-dimethoxyphenyl)ethene reacts 200 to 500 times faster than 1, 1-diphenylethene with (4-iodophenyl)acetate acid difluoride[86]. In addition, the formation of rearranged product is further evidence of an ionic reaction (equation 18). The addition of phenyliodine(III)difluoride to 1, 3-butadiene and 2, 3-dimethyl-1, 3-butadiene in the presence of BF_3:etherate forms mainly the 1, 4-difluoro adduct[87]. This is in contrast to the addition of XeF_2 under the same conditions where the 1, 2 difluoro adducts are the major or exclusive products.



(18)

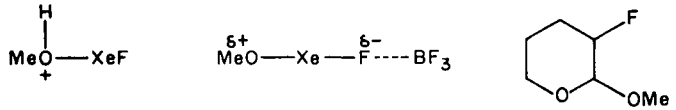
The addition of XeF_2 to alkenes is usually carried out in an inert solvent such as CH_2Cl_2. When methanol is used as a solvent, the reaction becomes very complicated. Xenon difluoride reacts with methanol to form an unstable electrophilic species CH_3OXeF which, in the presence of a proton catalyst, reacts with an alkene such as indene as shown in equation 19[88].

The product regiochemistry is reversed if BF_3:etherate is added to the reaction mixture. It is proposed that in the presence of a proton catalyst the intermediate **22** is formed in which the fluorine is the more electropositive center. When BF_3:etherate is the catalyst, a complex with CH_3OXeF is formed (**23**) in which the oxygen is the more electropositive



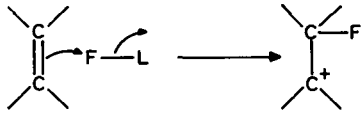
(19)

atom. As a result, the position of attack of the alkene changes depending on the catalyst. This dual behavior of XeF_2 with alkenes in methanol occurs with most alkenes. Exceptions are extremely reactive alkenes such as dihydropyran. In this case reaction of XeF_2 with the alkene is faster than with methanol and the only product formed is **24**.



(22) **(23)** **(24)**

In summary, the mechanism of these fluorination reactions is not well established. The regiochemistry of the products of reactions carried out in polar solvents and/or in the presence of Lewis-acid catalysts is consistent with the formation of carbocation intermediates[77,89]. The mechanism in equation 20 has been proposed[75,77]. Nucleophilic displacement by the alkene at the fluorine displaces the group bonded to the fluorine to form a reactive α-fluoro carbocation which then rapidly reacts in a predominantly *syn* manner. There is no evidence available for a donor–acceptor complex between any fluorine-containing reagent and an alkene which is consistent with this concerted mechanism (path a in Figure 2).



(20)

Mechanisms involving radical cations[84,90] and free radical[78] intermediates have also been proposed. This latter mechanism accounts well for the addition of CF_3OF to electron-poor alkenes under anaerobic conditions in solvents of low polarity[91] as well as photochemical reactions of XeF_2 with alkenes[92,93].

B. Chlorine and Chlorine-containing Compounds

The essential details of the ionic mechanism of chlorine addition to alkenes remain unchanged since the previous review[1]. The general mechanism, illustrated in Figure 6 for the chlorination of styrene, was first proposed by Poutsma[94]. A molecular complex **25**, contact ion-pair **26** and a solvent separated ion-pair **27** are all intermediates in this mechanism. Recent work has clarified certain features of this mechanism.

A small or negative activation energy for the reaction of chlorine and alkenes in nonpolar solvents is evidence that the molecular complex (**25**) is on the reaction coordinate[95,96]. A number of studies of the effect of solvent on the rate of chlorination have been reported[97,98]. The rate laws are first order in chlorine and first order alkenes in solvents of widely different polarity (hexane to methanol). The rate of chlorination in nonpolar solvents such as CCl_4 is slower than in more polar solvents such as acetic acid. Addition of water to acetic acid increases the rate of addition[99]. These data are consistent with a mechanism in which charge development occurs in the rate-determining state.

Reliable kinetic data in methanol at 25 °C, obtained by couloamperometry[100], for the chlorination of four simple alkenes have been reported[101]. The rate constants, which span a range of 10^3, are correlated by the Taft equation with $\rho^* = -2.9$. There is a very good linear relationship, with a near unit slope, between the rates of bromination and chlorination for the four alkenes under identical conditions.

The effect of added salts on the product distribution of chlorine addition to alkenes provides evidence for the type(s) of ion-pairs involved in the reaction. The products of chlorination of several ring- and side-chain substituted styrenes have been determined in anhydrous acetic acid in both the presence and absence of perchlorate, chloride and acetate salts[102]. The products formed are 1,2-dichlorides, 1-acetoxy-2-chlorides and chloroalkenes formed by an addition–elimination reaction (Figure 7). The regiochemistry of the addition products is exclusively Markownikoff and the addition–elimination products are formed with high stereoselectivity. Both types of addition products are formed nonstereospecifically. The product distribution and stereoselectivity are remarkably insensitive to added lithium perchlorate, lithium chloride or sodium acetate as shown in Table 5. The results are explained in terms of products formed from a contact ion-pair consisting of an open β-chlorobenzylic cation and a tightly held chloride counterion. Consistent with this view is the fact that chlorination of *E*- and *Z*-1-phenylpropenes forms different product distributions. Thus two different contact ion-pairs are formed that are not easily interconverted. Consistent with this view is the rate law of chlorine addition to ring substituted sytrenes which is second order overall and the fact that the rate constants correlate well with σ^+ with $\rho^+ = -3.22$. Thus, products are formed primarily from the contact ion-pair (**26**) in the addition of chlorine to styrene derivatives in acetic acid as solvent. This is in contrast to bromination of these same alkenes in acetic acid where both solvent-separated (**27**) and contact ion-pairs (**26**) are important in the product-determining step[103].

A number of reagents are known that can be formally regarded as a molecule of chlorine in which one chlorine atom has been replaced by an electronegative group or atom. The chlorine atom in these molecules is more electrophilic than in Cl_2 because of C—L bond is more polar and/or L is a better leaving group than Cl^-.

One examples is chlorine monofluoride (ClF) which is formed on mixing chlorine and fluorine gases. It reacts with a variety of halogenoethylenes in inert solvents such as freon or $CHCl_3$ to form the corresponding chlorofluoro adducts[104]. The products are formed in a nonregiospecific but *anti* stereospecific manner. A typical example is shown in equation 21. The data are consistent with an ionic mechanism involving a chloronium ion intermediate.

Alkyl hypochlorites (ClOR) are formally compounds in which one atom of a chloride molecule is replaced by an alkoxy group. They are known to react with alkenes in inert

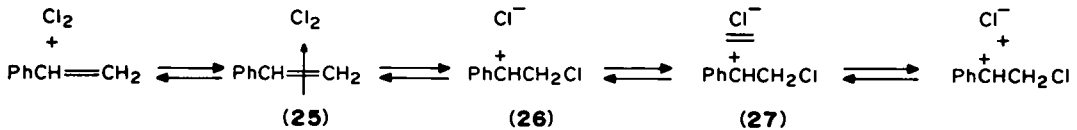


FIGURE 6. General mechanism of addition of chlorine to styrene

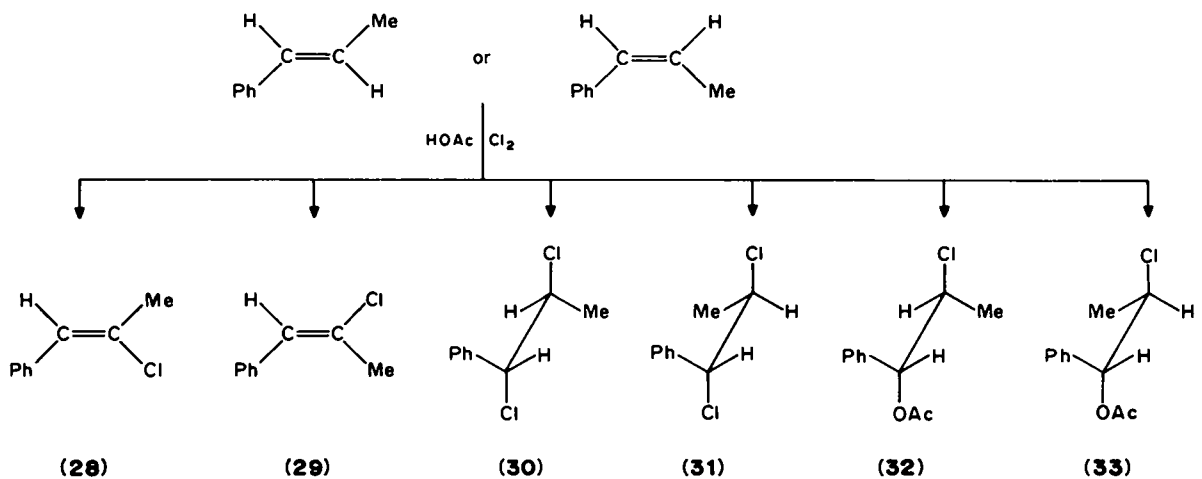
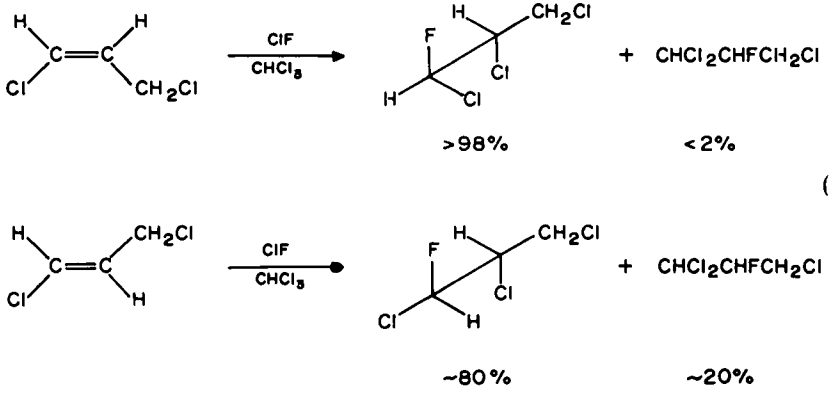


FIGURE 7. Products of addition of chlorine to *E*- or *Z*-1-phenylpropene

TABLE 5. Effect of added salts on products of addition of chlorine to *E*- or *Z*-1-phenylpropene in acetic acid

Salt	Conc. (M/L)	Products (%) 28	29	30	31	32	33
				E-1-Phenylpropene			
—	—	0.8	6	24	39	21.5	8.5
NaOAc	0.1	0.7	7	24	39	29[a]	
LiCl	0.1	0.7	6	25	38	30[a]	
LiCl	0.2	0.4	5	26	37	31[a]	
LiCl	1.0	0.4	4	31	34	21	8
$LiClO_4$	0.1	0.3	4	22	38	36[a]	
$LiClO_4$	1.0	0.4	4	12.8	36	31	15
				Z-1-Phenylpropene			
—	—	7	1.9	47	14	14	16
NaOAc	0.1	6.5	1.8	46	15	30[a]	
LiCl	0.1	6.5	1.9	45.5	16	30[a]	
LiCl	0.2	5.5	2	44.5	15.5	32.5[a]	
LiCl	1.0	5	1	42	24	13	15.5
$LiClO_4$	0.1	5.9	1.5	44	13	36[a]	
$LiClO_4$	1.0	4.4	1.2	37	13.5	19	25.5

[a]In these runs the *erythro* and *threo* isomers were not separated.



(21)

solvents but usually by a free radical mechanism[105]. The mechanism can be changed to an ionic one by carrying out the reaction either in the presence of BF_3 or in a polar solvent. The majority of the work has been carried out with methyl and *t*-butyl hypochlorites[106,107].

Methyl hypochlorite reacts very slowly with alkenes in nonpolar solvents. The addition of either gaseous BF_3 or BF_3:etherate accelerates the addition and forms substantial amounts of fluorochloride products as well as methoxychlorides (equation 22)[106]. The regiochemistry of the products formed in equation 22 and the fact that reaction of methyl hypochlorite with *E*- and *Z*-alkenes forms products by *anti* stereospecific addition is

consistent with an ionic mechanism that involves a chloronium ion intermediate.

$$BuCH{=}CH_2 \xrightarrow[BF_3/CH_2Cl_2]{MeOCl} BuCHCH_2Cl + BuCHCH_2Cl + BuCHCH_2OMe \quad (22)$$
$$\qquad\qquad\qquad\qquad\quad | \qquad\qquad\quad | \qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\quad F \qquad\qquad\quad OMe \qquad\qquad\quad Cl$$

The mechanism of the reaction of N-chloro compounds with alkenes can also be changed from free radical to ionic by the use of BF_3[108]. Thus the reaction of the N-chloro compounds **34** to **36** with alkenes in the presence of BF_3 or BF_3:etherate forms mainly the

MeNHCl	$(Me)_2NCl$	$MeNCl_2$
(34)	**(35)**	**(36)**

fluorochlorides and chloroamines as products (equation 23). Rearranged fluorochlorides (1-chloro-3-fluoro; 1-chloro-4-fluoro; and 1-chloro-5-fluorohexanes) are formed as well in small amounts. These products are not formed by equilibration of 1-chloro-2-fluorohexane and are believed to be formed by hydride shifts in the intermediate carbocation.

$$BuCH{=}CH_2 \xrightarrow[BF_3/CH_2Cl_2]{MeNCl_2} ClCH_2CHBu + BuCHCH_2Cl \quad (23)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad | \qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad F \qquad\qquad\quad NHMe$$

Another way of increasing the electrophilicity of chlorine is to replace one chlorine of Cl_2 by a RSO_2O group. The reactions of a number of such reagents with alkenes have been reported.

The first example of an addition of such a compound is the low-temperature reaction of CF_3SO_2OCl with neat alkenes such as ethylene and a number of chloro- and fluoro-substituted derivatives (equation 24)[109]. Based on the low reactivity of perfluoropropene, it is proposed that this is an electrophilic addition. This result is inconsistent with a nucleophilic attack but is consistent with the slow reaction of a very strong electrophile. Products of addition to *E*- and *Z*-CFH=CFH are formed by *syn* stereospecific addition leading to the suggestion of a concerted cyclic transition state.

$$Cl_2C{=}CF_2 + CF_3SO_2OCl \rightarrow CF_3SO_2OCCl_2CF_2Cl \quad (24)$$

Recently, sulfur trioxide has been inserted into a chlorine molecule and between the N and Cl atoms of *N,N*-dialkylchloroamines. Sulfur trioxide reacts with chlorine in methylene chloride or freon at $-60\,^{\circ}C$ to form chlorine chlorosulfate[110] ($ClSO_3Cl$), a very reactive chlorinating reagent. It reacts with alkenes to form products by nonregiospecific and *anti* stereospecific addition. For example, it reacts with 1-hexene to form 24% of isomeric β-chloro alkylchlorosulfates and 41% of 1,2-dichlorohexane. It adds to cyclohexene to form (in addition to appreciable resin) 27% of the adduct with *anti* stereochemistry. In addition to simple alkenes, it also chlorinates less reactive alkenes such as methyl methacrylate and trichloroethylene.

Similarly, *N,N*-diethylchloroamine, *N*-chloropiperidine and *N*-chloromorpholine react with equimolar amounts of sulfur trioxide at -70 to $-50\,^{\circ}C$ in methylene chloride and then to alkenes to give dialkylsulfamates (equation 25)[111]. The products are formed by *anti* stereospecific addition with Markownikoff orientation. Addition to norbornene forms rearranged products as expected for an addition reaction involving cationic intermediates.

$$BuCH{=}CH_2 \xrightarrow[SO_3/CH_2Cl_2]{Et_2NCl} BuCHCH_2Cl \quad (25)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad OSO_2NEt_2$$

In summary, recent work on the mechanism of molecular chlorine addition to alkenes

has clarified a number of points. For example, it has been shown that the products of the reaction of molecular chlorine with alkenes in acetic acid are formed at the contact ion-pair stage. The major advance in this area has been to increase the reactivity of molecular chlorine by formally replacing a chlorine atom by a more electronegative element. In this way the range of alkenes that can be chlorinated has been increased. While the available data are consistent with a mechanism involving displacement by the alkene at chlorine, the lack of quantitative rate data makes it difficult to substantiate this mechanistic conclusion.

C. Bromine and Bromine-containing Compounds

Recent work on the reaction of bromine and alkenes confirms the major features of the mechanism reported in the previous edition of this review[1]. In addition, new and important features of the individual steps have been reported. The various nonradical mechanistic pathways for the reaction in which solvent is not incorporated into the product are given in Figure 8. An alkene–bromine donor–acceptor complex, either 1:1 or 1:2, is the first-formed intermediate in each path. Let us consider the evidence for each of these mechanisms.

The rate of addition of bromine to cyclohexene in 1,2-dichloroethene decreases with increasing temperature[112]. A negative activation energy is evidence that the reaction mechanism is complex[113]. This fact along with the appearance of its charge-transfer band is good evidence that the donor–acceptor complex is on the reaction coordinate of this reaction. The formation constant ($K_f = 0.47\ M^{-1}$) and molar absorptivity ($E_{CT} = 5520\ M^{-1}\,cm^{-1}$) at 287 nm and 25 °C were obtained for this donor–acceptor complex. At high cyclohexene concentrations, the decrease in the absorbance of this charge-transfer band follows a second-order rate law. The rate constant of this process decreases with increasing cyclohexene concentration as expected for a mechanism involving a donor–acceptor complex on the reaction coordinate.

Experimental data are available for both 1:1 and 1:2 alkene:bromine complexes from IR and Raman spectroscopy in solid solutions at −185 °C[114] and thermographic and UV[115] studies. Evidence for 2:1, 1:1, 1:2 and 1:3 alkene bromine aggregates has recently been obtained by an investigation of the adamantylideneadamantane/bromine system in 1,2-dichloroethane using stopped-flow and conventional UV-visible spectrophotometric techniques. The data were treated by a nonlinear least-squares procedure to yield the following values of the formation constants of all four species: $K_{21} = 1.11 \times 10^3\ M^{-2}$, $K_{11} = 2.89 \times 10^2\ M^{-1}$, $K_{12} = 3.23 \times 10^5\ M^{-2}$ and $K_{13} = 7.23 \times 10^6\ M^{-3}$. Conductivity measurements confirm that the 1:1 species is a molecular charge transfer complex while the other three are ionic in nature. The 1:2 and 1:3 species have been identified as the bromonium tribromide and bromonium pentabromide salts, respectively[116].

The donor–acceptor complexes **37** and **38** are the precursors of other intermediates which are either bromonium ions (**39** or **40**) or bromocarbocations depending on the alkene structure and the reaction conditions. These cations are part of ion-pairs in which the counter-ion is either a bromide ion (in **39**) or a tribromide ion (in **40**). Evidence has recently been presented that the counterion can also be a pentabromide ion especially when bromine concentration is high during the addition[116]. Numerous examples of stable bromonium ions have been reported[117].

The rate-determining step in nonradical reactions of bromine and alkenes is the disappearance of the donor–acceptor complex. This step has been considered irreversible in most kinetic analyses of the reaction[118]. Yet bromine is regenerated from the bromonium ion of adamantylideneadamantane which is prevented from forming 1,2-dibromo products by steric hindrance[119,120].

Other examples of reversible formation of a bromonium ion have been reported recently. The approach taken by these authors is to generate a bromonium ion by bromine

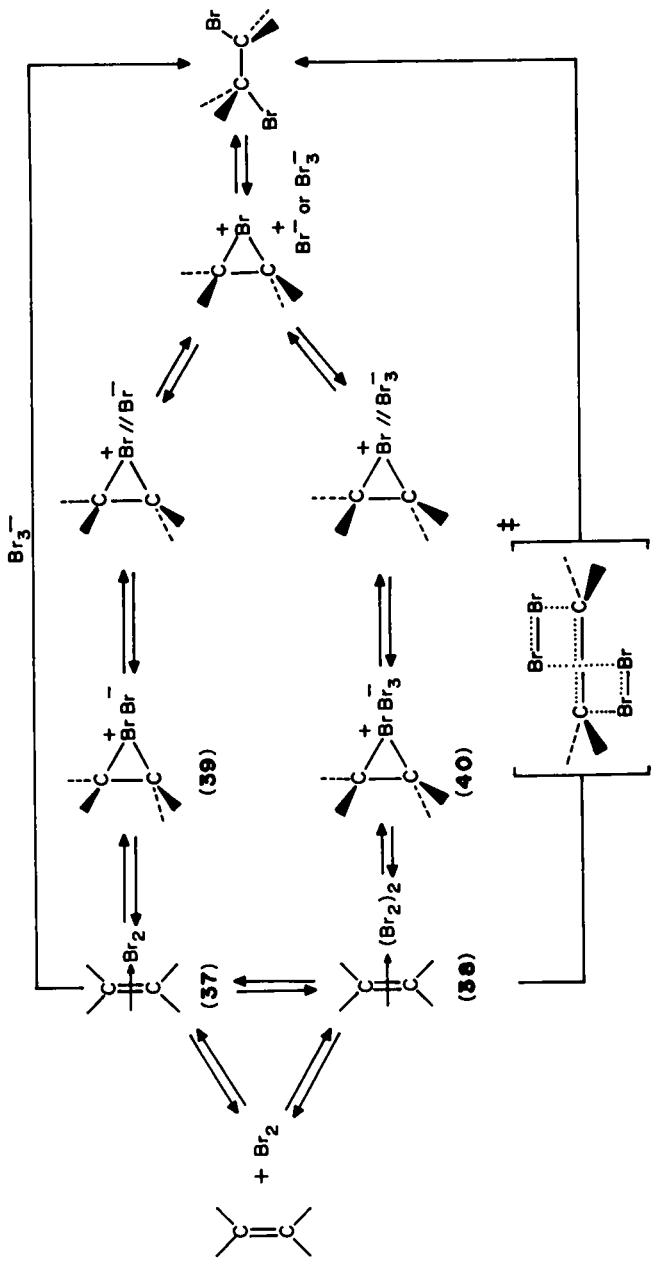
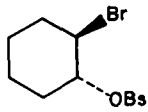


FIGURE 8. Nonradical mechanistic pathways for the reaction of bromine and alkenes in which solvent is not incorporated in the products

neighboring group participation in the presence of bromide ion. If bromonium ion formation is reversible, then alkenes and/or bromine scavanged products should be present at the end of the reaction. For example, the products of solvolysis of the *trans*-bromo brosylates **41** and **42** in glacial acetic acid containing bromide ion and an alkene as scavenger are given in Table 6[121]. The 1-acetoxy-2-bromides are the predominant products in both cases. Also formed are the cross products (**45** and **46** from **41**; **43** and **44** from **42**). These results are interpreted in terms of competitive bromide ion attack at both the carbon and bromine of the bromonium ion. The former process results in the *trans* dibromide while the latter forms bromine which is captured by scavenger alkene. Reaction of the cyclohexyl bromonium ion to form molecular bromine is 10–11 times more efficient than the same reaction of the cyclopentyl bromonium ion.



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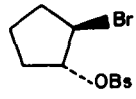
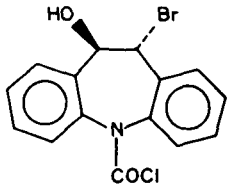


(42)

Similar results have been obtained from the reactions of bromohydrins **47**, **48** and **49** with gaseous HBr in 1,2-dichloroethane and in $CHCl_3$ at 25 °C[122,123]. The bromonium-bromide ion intermediate generated in this reaction collapses to form dibromides but also releases bromine to form *5H*-dibenz[*b*, *f*]azepine-5-carbonyl chloride from **47**, and *E*-stilbene from **48** and **49**.



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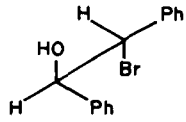
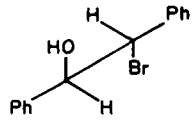


(48)



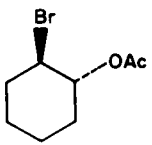
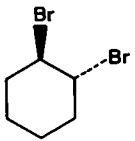
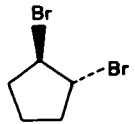
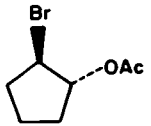
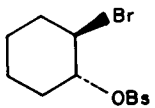
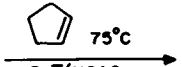
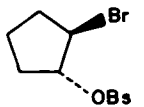
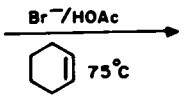
(49)

These three publications[121,122,123] provide strong evidence that in the reaction of bromine and alkenes the intermediate bromonium ion is formed reversibly. The results of Brown[121] indicate that the extent of such reversibility varies for different alkenes. Unless specifically taken into account, reversibility during bromination of alkenes introduces a severe complication into the kinetic studies and raises serious questions about the conclusions reached from the analysis of structure–reactivity data[124–130].

Bromine has been added to alkenes in many solvents whose polarity ranges from methanol[131] to CCl_4[132]. In hydroxylic solvents, the rate law is overall second order, first order in alkene and first order in bromine. In addition to its polarity, the role of a hydroxylic solvent is to provide specific electrophilic solvation by hydrogen bonding with the departing bromide ion of the donor–acceptor complex in the rate-determining step[133,134]. It has also been shown that there is a small nucleophilic contribution of the hydroxylic solvent in the rate-determining step of bromination[135,136]. In slightly polar aprotic solvents, the rate law is overall third order (second order in bromine). The second molecule of bromine is believed to assume the role of electrophilic solvation in the rate-determining step.

Reproducible data for the rates of bromination of alkenes in nonpolar solvents such as

TABLE 6. Product compositions

Reaction		% Product			
					
		43	**44**	**45**	**46**
 **(41)**		91.7	2.4	5.2	1.3
 **(42)**		0.7	0.35	4.1	94.7

hexane and CCl_4 are difficult to obtain, because trace impurities often catalyze the rapid free radical reaction. These difficulties are exemplified by the conflicting reports on the bromination of a number of alkenes in CCl_4[137–139].

The interpretation of the data for bromination in such nonpolar solvents at low temperatures in terms of an ionic mechanism has been challenged. Instead, a molecular mechanism involving a six-member transition state has been proposed (see Figure 8)[140]. On the other hand, Kochi[141] has found that the rates of bromination of alkenes and arenes in a variety of solvents (including CCl_4) can be correlated by a single free-energy relationship which relates the rate constant with a solvation term ΔG_R^S and the charge transfer transition energies $h\nu_{CT}$ (equation 26).

$$2.3RT \log k = (h\nu_{CT} + \Delta G_R^S) + \text{constant} \tag{26}$$

It is concluded from this relationship that the activation process of electrophilic bromination of both alkenes and arenes is equivalent to the formation of solvated ion-pairs.

Organic tribromide salts, such as pyridine hydrobromide perbromide (PHP) and tetrabutylammonium tribromide (TBAT), also add bromine to alkenes. These stable, easily prepared crystalline solids are more convenient to handle than liquid bromine. However, tribromide salts and molecular bromine often form different products when added to alkenes. For example, the addition of bromine to *E*-1-phenylpropene in CH_2Cl_2 occurs in an *anti* stereoselective manner while the addition of PHP to the same alkene forms products by *anti* stereopecific addition[142].

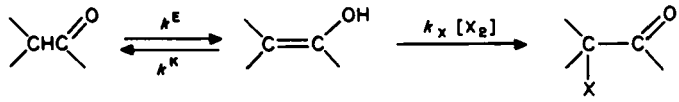
Evidence that these two brominating agents react by different mechanisms is available from a study of the rates of reaction of cyclohexene with molecular bromine and with TBAT in a number of solvents[143]. The rate law for addition of bromine is the usual overall third order (second order in bromine) while the rate law for reaction of TBAT is overall second order (first order in tribromide ion). The rate of addition of tribromide increases with increasing temperature while that of bromine decreases. The reaction of tribromide ion but not of bromine has a solvent kinetic isotope effect ($k_H/k_D = 1.175$) in $CHCl_3/CDCl_3$. These data are interpreted in terms of a mechanism involving the formation of an alkene:bromine 1:1 donor–acceptor complex in equilibrium with alkene and tribromide ion followed by rate- and product-determining nucleophilic attack by bromide ion on the donor–acceptor complex through a transition state that has more charge delocalization than the initial state.

In aqueous solutions, in the presence of bromide ion, both molecular bromine and tribromide ion brominate alkenes. Bromine is more reactive than tribromide ion toward most alkenes but reactivity differences are not large[144,145]. Aqueous micelles affect rates of bimolecular reactions by acting as a reaction medium different than bulk solvent (a pseudophase)[146]. The effect of aqueous micelles on the rate of bromination of a number of very hydrophobic alkenes with added LiBr is due largely to a micellar charge effect and to a change in the equilibrium between bromine and tribromide ion[147]. For example, the equilibrium is in favor of tribromide ion in micelles of cetyltrimethylammonium bromide. Consequently the overall reaction is slower than in nonionic micelles of poly(oxyethylene)(23)lauryl ether or in anionic micelles of sodium dodecyl sulfate. Addition of tetrabutylammonium bromide to anionic or nonionic micelles perturbs their surface which assists binding of anions such as bromide or tribromide ion and slows the overall reaction.

Since kinetic data provide no information about the product-determining step, other techniques must be used. One attempt to evaluate the factors that influence the reaction of bromonium ions with nucleophiles has been reported[148]. The percent of solvent incorporated products and their regiochemistry formed in the addition of bromine in methanol containing 0.2 M NaBr to ethylene and its six methylated derivatives have been

determined. The percent of bromomethoxyalkane formed correlates well with the carbocationic character of the most substituted carbon atom of the bromonium ion. The charge distribution is evaluated from measurements of ^{13}C NMR chemical shifts of these bromonium ions stabilized in superacid media[149]. It is concluded from this correlation that the hardness of the site is the major factor in determining which of two competing nucleophiles is successful in reacting at a given site.

The halogenation of enols has been examined by studying the acid catalyzed halogenation of the corresponding carbonyl compound in aqueous solution at very low halogen concentration and high buffer concentrations (equation 27). Under these

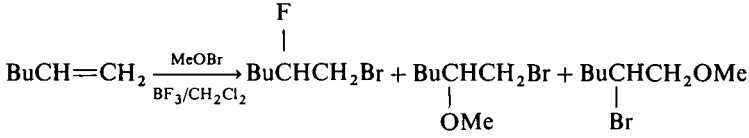


(27)

conditions, the rate is $k_X[X_2] \approx k^K$. The rates of halogenation under these condition are dependent on the concentration of the halogen but are independent of the identity of the halogen. The conclusion was reached from these data that the rate of halogenation of enols is diffusion controlled[150]. Recently, accurate values of $K_E = k^E/k^K$, free of any assumptions, have been determined[151] for many carbonyl containing compounds. Using these values of K_E, and the apparent second-order bromination rate constants k_2 ($k_2 = K_E k_{Br}$), it is possible to obtain experimental values of the rate constants of enol bromination[152]. The results are listed in Table 7. These rate constants vary with the enol structure in a way typical of electrophilic additions. Most instructive is the regular increase in the bromination rate constant shown by the substituted acetophenone enols (last five entries in Table 7). As the substituent becomes more electron releasing, the rate increases. While these rate constants are large, they are less that those found for the reaction of bromine in aqueous solution with other nucleophiles such as 4-bromophenoxide ion[153] ($7.8 \times 10^9\,M^{-1}s^{-1}$), the anion of malonitrile[154] ($8.3 \times 10^9\,M^{-1}s^{-1}$) and the anion of 3-methylucracil ($7.9 \times 10^9\,M^{-1}s^{-1}$)[155]. Furthermore, the low sensitivity of the reaction rate to substituent effects indicates that the reaction of bromine with enols in aqueous acid solution is almost but not quite a diffusion-controlled process. A similar conclusion has been reached for the halogenation of acetone and substituted acetophenones in alkaline solutions[156–158].

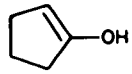
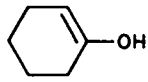
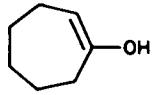
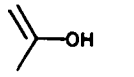
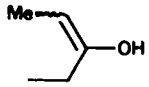
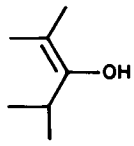
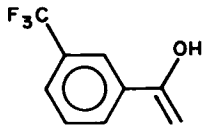
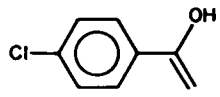
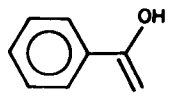
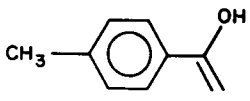
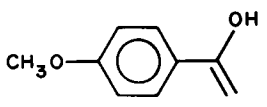
Bromine monochloride (BrCl) is more reactive towards alkenes than molecular bromine[159]. The regio- and stereochemistry of the products formed in the two reactions is very similar. Thus BrCl and bromine both add to *E*- and *Z*-1-phenylpropene in methylene chloride to form products of Markownikoff regiospecific but nonstereospecific addition (Figure 9)[160]. In contrast, the addition of tetramethylammonium dibromochloride (Me_4NBr_2Cl) forms both dibromo and bromochloro products by *anti* stereospecific and regiospecific Markownikoff addition. Bromination of alkenes by molecular bromine and organic tribromides show a similar different in product stereochemistry as was previously noted.

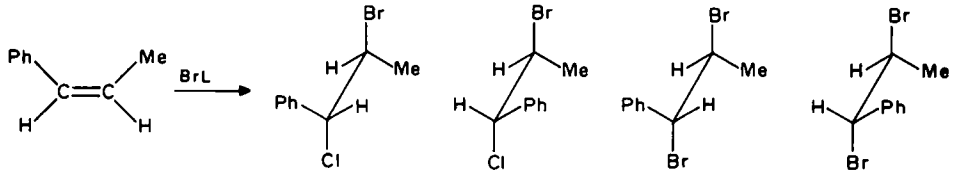
Methyl hypobromite and methyl hypochlorite exhibit similar behavior towards alkenes in the presence of BF_3 in nonpolar solvents[161]. The products formed in the addition of methyl hypobromite are the methoxybromides and the fluorobromides (equation 28).



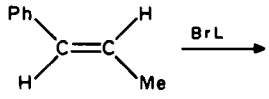
(28)

TABLE 7. Enolization constants K_E and rate constants k_{Br} for the reaction of simple enols with bromine in aqueous solution at 25 °C

Enol	pK_E	$k_{Br}(10^9\ M^{-1}\ s^{-1})$
	7.94 ± 0.01	4.4 ± 0.1
	6.39 ± 0.02	2.8 ± 0.2
	8.00 ± 0.01	4.0 ± 0.1
	8.33 ± 0.02	4.0 ± 0.4
	7.43 ± 0.02	2.8 ± 0.2
	7.52 ± 0.02	1.5 ± 0.1
	7.38 ± 0.02	2.0 ± 0.2
	7.77 ± 0.02	2.8 ± 0.2
	7.97 ± 0.03	3.3 ± 0.3
	8.34 ± 0.03	3.8 ± 0.4
	8.80 ± 0.02	4.3 ± 0.3



L				
Br	—	—	25.5	74.5
Cl	21	79	—	—
Me_4NBrCl	—	28	0.5	71.5



L				
Br	—	—	69	11
Cl	91.5	8.5	—	—
Me_4NBrCl	29	—	71	—

FIGURE 9. Product composition (%) of addition of bromine, bromine monochloride and tetraammonium dibromochloride to *E*- and *Z*-1-phenylpropene in CH_2Cl_2 at 25 °C

In summary, evidence in this section has been presented for each of the following:

1. Bromonium ions can react with bromide ion to form bromine and an alkene.
2. The activation process of electrophilic bromination of both alkenes and arenes is equivalent to the formation of solvated ion-pairs.
3. Bromine and organic tribromides react with alkenes by different mechanisms.
4. The reaction of bromine and enols and enolate anions in aqueous solution is almost but not quite a diffusion-controlled reaction.

D. Iodine and Iodine-containing Compounds

Evidence for both 1:1 and 1:2 alkene:iodine donor–acceptor complexes in the addition of iodine to alkenes has been presented[1]. In nonpolar solvents such as CCl_4 and hexane the rate law is usually fourth order overall, first order in alkene and third order in iodine. In more polar solvents such as acetic acid, the order is overall third order (second order in iodine). It still more polar solvents, a second-order overall rate law is observed (first order in iodine). It has been suggested that iodine must be polarized to react effectively with alkenes[162]. It does so by forming donor–acceptor complexes with alkenes, solvents and itself. The general mechanism shown in Figure 10 is based on data currently available.

As in the case of the mechanism of bromination and chlorination of alkenes, the rate-determining step is the disappearance of the donor–acceptor complex. This is evident from the reaction of iodine and 3,7-dimethylenebicyclo[3.3.1.]nonane (**50**) in CCl_4 to form 1-iodomethyl-3-iodoadamantane (**51**) (equation 29)[163–165]. The rate law is overall third order (second order in iodine). A charge transfer band is observed on mixing the reagents and there is a negative temperature dependence on the rate. The mechanism proposed

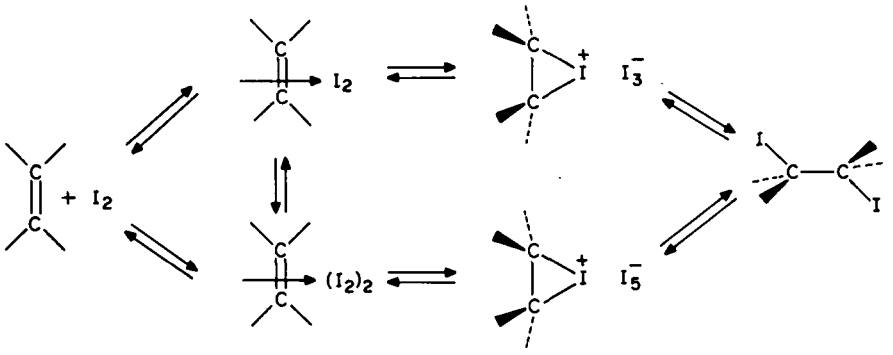
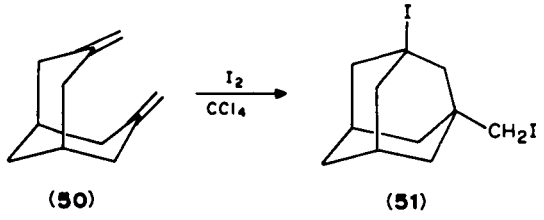


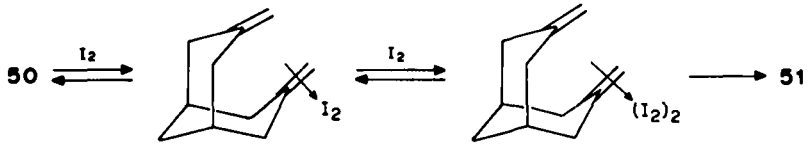
FIGURE 10. General mechanism for the reaction of alkenes and iodine

involves successive 1:1 and 1:2 alkene:iodine donor–acceptor complexes (equation 30). The uncomplexed double bond in the 2:1 complex is the internal nucleophile that reacts intramolecularly to form **51**. This must be the rate-determining step, since the fact that the overall rate law is second order in iodine rather than the usual rate law (third order in iodine) found in CCl_4 is evidence that the intramolecular attack by the double bond on the 1:2 alkene:iodine donor–acceptor complex is rate determining. Furthermore, a structure of the 1:2 alkene:iodine complex may be inferred from these data in which both iodine molecules are complexed to the same side of the double bond. This structure may be atypical, however, because of the proximity of the two double bonds.



(29)

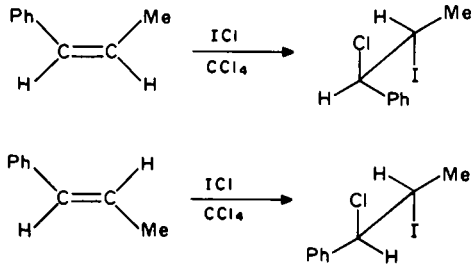
(50) **(51)**



(30)

The addition of iodine monochloride (ICl) to a number of α,β-unsaturated esters and amides has been studied in nitrobenzene, acetic acid and mixtures of the two solvents[166]. The rate law in these solvents is overall third order, first order in alkene and second order in ICl. The rate increases with increasing solvent polarity consistent with an ionic addition mechanism.

Evidence for donor–acceptor complexes in the addition of ICl to a series of simple alkenes in CCl_4 has been presented[167]. A new absorption band due to this complex is observed immediately on mixing ICl and the alkene. This band decreases rapidly with



(31)

time. The rate of the reaction decreases with increasing temperature, indicating that the complex is on the reaction coordinate. The products are formed by *anti* stereospecific addition and, in the case of *E*- and *Z*-1-phenylpropene, only products with Markownikoff orientation are formed (equation 31). Under conditions of $(\text{alkene})_0 > > (\text{ICl})_0$, the rate law is complex:

$$\frac{-\text{d[ICl]}}{\text{dt}} = \frac{k_{\text{expt}}(\text{alkene})(\text{ICl})^3}{[1 + C_2(\text{alkene})]^3}$$

where C_2 is K_{app} which is a measure of the formation constant or constants of the molecular complexes involved in the reaction. On the basis of analysis of the enthalpy changes during the reaction, it is concluded that both 1:1 and 1:2 alkene:ICl donor–acceptor complexes are involved in the mechanism prior to the rate-determining step. Under the experimental conditions used, C_2 is a good approximation of the formation constant of the first donor–acceptor complex involved in the reaction. By evaluating C_2 for the addition to a series of alkenes, it is possible to determine the effect of substituents on this formation constant[168]. The data are given in Table 8. It is clear from these data that the alkene–ICl complex stability increases as the hydrogen atoms of ethylene are successively replaced by alkyl groups. In two of the four series of alkenes, the nature of the

TABLE 8. Formation constants (C_2) for donor–acceptor complexes formed in the addition of ICl to various alkenes in CCl_4 at 25 °C

Alkene	R	$C_2(M^{-1})$
CH_2=CHR	Me	0.98 ± 0.050
	Et	2.43 ± 0.12
	i-Pr	4.62 ± 0.30
	t-Bu	1.58 ± 0.06
CH_2=C(Me)R	Me	27.2 ± 1.9
	Et	51.9 ± 8.0
	i-Pr	37.7 ± 9.1
	t-Bu	33.1 ± 7.5
Z-MeCH=CHR	Me	70.7 ± 7.5
	Et	101 ± 14
	i-Pr	55.2 ± 8.4
	t-Bu	112 ± 18
E-MeCH=CHR	Me	22.7 ± 0.6
	Et	43.8 ± 2.7
	i-Pr	26.7 ± 3.3
	t-Bu	1.23 ± 0.07
Me_2C=CHMe		458 ± 10
Me_2C=CMe_2		908 ± 12

alkyl substituent has little effect on C_2. Thus the values of C_2 for propene, 1-butene, 3-methyl-1-butene and 3, 3-dimethyl-1-butene are the same within experimental error. In the other series, the introduction of bulky substituents such as isopropyl and *tert*-butyl groups decreases the stability of the complex.

Iodine monochloride is a well-defined compound. However, many other iodine-containing reagents such as iodine thiocyanate (ISCN) and iodine acetate (IOAc) are not well characterized. There is some question as to their existence, since they are usually prepared by mixing iodine and a nucleophile in solution. This makes kinetic and mechanistic studies very difficult. However, great synthetic use has been made of the addition of iodine in the presence of added nucleophiles to functionalize alkenes[169,170]. Additional examples of this type have recently been reported.

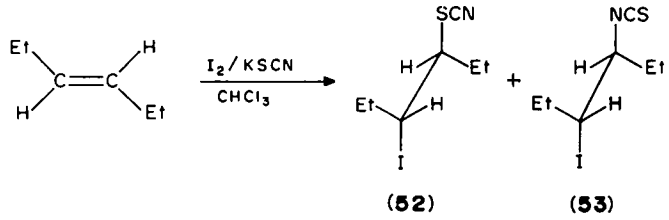
The reaction of simple alkenes such as cyclohexene, styrene and *E*-1-phenylpropene with iodine and water in 1:1 tetramethylenesulfone-chloroform occurs in an *anti*-stereospecific manner to form *vic*-iodohydrins in high yields[171]. If the water is replaced by fused sodium acetate, iodoacetates are formed instead, also by *anti*-stereospecific addition (equation 32).

$$PhCH{=}CH_2 \xrightarrow[I_2]{NaOAc} PhCHCH_2I \quad (OAc) \tag{32}$$

Iodosulfones can be prepared in a similar reaction[172]. Thus the reaction of a suspension of sodium benzenesulfinate in a solution of iodine and alkene in acetone in the dark at room temperature forms β-iodosulfones (equation 33). The fact that only the *anti*-Markownikoff isomer is formed as product is explained by steric hindrance. Attack at the more sterically hindered carbon of the iodonium ion is made difficult by the large size of the sulfinate ion. Similar *anti*-Markownikoff adducts have been observed for the addition of iodine isocyanate[173], iodonium nitrate[174] and arenesulfenyl halides[175] to alkenes.

$$HexCH{=}CH_2 \xrightarrow[I_2]{PhSO_2Na} HexCHCH_2SO_2Ph \quad (I) \tag{33}$$

A mixture of iodine and hydrated potassium thiocyanate in $CHCl_3$ reacts with alkenes such as *E*-3-hexene to form only the *erythro* isomers **52** and **53** (equation 34). The iodothiocyanates (**52**), the major products, are formed by kinetic control and can be isomerized to the thermodynamically more stable iodoisothiocyanates (**53**) by treatment with BF_3–etherate. The stereospecific *anti* addition suggests a mechanism involving an iodonium ion. Further evidence for such a mechanism is available from the addition to cyclohexene. In the presence of excess cyclohexene, the equilibrium between iodine, cyclohexene and 1,2-diiodocyclohexane is shifted to the side of the diiodide. When hydrated potassium thiocyanate is added to this solution, the iodothiocyanate is formed as well as a small amount of the iodoisothiocyanate. This is evidence that the thiocyanation



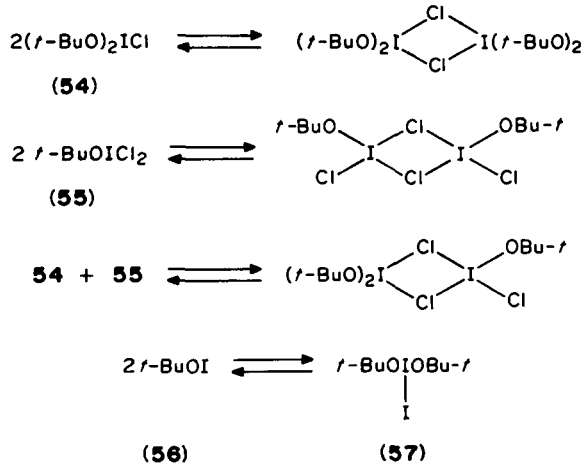
(52) (53) (34)

pathway involves initial formation of an iodonium ion which rapidly equilibrates with the diiodide. Subsequent reaction of the thiocyanate ion with the iodonium ion forms the observed products[176].

The addition of a mixture of iodine and thiocyanogen in benzene in the dark to alkenes forms mainly *vicinal* iodoisocyanates by an ionic mechanism[177]. Under irradiation with UV light the reaction occurs by a radical mechanism to form mainly *vicinal* iodothiocyanates. The relative facility for free radical reaction depends on the structure of the alkene. Alkenes such as *E*- and *Z*-3-hexene and cyclohexene that react rapidly with iodine and thiocyanogen show little evidence of reaction by a free radical mechanism under the influence of UV light. A radical mechanism competes successfully in the reaction of 3,3-dimethyl-1-butene and 4-methyl-1-pentene where the ionic reactions are relatively slow.

Alkenes react with a mixture of *tert*-butyl hypoiodite and BF_3:etherate by an ionic mechanism[178]. No fluorine containing products are formed in this reaction, unlike the BF_3:etherate catalyzed reaction of alkenes with *tert*-butyl hypochlorite[179] or *tert*-butyl hypobromite. The addition to isomeric *E*- and *Z*-alkenes is *anti* stereospecific while addition to 1-hexene forms products of both *anti*-Markownikoff and Markownikoff orientation. While the mechanism of this reaction probably involves an iodonium ion, the steps leading to its formation are unclear because the structure of the starting *tert*-butyl hypoiodite depends on its method of formation.

Three methods are usually used to prepare '*tert*-butyl hypoiodite'. They are (i) the reaction of *tert*-butyl hypochlorite with iodine, (ii) the reaction of *tert*-butyl hypochlorite with metal iodides and (iii) the reaction of potassium *tert*-butoxide with iodine[180]. The reagent obtained by the first method is different from that made by the latter two methods. The evidence for this statement is based on physical measurements (NMR, UV and IR) and chemical data (average molecular weight, homolytic reaction with cyclohexane and quantitative determination of iodine produced on hydrolysis). It is proposed that **54** and **55** which are in equilibrium with their dimers are formed in the first method (*t*-BuOCl and I_2). Both **54** and **55** are trivalent iodine species that contain O—I and I—Cl bonds. The reaction of *tert*-butyl hypochlorite with the two metal halides produces an equilibrium mixture of **56** and **57**. Structure **56** contains monovalent iodine while **57** contains both mono and trivalent iodine. The presence of equilibrium mixtures of these various species complicates any mechanistic study. Since trivalent iodine-containing compounds can react with alkenes[181], it is unknown which of the iodine atoms, the mono and/or trivalent ones of **54**, **55**, **56** or their dimers, is the reactive site.



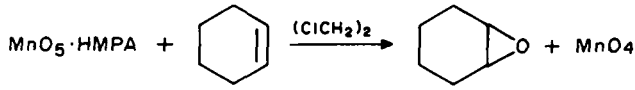
In summary, little new mechanistic information has been reported on the addition of iodine-containing compounds to alkenes since the last edition of this review[1]. It is generally assumed that their mechanism involves an iodonium ion, even though in most instances there is little evidence to support such a mechanistic conclusion.

IV. OXYGEN-, SULFUR- AND SELENIUM-CONTAINING COMPOUNDS

A. Oxygen-containing Compounds

A wide variety of oxygen-containing reagents are known that react with alkenes to form epoxides. These include metal peroxo complexes, dialkyldioxiranes, solutions of metal catalysts and H_2O_2 or alkyl hydroperoxides, and the organic peroxyacids. Numerous articles have recently appeared that review the reactions of many of these reagents with alkenes[182–189]. Consequently, only a few recent mechanistically important aspects of these reactions will be cited.

Alkenes react with molybdenum and tungsten peroxo complexes of the general formula $MO(OO)_2L^1L^2$ (M = Mo, W; $L^1 \cdot L^2$ = donor ligands such as pyridine, DMF or HMPA) to form epoxides. For example, $MoO_5 \cdot$HMPA which is highly soluble in organic solvents is an effective reagent for the selective epoxidation of alkenes at room temperature in aprotic solvents (equation 35)[190]. The reaction is stereospecific (*Z*-alkenes form *Z*-



(35)

epoxides and *E*-alkenes form *E*-epoxides) and the reactivity of the alkene increases with increasing numbers of electron-donating groups on the double bond. The mechanism shown in Figure 11 has been proposed[182]. The first step is the formation of a donor–acceptor complex (**58**) between the Mo^{VI} and the alkene. The next step is an intramolecular nucleophilic attack by the coordinated oxygen that results in the insertion of the alkene between the metal–oxygen bond. The resulting five membered dioxametallacycle (**59**) then decomposes by 1, 3 dipolar cycloreversion to form the epoxide and MoO_4. The rate law is consistent with such a mechanism[191] and the identity of the oxygen atom transferred was

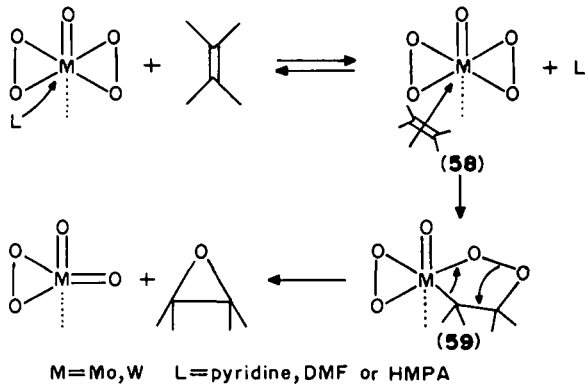
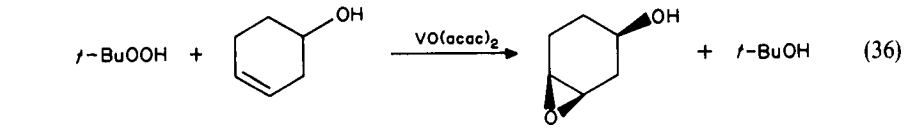


FIGURE 11. Mechanism of epoxidation of an alkene by metal peroxo complexes

established by O^{18} labeling studies[192]. A similar mechanism involving a dioxametallacycle has been proposed for a number of oxidation reactions involving other metal peroxy complexes[182].

A similar mechanism has been proposed for the epoxidation of alkenes by alkyl hydroperoxides catalyzed by d^0 metal complexes (Mo^{VI}, V^V and Ti^{IV}) (equation 36)[182]. Recently, the synthesis of a number of stable vanadium(V) alkylperoxidic complexes (e.g. oxo[*N*-(2-oxidophenyl)salicylidenaminatolvanadium(V) *t*-butylperoxide **60**) that epoxidize alkenes (equation 37) has provided evidence for such a mechanism[193]. This reaction exhibits the same characteristics as the metal catalyzed alkyl hydroperoxide epoxidation (equation 36). Both have the same order of reactivity, same stereoselectivity, same Michaelis–Menten kinetics, the same solvent effects and similar activation energies. Consequently, it is concluded that complexes such as **60** can be considered as good models for the vanadium catalyzed reaction of hydroperoxides and alkenes. The important feature of these mechanisms is the coordination of the alkene to the metal. The role of changing the nature of the metal and its ligands on the reactivity of these complexes has been recently reviewed[182].



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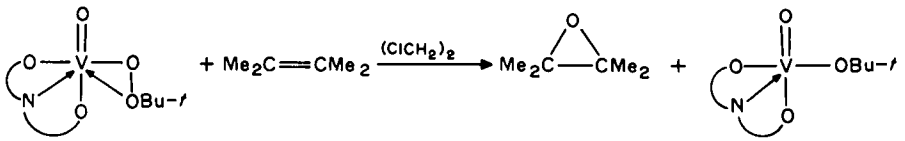
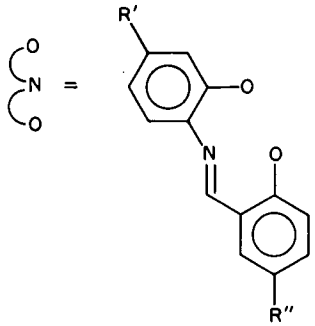
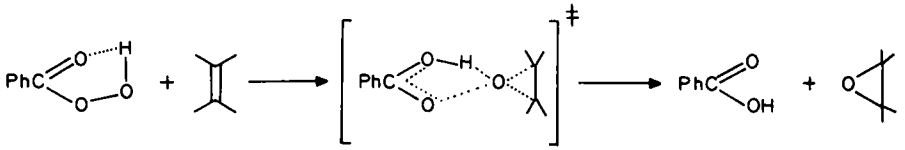


(**60**)



(37)

The mechanism originally proposed by Bartlett (the so-called 'butterfly mechanism') for the reaction of alkenes with peroxy acids is shown in equation 38[194]. This mechanism,



(38)

which involves nucleophilic displacement by the alkene at oxygen, has been questioned. An alternate mechanism similar to the one in Figure 11 has been proposed for this reaction, because of the fact that the reaction of three epoxidizing reagents, $MoO_5 \cdot HMPA$, metal catalyzed *t*-BuOOH and peroxy acids, exhibit similar order of reactivity and the same stereoselectivity[182]. This mechanism, illustrated in Figure 12, is a variation of the mechanism proposed by Kwart[195]. The intramolecular hydrogen-bonded peroxy acid is regarded as a potential hydroxy-substituted dioxirane (**61**). It is proposed that this dioxirane and the alkene form a donor–acceptor complex in the rate-determining first step of the mechanism (Figure 12). Nucleophilic attack on the alkene by the terminal peroxidic oxygen atom forms the 1,2-dioxolane (**62**) which decomposes to products. There are two major problems with this mechanism. Firstly, compounds such as **62** are unexpectedly stable and, on thermolysis at 100 °C, give only minor amounts of epoxide. Secondly, in the reaction with peroxy acids, the reactivity ratio norbornene/cyclohexene is much lower than is usually found for reagents that are believed to react by a cyclic five-membered transition state. To counter the first objection, Kwart proposed a modified

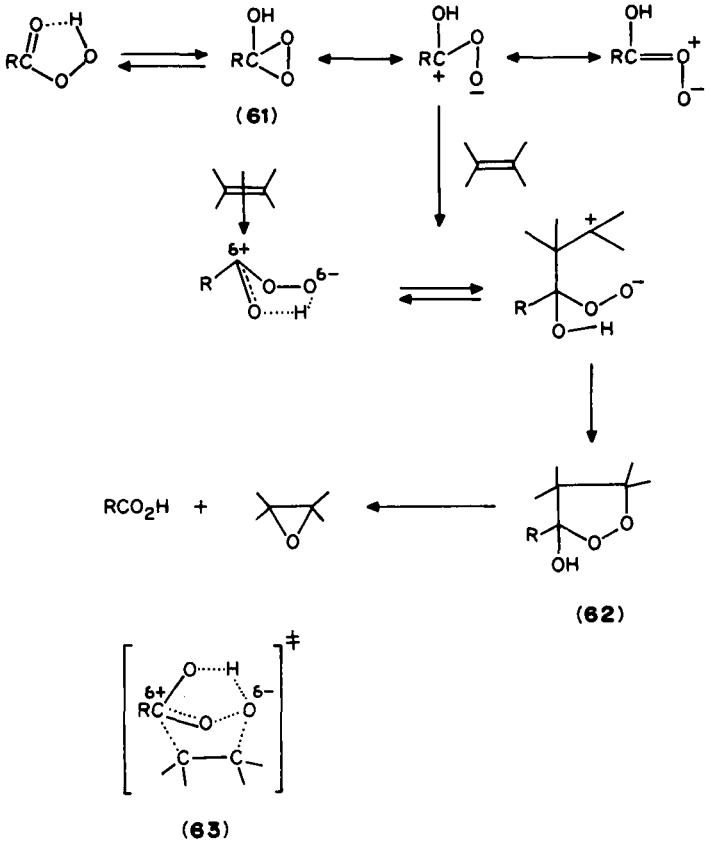
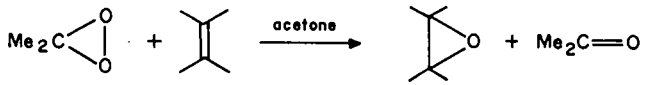


FIGURE 12. Proposed mechanism of the reaction of an alkene and peroxy acid involving the formation of a donor–acceptor complex in the rate-determining step

transition state (**63**) for the reaction[196]. As for the second objection, it has been suggested that reagents without a double bond in the sextet (such as **61**) should not necessarily show enhanced reactivity with bicyclic alkenes[197]. The mechanism in Figure 12 does account nicely for the fact that a clear distinction between the two carbon atoms of the alkene in the transition state has been observed by means of secondary kinetic deuterium isotope effect studies. The value $k_H/k_D = 0.82$ for the 2,2-d_2-4-phenylstyrene indicates that significant hybridization change occurs on C_2 while C_1 remains essentially unchanged[198].

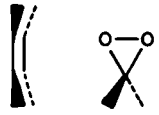
Dialkyldioxiranes, such as dimethyldioxirane (**64**), have been isolated and they do epoxidize alkenes as shown in equation 39[199]. The products are formed stereospecifically



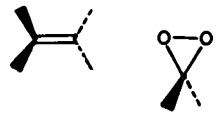
(39)

(**64**)

and the second-order rate constants, first order in each reagent, increase with increasing numbers of alkyl groups attached to the double bond. However, the mechanism proposed for this reaction is direct displacement by the alkene on the oxygen by either a planar (**65**) or spiro (**66**) transition state. The fact that *Z*-alkenes react faster than their *E*-isomers with dimethyldioxirane is taken as evidence for a spiro transition state.

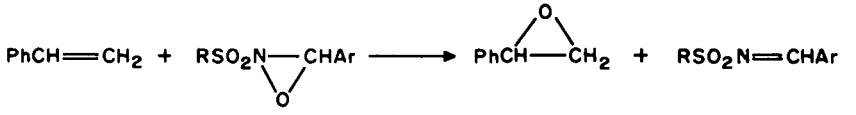


(**65**)



(**66**)

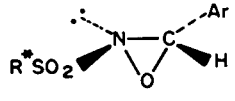
A planar transition state is favored for the reaction of oxaziridines (**67**) with alkenes to form epoxides (equation 40). This conclusion is based on the reaction of diastereomeric 2-



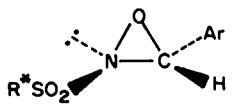
(**67**) (40)

sulfonyloxaziridines (−)-(*S*,*S*)-(**68**) and (+)-*R*,*R*-(**69**) with simple alkenes such as 2-methyl-2-pentene, *E*-stilbene, styrene and *E*-1-phenylpropene[200]. The configuration of the oxaziridine three-membered ring controls the stereochemistry of the product. The epoxides are formed with enantiomeric excesses of 12–40%. The results are explained in

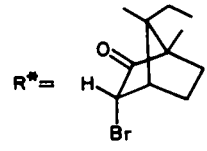
Ar = 2-chloro-5-nitrophenyl



(**68**)

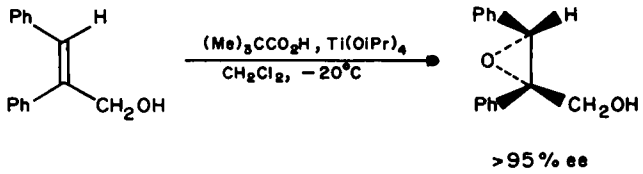


(**69**)



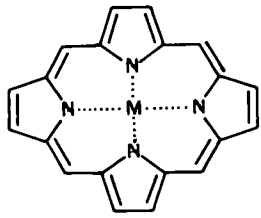
terms of a planar transition state in which steric effects between the substituents on the double bond and those on the oxaziridine ring are dominant. Such a planar transition state for this epoxidation reaction is supported by theoretical calculations[201].

A great deal of work has been reported on attempts to design reagents that will result in asymmetric epoxidations of alkenes and/or increase the *E*/*Z* selectivity of alkene epoxidations. Until recently, attempts at asymmetric epoxidations of alkenes were not very successful. Chiral peracids[202], chiral peroxymolybdenum V complexes[203], chiral hydroperoxides[204] and chiral oxaziridines[200] seldom produced enantiomeric excesses greater than 40%. One of the most successful is a simple method of metal catalyzed asymmetric epoxidation of allyl alcohols (equation 41)[189]. Enantiomeric excesses of 90–95% are frequently obtained[205].



(41)

Synthetic metalloporphyrins (**70**) act as catalysts for the epoxidation of alkenes (equation 42)[206]. To function as a catalyst, the metalloporphyrin must be converted into a metalloporphyrin-based oxidant. This is done by reaction with a number of oxygen donors including iodosylbenzene, hypochlorites, hydrogen peroxide, alkyl hydroperoxides or amine N-oxides[207–209]. Metalloporphyrins suffer from two limitations. Firstly they are difficult to synthesize and secondly they often have low turnover numbers. However, some have exhibited modest asymmetric induction in alkene epoxidation and *E*/*Z* alkene selectivity[210].



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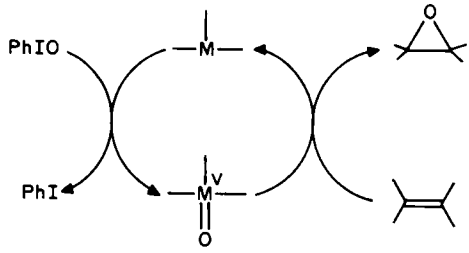


(42)

$M^V = O$ is a symbolic representation of the formal epoxidation state of the metalloporphyrin catalyst after oxidation by PhIO. No structural information is implied.

While synthetic metalloporphyrins are of limited practical application in alkene epoxidations, they are also catalysts for alkane hydroxylation. Consequently, they have received considerable attention as models of the enzyme cytochrome P-450. This subject has been recently reviewed[211,212].

To summarize, the epoxidation of alkenes by peroxy acids is a reaction that has been of great synthetic utility for over forty years. Yet the mechanism of this reaction is still the subject of debate. Attempts to synthesize reagents that will increase the *E/Z* alkene epoxidation selectivity and/or result in asymmetric epoxidation have already furnished valuable data about the structure of the rate-determining transition state. A great deal of work is being carried out on synthetic metalloporphyrins, not only as reagents for the epoxidation of alkenes but also as models to study the chemistry of cytochrome P-450. Further work along these lines can be anticipated.

B. Sulfur(II)-containing Compounds

Nucleophilic displacement reactions at S(II) are well known and have been reviewed[213]. A few of the many examples are given in Figure 13. The three mechanisms that have been proposed for this reaction are shown in Figure 14. The first (mechanism a) involves rate-determining formation of a sulfenium ion. The second (mechanism b) is a synchronous mechanism in which bond making between the nucleophile and S(II) occurs with S—X bond breaking. The third (mechanism c) is an addition–elimination mechanism. These three mechanisms differ only in the amounts of bond making and breaking at S(II) and therefore they are all variants of the same mechanism. Consequently, a Jencks–More O'Ferrall diagram can be drawn that incorporates these three mechanisms. This is illustrated in Figure 15 for the specific example of a symmetrical alkene acting as a nucleophile at S(II). At corner A of the diagram are located the starting compounds. The intermediate thiiranium ion is found at corner D. Breaking the S—X bond corresponds to movement along the edge AB to form the sulfenium ion, X^-, and alkene. Approaching the alkene and RSX without breaking the S—X bond corresponds to movement along the edge AE to form an episulfurane at corner E. Mechanism a corresponds to path a on the diagram while mechanisms b and c correspond to paths b and c.

The rate-determining transition state for the reaction of arenesulfenyl chlorides and

(a) $PhSSO_3^- + \overset{*}{S}O_3^{-2} \rightleftarrows PhS\overset{*}{S}O_3^- + SO_3^{-2}$

(b) $Ph_3CSOC_6H_4NO_2 + PhNH_2 \rightarrow Ph_3CSNHPh + 4\text{-}NO_2C_6H_4OH$

(c) $PhSSO_3^- + CN^- \rightarrow PhSCN + SO_3^{-2}$

FIGURE 13. Examples of nucleophilic displacement reactions at S(II)

(a) $RSX \rightarrow RS^+ + X^-$

$RS^+ + Nu^- \rightarrow RSNu$

(b) $RSX + Nu^- \rightarrow [Nu\cdots \overset{R}{\underset{|}{S}} \cdots X]^{\ddagger -} \rightarrow NuSR + X^-$

(c) $RSX + Nu^- \rightarrow R\underset{|}{\overset{X}{S}} - Nu \rightarrow RSNu + X^-$

FIGURE 14. Three possible mechanisms of a nucleophilic displacement reaction at S(II)

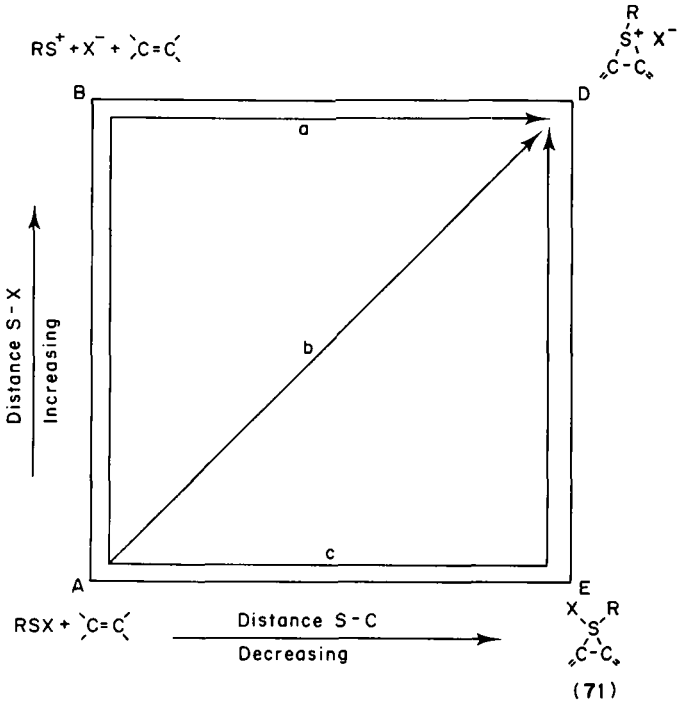


FIGURE 15. Reaction coordinate contour diagram for a nucleophilic displacement reaction at S(II) by a symmetrical alkene

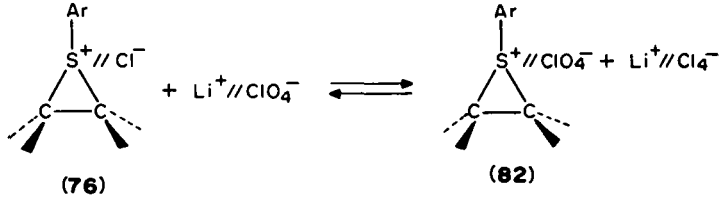
alkenes is located on this diagram. This was established by the use of heavy atom kinetic isotope effects. A value of $k^{12}/k^{14} = 1.022 \pm 0.044$ was obtained for the reaction of α C^{14} styrene and 2,4-dinitrobenzenesulfenyl chloride while a value of $k^{12}/k^{14} = 1.032 \pm 0.003$ was obtained for the corresponding reaction with β C^{14} styrene[214]. From these data, it is concluded that (i) bonding changes occur in both the α and β carbons in the rate-determining transition state and (ii) the structure of this transition state is bridged.

More information about the transition state can be obtained from structure–reactivity relationships. It has been found that substituents in the phenyl ring of arenesulfenyl chlorides have little effect on their rates of reaction with *E*- and *Z*-1-phenylpropene[215]. Small values (either positive or negative) of ρ or no correlation are characteristic of many reactions of arenesulfenyl chlorides[216]. The lack of a substituent effect is an indication that there is little change in the charge on sulfur during the reaction. A transition state in which C—S bond making and S—Cl bond breaking are about equal is in accord with this observation. A synchronous mechanism whose reaction path is along or near the diagonal AD is consistent with other work. There is still no experimental evidence for a mechanism involving dissociation of ArSCl to a sulfenium ion[217,218]. While many examples are known of sulfuranes containing a sulfur atom with both 10 valence shell electrons and four ligands bonded directly to it (10-S-4)[219], there is no evidence for a species such as **71**[219]. This suggests that corners B and E are relatively high in energy. Consequently, in the reaction of sulfenyl derivatives with alkenes the data are most satisfactorily explained by a rate-determining transition state that is located along or near the diagonal AD.

All data on the reaction of alkane- and arenesulfenyl chlorides and alkenes are consistent with the formation of a thiiranium ion as the first-formed intermediate. But thiiranium ions are also proposed as intermediates in the solvolysis and Markownikoff–*anti*-Markownikoff isomerization of *β*-chloroalkyl aryl sulfides and the alkylation of thiiranes. The general mechanism proposed several years ago that links these various reactions by means of a number of thiiranium ion–anion ion-pairs is given in Figure 16[1,220,221]. The upper sequence of reactions involving ion-pairs **72** and **73** and ion **74** is the general solvolysis scheme proposed by Winstein[222]. The lower sequence of ion-pairs is similar to that proposed by Poutsma and Kartch[223] and applied to the additions of arenesulfenyl chlorides to alkenes[224,225]. The ion-pairs **72** and **75** are contact ion-pairs and **73** and **76** are solvent-separated ion-pairs that differ only in the location of their counterion.

Before discussing recent work that has clarified certain aspects of this scheme, it is necessary to note that the absence of a standard definition of the term 'thiiranium ion' has led to some confusion about the mechanism of the reaction of arenesulfenyl chlorides to alkenes. Rather than using this term to describe only the dissociated ion **74**[224], it is preferable to restore the use of the term 'thiiranium ion' to designate a positively charged three-member sulfur-containing ring irrespective of the location of the counterion[226]. This is analogous to the conventional nomenclature originally introduced by Winstein, who referred to the carbocation portion of all ion-pairs as varieties of carbonium ions[227]. Therefore the cationic portion of ion-pairs **72**, **73**, **75** and **76** should all be called varieties of thiiranium ions. While there may be differences in the electronic structure of these ions, they all conform to this definition.

The evidence for the existence of ion-pairs **72**, **73** and **74** was given in the previous edition of this review[1]. The involvement of ion-pairs **75** and **76** in the addition of arenesulfenyl chlorides to alkenes has been inferred from the fact that addition of $LiClO_4$ in acetic acid causes a dramatic increase in solvent incorporated and rearranged products[224,225]. For example, the product composition of the addition of 4-chlorobenzenesulfenyl chloride to norbornene in acetic acid changes greatly on the addition of $LiClO_4$ as shown in Table 9[228]. Added $LiClO_4$ has no effect on the rate of the reaction[229]. This is consistent with involvement of $LiClO_4$ in the mechanism after the rate-determining first step. It is postulated that $LiClO_4$, which exists in acetic acid as a solvent separated ion-pair[230], exchanges partners with the solvent separated ion-pair **76** to form **82** (equation 43). This thiiranium ion-perchlorate ion ion-pair is responsible for the increase in rearranged and solvent incorporated products. It also forms, in certain cases, perchlorate products[231]. It appears from these data that, in acetic and nonpolar solvents, the mechanism of the reaction of arenesulfenyl halides and alkenes involves only the contact ion-pairs **72** and **75** after the rate-determining step.



(76) (82) (43)

Work continues on the reactions of stable thiiranium ions. They can be prepared and isolated by variations of the reactions in which thiiranium ions are proposed as intermediates. The difference is that to form a stable ion, the counterion must be a very poor nucleophile to ensure that it will not react with the thiiranium ion. The methods of preparation of these salts and their reactions have recently been reviewed[232].

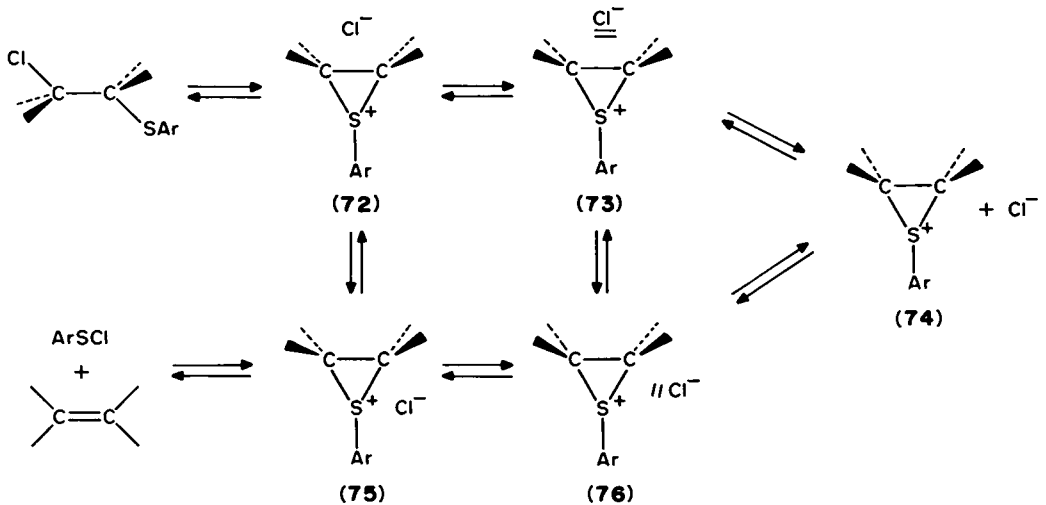
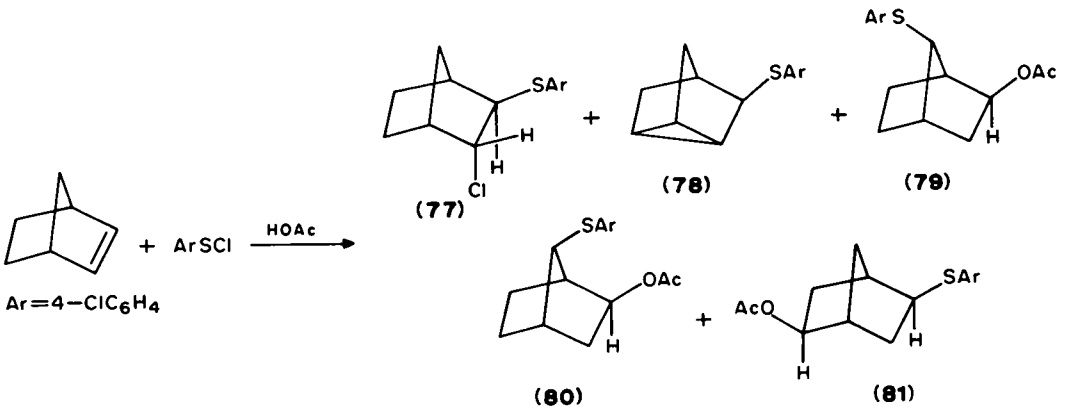
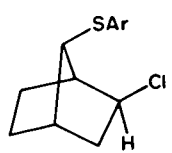


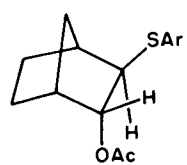
FIGURE 16. Common intermediates in the addition of arenesulfenyl chlorides to alkenes and reactions involving sulfur(II) as a neighboring group

TABLE 9. Effect of added $LiClO_4$ on the products of addition of 4-chlorobenzenesulfenyl chloride to norbornene in acetic acid



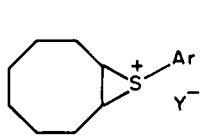
$[LiClO_4]$ $(10^{-4}$ M)	Products (%) 77	78	79	80	81	Others[a]
—	82	15	1.4	1.7	—	—
36	71	18	0.9	7.2	1.5	2.0
360	54	14	5.3	12.5	3.6	3.6
3600	27	10	18	27	5.2	4.7

[a] Mixture of 

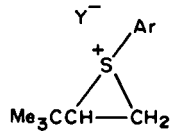
and 

Despite claims to the contrary[224,225], the products of the reaction of these stable thiiranium ions with nucleophiles are similar in many respects to those formed in the addition reactions of alkane- and arenesulfenyl chlorides to alkenes.

Both are capable of forming products that have undergone skeletal rearrangements. For example, the stable thiiranium ion **83** reacts with nucleophiles to form products of 1,5 hydride shift[233]. Rearranged products are formed after allowing the stable ion **84** to stand for 1.5 hours before it is reacted with chloride ion[234]. Rearranged solvent incorporated products are also formed in the addition of 2,4-dinitrobenzenesulfenyl chloride to norbornene in formic acid[235].



(83)

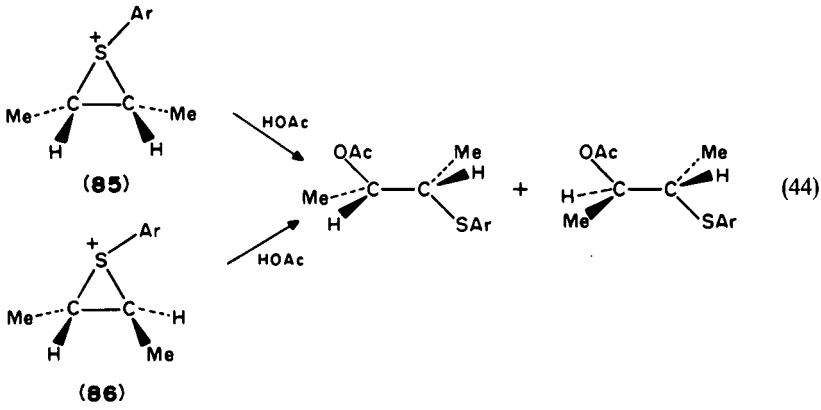


(84)

$Y^- = BF_4^-, SbF_6^-$

$Ar = 2,4-(NO_2)_2C_6H_4$

A second similarity is that nonstereospecific products are formed in both the reactions of stable thiiranium ions with nucleophiles and the addition of arenesulfenyl chlorides to alkenes. The reaction of the isomeric stable ions **85** and **86** with acetic acid at room temperature gives the same mixture of products (equation 44)[236]. Nonstereospecific products are also formed by the addition of 2,4-dinitrobenzenesulfenyl chloride to *E*- and *Z*-anethole[237] and 4-methoxy-β-deutereostyrene[238].



(85)

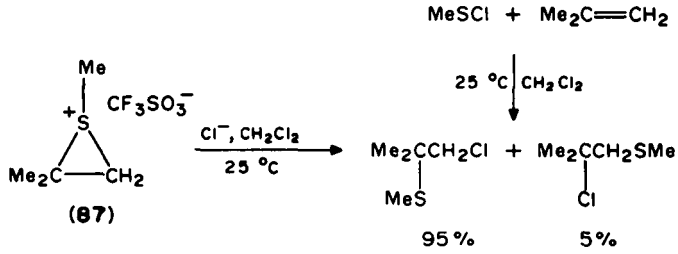
(86)

(44)

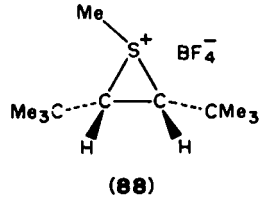
A third similarity is the regiochemistry of the products formed in the two reactions. The stable ion **87** forms the same proportion of regioisomers as formed by the addition of methanesulfenyl chlorides to methylpropene when the two reactions are carried out in the same solvents and at the same temperature (equation 45)[239].

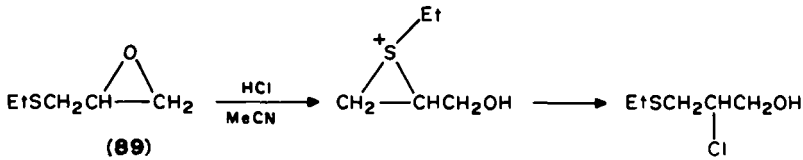
The fourth similarity is the ability of a thiiranium ion, either a stable one or one postulated as an intermediate, to react with chloride ion rather than the solvent. The absence of solvent incorporated products in the addition of arenesulfenyl chlorides to alkenes has been recognized[224,225] but the fact that stable thiiranium ions can also discriminate between chloride ion and solvent seems to have escaped notice. For example, lithium chloride reacts with the stable ion **88** in acetonitrile/CH_2Cl_2 to form products of attack by both chloride ion (80%) and acetonitrile (5%)[240]. Only products of the reaction of chloride ion are reported for the reaction of the stable ion formed by the reaction of the

epoxysulfide **89** with HCl in acetonitrile (equation 46)[241]. Thus stable ions, like their counterparts in the addition reaction, react preferentially with the stronger nucleophile.



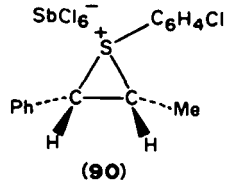
(45)





(46)

However, differences between the reactions of stable thiiranium ions and those proposed as intermediates have been cited[224,225]. It has been stressed that the reaction of 4-chlorobenzenesulfenyl chloride with *E*- and *Z*-2-butene gives different products by *anti*-stereospecific addition[242] while the reaction of the stable ions **85** and **86** with acetic acid gives the same product mixture. While this is a clear difference, it must be pointed out in all fairness that the two reactions occur under very different conditions. The addition reaction occurs instantly in 1,1,2,2-tetrachloroethane at 25 °C[243]. In contrast, the ions **85** and **86** were allowed to stand for 1.5 hours at 20 °C before reacting them with acetic acid. A thiiranium ion that is allowed to stand for long periods of time in the absence of a good nucleophile can undergo reactions that are not available to a thiiranium ion intermediate formed in the presence of a good nucleophile. This has been demonstrated by the reaction of the thiiranium ion **90**[244]. The time between the formation of **90** and its reaction with added chloride ion has a great effect on the stereochemistry of the product even at − 70 °C.



Thus allowing **90** to stand for a short time before reacting it with chloride ion results in products formed predominantly via a thiiranium ion. When the ion is allowed to stand for longer times before reacting it with chloride ion, products are formed via an open β-4-chlorophenylthioalkyl carbocation. It is clear from these data that meaningful conclusions about the similarities and/or differences of the reactions of stable thiiranium ions and thiiranium ion intermediates cannot be reached unless comparisons are made between reactions carried out under identical experimental conditions. Even then, the reactions of stable thiiranium ions may not be good models for the intermediates in the addition of arenesulfenyl chlorides to alkenes.

Synthetic uses have been made of the reaction of sulfenyl derivatives and alkenes to functionalize a double bond in a stereospecific manner. Examples are given in Figure 17. Particularly useful is the reaction of dimethyl(methylthio)sulfonium fluoroborate (**91**) with an alkene in CH_2Cl_2 followed by reaction with a variety of nucleophiles[245–247]. In this way a wide variety of β-substituted alkyl sulfides of known stereochemistry can be prepared.

The preparation of β-fluoro thioethers has also been accomplished by the reaction of benzenesulfenyl chlorides and alkenes in the presence of silver fluoride (equation 47)[248].

$$PhSCl + Me_3CCH{=}CH_2 \xrightarrow[MeCN]{AgF} Me_3CCHCH_2F \quad (47)$$
(SPh)

In summary, the reaction of sulfenyl derivatives with alkenes are examples of nucleophilic displacement reactions at sulfur(II). Their rate-determining step involves bond making between both carbons of the alkene and the sulfur atom with a concurrent bond breaking of the bond between sulfur and the leaving group to form a thiiranium ion. These ion, which can be prepared as stable entities, are also intermediates in reactions involving sulfur(II) as a neighboring group and the alkylation of thiiranes. These reactions

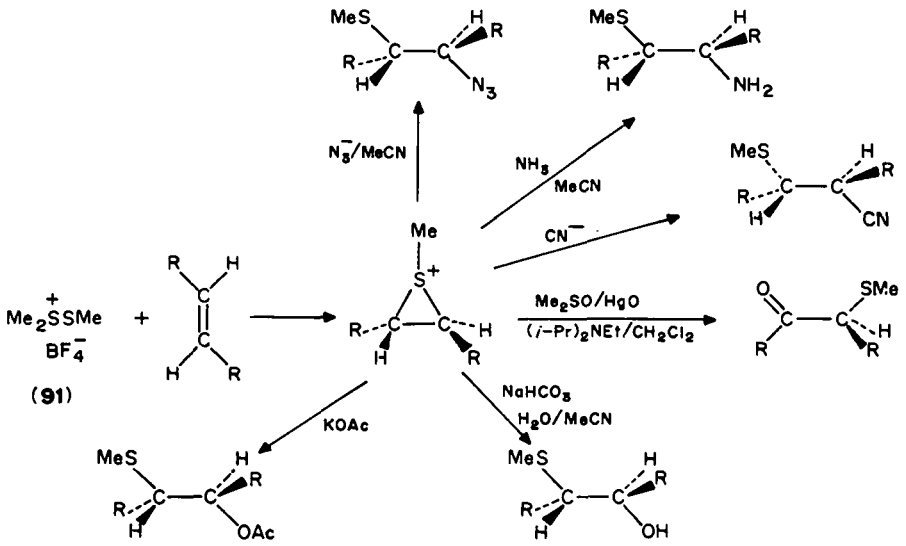


FIGURE 17. Functionalization of a double bond by the reaction of dimethyl(methylthio)sulfonium fluoroborate and an alkene followed by addition of a nucleophile

are linked together via a general mechanism involving a number of ion-pairs. Finally, comparisons between the reactions of stable thiiranium ions and those involved as intermediates should not be made unless the reactions being compared are carried out under identical experimental conditions.

C. Selenium(II)-containing Compounds

The reactions of areneselenenyl halides and alkenes have recently been reviewed[249]. Consequently, the emphasis in this section will be on a comparison of the reactions of alkenes and similar types of arenesulfenyl and selenenyl derivatives.

As expected, nucleophilic displacement at Se(II) is one of the fundamental reactions of Se(II)-containing compounds[250]. The rates of nucleophilic displacement at Se(II) compared to those at S(II) in similar type compounds depends on the nucleophile. For example, the ratio k_{Se}^{CN}/k_{S}^{CN} is 7×10^4 for the reactions of **92** and **93** with cyanide ion in a tris buffer in 90% acetonitrile/water at 25 °C[251].

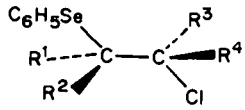
$PhSeSO_2Ph$ (92) $PhSSO_2Ph$ (93)

Such large differences are not observed in the reactions of arenesulfenyl and areneselenyl halides and alkenes as shown by the data in Table 10. One major difference is the effect of substituents on the rate of reaction. Substitution in the phenyl ring of ArSCl have little or no effect on the rate of reaction. In contrast, the data for the effect of substituents on the reaction of ArSeCl correlate with σ^+ to give ρ^+ values of -1.55 (*E*) and -1.39 (*Z*). These values can be compared with the effect of varying the substituent in the phenyl ring of *E*- and *Z*-1-phenylpropene on this same reaction. The values of ρ for the additions of PhSCl and PhSeCl to *E*- and *Z*-1-(4-X-phenyl)propene are very similar. For PhSeCl, ρ is -1.51 (*Z*) and -1.91 (*E*) in CH_2Cl_2 at 25 °C[253] while for ClC_6H_4SCl, ρ is -1.97 (*Z*) and -2.89 (*E*) in $C_2H_2Cl_4$ at 25 °C[1]. These data indicate that for the addition of ArSeCl, positive charge is developed at both the α carbon of the styrene and the Se atom in the transition state. In the transition state for the addition of ArSCl, positive charge is developed only at the α carbon. Little or no positive charge is developed at sulfur. This analysis suggests that in the reaction of ArSCl and 1-(4-X-phenyl)propenes, bond breaking and bond making to sulfur in the transition state are nearly equal. In the analogous reaction with ArSeCl, SeCl bond breaking is more advanced than CSe bond making in the rate-determining transition state.

TABLE 10. Second-order rate constants for addition of 4-substituted benzenesulfenyl and selenenyl chlorides to *E*- and *Z*-1-phenylpropene in CH_2Cl_2 at 25 °C

	Z-1-phenylpropene		*E*-1-phenylpropene	
X	ArSCl[252] k_2 ($M^{-1}s^{-1}$)	ArSeCl[253] k_2 ($M^{-1}s^{-1}$)	ArSCl[252] k_2 ($M^{-1}s^{-1}$)	ArSeCl[253] k_2 ($M^{-1}s^{-1}$)
CH_3O	8.75	48.2	27.6	98.2
CH_3	10.8	12.6	27.4	22.5
H	9.68	5.13	25.2	7.88
Cl	10.7	2.91	33.4	4.28
CF_3	11.2	0.583	26.1	0.733

TABLE 11. Second-order rate constants for the reaction of benzene-, 4-toluene- and 4-chlorobenzeneselenenyl chloride with 2-chloroalkyl phenyl selenides in CH_2Cl_2 at 25 °C



				$k_2(M^{-1}s^{-1})^a$ 4-XC_6H_4SeCl X =		
R^1	R^2	R^3	R^4	CH_3	H	Cl
H	H	H	H	0.092	0.089	0.061
H	H	H	CH_3	—	0.095	—
H	H	CH_3	CH_3	0.35	1.48	0.13
CH_3	H	CH_3	H	0.32	1.23	0.50
CH_3	H	H	CH_3	0.28	0.55	0.62
CH_3	H	CH_3	CH_3	—	0.21	—
CH_3	CH_3	CH_3	CH_3	—	1.92	—

[a]Rates reproducible to ± 5%.

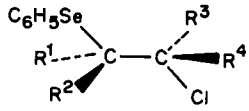
The selenium atom of 2-chloroalkyl phenyl selenides is also a nucleophile towards the selenium atom of areneselenenyl chlorides. The effect of substituents in the areneselenenyl chloride and changes in the structure of the selenide on the rate of the reaction, shown in equation 48, has been studied[254]. The data are given in Table 11. From these data, it is clear that there is no large substituent effect on the reaction. Varying the substituents in the 4-position of the phenyl ring of the areneselenenyl chloride has little effect on the rate. Replacing any two hydrogens on the methylene carbons of 2-chloroethyl phenyl sulfide by methyl groups does have a slight rate-enhancing effect. Replacing more than two hydrogens by methyl groups does not affect the rate appreciably. This lack of a large substituent effect leads to the conclusion that there is little or no charge on the selenium in the rate-determining transition state which suggests that bond making and bond breaking to it are nearly equivalent. This is in contrast to the reactions of alkenes with these same areneselenenyl chlorides, where it was concluded that the mechanism involves a transition state in which bond making to Se(II) lags behind SeCl bond breaking. Thus the structures of the rate-determining transition state for these two reactions differ. This is the first evidence that nucleophilic displacement reactions at Se(II) may indeed occur by a continuum of mechanisms[253].

$$PhSeCl + PhSeCH_2CH_2Cl \rightarrow PhSeSePh + ClCH_2CH_2Cl \quad (48)$$

The rates of reaction of 2-chloroalkyl phenyl selenides with benzeneselenenyl chloride have been compared to the corresponding reaction with alkenes. The data are given in Table 12[254]. The conclusion reached from these data is that a carbon–carbon double bond is a better nucleophile towards Se(II) than the selenium atom of 2-chloroalkyl phenyl selenide. In addition to mechanistic implications, this observation has practical significance for synthesis of organoselenium compounds. In general, the products of the reactions of arene- or alkaneselenenyl derivatives with a variety of compounds are themselves Se nucleophiles. As a result, these products can react with the starting selenenyl derivative causing an unwanted complication. This should be kept in mind when attempting the synthesis of selenium-containing compounds by nucleophilic displacement reactions at Se(II).

In summary, the mechanism of the reaction of areneselenenyl chlorides with alkenes is

TABLE 12. Comparison of rate constants for reaction of benzeneselenenyl chloride with alkenes and 2-chloroalkyl phenylselenides in CH_2Cl_2 at 25 °C[a]



R^1	R^2	R^3	R^4	$k_2(M^{-1}s^{-1})$	Alkene	$k_2(M^{-1}s^{-1})$
H	H	H	H	.089	$CH_2=CH_2$	498
H	H	H	CH_3	.095	$CH_3CH=CH_2$	4360
H	H	CH_3	CH_3	1.48	$(CH_3)_2C=CH_2$	3370
CH_3	H	CH_3	H	1.23	Z-$CH_3CH=CHCH_3$	1870
CH_3	H	H	CH_3	0.55	E-$CH_3CH=CHCH_3$	1040
CH_3	H	CH_3	CH_3	0.21	$(CH_3)_2C=CHCH_3$	1880
CH_3	CH_3	CH_3	CH_3	1.92	$(CH_3)_2C=C(CH_3)_2$	1230

[a]Rates reproducible to ± 5%.

similar in most respects to that of the reaction of the corresponding sulfenyl derivative. The major difference seems to be in the relative amounts of bond making and bond breaking in the two reactions.

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CHAPTER **12**

Mechanisms of base-catalyzed alkene-forming 1,2-eliminations

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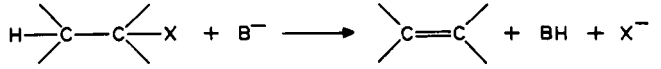
I. BACKGROUND

A. General Features

Elimination reactions encompass a very wide range of homogeneous and heterogeneous reactions, including 1,2, 1,3 and higher-order eliminations, dehalogenations, fragmentation and extrusion reactions, unimolecular reactions and pyrolyses, acid-catalyzed dehydrations, photochemical eliminations and reactions promoted by metals. Although the scope of this review is more limited than this, base-catalyzed 1,2-elimination reactions have been and continue to be the subject of extensive mechanistic study and have been important in helping develop a general understanding of organic reaction mechanisms and chemical reactivity[1-19]. These reactions are characterized by the loss of two atoms or groups from vicinal carbons with the formation of a carbon–carbon double bond (equation 1). With regard to numbering the chain, the carbons from which the leaving group and the electrophilic reagent depart (hydrogen in the cases covered here) are the α and β carbons, respectively.



(1)

The most common leaving groups in these reactions are halide ions, tosylate and trialkylammonium ions (the Hofmann elimination[20,21]), but a wide variety of other leaving groups are possible, and have been the subject of mechanistic study[22,23]. These include, but are not limited to, dialkylsulfonium ions, carboxylates, phenoxides, nitro, trialkylphosphonium ion, phenylseleno and sulfur leaving groups in various oxidation

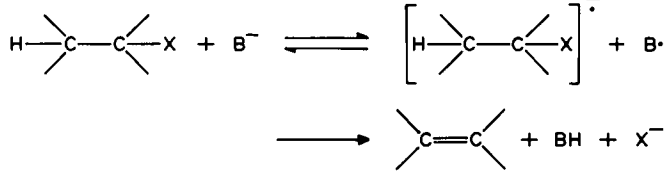
states[1-3,10]. Given sufficiently strong β-activation, very strongly basic conditions, or leaving groups constrained in strained ring systems, many 'poor leaving groups' will also leave, including oxyanions, amide and carbon leaving groups[22,23].

Substituents at the β carbon are common and may vary from simple alkyl groups to substituents that exert a strong polar or resonance effect on the developing charge in the transition state[24]. Some of the more extensively studied groups include aryl[25-28], carbonyl[29-32], sulfonyl[33,34], cyano[35-37], indenyl[38], fluorenyl[39,40] and nitro[41]. Substitution at the α position with alkyl or aryl groups is also common in these reactions, and both small and medium ring compounds[42-44] and bicyclic molecules[45-51] (especially the norbornyl system) have been intensely studied.

Alkoxide ions in their corresponding alcohols are still very popular as bases in mechanistic studies, but alkoxides in dipolar aprotic solvents such as DMSO[52], aprotic solvents such as ethers and benzene are also used. Eliminations catalyzed by hydroxide ion in mixtures of DMSO and water[53,54], by weak bases in dipolar aprotic solvents or thiolate ions in alcoholic solvents[55,56], by hydroxide ion in the presence of phase transfer catalysts[57], by metal amides[58], DBU[59], DBN[60], trityl potassium[61] and organolithiums further extend, but do not exhaust, the list of bases that have been successfully employed. Studies in aqueous solution are also important and, although rates of reaction are generally slower in aqueous solution than in less polar media (especially so for charged substrates), when possible, studies in aqueous solution complement studies in nonaqueous media. For example, studies of buffer catalysis can be more easily carried out and complications due to ion pairing and specific salt and medium effects are generally much less significant—although in less polar media the study of ion pairs as intermediates in these reactions are of substantial interest in their own right (see Section VII).

B. Summary of Recent Developments

The early mechanistic framework proposed by Hughes and Ingold[62-65] and coworkers 40 to 50 years ago of E1, E2 and E1cB mechanisms has stood the test of time although important refinements on it have been made. These include the discovery about 20–30 years ago of eliminations catalyzed by weak or soft bases, such as halide ions in dipolar aprotic solvents or thiolates in alcoholic solvents[66-68], and the recognition of the importance of ion pairs as intermediates in elimination reactions (the $E1cB_{ip}$ mechanism)[69]. A new mechanism of elimination has been proposed, although firm experimental evidence for it is apparently lacking. This mechanism, named (E2C-I), is expected to involve electron transfer from the base to the substrate with the resulting radical-anion intermediate breaking down to products (equation 2)[70,71].



(2)

Many other advances in our understanding of these reactions have evolved in recent years. The Valence-Bond Configuration Mixing Model has been applied to elimination reactions; this model generates the reaction coordinate by a linear combination of valence-bond configurations. The transition state is in turn described by a weighted average of valence-bond configurations based on the relative stabilities of these structures in the vicinity of the transition state. The model provides new and useful insights into elimination reactions and complements the More O'Ferrall–Jencks model of the E2 transition state.

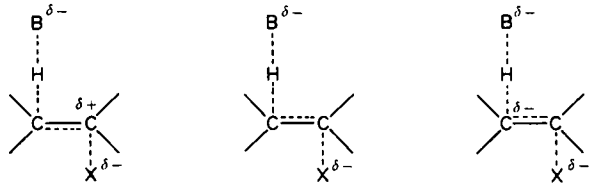
The latter model has evolved to the point that it is now used both to characterize transition state structures and reaction coordinates and to diagnose reaction mechanisms. These models taken together help to better understand the great variation in rates, mechanisms, orientation, geometrical isomerism and stereochemistry that are observed in these reactions. Isotope effect studies continue to be important in diagnosing mechanisms of eliminations and characterizing transition states in elimination reactions, as well as helping to better understand the role of tunneling and the nature of the proton transfer process. It has been suggested that the temperature dependence of kinetic isotope effects (or lack of it) can serve as a probe of linear or nonlinear proton transfer, but this view has not been generally accepted. Additional reports of the role of ion pairs as intermediates in elimination reactions have appeared, as have base-catalyzed eliminations in the gas phase. Anionic hyperconjugation has been suggested to be important in the proton transfer step of the E1cB mechanism; anionic hyperconjugation provides a unifying view of both E1cB and E2 reactions, but further blurs the distinction between these mechanisms. The role of strain in promoting elimination reactions has been investigated, and still more is now known about relative leaving group abilities, factors that influence reaction stereochemistry and the transition state of the controversial E2C mechanism. Finally, studies of the 'mechanistic borderline' between the E2 and E1cB mechanisms suggest that the concerted E2 mechanism may occur only when it is enforced, i.e., when the lifetime of the carbanion intermediate becomes vanishingly small.

I have tried in this chapter to emphasize important recent developments, and to describe some of the novel chemistry that has been observed in recent years. Some background information is however included in order to try to bring perspective to recent results, or to try and provide a balanced treatment of the subject.

C. Overview of the General Mechanisms[72]

1. The E2 and E1cB mechanisms

Of the second-order base-catalyzed reactions, the most general and well characterized ones are the stepwise E1cB mechanisms via free or ion-paired carbanion intermediates, and the concerted E2 mechanism in which both proton transfer and bond cleavage occur in a single step. Note though that in the latter, the degree of proton transfer and bond cleavage can vary over a wide spectrum of possible transition state structures, ranging from carbonium ion-like to carbanion-like (**1**–**3**). These two general mechanisms are depicted in Scheme 1.



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

The E1cB mechanism is further classified according to which step is rate-limiting. For example, the $E1cB_{irr}$ mechanism describes rate-limiting formation of the carbanion—proton transfer (k_1) is rate-limiting. The initially formed ion-pair, encounter-complex or ion-molecule complex will then rapidly break down to give products either directly (k_2) or

TABLE 1. IUPAC[a] and common symbolism for naming mechanisms of elimination reactions

IUPAC symbolism	Common symbolism
$A_{xh}D_HD_N$	E2
$A_{xh}D_H^{\ddagger} + D_N$[b]	$E1cB_{irr}$[c]
$A_{xh}D_H + D_N^{\ddagger}$	$E1cB_{rev}$[d]
$A_{xh}D_H^{\ddagger}D_N^{\ddagger}$[e]	$E1cB_{ip}$[f]
$A_{xh}D_h$ + intra-$D_HD_NA_n$[g]	ylide or α'-β eliminations[h]
$D_N^{\ddagger}A_{xh}D_H^{\ddagger}$	$E2_{ip}$[i]
$A_{xh}D_H + D_NA_hD_{xh}^{\ddagger}$	E2cB[j]
cyclo-$D_HD_NA_n$[k]	E_i (unimolecular)
$D_N^{\ddagger} + A_{xh}D_H$	E1
$A_{xh}D_HD_N(A_N)$[l]	E2C
$1/A_{xh}D_H + 1/D_N + \frac{1}{2}/A_HD_H$[m]	apparent 1,2-elimination, via a carbene intermediate (1,1-elimination followed by a 1,2-hydrogen shift)

[a]Commission on Physical-Organic Chemistry IUPAC to be published in *Pure and Applied Chemistry*; see reference 72.

[b]The ‡ symbol is optional; it may be added to indicate which step in a multi-step mechanism is rate-limiting.

[c]See Section, I.C.1.

[d]Or the $E1_{anion}$ mechanism if the carbanion intermediate is formed irreversibly; see Sections I.C.1–3.

[e]The * symbol means that the intermediate is short-lived, so that it is not in equilibrium with its surroundings.

[f]See Section I.C.1.

[g]The *intra* term means that the process is intramolecular.

[h]See Section I.C.3.

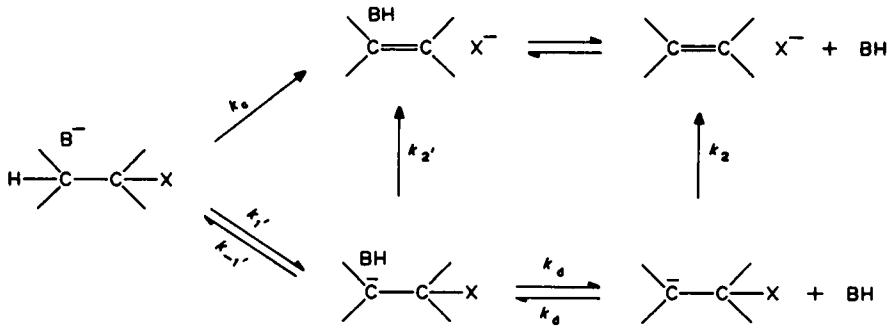
[i]See Section I.C.2 and equation 3.

[j]See Section I.C.3 and References 83 and 168; this mechanism corresponds to rate-limiting breakdown of a carbanion intermediate in which leaving-group expulsion is general acid catalyzed.

[k]The *cyclo* term means that this is a pericyclic reaction.

[l]The E2C mechanism (see Section I.C.2) is like the E2 mechanism but includes an interaction between the base catalyst and the α carbon that has been described as either weakly covalent or electrostatic—this weak interaction (it does not lead to bond formation) has been denoted above by '(A_N)'.

[m]The numbering here is used to indicate that a rearrangement has taken place—the base catalyst abstracts a proton from the 1 position, followed by loss of a nucleofuge, also from the 1 position, and a shift of a hydrogen from the 1 to the 2 position.



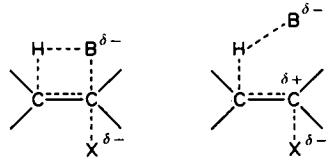
SCHEME 1

via the free carbanion (k_2). On the other hand, the E1cB$_{rev}$ mechanism involves rate-limiting expulsion of the leaving group from a free carbanion (k_2) that is in equilibrium with starting materials.

Other variations on the E1cB mechanistic theme include the E1cB$_{ip}$ mechanism in which $k_{2'}$ is rate-limiting. This mechanism will be observed if the ion-pair intermediate breaks down to products faster than the conjugate acid of the base diffuses away (k_{-d}), and the first step is at equilibrium. The E1cB$_{ip}$ mechanism is a preassociation mechanism in the reverse direction[73]. That is, because of the short lifetime of this intermediate, in the reverse direction, the alkene, nucleophile and catalyst will preassociate before nucleophilic addition to the alkene takes place. A possible variation on the E1cB$_{ip}$ mechanism is one in which the ion pair and the free carbanion are at equilibrium (hence hydrogen–deuterium exchange into the substrate would be observed, as would a rate depression by added BH), but $k_{2'}$ is rate-limiting, so that the equilibrium with the free carbanion would be a nonproductive side-reaction that does not result in product formation (alkene formation via both the ion-paired and free-carbanion intermediates is also theoretically possible). If breakdown of the ion pair to give products ($k_{2'}$) is comparable to the rate at which it is protonated to regenerate starting materials (there is significant internal return), then the reaction will show many of the same characteristics of the concerted E2 mechanism (see Section VII.A)[74], because both proton transfer and bond cleavage would be partly rate-limiting and exchange with solvent would normally be precluded due to the short lifetime of the ion pair.

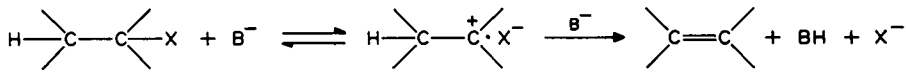
2. *The E2C mechanism*

The E2C mechanism is, like the E2 mechanism, concerted, but differs from the E2 mechanism in that the base may interact with both the β proton and the α carbon in the transition state (**4**)[75]. Based on results that will be summarized in Sections V.A, V.C and V.D, the E2C mechanism was proposed by Parker and Winstein[75,76] to account for weak or 'soft' base-catalyzed elimination reactions of secondary and tertiary halides and tosylates, normally carried out in dipolar aprotic solvents such as acetone or DMSO with tetrabutylammonium halide salts, or in alcoholic solvents using thiolate ions, although a number of other bases were suggested to follow it as well. In 1976 McLennan reviewed these reactions and concluded that the interaction between the base and the α carbon is electrostatic rather than covalent (**5**)[9].



(4) **(5)**

Bunnett has argued, however, that these reactions can be accommodated within the normal spectrum of E2 transition states[77–81], and Bordwell has proposed an E2$_{ip}$ mechanism in certain cases (see Section V)[14]. The E2$_{ip}$ mechanism involves rate-limiting deprotonation by the base of a carbonium ion intermediate or ion pair (equation 3).

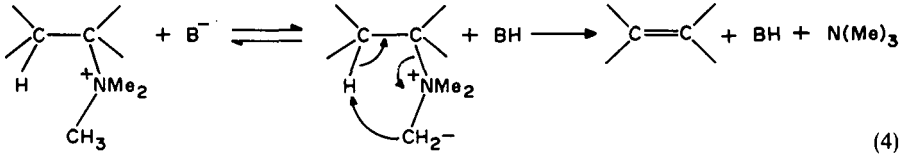


(3)

3. *Other base-catalyzed mechanisms*

For relatively acidic substrates, or for moderately acidic substrates in strongly basic media, a carbanion may form rapidly and irreversibly in the first step of the reaction followed by slow rate-limiting expulsion of the leaving group (the $E1_{anion}$ mechanism)[82]. Although the $E1_{anion}$ mechanism will normally follow a first-order rate law, for relatively poor leaving groups such as alkoxides and hydroxide, for example, general acid catalysis of leaving group expulsion will result in overall second-order kinetics[83].

Other base-catalyzed 1,2-elimination reactions include reactions that proceed via an α'-β elimination (the ylide mechanism)[84]. This mechanism involves initial abstraction of the α' proton (the ′ refers to that part of the molecule into which elimination does not occur), followed by abstraction of the β proton via a cyclic transition state; it is characterized by the incorporation of a β-deuterium label into the leaving group and is expected to follow *syn* stereochemistry (equation 4). For trialkylammonium ion derivatives the ylid mechanism is generally important only under very strongly basic conditions, for example, using metal alkyls or aryls[85], but sulfonium ions appear to be more prone to react via this mechanism[86]. Under very strongly basic conditions apparent 1,2-eliminations can also occur via a carbene that is formed as a result of α elimination followed by hydrogen migration. This mechanism is characterized by the formation of products that are indicative of carbene intermediates: cyclopropane formation, etc.[10].



(4)

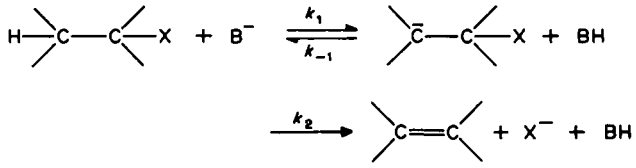
II. THE $E1cB_{irr}$ MECHANISM

A classic problem in diagnosing mechanisms of elimination reactions has been distinguishing between the $E1cB_{irr}$ mechanism and the E2 mechanism in which the transition state is carbanion-like (E1cB-like). An E2 mechanism will show many of the same characteristics of an $E1cB_{irr}$ mechanism, including second-order kinetics, primary kinetic isotope effects and general base catalysis, the absence of substrate epimerization and hydrogen–deuterium or tritium exchange, and, if the E2 transition state is carbanion-like, small leaving group effects. E2 reactions can also proceed with a mixture of *syn* and *anti* stereochemistry (see Section III.G). Of the methods employed to distinguish between these mechanisms, those that have proven most useful include measuring isotope effects at the β and α positions (see Section III.A), studies of general base catalysis coupled with element or other leaving-group effects based on structure–reactivity parameters (see Sections II.B.1 and II.B.2), changes in rate-limiting step that are brought about by increasing concentrations of buffer acids (see Section II.A), structure–reactivity interaction coefficients (see Section III.D), comparing rates of reaction with estimated rates of substrate deprotonation (see Section II.C) and, in some cases, stereochemistry (i.e., stereospecificity in systems where an intermediate carbanion is not expected to maintain the substrate's configuration). Below, some of these methods are reviewed in the light of recent work that either complements or, in some cases, challenges these approaches.

A. Changes in Rate-limiting Step

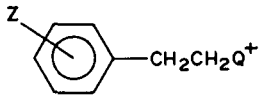
A change in rate-limiting step provides strong evidence for a mechanism involving a free-carbanion intermediate [as does hydrogen–deuterium or tritium exchange, or substrate

epimerization that occurs faster than elimination (*pace* Breslow[87]) although, under some conditions, exchange with either retention or inversion of configuration is possible at the ion pair, or asymmetrically solvated carbanion stage[88]]. A change in rate-limiting step with increasing concentrations of buffer will normally manifest itself as a change in slope of a plot of k_{obsd} against buffer base concentration. If it can be demonstrated that this change in slope cannot be accounted for by specific salt or medium effects[89], then this behavior reflects a change in rate-limiting step, from rate-limiting formation of the carbanion at low buffer concentrations, to rate-limiting expulsion of the leaving group at high buffer concentrations.



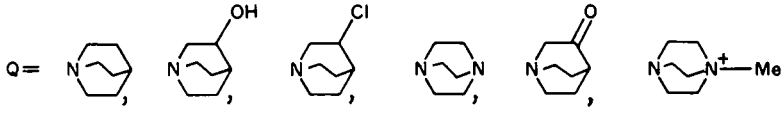
(5)

A new criterion for diagnosing the $E1cB_{irr}$ mechanism has been proposed that is related to a change in rate-limiting step[90,91]. In this method, the effect of increasing buffer concentration on the initial rates of elimination is determined in both deuterated and unlabeled solvents. Under conditions in which k_{-1} and k_2 are comparable (equation 5), the reaction rate will increase more rapidly as a function of increasing buffer base concentration in the deuterated than in the unlabeled solvent. This is so because the rate at which the carbanion intermediate is protonated will be slowed in the deuterated solvent, because of a primary hydrogen isotope effect that is associated with the proton transfer reaction. The change in rate-limiting step will therefore occur at lower buffer base concentrations for the reaction in the unlabeled solvent. For example, for the acetohydroxamic buffer catalyzed reaction of 2-(*p*-nitrophenyl)ethylquinuclidinium ion (**6**, Z = *p*-NO_2) in water and deuterium oxide, at *ca* 0.5 M buffer concentration, an enlarged inverse *solvent* isotope effect of 7.7 was observed as a result of this effect[90,91]. A related effect has previously been demonstrated by comparing the initial rates of elimination of unlabeled substrates in deuterated solvent and deuterated substrates in unlabeled solvent for elimination reactions of fluorenyl derivatives[32,92,93]. For example, biphasic kinetics (as a result of H–D exchange into the substrate) and enlarged primary kinetic hydrogen isotope effects on the initial rates of reaction were observed[32,92].



(**6**)

Z= *p*-NO_2, *p*-CN, *p*-Ac, *m*-NO_2, *m*-CF_3, *m*-Cl, H



An E1cB mechanism for the reaction of **6**, Z = *p*-NO_2, was independently established by showing that hydrogen–deuterium exchange into the substrate occurred faster than elimination. Furthermore, plots of k_{obsd} against acetohydroxamic acid buffer con-

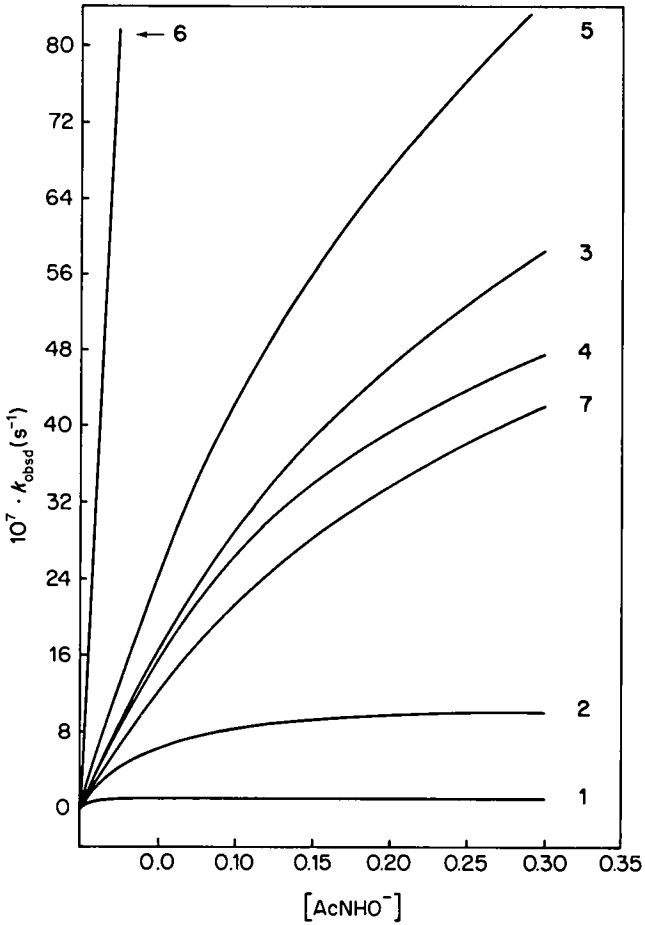


FIGURE 1. Dependence of k_{obsd} on the concentration of acetohydroxamate concentration for the reactions of compound **6**, Z = *p*-NO_2, where **1** = quinuclidine, **2** = 3-quinuclidinol, **3** = Dabco, **4** = 3-chloroquinuclidine, **5** = 3-quinuclidinone and **6** = *N*-methylDabco, and **7** = trimethylammonium in water at 25 °C and I = 1.0 (KCl). The lines were calculated from equation 6 and the experimentally determined rate constants. Reprinted with permission from J. R. Keeffe and W. P. Jencks, *J. Am. Chem. Soc.*, **105**, 265 (1983). Copyright (1983) American Chemical Society

centrations yielded curves that varied with changes in the leaving group (Figure 1)[90,91]. The curvature in Figure 1 becomes less pronounced with decreasing pK_a of the leaving group, in which the lines were calculated using experimentally derived rate constants from equation 6[90,91] (the experimental points were omitted for simplicity, but fit the curves well), in which k_{OH^-}, k_B, k_W and k_{BH} are the second-order rate constants for hydroxide and buffer-catalyzed reactions, and for protonation of the intermediate carbanion by H_2O and

buffer acids, respectively. The decreasing curvature with decreasing pK_a of the leaving group is consistent with an E1cB mechanism in which the $k_2/k_{-1}[BH]$ partitioning ratio

$$k_{obsd} = k_2(k_1^{OH}[OH^-] + k_1^{B}[B])/(k_{-1}^{H_2O} + k_{-1}^{BH}[BH] + k_2) \quad (6)$$

increases with decreasing pK_a of the leaving group: k_2 is more sensitive to changes in the leaving group than is k_{-1}. If specific salt or medium effects were contributing in a significant way to this curvature, then systematic changes in the curvature as a function of leaving group pK_a would not be expected. Furthermore, the curvature becomes less pronounced when increasing amounts of ethanol[92] or DMSO[94] are mixed with water, consistent with an increase in the $k_2/k_{-1}[BH]$ partitioning ratio with decreasing solvent polarity, as expected for a reaction of this charge type. These results, however, contrast with reports that support an E2 mechanism for the hydroxide ion catalyzed reaction of N-(2-(*p*-nitrophenyl)ethyl)trimethylammonium ion in water at 100 °C: α-carbon isotope effects of 1.078[95] or 1.026[96] and a leaving-group nitrogen isotope effect of 1.024[97]. The results discussed above, however, establish an E1cB mechanism. They suggest that the isotope effects are in error, although it is also possible[91,92] that there is a change from an E1cB mechanism at 25 °C (where the kinetics were measured) to an E2 mechanism at 100 °C (where the isotope effects were measured), or an important contribution of anionic hyperconjugation in the proton transfer step of the $E1cB_{irr}$ mechanism[98,99] (see Section II.B.1).

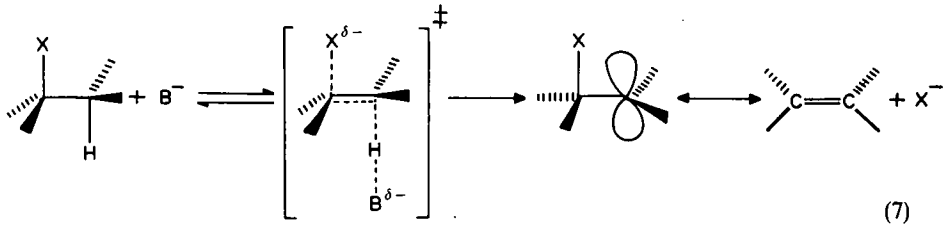
B. Leaving-group Effects

1. The element effect

Because the bond to the leaving group is envisioned to be intact in the rate-limiting step of the $E1cB_{irr}$ mechanism, it has been assumed that the leaving group will exert only a polar or inductive effect on the rate of the elimination reaction. This effect would result from an electrostatic interaction between the leaving group and a partially charged β carbon, and suggests little or no change in the force constant of the α-carbon leaving-group bond[32,100]. This view has led to the use of halogens as leaving groups for diagnosing mechanisms in these and related reactions—Bunnett's element effect criterion of mechanism[101]. The element effect criterion of mechanism presumes that because the bond to the leaving group is intact in the rate-limiting step of the $E1cB_{irr}$ mechanism, the order of halogen mobilities ought to be F > Cl > Br > I, an order that reflects the expected polar effects of the halogens. On the other hand, for mechanisms which involve partial cleavage of the leaving-group bond (such as the $E1cB_{ip}$, E2, $E2_{ip}$ and $E1cB_{rev}$ mechanisms), the order of halogen mobilities ought to reflect the relative strengths of the carbon–halogen bonds that are cleaved: I > Br > Cl > F. Although the element effect has proven a useful qualitative measure of leaving-group bond cleavage in these and other reactions, Stirling has pointed out that in protic solvents, differences in solvation energies and electron affinities tend to promote cleavage of the *stronger* carbon–halogen bond[102]. For example, based on a difference in solvation energies, electron affinities and heterolytic bond dissociation energies of Cl and Br in water, a bell-shaped dependence of the k_{Br}/k_{Cl} ratio on the extent of carbon–halogen bond cleavage has been predicted[102,103].

Another and more fundamental challenge to the element effect criterion of mechanism is based on the work of Hoffman, Radom, Pople, Schleyer, Hehre and Salem[104] on hyperconjugative stabilization of anions. Based on this work, Ahlberg and Thibblin have suggested that hyperconjugation in the proton transfer step of the $E1cB_{irr}$ mechanism may be important (equation 7)[98,99]. If this is true, and if hyperconjugation increases in the order F < Cl < Br < I[105], then an $E1cB_{irr}$ mechanism will show many of the same characteristics of and E2 mechanism: significant leaving group and leaving-group isotope

effects, partial C—C double bond formation, and, perhaps, stereospecific *anti* elimination because a coplanar arrangement of the β proton and leaving group would be the favored conformation[104,106]. This is an extremely interesting view that provides a unifying interaction for both E1cB and E2 reactions. *Ab initio* calculations on β-substituted ethyl anions show that anionic hyperconjugation results in large barriers to rotation around the carbon–carbon bond, and hyperconjugation in β-substituted ethyl anions has also been invoked to explain the retention of configuration that is commonly observed in a variety of nucleophilic vinylic substitution, epoxidation and cyclopropanation reactions of substrates with weakly to moderately activating substituents and good leaving groups[107–109]. It is difficult, however, to experimentally distinguish between the E2 mechanism and the E1cB mechanism in which there is interaction between the β-electron pair and C—X orbitals. Some evidence that bears on this problem involves elimination reactions of substrates in which the fluoride derivative is more reactive than the chloride, the order expected for the classical $E1cB_{irr}$ mechanism. For example, the fluoride derivative is more reactive than the chloride in the ethoxide ion catalyzed elimination reaction of 2-(phenylsulphonyl)ethyl halides in ethanol ($k_F/k_{Cl} = 1.1$)[35], (7), the potassium *t*-butoxide catalyzed elimination reactions in *t*-butanol of *trans*-1,2-dihalogenoacenaphthenes ($k_F/k_{Cl} = 6.2$ and 10 in the presence and absence of 18-crown-6-ether, respectively)[110], (8), *trans*-2,3-dihalo-2,3-dihydrobenzofurans ($k_F/k_{Cl} = 2.3$ and 4.2 in the presence and absence of crown ether, respectively)[111–113], (9), 1,2-dihalo-1,2-diphenylethanes ($k_F/k_{Cl} = 10$ for *syn* elimination in the absence of crown ether)[114], (10), and the methoxide ion catalyzed elimination in methanol of 9-halogeno-9,9′-bifluorenyls ($k_F/k_{Cl} = 1.6$)[115], (11).



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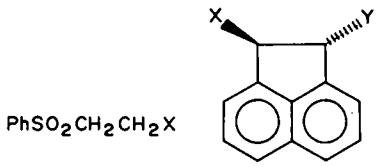
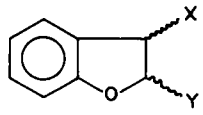


(7)

(8)

X = Cl, F

Y = Cl, F



(9)

X = Cl, F

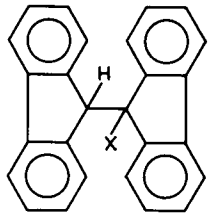
Y = Cl, F

PhCH(X)CH(Y)Ph

(10)

X = Cl, F

Y = Cl, F



(11)

PhCH(Y)CH(X)COOMe

(12)

X = Cl, Br

Y = F, Cl

A k_{Cl}/k_{Br} ratio slightly greater than 1 (1.2) has also been reported for the methoxide ion catalyzed elimination reactions of methyl 2,3-dihalogeno-3-phenylpropanoates in methanol solution[116,117], (**12**).

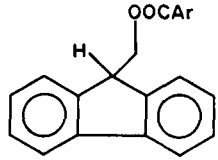
If hyperconjugation is important in these cases, the fluoride derivative would be expected to be less reactive than the chloride, and the chloride, perhaps, more reactive than the bromide. Relative to β-substituted ethyl anions in the gas phase, the strongly electron-withdrawing groups at the β carbon of these substrates and solvation of the negative charge will reduce the need for hyperconjugation[108,118]. If hyperconjugation is important in elimination reactions in solution, substrates that react by the $E1cB_{irr}$ mechanism (independently established) should be found which show heavy-atom leaving-group, or secondary α-carbon or hydrogen isotope effects.

2. *Structure–reactivity parameters*

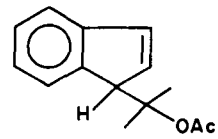
A probe of leaving-group effects that may provide a more direct measure of the extent of leaving-group bond cleavage than the element effect is based on a family of leaving groups of constant steric effects and leaving atom. Such studies result in structure–reactivity parameters such as β_{lg} or ρ_{lg}, obtained from the slopes of plots of log k against the pK_a of the leaving group or against the appropriate Hammett substituent constant where substitution is made in the leaving group[119]. Qualitatively, small sensitivities to changes in the pK_a of the leaving group are expected for the $E1cB_{irr}$ mechanism, whereas larger effects are expected if the leaving-group bond is significantly cleaved in the transition state[32,100]. As noted above, the classical problem with this criterion of mechanism is that small leaving-group effects are consistent with both the $E1cB_{irr}$ mechanism and the concerted E2 mechanism in which the α-carbon leaving-group bond is only slightly cleaved. For example, for the elimination reactions in 28 mole% DMSO in water of *N*-(2-arylethyl)quinuclidinium ions, (**6**), β_{lg} changes from $-0.15: -0.17: -0.16: -0.20: -0.22: -0.23: -0.26$ as the β-phenyl substituent is varied from *p*-NO_2CH_4:*p*-NCC_6H_4:*p*-$CH_3COC_6H_4$:*m*-$NO_2C_6H_4$:*m*-$CF_3C_6H_4$:*m*-ClC_6H_4:Ph, respectively[94]. The small value of β_{lg} for the *p*-NO_2 derivative is consistent with the $E1cB_{irr}$ mechanism (see Section II.A) in which the better leaving groups stabilize the carbanionic-like transition state of a rate-limiting proton transfer. However, the small values of β_{lg} that are associated with the reactions of the *p*-NCC_6H_4, *p*-$CH_3COC_6H_4$ and *m*-$NO_2C_6H_4$ derivatives refer instead to an E2 mechanism (see Section III.D.1.b) in which only a slight amount of leaving-group bond cleavage has taken place. Because the transition state of the E2 reactions of these latter substrates change as a function of base strength, the values of β_{lg} for the reactions catalyzed by weaker bases now show a break from a small value characteristic of the $E1cB_{irr}$ mechanism for the *p*-NO_2 derivative, to larger values characteristic of the E2 mechanism for the other derivatives. For example, β_{lg} changes from $-0.13: -0.34: -0.29: -0.35: -0.36$ for the $(CF_3)_2CHO^-$ catalyzed reactions (apparent $pK_a = 11.2$ in this solvent) and from $-0.13: -0.25: -0.21: -0.29: -0.27$: for the $CF_3CH_2O^-$ catalyzed reactions (apparent $pK_a = 14.5$) of the *p*-$NO_2C_6H_4$:*p*-NCC_6H_4:*p*-$CH_3COC_6H_4$:*m*-$CF_3C_6H_4$:*m*-ClC_6H_4 derivatives, respectively.

Larger values of β_{lg} and ρ_{lg} than expected for an $E1cB_{irr}$ mechanism have recently been reported for the probable $E1cB_{irr}$ reactions of **13** (β_{lg} and $\rho_{lg} = -0.27$ and -0.42, respectively, whereas, for example, $\beta_{lg} = -0.18$ for the $E1cB_{irr}$ reactions of 4-benzoyloxybutan-2-ones[100]). This apparent enhancement in β_{lg} and ρ_{lg} has been tentatively attributed to a hydrophobic interaction between the aryl and fluorenyl groups that brings the benzoate groups closer to the site of charge at the β carbon. An $E1cB_{irr}$ mechanism was assigned to **13**[115,120] based on primary kinetic isotope effects in the range of 6–8, general base catalysis, the near identity of the rate constants for elimination with the expected rate constants for simple proton transfer, evidence that the related

9-halogeno-9,9′-bifluorenyls[115], (11), with the better halide leaving groups, react at the E2–E1cB borderline, and absolute rates of reaction that are comparable to those of the similarly activated and related 1-(1-acetoxy-1-methylethyl)indene, (14), for which an E1cB mechanism has been unambiguously established (see Section VII.B)[99,121].



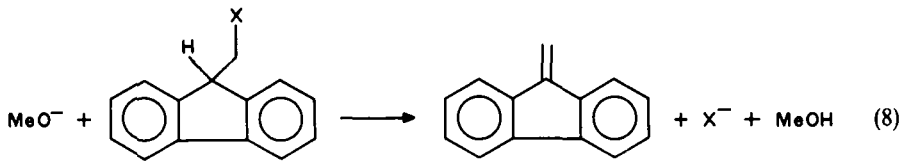
(13)



(14)

C. Rates of Proton Transfer

Another criterion of mechanism that has been applied in diagnosing the $E1cB_{irr}$ mechanism is one in which the rate of elimination is compared to the expected rate of proton transfer. The rates of proton transfer are normally estimated for substrates that undergo elimination reactions by extrapolating a Taft plot constructed from rates of proton transfer (measured by hydrogen or tritium exchange reactions) of substrates that do not undergo elimination, normally owing to the presence of poor leaving groups. Large primary hydrogen–deuterium or hydrogen–tritium isotope effects help show that the rate of the exchange reaction measures the rate of proton transfer and not diffusion. For reactions that show large accelerations compared to the expected rate of proton transfer, the acceleration is taken as evidence for a new and more favorable reaction pathway: the E2 mechanism. A classic example of this approach that has recently been reinterpreted is the study of the methoxide ion catalyzed elimination reactions of 9-(X-methyl)fluorenes in methanol solution (equation 8)[122]. A plot of log k against σ^* gives a line of slope 2.25 (this has been revised upward[120] to 2.6 by including new data for a series of carboxylate leaving groups) including points for X = H, Me, Ph and OH, substrates for which rates of hydrogen–tritium exchange are available and which are corrected for a primary hydrogen–tritium isotope effect estimated to be around 15.4 (evidence for the lack of significant amounts of internal return in the exchange reaction). Rates of elimination for X = PhS, Cl, Br, I, TsO, AcO and SO_2Ph when plotted on this graph show positive deviations from the Taft correlation. A large deviation of over two orders of magnitude is observed for the iodide, and deviations of approximately 100-fold are observed for the Br, Cl, TsO and $PhSO_2$ derivatives, consistent with a change to a new reaction mechanism (E2). Smaller deviations are observed for the PhS and AcO derivatives (less than 10-fold), so that the mechanistic assignments in these cases are less certain. Thibblin[123] has recently reinterpreted the Taft plot in this and other systems in terms of the model, described above, in which hyperconjugation between the carbanionic center and the carbon-leaving group bond is important (see Section II.B.1) in the transition state of the $E1cB_{irr}$



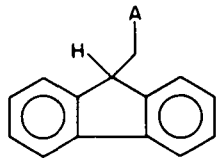
(8)

mechanism. These data have been fitted to equation 9.

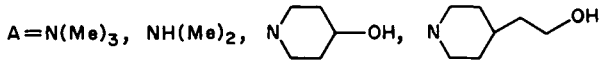
$$\log k = \sigma^*\rho^* + lL \tag{9}$$

In Thibblin's equation, the $\rho^*\sigma^*$ term measures the polar effect of the leaving group, whereas the lL term is a measure of a system's sensitivity to changes in leaving-group ability. A set of L parameters were obtained by using the 9-(X-methyl)fluorene system as a standard (l set = 1.0). It is further assumed that for $E1cB_{irr}$ reactions, the Taft term will be a constant for changes in the leaving group, resulting in linear plots of equation 9, but for E2 reactions this term will vary in accord with the variable transition state theory, resulting instead in curved plots. Data from five systems are treated in this way. For fluorenyl and 1-(2-X-2-propyl)indenyl derivatives, for which linear plots are observed, the data are unfortunately limited—three data points—so it is difficult to draw any conclusions in these cases. For the three other systems a linear plot is obtained for the 2-(phenylsulfonyl)ethyl system[35] with $l = 0.88$ and $\rho^* = 4.89$, but curved plots are evident for both the 2-phenylethyl[25,28] and 1-hexyl systems[124]. The observed curvature in these latter two systems is in line with the E2 mechanism that has been proposed for these compounds based on other evidence. The linear plot observed for the 2-(phenylsulfonyl)ethyl system has been interpreted to indicate an $E1cB_{irr}$ mechanism for the Cl, Br, I, TsO and OAc derivatives. An $E1cB_{irr}$ mechanism has been independently assigned to the F, TsO and AcO derivatives because these compounds adhere to a Taft plot based on rates of proton transfer, and because β-primary hydrogen isotope effects are the same for these leaving groups ($k_H/k_D = 2.0$)[35]. However, an E2 mechanism was assigned to Br and I (Cl was considered to be a borderline case) based on positive deviations from the Taft plot of 1.0 and 1.9 log units, respectively, and because of changes in k_H/k_D ($k_H/k_D = 3.6$, 5.0 and 5.6 for the Cl, Br and I, respectively[34a,35]). These systematic changes in k_H/k_D are consistent with a variable E2 transition state structure, but are more difficult to reconcile with an $E1cB_{irr}$ mechanism[35]. Furthermore, it is also possible that the linear plots observed in these cases are a result of using a similarly strongly activated system (the fluorenyl system) to define the L parameter[115]: systems which react near the E2–E1cB borderline so that ρ^* may show only a small or neglible dependence on changes in leaving-group ability.

For the reaction of *N*,*N*-dimethyl(fluoren-9-yl-methyl)amine, (**15**), A = $N(Me)_2$, an E1cB mechanism has been established based on curvilinear plots of k_{obsd} against hydroxide ion and tertiary amine buffer concentrations (and the pH dependencies of the buffer plots) that are consistent with a change in rate-limiting step (from deprotonation of the substrate to loss of the leaving group with increasing hydroxide ion concentration, and deprotonation of the zwitterionic N-protonated fluoren-9-yl carbanion intermediate to loss of the leaving group with increasing buffer concentration), and by concurrent exchange and elimination for the methoxide ion catalyzed reaction in MeOD[92,125].



(**15**)



Similar changes in rate-limiting step with increasing hydroxide ion and tertiary-amine buffer concentrations have also been reported for derivatives of **15**, in which A = 4-hydroxypiperidine and *N*-(2-hydroxyethyl)piperazine[125]. It is surprising, therefore, that for the methoxide ion catalyzed elimination reaction in methanol of **15**, in which A = $\overset{+}{N}(Me)_3$, the rate constant shows a 10^5 positive deviation from the Taft plot that is based on the ionization rate constants of 9-substituted-fluorenes using $\sigma^1 = 0.92$ for the trimethylammonium group[126]. The buffer curvature observed with the other amine leaving groups is much weaker for the trimethylammonium ion derivative, but is apparent in aqueous dimethylaminoacetonitrile buffer solutions. The relatively weak curvature observed in this buffer plot does not appear to be a result of specific salt or medium effects, because when the reaction is run in D_2O the plot is now linear; this result is consistent with a slower protonation of the zwitterionic N-protonated fluoren-9-yl carbanion intermediate, because of a primary kinetic isotope effect, so that there is no change in rate-limiting step in D_2O. The weaker buffer catalysis for the trimethylammonium ion than the other amine derivatives is consistent with steric acceleration of leaving-group departure for the larger trimethylammonium ion leaving group. On balance, therefore, an E1cB mechanism is likely for the trimethylammonium ion derivative; the large deviation that is observed from the Taft plot for this substrate has therefore been attributed to the sensitivity of σ^* values for charged groups to the solvent's polarity[127], and to relief of ground state strain (the ionization of 9-substituted fluorenes is known to be accelerated by γ-substituents[128]).

III. THE E2 MECHANISM

A. Hydrogen Isotope Effects

Measurements of primary kinetic isotope effects are commonly made in E2 and $E1cB_{irr}$ reactions as a measure of the extent of proton transfer in the transition state as described originally by Westheimer and by Melander[129,130]. However, primary kinetic isotope effects can be affected by a number of other factors too, such as proton tunneling[131], nonlinear proton transfer[132,133], internal return[88,134] and the coupling of heavy-atom motion with proton transfer along the reaction coordinate[135,136].

The existence of proton tunneling is normally indicated by the observation of abnormally large isotope effects[137,138] or abnormal Arrhenius parameters—$A_H/A_D < 0.7$[131,139,140] and $E_D - E_H > 1.2$ kcal mol^{-1}, although abnormally large hydrogen isotope effects in elimination reactions have also been shown to result when there is competition between two processes having different isotope effects but which follow a common rate-limiting step (see Section VII.B), and elimination reactions that show significant amounts of internal return can also give rise to anomalous Arrhenius parameters of this magnitude[141]. Based on the criterion of anomalous Arrhenius parameters, it appears as if tunneling commonly contributes to primary kinetic isotope effects in elimination reactions that lie within the normal range ($k_H/k_D = 2$–8 at 25 °C). For example, for the elimination reactions of (2-(*p*-trifluoromethylphenyl)ethyl)-trimethylammonium ion in DMSO–water mixtures, $E_H - E_D = 1.78$–2.2 and $A_H/A_D = 0.42$–0.21[142]. Similarly, abnormal Arrhenius parameters indicative of tunneling have also been observed for the ethoxide ion catalyzed elimination reactions 1-bromo-2-phenylpropane[143], 2-phenylethyl bromide, tosylate, and dimethylsulfonium ion in ethanol[144], *N,N*-dimethyl-*N'*-propyl-*N''*-isobutyl ammonium ion, in 50% 1-butanol-DMSO[145], and 3-methyl-2-butyl-*p*-nitrobenzenesulfonate[146].

Tunneling appears to also affect the magnitude of secondary β-hydrogen isotope effects. For example, for the hydroxide ion catalyzed elimination reactions of (2-phenylethyl)trimethylammonium ion in DMSO–water mixtures, and for the *t*-butoxide ion catalyzed reactions of 2-phenylethyl tosylate and bromide in *t*-butanol, $(k_H^H/k_H^D)_\beta$[147]

= 1.17[148–150], 1.16 and 1.18 (all at 50 °C), respectively, isotope effects that are larger than the calculated equilibrium isotope effect[151,152] of 1.13 at 50 °C for the conversion of a C—CHD—C to a C=CD—C group. Based on these results model calculations were undertaken; models in which there is coupling between the stretching and bending motions of the transferred and nontransferred hydrogens give results that are in good agreement with experiment, and consistent with a contribution from tunneling to the secondary β-hydrogen isotope effects[153]. The calculations also suggest new criteria for tunneling: anomalous Arrhenius preexponential factors, as well as a breakdown in the expected relationship between hydrogen, deuterium and tritium secondary β-isotope effects.

Although nonlinear proton transfers can result in reduced isotope effects in elimination reactions[132,133] the proton transfer component in elimination reactions has in general been assumed linear, unless there are mechanistic reasons to assume otherwise (for example, E2C eliminations or eliminations via cyclic transition states—such as the Cope elimination). In a number of cases, however, Kwart has challenged this assumption using the temperature dependency of primary kinetic isotope effects as a probe to diagnose instances of linear or nonlinear proton transfer[154]. A nonlinear proton transfer is suggested to show isotope effects that are temperature independent and associated with extraordinarily large values of A_H/A_D, much greater than $2^{1/2}$. However, this approach has been criticized by a number of workers on both theoretical and experimental grounds[155–158]. For example, model calculations at the MNDO level of the temperature dependence of the primary hydrogen isotope effect for the transition state in the intramolecular proton transfer reaction of monoprotonated methylenediamine ion suggest that the Arrhenius preexponential factor A_H/A_D is normal[155], and for the [1, 5] sigmatropic shift of *cis*-1, 3-pentadiene, model calculations suggest that temperature-dependent isotope effects are expected, even for transition states involving bent proton transfer[159]. Furthermore, for the hydrogenolysis of octyllithium, which is believed to proceed via a four-centered transition state, a small but real temperature dependence is observed[156,160]. Bogus temperature-independent isotope effects can also arise as a result of side-reactions[159,161], and temperature-independent isotope effects have been observed for elimination reactions in the phenylethyl series (e.g., $PhCHBrCF_2Br$, *p*-$ClPhCHClCF_2Cl$, $PhCHClCF_2Cl$ and $PhCHBrCH_2Br$), but have been interpreted instead in terms of internal return that varies as a function of temperature[141].

The contribution of heavy-atom motion to motion along the reaction coordinate is also predicted to give rise to depressed hydrogen isotope effects[135,136,163]. For example, model calculations show that such coupling increases the isotopic sensitivity of the real vibrations of the transition state. The hydroxide ion catalyzed reaction of (2-phenylethyl)trimethylammonium ion in DMSO–water mixtures has been cited as an example of this effect[163]. In this reaction k_H/k_D goes through a maximum with increasing concentration of DMSO in DMSO–water mixtures: k_H/k_D changes from 3.22:3.88:4.75:5.21:4.94:4.84:4.44:3.83 as the DMSO concentration is increased from 17.1:22.8:30.0:34.3:40.6:44.5:50.6:57.1 mole%, respectively. The k_H/k_D maximum that is observed at 30–40% DMSO corresponds to an isotope effect of only 3.08 after the observed isotope effect has been corrected for tunneling, a value that is much smaller than expected if the isotope effect maximum corresponds to a proton that is symmetrically placed in the transition state (for proton transfer between a carbon acid and an oxygen base a symmetrical transition state corresponds to 0.38 proton transfer to the base). However, there is a discrepancy between these results and the large Bronsted β values > 0.9 that have been observed for the reactions of the closely related (2-arylethyl)quinuclidinium ions, (**6**), in 28 mole% DMSO in water[94] (28 mole% DMSO is close to the solvent composition where the isotope effect maximum is observed). These large β values are consistent with a solvent isotope effect of 1.79 (k_{OD}/k_{OH}) at 80 °C that has

been reported for the reaction of (2-phenylethyl)trimethylammonium ion in water and deuterium oxide[164]. This solvent isotope effect corresponds to a β_I[165] value of 0.92 based on a limiting value of 1.88 for this isotope effect at 80 °C[164]. Although Bronsted's β and β_I values show good agreement for this reaction, values of β_I do not generally correlate with Bronsted β values[92]. The solvent isotope effect, k_{OD}/k_{OH}, may not be a reliable measure of the extent of proton transfer in the transition state, because changes in bonding of both the lyoxide's covalently bound hydrogen and the hydrogens of the solvent that make up the lyoxide ion's immediate solvation shell are believed to contribute to the isotope effect[93,166]. Nevertheless, the large Bronsted β values observed in the reactions of the 2-(arylethyl)ammonium ions show that significant primary kinetic isotope effects can be observed for transition states in which the proton is extensively transferred to the base, and are consistent with the conclusion that proton tunneling contributes to the primary kinetic isotope effect in these systems[94]. It has been suggested that this discrepancy between the primary kinetic isotope effect maximum and the large β values may be related to the fact that electron delocalization from carbon can lag behind other processes such as proton transfer[167]. If this is the case here, the increased electron density on carbon that would result may be large enough to balance that on the base, so that the symmetric vibration of the 3-centered transition state is insensitive to isotopic substitution[94].

Bronsted β values for general base catalysis complement measurements of primary kinetic isotopes effects—they can help resolve the ambiguity associated with small isotope effects—is the transition state early or late with respect to proton transfer? They are also useful in distinguishing among possible elimination mechanisms; for example, when a reaction can be studied in buffered solution, general base catalysis with Bronsted β values ranging from 0 to 1 will be observed for the $E1cB_{irr}$, E2 and $E1cB_{ip}$ mechanisms[168], with β near one for the $E1cB_{ip}$ mechanism, because the proton is fully transferred to the base in the transition state of this mechanism. General base catalysis with β near one is experimentally distinguishable from specific base catalysis[169], because hydroxide and alkoxide ions show negative deviations from the Bronsted equation for proton transfers from carbon acids (the hydroxide ion anomaly[170]) that has been attributed to a solvation effect[171].

Although α-secondary hydrogen isotope effects, $(k_H/k_D)_\alpha$, greater than 1 are expected in elimination reactions as the hybridization at the α-carbon changes[172] from sp^3 to sp^2, surprisingly, *inverse* α-secondary hydrogen isotope effects have recently been reported for the *t*-butoxide ion catalyzed elimination reactions of 2-phenylethyl chloride and fluoride at low base concentration (less than 0.2 M, $(k_H/k_D)_\alpha = 0.8–0.86$)[173]; at higher base concentrations and in the presence of 18-crown-6 ether, normal $(k_H/k_D)_\alpha$ values were observed [$(k_H/k_D)_\alpha = 1–1.17$]. It was argued that at low base concentrations a significant contribution from *syn* elimination could give rise to an increase in the α-C—H out-of-plane bending frequencies in the transition state and result in inverse isotope effects, whereas at higher base concentrations this transition state was considered less important because of the possible formation of ion aggregates. But the *syn*-elimination reaction of 2-(Phenylethyl)dimethylamine oxide in 90 mole% DMSO–water solution shows a large normal α-secondary hydrogen isotope effect[175].

B. E1-like E2 Transition States

In general, base-catalyzed E2 reactions show positive Hammett ρ values, as do the corresponding $E1cB_{irr}$ reactions, consistent with a build-up of negative charge on the β carbon in the transition states of these reactions. There are relatively few documented examples of E2 mechanisms that proceed via the E1 end of the E2 transition state spectrum—E2C reactions show only a small sensitivity to changes in substituents in an α-phenyl group (see Section V.A). Reactions of 1-arylethyl derivatives may however provide

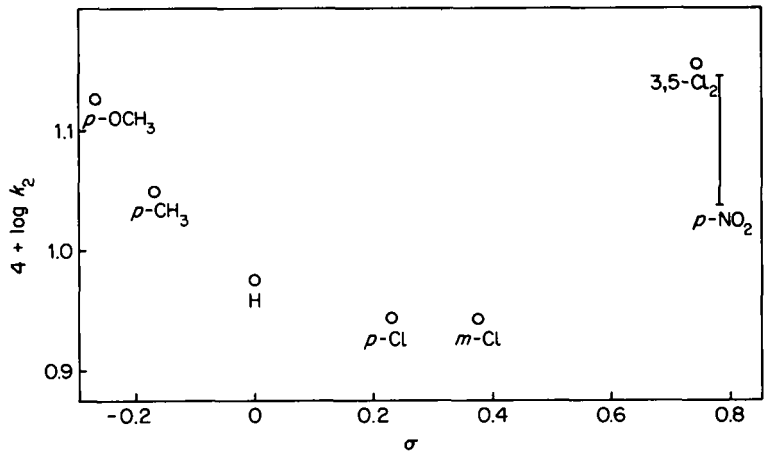
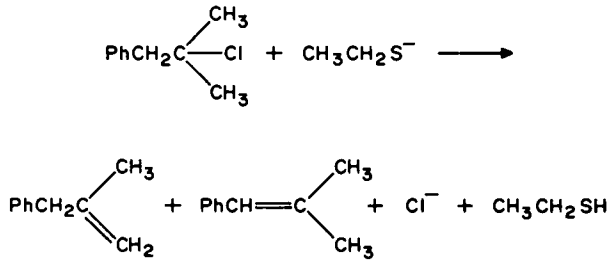


FIGURE 2. Log of the rate constant for the ethanethiolate ion catalyzed elimination of $ArCH_2CMe_2Cl$ to form $ArCH{=}CMe_2$ against Hammett's σ values in methanol at 75.8 °C. Reprinted with permission from J. F. Bunnett, S. Sridharan and W. P. Cavin, *J. Org. Chem.*, **44**, 1463 (1979). Copyright (1979) American Chemical Society

examples of this class of E2 reactions. For example, consider the ethanethiolate ion catalyzed elimination reaction of benzyldimethylcarbinyl chlorides in methanol to give the conjugated alkene (equation 10)[175]. Although the spread in rate constants is very small, Figure 2 shows a curved Hammett plot for the reaction with the left and right parts of the plot corresponding to ρ values of *ca* -0.4 and 0.5, respectively. This result is consistent with an E2 mechanism in which there is a shift from transition states with net positive charge to ones with net negative charge as the β-phenyl substituent becomes more electron-withdrawing. The elimination reaction of this same substrate to give the unconjugated alkene also shows a negative ρ value ($\rho = -0.7$) and evidence of curvature based on a positive deviation from the Hammett correlation of the 3,5-dichloro derivative. For these ethanethiolate ion catalyzed reactions an E2C reaction was not considered tenable[175]. For the reaction catalyzed by the stronger base, methoxide ion, ρ is only -0.07, consistent with a movement towards a transition state with less carbonium ion character for the reaction catalyzed by the stronger base[81,176]. For the reaction that leads to the conjugated alkene, $\rho = 1.2$, despite the fact that the α carbon is a tertiary center, chloride a good leaving group and methanol a relatively polar solvent[81,176]. Apparently for this reaction, the combination of the relatively strong methoxide ion base and a β-phenyl group shifts the transition state to the carbanion-like end of the transition state spectrum. A curved Hammett plot with a distinct minimum has also been observed for the elimination reactions of 1-arylethyl chloride (but not the bromides), catalyzed by *t*-butoxide ion in *t*-butyl alcohol to which 10% DMSO had been added[177], and the acetate-catalyzed elimination reaction of *threo*-3-chloro-3-(4-substituted-phenyl)-1,2-diphenylpropan-1-one in a 4:1 DMSO–MeOH solvent[178]. For these compounds the left arms of the curves correspond to negative ρ values [based on the *p*-methyl and *p*-MeO compound for the 1-arylethyl derivatives, and the *p*-MeO compound for the 3-(4-substituted-phenyl)-1,2-diphenylpropan-1-ones], that is consistent with an E1-like E2 transition state for these substrates.



(10)

C. The More O'Ferrall–Jencks Model of the E2 Transition State

There exist a variety of models that attempt to understand the relationship between transition state structure and changes in the energies of reactants and intermediates[179]. Of these models, the model first popularized by More O'Ferrall[180] for elimination reactions and later extended by Jencks[181,182] has proved especially fruitful in aiding thinking about structure–reactivity effects in elimination reactions. The Valence Bond Configuration Mixing Model has also recently been applied to elimination reactions and lends important new insights into these reactions[70,71]. Aspects of these models with regard to E2 and $E1cB_{irr}$ elimination reactions are discussed below.

The main features of the More O'Ferrall–Jencks model as applied to elimination reactions are to characterize the E2 transition state, including the orientation of the reaction coordinate and the surface curvatures in the vicinity of the saddle point, and to diagnose reaction mechanisms[180–182]. A More O'Ferrall–Jencks diagram is shown in Figure 3 for elimination reactions of substituted 2-phenylethyl derivatives, substrates for which the most extensive amount of structure–reactivity data are available. In Figure 3, the substrate and base are located in the upper right-hand corner and the products in the lower left-hand corner of the diagram. Proton transfer occurs along the x axis and bond cleavage along the y axis. A diagonal axis may be drawn between the carbonium ion and carbanion intermediates in the lower right- and upper left-hand corners of the diagram, respectively, that provides a measure of transition state charge and changes in that charge[182]. Jencks has utilized experimentally derived structure–reactivity parameters such as Bronsted's β values (or solvent isotope effects), β_{lg}, ρ_{lg} (or heavy-atom leaving-group isotope effects) and Hammett ρ values to define the scales of the x, y and diagonal axes, respectively. The y and diagonal axes may then be scaled to values of 0 to 1 and + 1 to − 1, respectively, if the structure–reactivity parameters or isotope effects that are derived from kinetic measurements can be normalized relative to their equilibrium values[182]. If these equilibrium values are known or can be estimated, the 'effective charges'[179,183] on the atoms in the transition state are then derived and may be used to map out the position of the transition state on the diagram. This approach has recently been used to map out the transition state structure for the elimination reactions of *N*-(2-arylethyl)quinuclidinium ions in 60 volume% DMSO in water, in which the transition state lies near the well for the carbanion in the upper left-hand corner of the More O'Ferrall–Jencks diagram[94]: extensive proton transfer to the base catalyst and little C—N bond cleavage; this transition state structure, based on values of β, β_{lg} and Hammett ρ values, is consistent with transition state structures derived from measurements of isotope effects[1,26,184–186] and transition state structures derived by kinetic isotope effect calculations utilizing the extensive set of kinetic isotope effects that have been reported for the closely related (2-arylethyl)trimethylammonium ion system[187].

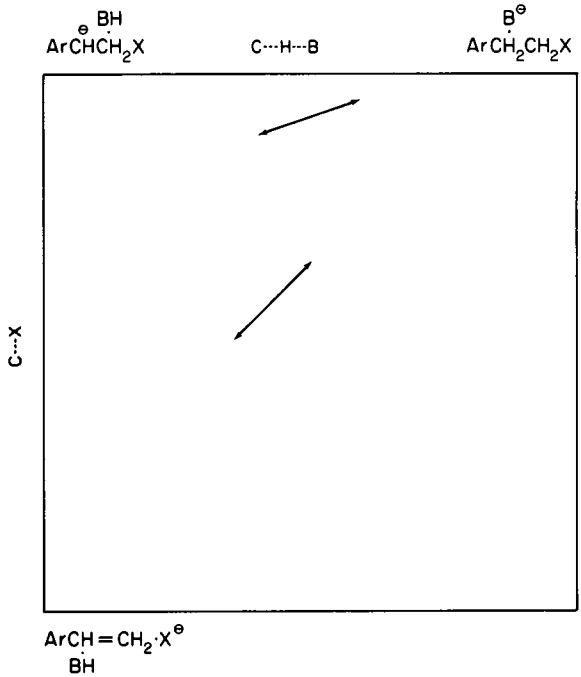


FIGURE 3. More O'Ferrall–Jencks energy diagram for the base-catalyzed β-elimination reactions of 2-arylethyl derivatives. The x and y axes correspond to proton transfer and carbon leaving-group bond cleavage, respectively. Two reaction coordinates are drawn: one that has a major component of proton transfer that lies near the E1cB borderline, the other representing a more 'central' E2 transition state that has significant components of both proton transfer and carbon leaving-group bond cleavage

According to the model as described by Jencks and Jencks,[182] changes in reactant structure will result in changes in the structure of the E2 transition state that depend on both the orientation of the reaction coordinate (near the saddle point) as well as the surface's curvature parallel and perpendicular to it, assuming linear perturbations across the surface[182]. Thornton showed that as a consequence of the curvatures around the saddle point, transition states will have a tendency to become more like a destabilized reactant, product or intermediate when the perturbation acts along the reaction coordinate and across an energy maximum (a Hammond or parallel effect), but will have the opposite tendency, that is, to become less like a destabilized reactant, product or intermediate when this perturbation acts perpendicular to the reaction coordinate and across an energy minimum (an *anti* Hammond or perpendicular effect)[188]. Cram, Greene and Depuy in 1956 recognized the variableness of the E2 transition state[189], as did Bunnett who emphasized that substituent changes that favor a particular part of the overall reaction (such as proton transfer or bond cleavage) tend to promote a greater contribution from that process in the transition state[16,19]. It is important to note that this model assumes that the structural perturbations are small and linear across the reaction

surface. Therefore, large perturbations, such as changes in solvent, and large structural changes, such as those that introduce variable steric effects, can result in large movements of the transition state that may not be accommodated by the theory. Furthermore, transition state imbalance or imperfect synchronization[167,190] changes in mechanism, solvation effects, and changes in rate-limiting step in a multistep reaction can also give rise to changes in structure–reactivity parameters and isotope effects[179]. Although steric effects are not explicitly treated in this model, the nonadditivity of β-methyl groups on the rates of the elimination reactions of $RN(Me)_3^+$ derivatives, in which R is changed from Et to Pr to *i*-Bu, provides an interesting example of how steric effects can give rise to changes in transition state structure that have interesting consequences for elimination reactions[145]. For example, although a 9.2-fold decrease in rate is observed for a change in R from Et to Pr, addition of a second methyl group to the β position results in only a 1.55-fold rate reduction (a change in R from Pr to *i*-Bu; rates are statistically corrected). This result is consistent with a shift to a more olefin-like transition state for the derivative with R = *i*-Bu that results in order to relieve the nonbonded interactions between the $N(Me)_3$ group and the two β-methyl groups that would occur in the transition state of an E1cB-like E2 reaction that is normally preferred for Hofmann eliminations[145]. The net result is that the *i*-Bu derivative reacts faster than expected because of a favorable interaction with the developing double bond. A similar effect is likely for the elimination reaction of *cis*-(2-alkylcyclohexyl)trimethylammonium ions in which the Saytzev product predominates[145,191]. The evidence for this view is based on an increase in the $(k_T/k_H)_\alpha$ isotope effect for elimination from 1.108:1.150:1.216 as the R group is varied from Et:Pr:*i*-Bu, and the fact that for the analogous, but less hindered, dimethylsulfonium ions β-methyl substitution *is* additive. Furthermore, two alternative explanations for these results were tested and found wanting: (1) there is no significant change from *anti* to *syn* elimination for the *i*-Bu derivative, and (2) there is no evidence for increased proton tunneling for the Et derivative.

D. Interaction Coefficients

Perturbations of the E2 transition state result from three basic structural changes: (1) changes in base strength, (2) changes in the leaving group and (3) changes in substituents at the α and β carbons. Structural perturbations of the E2 transition state are normally classified according to the effects on transition state structure that result from these changes. The system employed by Jencks based on structure–reactivity interaction coefficients appears, however, to be a more systematic way of classifying these effects[179,182]. The Jencks interaction coefficients not only provide a quantitative measure of changes in structure–reactivity parameters and transition state structure that can be used to map out the transition state and the curvature of the surface in the vicinity of the saddle point, but also define relationships between changes in one parameter and changes in another that are not always apparent.

1. The interaction between the base catalyst and the leaving group

a. General. The interaction between the base catalyst and the leaving group can be defined by the p_{xy} coefficient[182]. The p_{xy} coefficient is described by equation 11, in which β is Bronsted's β value, β_{lg} is the slope of a plot of log *k vs* pK_a of the leaving group (pK_{lg}), and pK_{BH} is the pK_a of the base catalyst. Other measures of the extent of proton transfer and carbon leaving group-bond cleavage in the transition state, such as solvent and heavy-atom isotope effects, or ρ_{lg}, have been employed instead. Jencks has discussed the complementary nature of this and other interaction coefficients[179,182]. For example, equation 11 requires that changes in β values as a function of changes in the leaving group

be proportional to changes in β_{lg} as a function of changes in catalyst pK_a. Experimentally, a positive p_{xy} coefficient for elimination reactions corresponds to an increase in β for the reactions of substrates with poorer leaving groups, as well as an increased sensitivity to changes in leaving-group ability for reactions catalyzed by weaker bases[94].

$$p_{xy} = \partial\beta/\partial pK_{lg} = \partial\beta_{lg}/\partial pK_{BH} \tag{11}$$

b. Diagnosing mechanisms. The interaction between the base catalyst and the leaving group also serves to illustrate the value of the More O'Ferrall–Jencks model in diagnosing reaction mechanisms. This is based on the expectation that the orientations of the reaction coordinates for E2 and $E1cB_{irr}$ reactions should differ, so that the corresponding transition states may respond differently to changes in reactant and catalyst structure and reaction conditions[94]. For example, a stepwise E1cB mechanism in which proton transfer is rate-limiting ($E1cB_{irr}$) has a horizontal reaction coordinate on a More O'Ferrall–Jencks energy diagram, whereas the reaction coordinate of the concerted E2 reaction which involves both proton transfer and bond cleavage is expected to have some diagonal character. For the diagonal reaction coordinate of an E2 mechanism, an increase in base strength will raise the energy of the right side of the diagram, so that a net decrease in carbon leaving-group bond cleavage is expected ($p_{xy} > 0$). On the other hand, for the horizontal reaction

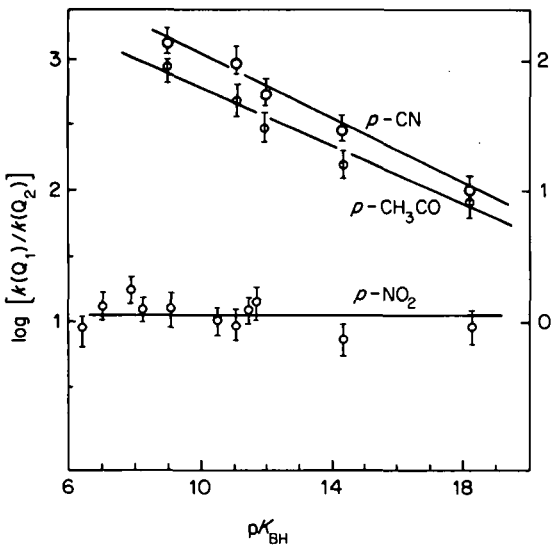


FIGURE 4. The change in the dependence of the rate on the pK_a of the leaving quinuclidine with changing pK_a of the base catalyst for the **6**, *p*-MeCO and *p*-CN derivatives for which Q_1 = *N*-methyl-Dabco and Q_2 = Dabco, and for the *p*-NO_2 derivative for which Q_1 = *N*-methyl-Dabco and Q_2 = quinuclidine, in 60 vol% DMSO in water at 40 °C, I = 0.30 (KCl). The left ordinate scale is for the *p*-NO_2 derivatives, and the right scale for the *p*-MeCO and *p*-CN derivatives. Reprinted with permission from J. R. Gandler and W. P. Jencks, *J. Am. Chem. Soc.*, **104**, 1937 (1982). Copyright (1982) American Chemical Society

coordinate of an $E1cB_{irr}$ mechanism, raising the energy of the right side of the diagram should result in little or no change in carbon leaving-group bond cleavage ($p_{xy} = 0$). This expected difference in behavior is realized in elimination reactions of 2-(arylethyl)quinuclidinium ions, (**6**), in 28 mole% DMSO in water[94]. For example, Figure 4 shows that for the elimination reactions of the *N*-(2-(*p*-nitrophenyl)ethyl)quinuclidinium ion derivatives the sensitivity of the reaction to the pK_a of the leaving quinuclidine is independent of the pK_a of the base catalyst over 12 pK_a units of catalyst strength ($p_{xy} = 0$), whereas the sensitivity of the reaction to the pK_a of the leaving quinuclidine increases with decreasing pK_a of the base catalyst ($p_{xy} > 0$) for the reactions of the *p*-acetyl and *p*-cyano derivatives. An increased sensitivity to the pK_a of the leaving group for reactions catalyzed by weaker bases ($p_{xy} > 0$) was also observed for reactions of the unsubstituted, *m*-chloro and *m*-trifluoromethyl compounds. For example, for the reactions of the *N*-(2-(*m*-chlorophenyl)ethyl)quinuclidinium ion derivatives, $\beta_{lg} = -0.23$, -0.27 and -0.36 for catalysis by OH^- (apparent $pK_a = 18.3$ in this solvent), $CF_3CH_2O^-$ (apparent $pK_a = 14.5$) and $(CF_3)_2CHO^-$ (apparent $pK_a = 11.2$), respectively. These results are consistent with a change from an $E1cB_{irr}$ mechanism for the *p*-nitro derivative to an E2 mechanism for the other 2-arylethyl compounds. Independent evidence for an E1cB mechanism for the *p*-nitro derivative was cited in Section II.A, and an E2 mechanism for the other 2-arylethyl derivatives is based on analogy with the closely related (2-arylethyl)-trimethylammonium ions: the elimination reactions of the *p*-MeO, unsubstituted, *p*-Cl and *p*-CF_3 derivatives show both primary kinetic hydrogen isotope effects and leaving-group nitrogen isotope effects[184], and the unsubstituted compound undergoes exclusive *anti* elimination[192].

Complementary structure–reactivity behavior is also expected as a result of changes in the leaving group (equation 11). For example, as the leaving group is made poorer an increase in proton transfer (β) is expected for an E2 mechanism ($p_{xy} > 0$), but for an $E1cB_{irr}$ mechanism no change in proton transfer is expected ($p_{xy} = 0$)[94]. This effect has also been observed in elimination reactions of *N*-(2-(*p*-nitrophenyl)ethyl)quinuclidinium ions[94]. For example, for the reaction of *N*-2-(*p*-nitrophenyl)ethyl)quinuclidinium ion the sensitivity of the reaction to the basicity of the catalyst (β) is independent of the pK_a of the leaving quinuclidine over a range of 8 pK_a units ($\beta = 0.67$, $p_{xy} = 0$). On the other hand, for the reactions of *N*-(2-phenylethyl)quinuclidinium ions there is an increased sensitivity to the basicity of the catalyst with poorer quinuclidine leaving groups ($p_{xy} > 0$). Similar effects have been observed before in other systems. For example, constant primary hydrogen isotope effects of 2.0 have been reported for the reactions of 2-(phenylsulphonyl)ethyl derivatives as the leaving group is changed from F to AcO to TsO ($p_{xy} = 0$, $E1cB_{irr}$ mechanism)[33]. On the other hand, for the reactions of 2-(phenylsulfonyl)ethyl halides in ethanol, the primary hydrogen isotope effects increase from 2.0 to 3.6 to 5.0 to 5.6 as the leaving group is changed from F to Cl to Br to I[33,34a,35]. The increasing values of these isotope effects are consistent instead with an E2 mechanism[33,35], and an increase in the degree of proton transfer for the better leaving groups ($p_{xy} > 0$), because in this system it is likely that the proton is more than half-transferred to the base in the transition state.

Both positive (E2 mechanism) and zero ($E1cB_{irr}$ mechanism) p_{xy} coefficients have also been observed for the elimination reactions of *cis*- and *trans*-2,3-dihalo-2,3-dihydrobenzofurans[111], (**9**). For example, values of $k_{Cl}/k_F < 1$ (0.16 and 0.10) are observed for the *t*-butoxide catalyzed *syn* elimination reactions in *t*-butanol of the X = Cl, Y = Cl and F derivatives, in the presence and absence of 18-crown-6-ether, respectively. For these same derivatives, the primary kinetic isotope effect and the rate constant ratio for the 5-Cl and unsubstituted compound (for substitution in the benzene ring) are invariant (p_{xy} and $p_{xy'} = 0$; see Section III.D.2) as the leaving group is changed from Br to Cl to F($k_H/k_D = 3$ and $k_{5Cl}/k_H = 15$). An E2 mechanism may apply, however, to the reaction of the X = Cl, Y = Br derivative based on a twofold decrease in the k_{5Cl}/k_H ratio (in the absence of crown

ether), and a k_{Br}/k_{Cl} ratio of about 4[111]. On the other hand, for the ethoxide ion catalyzed *syn* elimination reactions of these same derivatives in ethanol both the primary hydrogen isotope effect and the k_{5Cl}/k_H ratio vary, with the isotope effect decreasing and the k_{Cl}/k_H ratio increasing as the leaving group is made poorer in the order Br, Cl and F (corresponding to a positive p_{xy} and negative $p_{yy'}$ coefficient). Furthermore, the k_{Cl}/k_F ratio is now > 1 (2.2 for the reaction of the X = Cl, Y = Cl and F derivatives). These results are consistent with a change to an E2 mechanism for the reaction of these compounds catalyzed by the weaker ethoxide ion, although the authors still prefer an E1cB mechanism for the reaction of the X = Cl, Y = F derivative—a change to the E1cB mechanism is also suggested for the 5-Cl, X = Cl, Y = Cl derivative based on a k_{Cl}/k_F ratio of 0.98.

c. Other positive p_{xy} interaction coefficients. Positive p_{xy} interaction coefficients are common in E2 reactions. For example, for the reaction of 2-(*p*-nitrophenyl)ethyl halides in 60 volume% DMSO in water, Bronsted β values increase from 0.55 to 0.67 to 0.76 as the leaving group is changed from Br to Cl to F, respectively ($p_{xy} > 0$)[94]. In this same study, the leaving-group effect was observed to increase for the reactions catalyzed by weaker bases; the Br:Cl:F rate ratio changes from 22:4:1 for hydroxide ion catalysis (apparent pK_a = 18.7 in this solvent), to 52:5.5:1 for catalysis by $CF_3CH_2O^-$ (apparent pK_a = 14.5), to 154:8:1 for catalysis by $(CF_3)CHO^-$ (apparent pK_a = 11.2). These results mean that there is an increase in leaving-group bond cleavage for the reactions catalyzed by weaker bases ($p_{xy} > 0$). Bronsted β values also increase as the leaving group is made poorer in the hydroxide ion catalyzed reactions of 2-(2,4-dinitrophenyl)ethyl halides in aqueous solution[193]. The β values are 0.42, 0.46, 0.54 and 0.54 for the I, Br, Cl and F, derivatives, respectively. A corresponding increase in the element effect for the reactions catalyzed by weaker base catalysts was also observed. The identical β values observed for the Cl and F substrates may signify a change to an E1cB mechanism for the reaction of these compounds. Previous examples of these effects also include: the increase in the solvent deuterium isotope effect for the reactions of 2-(*p*-(trimethylammonium)phenyl)ethyl halides as the leaving group is varied from Br to Cl to F[185], and the decrease in the primary kinetic isotope effect as the leaving group is made poorer for the ethoxide catalyzed reactions of 2-phenylethyl derivatives in ethanol[26]. For this latter reaction, the isotope effects are 7.1, 5.7, 5.1 and 3.0 for the Br, TsO, $^+SMe_2$ and $^+NMe_3$ leaving groups, respectively. Although abnormal Arrhenius parameters for elimination reactions of 2-phenylethyl bromide, tosylate and dimethylsulfonium ion catalyzed by ethoxide ion in ethanol suggest that proton tunneling contributes to the isotope effects in these reactions[144], the decrease in the isotope effect as the leaving group is made poorer in this series is still evident after factoring out the contribution from tunneling using Bell's equations.

For the reactions of 2-(phenylethyl)dimethylsulfonium ion[194,195] and $(p\text{-}ClC_6H_4)_2CHCHCl$[196] decreases in the sulfur and chlorine leaving-group isotope effects are observed (consistent with decreasing amounts of carbon leaving-group bond cleavage) as the medium basicity increases with increasing concentrations of DMSO in mixtures of DMSO and water. Surprisingly, however, the nitrogen isotope effect for the reaction of (2-phenylethyl)trimethylammonium ion does not decrease significantly as the concentration of DMSO increases: the ratio of 1.0087 in water does drop to 1.007 in 22.8 mole% DMSO, but then levels off at values between 1.006 and 1.007 for DMSO concentrations up to 57 mole%[197]. For the elimination reaction of (2-arylethyl)dimethylsulfonium ion, the sulfur isotope effect varies from 1.0074 in water to 1.0025 in 43 mole% DMSO. Although these changes in the sulfur isotope effect indicate that cleavage of the carbon–sulfur leaving-group bond decreases with increasing medium basicity, these changes do not give rise to corresponding changes in the α-carbon isotope effect. For example, for the reaction of (2-arylethyl)dimethylsulfonium ions, the α-carbon isotope effect only varies between 1.020 and 1.029 as the DMSO concentration is changed from 30 to 50 mole% DMSO—for this same

change in solvent, a decrease in the sulfur isotope effect from 1.0043 to 1.0025 is observed. This invariance in the α-carbon isotope effect has been ascribed to the partial carbon–carbon double bond that is forming in the transition state at the same time the carbon–sulfur bond is breaking[198]. This same effect has also been invoked to explain the invariance in the α-carbon isotope effect (an effect of about 4.6% was observed) as the β-phenyl substituent is changed from *p*-Me:H:*p*-Cl in the methoxide ion catalyzed reactions of 2, 2-diaryl-1, 1, 1-trichloroethane, and for the invariance in the β-carbon isotope effect (*ca* 4.2%) as the β-phenyl substituent is made more electron-withdrawing in elimination reactions of (2-phenylethyl)trimethylammonium ion[199].

2. *The interaction between the leaving group and a β-activating substituent*

The interaction between the leaving group and the β-activating substituent can be described by the $p_{yy'}$ coefficient[182]. The $p_{yy'}$ coefficient is defined by equation 12, in which ρ corresponds to the Hammett ρ value for substitution in the β-activating group. This relationship describes both the change in the sensitivity of the rate of reaction to the nature of the leaving group with changing substituents in a β-activating group, and the complementary change in the sensitivity of the rate of reaction to substituents on the β-activating group as the structure of the leaving-group is varied. Experimentally, a negative $p_{yy'}$ coefficient for elimination reactions corresponds to an increase in ρ values for reactions of substrates with poorer leaving groups, and a corresponding decreased sensitivity to changes in the leaving group for reactions in which the β-activating group is more strongly electron-withdrawing[94].

$$p_{yy'} = \partial\beta_{lg}/\partial\sigma = -\partial\rho/\partial pK_{lg} \tag{12}$$

This effect is also apparent in the reactions of (2-arylethyl)quinuclidinium ions where β_{lg} is observed to increase (becomes less negative) as the β-phenyl substituent is made more electron-withdrawing[94]. Thus, for the hydroxide ion catalyzed reactions, values of β_{lg} of −0.25, −0.23, −0.22, −0.20, −0.16, −0.17 and −0.14 were reported for the H, *m*-Cl, *m*-NO_2, *p*-AcO, *p*-CN and *p*-NO_2 derivatives, respectively. These data correspond to a negative $p_{yy'}$ coefficient, and describe a decrease in carbon–nitrogen bond cleavage as the β-phenyl substituent is made more electron-withdrawing. This result is consistent with an E2 mechanism, because a decrease in carbanion stability will result in a shift in transition state structure towards the bottom of the energy diagram, whereas little or no change in leaving-group bond cleavage is expected for the horizontal reaction coordinate of an $E1cB_{irr}$ mechanism. The decrease in the leaving-group nitrogen isotope effect with increasing electron-withdrawing power of the β-phenyl substituent for the ethoxide ion catalyzed elimination reactions of (2-arylethyl)trimethylammonium ions provides another example of this effect[184], as does the decrease in the Br:Cl:F rate constant ratio from 4100:60:1 for 2-phenylethyl halides[25] to 46:4:1 for 2-(*p*-nitrophenyl)ethyl halides[94], and the decrease in α-secondary deuterium isotope effects from 1.047 to 1.043 to 1.017 for elimination reactions of the *p*-MeO, H and *p*-Cl derivatives of 2-phenylethyl tosylate, respectively[200]. Secondary α-deuterium isotope effects have also been observed to decrease from 1.37:1.30:1.22:1.08 with increasing electron-withdrawing power of a β-phenyl substituent for the methoxide ion catalyzed reactions of the *p*-Me, H, *p*-Cl and *p*-NO_2 derivatives of 1-phenyl-2-aryl-1-chloroethane, respectively[201]. For the methoxide ion catalyzed reactions of 1, 1-dichloro-2, 2-diarylethanes[202] in methanol, the decrease in the intramolecular chlorine leaving-group isotope effect from 1.0038:1.0035:1.0023:1.000 as the β-phenyl substituent is varied from MeO:H:Cl:NO_2 also shows that there is less cleavage of the carbon–chlorine bond for the reactions of the more activated substrates. The isotope effect of 1.000 for the *p*-nitro compound suggests an $E1cB_{irr}$ mechanism (with a

very early transition state for expulsion of the chloride ion from the carbanion), but it has recently been reported that this same reaction shows an α-carbon isotope effect of 1.024[203].

The complementary $p_{yy'}$ relationship described by equation 12 is manifested in an observed increase in Hammett ρ values as the leaving group is made poorer for the reactions of the 2-(arylethyl)quinuclidinium ions. For example, $\rho = 3.3$ and 3.9 for the hydroxide catalyzed reaction of *N*-methyl-Dabco ($pK_a = 3.0$) and Dabco ($pK_a = 8.9$) derivatives, respectively[94]. For the reactions catalyzed by trifluoroethoxide, ρ values of 3.5 and 4.3 were observed for the *N*-methyl-Dabco and Dabco derivatives. An increase in Hammett ρ values with decreasing leaving-group ability of the halide in the series I (2.07), Br (2.14), Cl (2.61) and F (3.12) corresponds to the same effect for elimination reactions of 2-arylethyl halides catalyzed by ethoxide ion[25b]. Values of ρ also increase as the leaving benzenesulfonate is made more basic in the reactions of 2-arylethyl-*p*-benzenesulfonates catalyzed by *t*-butoxide ion in *t*-butyl alcohol[204], and secondary α-hydrogen isotope effects decrease from 1.047:1.043:1.017 as the β-aryl group is changed from *p*-MeOPh to Ph to *p*-ClPh, respectively, for the elimination reactions of 2-phenylethyl tosylates[200].

Substitution of α-alkyl groups or aryl groups tends to lower ρ values measured using substituted β-phenyl substituents. For example, $\rho = 2.6$ and 1.98 for the ethoxide ion catalyzed reactions in ethanol of 2-arylethyl chlorides[25b] and 2-aryl-1-phenyl-1-chloroethanes[1], respectively. For the methoxide ion catalyzed reactions in methanol of 1, 1-dimethyl-2-arylethyl chloride, $\rho = 1.0$–1.2[81,176]. Similarly, ρ declines from 2.27 to 1.81 to 1.32 for the ethoxide ion catalyzed reactions of 2-arylethyl tosylates, and their β- and α-methyl substituted derivatives, respectively (a similar trend was also reported for the corresponding bromides)[205]. These results are consistent with an E2 mechanism in which groups which promote carbon–chlorine bond cleavage and which stabilize an incipient double bond make the transition state less carbanion-like.

3. *The interaction between the base catalyst and a β-activating substituent*

The interaction between the base catalyst and the β-activating substituent can be described by the $p_{xy'}$ interaction coefficient (equation 13)[182].

$$p_{xy'} = \partial\beta/\partial\sigma = \partial\rho/\partial pK_{BH} \tag{13}$$

This coefficient describes a change in the amount of proton transfer as measured by Bronsted β values and hydrogen or solvent isotope effects with changes in the β-activating group, as well as the complementary changes in Hammett ρ values with changes in catalyst strength. Experimentally, a negative $p_{xy'}$ interaction coefficient for elimination reactions means that β decreases with increasing electron-withdrawing power of the β-activating group, and ρ values are *smaller* for reactions catalyzed by stronger bases, whereas a positive $p_{xy'}$ coefficient means that β increases with increasing electron-withdrawing power of the β-activating group and ρ values are larger for catalysis by stronger bases[94]. It has been claimed that as a β-substituent becomes better able to stabilize a carbanion intermediate, proton transfer to the base catalyst generally increases ($p_{xy'} > 0$)[4,70], but both positive and negative $p_{xy'}$ coefficients have been reported in elimination reactions (Sections III. D.3.a and III.D.3.b).

a. Positive $p_{xy'}$ coefficients. Positive $p_{xy'}$ coefficients in elimination reactions have been observed in a variety of systems. For example, the Bronsted β value increases from 0.51 to 0.61 as the β-phenyl substituent is changed from phenyl to *p*-nitrophenyl in the reactions of 2-arylethyl bromides[94]. An increase in Bronsted β values with increasing electron-withdrawing power of a β-substituent has also been previously reported for elimination reactions of 2-arylethyl bromides catalyzed by unbuffered phenoxide ions in ethanol[206], and for the reactions of 2-(arylethyl)sulfonyl chlorides catalyzed by tertiary amines in

acetonitrile[207]. These effects correspond to an increase in proton transfer with increasing electron-withdrawing power of the β-phenyl substituent, a positive $p_{xy'}$ coefficient and a diagonal reaction coordinate on a More O'Ferrall–Jencks energy diagram. Other examples of positive $p_{xy'}$ coefficients that have been documented before in the literature include the elimination reactions of 1-arylethyl chlorides. For example, the Hammett plot for these reactions is curved with both electron-donating and electron-withdrawing substituents accelerating the reaction[177]; for the bromide derivative, however, the acceleration by electron-donating groups is not apparent, with the *p*-methyl derivative reacting only 7% faster than the unsubstituted compound[208]—for the chlorides, the *p*-methyl compound reacts 8 to 13 times faster than the unsubstituted compound. The increase observed in the β-carbon isotope effects from 1.038:1.058:1.068 for the *p*-methyl, unsubstituted and *p*-chloro derivatives, respectively, is consistent with increased C—H bond cleavage and a more carbanionic transition state as the β-phenyl substituent is made more electron-withdrawing ($p_{xy'} > 0$)[177]. For a diagonal reaction coordinate, however, a change to a better leaving group is expected to result in a net shift to the right side of the diagram and a net decrease in ρ. If the *p*-MeO and *p*-Me derivatives of the chloride compound already react via an E1-like transition state, then the *p*-Me-substituted bromide should accelerate the reaction relative to the unsubstituted bromide even more strongly than it does for the 1-arylethyl chlorides, but just the opposite result is found. It is possible that the curvature observed in these reactions reflects a 'dual-interaction mechanism'[209] rather than a shift in the E2 transition state structure. That is, the transition state has a net negative charge as a result of the base (*t*-butoxide ion) being there, so electron-withdrawing substituents accelerate the reaction, but substituents capable of direct resonance interaction with a partially formed carbonium ion react at rates faster than expected based solely on the polar effect of these substituents. Similar effects have been shown to operate for S_N2 reactions of benzyl derivatives and the base-catalyzed breakdown of carbonyl bisulfite addition products[209], and have been quantified using a modified form[210a] of the Yukawa–Tsuno equation [210b]. It is not clear, however, why Hammett curvature is not observed for the bromide derivatives.

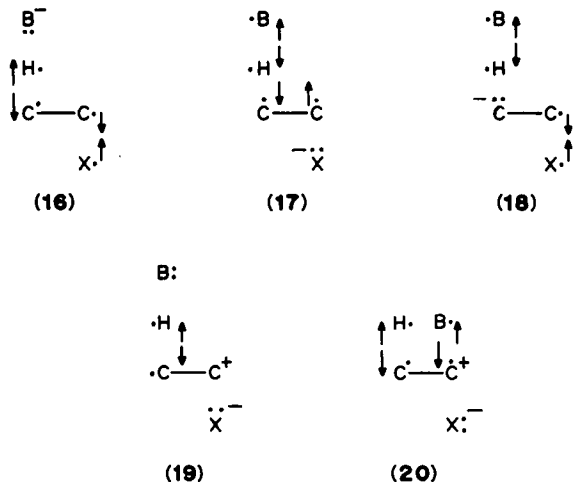
b. Negative $p_{xy'}$ coefficients. Negative $p_{xy'}$ interaction coefficients have also been observed in a number of different systems. For example, a negative $p_{xy'}$ coefficient is observed for elimination reactions of (2-arylethyl)ammonium ions based on β-primary hydrogen isotope effects that increase from 2.64 to 4.16 as the β-aryl substituent is changed from *p*-MeO to *p*-CF_3[184]. The large solvent isotope effects [$k_{OH}/k_{OD} = 1.6$–1.7 for reactions of the (2-arylethyl)trimethylammonium ions[165,185]] and Bronsted β values > 0.66 for the reactions of *N*-(2-arylethyl)quinuclidinium ions[94] indicate a proton that is more than half-transferred to the base in the transition state of these reactions, and mean that the increasing isotope effects observed correspond to decreasing degrees of proton transfer to the base catalyst in the transition state ($p_{xy} < 0$)[94,184,185]. Bronsted β values also show a small decrease as the β-phenyl substituent becomes more electron-withdrawing for the elimination reaction of *N*-(2-arylethyl)quinuclidinium ions in 60 volume% DMSO in water[94]. Hammett ρ values increase, however, from 3.8 to 4.2 for base catalysis by *p*-nitrophenoxide and phenoxide ion, respectively, for the reactions of (2-arylethyl)trimethylammonium ions in DMF[211] ($p_{xy'} > 0$), so changes in solvent can give rise to changes in the magnitude and even sign of interaction coefficients. Increases in primary β-hydrogen isotope effects as the β-phenyl group is made more electron-withdrawing have also been observed for elimination reactions of (2-arylethyl)-dimethylsulfonium ions[212] and 1-phenyl-2-arylethyl chlorides[201], although for the chlorides it is not known whether the proton is more or less than half-transferred to the base in the transition state. For the reactions of 2-arylethyl bromides, although β increases from 0.51 to 0.61 as the β-phenyl group is changed from Ph to *p*-NO_2Ph ($p_{xy} > 0$)[94,206], for

the 2,4-$(NO_2)_2$Ph derivative β decreases to 0.46 ($p_{xy} < 0$)[193]. This inversion in the trend of β with increasing electron-withdrawing power of the β-phenyl substituent could be due to a steric effect of the *o*-NO_2 group, but the rate constant for the hydroxide ion catalyzed reaction of this substrate fits a Hammett plot based on rate constants for the reactions of other *para*- and *meta*-substituted derivatives using a σ^- value of 1.24 for the *o*-NO_2 group that is based on the ionization of phenols[213]. The inversion in β values can be understood as resulting from a change in the E2 transition state and a clockwise rotation of the reaction coordinate relative to the proton transfer axis that must occur at the E2–E1cB borderline (Figure 3): from a diagonal reaction coordinate for the phenylethyl derivative ($p_{xy} > 0$) to one with a major component of proton transfer for the nitro-activated compounds ($p_{xy} < 0$).

E. The Valence-bond Configuration Mixing Model

The Valence-Bond Configuration Mixing Model of Pross and Shaik generates reaction coordinates by a linear combination of valence-bond electron configurations[70,71]. The transition state structure is therefore dependent on a mixing of electronic configurations of the reactants, products and potential intermediates in proportion to their relative stabilities in the vicinity of the transition state—near where the avoided crossing occurs. The Valence-Bond Configuration Mixing Model appears to be in general accord with predictions based on the More O'Ferrall–Jencks model described above. However, the negative p_{xy}, coefficients that have been reported in elimination reactions (Section III.D.3.b) are not consistent with predictions based on the Valence-Bond Configuration Mixing Model. This latter model predicts that a more electron-withdrawing β-substituent that stabilizes the carbanion intermediate will result in a net *increase* in proton transfer, because the transition state is expected to look more like the carbanion in which the C—H bond is completely broken.

For elimination reactions the basis set of valence-bond electronic configurations are represented by structures **16**–**20**, where **16** represents the electronic configuration of the reactant, **17** the product alkene, **18** and **19** the potential carbanion and carbonium ion intermediates, respectively, and **20** the product of nucleophilic substitution[70,71].



The mechanistic pathways available for elimination reactions may be constructed by qualitatively generating the reaction profiles in the way described above. For example, the reaction coordinate of a synchronous E2 mechanism is generated from a simple mixing of reactant and product configurations. Similarly, the reaction coordinate of an E1cB–E2 mechanism is generated when significant mixing of the carbanion configuration occurs; when the carbanion configuration becomes more stable than both the reactant and product configurations near their expected crossover point, a discrete intermediate is expected to form (an E1cB mechanism)[70,71]. It is interesting that this model suggests that stepwise mechanisms via discrete intermediates will occur when these intermediates are stable. This hypothesis is in accord with the conclusion of Jencks, based on experimental data, that a number of classes of reactions inherently favor stepwise mechanisms: concerted mechanisms appear to occur only when they are enforced—when the lifetime of the potential intermediate becomes vanishingly small, so that the intermediate has no significant lifetime[73].

F. Conclusions

In conclusion, the following generalizations concerning the variableness of the E2 transition state appear warranted.

(1) E2 reactions show positive p_{xy} coefficients; changing to a poorer leaving group results in increased proton transfer; changing to a weaker base catalyst results in increased carbon leaving-group bond cleavage.

(2) E2 reactions show negative p_{xy} coefficients; changing to a poorer leaving group results in more carbanion character; changing to a more electron-withdrawing β substituent results in less carbon leaving-group bond cleavage.

(3) E2 reactions show both positive and negative p_{xy} coefficients; changing to a more electron-withdrawing β-activating group may either increase or decrease proton transfer, and changing to a weaker base catalyst may either increase or decrease carbanion character. There is some evidence that substrates that react at or near the E1cB borderline show negative p_{xy} coefficients, characteristic of reaction coordinates that have a large component of proton transfer.

G. Stereochemistry

1. Background

Many structural and environmental factors are known to be able to affect the stereochemical course of elimination reactions, including the leaving group and base catalyst, the size of alkyl substituents, ring size and structure (for the reactions of cyclic and bicyclic molecules), solvent polarity, the presence or absence of metal cations and crown ethers, the structure of the product alkene, and the polar and resonance effects of β substituents[5,15].

A number of theories have been advanced to explain how these factors influence reaction stereochemistry. The most firmly established ones are:

(1) Ion-paired or associated bases have been shown to promote *syn* eliminations of substrates with neutral leaving groups (e.g. halides and tosylate), probably via a cyclic transition state in which the metal cation assists leaving-group departure[44b,214–216]. These interactions are favored by strong bases in nonpolar solvents (for example, potassium *t*-butoxide ion in benzene is particularly effective in promoting *syn* eliminations), but disfavored by more polar solvents (MeOH, DMSO, etc.), the presence of crown ethers and tetraalkylammonium salts, all of which promote the formation of free or solvent separated base. On the other hand, the increasing amounts of *syn* elimination that

have been observed in reactions of trialkylammonium ion derivatives as the polarity of the solvent decreases[218] have been attributed instead to stronger electrostatic interactions between the *free* alkoxide and trialkylammonium ion (formed as a result of a metathesis between the substrate and the ion-paired base) in the transition state for *syn* elimination[217] (the interaction between the ion-paired alkoxide and trialkylammonium ion is expected to be destabilizing[44a,217a,219]).

(2) Stereoelectronic effects favoring *syn* and *anti* periplanar conformations over all others are important; they are most visible in reactions of cyclic and bicyclic compounds, in which free-rotation around carbon–carbon single bonds is hindered or restricted[220].

(3) Compared with the formation of disubstituted *trans* alkenes, eclipsing of alkyl groups in the transition state for the formation of *cis* and trisubstituted alkenes is believed to contribute to the smaller amounts of *syn* elimination that are normally observed in these cases[221].

(4) Steric hindrance to abstraction of the β proton[222,15b] and/or release of ground-state conformational strain[223] are believed to be partly or entirely responsible for increases in the percentage of *syn* elimination that are observed in acyclic systems for reactions of trialkylammonium ion[221d,224] and tosylate[221a] derivatives with increasing size of β'- and γ-alkyl substituents, and steric hindrance to abstraction of the intra-annular proton is believed to be responsible for the *syn–anti* dichotomy (*trans* alkene formed by *syn* elimination and *cis* alkene formed largely or exclusively by *anti* elimination) that is observed in medium ring to larger ring systems (and to a lesser extent in acyclic systems as well for trialkylammonium ions derivatives)[43b,44a,44b,44d,217b,221c,224,225].

(5) Both experimental[46,220,226] and theoretical evidence[70,227–229] suggests that *syn* eliminations have more carbanionic-like transition states than *anti*, so that changes in substrate structure and reaction conditions that give rise to changes in transition state structure can also affect reaction stereochemistry[44a,217c,230].

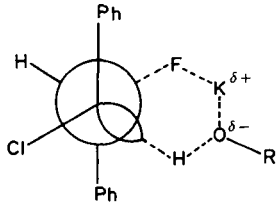
The reader is referred to other reviews for a more detailed discussion of these factors and their effect on orientation and *cis/trans* olefin ratios[4,5]; we limit ourselves here to discuss some recent observations that tend to complement previous results but, in some instances, also extend the scope of previous investigations.

2. *Stereochemistry, mechanism and transition state structure*

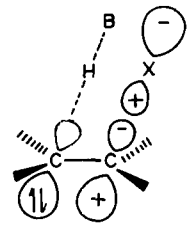
Recent work from Baciocchi's laboratory shows that near the E2–E1cB borderline a change in mechanism can be brought about by a change in reaction stereochemistry[110–114]. For example, for the elimination reactions of *meso*- and *erythro*-1,2-dihalo-1,2-diphenylethanes (**10**), both *syn* and *anti* elimination is observed for the reactions catalyzed by *t*-butoxide ion in *t*-butanol in the presence and absence of crown ether, although in the presence of crown ether only small amounts of *syn* elimination are observed for reactions with fluoride as the leaving group (5 and 13% for F and Cl activation, respectively, and none for Cl as leaving group)[114]. It is significant *syn* elimination is observed in this system—up to 95% *syn* elimination for the X = Cl, Y = F derivative in the absence of crown ether, because earlier evidence suggested that β-halogeno-activated and β-phenyl-activated derivatives show little or no propensity for *syn* elimination; the elimination reactions of *meso*- and *dl*-4,5-dichlorooctane and *meso*-3,4-dibromo-2,5-dimethylhexane provide a dramatic example of this view: these substrates have been reported to give quantitative *anti* elimination even with potassium *t*-butoxide ion in benzene (or toluene), whereas under the same conditions for the reaction of the related 5-decyl chloride, 65% of the *trans*-5-decene formed is formed by *syn* elimination[231].

The element effect for *syn* eliminations of the X = Cl, Y = Cl and F derivatives of diphenylethane in the absence of crown ether is 0.1 (k_{Cl}/k_F), whereas it is 11 for the corresponding *anti* eliminations. In the presence of crown ether, $k_{Cl}/k_F = 3.0$ for *anti*

elimination, and although a value is not reported for *syn* elimination the ratio is probably greater than 4, because a value of less than 4 would mean that more than 10% of the reaction of the X = Cl, Y = Cl compound would follow *syn* stereochemistry, but none was detected (a 5% yield of the product of *syn* elimination was detected for the reaction of the *meso*-2, 3-difluoro derivative). These results are consistent with an $E1cB_{irr}$ mechanism for *syn* elimination (at least for the reaction of the X = Cl, Y = F derivative in the absence of crown ether—no deuterium incorporation into unreacted substrate was observed in these reactions[114]). On the other hand, for *anti* elimination, the mechanism appears to be E2[114]. It was argued that the carbanion formed as a result of abstraction of the *syn* proton can be stabilized by favorable coordination between the base counterion (K^+) and the leaving group, (**21**), so that these carbanions may have sufficient lifetimes to exist because of an unfavorable torsional angle between the β-electron pair and the leaving group. On the other hand, a carbanion formed by abstraction of an *anti* proton could not benefit from such stabilization, and would therefore be expected to have a shorter lifetime, so that the concerted mechanism may be enforced[114].



(21)



(22)

Similar results have previously been reported for elimination reactions of *cis*- and *trans*-1, 2-dihalogenoacenapthenes[110], and *cis*- and *trans*-2, 3-dihalo-2, 3-dihydrobenzofurans[111,113], although for the benzofuran derivatives both E1cB and E2 *syn* eliminations were observed, with the leaving group, β-activating group and solvent affecting the mechanistic course of the reactions.

These changes observed in reaction mechanism are also consistent with the view that *syn* eliminations proceed through more carbanionic-like transition states than *anti*. For example, based on *ab initio* calculations and frontier molecular orbital theory, Bach showed that for the reaction of ethyl fluoride with hydride ion, the 'displacement' of the leaving group (X) by the β-electron pair involves an interaction between the C—X σ^* orbital and the electrons of the C—H bond, (**22**), a process that is favored by a carbanionic-like transition state in which inversion of configuration at the β carbon can occur in order to maximize orbital overlap[228].

Similarly, the Valence-Bond Configuration Mixing Model predicts that electron-withdrawing groups at the β position will result in a more carbanionic-like transition state, (**19**), that should favor *syn* elimination, because in **19** electron transfer is to the C—H bond where the requirement for *anti* elimination may be relaxed, allowing the *syn*-elimination pathway to become more competitive[70]. The less developed double bond of carbanion-like (or reactant-like) transition states is also expected to relax the requirement for *anti* elimination[221d]. These results affirm Ingold's analysis that *syn* eliminations should be relatively favored by carbanionic-like E2 transition states, because inversion of configuration at the β carbon could then occur, making the displacement of the leaving group at the α carbon formally equivalent to a Walden inversion at that center[227].

Experimental support for these views has been largely derived from cyclic tosylate derivatives, but has recently been extended to acyclic trialkylammonium ions. For

example, Hammett ρ values are larger for *syn* than *anti* eliminations[232] for the *t*-butoxide ion elimination reactions of *cis*- and *trans*-2-phenylcyclopentyl tosylate[220a] (2.8 vs. 1.5), 2-phenylcyclobutyl tosylate (2.9 vs. 2.2)[46,220a] and 3-aryl-2-norbornyl tosylates[46] (3.1 vs. 2.6—*exo–syn* vs. *exo–anti*) in *t*-butanol solution, and for the hydroxide ion catalyzed elimination reactions in 50% DMSO–water of **23**, in which $R^1 = (CH_3)_2CH$ and $R^2 = Ar$, $\rho_{syn} = 3.69$ and $\rho_{anti} = 3.02$[226].

$$R^1R^2CHCH_2\overset{+}{N}(Me)_3$$

(23)

$R^1 = i\text{-Pr}, Ph$

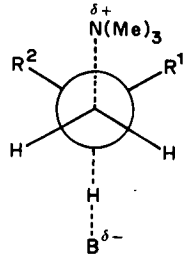
$R^2 = Ph, p\text{-An}$

These results show that changes in stereochemistry can occur due to changes in the polar and resonance effects of substituents. Other examples of this effect appear to be the elimination reactions of *erythro*- and *meso*-1,2-diphenyl-1,2-dihalogenoethanes where more *syn* elimination is observed for the Cl-activated elimination with fluoride rather than chloride as leaving group (95% vs. 13%), and more is observed when the β position is activated by Cl rather than F (13% vs. 0% with Cl as leaving group, and 95% vs. 32% with fluoride as leaving group)[114], and for the potassium *t*-butoxide ion promoted elimination reactions of 5-decyl-6-deuterio-derivatives in benzene (producing *trans*-5-decene), where the percentage of *syn* elimination increases from 27% to 33% to 65% to 88% to 92% as the leaving group is changed from TsO:Br:Cl:F: $^+N(Me)_3$, respectively[230a,233]. These results are consistent with increasing amounts of *syn* elimination for the reactions of substrates with poorer leaving groups that are brought about by a shift to a more carbanionic-like E2 transition state[234], and for the reactions of substrates with stronger β-activating groups that are brought about by a larger increase in the *syn* than the *anti* rate constant (an α-Cl better stabilizes and sp^2 carbanion than an α-F[235]; for example, dehydrofluorination of *trans*-2-fluoro-3-chlorobenzofuran proceeds *ca* 8×10^3 times faster than dehydrofluorination of *trans*-2-fluoro-3-fluorobenzofuran, and dehydrochlorination of *trans*-2-chloro-3-chlorobenzofuran proceeds *ca* 2×10^3 times faster than *trans*-2-chloro-3-fluorobenzofuran[111]). The increase observed in the *trans/cis* alkene ratio from 0.04:1.7:4.9 for the reaction of cyclooctyltrimethylammonium ion in DMSO as the basicity of the base catalyst increases from PhO^-:MeO^-:$(CH_3)_3O^-$ may provide another example of this effect[44a], but one in which increasing strength of the base catalyst promotes a more carbanion-like transition state (the same trends were also observed in *t*-butyl alcohol, methanol and benzene for the cyclooctyl derivative, and for the reactions of other cyclotrialkylammonium ions, ranging from 9–14 ring carbons)[44a]. However, for the reactions of the *erythro*- and *meso*-1,2-diphenyl-1,2-dihalogenoethanes and the decyl halides and tosylate, the importance of base association is evident, because the percentages of *syn* elimination drop for the potassium *t*-butoxide ion reactions of the decyl derivatives in DMSO, and in the presence of crown ether for the reactions of the 1,2-diphenylethane derivatives, although even under these conditions the trends noted above are apparent. For example, the percentages of *syn* elimination drop to 3.7%, 2.5%, 6% and 11% for the reactions in DMSO of decyl tosylate, bromide, chloride and fluoride, respectively—the percentage of *syn* elimination for the trimethylammonium ion derivative remains unchanged at 94% under these conditions, consistent with a metathesis between the substrate and the ion-paired base to form a trimethylammonium ion–alkoxide pair which is the reactive species in both solvents[44a,217]. For the reactions of the diphenylethanes, the percentages of *syn* elimination drop to 13% and 0% for the chloride-activated elimination with fluoride and chloride as leaving groups, and to 13% and 5% for the reaction in which chloride and fluoride, respectively, activate loss of fluoride ion.

3. Steric effects

As noted above, it is known that the size of β'-and γ-alkyl substituents can influence the stereochemical course of elimination reactions. For example, only small or negligible amounts of *syn* elimination are observed for primary substrates, but increasing amounts of *syn* elimination are observed as the size of the β' and γ substituents increase; for example, whereas the *t*-butoxide ion promoted elimination in *t*-butanol of 2-deuterio-1-decyltrimethylammonium ion yields only 7% of the *syn*-elimination product[236], the 2-hexyl derivative yields 15%, the 3-hexyl[221d] 80% and the 5-decyl[221c] 89% of the product of *syn* elimination[237]. The role of steric effects in promoting *syn* eliminations is further underscored by a recent report that primary alkylammonium ions undergo large amounts of *syn* elimination even in DMSO–water mixtures, if there are two sizable β substituents[238]. For example, for the hydroxide ion catalyzed reactions of **23** in 50% DMSO–water, the amounts of *syn* elimination are 68.5, 61.9 and 26.5 for compounds in which R^1 and R^2 are Ph and *i*-Pr, Ph and *p*-MeOPh, and Ph and Me, respectively. In these cases steric effects appear to be more important than electronic ones, because there is little change in the amount of *syn* elimination when an isopropyl group is replaced by a second aryl group (*p*-MeOPh)[238].

It was suggested that the increase in *syn* elimination observed for substrates with two sizable β substituents is due to a destabilizing steric interaction between these substituents and the bulky trimethylammonium group in the *anti* transition state, (**24**)[238].



(**24**)

4. Syn eliminations promoted by 'complex base'

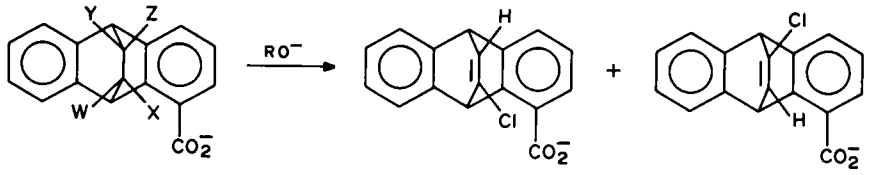
'Complex base', a mixture of $NaNH_2$–NaOBu-*t* in THF[239], promotes *syn* eliminations (a heterogeneous reaction) in which the normal E2 order of halogen leaving-group abilities (Br > Cl > F) is changed, with fluoride better than chloride, and chloride and bromide having comparable leaving-group abilities[240–242]. For example, for the *syn*-elimination reactions of *trans*-1-bromo-2-chlorocycloalkanes (cyclobutane, cyclopentane, cyclohexane, cycloheptane and cyclooctane), the ratios of 1-bromocycloalkenes to 1-chlorocycloalkenes are 1.2, 1.3, 1.9, 0.85 and 0.54, respectively, for the reactions promoted by 'complex base', and 0.18, 0.20, 0.042, 0.19 and 0.16, respectively, for the reactions promoted by potassium *t*-butoxide ion in *t*-butanol[240]. For the complex-base promoted eliminations of *trans*-1-chloro-2-bromoacenapthene and *trans*-1-bromo-2-chlorocyclopentane, the ratio of 1-bromo to 1-chloroalkenes formed is *ca* 1.3 for both substrates. It has been reported, however, that *trans*-1,2-bis(*p*-toluenesulfonyl)cyclohexane does not undergo *syn* elimination with 'complex base'[239]. Dehydrofluorinations are particularly favored when *syn* eliminations are promoted by 'complex base'. For example, for the reactions of *trans*-1-chloro-2-fluorocyclohexane and *trans*-1-bromo-2-fluorocyclohexane, the products formed in 85% yields are 1-chloro and 1-bromocyclohexenes—no

1-fluorocyclohexene is detected[241]. This work has recently been extended to the reaction of *trans*-2-chloro-3-fluoro-2, 3-dihydrobenzofuran where a 97% yield of 2-chloro-benzofuran was reported[242]; this latter result contrasts with the exclusive formation of 3-fluorobenzofuran when the elimination is promoted by ethoxide ion in ethanol or *t*-butoxide ion in *t*-butanol (in the presence and absence of crown ether)[111].

The reversal or change in the normal E2 order of halogen leaving-group abilities that is observed for 'complex-base' catalyzed *syn* eliminations has been attributed to an E2 mechanism in which associated or ion-paired NH_2^- (Na^+) provides electrophilic assistance to leaving-group departure, of the kind originally proposed for alkoxide ion promoted *syn* eliminations[15], but stronger. This type of transition-state electrostatic interaction is underscored by the fact that the 1.9:1 ratio of 1-bromocyclohexene to 1-chlorocyclohexene formed in the 'complex-base' catalyzed reaction of *trans*-1-bromo-2-chlorocyclohexane drops to 0.031 in the presence of 15-crown-5-ether, and for the reactions of both *cis*-1-bromo-2-chlorocyclohexane and 1-chloro-1-bromocyclohexane, 99% of the product is 1-chlorocyclohexene[241].

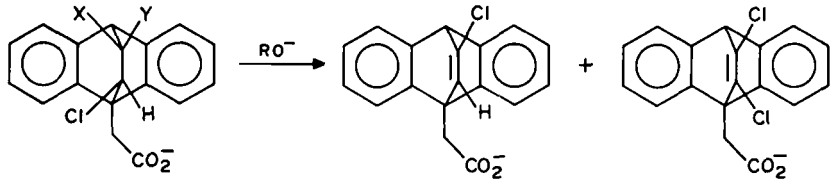
5. *Remote substituent effects and intramolecular eliminations*

Syn and *anti* eliminations from the four isomeric 11,12-dichloro-9,10-dihydro-9,10-ethano-1-anthroic acids, **25–28** to produce alkenes **29** and **30** have been studied under a variety of base/solvent conditions[243]. The observed regioselectivities (defined as the **30/29** product ratio) were explained in terms of an electrostatic model in which product yields were attributed to differences in electrostatic repulsion energies between the carboxylate and oxyanion base in the respective transition states (this interpretation requires an E1cB-like E2 transition state in which there is little charge on the leaving chloride ion)[244]. For example, for the potassium *t*-butoxide ion promoted elimination reactions of **25**, **26**, **27** and **28** in *t*-butanol solutions, in the presence of an equivalent of 18-crown-6-ether to promote free-base formation, the **30/29** product ratio changes from 2.4:13.3:24:1.7, respectively. These results show that the protons most remote from the carboxylate group are preferentially abstracted (the Y and Z protons). Similarly, for the reactions of **31** and **32**, under the same conditions, the **33/34** product ratios are 19 and 49, respectively (intramolecular β elimination was not observed). Steric effects are probably not significant in this latter system, because for reactions of the 9-methyl derivative of **32** the product ratio is *ca* 1.



(29) **(30)**

(25) X=Z=Cl; W=Y=H
(26) X=Y=H; W=Z=Cl
(27) X=Y=H; W=Z=Cl
(28) X=Y=Cl; W=Z=H



(31) X=H, Y=Cl (33) (34)

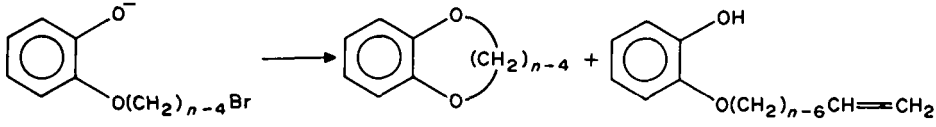
(32) X=Cl, Y=H

Product ratios in the anthroic acid system were fitted to a model in which total repulsive energies for the competing transition states were calculated using Coulumb's law, in which the effective dielectric constant and the charge on the oxyanion base and the β carbon were variables. The data are best fitted with a transition state model in which the effective dielectric constant is 13.7 *D*, and the oxyanion base and β carbon have fractional charges of 0.85 and 0.15, respectively. The common transition state structure suggested by this model, indicating a small amount of proton transfer and charge build-up on the β carbon for both *syn* and *anti* eliminations, contrasts with results described earlier (see Section III.G.2).

For the KOH and NaOH promoted *anti* eliminations of **25** and **26** in methanol solution, and in the presence of crown ether, the **30**/**29** product ratios from **25** are 2.3 and 3.5, and from **26**, 1.0 and 1.2, respectively. In the absence of crown ether, the product ratios are all *ca* 1. These results are also consistent with the electrostatic model in which electrostatic effects are smaller in methanol than in *t*-butanol solution, and small or negligible in the absence of crown ether, conditions under which the base is in an associated state[243]. However, for the reactions of **25**–**28** promoted by potassium *t*-butoxide ion in THF, it is not clear why for the reaction of **28** the regioselectivity is higher in THF (13.3) than in *t*-butanol (1.7), or why for the reaction of **27** regioselectivities are *ca* equal in the two solvents, 19 and 24, respectively[243].

Although many kinetic studies of intramolecular substitutions and proton transfers have been reported[245] there have been relatively few reports of intramolecular elimination reactions. A particular systematic and thorough study has been reported by Mandolini and coworkers. They studied the effect of increasing ring size on intramolecular β-elimination reactions of *o*-(ω-bromoalkoxy)phenoxides in 99% DMSO (equation 14, ring sizes 6–10 and 14)[246]. This study is also important because it apparently provides the first systematic model for intramolecular vs. intermolecular proton transfers in which a wide range of ring sizes could be studied.

Effective molarities (EM) for the elimination reactions were obtained by comparing the intramolecular reaction with the intermolecular reaction of guaiacolate ion with decyl bromide. Although intramolecular substitution is kinetically favored by factors of *ca* 10–40, the EM are generally higher for the elimination reactions: $EM_E/EM_S = 0.2, 4, 13, 49, 4$ and 6 for $n = 6$-, 7-, 8-, 9-, 10- and 14-membered rings, respectively. The rate profiles for both elimination and substitution are similar: there is a general decrease in log k_{intra} from



(14)

6- to 10-membered rings (*ca* 4×10^3 for elimination and *ca* 1×10^4 for substitution), with the 10- and 14-membered rings reacting at about the same rate. The majority of the difference in EM values for rings 7, 8 and 10 can be accounted for because there is one less rotor frozen-out in the transition state for elimination than substitution. This has been shown to correspond to *ca* 4 e.u. for rings of this size[247,248]. For $n = 6, 9$ and 14 where EM_E/EM_S values equal 0.2, 49 and 5, respectively, alternative explanations were advanced based on a combination of effects: relief of medium ring strain in the transition state of the elimination reaction, and the requirement for a bent proton transfer in forming the 6-membered transition state for elimination.

IV. ELIMINATIONS IN THE GAS PHASE

Base-catalyzed elimination reactions in the gas phase have been studied in recent years by both Ion-Cyclotron-Resonance (ICR) and Flowing-Afterglow methods (FA)[249–255]. A variety of substrates have been investigated including acyclic and cyclic ethers[250,251], thioethers[252], alkyl fluorides[249,253], carboxylic acid esters[254] and substituted 1,3-dithianes and dithiolanes[255].

A. Ethers and Thioethers

Ethyl ether (as well as other acyclic ethers) reacts with hydroxide and amide ions in the gas phase to produce both free ethoxide ion (alkoxide ions) and ethoxide ion (alkoxide ions) clustered with water or ammonia, respectively (equation 15)[250]. For example,

$$CH_3CH_2OCH_2CH_3 + B^- \begin{cases} \longrightarrow CH_3CH_2O^- + BH + CH_2{=}CH_2 \\ \longrightarrow CH_3CH_2O^-(BH) + CH_2{=}CH_2 \end{cases} \quad (15)$$

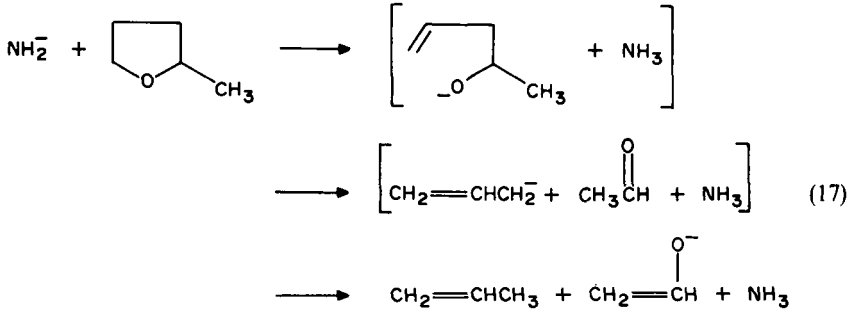
$CD_3CD_2OCD_2CD_3$ reacts with OH^- to produce an ion of $m/z = 69$ consistent with the formation of $CD_3CD_2O^-(HOD)$ via an elimination reaction[250]. For the reaction of ethyl ether with $^{18}OH^-$ (generated in the absence of water) in an ICR spectrometer, no ^{18}O-labeled ethoxide ion is produced, and collision-induced dissociation of the ion at $m/z = 65$ shows loss of H_2O^{18}, consistent with the formation of $CH_3CH_2O^-(H_2O^{18})$[253]. Furthermore, although ethyl ether reacts rapidly with both hydroxide and amide ions to produce ethylene and ethoxide ion (both free and clustered with ammonia or water), under the same conditions, methyl ether and methyl noepentyl ether react very slowly, and cyclic ethers such as THF react to produce M-1 anions that are not a result of deprotonation of the α hydrogen (for example, 2, 2,5 5-tetradeuteriotetrahydrofuran reacts with amide ion to produce $CD_2{=}CHCH_2CD_2O^-$, the product expected of 1,2-elimination)[250]. It appears therefore that for the reactions of ethers (and thioethers) in the gas phase, eliminations are strongly favored over substitutions unless there are no β hydrogens so that elimination cannot occur, the reaction is endothermic, or an *anti*-periplanar arrangement of the β hydrogen and the leaving-group is not possible (see below).

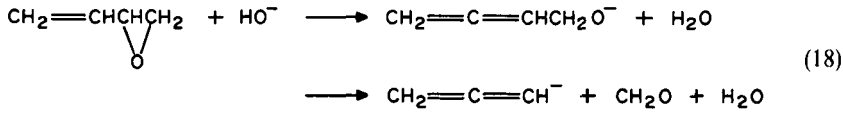
Reactions subsequent to the primary processes, such as fragmentations, eliminations and cluster formation often occur. For example, in addition to the three 'normal' products of elimination that are expected and observed for the base-catalyzed reaction of the methyl ethyl ether of ethylene glycol using the FA method, acetaldehyde enolate is also produced: in 50% yield for the reaction with hydroxide ion and in 20% yield for the reaction with amide ion[250]. The acetaldehyde enolate product is suggested to arise from further elimination within the product complex as shown in equation 16[250]. The lower yield of

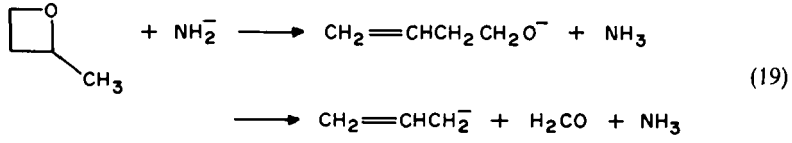
$$[CH_2{=}CHOCH_2CH_3 + CH_3O^-] \longrightarrow CH_2{=}CHO^- + CH_2{=}CH_2 + CH_3OH \quad (16)$$

$CH_2{=}CHO^-$ in the reaction with amide ion is consistent with the view that product complexes of more exothermic reactions (the reaction with amide ion, for example) have shorter lifetimes and, therefore, less time for further reaction before they dissociate[250]. The higher yields of clustered alkoxide ions than free alkoxide ions for the reactions catalyzed by HO^- compared to NH_2^- may result for the same reason, although for the reaction of HO^- with ethyl ether and F^- with ethyl sulfide, different primary kinetic isotope effects have been observed for pathways producing free ($k_H/k_D = 2.20$) and clustered ethoxide ion ($k_H/k_D = 1.55$), and free ($k_H/k_D = 1.62$) and clustered thioethoxide ion ($k_H/k_D = 1.98$), respectively[251,252]. These different isotope effects, and the fact that the isotope effects were insensitive to the translational energy of the base, were taken to mean that the two ions are produced via distinct pathways: the free ethoxide ion (thioethoxide ion) via an *anti*-periplanar arrangement, and the clustered ethoxide ion (thiophenoxide ion) via a *syn*-periplanar arrangement in which OH^- or HF stabilizes the departing ethoxide (thioethoxide) ion[251,252]. This type of interaction may also be favored, because it does not require reorganization of the product complex in order to stabilize the alkoxide or thioalkoxide ion by cluster formation. A *syn*-periplanar arrangement has also been suggested for the base-catalyzed elimination reactions of fluoroalkanes in which BHF^- ions are produced (where BH is the conjugate acid of the catalyzing base)[249,253].

Other secondary reactions (generally driven by the reaction's exothermicity or by ring strain) are shown in equations 17–19[250]. For example, 2-methyltetrahydrofuran yields the enolate of acetaldehyde (equation 17).







The monoepoxide of butadiene yields the allenyl anion (equation 18), and 2-methyloxetane undergoes reaction with amide ion (FA) to produce 47% of the allyl ion in addition to the normal products of elimination (equation 19).

The available evidence suggests that, like elimination reactions in solution, elimination reactions in the gas phase are also under stereoelectronic control. For example, although 2-methyloxetane undergoes facile elimination, oxetane itself does not, but undergoes a slow substitution reaction instead, followed by a fragmentation[250]. Ethylene oxide reacts similarly. These results are consistent with the requirement for coplanarity of the β hydrogen and the leaving-group in these reactions (both THF and THP undergo elimination as expected)[250].

The ylide mechanism (α'-β-eliminations) has also recently been observed in the gas phase. For example, using the FT–ICR method[252], for the reaction of $CD_3CD_2SCH_2CH_3$ with NH_2^- ion, 28% of the product is CD_3CHDS^- and 65% CH_3CHDS^-, product ions that result from hydrogen shifts from the β to the α' carbon. The proton transfer step in these reactions must be irreversible, because there is no hydrogen–deuterium exchange between the substrate and NH_2^- (for example, no CD_3CHDS^- is formed in the reaction of $CD_3CD_2SCD_2CD_3$ with NH_2^-)[252]. The ylide mechanism is not observed for the reactions catalyzed by HO^-, F^- or MeO^-.

B. The E2 Transition State

Primary kinetic isotope effects, secondary α hydrogen and leaving-group isotope effects have been reported as a function of base strength for the elimination reactions of ethyl ether and ethyl sulfide using the FT–ICR method[251,252]. Primary kinetic isotope effects increase from 2.2:3.5:4.03:5.60 as base strength increases from OH^-:$EtNH^-$:$MeNH^-$:NH_2^-, respectively, for the reactions of ethyl ether that produce free ethoxide ion (equation 15)[251]. The primary kinetic isotope effects reported for the reactions catalyzed by NH_2^- and OH^- under these conditions compare satisfactorily with the primary kinetic isotope effects reported for these same reactions using the FA method[250]: 5.5 and 2.1, respectively. These primary kinetic isotope effects coupled with the fact that the NH_2^- reaction shows no significant $k(OC_2H_5)/k(OC_2D_5)$ leaving-group isotope effect, whereas the hydroxide ion reactions does—$k(OC_2H_5)/k(OC_2D_5) = 1.05$ and 1.10 for reaction producing free and clustered ethoxide ion, respectively—were interpreted within the framework of the variable E2 transition state model in which the NH_2^- reaction is $E1cB_{irr}$ or E1cB-like, and the hydroxide ion reaction more central or product-like with significant cleavage of the leaving-group bond and a proton that is more than half-transferred to the hydroxide ion in the transition state. For the reaction of ethyl sulfide a similar analysis was carried out. In this case, a complete set of isotope effects could not be obtained for the reactions catalyzed by amide ions, because of the incursion of α'-β-elimination, nor for the reactions catalyzed by HO^-, because of hydrogen–deuterium exchange at the α position. However, a similar decrease in primary kinetic isotope effects was observed as the base strength was decreased from MeO^- ion to F^- ion: $k_H/k_D = 2.43$ and 1.68, respectively[252] (1.98 for the formation of clustered thiophenoxide ion). The absence of a significant secondary α hydrogen or leaving-group isotope effect for the reaction catalyzed by MeO^- ion is consistent with an $E1cB_{irr}$ or E1cB-like E2 transition state. An E2C mechanism was however suggested for the F^- catalyzed reaction producing free thioethoxide ion based on a very large α-hydrogen isotope effect of 1.30 per deuterium, and a small primary kinetic isotope effect of 1.68. Large secondary α-hydrogen isotope effects and small primary kinetic isotope effects of this kind are characteristic of E2C reactions in solution (see Section V.A below). A larger primary kinetic isotope effect (1.98), smaller α-secondary effect (1.16) and larger leaving-group effect (1.23) for the reaction producing EtS^-(HF) was taken to mean that this reaction proceeded instead with *syn* elimination through a cyclic 5-membered transition state.

C. Alkyl Fluorides

Beauchamp and coworkers were the first to demonstrate the feasibility of carrying out base-catalyzed alkene-forming eliminations in the gas phase[253]. They studied base-catalyzed reactions of fluorinated alkanes[249a]. Three important reaction channels were observed: production of BHF^- via an elimination reaction, formation of a carbanion by proton transfer and, in some cases, generation of fluoride ion via either separation from BHF^- or possibly by substitution (equation 20).

$$CD_3O^- + CD_3CH_2F \longrightarrow \begin{cases} CD_3ODF^- + CD_2{=}CH_2 \\ FCH_2CD_2^- + CD_3OD \\ F^- + CD_2{=}CH_2 + CD_3OD \\ \text{or} \\ F^- + CD_3OCH_2CD_3 \end{cases} \quad (20)$$

Further reactions of these ions were also observed. For example, F^- ion effects elimination of HF, and BHF^- transfers F^- to the starting material. The initial elimination reaction was suggested to take place with *syn* stereochemistry via a 5-membered transition state. *Ab initio* calculations for the reaction of ethyl fluoride with fluoride ion indicate that elimination is expected to be favored over substitution. The reaction is expected to follow a concerted mechanism after formation of a cluster between fluoride ion and the substrate in which the fluoride ion interacts with the β hydrogen and weakens both the C—H and C—F bonds. The concerted mechanism is favored because the fluoroethyl carbanion is calculated to be unstable with respect to expulsion of fluoride ion[256]. For more heavily fluorinated derivatives an E1cB mechanism is favored. Elimination is believed to be favored over substitution, because the cluster in which fluoride ion attacks the β hydrogen is the preferred one. However, for the reactions of ethyl bromide and cyclohexyl bromide with chloride ion, it was concluded that substitution is the favored process[257,258].

Elimination reactions have also been reported for reactions of alkyl esters catalyzed by HO^-, F^- and NH_2^- in the gas phase[254]. For example, the 3.4-fold increase in rate for the fluoride ion catalyzed reaction of ethyl compared to methyl formate is consistent with a contribution from an elimination reaction to the overall reaction of this substrate[254] (analysis of the neutrals produced in this reaction were consistent with the formation of ethylene rather than ethyl fluoride). Elimination reactions competing with reactions involving acyl-oxygen cleavage as well as S_N2 substitutions were also observed for the OH^-, F^- and NH_2^- catalyzed reactions of other alkyl esters capable of β elimination. Two mechanisms of elimination were considered: an apparent E2 elimination, and an elimination proceeding via a cyclic 6-membered transition state.

V. THE E2C MECHANISM

A. Background

As discussed in Section III.C, More O'Ferrall–Jencks energy diagrams help to characterize mechanisms and transition state structures in elimination reactions ranging from the E1 to the E1cB extremes. However, for weak or 'soft base' catalyzed elimination

reactions of many unactivated secondary and tertiary halides and tosylates, transition state structures have been proposed[76a] that are difficult to accommodate on these diagrams. These reactions, designated E2C[259], are notable in a number of respects, but, perhaps most striking, is that weak bases can promote elimination reactions at rates comparable or greater than much stronger bases do[60–68]. For example, for the reactions of cyclohexyl tosylate in acetone, chloride ion is 12 times more reactive than *p*-nitrophenoxide ion and only 2.4 times less reactive than acetate ion[75a], despite an estimated difference in DMF solution of 10^{14} in basicities[260].

In general, some of the other major characteristics of these reactions are: a very strong preference for *anti* elimination[55,75a,261], small primary kinetic isotope effects (in the range of 2–4)[262], β-substituents which in general accelerate reaction (for example, a β-phenyl or β-methyl group are about equally effective in promoting reaction)[261a], α-substituents which in general accelerate reaction, but ρ values for substitution in an α-phenyl group that are small (negative) or negligible[263], '*anti*-diaxial' eliminations that are only slightly more favorable than '*anti*-diequatorial' ones in cyclohexyl derivatives[75a], large secondary hydrogen isotope effects at both the α and β positions ($k_H/k_D = ca\ 1.1–1.2$)[263a,264–266], strong Saytzeff orientation (the requirement for *anti* elimination is, however, more important), and a preference for the formation of *trans* rather than *cis* olefins, with both Saytzeff/Hofmann and *trans/cis* alkene ratios sometime exceeding their equilibrium values[267–269].

Based on these results (and other results to be discussed below), Parker and Winstein proposed an alkene-like transition state, **4**, in which the base interacts covalently with both the α carbon and β hydrogen[55,56,75,76]. In 1975, McLennan argued[9] that the interaction between the base and the α carbon should be viewed as being primarily electrostatic in nature, and proposed transition state **5** as an alternative to **4**. Transition state **5**[270] also differs from **4** in that it has a less-developed double bond (because the proton is viewed as being only slightly transferred to the base), and an α carbon that has some carbocation character, although the charge is suggested to be effectively reduced by electrostatic interaction with the base, so that ρ values for substitution on an α-aryl group are small or negligible[263]. The enhanced reactivities of weak bases is attributed instead to stronger electrostatic interactions between these bases (e.g., chloride and bromide) and a positively charged α-carbon than with neutral bases, or bases such as acetate or aryloxide ions in which the charge is delocalized[9,271]. The enhanced reactivity of thiolate ions is ascribed to their greater polarizability.

Transition state **4** depicts a transition state with considerable double-bond character. This is supported by substituent effects at both the α and β positions in acyclic and alicyclic systems[75a,261a], large Saytzeff/Hofmann and *trans/cis* ratios, and large secondary hydrogen isotope effects at the α, β and β' positions, although measurements of β- and β'-isotope effects have been generally limited to cyclohexyl derivatives. Furthermore, for the bromide-catalyzed elimination reactions in acetone of $R^1CH_2CH(X)R^2$ derivatives (X = OTS and Br)[268], rates of formation of the Saytzeff olefins are roughly linearly related to the double-bond stabilization energies[272] of the R^1 and R^2 substituents.

Some of these results are, however, ambiguous, because product ratios in these reactions may be affected by other factors too, such as steric interaction between the leaving group and base[9] or α-alkyl group (that hinders free rotation of an α-alkyl group)[273], and relief of ground-state steric interactions[261a] as the hybridization of the α and β carbons change from sp^3 to sp^2. Furthermore, there is evidence in some systems that contradicts a transition-state model with a well-developed double bond. For example, for the thiophenoxide ion catalyzed elimination reactions in ethanol of cyclohexyl tosylate, bromocyclohexane, chlorocyclohexane, *t*-butyl chloride and 4-heptyl bromide, Bronsted β values for general base catalysis of 0.27, 0.36, 0.39, 0.17 and 0.39, respectively, have been observed[274,275]. These β values are consistent with a proton that is less than half-

transferred to the base, and a double bond that is only partly developed in the transition states for the reactions of these substrates.

Transition state **5** is favored over **4** by the relative insensitivity of these reactions to steric effects (see below), and by the fact that the neutral base, triphenylphosphine, is relatively poor in promoting elimination of cyclohexyl tosylate (relative to its ability to promote substitution)[271]. In transition state **5** the base is far removed from the α carbon, so that steric effects are expected to be minimal, and transition state **5** requires an anionic base to provide the necessary transition-state stabilization. On the other hand, transition state **4** makes no distinction between neutral and anionic bases. The fact that thiourea behaves like anionic bases do in its reaction with cyclohexyl tosylate in ethanol and *t*-butyl alcohol solutions (as defined by the elimination/substitution product ratio) is attributed to delocalization of the nitrogens' nonbonded electron pairs onto sulfur[271b]. Transition state **5** is however difficult to reconcile with the report that, for the acetate-catalyzed reaction of cyclohexyl tosylate in acetone solution, the secondary β′- and γ-hydrogen isotope effects are equal[266] (suggesting a symmetrical transition state), although McLennan points out that in this system the β′ isotope effect could be the result of hyperconjugative interaction with a developing positive charge, whereas the γ effect could be steric in origin[276].

On the other hand, a different view of these reactions has been advocated by Bunnett, who has argued that an interaction between the base and the α carbon is not required by the data; in other words, it is argued that these reactions can be adequately accommodated within the classical spectrum of E2 transition states[16,19,77–81]. According to this view, the 'E2C' transition state would be classified as either olefin or carbonium ion-like. The insensitivity of these reactions to steric effects in both the substrate and nucleophile support the view that the interaction between the base and the α carbon is either very weak or negligible[80]. For example, there is a lack of sensitivity to bulky substituents in the nucleophile for the reactions of alkyl thiolates with 2-methyl-2-butyl bromide[81,277], and rate constants for E2C reactions are often faster for tertiary than secondary substrates and not sensitive to the size of α-substituents[79,80,261a]. On the other hand, these facts may be taken to underscore the differences between S_N2 and E2C transitions states: the longer and weaker base–α carbon bond in the E2C reaction, the hybridization change from sp^3 to sp^2 at the α carbon (and β carbon), and the ability of α-alkyl substituents to stabilize a transition-state double bond, with the latter two factors working to increase the rate of E2C reactions[261a]. Solvation effects are also suggested by Bunnett to be important. For example, the greater reactivities in alcoholic solvents of thiolate than alkoxide ions under E2C conditions is attributed to the larger solvation energies of alkoxides than thiolate ions and a transition state that is early with respect to proton transfer[77,81,278].

Other alternatives to transition states **4** and **5**, such as a carbonium ion-like E2 transition state, and a mechanism in which the rate-limiting step is deprotonation of a carbonium ion ion-pair (the $E2_{ip}$ mechanism)[12,14a], are difficult to support as general mechanisms, because of the small sensitivity of the rate of E2C reactions to α-substituents, including a small sensitivity to changes in substituents in an α-phenyl group. For example, for the $(Bu)_4N^+Br^-$ catalyzed elimination reactions of 1-bromo-1-arylpropanes in acetone solution, the rate constants span a range of only 4.1 from the *m*-NO_2 to *p*-Me substituted derivatives, and the correlation of log *k* against σ^+ (or σ) is poor[263]. It is also possible that the Hammett plot is curved with a ρ value of *ca* 0 for the *m*-NO_2, *m*-Cl and unsubstituted derivatives, increasing to a negative ρ value of *ca* −0.8 for the *m*-Me, *p*-Cl, *p*-F and *p*-Me substituted compounds, consistent with a shift to a transition state with some positive charge on the α carbon for substrates with α-substituents that are able to accommodate that charge, although even in this case the correlation is poor (correlation coefficients equal to 0.91 and 0.74 when the rate constants for the *p*-Me, *p*-F, *m*-Me, *p*-Cl, unsubstituted and *m*-Cl compounds are plotted against σ^+ and σ, respectively).

B. The Valence-bond Configurational Mixing Model

The recent analysis by Pross and Shaik of elimination reactions using the Valence-Bond Configuration Mixing Model lends theoretical support to the E2C mechanism[70,71]. The transition state for an E2C mechanism is viewed as resulting from mixing the corresponding S_N2 valence-bond configuration into the wave function that describes the elimination transition state; the result is that the elimination transition state takes on some of the character of an S_N2 reaction: covalent interaction between the base and the α carbon. This is expected to occur when the substrate is weakly acidic, has a good leaving group (which is a good electron acceptor), is sterically hindered (thus retarding direct substitution), and the base nucleophilic, conditions suited for weak base catalyzed reactions[70]. According to this view, the EC2 transition state should be looser than the S_N2 transition state, because the E2C transition state will also include the valence-bond configuration of the product alkene in which there is no base–α carbon interaction. This conclusion supports the view that E2C eliminations are less sensitive to steric effects than the analogous S_N2 reactions, because of a weak base–α carbon interaction[80,279].

If the S_N2 configuration is very stable at the transition state, an intermediate radical anion is expected to form and could expel the leaving-group[70,71]. This would represent a new mechanism of elimination, named E2C-I, that would compete with E2 or E1cB reactions. Figure 5 illustrates a revised E2 transition-state spectrum according to the Valence-Bond Configuration Mixing Model.

The strong tendency for *anti* eliminations that is observed in these reactions has also been taken to support transition state **4**, because in this transition state, backside attack of the base on the α carbon would be favored. The Valence-Bond Configuration Mixing Model lends support to this view, because **20** would be a major contributing structure to the structure of the E2C transition state; structure **20** involves electron transfer from the base to the leaving-group, a process that may be strongly favored from the backside[70].

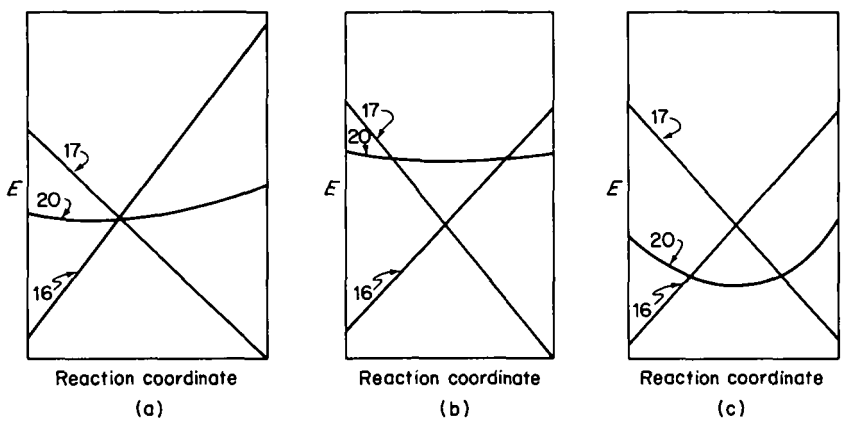


FIGURE 5. The E2H–E2C–E2C-I spectrum is shown with the aid of the valence-bond configurations **16**, **17** and **20**. (a) An E2C mechanism in which **16**, **17** and **20** have comparable energies in the vicinity of the transition state. (b) An E2H mechanism in which **20** is higher in energy than **16** and **17** in the vicinity of the transition state. (c) An E2C-I mechanism in which **20** is more stable than **16** and **17** in the vicinity of the transition state. Reprinted with permission (numbers corresponding to structures **16**, **17** and **20** have been changed) from A. Pross and S. Shaik, *J. Am. Chem. Soc.*, **104**, 187 (1982). Copyright (1982) American Chemical Society

However, this result does not distinguish **4** or **5** from the other possible mechanisms, because the *anti* stereochemistry observed could also be a consequence of the fact that *syn* eliminations are disfavored for weak base catalyzed reactions in polar solvents, and for reactions in which the transition state lacks carbanion character—conditions characteristic of E2C eliminations (see Section III.G for other factors that can influence the stereochemistry of elimination reactions).

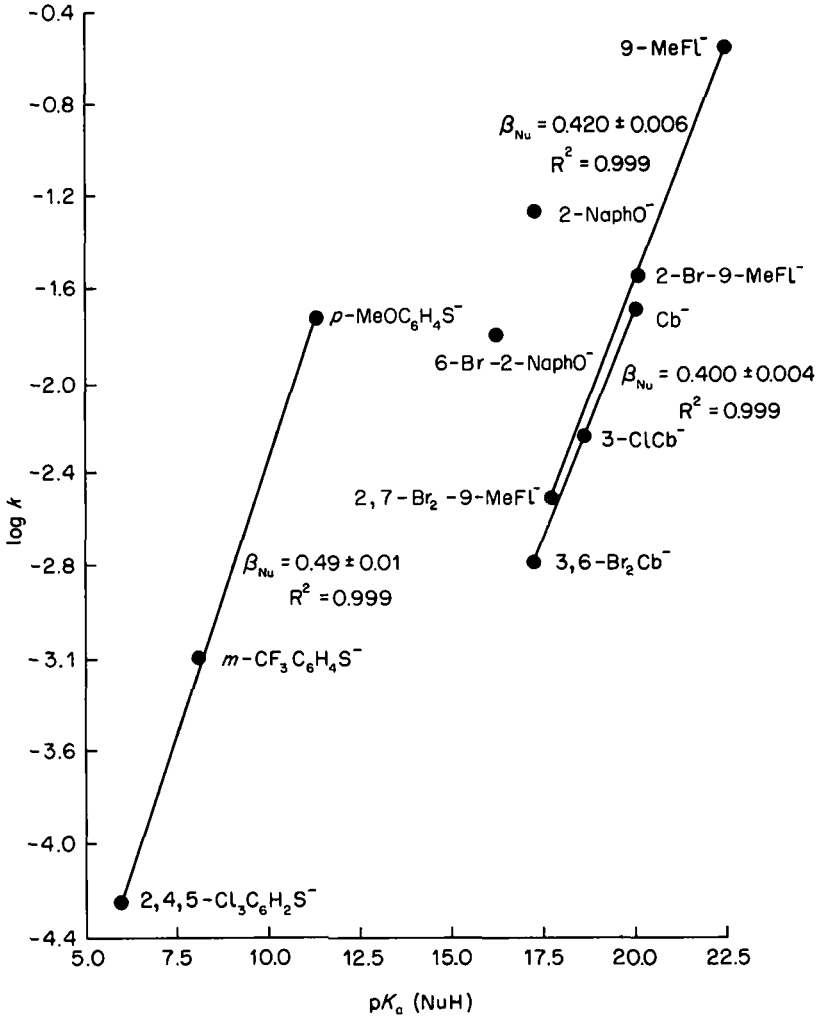


FIGURE 6. Plots of the second-order rate constants ($\log k$) against pK_a values for the reactions of benzenethiolates ions, 2-napthoxide ions (2-NaphO$^-$), 9-methylfluorene carbanions (9-MeFl$^-$) and carbazole nitranions (Cb$^-$) with cyclohexyl bromide in DMSO solution at 25 °C. R^2 is the square of the correlation coefficient. Reprinted with permission from F. G. Bordwell and S. R. Mrozack, *J. Org. Chem.*, **47**, 4815 (1982). Copyright (1982) American Chemical Society

C. Rate Correlations

One of the strongest arguments that has been made in support of transition states such as **4** or **5** (particularly **4**) are the correlations sometimes observed between E2C and S_N2 rate constants[12,75b]. For example, for the classic E2C substrate, cyclohexyl tosylate, a plot of $\log k_E$ for elimination against $\log k_S$ for concurrent substitution, is linear with slope 1.0[76a]. Likewise, a plot of $\log k_E$ for reactions of *t*-butyl bromide against $\log k_S$ for reactions of cyclohexyl tosylate also results in a good correlation with slope 1.0[76b] (for *t*-butyl bromide, substitution does not compete well with elimination under these conditions). However, for the reactions of cyclohexyl bromide in DMSO, rates of dehydrobromination do not correlate with rates of S_N2 substitution of a model S_N2 substrate, benzyl bromide[280]. The elimination reactions of cyclohexyl bromide in DMSO, promoted by oxyanions (2-napthoxides, 2-NaphO$^-$), thianions (benzenethiolates, ArS$^-$), nitranions (carbazoles, Cb$^-$) and carbanions (9-methylfluorenes, 9-MeFl$^-$), give relative reactivities (obtained by extrapolating the Bronsted plots to a common pK_a value, Figure 6) of: ArS$^-$ > 2-NaphO$^-$ > Cb$^-$ > 9-MeFl$^-$, an order that is different from the order for the S_N2 reactions of these same nucleophiles with benzyl bromide in the same solvent. For the S_N2 reactions, the reactivity order is: ArS$^-$ > 9-MeFl$^-$ > 2-NaphO$^-$ > Cb$^-$. However, the oxyanions, nitranions and carbanions studied in this work are considerably more basic than the arenethiolates (*ca* 5 to 11 pK_a units more basic than the most basic arenethiolate studied, 4-MeOphS$^-$, which has a pK_a value of 11.2 in DMSO), whereas the pK_a values for the other classes of bases studied range from 17 to 22—much more basic than halide ions, the traditional promoters of E2C reactions. Poor correlations of elimination and substitution rate constants have, however, also been observed for reactions of cyclohexyl bromide and *cis*-2-methylcyclohexyl tosylate (excluding the points for azide and ethoxide ions which are known to deviate)[75a]. For the reactions of cyclohexyl bromide it was argued that because bromide is a poorer leaving-group than tosylate, cyclohexyl bromide will react through a tighter or more E2H-like transition state than cyclohexyl tosylate, so that the correlation of substitution and elimination rate constants is expected to be poorer.

Nevertheless, these observations weaken the hypothesis that transition states such as **4** have general applicability[12], although transition state **5** remains a viable structure—the lack of correlations between log k_E and pK_a values in these reactions (and the better correlations that are sometimes observed against rates of substitution) were originally taken as evidence against an E2 mechanism for which a good Bronsted correlation was expected, and in support of a transitions state such as **4**[76a]. However, it is now known that different families of catalysts often give rise to different Bronsted lines, even in reactions involving only proton transfers[281–283]. The scatter observed in plots of log k_E against pK_a for weak base-catalyzed reactions is almost certainly partly or entirely due to this factor.

D. Temperature Dependence of Primary Hydrogen Isotope Effects

Because proton transfer to the base must be nonlinear in the transition state of an E2C mechanism in which the base interacts with the α carbon, the temperature dependence of primary kinetic isotope effects has been proposed as a criterion to identify this mechanism (for criticisms of this approach, see Section III.A)[154]. Based on this criterion of mechanism, an E2C mechanism has been proposed for a number of bromide and tertiary-amine catalyzed reactions of 2-phenylethyl derivatives in acetonitrile solution. For example, for the fluoride-catalyzed elimination reactions of 2-phenylethyl tosylate, bromide and dimethylsulfonium ion, an E2C mechanism was proposed based on primary kinetic isotope effects that are independent of temperature and A_H/A_D values that are much larger than the theoretical value of $2^{1/2}$—values range from 3.6 to 6.6; furthermore, the magnitude of A_H/A_D was taken proportional to the angle

of hydrogen transfer[284]. On the other hand, an E2 mechanism with proton tunneling was suggested for the trimethylammonium ion derivative, because the primary kinetic isotope effect now shows a large temperature dependence with an A_H/A_D value much less than $2^{1/2}$ (0.212)[285].

Based on the same criterion of temperature-independent primary kinetic isotope effects and anomalously large A_H/A_D values, E2C mechanisms have also been suggested for the bromide-catalyzed reactions in acetonitrile of *erythro*- and *threo*-1-phenyl-1-propyl-2-d_1-*p*-nitrobenzoates[286], and for the bromide and tertiary-amine catalyzed reactions (Proton Sponge, DBN and Dabco) of ethyl-2-bromo-3-phenylpropionate and methyl-2-bromo-2-methyl-3-phenylpropionate[265]. A common reaction intermediate was suggested for the bromide-catalyzed eliminations of the *erythro*- and *threo*-1-phenyl-1-propyl-2-d_1-*p*-nitrobenzoates, based on identical product ratios of *E*-PhCH=CDMe and *E*-PhCH=CHMe alkenes from both the *erythro* and *threo* isomers: 67% and 33% of these alkenes, respectively. The authors resurrected the idea of a trigonal-bipyramid carbon intermediate. An E2C mechanism with a trigonal-bipyramid intermediate has also been suggested for the reaction of a 50:50 mixture of *threo*- and *erythro*-ethyl-2-bromo-3-phenyl-3-deuterio-propionate. In this case, the intermolecular primary kinetic isotope effect and intramolecular isotope effect are equal (2.6); an intramolecular primary kinetic isotope effect of 2.6 is surprising, because the isotope effect was calculated from the relative amounts of deuterated and undeuterated alkenes produced after the reaction was allowed to go to completion—only the *trans* isomer was formed. If only *anti* elimination had occurred (as would be expected for a *bona fide* E2C reaction), then a primary kinetic isotope effect of 1.0 is expected. These are very surprising results, but it is difficult to see why an E2C mechanism would be favored for many of these compounds because 2-phenylethyl systems have a strong tendency to react via E1cB–E2 transition states as illustrated most forcefully by the large positive Hammett ρ values that have been reported in both polar[1] and dipolar aprotic[211] solvents, and because fluoride ion, DBN, Dabco and Proton Sponge are not expected to be good E2C bases—for example, it is difficult to see how, in a transition state such as **4**, an amine base could simultaneously abstract a proton and covalently interact with the α-carbon atom.

VI. THE E1cB$_{rev}$ MECHANISM

A. General

The E1cB$_{rev}$ mechanism involves rate-limiting breakdown of a free carbanion. A number of substrates that follow the E1cB mechanism were discussed in Section II. E1cB$_{rev}$ mechanisms have also recently been proposed for elimination reactions of 2,2-di(*p*-nitrophenyl)-1,1,1-trifluoroethane catalyzed by either methoxide in methanol or ethoxide ion in ethanol[287] (however, the primary kinetic isotope effect of 5.4 and the lack of hydrogen–deuterium exchange for the reaction catalyzed by *t*-butoxide ion in *t*-butanol is consistent with a change to either an E1cB$_{irr}$ or E2 mechanism for the reaction under these conditions), and for the elimination reactions of 2-halogeno-3-methoxy-1,3-diphenylpropan-2-ones and the related methyl propionate esters[116,288].

B. Leaving-group Ability

1. Acyclic systems

In a now classic study of leaving-group abilities in elimination reactions, Stirling utilized the ethoxide-catalyzed E1cB$_{rev}$ reactions of 2-(phenylsufonyl)ethyl and 2-cyanoethyl derivatives in ethanol to formulate a scale of relative leaving-group abilities

(nucleofugalities) from the carbanions formed as intermediates in these reactions[22]. No general correlation was found between leaving-group ranks and pK_a, carbon leaving-group bond strengths or nucleophilic reactivities towards carbon (as defined by the Swain–Scott relationship) when a variety of leaving groups from different families were compared. A recent reexamination of the data for the 2-(phenylsulfonyl)ethyl derivatives indicates, however, that a much better correlation exists than previously thought between leaving-group rank and pK_a when a very large reactivity range is explored (Figure 7)[289], although large deviations from the correlation are still noted—carbon leaving groups are particularly poor for a given pK_a, whereas methoxide, phenoxide and $PhN(Me)_2$ are more reactive than expected. The $E1cB_{rev}$ mechanism was assigned to substrates in these series when either primary kinetic isotope effects near one were measured, and/or hydrogen–tritium exchange into the substrates occurred faster than elimination under the reaction conditions[22]. The calculation of the leaving-group scale is based on the reasonable assumption that the rates of protonation of the carbanion intermediates

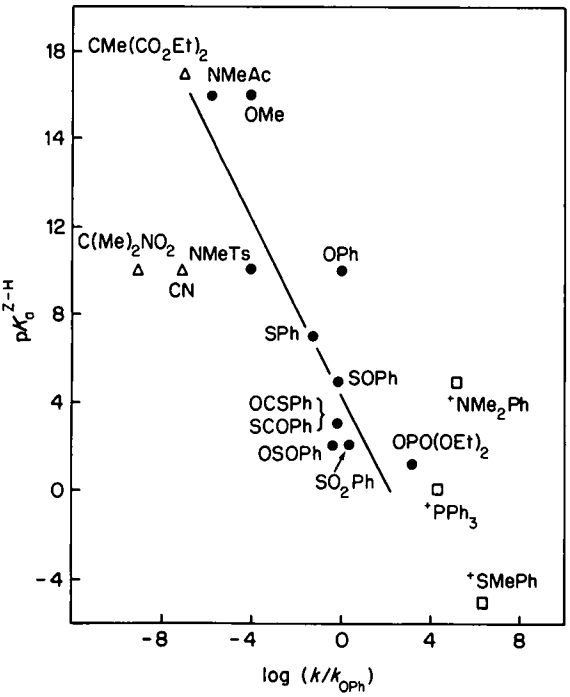
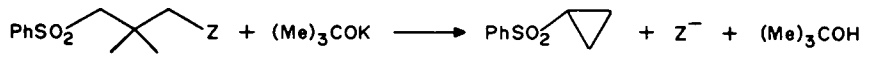


FIGURE 7. Plot of the pK_a of the leaving-group against $\log(k/k_{OPh})$, where k_{OPh} and $\log k$ are rate constants for the ethoxide ion catalyzed elimination in ethanol of 1-phenoxy-2-(phenylsulfonyl)ethane and 1-*Z*-(2-phenylsulphonyl)ethanes, respectively. The regression line was fit to the data for eleven *Z* groups (solid circles). Rate constants for the three carbon leaving groups (open triangles) are minimum values. The three onium ion leaving groups are denoted by open squares. Reprinted with permission from D. B. Boyd, *J. Org. Chem.*, **50**, 885 (1985). Copyright (1985) American Chemical Society

(k_{-1}[BH]) are near the diffusion-controlled limit, and therefore changes in the leaving-group will have a small or negligible affect on these rate constants. Hence, relative values of k_1 (the proton transfer rate constants), are proportional to relative values of k_2, the rate constants for expulsion of the leaving-groups from the intermediate carbanions. Stirling defined a leaving-group scale equal to log $(k_{obsd}/k_1) + 11$, in which values of k_1 were obtained either from directly measured detritiation rates, or by extrapolation of Taft plots based on rates of detritiation (in both cases, rate constants were corrected for primary tritium isotope effects). The range of nucleofugalities in these systems in large (10^{14}). With phenylsulfonyl activation, for example, nucleofugalities range from sluggish carbon nucleofuges such as $CMe(SO_2Et)_2$ and $CMe(CO_2Et)_2$ with ranks of -3.6 and -3.7, to the relatively good PhSe and $PhNMe_2$ nucleofuges with ranks of 10.4 and 9.2. Leaving groups much better than these, such as the commonly employed bromide, chloride, iodide, acetate and tosylate leaving groups, cannot generally be given a quantitative rank because of changes in mechanism for substrates with these leaving groups: from the $E1cB_{rev}$ mechanism for substrates from which rankings can be obtained as noted above, to either the $E1cB_{irr}$ mechanism in which leaving-group bond cleavage is no longer part of the rate-limiting step, or the E2 mechanism, in which bond cleavage becomes coupled to proton transfer. In both of these latter cases, the observed rates of reaction no longer provide a reliable measure of nucleofugalities.

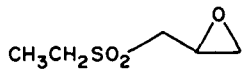


(21)

Leaving-group rankings have also been reported for 1,3-eliminations of a phenyl sulfonyl activated system (equation 21)[290]. This is an interesting system because the potassium *t*-butoxide detritiation rate constants in *t*-butyl alcohol for the Cl and OTs, as well as the SO_2Ph, SPh and OPh derivatives are faster than 1,3-elimination under the same reaction conditions ($E1cB_{rev}$). This behavior contrasts with the corresponding phenylsulfonyl activated 1,2-eliminations (conducted, in general, in ethanol solution) in which the chloride and tosylate follow either an E2 or an $E1cB_{irr}$ mechanism[33,34a]. This is understandable if there is less driving force for leaving-group expulsion in 1,3- rather than 1,2-eliminations, and because rates of leaving-group expulsion are expected to be slower in *t*-butanol than in ethanol solutions. Kinetic problems were identified: for example, detritiation and dedeuteration rate constants for substrates with $Z = PhSO_2$ and H are about equal, suggesting that internal return may be contributing to the rate of the exchange reactions under these conditions. A plot of leaving-group ranks for these 1,3-eliminations (for the leaving groups noted above) against pK_a values measured or estimated in *t*-butyl alcohol shows a good correlation (with a large slope of -0.8), over *ca* 11 orders of magnitude in leaving-group rank and 16 pK_a units.

2. *Alicyclic systems*

The effect of strain in the leaving group on reactivity has also been explored and large rate accelerations noted[23]. In a number of cases the accelerations are large enough to effect a change in mechanism. For example, elimination of **35** in which the oxyanion leaving group is incorporated into a 3-membered ring reacts *ca* 10^6 faster than $PhSO_2CH_2CH_2OMe$ in which it is not[291]. An E2 mechanism is suggested for **35** based on a primary kinetic isotope effect of 2.5 and an elimination rate constant that is much larger than estimated for rate-limiting proton transfer[291]. Similarly, when the sulfur analogue of **35** was studied, namely **36**, a rate acceleration of 9.7×10^5 was observed and, as with the oxirane derivative, the observed enhancement in leaving-group ability associated with the



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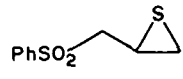
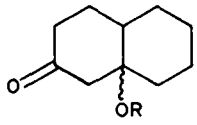


(36)

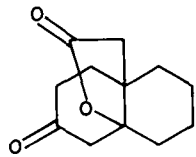
strained ring system leads to a change from an E1cB$_{rev}$ mechanism for $PhSO_2CH_2CH_2SEt$ to an E2 mechanism for the thiirane derivative based on a primary kinetic isotope effect of 3.2 and an elimination rate constant that is 2×10^3 larger than the estimated rate constant for proton transfer[292].

Mayer and Spencer have also demonstrated a change from an E1cB mechanism for the reaction of substrate, **37**, R = MeCO (for isomers with both *cis* and *trans* ring-fusions)[168a,b,293] to an E2 mechanism for the reaction of lactone **38**[294] that was ascribed to an acceleration of leaving-group expulsion due to strain in the lactone ring. Evidence for an E2 mechanism for **38** was based on rate accelerations of 50- to 10^4-fold for the hydroxide ion and substituted quinuclidine promoted elimination reactions of **38** relative to **37**, R = MeCO (*cis* ring-fusion), and a decrease in the Bronsted β value for general base catalysis from 0.69 to 0.42. Little difference in Bronsted β values, and only a small difference in rate that is consistent with a small difference in the polar effect of a OH and MeCOO group, were observed for the base-catalyzed reactions of **37**, R = MeCO and H. An X-ray crystal structure shows that the lactone **38** exists in a conformation in which the β proton and the C—O bond are *anti* periplanar; the C—O bond may be slightly elongated (1.486 Å), consistent with an enhanced reactivity[295]. Both **37**, R = H and **39** were shown to follow the E1cB mechanism based on changes in rate-limiting step with increasing buffer concentration. That the β-alkoxy ketone is also probably strained is shown by a rate constant for expulsion of the alkoxide ion from **39** that is at least 25 times greater than from **37**, R = H.



(37)

R=COMe, H



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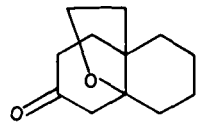
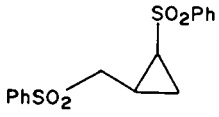


(39)

An acceleration of *ca* 10^9 (this has been revised downward[296,297] from a previous estimate of $10^{11.7}$) was calculated for the case in which a carbon leaving group, represented by **40**, is constrained to a 3-membered ring and compared with the related unstrained compound **41**[298]. For the reaction of **40**, it was demonstrated that the rate-limiting step is cleavage of the cyclopropane ring, although the overall reaction is multistep and leads to $PhSO_2CH_2CH(OEt)CH_2CH_2(OEt)$. This latter compound is formed as a result of isomerization of $PhSO_2CH{=}CHCH_2CH_2SO_2Ph$ followed by elimination of $PhSO_2^-$, and addition of 2 equivalents of ethanol to the resulting diene. The estimate of the acceleration noted above is crude, because **41** does not react under the reaction conditions (EtO^- in ethanol), so its reactivity had to be estimated in a roundabout way: the rate of elimination of $PhSO_2CH_2CH_2C(Me)(SO_2Et)_2$ was studied in *t*-butanol catalyzed by *t*-butoxide ion, and corrections made both for the effect of having a leaving group that is now stabilized by two phenylsulfonyl groups and for the effect of changing solvents from ethanol to *t*-butanol.



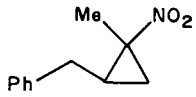
(40)

$PhSO_2CH_2CH_2CH(Me)SO_2Ph$

(41)

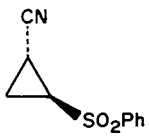
A second estimate of the rate of reaction of **41** in ethanol was obtained from the rate of elimination of $(MeSO_2)_2CHCH_2C(Me)(SO_2Et)_2$ in ethanol after corrections were made for both leaving-group and activating-group differences between the two substrates. These estimates for the reactivity of **41** differ by a factor of $10^{1.5}$, but nevertheless provide a rough measure of the extent of the rate acceleration. This acceleration corresponds to release of *ca* 46% of the strain energy of the cyclopropane ring, where the strain energy is defined as the excess enthalpy of the strained system determined from heats of combustion versus the enthalpy calculated using group equivalents obtained from unstrained molecules[299].

Although E2 mechanisms are uncommon for substrates with carbon leaving groups, if the rate of leaving-group expulsion is enhanced enough by ring strain, an E2 mechanism becomes possible. Such may be the case for the elimination reaction of **42** for which a rate acceleration of $10^{7.6}$ has been reported by comparing **42** with $PhSO_2CH_2CH_2C(Me)_2NO_2$[292]. Elimination from the cyclopropane derivative occurs about 20 times faster than the estimated rate of the proton transfer step so an E2 mechanism may be operating here[292].



(42)

Constraining a leaving group to a 4-membered ring also results in large rate accelerations over acyclic models, but these accelerations are not as large as those observed for 3-membered rings[300,301]. For example, the 3-ring/4-ring ratio is 4840 and 57,600 when comparing **43** with **44**, and **45** with **40**, respectively. Both the cyano and phenylsulfonyl substituted cyclobutanes react with rate-limiting ring opening. The reactivity differences between three- and four-membered rings are ascribed to differences in the rates at which these rings open, and to calculations[302,303] that suggest that the reduction of the excess enthalpy of the cyclobutane derivatives fall off more slowly as a function of cleaving the carbon–carbon ring bond than for the cyclopropanes.



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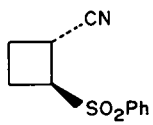

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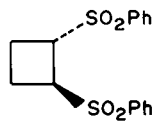

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VII. THE E1cB$_{ip}$ MECHANISM

A. 2-Phenyl-activated Systems

A new approach to diagnose an ion-pair mechanism in which both reprotonation and breakdown of the ion-pair occur at comparable rates is based on measuring leaving-group

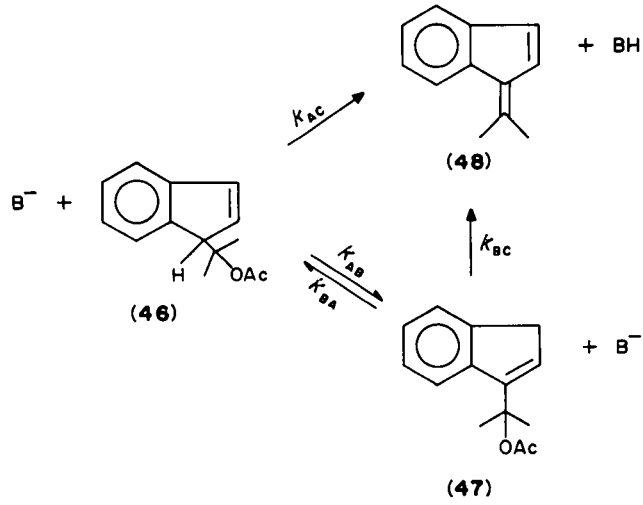
(chlorine was used) or α-carbon isotope effects for both β-deuterated and unlabeled substrates[141,304]. If k'_2 and k_{-1} are comparable (Scheme 1), then the leaving-group isotope effect (or α-carbon isotope effect) should be significantly smaller for the deuterated compared to the unlabeled substrate, because the k_{-1} step could be slowed by a primary hydrogen isotope effect. For example, for the elimination reactions in ethanol of $PhCH(CH_3)CH_2Cl$, $k^{35}/k^{37} = 1.00590$ and 1.00507 for the unlabeled and deuterated compounds, respectively; this fact, coupled with a primary kinetic isotope effect of 5.37, means that the mechanism in this case is probably E2[305]. Similarly, α-carbon isotope effects for elimination reactions of $PhC(CH_3)CH_2I$ are, within experimental error, the same (*ca* 1.03) for the deuterated and unlabeled compounds[304]. For the elimination reactions of $PhCHClCF_2Cl$ and $PhCHClCH_2Cl$, however, k^{35}/k^{37} is significantly smaller for the deuterated compared to the unlabeled substrate (1.01255 vs. 1.01025 and 1.00978 vs. 1.00776, respectively, in methanol solutions), results that are consistent with a mechanism involving significant amounts of internal return, although the differences in the isotope effects were reported to be much smaller than that expected based on model calculations[304].

Based on a variety of evidence, including anomalous Arrhenius parameters (e.g. temperature-independent primary kinetic isotope effects and curved Arrhenius plots), Hammett ρ values, the magnitude and temperature dependency of primary kinetic isotope effects, leaving-group isotope effects, yields of nucleophilic addition and vinylic substitution products from reactions of alkoxides with alkenes, and enlarged rate-constant ratios for reactions in *t*-butanol and ethanol solutions catalyzed by potassium *t*-butoxide and ethoxide ions, Koch has proposed an $E1cB_{ip}$ mechanism or an $E1cB_{ip}$ mechanism in which k_{-1} and k'_2 are comparable for a number of α- and β-halogenated 2-phenylethyl derivatives[74b,162,141,304–308]. An $E1cB_{ip}$ mechanism in which k'_2 and k_{-1} are comparable is expected to show many of the same characteristics of a concerted E2 mechanism—lack of exchange, significant primary kinetic isotope effects, leaving-group effects, and possibly even stereospecific reactions if the hydrogen-bonded intermediate maintains the substrate's configuration[74a]. Furthermore, changes in substrate structure and reaction conditions may give rise to changes in isotope effects and structure–reactivity parameters that are due to changes in the amount of internal return in this mechanism, but equivalent in kind to the changes in these parameters that are associated with a variable E2 transition-state structure. Although this mechanism must exist, and a number of examples of it were cited above (e.g. the ethoxide and methoxide ion catalyzed elimination reactions of $PhCHClCF_2Cl$ and $PhCHClCH_2Cl$), its weakness as a general mechanism is that k'_2 and k_{-1} must be comparable in magnitude (within a factor of 50 or so of each other); if not, then the steady-state rate expression simplifies to a form where either k_1 or k'_2 is rate-limiting.

B. Indenyl Systems

Ahlberg, Thibblin and coworkers have studied tertiary-amine and oxyanion catalyzed reactions of 1-(1-substituted-1-methylethyl)indenes, **46**, in methanol in which 1,2-elimination to form **48**, 1,3-proton transfer to form **47**, and 1,4-eliminations (**47** to **48**) occur competitively (Scheme 2)[309].

For the reaction of the acetate with a variety of tertiary amine bases (triethylamine, *N*-ethylpiperidine, quinuclidine and Dabco) little or no hydrogen–deuterium exchange into **48**, **46** or **47** was observed, although at high buffer concentrations of quinuclidine and Dabco, 17 and 12 atom%, respectively, incorporation of hydrogen into **48** was detected[121]. Hydrogen incorporation into **47** of 9 and 18 atom% has also been reported for the Dabco-catalyzed reaction in the presence of 0.005 and 0.50 M Dabco H^+[310], and 13 and 20 atom% incorporation for the *p*-nitrophenoxide-catalyzed reactions at 0.24 and 0.71 M



SCHEME 2

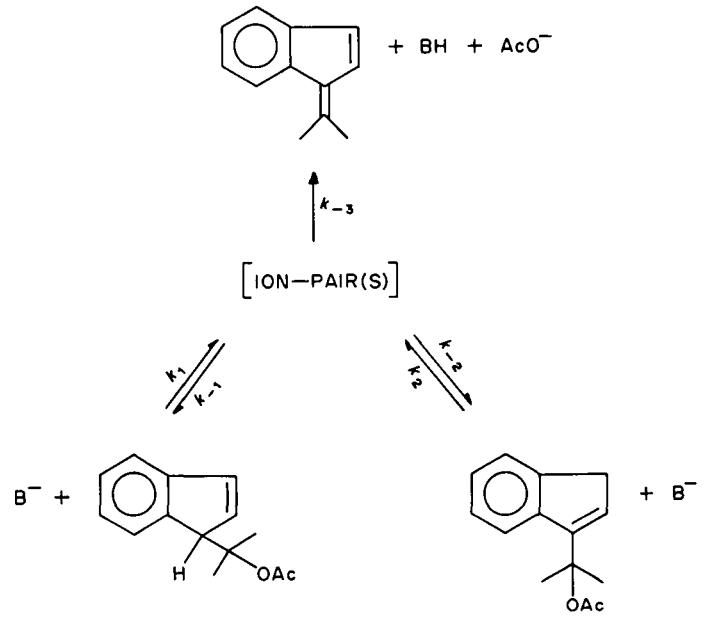
p-nitrophenol buffer concentrations, respectively[311]. These results indicate that the three processes occur, in general, without large amounts of H–D exchange and, for many bases, little or no exchange is observed. For the 1,4-elimination reaction of **47** small primary kinetic isotope effects were observed: $k_H/k_D = 1, 3, 1.3, 1.6, 1.0$ and 2.5 for the triethylamine, *N*-ethylpiperidine, quinuclidine, Dabco and *p*-nitrophenoxide catalyzed reactions, in methanol, respectively. These small primary kinetic isotope effects are consistent with a mechanism involving significant amounts of internal return. The primary kinetic isotope effects associated with the disappearance of **46** are 7.3, 7.0, 7.1, 5.2, 6.5 and 5.2 for the triethylamine, *N*-ethylpiperidine, quinuclidine, Dabco, methoxide and *p*-nitrophenoxide[311] ion catalyzed reactions, respectively. These primary kinetic isotope effects are consistent with a rate-limiting proton transfer reaction, either via an $E1cB_{irr}$ or E2 mechanism. A Bronsted β value of 0.53 for the oxyanion-catalyzed reactions (based on three points), and of 0.47 for the amine-catalyzed reactions (based on two points) are consistent with the large primary kinetic isotope effects observed for these reactions and a proton that is about half-transferred in the transition state.

An E1cB mechanism was favored for these reactions, because the primary kinetic isotope effects for the 1,3-proton transfer reactions were enlarged: > 13, 14.7, 18.1, 7.9 and 12.2 for the triethylamine, *N*-ethylpiperidine, quinuclidine, Dabco and *p*-nitrophenoxide ion catalyzed reactions, respectively (the methoxide catalyzed reaction does not yield significant amounts of rearranged product). The primary kinetic isotope effects for the 1,2-elimination reaction were apparently attenuated, with values of 2.5, 2.6, 4.0, 1.9 and 3.6 for the reactions of these same bases. These primary kinetic isotope effects are consistent with Scheme 3, in which the three processes are coupled via a common intermediate. This follows from the steady-state rate equation for this type of system (equations 22–24), in which k_{AB}, k_{AC} and k_{BC} correspond to the apparent rate constants for

$$k_{AB} = k_1 k_{-2}/(k_{-1} + k_{-2} + k_{-3}) \quad (22)$$

$$k_{AC} = k_1 k_{-3}/(k_{-1} + k_{-2} + k_{-3}) \quad (23)$$

$$k_{BC} = 2k_2 k_{-3}/(k_{-1} + k_{-2} + k_{-3}) \quad (24)$$



SCHEME 3

the 1,3-proton transfer, 1,2 and 1,4-elimination reactions, respectively. These equations can be transformed into equations 25–27 which describe the primary kinetic isotope effects for these three processes in terms of the rate constants for the mechanism's elementary steps[312].

$$\frac{k^{H}_{AB}}{k^{D}_{AB}} = \frac{k^{H}_{1}}{k^{D}_{1}}\left(\frac{k^{D}_{-3}}{k^{D}_{-2}} + \frac{k^{D}_{-1}}{k^{D}_{-2}} + 1\right)\Big/\left(\frac{k^{H}_{-1}}{k^{H}_{-2}} + \frac{k^{H}_{-3}}{k^{H}_{-2}} + 1\right) \tag{25}$$

$$\frac{k^{H}_{AC}}{k^{D}_{AC}} = \frac{k^{H}_{1}}{k^{D}_{1}}\left(\frac{k^{D}_{-2}}{k^{D}_{-3}} + \frac{k^{D}_{-1}}{k^{D}_{-3}} + 1\right)\Big/\left(\frac{k^{H}_{-1}}{k^{H}_{-3}} + \frac{k^{H}_{-2}}{k^{H}_{-3}} + 1\right) \tag{26}$$

$$\frac{k^{H}_{BC}}{k^{D}_{BC}} = \frac{k^{H}_{2}}{k^{D}_{2}}\left(\frac{k^{D}_{-2}}{k^{D}_{-3}} + \frac{k^{D}_{-1}}{k^{D}_{-3}} + 1\right)\Big/\left(\frac{k^{H}_{-1}}{k^{H}_{-3}} + \frac{k^{H}_{-2}}{k^{H}_{-3}} + 1\right) \tag{27}$$

The isotope effect on k_{-3} is expected to be small and approximately equal to 1, because this step does not involve transfer of a proton. Therefore, the primary kinetic isotope effect on k_1 for the 1,3-proton transfer reaction should be amplified, whereas attenuated primary kinetic isotope effects are expected for the 1,2- and 1,4-elimination rate constants, k_{AC} and k_{BC}, respectively. The amplification is a result of elimination competing with rearrangement (with both reactions having the same rate-limiting step), and will increase in magnitude with increasing amounts of elimination (relative to 1,3-proton transfer) and/or decreasing amounts of internal return. Even larger primary kinetic isotope effects than noted above were reported for the quinuclidine catalyzed reactions of *erythro*- and *threo*-1-(acetoxyethyl)indenes: primary kinetic isotope effects of 39 and 30, respectively, for the 1,3-proton transfer reactions of these substrates. A value of 89 ($\pm$ 25) has been reported for the quinuclidine-catalyzed reaction of the acetate in 35 weight% DMSO in water, a value that must be close to the theoretical maximum for this scheme, namely $k^{H}_{1}/k^{D}_{1}(k^{H}_{-2}/k^{D}_{-2})$, with

little or no internal return, accompanied by only small amounts of rearranged product (approximately 0.71% for the reaction of the deuterated substrate). An alternative explanation for these large primary kinetic isotope effects is that proton tunneling is occurring in the 1,3-proton transfer reactions. This was, however, considered unlikely because a normal primary kinetic isotope effect of 7.1 was observed for the 1,3-proton transfer reaction of the methoxy derivative catalyzed by *N*-ethylpiperidine—this substrate does not undergo a 1,2-elimination so that the 1,3-proton transfer reaction can be studied directly[121].

Solvent effects and structure–reactivity effects are also consistent with Scheme 3. For example, the ratio of elimination to rearrangement of **46** increases as the solvent's polarity increases—from methanol to mixtures of MeOH and water, and DMSO and water, and as the pK_a of the base catalyst increases. For example, for the reaction of the acetate derivative, in order of decreasing yields of rearranged product we have: pyridine > Dabco > triethylamine, > *N*-ethylpiperidine > quinuclidine >, and *p*-nitrophenoxide > phenoxide > methoxide ion, the same qualitative order of increasing base strength and decreasing ability to protonate an intermediate carbanion. The primary kinetic isotope effects for the overall reaction also increase for the reactions catalyzed by the stronger bases. These results taken together are consistent with Scheme 3, and with less internal return and less rearrangement for the reactions catalyzed by the stronger bases, and for reactions carried out in the more polar solvents (a more polar solvent should favor breakdown of the ion pair via the k_{-3} route for electrostatic reasons).

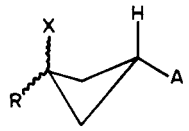
Scheme 3 has recently been expanded to accommodate two ion-pair intermediates[38]. The additional ion-pair intermediate was proposed because **46** and **47** produce intermediates that behave differently, and give ratios of isotope effects for the ionization of **46** and **47** that are significantly larger than expected. For example, for the Dabco-catalyzed reaction in DMSO/water mixtures, **46** gives about 55% of **48** while **47** produces an intermediate that is reprotonated to regenerate **47** faster than it eliminates to give **48**. This result also requires that the two ion-pair intermediates are not in equilibrium[311].

An interesting but difficult question about $E1cB_{irr}$ reactions is whether it is the initially formed ion pair or the free carbanion that breaks down to products. In a recent paper, Thibblin argues that for the Dabco-catalyzed 1,2-elimination reaction of **46** it is the ion pair rather than the free carbanion that breaks down to **48**[313]. It is reasonably argued that if the acetoxy group is expelled from a free carbanion, then significant amounts of hydrogen–deuterium exchange must be observed for the methoxy derivative, because this derivative does not eliminate under the reaction conditions but only gives rearranged product **47**. Since no exchange is observed for the reaction of the methoxy derivative, it is concluded that elimination of the acetoxy group occurs directly from the ion pair. The pyridine-catalyzed reaction of the chloro derivative is suggested to follow the same mechanism, because chlorine is a better leaving group than acetoxy and pyridinum ion is a stronger hydrogen-bond donor than $DabcoH^+$[38]. Therefore, the ion-pair intermediate should expel chlorine even faster than the acetoxy group relative to the rate of dissociation to the free carbanion.

Interestingly, an $E1cB_{ip}$ mechanism is also suggested for the reaction of the chloro derivative (catalyzed by pyridine in methanol), based on an enlarged primary kinetic isotope effect of 14.6 for the 1,3-proton transfer reaction of this derivative[38]. A second ion-pair intermediate has also been suggested for this reaction, based on the fact that the enlarged isotope effect on the 1,3-proton transfer reaction is smaller than expected.

C. Other Systems

The *t*-butoxide ion catalyzed elimination reactions of 1,3-disubstituted cyclobutanes, **49–53**, to give 1,3-disubstituted bicyclobutanes have recently been reported[314]. For



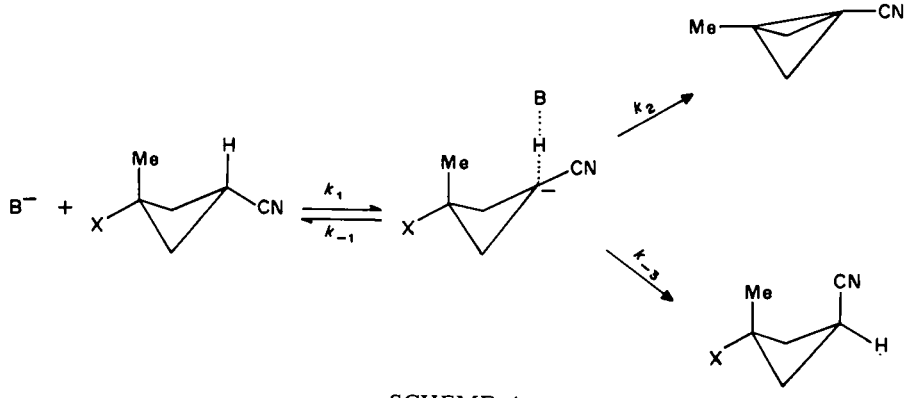
(**49**) A=CN, R=H, X=Cl
(**50**) A=CN, R=Cl, X=Cl
(**51**) A=CN, R=Me, X=Cl
(**52**) A=CN, R=Me, X=Br
(**53**) A=PhCO, R=H, X=Cl

compounds **49** and **51** isomerization was observed to compete with elimination (k_{isom} is approximately equal to k_{elim} for these compounds). Although compound **50** cannot isomerize, it showed hydrogen–tritium exchange when the reaction was conducted in tritiated *t*-butyl alcohol.

Element effects of 70 and 30 were reported for the *syn* and *anti* eliminations of compounds **51** and **52**, respectively. These effects are not consistent with an $E1cB_{rev}$ mechanism in which k_2 is approximately equal to k_{-1} for the chloride, but $k_2 > k_{-1}$ for the bromide (see equation 5), because such a mechanism cannot reasonably account for element effects of the magnitude observed. For such a mechanism, the element effect is

$$k_{Br}/k_{Cl} = k_2^{Br}(k_{-1} + k_2^{Cl})/k_2^{Cl}(2k_{-1} + k_2^{Br})$$

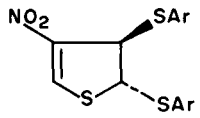
for which a maximum element effect of 3.8 can be calculated based on $k_{isom} = 0.027\,M^{-1}s^{-1}$ and $k_{elim} = 0.025\,M^{-1}s^{-1}$ for the chloride, **51**, and $k_2^{Br} > k_{-1}$ for the bromide. This is much smaller than the observed effect of 70 for *syn* elimination. It was suggested instead that the mechanism is $E1cB_{ip}$ (Scheme 4), at least for the chloride—there could still be a change in rate-limiting step (to k_1) for the bromide. For the isomerization reaction of *cis*- and *trans*-methoxy or *t*-butoxycyclobutanecarbonitrile, the primary kinetic isotopic effect is *ca* 1[315]. This suggests a mechanism for the isomerization reaction that involves internal return and in which proton transfer is not rate-limiting. It is also possible that the bromide substrate reacts via an E2 mechanism, although concerted 1,3-eliminations are generally less favorable than stepwise ones (see below and Section VI.B.).



SCHEME 4

The carbonyl activated substrates, **53**, do not isomerize and only undergo elimination. They also show a small k_{syn}/k_{anti} rate constant ratio of 1.3, and eliminate with significant primary kinetic isotope effects, 5.1 and 3.9, respectively. These results suggest a different mechanism for the carbonyl activated system, either E2 or $E1cB_{irr}$. An $E1cB_{irr}$ mechanism was favored by the authors, because of the small k_{syn}/k_{anti} ratio, and a small effect on the rate constant of added 18-crown-6-ether. These results support the view that concerted 1, 3-eliminations do not compete with their stepwise counterparts[316]. It is likely that rate constants for expulsion of leaving groups from carbanions are much smaller for 1, 3- than 1,2-eliminations. It may be that concerted 1,3-eliminations are unfavorable because the intermediate carbanions in these processes have significant lifetimes so that the stepwise mechanisms prevails, even for substrates with good leaving groups.

Other recent examples of systems for which an $E1cB_{ip}$ mechanism has been established or is possible include the methoxide ion catalyzed reactions of *erythro-* and *threo-* $PhCH(Cl)CMe(Et)NO_2$ in methanol, which show a small primary kinetic isotope effect of 1.6, and hydrogen–deuterium exchange or substrate epimerization. This reaction also shows significant amounts of *syn* elimination (approximately 40–60%)[317], so that, if the mechanism is $E1cB_{ip}$, the ion pairs maintain their structural identity and do not interconvert more rapidly than they eliminate[318]. An $E1cB_{ip}$ mechanism is also likely for the tributylamine-catalyzed reactions of *trans*-2, 3-bis(arylthio)-4-nitro-2, 3-dihydrothiophenes[319], **54**, and *trans*-2, 3-bis(mesitylthio)-4-nitro-2, 3-dihydrothiophene[320], **55**, in toluene, and the reaction of 1, 1, 1-trifluoro-2, 2-bis-(*p*-nitrophenyl)ethane catalyzed by piperidine or pyrrolidine in dipolar aprotic solvents[321], a reaction in which the elimination product reacts further with base to form mono and dienamine products. The $E1cB_{ip}$ mechanism has also been proposed for the expulsion of methoxide from 1-methoxyacenapthene[215], and of fluoride ion from 2-methyl-3-phenyl-1, 1, 1-trifluoropropane catalyzed *t*-butoxide ion in *t*-butanol[322], for the reaction of $ArC(CN)_2CH(CN)_2$ in chloroform catalyzed by amine bases[36], and for the triethylamine catalyzed reactions of $PhSO_2C(R^1R^2)CHFSPh$ in benzene[323] and $PhSO_2CH_2CH_2F$ in acetonitrile and benzene[34a].



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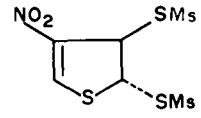

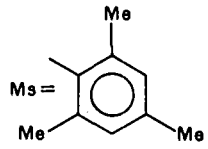

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VIII. ACKNOWLEDGMENTS

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72. Although the common symbolism for representing mechanisms of elimination reactions (i.e. E2, E1cB, etc.) will be used here, the Commission on Physical-Organic Chemistry of IUPAC has recently proposed a new symbolism (Table 1). The IUPAC symbolism describes the properties of a given mechanistic model more completely than the classical symbolism, and does so in a way that is easier to remember, once the rules are known. In the IUPAC system, atoms are first classified as either core, peripheral or carrier atoms. For elimination reactions, the core, peripheral and carrier atoms correspond to the α and β carbons, the β hydrogen and leaving group, and the base catalyst, respectively. This classification provides a frame of reference for defining the flow of electrons in a given reaction.

Bond formation and bond cleavage are represented by A (for association) and D (for dissociation), respectively; subscripts are then used to indicate whether a process involves an electron-rich or electron-deficient species, or hydrogen, and whether it occurs at a core, peripheral or carrier atom. For example, A_N, A_E and A_H represent bond formation at a core atom (this is denoted by using *upper case* N, E and H) of a nucleophilic species, an electrophilic species and hydrogen, respectively. Likewise D_N, D_E and D_H represent the corresponding bond cleavages. Similarly A_n, A_e and A_h (or A_{xh}), and D_n, D_e and D_h (or D_{xh}) represent these same processes occurring at peripheral *or* carrier atoms (this is denoted by using *lower case* n, e and h). The A_h and D_h terms are used when the proton transfer is to and from a peripheral atom, and the 'x' is included when the proton transfer is to and from a carrier atom (e.g. A_{xh} or D_{xh})—this distinction is useful in identifying the site of catalysis in some cases. Based on this system, for example, an E2 mechanism is described as an $A_{xh}D_HD_N$ process—proton transfer to the base catalyst (A_{xh}), with loss of a proton (D_H) and a leaving group (D_N) from core atoms—the β and α carbons, respectively. The absence of punctuation means that the process is concerted. Discrete steps are separated by a + sign. For example, and E1cB mechanism is described as an $A_{xh}D_H + D_N$ process—proton transfer from the substrate (D_H) to the base catalyst (A_{xh}), followed by leaving-group expulsion (D_N). Table 1 lists both IUPAC and common symbolism for representing mechanisms of base-catalyzed elimination reactions. Some additional features of the IUPAC system are explained in the footnotes to Table 1.
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